ALZHEIMER'S DISEASE & OTHER DEMENTIAS: BASIC/REFRESHER INFORMATION & CURRENT UPDATES FOR THE AGING NETWORK ON SYMPTOMS, DIAGNOSES AND TREATMENTS

May 9, 2012

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National Institutes of Health

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Alzheimer's Disease & Other Dementias: Basic/refresher information & current updates for the Aging Network on symptoms, diagnoses and treatments

May 9, 2012

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What is Dementia?
How is Dementia Diagnosed?
What are the different Types of Dementia?

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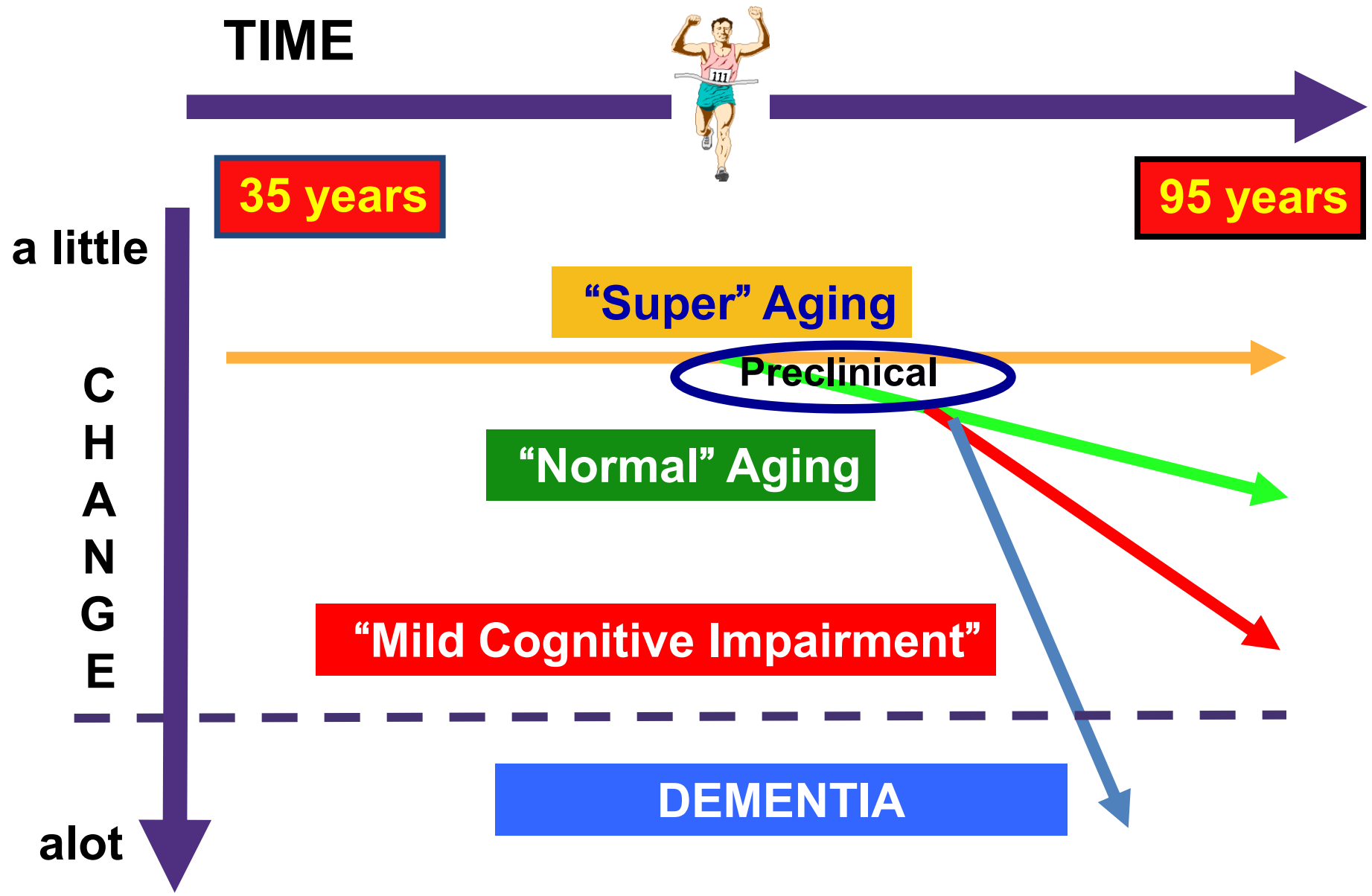
PATHWAYS OF AGE-RELATED COGNITIVE CHANGE: A Race Against Time



WHAT IS DEMENTIA?

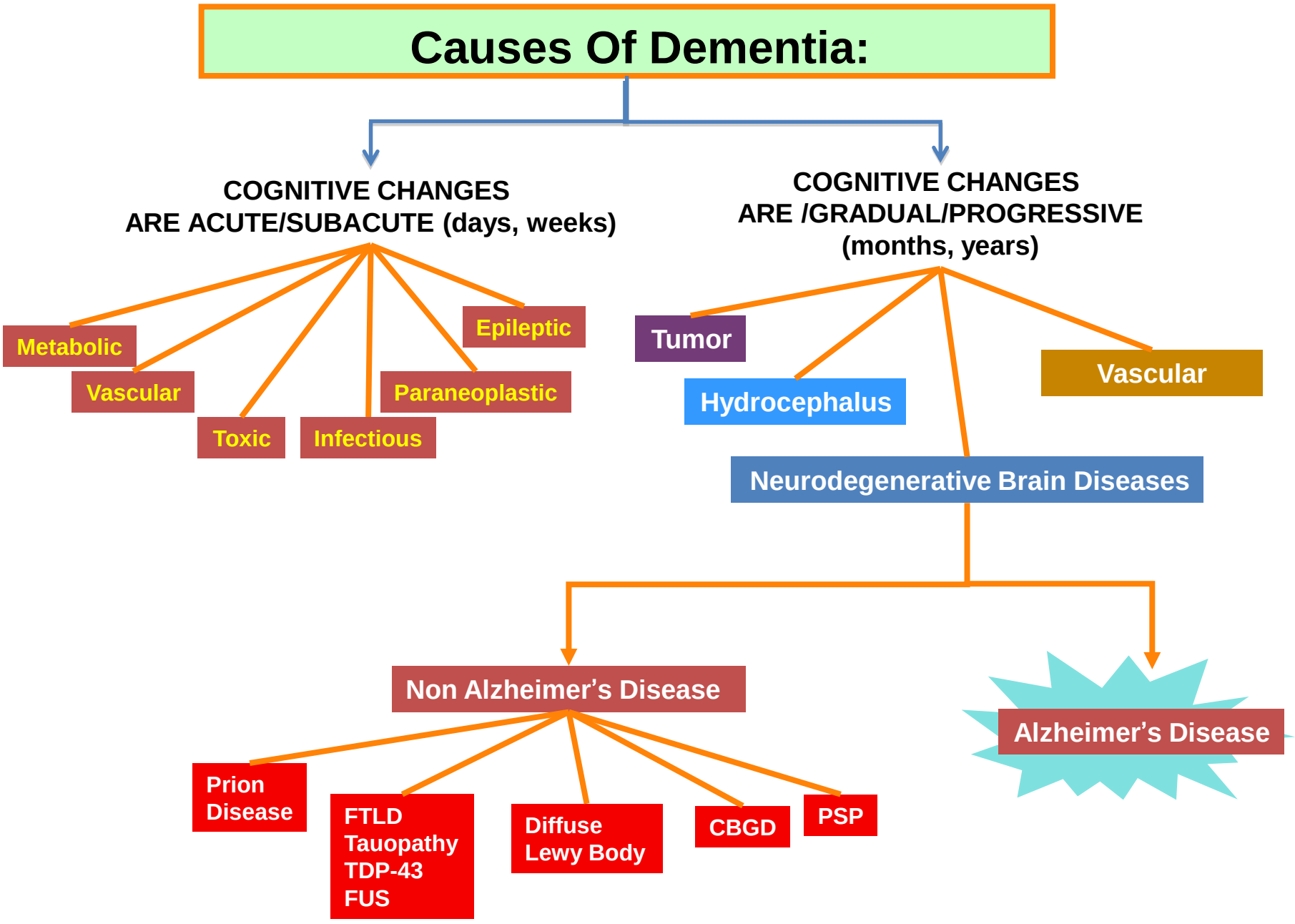
DEMENTIA: A Description of a Condition (Clinical Syndrome) With *Many* Causes

1) INITIALLY UNNOTICED (insidious), progressive decline in cognition and/or behavior *from a prior level of functioning*

2) Decline in *one or more*: memory, reasoning, language, visual perceptual processes, executive functions, social-interpersonal behaviors, personality; memory most common

3) Interferes with customary activities and social relationships, causing dependence, alienation

4) Caused by brain disease


Causes Of Dementia:
COGNITIVE CHANGES
ARE ACUTE/SUBACUTE (days, weeks)
COGNITIVE CHANGES
ARE /GRADUAL/PROGRESSIVE
(months, years)
Metabolic
Vascular
Toxic
Infectious
Paraneoplastic
Epileptic
Tumor
Hydrocephalus
Vascular
Neurodegenerative Brain Diseases
Non Alzheimer's Disease
Alzheimer's Disease
Prion Disease
FTLD
Tauopathy
TDP-43
FUS
Diffuse
Lewy Body
CBGD
PSP

How Is Dementia Diagnosed?

EVALUATION FOR SUSPECTED DEMENTIA

Clinical examination by clinician skilled in dementia (behavioral neurologist, neuropsychologist, geriatrician, psychiatrist):

- **Is this a change from usual way of functioning?**
- **Has it interfered with *customary* daily living activities**
- **and interpersonal relationships?**
- **When did it start? Did it start slowly or rapidly?**
- **Has it progressed, stayed the same, gotten better?**
- **What is the medical history?**
- **What is the psychiatric history?**

EVALUATION FOR SUSPECTED DEMENTIA

Brain Imaging:

- **Brain Structure: MRI or CT scan (Rule out tumor, stroke, other causes of dementia)**
- **Brain Function: Positron Emission Tomography to find patterns of brain dysfunction associated with different causes of dementia**

- **Blood tests (Exclude potentially reversible conditions)**

- **Neuropsychological examination**
  - The only marker of the cognitive dysfunction

Activities of Daily Living Questionnaire (ADL-Q)

Johnson, Barion, Rademaker, Rehkemper, Weintraub, ADAD, 2004

Self-Care	**Employment/Recreation**
Household Care	**Travel**
Shopping/Money	**Communication**

Recreation

0 = Same as usual

1 = Engages in recreational activities less frequently

2 = Has lost some skills necessary for recreational activities (e.g., bridge, golfing); needs coaxing to participate

3 = No longer pursues recreational activities

9 = Never engaged in recreational activities OR don't know

Mild=0-33%; Moderate=34-66% Severe=>66%

Important for Diagnosing Dementia

Staging Dementia Severity
Mild, Moderate, Severe

TESTS FOR PATIENTS:

Mini Mental State Examination (MMSE)
Blessed Dementia Scale (BDS)
Montreal Cognitive Assessment (MoCA)

OBSERVER RATINGS

Clinical Dementia Rating Scale (CDR)

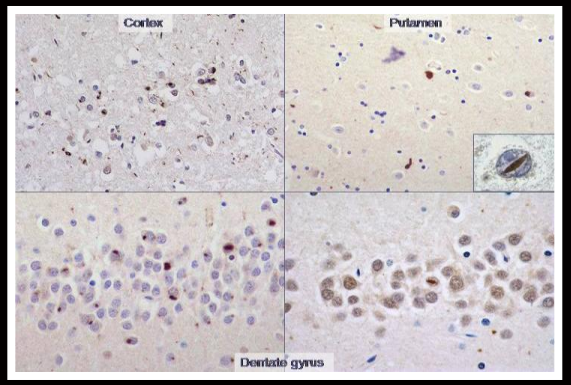
EVALUATION FOR SUSPECTED DEMENTIA

The definitive diagnosis of the disease causing the dementia still relies on post mortem brain autopsy

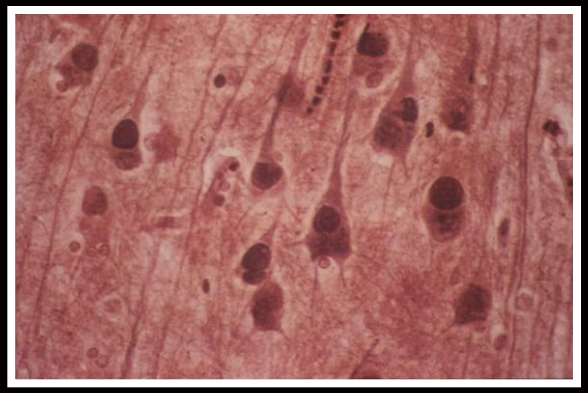
The brain autopsy shows the cell and protein abnormalities that caused brain cells to die and cause dementia

AUTOPSY DIAGNOSIS BASED ON NERVE CELL ABNORMALITIES

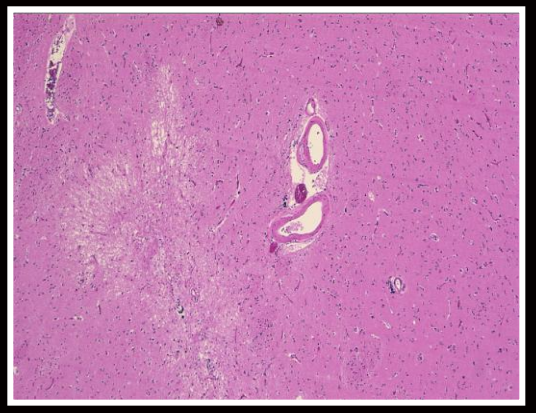
Frontotemporal Lobar Degeneration With TDP-43 Proteinopathy



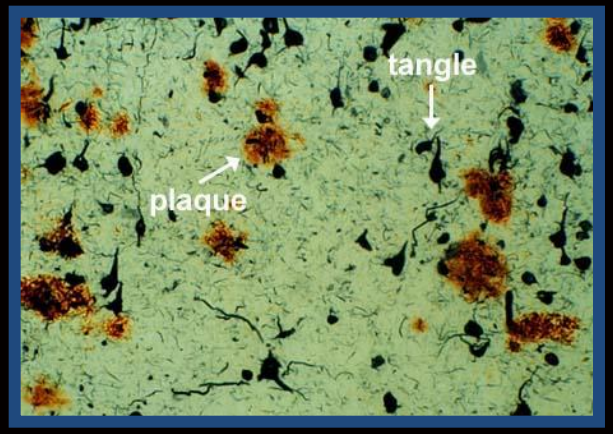
Frontotemporal Lobar Degeneration With Tau Inclusions - e.g. Pick's disease

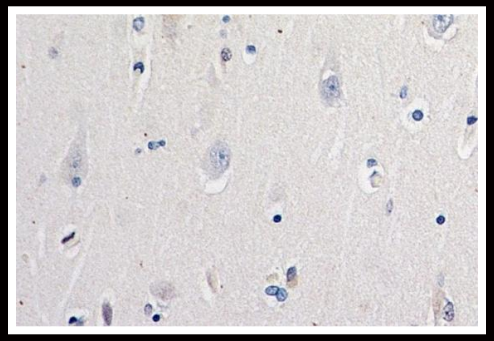


Microinfarct "Mini Stroke"



