Advancements in the Early Detection of Dementia

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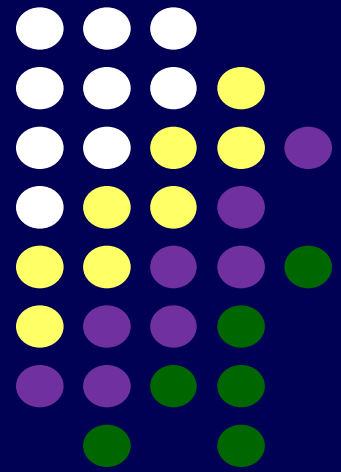
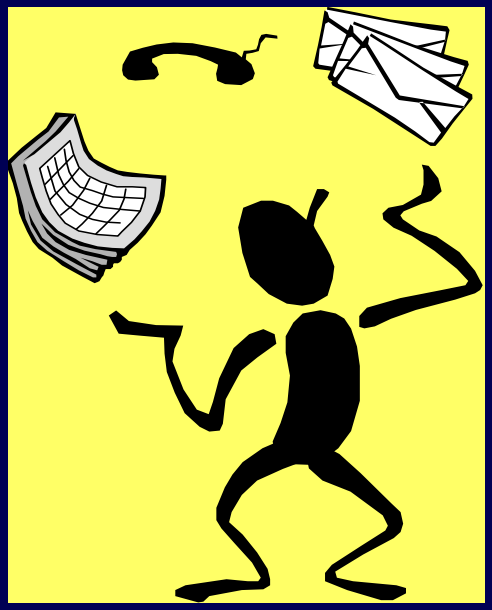


Dementia Is . . .

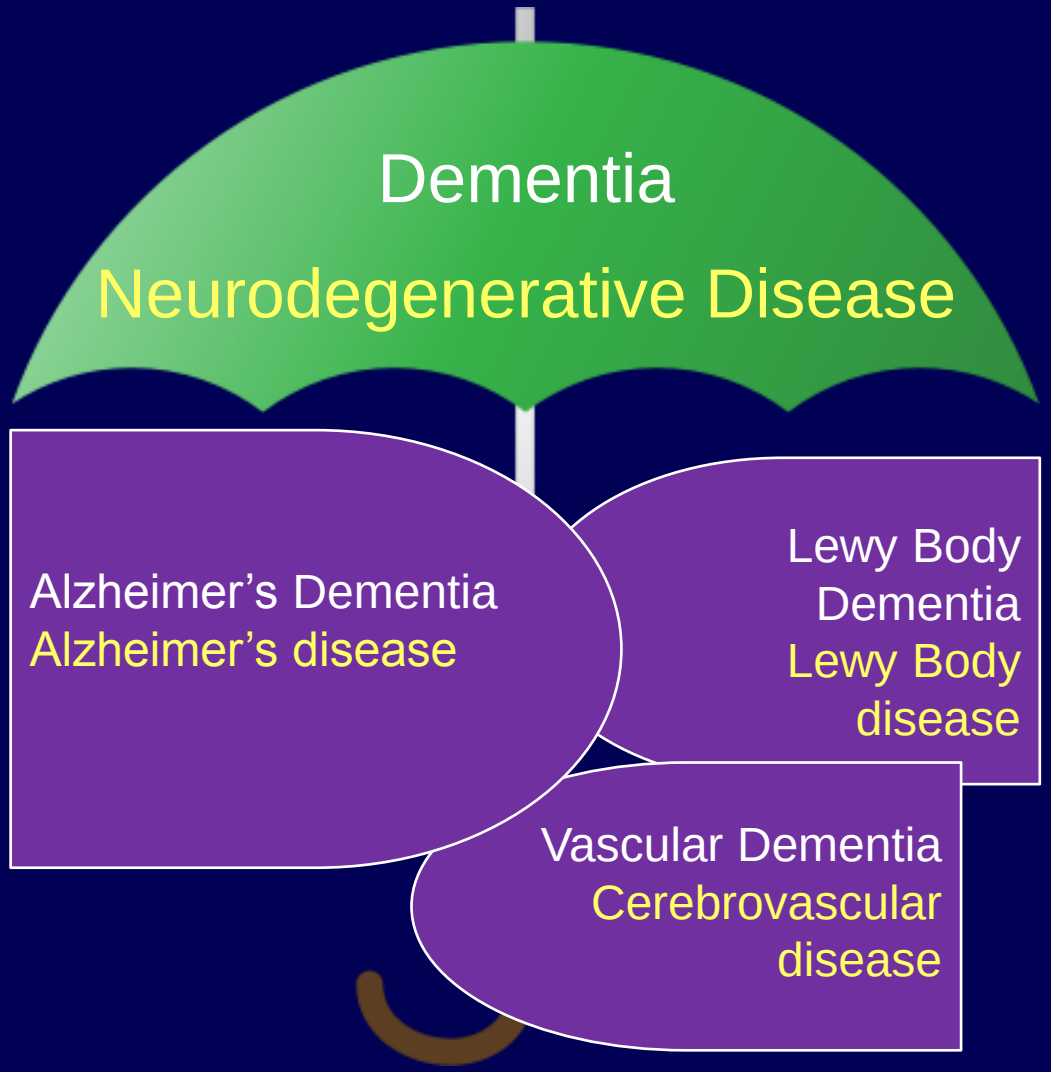
A significant, chronic loss in some aspect of mental function (often memory) and/or behavior, involving structural damage which causes functional decline and gets worse with time



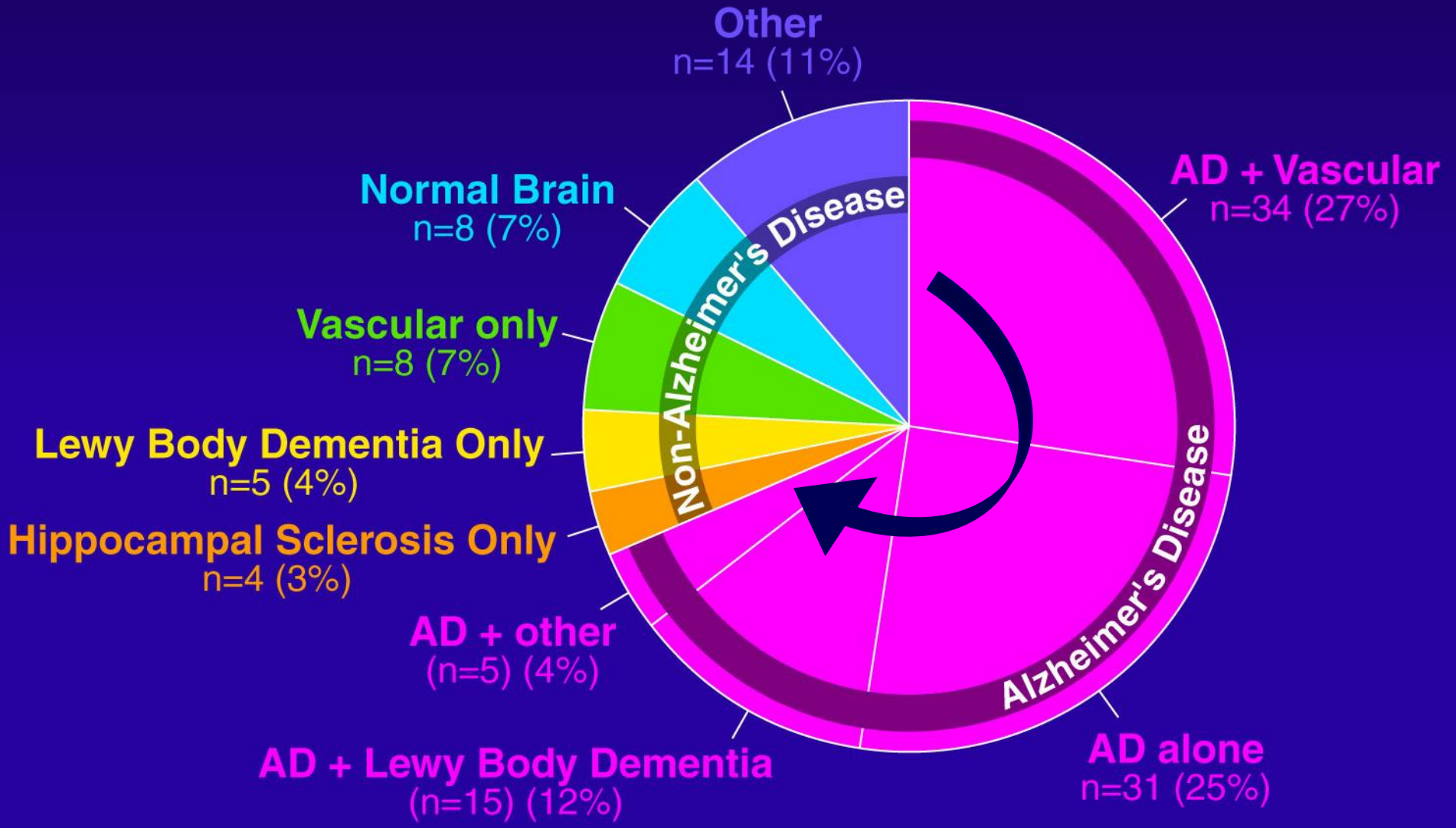
Daily Living Skills

- ✓Significant
  - functional consequences
- ✓Chronic
  - insidious onset and progressive course
- ✓Loss
  - new impairments (not lifelong)
- ✓Structural Damage
  - neurons die

Primary Causes of Sporadic Dementia in Older Adults



Neuropathological Diagnosis in 124 Community-based Incident Dementia Cases



Lim, et al. *J Am Geriatr Soc*. 1999 May;47(5):564-9.

Definite Alzheimer's Disease

- Examination of brain tissue
  - Amyloid plaques
  - Neurofibrillary tangles
- Present in brain in a certain density & distribution

NINCDS-ADRDA Criteria from 1984 consensus group

Neuropathology of Alzheimers

Two hallmarks: **amyloid plaques and neurofibrillary tangles**

- Amyloid plaques are extracellular aggregations of the Aβ peptide that are found throughout the brain
  - Begin as oligomers which are not cleared well
  - Aggregate and deposit – becoming small diffuse plaques and dense core plaques
- NFTs occur due to hyperphosphorylation of the MAP tau
  - Leads to destabilization of axons, impairment of transport, degeneration, dysfunction, and death
  - Creates paired helical filaments, key component of NFTs
- Aβ first, then tau, but it's tau that correlates with symptom expression

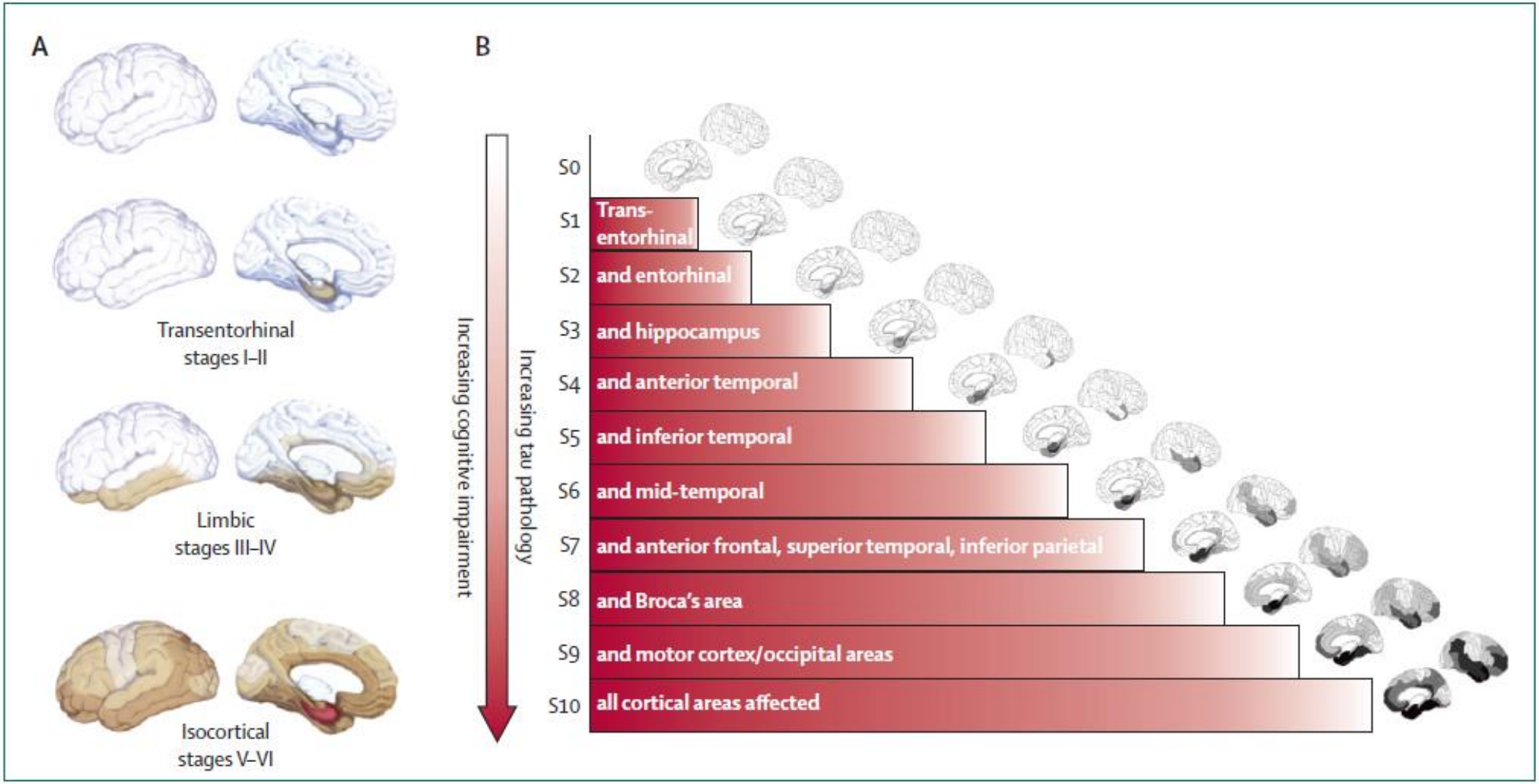
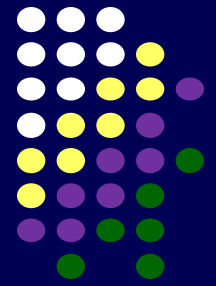
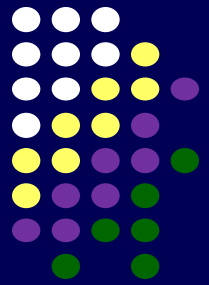