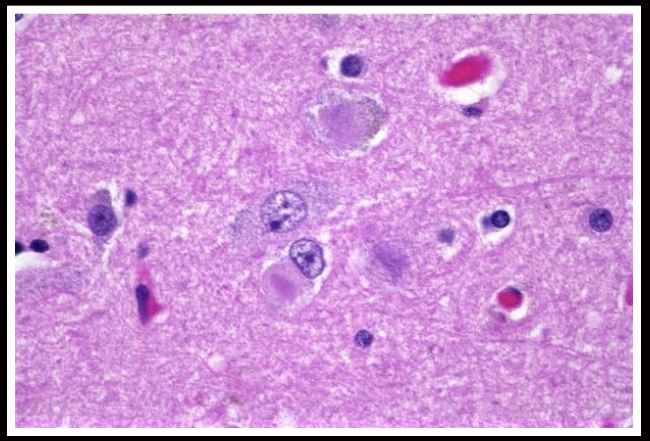
Plaques and Tangles- "Alzheimer's Disease"





NORMAL BRAIN TISSUE

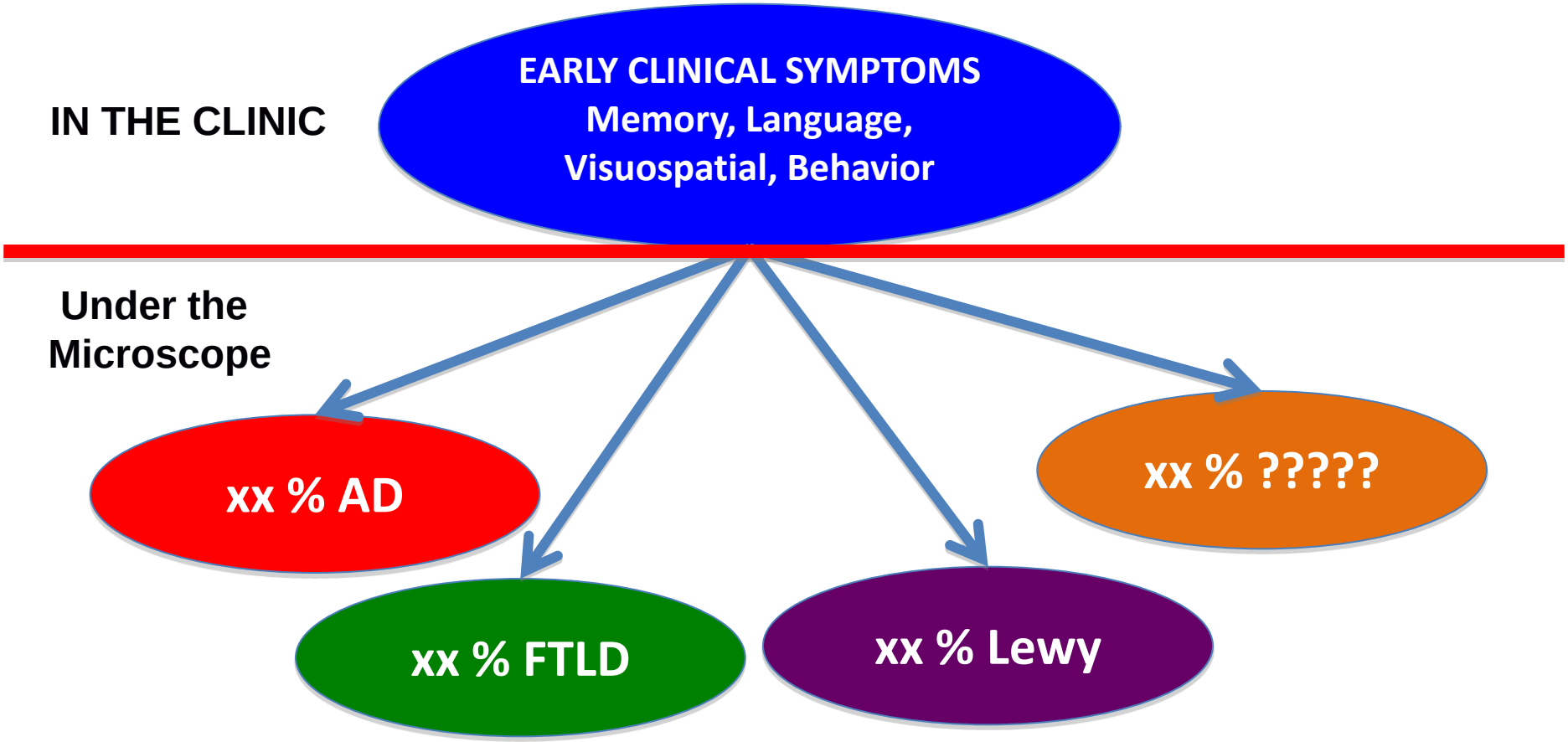
Cortical Lewy Body Disease



Courtesy Eileen Bigio MD NORTHWESTERN CNADC

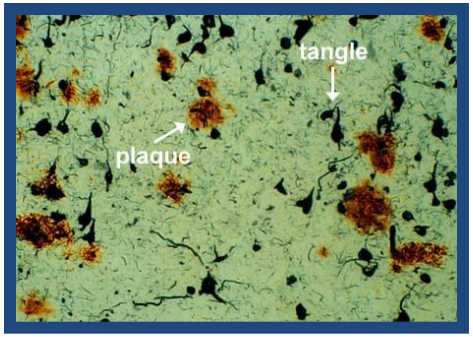
What are the different Types of Dementia? "Differential Diagnosis"

There is no 1:1 correspondence between the dementia symptoms and the neuropathology at post mortem
BUT there are well-established correlations



Dementia Diagnoses: BASED ON THE EARLY CLINICAL SYMPTOMS

1) Dementia of the Alzheimer Type:
Initial Symptom most often Short Term Memory Loss: Forgets conversations; repetitive comments/questions. Also reduced motivation.
Later Symptoms: word-finding difficulty, visual perception disorders, reasoning problems

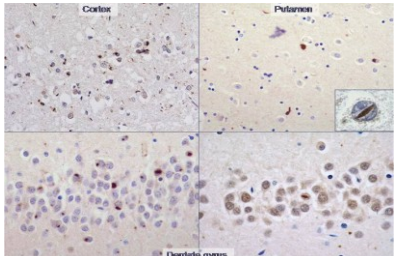


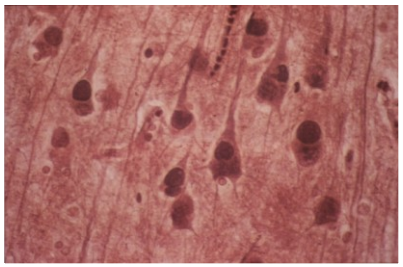
Brain Autopsy:
90%- have AD neuropathology
10%-other pathology

Slides courtesy E. Bigio, MD

2) Dementia of the Frontotemporal Lobar Degeneration Type: Two main clinical forms:

a) Primary Progressive Aphasia: Early Symptoms: Word-finding deficits; Later Symptoms: reading, spelling errors; behavioral changes; short term memory loss





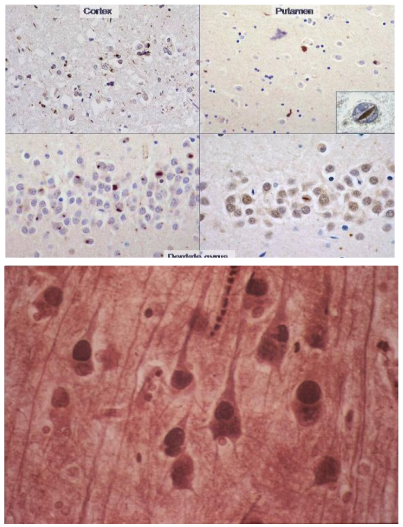
Brain Autopsy:
70% have FTLD neuropathology (Tauopathy, TDP 43 proteinopathy, other)
30% Alzheimer's neuropathology

Slides courtesy E. Bigio, MD

b) Behavioral Variant Frontemporal Dementia;

Early symptoms: personality change, poor judgment, inappropriate emotions, odd food habits

Later Symptoms: memory loss; also can have motor symptoms (tremor, etc.)



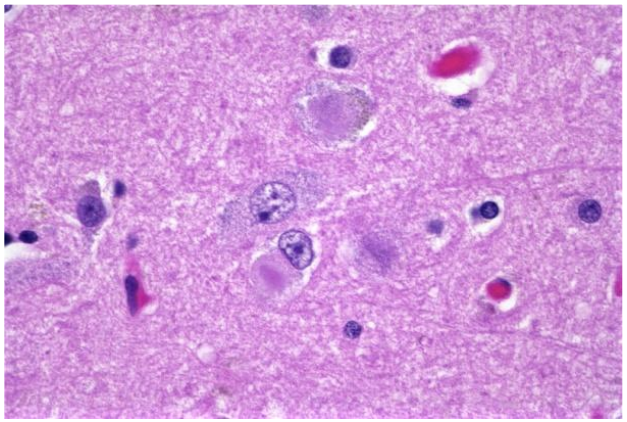
Brain Autopsy:

70% have FTLD neuropathology (Tauopathy, TDP 43 proteinopathy, other)

30% Other, *including* AD neuropathology

Slides courtesy E. Bigio, MD

3) Lewy Body Dementia: Prominent visuospatial deficits; visual hallucinations (usually *pleasant, non threatening*); symptoms fluctuate; motor symptoms (parkinson-like)



Brain Autopsy:

***53% Cortical Lewy Body Disease**

26% AD neuropathology

21% other

*** Based on Nelson et al,J Neurol, 2010**

Slides courtesy E. Bigio, MD

4) Vascular Dementia:
Many types of symptoms: aphasia, behavior, executive functions, motor symptoms; depend on brain location of stroke

Related to chronic cardio and cerebrovascular risk factors (heart disease, hypertension, high cholesterol); progressive loss of function due to multiple successive cerebrovascular events ("mini strokes")

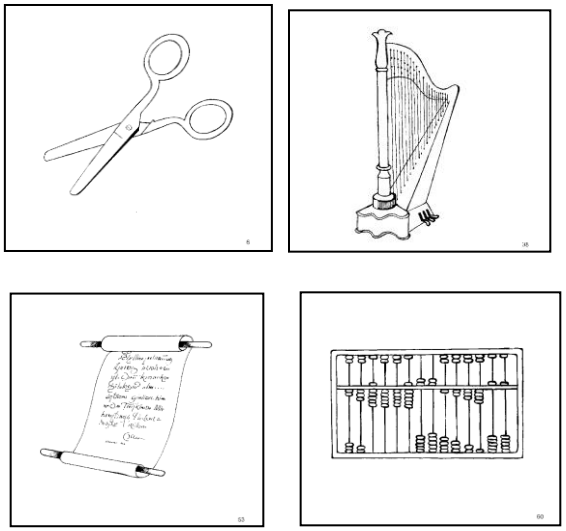
5) Prion Disease ("Mad Cow"):
Rapid course; may be accompanied by severe sleep disorder; myoclonic jerks of the body

Neuropsychological Battery: Shows the profile of cognitive deficits *and* strengths

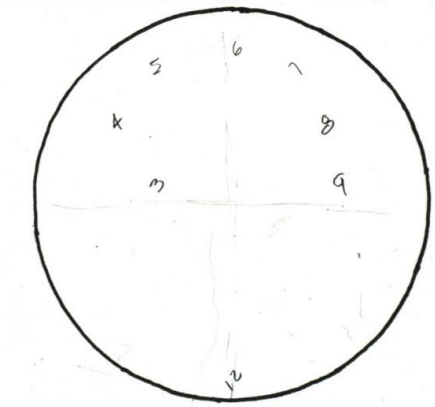
Neurocognitive Domains Are Related to Different Brain Networks

- Attention
- Executive Functions
- Mood/Affect/Behavioral Scales
- Memory
- Language
- Visuospatial
- Reasoning

NEUROPSYCHOLOGICAL TESTS OF COGNITIVE FUNCTIONS



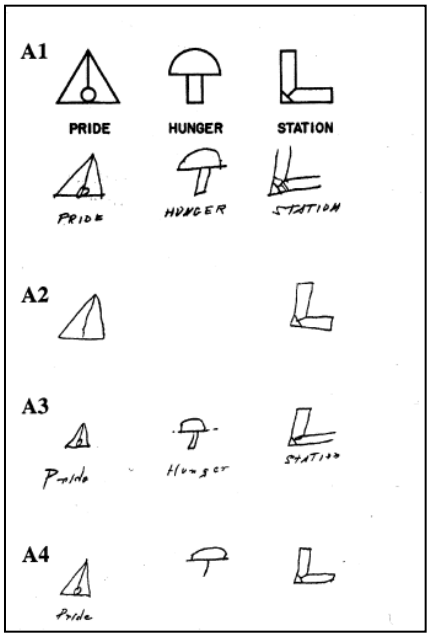
Language (Naming)



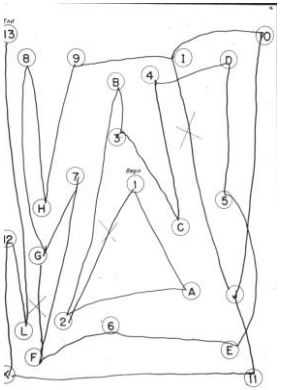
Visuospatial

1-8-5-7-9-3

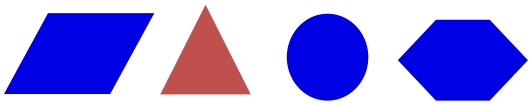
Attention



Retentive Memory



Executive



1 2 3 4

Reasoning

DEMENTIA

1) EARLY clinical symptoms (neuropsychological, neurological, and psychiatric) tell Which Part of the Brain is not working properly

2) The post mortem brain autopsy tells what disease is attacking those parts of the brain in early stages

3) All diseases progress to eventually affect many brain regions and, correspondingly, all dementias progress to affect all cognitive and behavioral functions

4) BUT, the earliest symptoms are most helpful in predicting the post mortem neuropathology AND advising patients and caregivers on management

THE END

RUSH UNIVERSITY MEDICAL CENTER

IT'S HOW MEDICINE SHOULD BE

Webinar #1

Alzheimer's Disease & Other Dementias – Diagnosis

Raj C. Shah, MD

Asst. Prof., Family Medicine and Rush Alzheimer's Disease Center

Medical Director, Rush Memory Clinic

Education and Information Transfer Core Leader, Rush Alzheimer's Disease Core Center

Wednesday, May 9, 2012

12:30 – 2:00pm CST

Disclosures

I receive or have recently received research support from the NIH [P30 AG101061 (Education and Information Transfer Core Leader), P01 AG009466 (Co-investigator, Administrative Core), U01 AG010483 (Site Investigator), U01AG024904 (Site Co-investigator), and U01 AG029824 (Coinvestigator)] and from the Illinois Department of Public Health Alzheimer's Disease Assistance Center Grant.

I receive or have recently received research support as Site PI or Site Subinvestigator from Ceregene, Inc., Danone Research B.V., Eisai, Inc., Elan Pharmaceuticals,Inc., Genentech, Inc., Merck & Co., Inc., Metabolic Solutions Development Company, Pamlab, L.L.C., Orasi, Inc., and Pfizer, Inc.; and

I serve on the Board of Directors of the Alzheimer's Association – Greater Illinois Chapter;

I recently served on a research advisory panel for Accera, Inc. and a Clinical Advisory Panel for Nutricia North America;

Objectives

- What is dementia
- Types of dementia
- **Risk factors**
- **Diagnosing dementia**
- Drug & non-drug treatments, drug discovery research
- Federally-funded sources for more information

Case Example

At your work, a 75 year-old client mentions that he is concerned about memory loss. He reports a family history of Alzheimer's disease, with dementia affecting three living first-degree relatives in their 60s. His difficulties are not apparent to his spouse or close friends, but he is noticing a change in his ability to rely on his thinking to perform his daily activities.

- Should he seek a cognitive evaluation?

Today's Discussion – Part 1

- Who should seek an evaluation?
- When should one seek an evaluation?
- Why seek an evaluation early?
- Where can one get an evaluation?
- What to expect from an evaluation?
- How is an evaluation conducted?

Today's Discussion – Part 2

- What a health provider may diagnose after a memory evaluation?

Evaluating Cognition: Who?

- Who should seek an evaluation?
  - Persons with clinical risk factors for dementia

Evaluating Cognition: Who?

- Risk Factors for Dementia
  - Non-Modifiable
    - Advancing Age
    - Family History
    - Genetic Factors (Apolipoprotein E ε4)

Evaluating Cognition: Who?

- Risk Factors for Dementia
  - Modifiable
    - Cardiovascular disease risk factors
      - High blood pressure
      - Diabetes
      - Cholesterol
      - Smoking
    - Head trauma (traumatic brain injury)
    - Unhealthy lifestyle choices
      - Lack of physical and cognitive activity
      - Poor nutrition
      - Low social engagement

Evaluating Cognition: When?

- When should one seek an evaluation?
  - When experiencing cognitive concerns that are affecting their quality of life and function
  - When experiencing cognitive concerns more frequently

Evaluating Cognition: Why?

- Why seek an evaluation early?
  - Define current cognitive status
  - Determine treatable conditions
  - Provide piece of mind

Evaluating Cognition: Where?

- Where can one get an evaluation?
  - Primary Health Care Provider
  - Neurologist
  - Psychiatrist
  - Geriatrician
  - Neuropsychologist

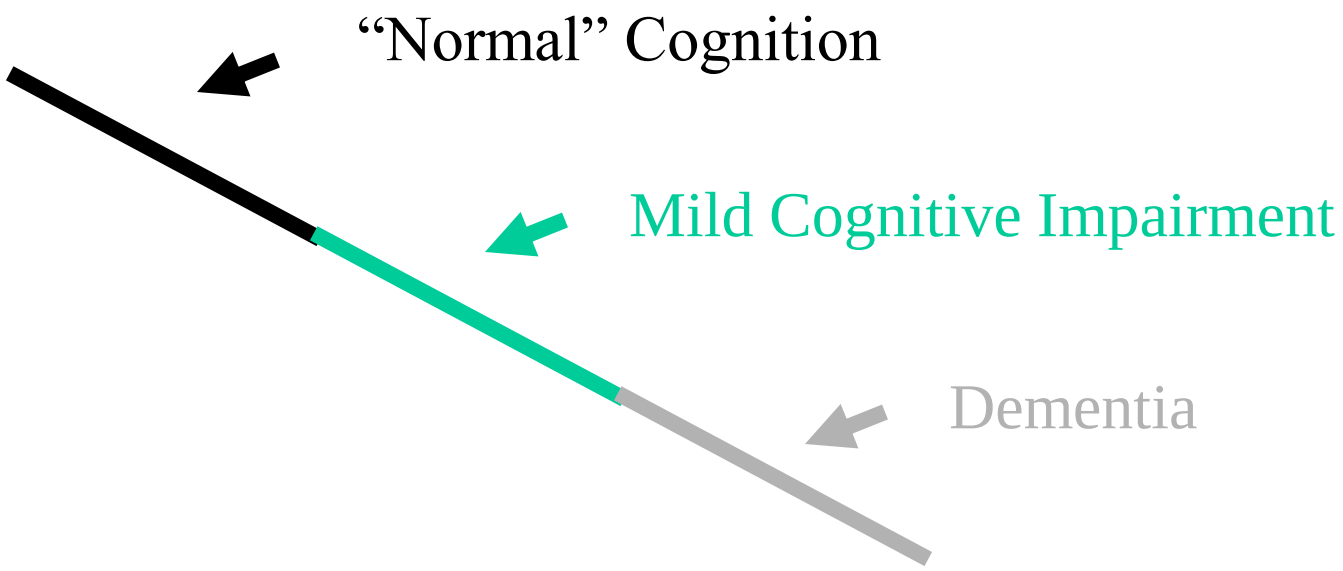
Evaluating Cognition: Where?

- Where can one get an evaluation?
  - Private Practice
  - Community Hospitals
  - Academic Health Centers

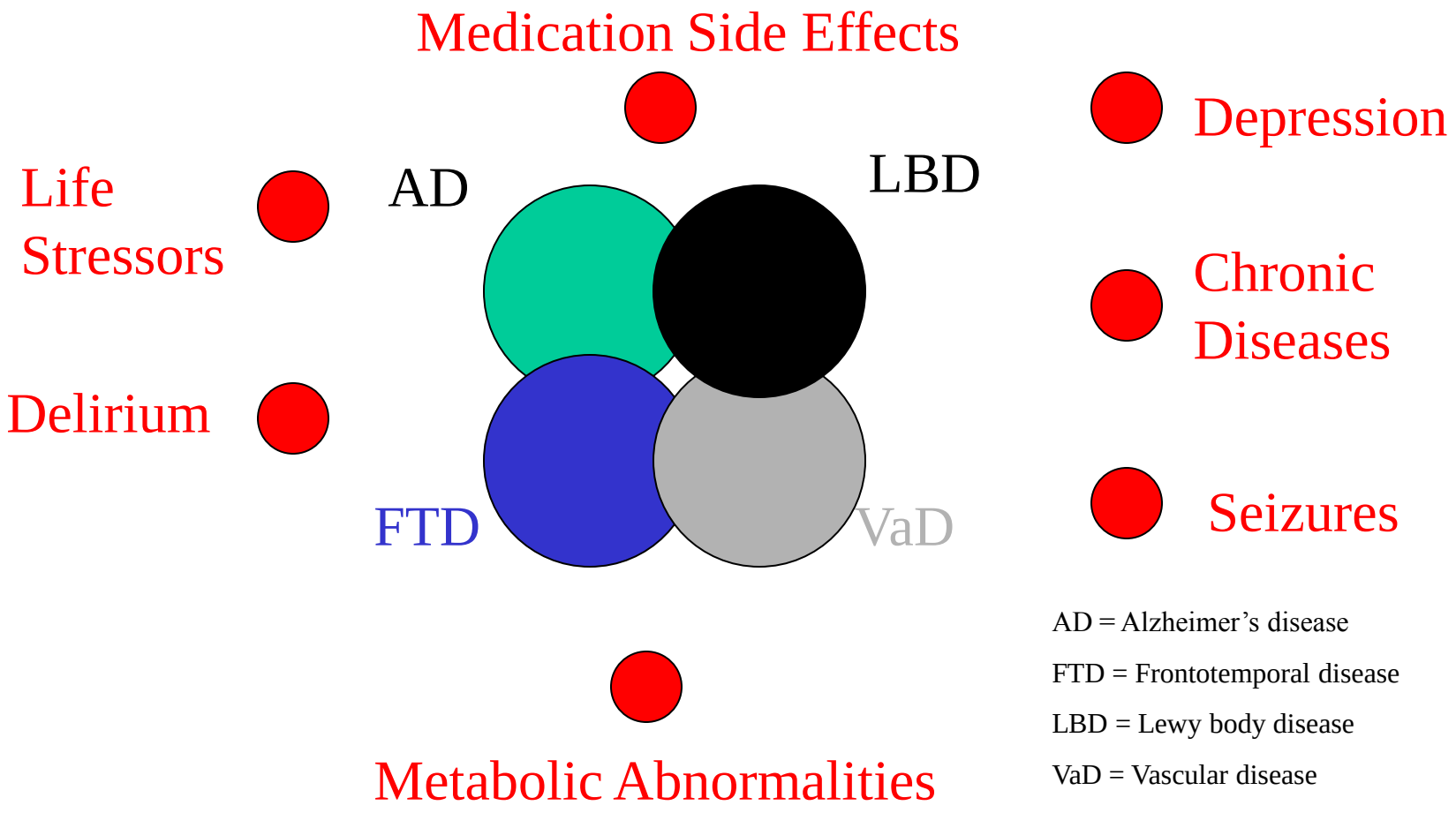
Evaluating Cognition: What?

- What to expect from an evaluation?
  - The health care provider listened to the cognitive concerns
  - A statement of where a person is on the cognitive spectrum from normal memory to Mild Cognitive Impairment to dementia
  - If a dementia is diagnosed, a statement about the primary cause for the dementia

Evaluating Cognition: What?



Evaluating Cognition: What?



AD = Alzheimer's disease

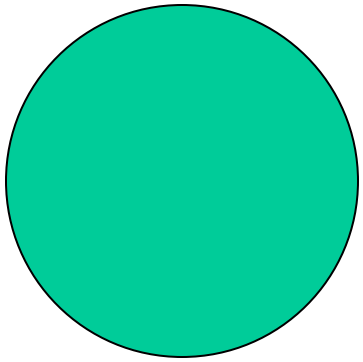
FTD = Frontotemporal disease

LBD = Lewy body disease

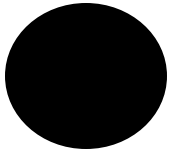
VaD = Vascular disease

Evaluating Cognition: What?

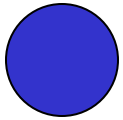
Alzheimer's Disease



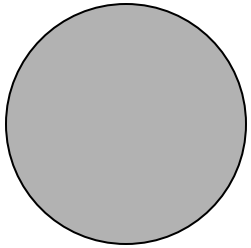
Lewy Body Disease



Frontotemporal Disease



Vascular Disease

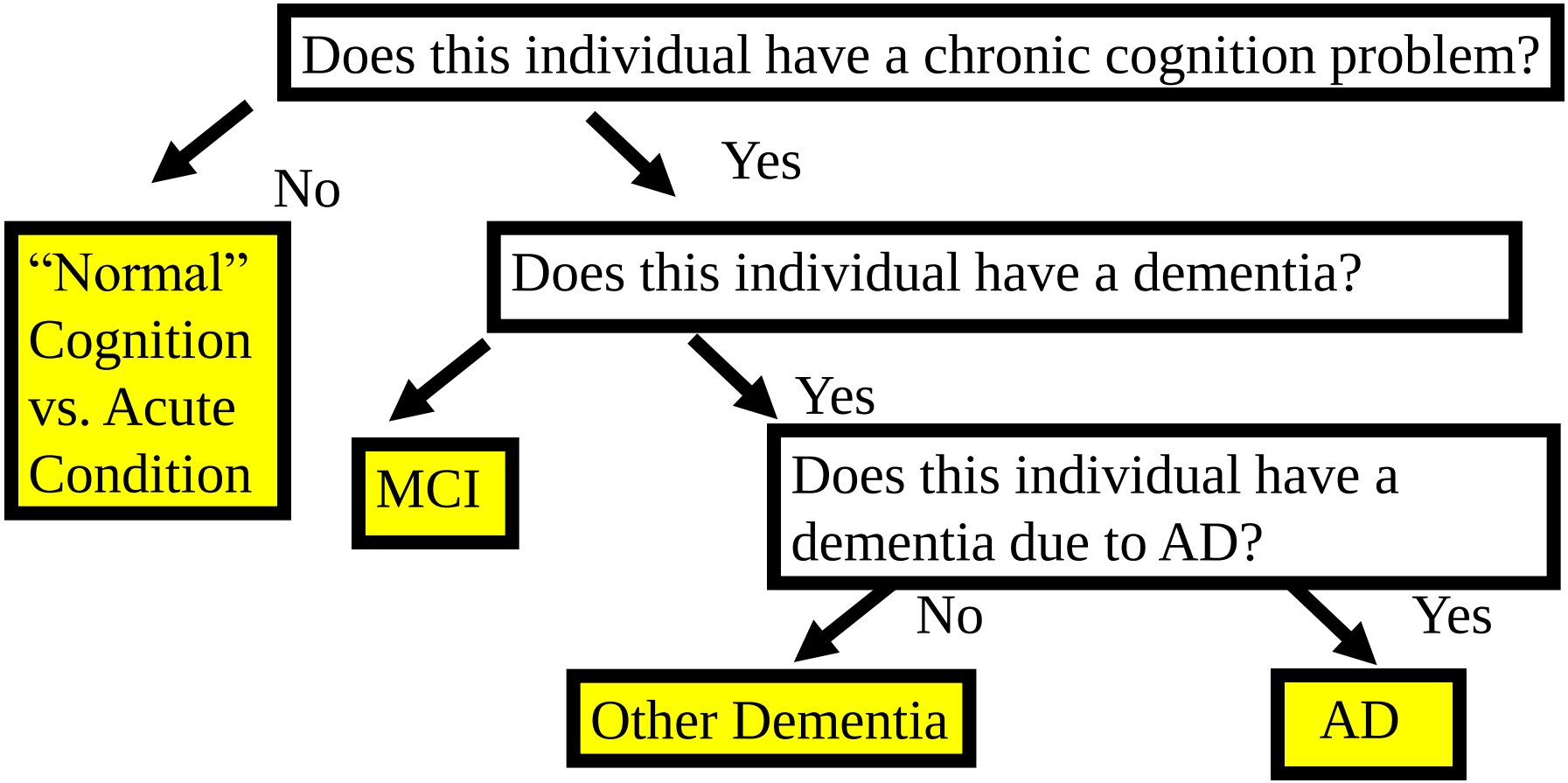


Evaluating Cognition: How?

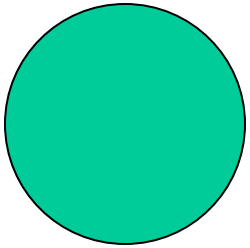
- How is an evaluation conducted?
  - Cognitive History of Present Illness*
  - Memory Review of Systems*
  - Depression Screening*
  - Functional Assessment*
  - Medication Review
  - Family History
  - Review of Support Network
  - Pen and paper tests of thinking function
  - Physical Examination
  - Common blood tests (thyroid, vitamin B12 levels)
  - Brain Imaging (if necessary)

*Helpful to confirm with an person who knows the individual with thinking concerns well

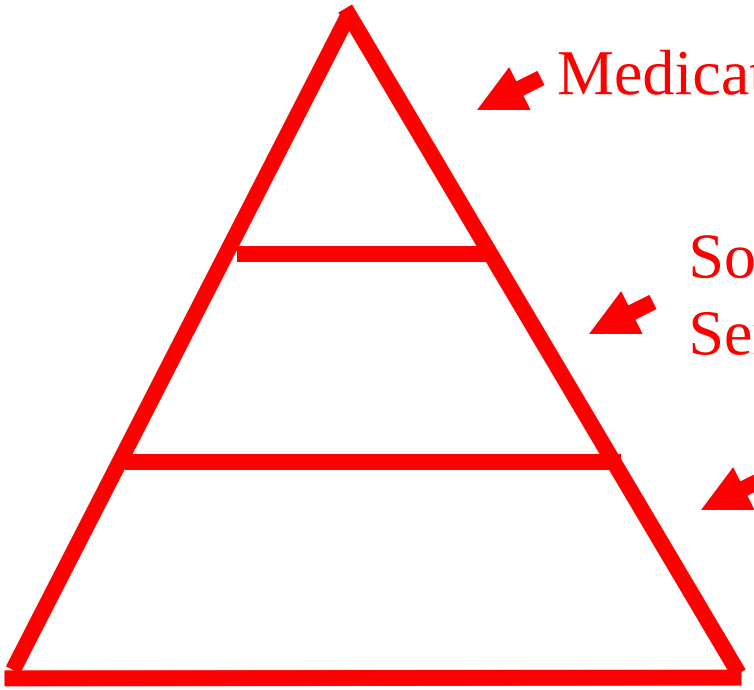
Evaluating Cognition: How?