Figure 2: **Progression of tau deposition in Alzheimer's disease according to Braak and Braak[1] or Delacourte[36] staging**
Stereotypical regional tau deposition in the brain according to the six stages described by Braak and Braak[1] (A) and the ten stages described by Delacourte[36] (B). A sequential and hierarchical neurocognitive profile is closely associated with the progression of tau aggregation and deposition. Patients with transentorhinal and limbic accumulation of tau (Delacourte stages 1–4 or Braak and Braak stages I–III) are asymptomatic for a protracted period; incipient and subtle memory loss (Delacourte stages 5–6 or Braak and Braak Stage IV) is followed by objectively measured progressive cognitive impairment reflecting the spread of tau deposits into isocortical unimodal and multimodal association areas (Delacourte stages 7–10 or Braak and Braak stages V–VI).[1] Part A adapted from Braak and Braak;[1] part B adapted from Delacourte and colleagues,[36] by permission of Wolters Kluwer Health.

Genetics of Alzheimer's disease



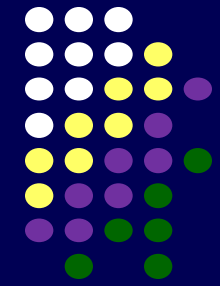
- Only one consistent association for sporadic AD
  - E4 allele of APOE (gene found on ch19)
    - Betram, et al., Nature Genetics, 39(1), January 2007
- Early-onset familial AD – rare autosomal dominant mutations - <5% of all cases
  - APP gene is mapped to chromosome 21
    - Trisomy 21 – Down Syndrome and AD by age 30
  - Major disease locus on ch14
    - Presenilin 1
    - Presenilin 2 – more recently found on ch1
  - Tau gene (FTD and associated tauopathies) on ch17
    - Goedert, et al., Science, 314, 777, 2006



Alzheimer’s disease is the 6th leading cause of death in the U.S.

DEMENTIA AFFECTS EVERYONE

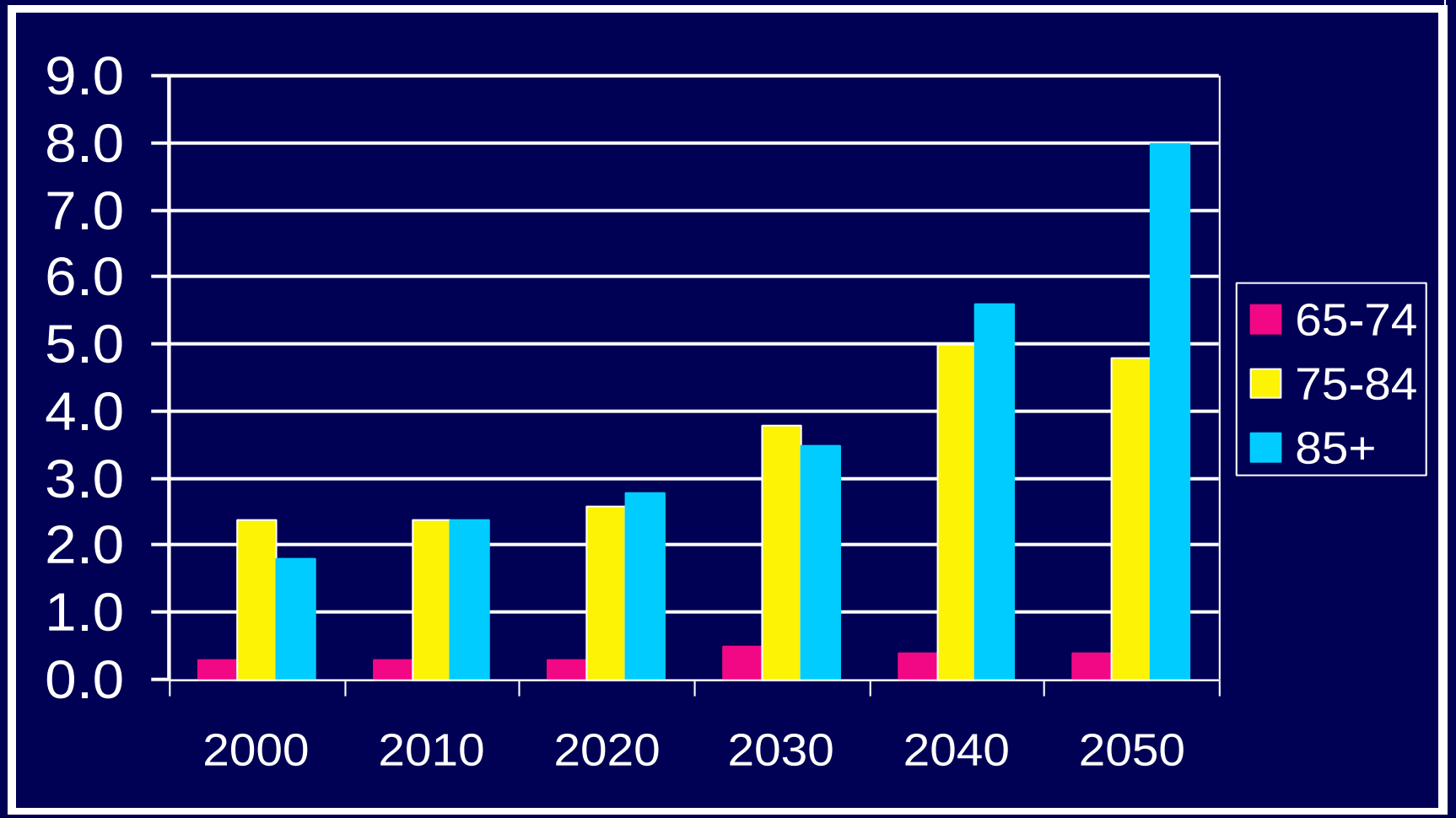
Aging Population → Dementia Epidemic



- In 2010, older adults 65+ were ~13% of the U.S. population
- By 2030, it's expected to be ~20%
- An estimated 72 million older Americans
  - 26% percent of physician office visits
  - A third of all hospital stays and of all prescriptions
  - Almost 40% of all emergency medical responses
  - 90% of nursing home residents
- 5.3 million Americans of all ages have AD in 2015
- WA state: 40% increase in people with AD over the next 10 years

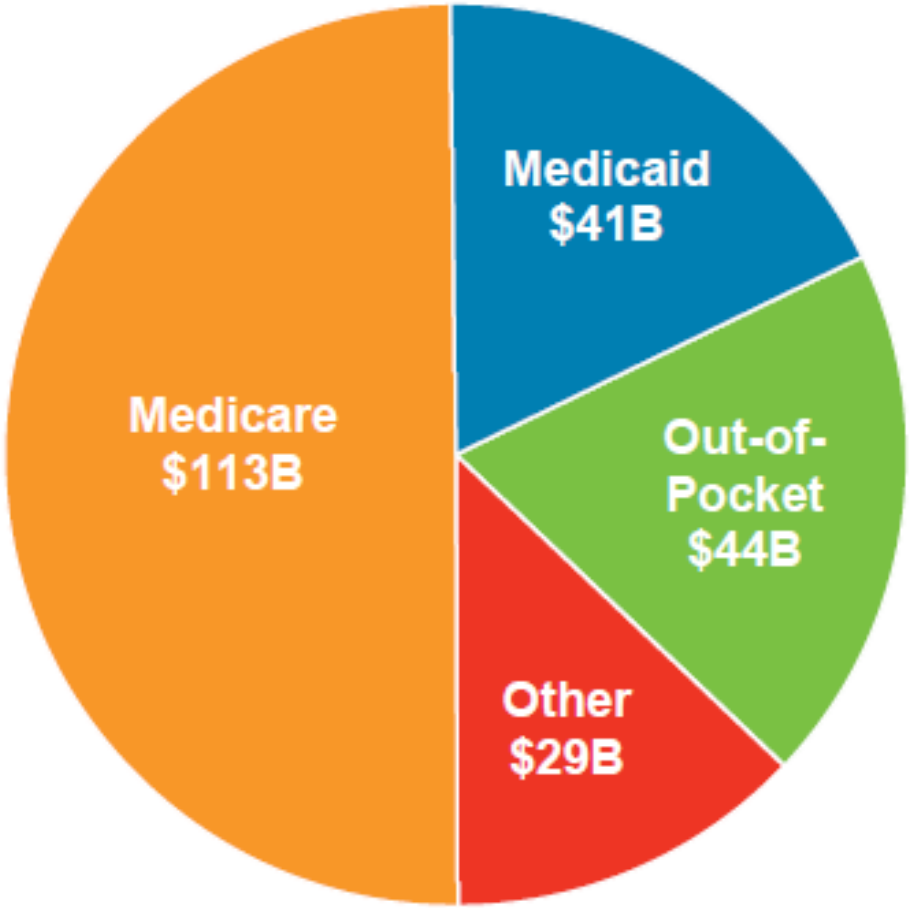
As reported in the 2015 Alzheimer's Disease Facts and Figures from the Alzheimer's Association

Prevalence of AD in the US



Hebert, et al, 2003, Archives of Neurology

2015 Costs of Alzheimer's = $226 Billion

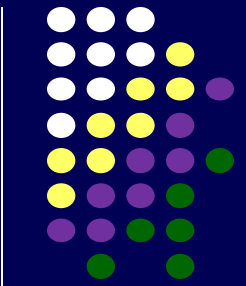


Total does not add due to rounding.