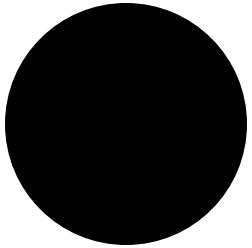


Treatment After Diagnosis



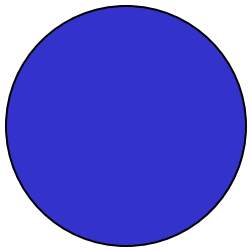
Cognition



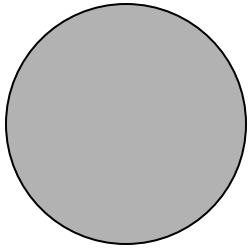


Behaviors

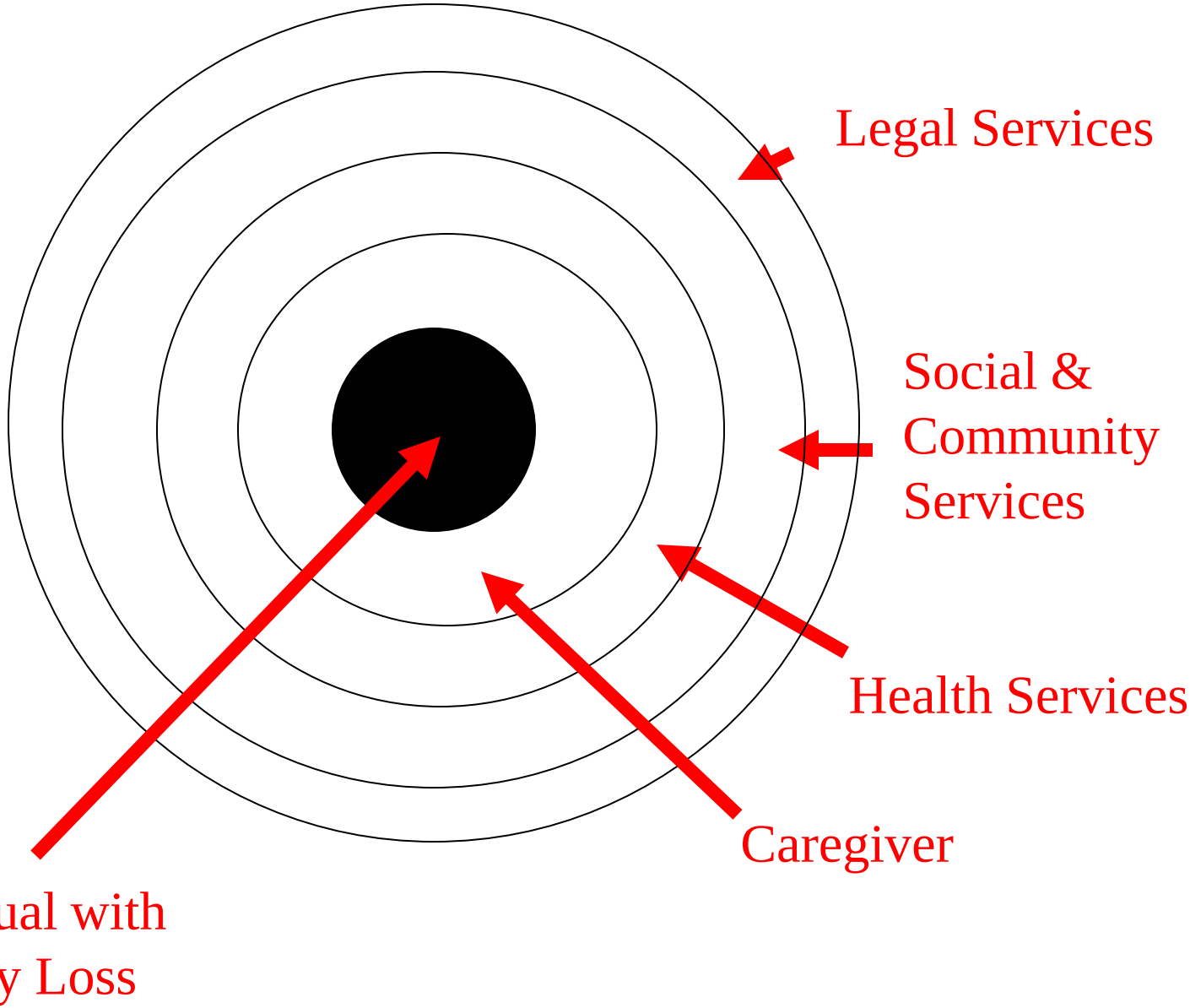
Functionality



Caregiver Burden



Treatment After Diagnosis



Conclusion

- Diagnosing cognitive disorders early will provide the most benefit.
- The diagnosis of individuals with cognitive concerns requires an integrated and team approach.
- Helping persons know what to expect in a cognitive evaluation can help in making sure they get the best health information for their needs as possible.

RUSH UNIVERSITY MEDICAL CENTER

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UPDATE ON ALZHEIMER'S DISEASE CLINICAL TRIALS

Laurie Ryan, PhD
Program Director, Alzheimer's Disease Clinical Trials
Dementias of Aging Branch
Division of Neuroscience
National Institute on Aging, National Institutes of Health

National Institute on Aging

Financial Disclosures

- I have no financial relationships to disclose

Currently FDA Approved Treatments for AD

- The U.S. Food and Drug Administration (FDA) has approved two types of medications to treat cognitive symptoms of AD.

- Provide temporary cognitive improvement and deferred decline in some patients

Currently Approved Treatments for AD

- Cholinesterase Inhibitors
  - Donepezil (Aricept)
  - Rivastigmine (Exelon)
  - Galantamine (Razadyne)

- Memantine (Namenda)

Failure of AD Candidate Therapeutics in the Clinic

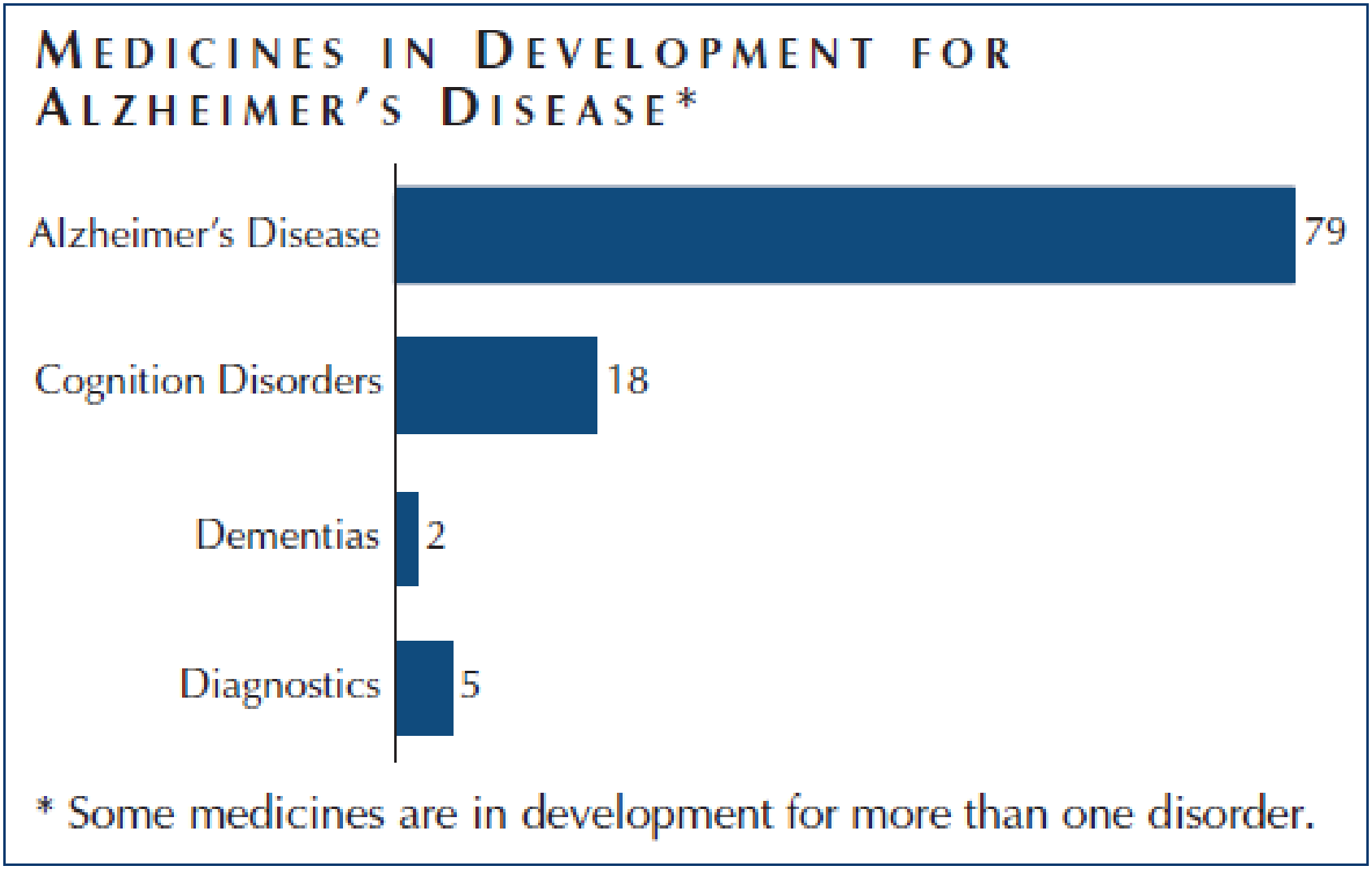
Phase III randomized, placebo controlled , double-blind clinical trials

Agent	Target/Mechanism	Outcome
Atorvastatin	HMG CoA reductase	Negative
Dimebon	Mitochondrial function	Negative
LY450139	Gamma secretase	Negative
NSAIDs	Inflammation	Negative
Phenserine	Cholinesterase/Amyloid	Negative
Rosiglitazone	PPAR gamma agonist	Negative
Simvastatin	HMG CoA reductase	Negative
Tarenflurbil	Gamma secretase	Negative
Xaliproden	Serotonin antagonist	Negative

The most common reasons for Phase III failure: *lack of efficacy and toxicity.*

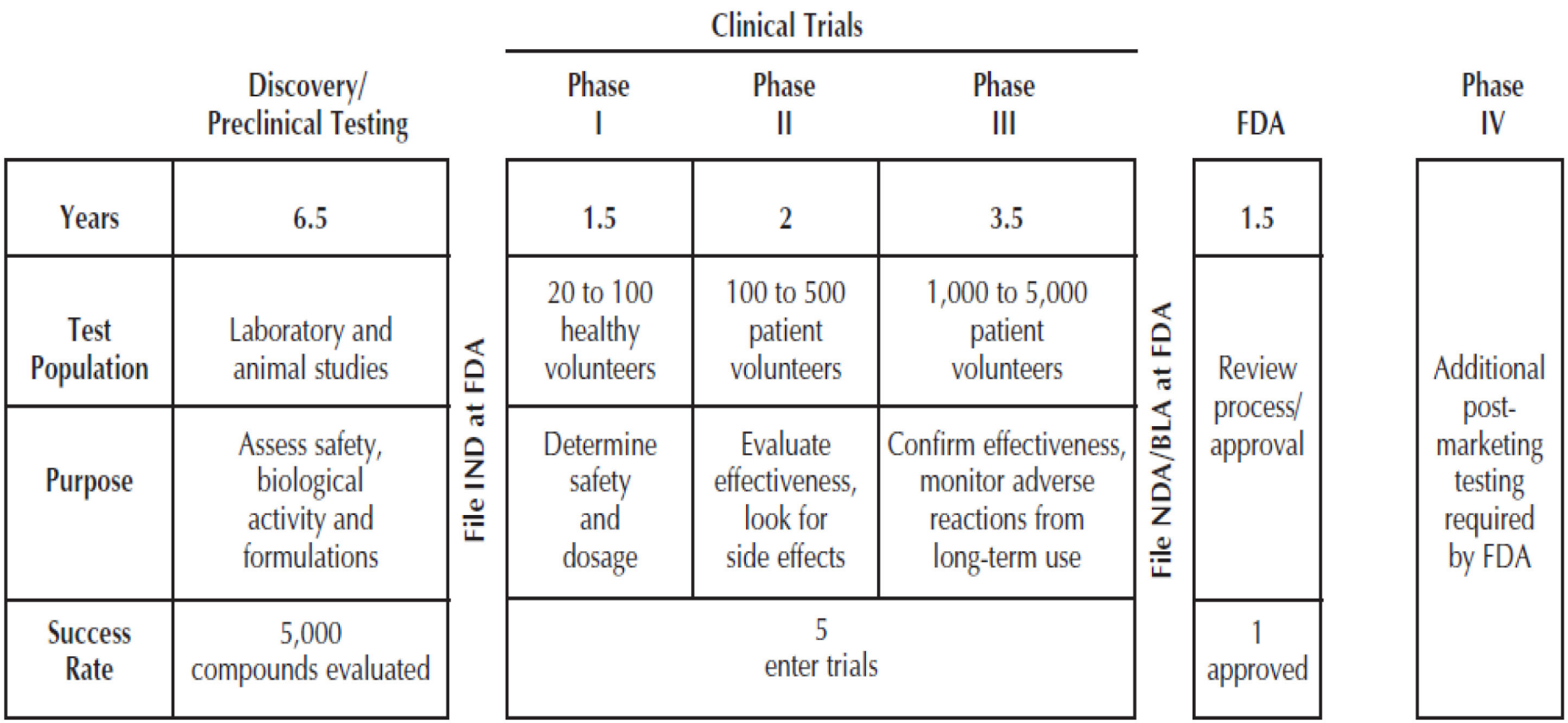
- If no new medicines are found to prevent, delay or stop the progression of Alzheimer's disease, the number of afflicted in America will jump to 13.5 million by 2050 (Alzheimer's Association).

- Costs for care for Alzheimer's patients will increase five-fold to $1.08 trillion a year. That is about 25 times more than the 2010 budget for the Department of Homeland Security.



From Medicines in Development for Alzheimer's Disease 2010
PhRMA; phrma.org

THE DRUG DISCOVERY, DEVELOPMENT AND APPROVAL PROCESS



It takes 10-15 years on average for an experimental drug to travel from the lab to U.S. patients. Only five in 5,000 compounds that enter preclinical testing make it to human testing. One of these five tested in people is approved.

Medicines in Development for Alzheimer's Disease 2010; PhRMA; phrma.org

Disease Modification

- An improved understanding of the pathogeneses of AD has led to the identification of numerous therapeutic targets

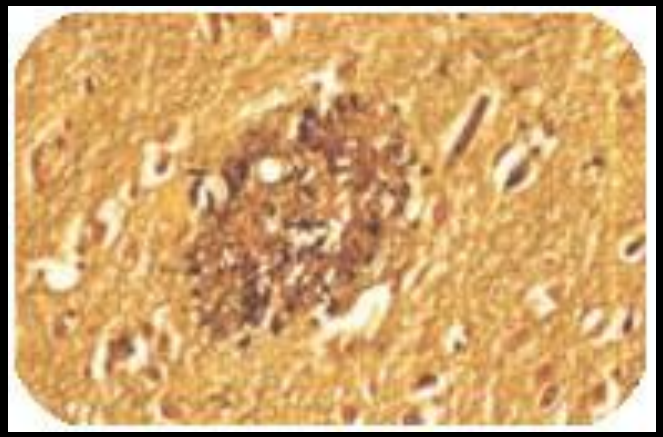
- Many of these targets have been validated in proof of concept studies in preclinical animal models, and a number are being tested in human clinical trials.

AD and the Brain

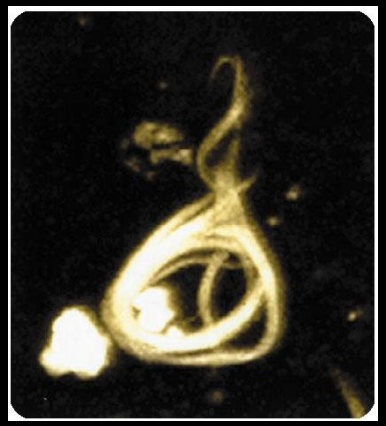
Plaques and Tangles: The Hallmarks of AD

The brains of people with AD have an abundance of two abnormal structures:

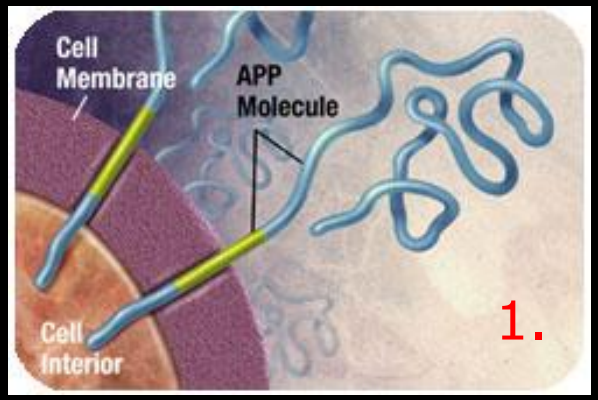
- beta-amyloid plaques, which are dense deposits of protein and cellular material that accumulate outside and around nerve cells
- neurofibrillary tangles, which are twisted fibers that build up inside the nerve cell

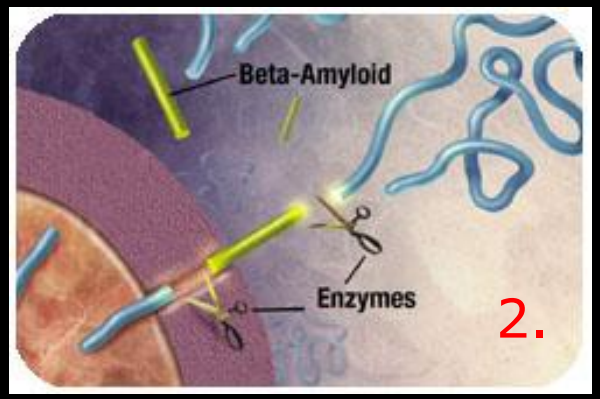


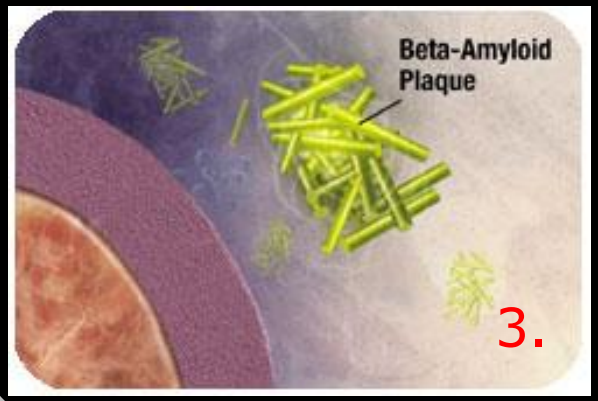
An actual AD plaque



An actual AD tangle







AD and the Brain

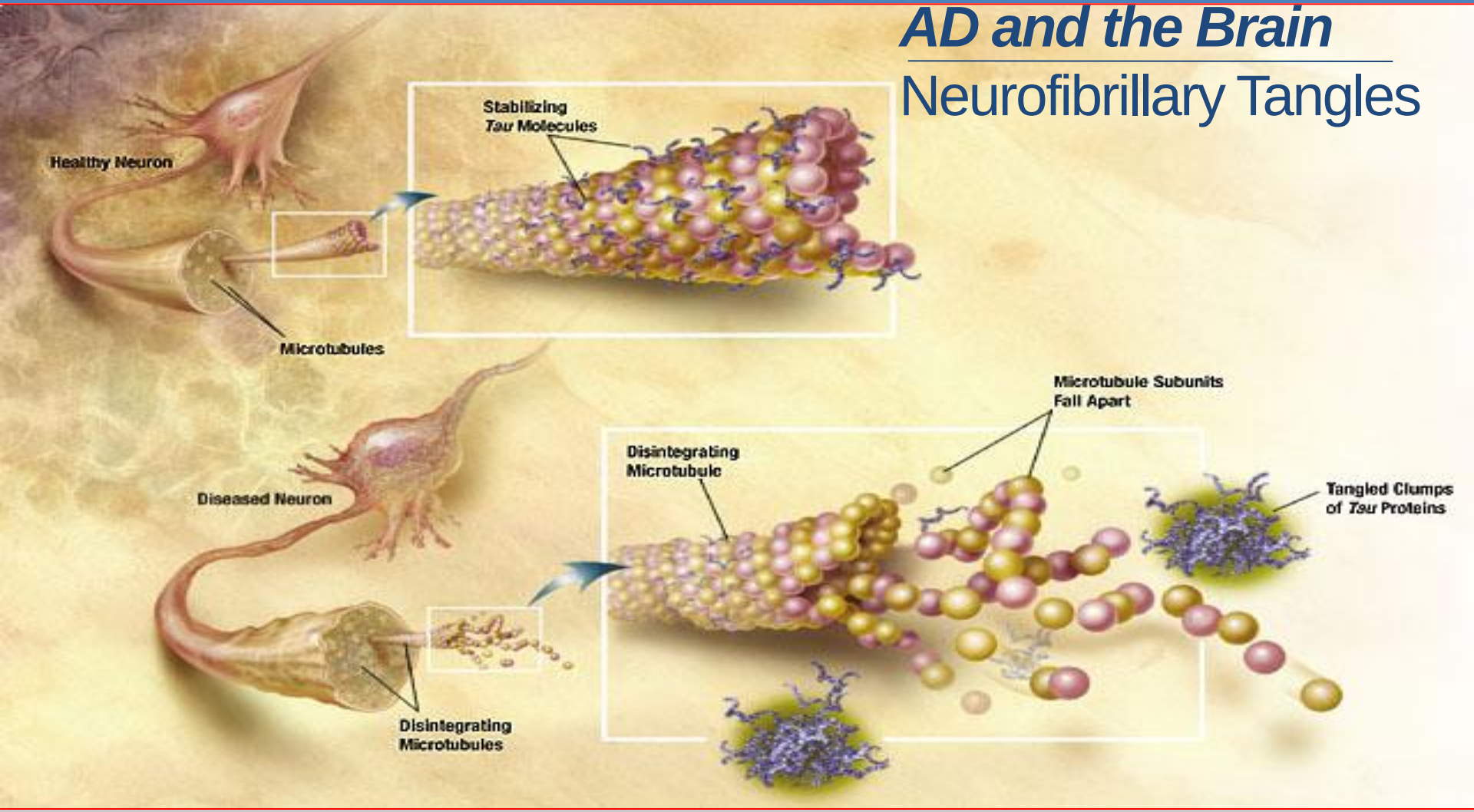
Beta-amyloid Plaques

Amyloid precursor protein (APP) is the precursor to amyloid plaque.

1. APP sticks through the neuron membrane.
2. Enzymes cut the APP into fragments of protein, including beta-amyloid.
3. Beta-amyloid fragments come together in clumps to form plaques.

AD and the Brain

Neurofibrillary Tangles

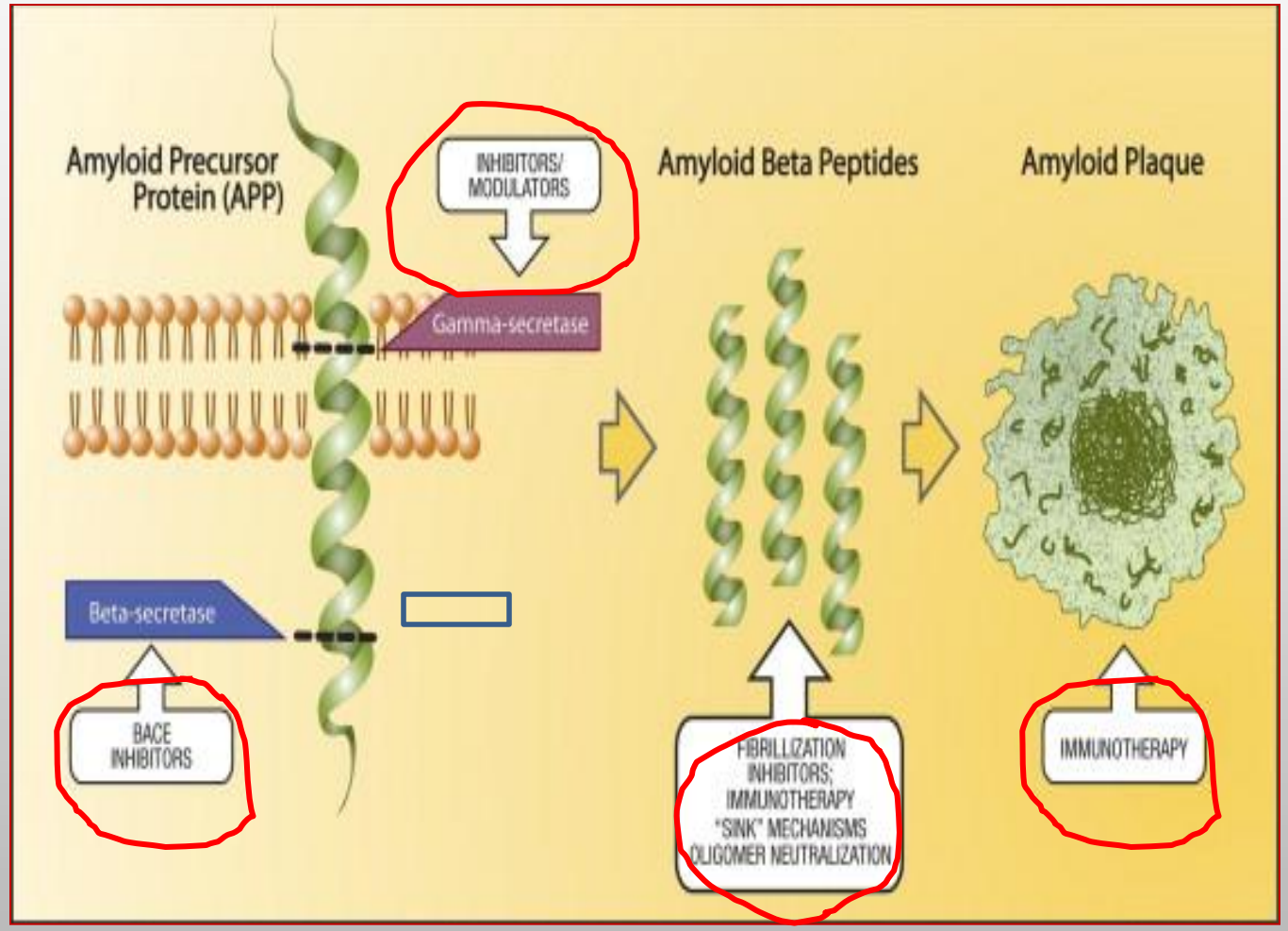


Neurons have an internal support structure partly made up of microtubules. A protein called *tau* helps stabilize microtubules. In AD, *tau* changes, causing microtubules to collapse, and *tau* proteins clump together to form neurofibrillary tangles.

Avenues for New AD Therapies

- **Prevent build up of plaque (anti-amyloid)**
  - slow or prevent amyloid production by inhibiting clipping enzymes or by vaccine therapy
  - slow aggregation into plaques
  - dissolve plaques
  - increase clearance
- **Prevent build up of paired helical filaments (tau focused)**
  - slow or prevent tau aggregation and dysfunction
  - dissolve paired helical filaments
- **Prevent brain cell dysfunction and death**
  - slow or prevent oxidative stress, inflammation, reduced blood flow
  - increase levels of protective molecules in brain
  - maintain viable connections between cells

Amyloidogenic Pathways: Possible Therapeutic Targets



Salloway, S. et al. *Alzheimer's and Dementia 2008; 4: 65-79*

Aβ Immunotherapy

- Altering Aβ deposition by inducing a humoral immune response to fibrillar Aβ42 (active) or administering anti-Aβ antibodies (passive)

AN1792: Active Immunization

- Initial human clinical trial was halted due to a meningoencephalitis in 6% of treated subjects.
- Leading hypothesis, supported by some recent experimental data: SAE attributable to an autoreactive T-cell response against Aβ.
- Passive immunization approaches do not initiate this type of response; in human trials
- Alternative active immunization strategies are in human trials

AN1792: Active Immunization

- **AN1792 4½ year follow-up:**
  - After active immunization was D/C'd, researchers continued to follow the participants.
  - Patients who developed antibodies to Aβ continued to show detectable Aβ antibodies and less decline in activities of daily living (ADL) compared to placebo treated patients.

Vellas et al. *Curr Alzheimer Res.* 2009 Apr;6(2):144-51

PASSIVE IMMUNIZATION :

IVIg – Intravenous Immunoglobulin (Gammagard)

Purified human immunoglobulin preparation recently found to contain polyclonal anti-Aβ antibodies

PHASE II: 24 patients with mild to moderate AD, one of four doses of IVIg or placebo for 24 mos.

RESULTS: Treatment with IVIg over nine months resulted in statistically significant improvements on both cognitive and global clinical measures; FDG-PET: treated groups were observed to show 16% higher brain metabolism (hippocampus, temporal-parietal regions) after treatment compared to placebo

SAFETY: No significant side effects

PHASE III: supported by the NIA through the Alzheimer's Disease Cooperative Study (ADCS), and Baxter, N=390

Aβ Immunotherapies in development.