As reported in the 2015 Alzheimer's Disease Facts and Figures from the Alzheimer's Association

Alzheimer's is a young(er) person's disease -- so get to work

By Dr. Sanjay Gupta, CNN Chief Medical Correspondent
Updated 2:10 PM ET, Fri November 6, 2015

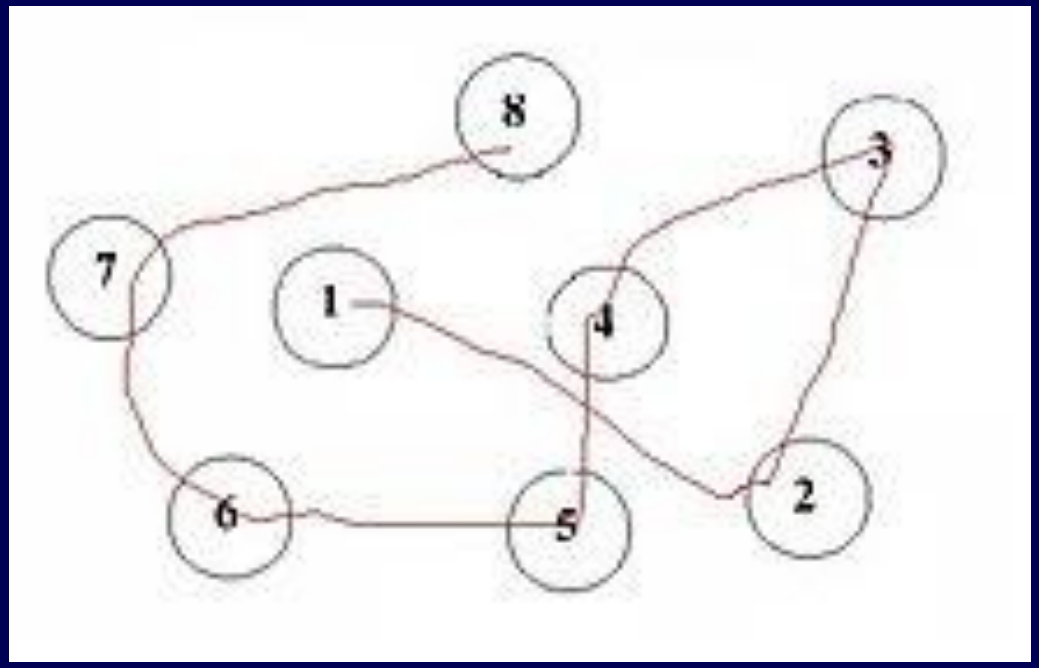


By 2040, it's estimated that Alzheimer's will consume almost 25% of Medicare's budget.

- Funding to battle the disease has not kept pace. Alzheimer's research was promised a mere $580 million in NIH funding; cancer is slated for more than $5 billion, AIDS is getting $3 billion and cardiovascular disease nearly $2 billion.

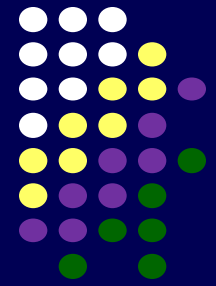
Alzheimer's Association researchers did the math: Uncle Sam needs to spend $2 billion a year to get a treatment in 2025 that would delay the onset of Alzheimer's by five years.

- That would reduce the number of people with Alzheimer's by 42% in 2025 and save $220 billion within the first five years alone.



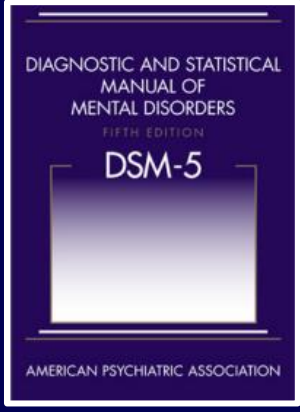
CLINICAL DIAGNOSIS

Diagnostic Criteria for Dementia



- NINCDS/ADRDS evolved to NIA/NIH and AA
  - 1984 criteria
  - 2011 updated/research driven
- APA - DSM
  - DSM IV (1994) and IV-TR (2000)
  - DSM 5 (2013)
- WHO - ICD
  - Frequently updated – billing
  - ICD-9 just discontinued for Medicare/Medicaid
  - ICD-10 - current; already working on ICD-11

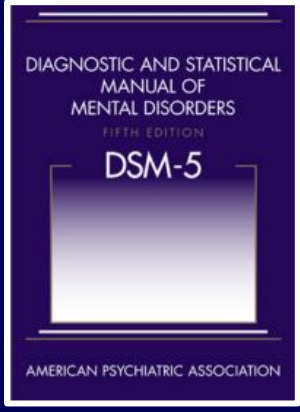
DSM 5: Neurocognitive Disorders



- Decline from a previous level of functioning as opposed to a deficit.
- DSM-IV terminology required the presence of memory impairment for all of the dementias.
- First establish the presence of a neurocognitive disorder and then determine whether the neurocognitive disorder is mild or major.

Mild Neurocognitive D/O:

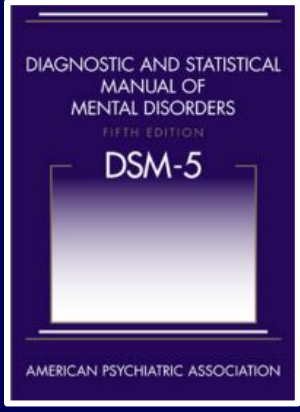
- There is evidence of modest cognitive decline from a previous level of performance in one or more of the domains outlined above based on the concerns of the individual, a knowledgeable informant, or the clinician; and a decline in neurocognitive performance, typically involving test performance in the range of one and two standard deviations below appropriate norms (ie, between the third and 16th percentiles) on formal testing or equivalent clinical evaluation.
- The cognitive deficits are insufficient to interfere with independence (eg, instrumental activities of daily living, like more complex tasks such as paying bills or managing medications, are preserved), but greater effort, compensatory strategies, or accommodation may be required to maintain independence.



DSM 5: Neurocognitive Disorders

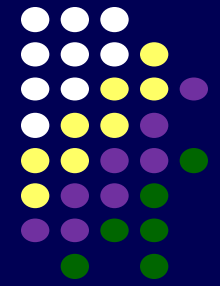
- **Major Neurocognitive D/O**
  - There is evidence of substantial cognitive decline from a previous level of performance in one or more of the domains outlined above based on the concerns of the individual, a knowledgeable informant, or the clinician; and a decline in neurocognitive performance, typically involving test performance in the range of two or more standard deviations below appropriate norms (i.e., below the third percentile) on formal testing or equivalent clinical evaluation.
  - The cognitive deficits are sufficient to interfere with independence (ie, requiring minimal assistance with instrumental activities of daily living).
  - The cognitive deficits do not occur exclusively in the context of a delirium.
  - The cognitive deficits are not primarily attributable to another mental disorder (e.g., major depressive disorder, schizophrenia).
  - Next, indicate etiology

Alzheimer's Dementia – DSM-5



- Major or Mild Neurocognitive Disorder:
  - Dementia? Y or N
- All 3 of the following are present:
  - Clear evidence of a decline in memory and at least 1 other cognitive domain (based on hx or NP testing)
  - Steadily progressive, gradual decline
  - No evidence of mixed etiology
- Probable AD – if there is evidence of a causative AD genetic mutation from either genetic testing or family history

Neuropsychology of AD



- Tests
  - Consider age of subject and overall health/energy
  - Consider adjusting measures administered based on referral question (e.g., first diagnosis vs. current function)
- Normative populations
  - Limited normative information for 90+
  - Non-native English speakers
  - Ethnicity/Cultural differences
- Premorbid estimates
  - Individualized benchmark

Mr. Jones

Name: [redacted]
DOB: [redacted]/19
Occupation: re

ESTIMATE (

WRAT
-1 SD:
Barona: 117.0

VERBAL MEMORY

WMS-IV LM - Version A/B

	Raw	*SS*	*%ile*
LM I Recall (53)	15	7	16th
LM II Recall (39)	0	3	1st
LM II Recog (23)	11	x	3-9th

CVLT -II-short	*Raw*	*Standard*
Total 1-4 (36)	9	
Trial 1	0	-3.5
Trial 4	4	-2
SD Free Recall	0	-2.5
LD Free Recall	0	-1.5
LD Cued Recall	0	-2.5
Repetitions	0	-0.5
Free Recall Intrusions	11	5
Cued Intrusions	0	-0.5
Recognition Hits	x	x
False Positives	x	x
0/2/3/4		

VISUAL MEMORY

WMS-IV VR	*Raw*	*SS*	*%*
VR I Recall	18	8	25th
VR II Recall	0	4	3rd
VR II Recognition	x	x	x

BVMT	*Raw*	*z*	*%*
Total	6	-2.4	<1st
Delayed	0	<-3	<1st
2/2/2			

ABSTRACTION	*Raw*	*SS*	*%*
Similarities	19	9	37th
Matrix Reasoning	x	x	x

VISUO-SPATIAL	*Raw*	*SS*	*%ile*
Block Design	24	11	63rd
VR II Copy	42	x	51-75th

Target Cancellation – time: 220" errors: 1 omission

ATTENTION/CONCENTRATION

Digit Span	*Span*	*Raw*	*SS*	*%ile*
Digits Forward	7	11	1.3	
Digits Reverse	4	7	-0.1	
Digits Sequence	0/5	0/7		
Digit Span Total		18/25	8/12	25th/74th

Trailmaking Test	*Sec*	*z*	*%ile*
Part A (Errors= 0)	36	0.95	84th
Part B (Errors= 2)	dc		<1st

LANGUAGE	*Raw*	*z*	*%ile*
BNT	49	-0.26	40th
FAS	32	-0.4	35th
Animal Naming	11	-1.2	12th
Writing	2		

FUNCTIONAL SCALES

OARS Instrumental ADL (patient)	10/14
OARS Instrumental ADL (collateral)	8 /14
OARS Physical ADL (patient)	14 /14
OARS Physical ADL (collateral)	14 /14

MOOD

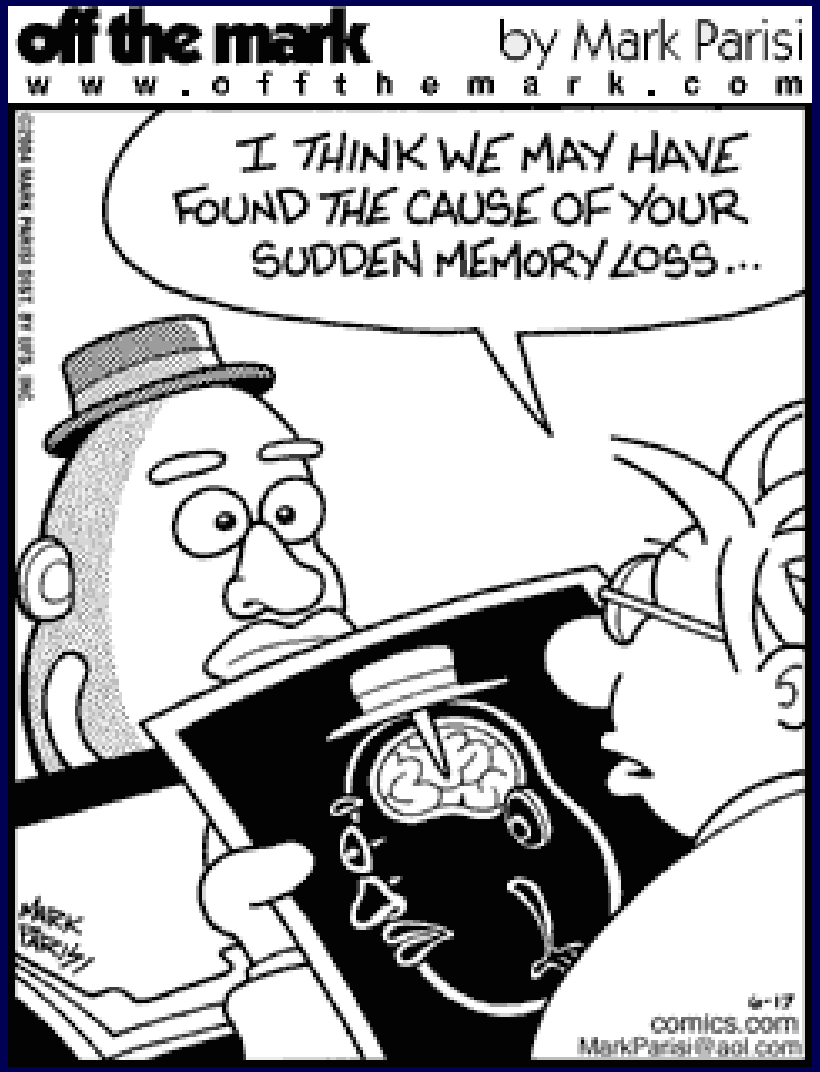
GDS 00 /30

EFFORT	*Raw*	*Effort*
Dot counting	21	Y
Reliable Digit Span	11	Y
CVLT Forced Choice	6/9	N

How is Dementia Typically Diagnosed?

- Minimum work-up includes:
  - History and physical examination
  - Mental status testing
  - Basic laboratory panel
- Recommended work-up includes:
  - Brain CT or MRI
  - Neuropsychological examination
  - Neurological examination
  - Psychiatric consultation

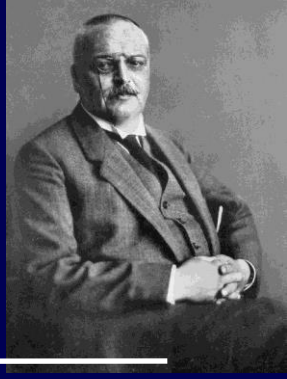
BIOMARKERS?



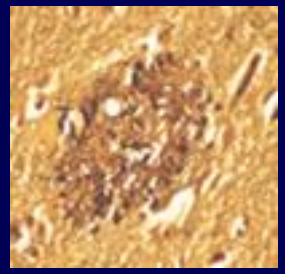
. . . To help us move forward

WHERE HAVE WE BEEN?

Timeline History of AD - early



- 1901-1906 Dr. Alzheimer observes 51 year old female, Auguste D., of Frankfurt, Germany
  - cluster of symptoms including: – Aphasia – Disorientation – Unpredictable behavior – Paranoia – Auditory hallucinations – Pronounced psychosocial impairment
- 1906 Dr. Alzheimer published histological changes associated with AD

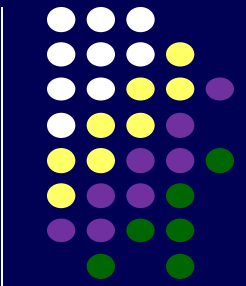


Amyloid plaques
- aggregated beta-amyloid

Neurofibrillary tangles
- hyperphosphorylated tau

- 1910 Emil Kraepelin names “Alzheimer’s Disease”

1910-1960s AD remains little known disease



- 1974-1975 Establishment of the National Institute of Health/ National Institute on Aging
- 1976 Biochemical changes in brain associated with AD
- 1979 Alzheimer's Association founded
- 1980s Research-Clinical trials
  - AD Becomes Social Movement
  - Research on biochemistry of toxic proteins of plaques and tangles
- 1987 Rita Hayworth dies of AD
- 1993 Cognex is first FDA approved drug to treat AD
- 1994 Possible effect of estrogen on AD is postulated
- 1996 Aricept FDA approved

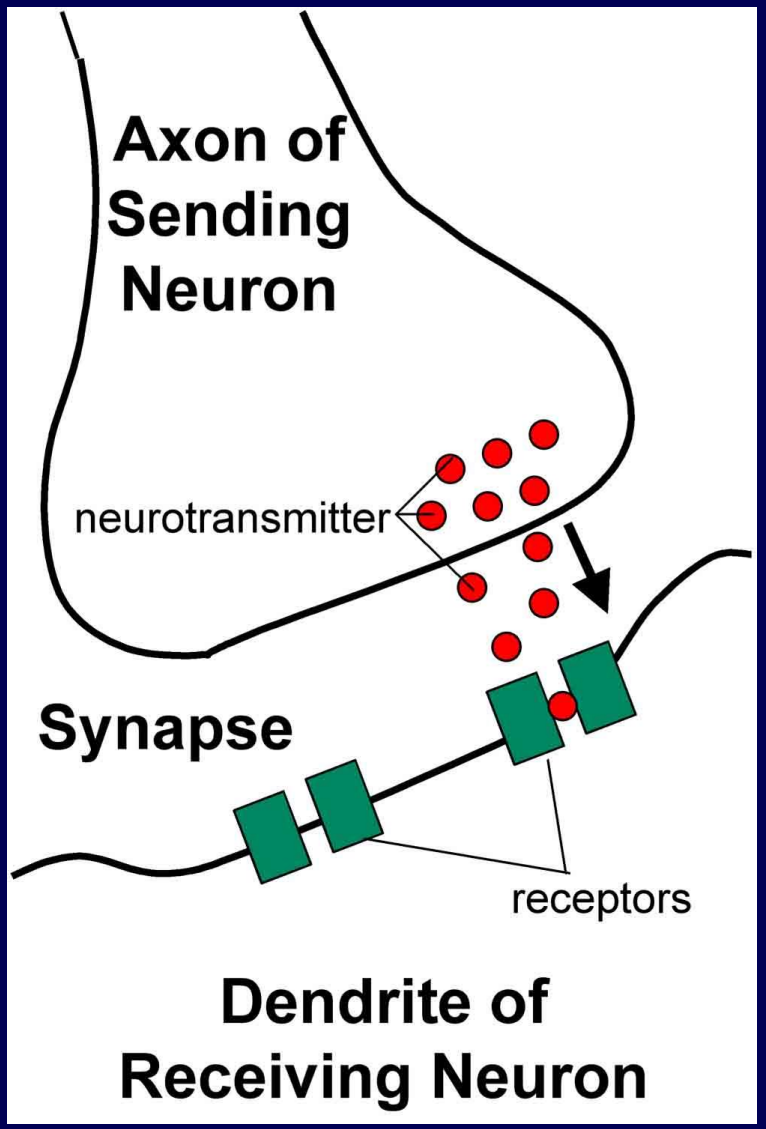
- 1997 Effect of antioxidants on AD studied
- 1999 Genetic mutations linked to programmed cell death of neurons
  - Development of techniques leading towards direct genetic manipulation for treatment of AD
  - First anti-AD vaccine tested
- 2000 Exelon FDA approved to treat AD
  - Brain imaging used to study AD
- 2001 Razadyne (previously Reminyl®) FDA approved
- 2002 Clinical trial of anti-Alzheimer's disease vaccine conducted
- 2003 Namenda FDA approved
- 2004 President Reagan dies of AD
  - Diabetes linked with increased risk of Alzheimer's

Current FDA-Approved Medications

Acetylcholinesterase Inhibitors		
tacrine	*Cognex®*	*hepatotoxic*
donepezil	Aricept®	1 month
galantamine	Razadyne®	4 months
rivastigmine	Exelon®	4 months; patch
NMDA receptor antagonist		
memantine	Namenda®	1 month; approved for mod-severe AD
Adjunct Therapies (off label)	Antidepressants Antipsychotics	SSRIs, mirtazapine risperidone, quetiapine

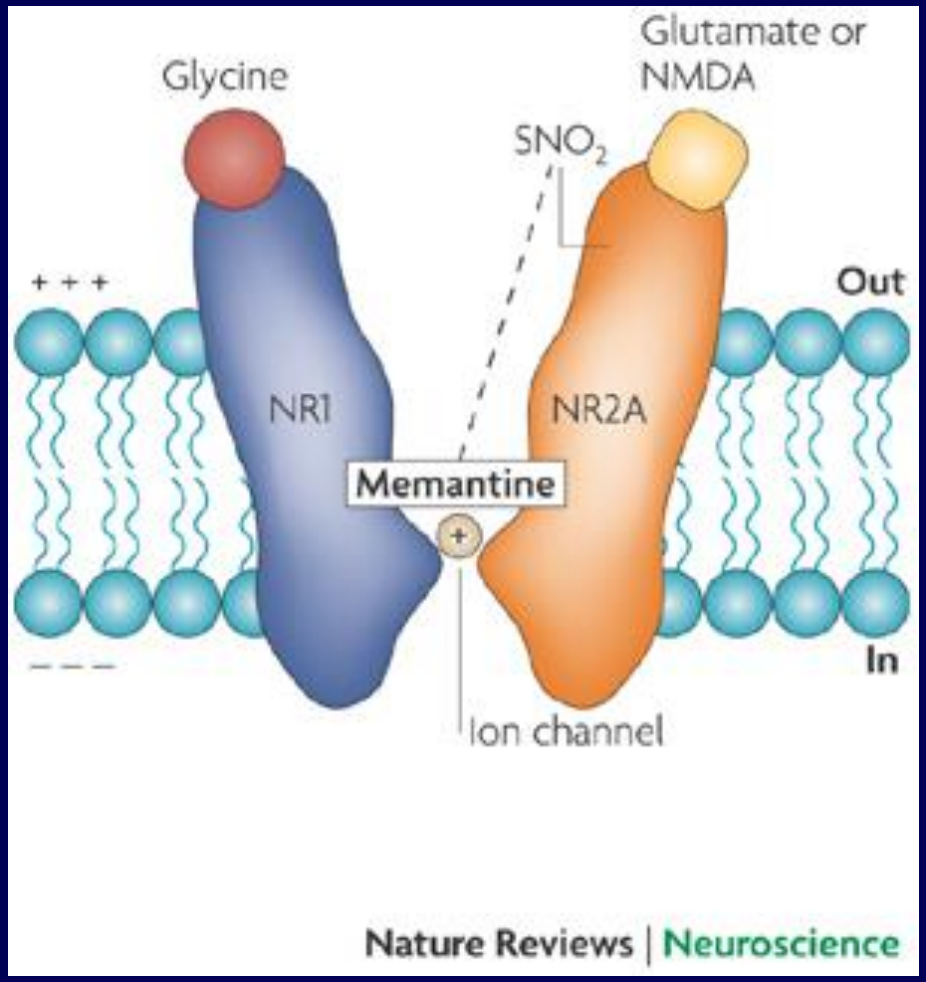
Acetylcholinesterase Inhibitor

- Acetylcholine is a neurotransmitter – part of cholinergic system of the brain
- Damage to the cholinergic (acetylcholine-producing) system in the brain has been shown to be plausibly associated with the memory deficits associated with Alzheimer's disease



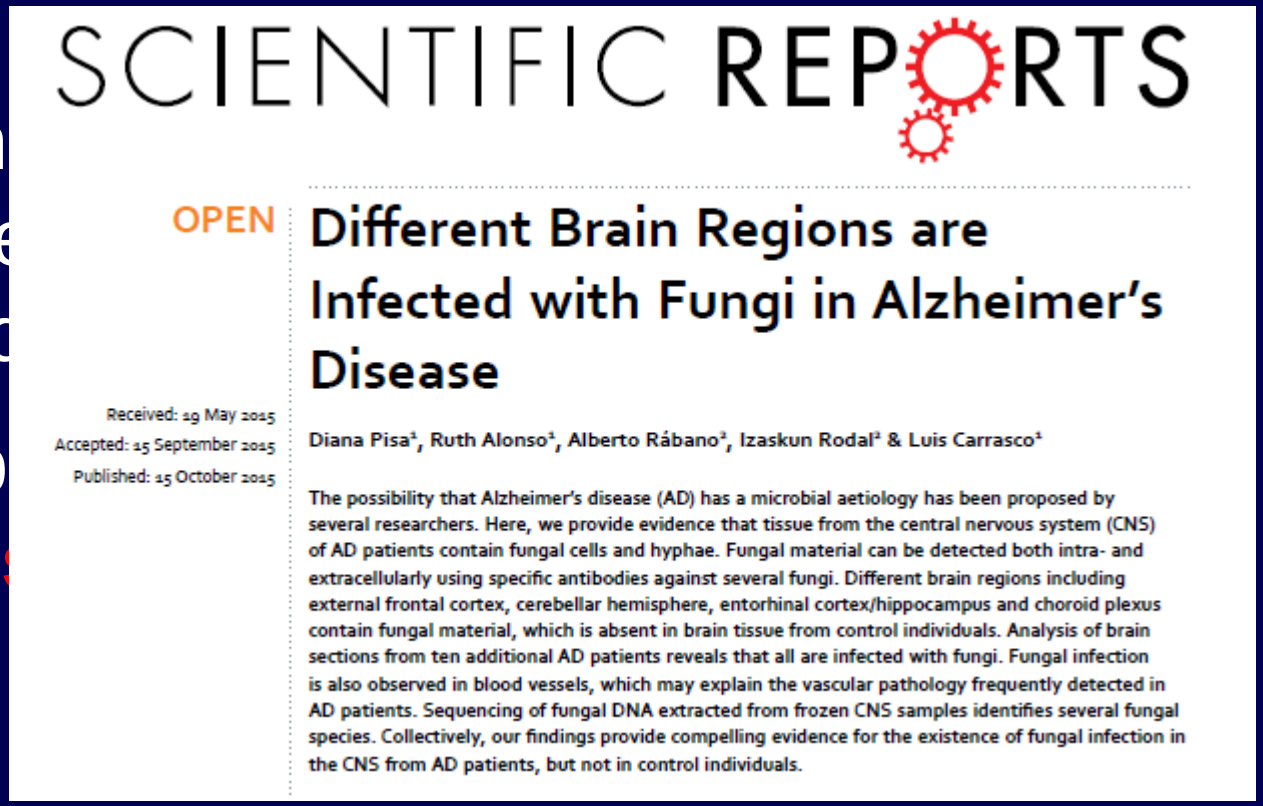
Memantine – NMDA receptor antagonist

- NMDA receptor responds to glutamate (the main excitatory neurotransmitter in the central nervous system)
- NMDA receptors have an important physiological role in learning and memory, but receptor overactivation owing to increased glutamate release leads to excessive calcium entry, triggering neuronal death - 'excitotoxicity'



Do we have a cure or tx for AD?