Drug Name	Sponsor	Characteristics		Phase
Monoclonal Antibodies		*Epitope**	*Isotype*	
Bapineuzumab (AAB-001)	Janssen/Elan/Pfizer	1–5 (free N- terminus)	IgG1	III
Solanezumab (LY2062430)	Eli Lilly	13–28	IgG1	III
PF-04360365	Pfizer	33–40 (free C- terminus)	IgG2	II
MABT5102A	Genentech	NP	NP	I
GSK933776A	GlaxoSmithKline	NP	NP	I
Gantenerumab (R1450/RO4909832)	Hoffmann-La Roche	NP	IgG1	I
Intravenous Immunoglobulin				
Gammagard	Baxter; NIH Alzheimer's Disease Cooperative Study			III
Octagam	Octapharma			II
Active Vaccines		*Fragment**		
CAD106	Novartis	1–6		II
ACC001	Pfizer	1–7		II
UB311	United Biochemical	1–14		I
V950	Merck	NP		I
AD01/AD02	Affiris	**		I

Kerchner & Boxer *Expert Opin Biol Ther.* 2010 July; 10(7): 1121–1130

AD Neuropathology

- A growing body of evidence suggests that the underlying pathology precedes the onset of clinically detectable AD by a decade or more

- By the time a patient is diagnosed, there is thought to be massive neuronal loss and widespread pathology

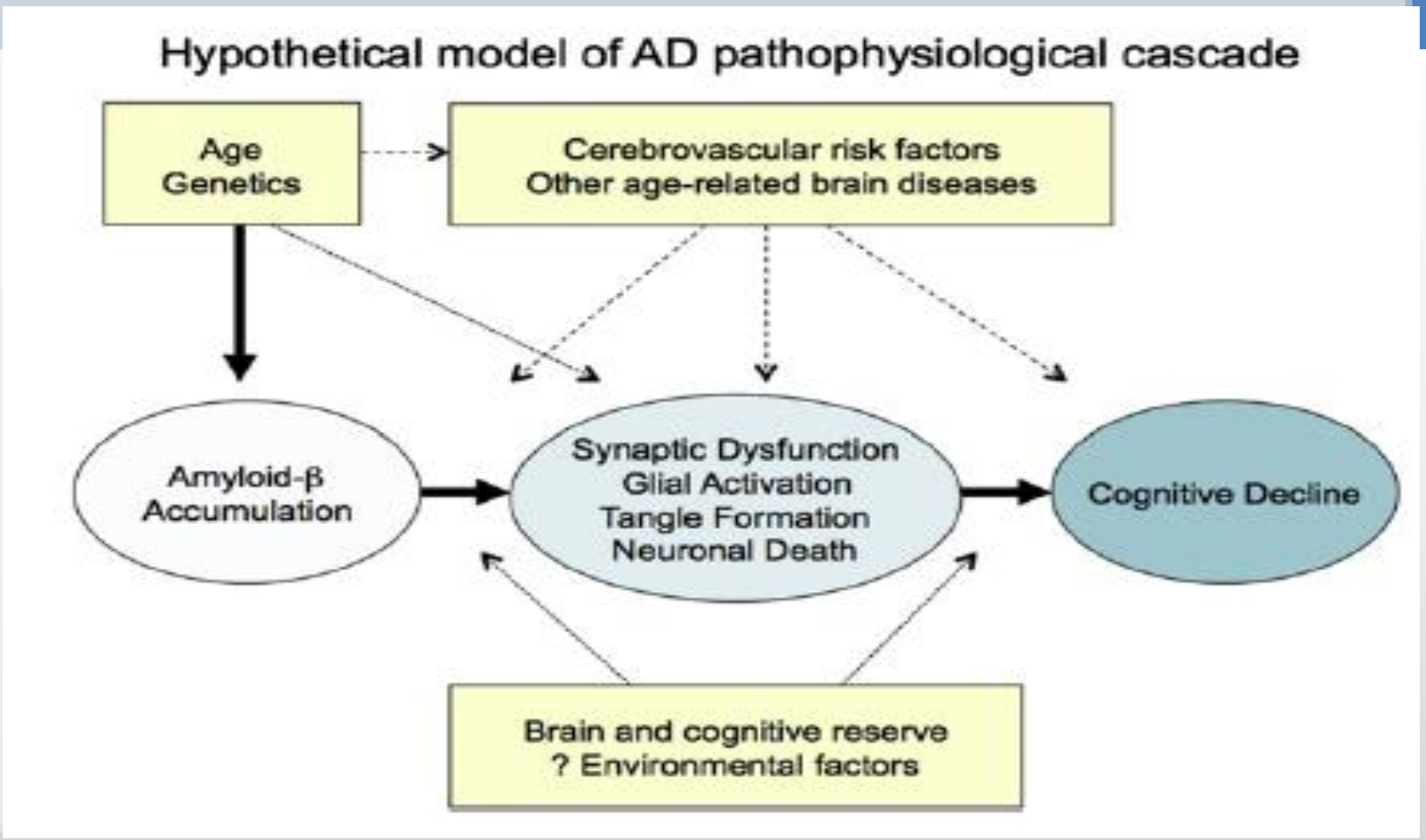


Fig. 2. Hypothetical model of the Alzheimer's disease (AD) pathophysiological sequence leading to cognitive impairment. This model postulates that Aβ accumulation is an "upstream" event in the cascade that is associated with "downstream" synaptic dysfunction, neurodegeneration, and eventual neuronal loss. RA Sperling et al. http://dx.doi.org/10.1016/j.jalz.2011.03.003

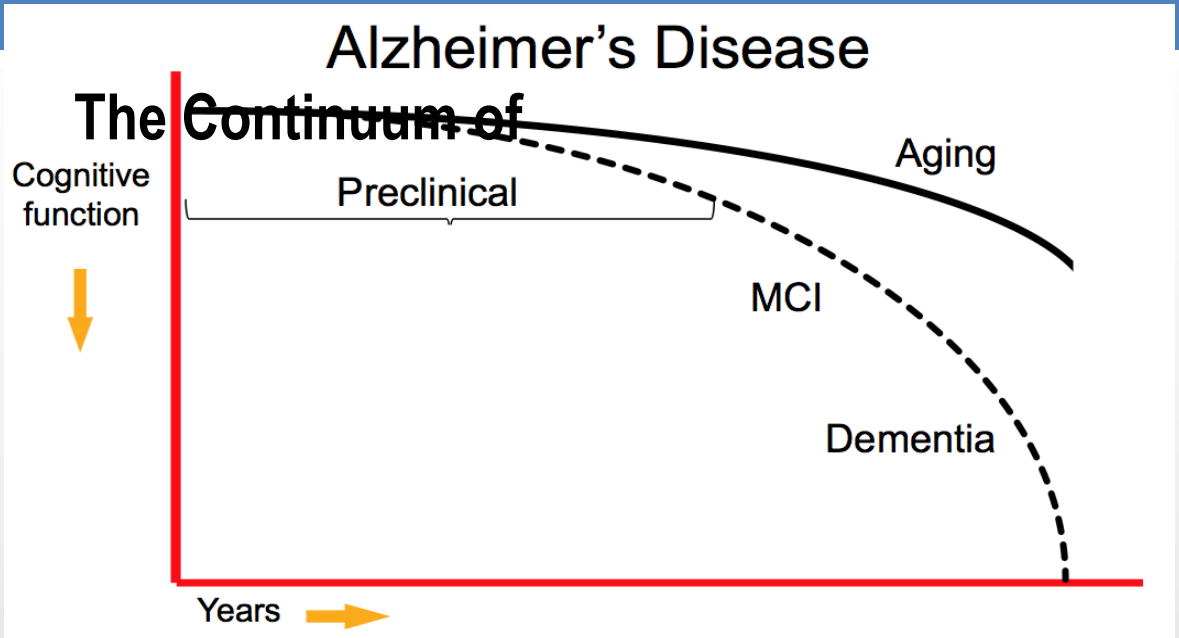


Fig. 1 The stage of preclinical AD precedes mild cognitive impairment (MCI) and encompasses the spectrum of presymptomatic autosomal dominant mutation carriers, asymptomatic biomarker-positive older individuals at risk for progression to MCI due to AD and AD dementia, as well as biomarker-positive individuals who have demonstrated subtle decline from their own baseline that exceeds that expected in typical aging, but would not yet meet criteria for MCI.

RA Sperling et al

http://download.journals.elsevierhealth.com/pdfs/journals/1552-5260/PIIS1552526011000999.pdf

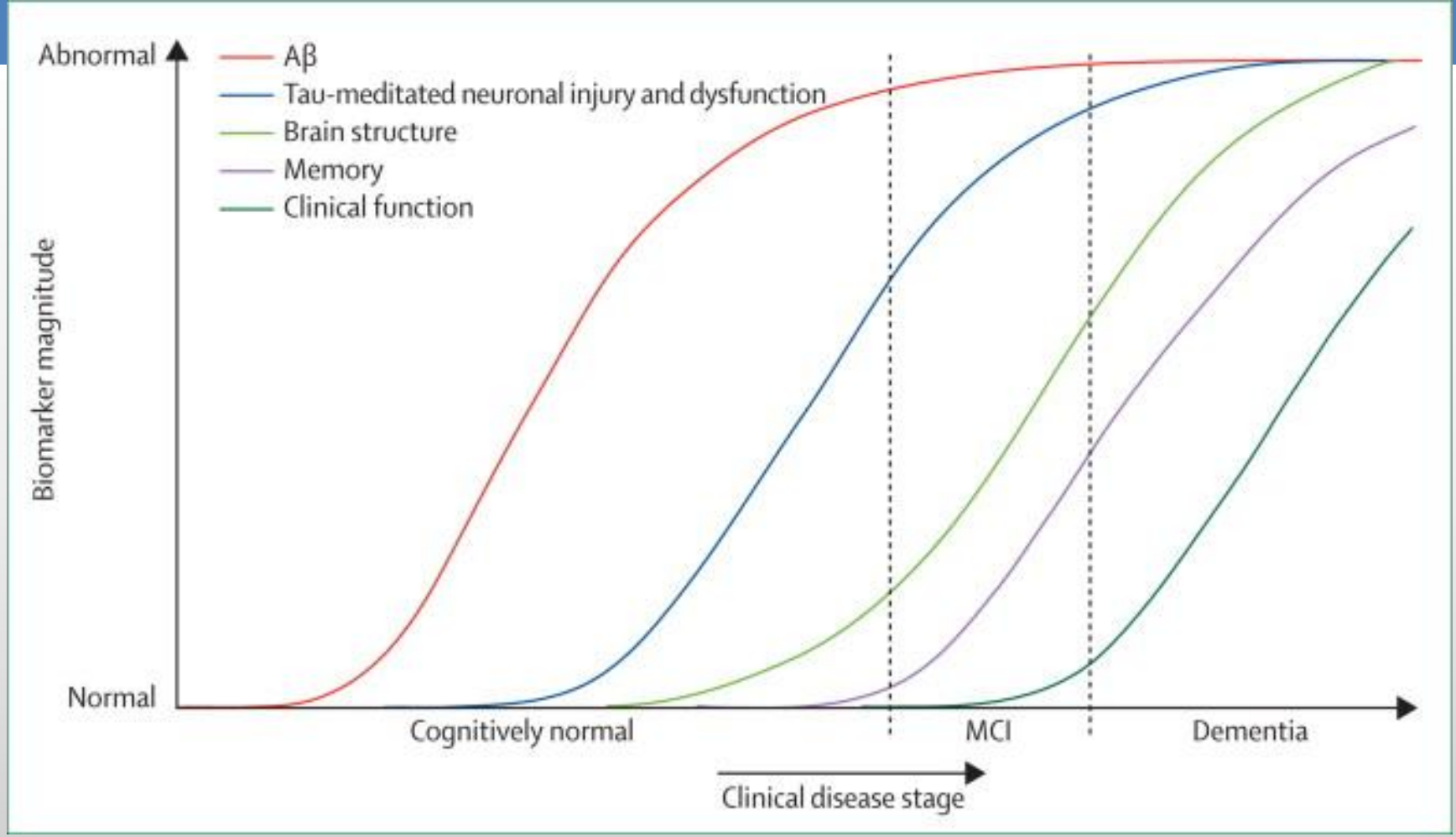


Figure 2. Dynamic biomarkers of the Alzheimer's pathological cascade Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment. Jack et al *Lancet Neuol* 2010

COMMENTARY

ALZHEIMER'S DISEASE

Testing the Right Target and Right Drug at the Right Stage

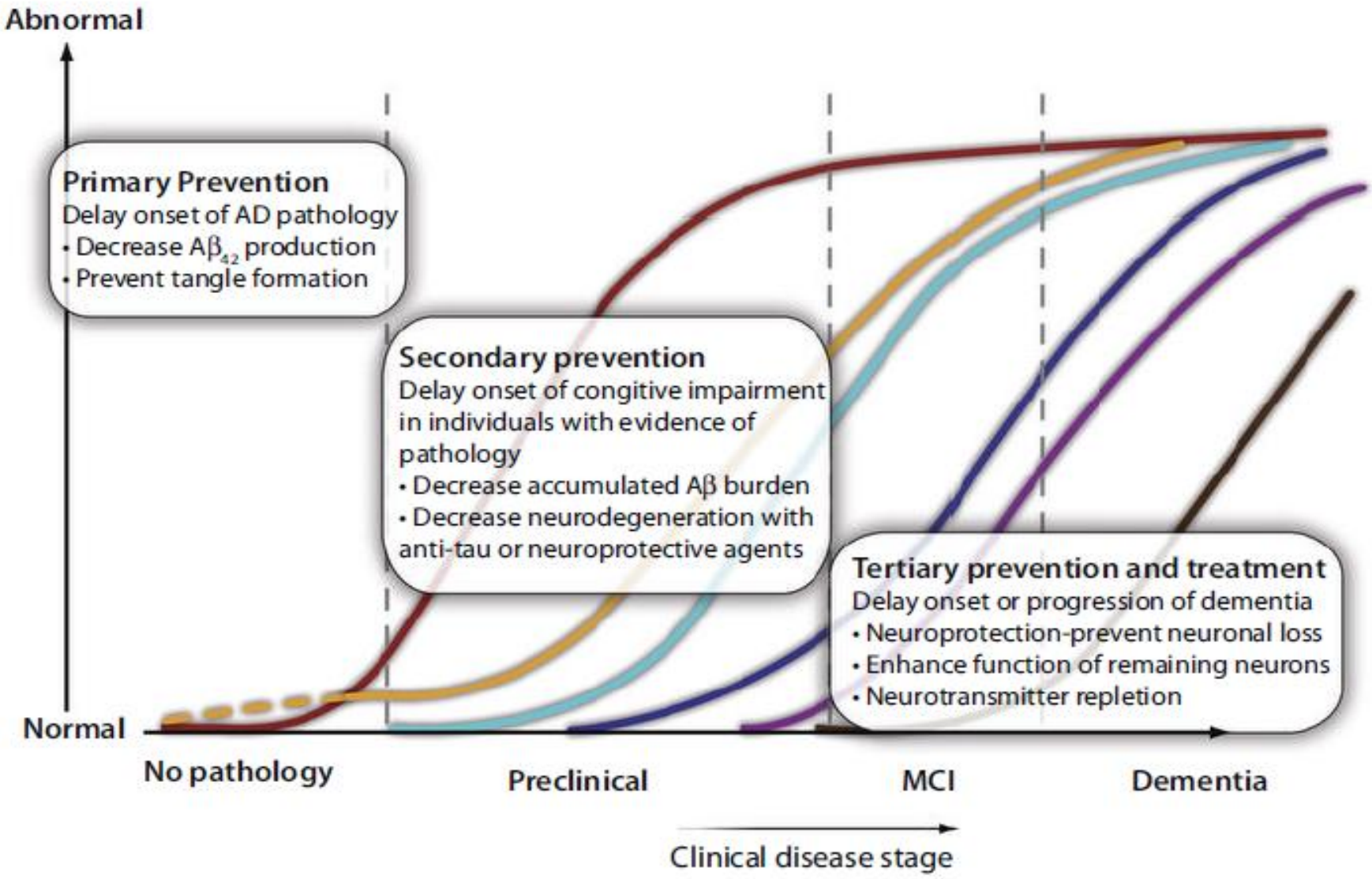
Reisa A. Sperling,[1*] Clifford R. Jack Jr.,[2] Paul S. Aisen[3]

Alzheimer's disease (AD) is the only leading cause of death for which no disease-modifying therapy is currently available. Recent disappointing trial results at the dementia stage of AD have raised multiple questions about our current approaches to the development of disease-modifying agents. Converging evidence suggests that the pathophysiological process of AD begins many years before the onset of dementia. So why do we keep testing drugs aimed at the initial stages of the disease process in patients at the end-stage of the illness?