- No cure and the originating cause of AD is not fully understood
- Effective interven
  status to a degree
  health care provid
- In the case of a p
  "improvement" = s



SCIENTIFIC REPORTS

OPEN

Different Brain Regions are Infected with Fungi in Alzheimer's Disease

Received: 19 May 2015
Accepted: 15 September 2015
Published: 15 October 2015

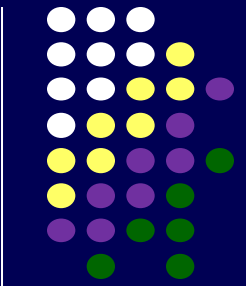
Diana Pisa[1], Ruth Alonso[1], Alberto Rábano[2], Izaskun Rodal[2] & Luis Carrasco[1]

The possibility that Alzheimer's disease (AD) has a microbial aetiology has been proposed by several researchers. Here, we provide evidence that tissue from the central nervous system (CNS) of AD patients contain fungal cells and hyphae. Fungal material can be detected both intra- and extracellularly using specific antibodies against several fungi. Different brain regions including external frontal cortex, cerebellar hemisphere, entorhinal cortex/hippocampus and choroid plexus contain fungal material, which is absent in brain tissue from control individuals. Analysis of brain sections from ten additional AD patients reveals that all are infected with fungi. Fungal infection is also observed in blood vessels, which may explain the vascular pathology frequently detected in AD patients. Sequencing of fungal DNA extracted from frozen CNS samples identifies several fungal species. Collectively, our findings provide compelling evidence for the existence of fungal infection in the CNS from AD patients, but not in control individuals.

Diagnostic and Treatment Challenges

- Pathological changes can begin up to 20 years before noticeable by self & others
  - early identification
  - importance of prevention …
- Comprehensive assessment is essential
  - rule out other causes of impairment and decline
- Not all dementia is AD
  - clinical presentations can be similar
  - screening or brief cognitive tests are insufficient

What's the hold up?

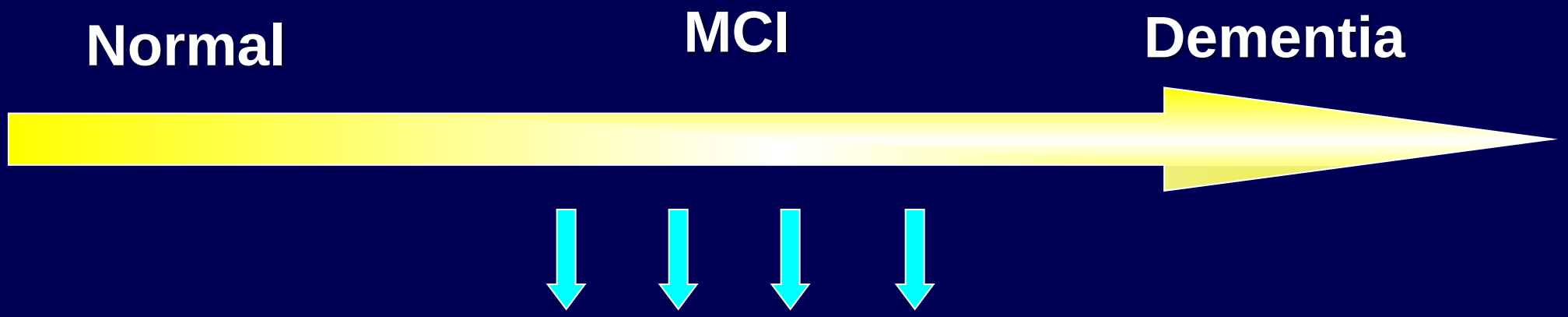


- Is therapy being implemented too late?
  - Early detection

- Is the therapeutic strategy not appropriate?
  - Need a better understanding of the pathological mechanisms

Either way, early detection of prodromal AD is a major goal to help researchers find a cure

Mild Cognitive Impairment



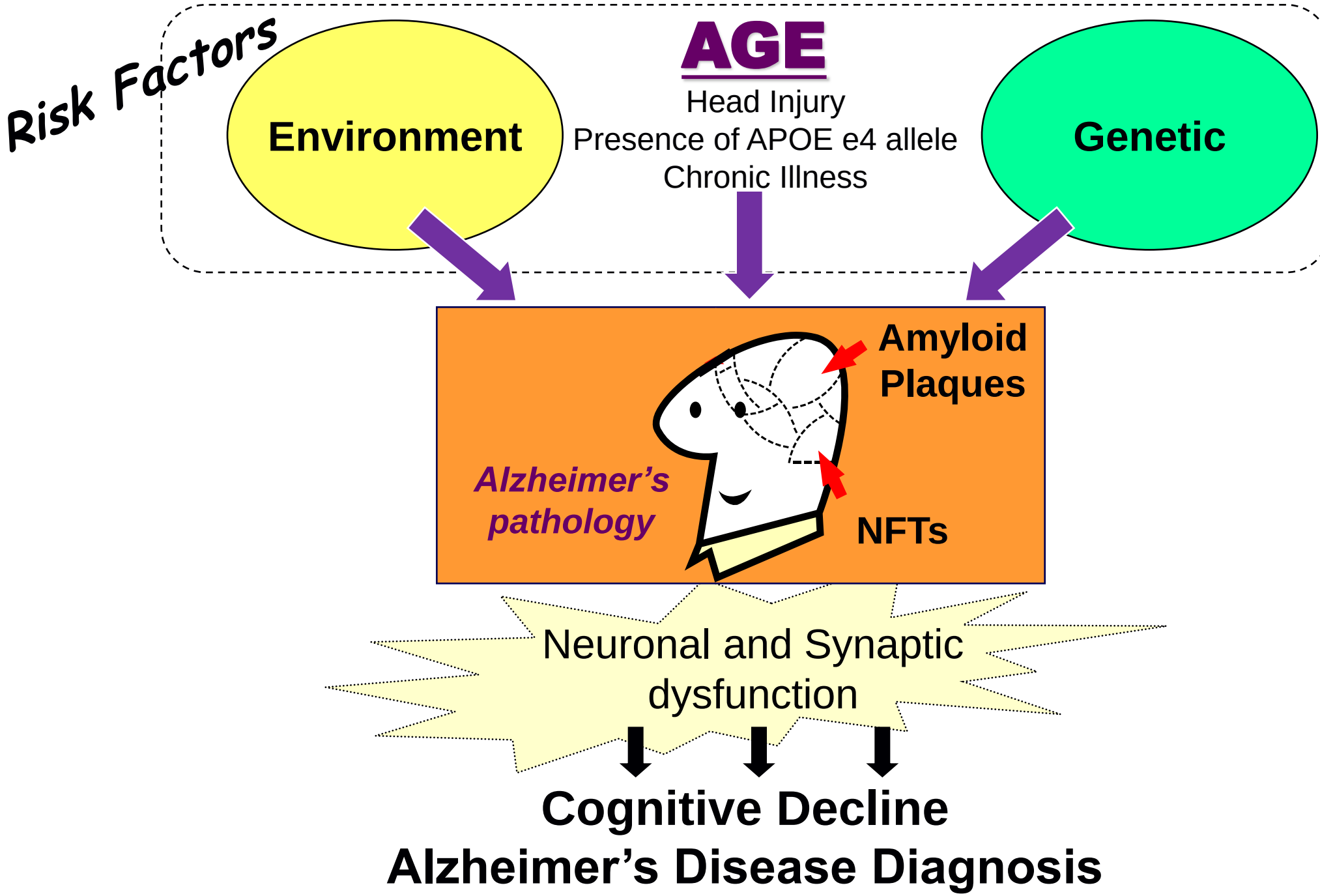
Pre-MCI?

An ideal point of intervention?