Implications for the development of effective treatments

- Suggests that researchers should begin to
  - 1) target selected therapies to specific stages of AD and
  - 2) think about the disease in terms of primary, secondary, and tertiary prevention rather than lumping together all disease-modifying treatments across the disease spectrum (see figure 1)

RA Sperling et al www.ScienceTranslationalMedicine.org Nov 2011 Vol 3



www.ScienceTranslationalMedicine.org 30 November 2011 Vol 3 Issue 111 111cm33

Implications for the development of effective treatments

- It is hoped that the advances in pre-clinical detection of AD will enable earlier, more effective treatment,
  - nearly all of therapeutic gains in cancer, cardiovascular disease, osteoporosis, and diabetes involve treatment before significant clinical symptoms are present

- It is possible that promising drugs, particularly amyloid-modifying agents, may fail to affect the clinical course of AD at the stage of dementia or even MCI, when the neurodegenerative process is well established, but may be beneficial at the earliest stages of the AD, before the onset of symptoms

RA Sperling et al http://download.journals.elsevierhealth.com/pdfs/journals/1552-5260/PIIS1552526011000999.pdf; RA Sperling et al www.ScienceTranslationalMedicine.org Nov 2011 Vol 3

PRESYMTOMATIC

Trials in Development

Anti-Amyloid treatment in Asymptomatic AD (A4 Trial)

- Alzheimer's Disease Cooperative Study (ADCS)
- Clinically normal older individuals (> age 70) Aβ+ on PET imaging
- Treat with biologically active compound for 3 years in a randomized, double-blind, placebo-controlled trial

http://www.alzforum.org/new/detail.asp?id=3014

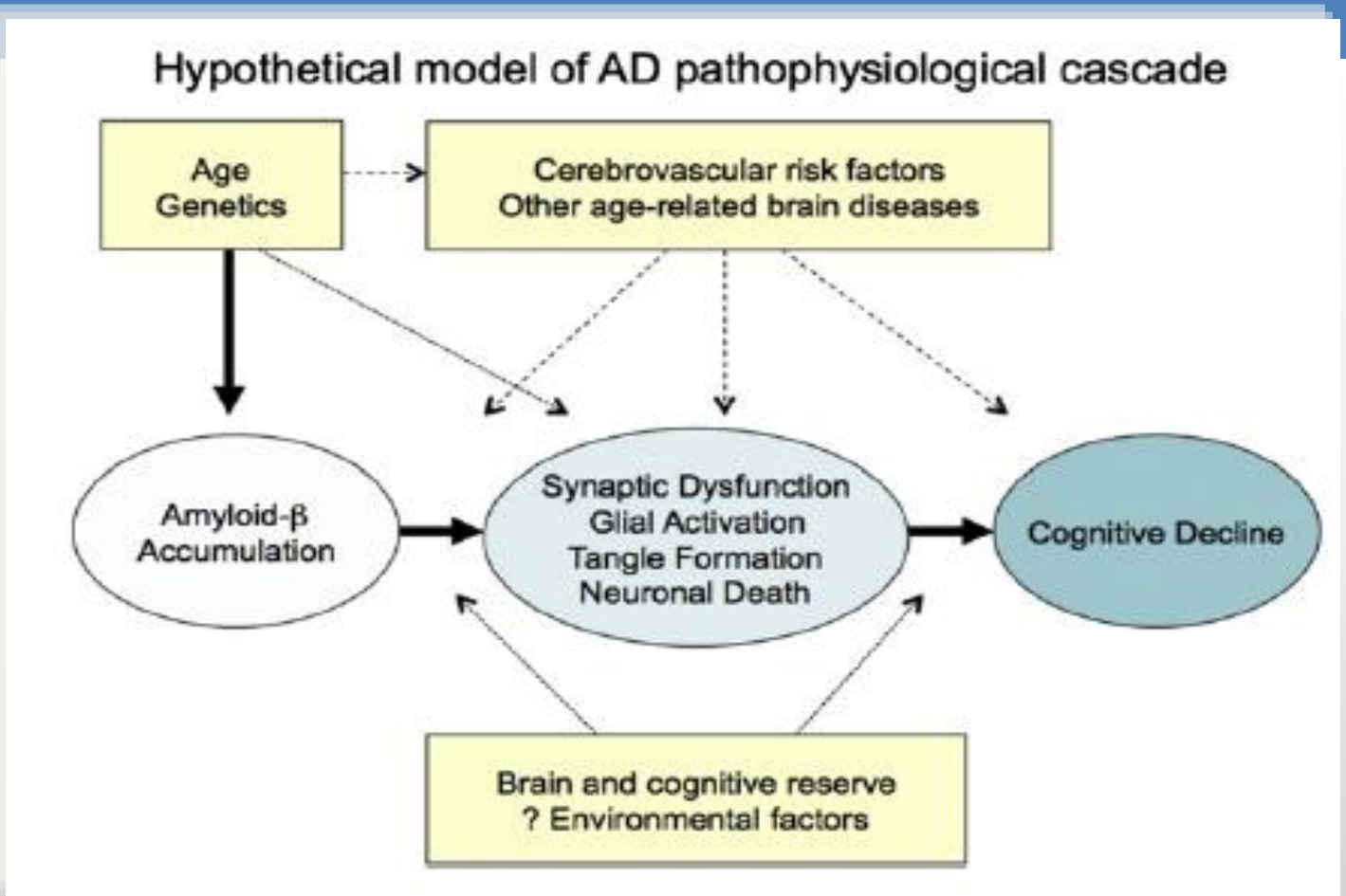


Fig. 2. Hypothetical model of the Alzheimer's disease (AD) pathophysiological sequence leading to cognitive impairment. This model postulates that Aβ accumulation is an "upstream" event in the cascade that is associated with "downstream" synaptic dysfunction, neurodegeneration, and eventual neuronal loss. RA Sperling et al. http://dx.doi.org/10.1016/j.jalz.2011.03.003

A4 Trial Aims

- To determine whether decreasing Aβ burden will slow the rate of cognitive decline in clinically normal older Aβ+ individuals at risk for progression to MCI and AD dementia

- To investigate the impact of anti-Aβ treatment on “downstream” markers of neurodegeneration, and explore whether there is a “critical window” for anti-Aβ therapy within the preclinical stages of AD

- To develop more sensitive outcome measures to improve the efficiency of future secondary prevention trials

http://www.alzforum.org/new/detail.asp?id=3014

DIAN Coordinating Center at Washington University

DIAN
Dominantly Inherited Alzheimer Network

Goals

Enroll 400 individuals from families with a known pathogenic mutation for AD

Longitudinally study carriers in comparison with sibling non-carriers for rate and sequence of AD biomarker changes prior to expected AAO of AD

Performance Sites

US: Washington Univ (Bateman), MGH/BWH (Sperling), Butler Hosp/Brown Univ (Salloway), Columbia Univ (Mayeux), Indiana Univ (Ghetti), UCLA (Ringman)

UK: Institute of Neurology, Univ College London (Rossor)

Australia: Prince of Wales Medical Research Institutes, Sydney (Schofield), Mental Health Research Institute, Melbourne (Masters), Edith Cowan Univ , Perth (Martins)

Washington University in

DIAN Clinical Trials

- Compare three different drugs to a shared placebo group
- Determine whether the drugs have positive effects (AD biomarkers)
- First phase would go on for two years, at which point drugs that have positive effects would be considered for longer-term cognitive endpoint studies

http://www.alzforum.org/new/detail.asp?id=3009

Alzheimer's Prevention Instrument (API)

- Cognitively normal individuals with AD-causing genetic mutation causing early-onset AD (*presenilin 1* (PS1) *E280A* mutation carriers), from the world's largest early-onset AD kindred, located in Antioquia, Colombia, as well as individuals with AD-causing genetic mutations from the US.

- Columbian kindred includes about 5,000 people with a sufficient number of presymptomatic carriers in the targeted age group to make it possible to relate a treatment's effects on both biomarker and clinical endpoints within 2–5 years.

Reiman et al. *Journal of Alzheimer's Disease* 26 (2011) 321–329

API

- 24 months double-blind, randomized, placebo-controlled trial using biomarker (amyloid PET, FDG PET, volumetric MRI, CSF), and cognitive endpoints

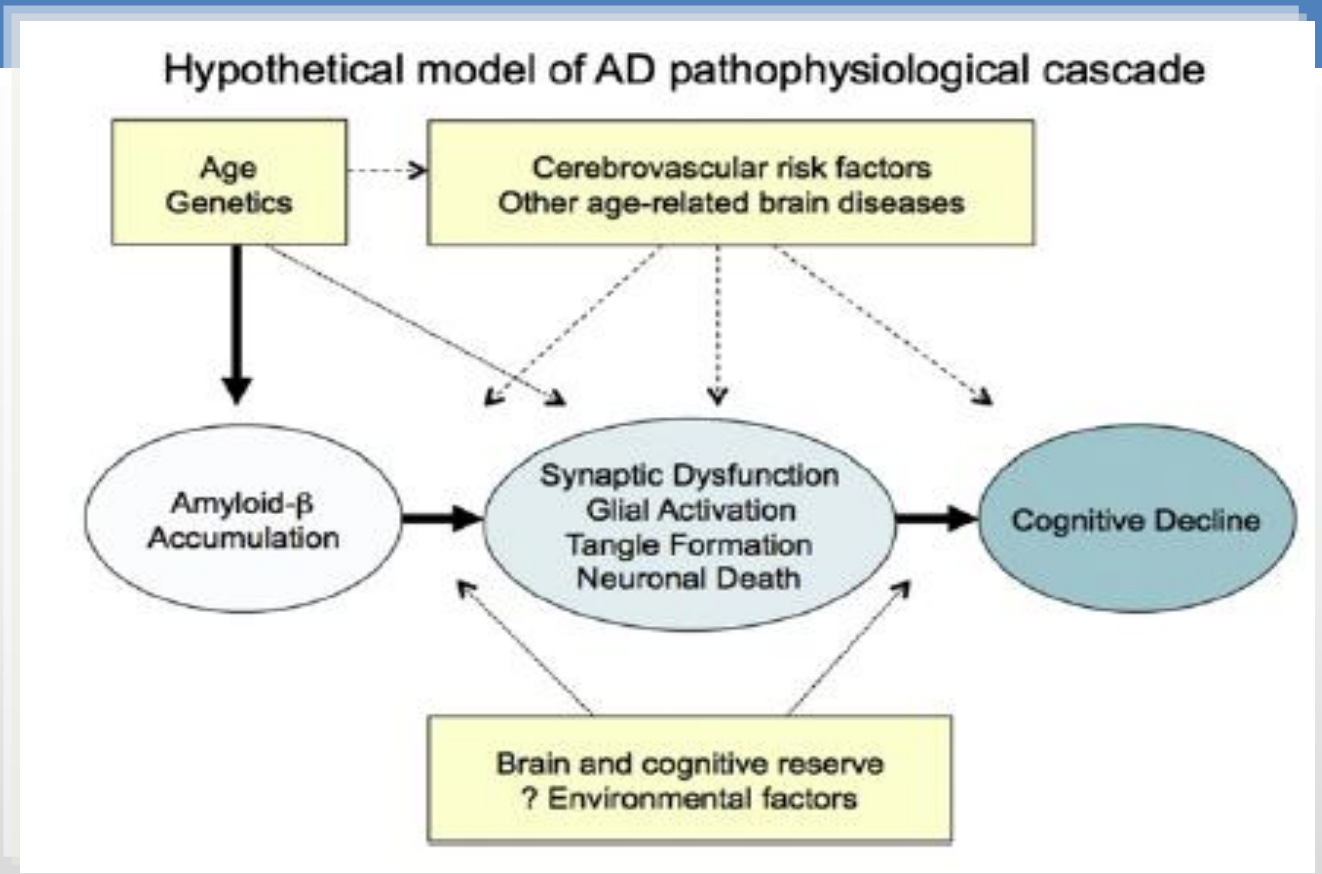
- If after two years, the treatment does not show positive effects on AD biomarkers, the trial would be discontinued, and the participants would be eligible to participate in a trial of the next most promising AD-modifying treatment

- If, however, the treatment is positive, the trial would be continued to assess effects on cognitive functioning

Reiman et al. *Journal of Alzheimer's Disease* 26 (2011) 321–329

Targeting Tau

- Increased phosphorylation of the tau protein appears to be a pivotal event in the pathogenesis of AD.
  - Like deposition of Aβ in plaques, accumulation of hyperphsophorylated tau as paired helical filaments within neurofibrillary tangles is a hallmark of AD pathogenesis (Lee and Trojanowski 1992; Selkoe 2001).
  - Hyperphosphorylation of tau is known to interfere with the ability of tau to stabilize and promote the assembly of microtubules (Lee *et al*. 2001; Geschwind 2003).