We need more options to assist research

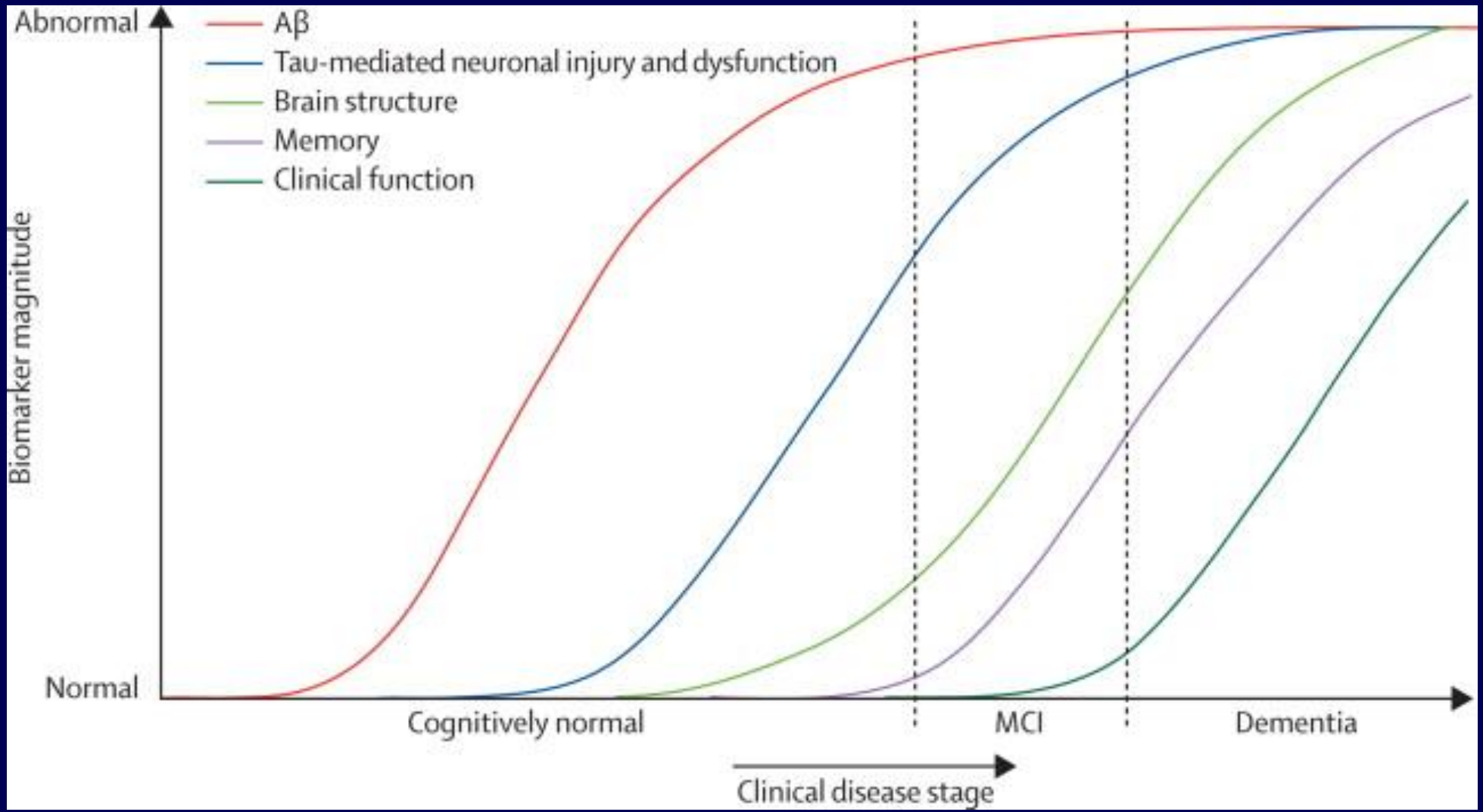
EARLY DETECTION

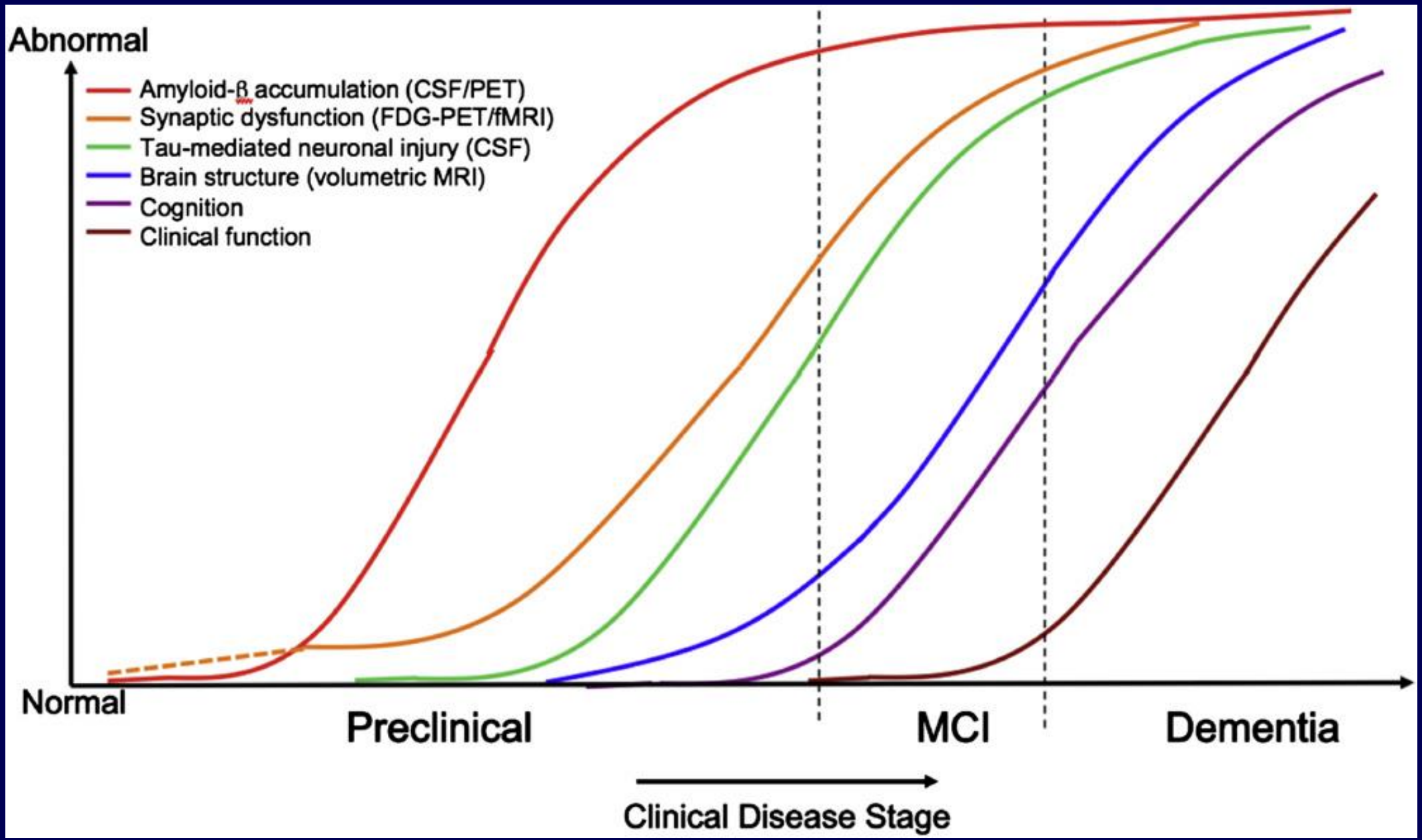
Before paper and scissors


Risk Factors
Environment
AGE
Head Injury
Presence of APOE e4 allele
Chronic Illness
Genetic
Amyloid Plaques
Alzheimer's pathology
NFTs
Neuronal and Synaptic dysfunction
Cognitive Decline
Alzheimer's Disease Diagnosis

Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade.

Jack, et al. 2010. Lancet



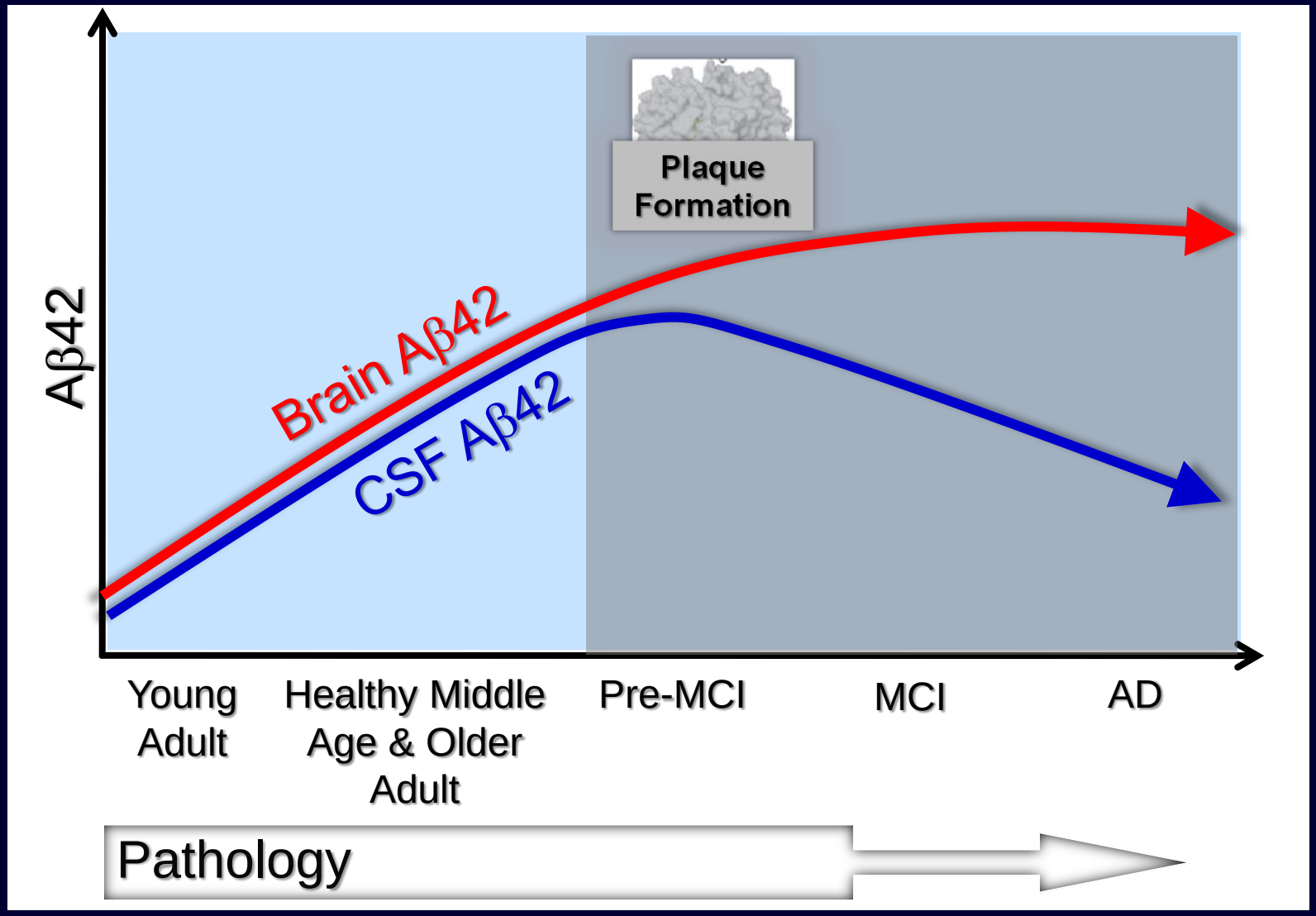


Sperling, et al., 2011 – adapted from Jack, et al., 2010

Biomarkers for Diagnosis of AD

- CSF markers
  - β-amyloid protein ($a\beta_{1\text{-}42}$)
    - $A\beta_{40}$ and $A\beta_{42}$
  - Total tau
  - Phosphorylated Tau (P Tau)
- MRI – structural and *functional*
  - Cortical thickness mapping/volume of medial temporal lobe
  - Ventricular volume as evidence for atrophy
- PET imaging

Model of Aβ Changes - Health to AD



Craft, S. figure from Trittschuh 2012 presentation

Diagnosis-Independent Alzheimer Disease Biomarker Signature in Cognitively Normal Elderly People

De Meyer, Shapiro, Vanderstichele, Vanmechelen, Engelborghs, De Deyn, Coart, Hansson, Minthon, Zetterberg, Blennow, Shaw, Trojanowski; for the Alzheimer's Disease Neuroimaging Initiative

Archives of Neurology, 67, August 2010

- Used Mixture Model classification to determine an **AD signature**

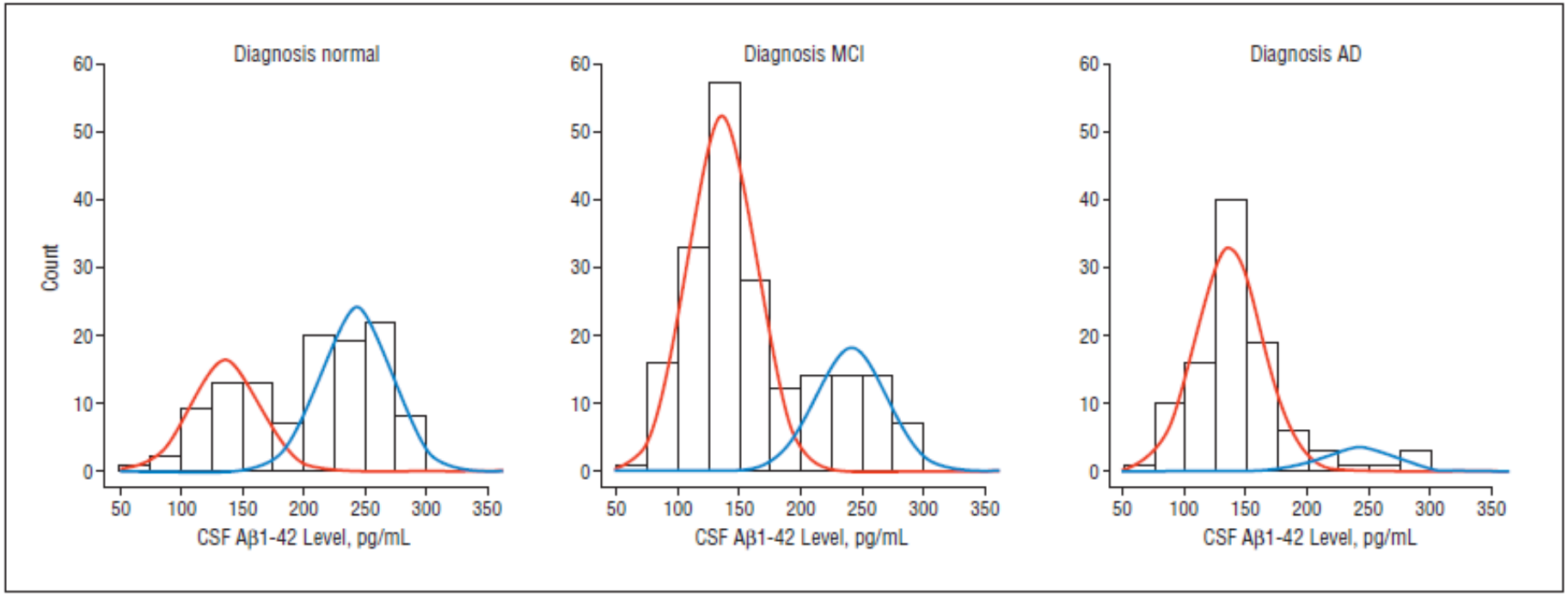


Figure 2. Cerebrospinal fluid–derived β-amyloid protein 1-42 (CSF Aβ1-42) mixture model applied to the clinically diagnosed subject groups. AD indicates Alzheimer disease; MCI, mild cognitive impairment.

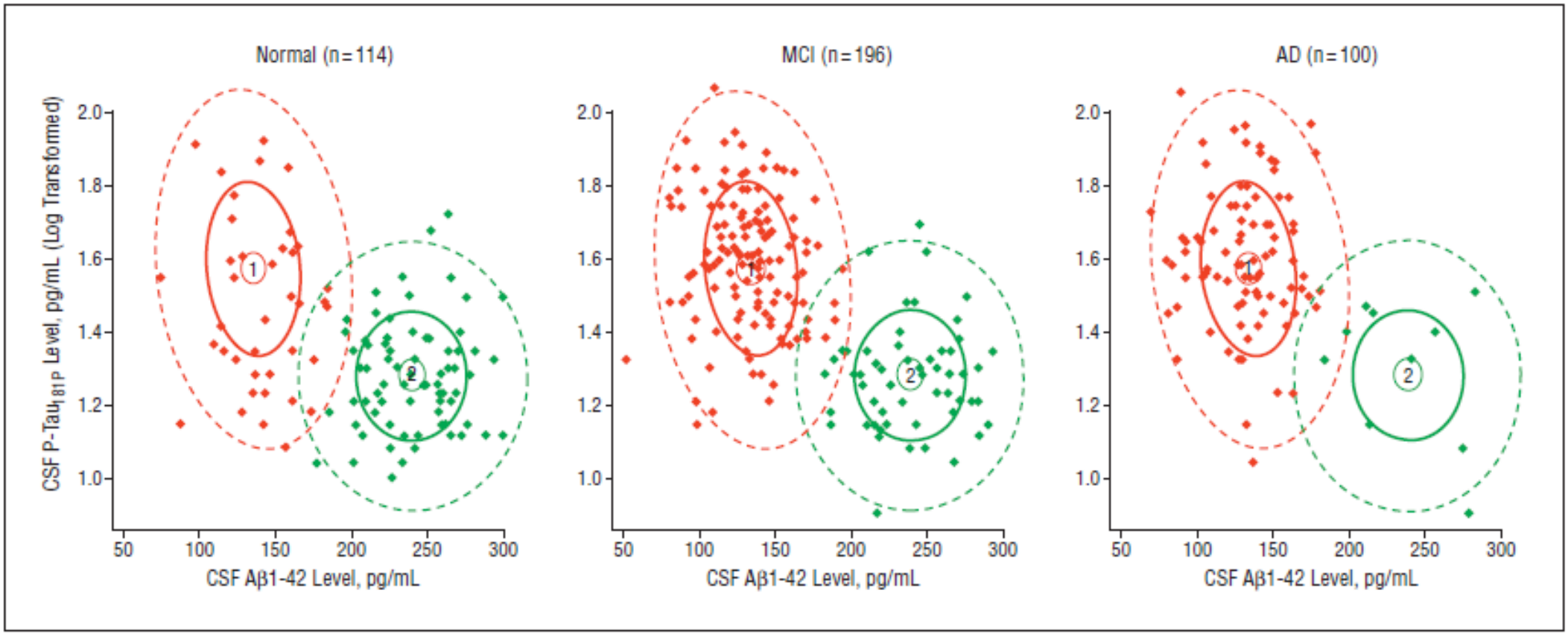


Figure 4. A combined cerebrospinal fluid–derived β-amyloid protein 1-42 (CSF Aβ1-42)/CSF phosphorylated tau_{181P} (CSF P-Tau_{181P}) mixture model applied to the subject groups. Densities of each signature are represented with confidence ellipses, and signature membership of the subject based on the mixture is indicated with the corresponding color (signature 1 is the Alzheimer disease [AD] signature [red]; signature 2 is the healthy signature [green]). MCI indicates mild cognitive impairment.

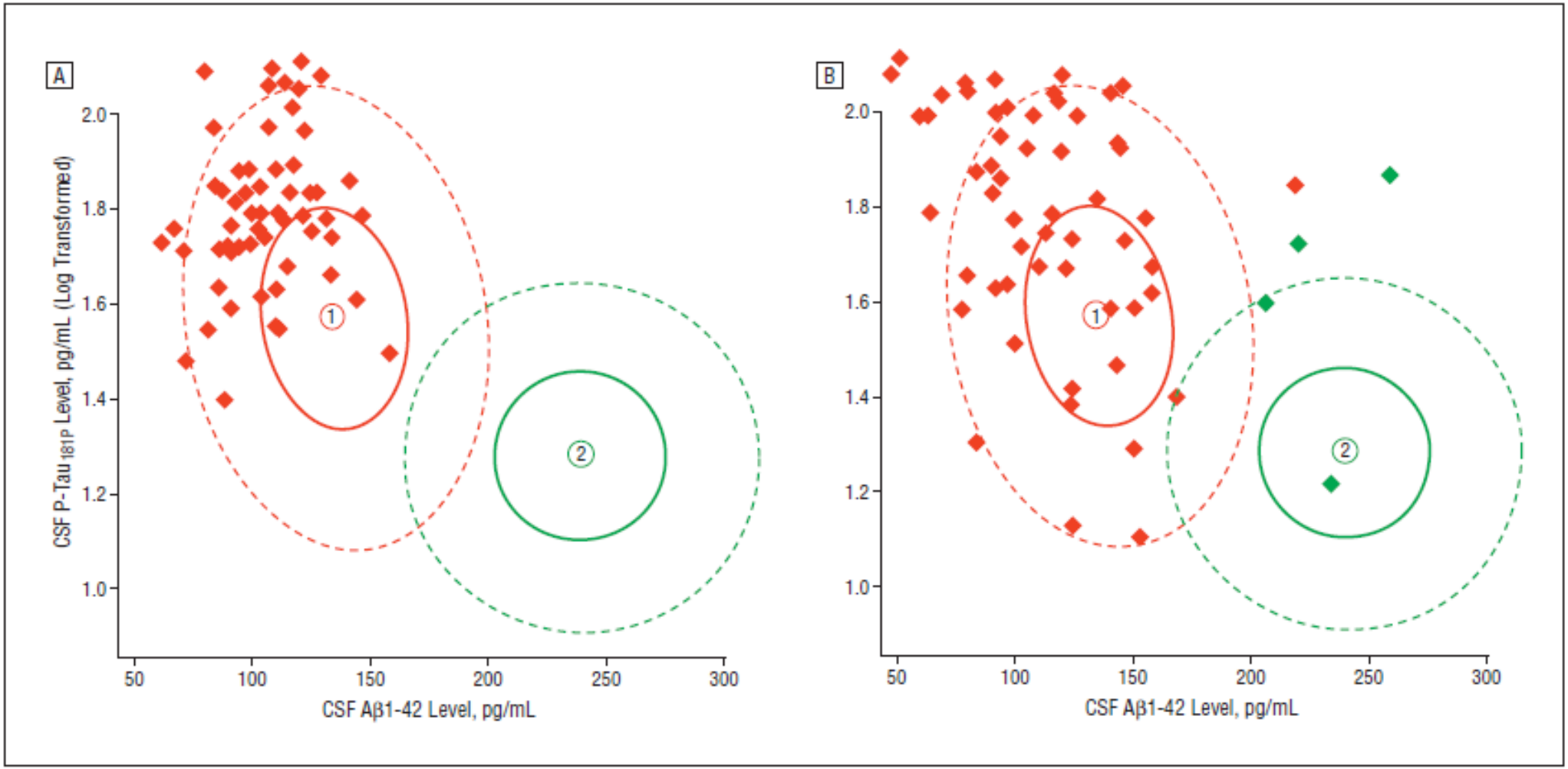
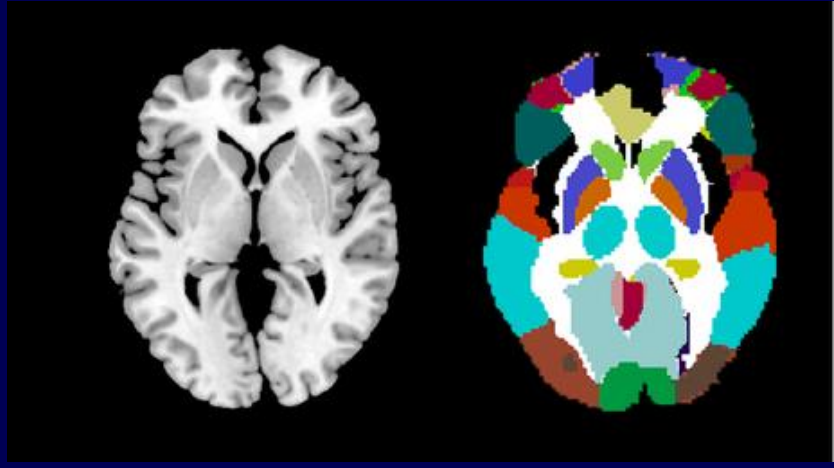


Figure 5. Validation of the combined cerebrospinal fluid–derived β-amyloid protein 1-42 (CSF Aβ1-42)/CSF phosphorylated tau_{181P} (CSF P-Tau_{181P}) mixture model in 2 data sets. A, Patients with mild cognitive impairment who developed Alzheimer disease within 5 years after the CSF sample.[2] B, Patients with autopsy-confirmed Alzheimer disease with mostly less than 1 year between CSF sample and autopsy (n=68).[12] Signature 1 is the Alzheimer disease signature (red); signature 2 is the healthy signature (green).

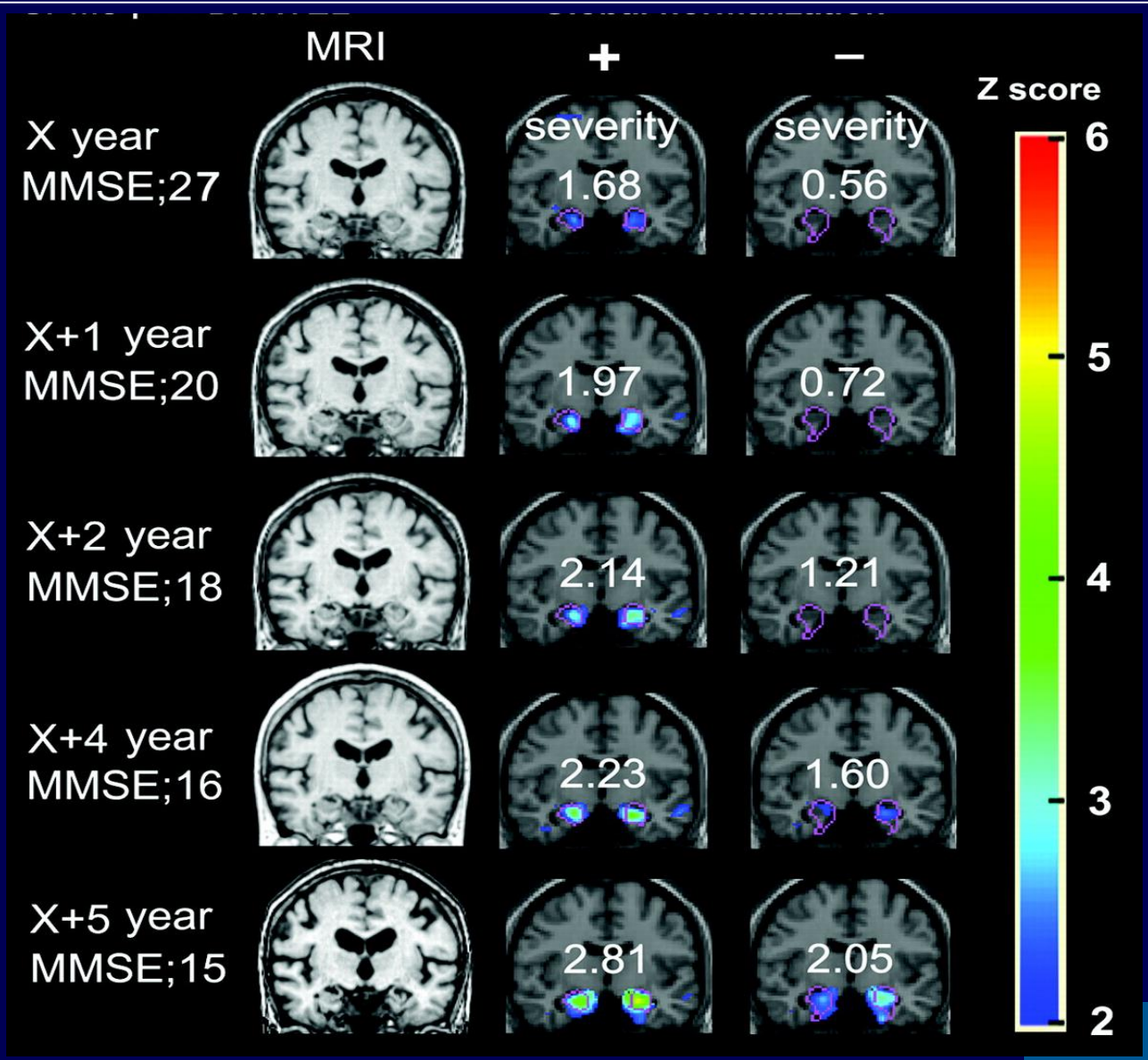
- 100% predictive in people who already had a memory problem

MRI - structural



- Manual tracing
  - Utilized to extract volumetric and morphometric characteristics
  - Manual tracing of regions of interest and medial temporal atrophy scores
- Semi-Automated and Automated techniques have been developed
  - Voxel-based morphometry
  - Cortical thickness mapping

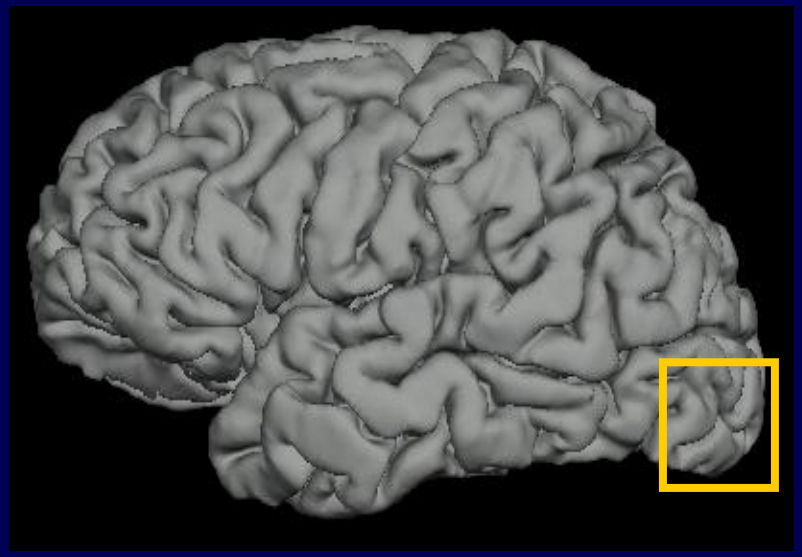
Longitudinal VBM studies by using SPM8 plus DARTEL. A 63-year-old woman with an MMSE score of 27 at the first visit was followed up for 6 years.