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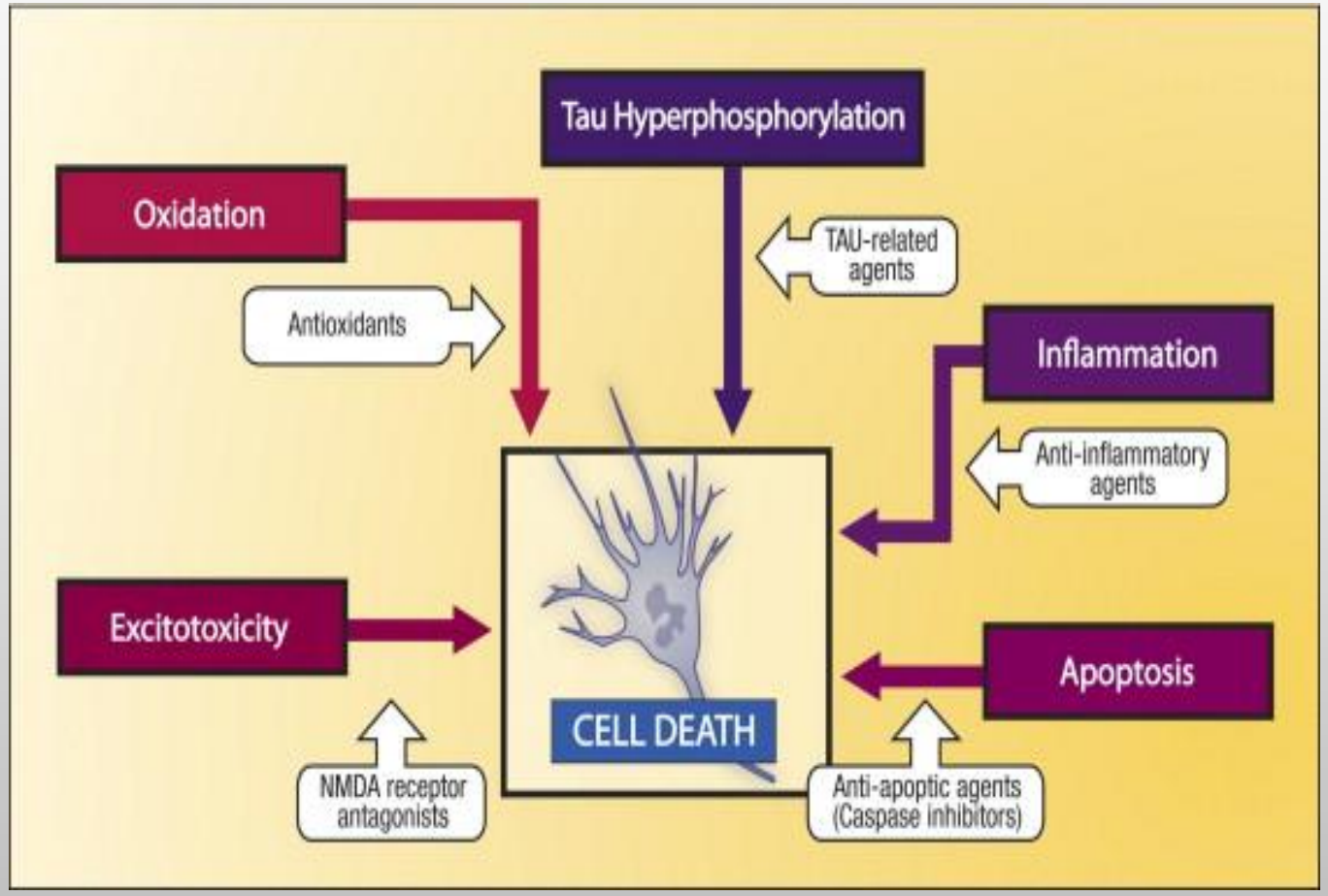
Tau Focused Strategies

- Although not ignored as a therapeutic target, tau has not received as much attention until recently.

- General strategies for altering tau accumulation include: microtubule stabilizing agents, kinase inhibitors, aggregation inhibitors and methods to enhance clearance of either soluble tau or tau aggregates via chaperones (e.g. HSPs, CHIP) or proteases (e.g. the proteasome).

Bunden, Trojanowski, & Lee. *Rev Drug Discov.* 2009 October; 8(10): 783–793

Secondary Pathways: Possible Therapeutic Targets



Salloway, S. et al. Alzheimer's and Dementia 2008; 4: 65-79

Alternative Strategies Towards Disease Modification

- Both chronic inflammation and oxidative stress are likely to contribute to the degenerative process (Akiyama *et al*. 2000).

- However, to date, treatments targeting these processes (e.g, NSAIDs, Vitamin E, B vitamins, DHA) have not shown effectiveness in human trials.

Neuroprotective/Restorative Strategies: Neurotrophins

- Growth factors potently influence neuronal survival and function. They exhibit broad activity against a multitude of toxic mechanisms

- Growth factors offer the potential to treat neurodegenerative disorders

- Gene delivery seems to meet the need for accurately targeted, regionally restricted, safe, and long-term neurotrophin delivery to the brain.

Tuszynski, *ADAD,* 21, 2007

Neuroprotective/Restorative Strategies: Neurotrophins

- Nerve Growth Factor (NGF): Hypotheses - NGF will protect cholinergic neurons in the pathogenic environment of the AD brain, targeting of the cholinergic system will be sufficient to meaningfully benefit quality of life in patients.

  Tuszynski, *ADAD,* 21, 2007

- <u>NIA Funded Gene Therapy Trial – AAV-NGF:</u>
  - Phase II NGF placebo controlled trial to restore function to degenerating cholinergic neurons; effect on cognition, brain metabolism, safety/tolerability in AD

AD RISK AND INTERVENTIONS

AD Risk Factors

Age
Head Injury
High Blood Pressure
High Cholesterol
High Homocysteine
Diabetes
Diet
Education
Exercise
Social Interaction

Diet and Exercise

- **Mediterranean Diet (MeDi) adherence and physical activity (PA) on AD risk**
  - Prospective multi-ethnic cohort study of 1880 community-dwelling elders without dementia living in New York, New York, with both diet and physical activity information available
  - Results: Risk for incident AD was lower for both higher MeDi adherence and more PA.
  - Adoption of both physical activity and healthy nutrition seem to be independently associated with low risk for AD

Scarmeas, N. et al. *JAMA* 2009;302:627-637

Exercise

- **Home-based Physical Activity**
  - 170 community-dwelling older adults from the Perth Metropolitan area, who were free of dementia, but had subjective memory complaints or Mild Cognitive Impairment
  - Randomized controlled trial of a 24-week physical activity intervention vs. usual care conducted between 2004 and 2007 in metropolitan Perth, Western Australia. Assessors of cognitive function were blinded to group membership.
  - Results: Modest improvement in cognition over 18 months. The effect of exercise was apparent by 6 months and persisted at the 12 and 18-months assessments

Lautenschlager et al *JAMA* 2008

Diabetes Treatment

- Research has suggested that AD and diabetes/insulin resistance are closely related. For example, AD is associated with reduced brain insulin signaling and low levels of insulin in cerebrospinal fluid (CSF). These deficiencies may reduce or eliminate insulin's beneficial roles in the brain.

- **Diabetes Medications:**
  - Postmortem study: 124 older adult diabetic patients and 124 non-diabetic older adult controls

  - Found that those treated with both **insulin and oral diabetic agents** had significantly fewer amyloid plaques (as much as 80 percent) than patients with other medication statuses (none, or only insulin or oral anti-diabetic medication) or non-diabetic controls. Beeri et al., *Neurology*. 2008; 71(10): 750–757

NIA Funded Trials Targeting Diabetes/Insulin Resistance

- Intranasal insulin: Effects on cognition, cerebral glucose metabolism, markers of AD pathology, neuroendocrine functions in AD. Completed

- Insulin Sensitizing Agents:
  - Pioglitazone and Exercise: Effects of the medication or exercise on cognition, inflammation, insulin resistance in individuals with MCI and Metabolic Syndrome. Ongoing
  - Metformin: Effects on cognition, brain metabolism in overweight/obese individuals with MCI. Ongoing

Intranasal Insulin

- Restoring normal insulin function in the brain may provide therapeutic benefits to adults with AD.
- The SNIFF-120 trial was a 4-month, randomized, double-blind trial of placebo vs 2 doses of intranasal insulin (20 or 40 IU).
- 104 patients with AD or amnestic MCI participated; patients with diabetes were excluded.

Craft, et al. *Arch Neurol*. 2012 January ; 69(1): 29–38.

Intranasal Insulin

- Results: 20 IU dose of insulin delayed story recall significantly improved compared to placebo, as did functional status.
- Improvements in delayed memory recall persisted for 2 mos. after treatment ended.
- Improved memory and functional status with insulin were associated with an improved AD biomarker profile.
- Also, compared with placebo patients, those in the insulin groups showed preserved glucose metabolism on FDG PET scanning in areas affected by AD pathology.

Craft, et al. *Arch Neurol.* 2012 January ; 69(1): 29–38.

Treatment Approaches For Neuropsychiatric Symptoms In AD

Spectrum of Neuropsychiatric Symptoms in AD

- Apathy
- Depression
- Sleep Disturbance
- Anxiety
- Agitation and Aggression
- Psychosis

Prevalence of Neuropsychiatric Symptoms in AD

- Behavioral changes/neuropsychiatric symptoms commonly accompany AD, although they are not required for diagnosis

- Prevalence is high, varying from about 60% of individuals in population-based studies , up to 92% in clinical samples

Lykestsos, et al. *Int J Geriatr Psychiatry* 2001; Fernandez-Martinez, et al. *Curr Alz Res* 2008

- These symptoms are often multiple and simultaneous in dementias
- Contribute to patient distress, add to caregiver burden, increase medical care and costs, and often precipitate institutionalization in nursing homes
- Tend to increase in prevalence and severity as the disease progresses
- Are associated with more rapid cognitive decline
- Assal & Cummings, *Curr Opin Neurol* 2002; Beier *Pharmacotherapy* 2007, Bruen, et al *Brain 2008*

Pharmacologic Interventions for Neuropsychiatric Symptoms in AD

- No drugs are specifically approved by the U.S. Food and Drug Administration (FDA) to treat neuropsychiatric dementia symptoms.

- The drugs currently used are **“off label”**, a medical practice in which a physician may prescribe a drug for a different purpose than the ones for which it is approved.

Antipsychotics

- Atypical and conventional antipsychotics have been used to treat agitation, aggression, and psychosis in AD and other dementias
  - Atypical, Ex: clozapine (Clozaril)
  - Conventional, Ex: haloperidol (Haldol)

- However these medications are associated with an **increased risk of mortality and cerebrovascular events** in older dementia patients

Gianluca et al *Pharmacol Res* 2008

U.S. Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

Information for Healthcare Professionals
Antipsychotics

FDA ALERT [6/16/2008]: FDA is notifying healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis.

In April 2005, FDA notified healthcare professionals that patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. Since issuing that notification, FDA has reviewed additional information that indicates the risk is also associated with conventional antipsychotics.

Information for Healthcare Professionals
Antipsychotics (cont.)

Antipsychotics are not indicated for the treatment of dementia-related psychosis.

FDA is requiring the manufacturers of conventional antipsychotic drugs to add a ***Boxed Warning*** **and** ***Warning*** to the drugs' prescribing information about the risk of mortality in elderly patients treated for dementia-related psychosis similar to the *Boxed Warning* and *Warning* added to the prescribing information of the atypical antipsychotic drugs in 2005.*

Serotonergic Antidepressants in AD

- Ex: citalopram (Celexa), fluoxetine (Prozac), paroxeine (Paxil), sertraline (Zoloft)
- RCTs have demonstrated modest effects in treating depression associated with AD*
- Fairly well tolerated
- One small RCT using citalopram demonstrated reduced agitation in AD patients†
- A large NIA-funded multi-site double-blind RCT of citalopram for agitation in AD began in 2009.

*Beier *Pharmacotherapy* 2007; Sink, Holden, & Yaffe *JAMA* 2005

†Pollock et al. *AJP* 2002

Non-pharmacologic Interventions

- Non-pharmacologic strategies are the cornerstone of the management of AD–related neuropsychiatric symptoms
- The cumulative research to date suggests these interventions may be efficacious:
- the majority of trials have been small and the effects modest

Ayalon et al. Arch Intern Med 2006; Ballard & Corbett, *CNS Drugs* 2010; Beier *Pharmacotherapy* 2007

‘Cocktail’ Approach

- Likely that multimodal therapy or ‘cocktail’ may be needed to significantly impact the clinical course of AD.

- E.g. a cocktail of therapies that target tau, Aβ, inflammation and cognitive symptoms, may be more efficacious than monotherapy.

Ongoing NIA Funded Clinical Trials

- Currently support over 30 active clinical trials, including both pilot and large scale trials, of a wide range of interventions to prevent, slow, or treat AD and/or MCI.

- 6 primary and 7 secondary prevention trials. Of the 6 primary prevention trials, 2 are NIA-funded cognitive/AD measure add-ons to large NIH primary prevention trials that address a variety of other primary outcomes.

TABLE 1. Ongoing Alzheimer's Disease/Mild Cognitive Impairment Prevention Trials Funded by NIA

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	TYPE OF TRIAL	ANTICIPATED COMPLETION DATE
		Nutritional			
AREDS2 (Age-Related Eye Disease Study 2)*	John Paul San Giovanni (Study Director), NEI	Macular xantho-phylls (lutein and zeaxanthin) and/or omega-3 fatty acids (DHA and EPA)	People age 50-85 with age-related macular degener-ation (AMD) in both eyes or advanced AMD in one eye	Primary Prevention	2015
PREADVISE (Prevention of Alzheimer's Disease by Vitamin E and Selenium)†	Frederick Schmitt, University of Kentucky	Vitamin E, selenium, vitamin E + selenium	Men age 60-90	Primary Prevention	2014
Vitamin E in Aging Persons with Down Syndrome	Arthur Dalton, Institute for Basic Research in Developmental Disability	Vitamin E	People age 50+ with Down syndrome, at high risk of developing Alzheimer's disease	Primary Prevention	2012
		Hormones			
ELITE (Early Versus Late Intervention with Estradiol)	Howard Hodis, University of Southern California	17β-estradiol	Healthy early (less than 6 years) or late (10 years +) menopausal woman	Primary Prevention	2014
SMART (Somatotrophics, Memory, and Aging Research Trial)	Michael Vitiello, University of Washington	Growth hormone releasing hormone (GHRH)	People with mild cognitive impairment and healthy older adults age 55-80	Secondary Prevention	2011
Testosterone Supplementation in Men with MCI	Monique Cherrier, University of Washington	Testosterone	Older men with MCI and low testosterone	Secondary Prevention	2011
		Cardiovascular			
ASPREE (Aspirin in Reducing Events in the Elderly)	Richard Grimm, Berman Center for Outcomes and Clinical Research; John McNeil, Monash University	Aspirin	Healthy adults age 70+	Primary Prevention	2017

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Federally-funded sources for more information on Alzheimer's disease and other dementias: NIA funded

- **Alzheimer's Disease Education and Referral Center (ADEAR)**, http://www.nia.nih.gov/alzheimers or 1-800-438-4380 (Mon-Fri, 8:30 am-5:00 pm Eastern Time): research-based information on Alzheimer's disease and other dementias for the general public, social service & health care professionals, with links to
  - Find an Alzheimer's Disease Research Center
  - Learn more about Alzheimer's Clinical Trials that are currently recruiting
  - Access recent news articles and free publications, and more

Federally-funded sources for more information on Alzheimer's disease and other dementias: NIA funded

- **NIH Senior Health**, http://nihseniorhealth.gov
  - A-Z Health Topics Index to access information, videos, quizzes and more on Alzheimer's disease and other topics
- **Health & Aging information**, http://www.nia.nih.gov/health
- **Information on Alzheimer's and aging in Spanish,** http://www.nia.nih.gov/espanol

Thank You!

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National Institute on Aging

Federally-funded sources for more information on Alzheimer's disease and other dementias: AoA funded

- **National Alzheimer's Call Center** (Alzheimer's Association is the grantee): call the 24/7 Helpline at 1.800.272.3900 or http://www.alz.org/
  - Talk to an Information Specialist or master's prepared Care Consultant 24/7 about Alzheimer's disease, dementia or related caregiving issues
  - Access on-line tools, Message Boards (on-line supportive community), TrialMatch and more

Administration on Aging

Federally-funded sources for more information on Alzheimer's disease and other dementias: AoA funded

- **Eldercare Locator** (n4a is the grantee): call 1.800.677.1116 Mon-Fri 9am - 8pm ET or http://www.eldercare.gov/eldercare.net/public/resources/topic/Alzheimer_Disease.aspx for assistance finding specific information and supportive services available from local aging network organizations

- **Administration on Aging, ADSSP**: http://www.aoa.gov/AoARoot/AoA_Programs/HPW/Alz_Grants/index.aspx has information for professionals in the field of aging, including a Resource Compendium, links to find locations of Alzheimer's Disease Supportive Services Program (ADSSP) grantees & more

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QUESTIONS?