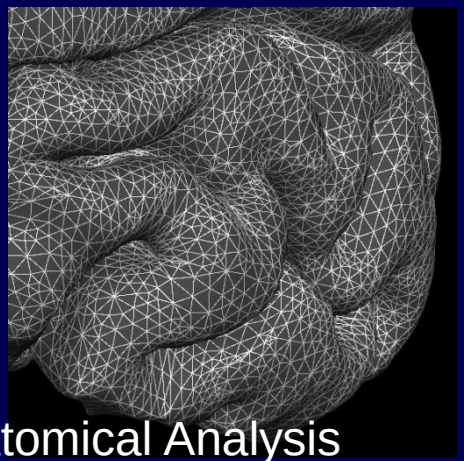


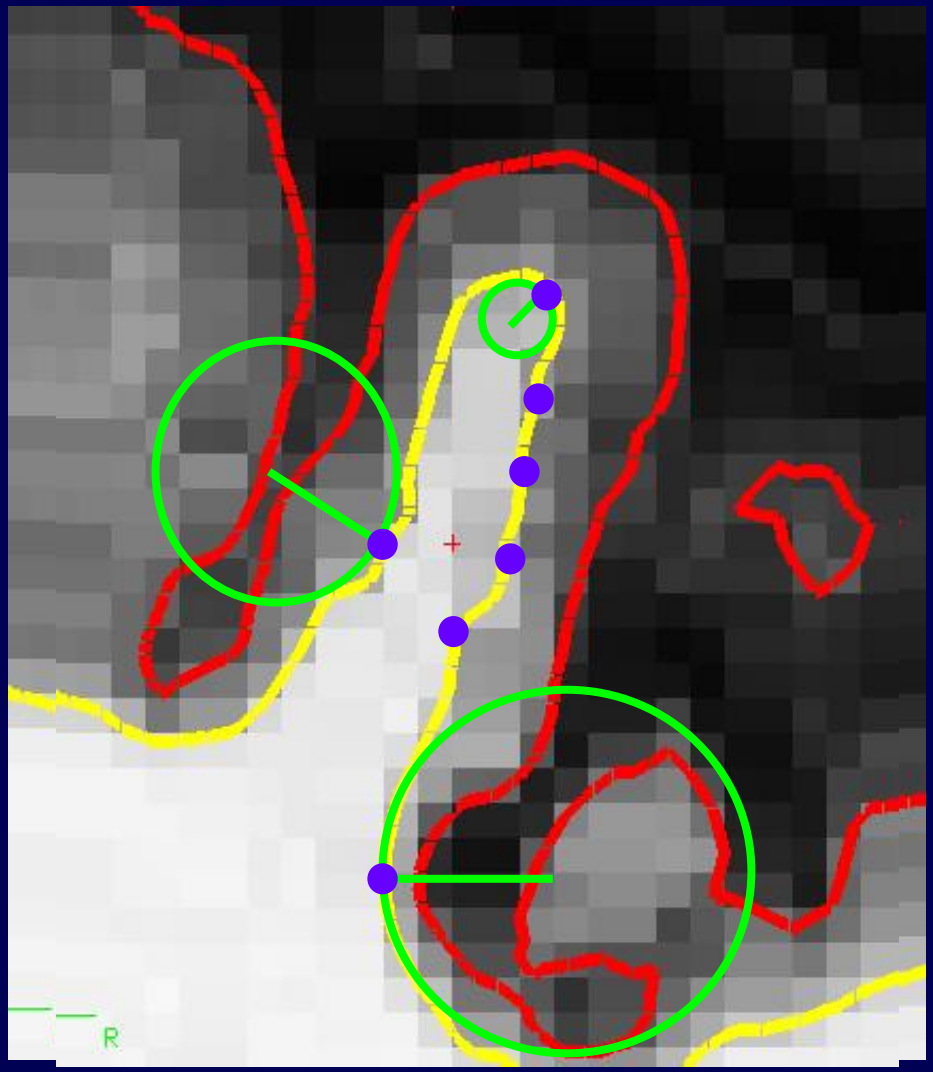
H. Matsuda et al. AJNR Am J Neuroradiol 2012;33:1109-1114

AJNR
AMERICAN JOURNAL OF NEURORADIOLOGY

Cortical Thickness Mapping



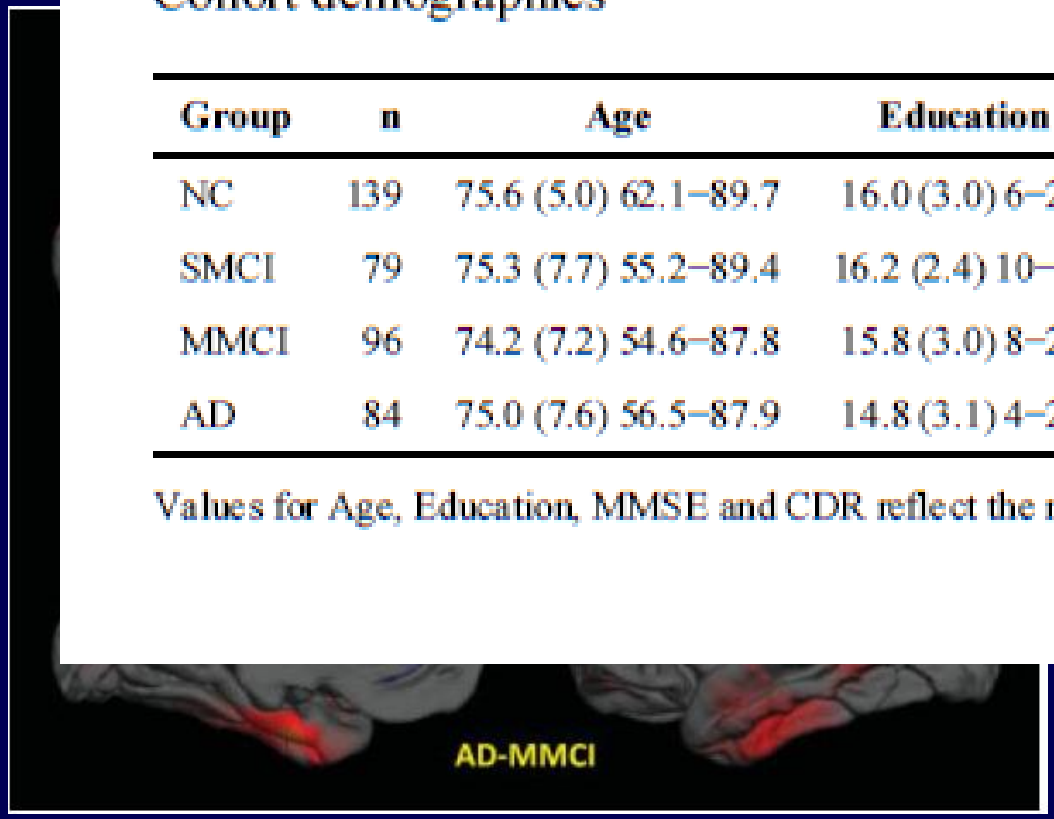




FreeSurfer: Automated Anatomical Analysis

surfer.nmr.mgh.harvard.edu

Structural MRI Biomarkers for Preclinical and Mild Alzheimer's Disease



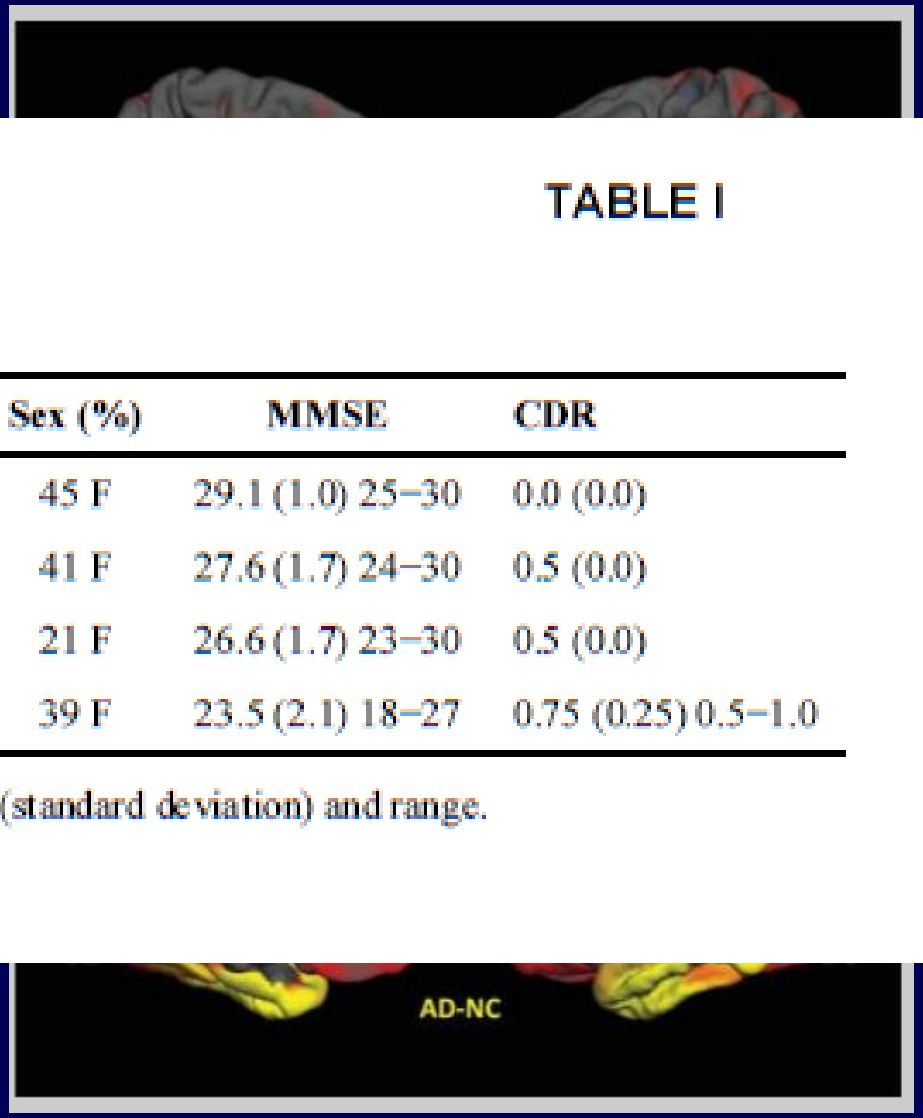


TABLE I

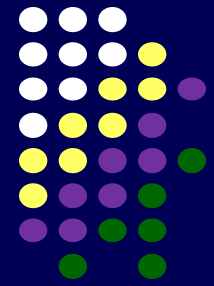
Cohort demographics

Group	n	Age	Education	Sex (%)	MMSE	CDR
NC	139	75.6 (5.0) 62.1–89.7	16.0 (3.0) 6–20	45 F	29.1 (1.0) 25–30	0.0 (0.0)
SMCI	79	75.3 (7.7) 55.2–89.4	16.2 (2.4) 10–20	41 F	27.6 (1.7) 24–30	0.5 (0.0)
MMCI	96	74.2 (7.2) 54.6–87.8	15.8 (3.0) 8–20	21 F	26.6 (1.7) 23–30	0.5 (0.0)
AD	84	75.0 (7.6) 56.5–87.9	14.8 (3.1) 4–20	39 F	23.5 (2.1) 18–27	0.75 (0.25) 0.5–1.0

Values for Age, Education, MMSE and CDR reflect the mean (standard deviation) and range.

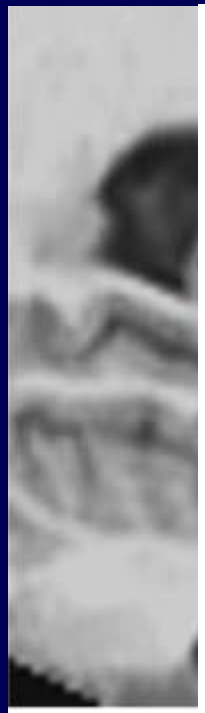
Fennema-Notestine, et al, Human Brain Mapping, 2009

MRI General Findings



- Structural imaging markers can detect early AD with good accuracy [Frisoni, et al, 2010; Cuingnet, et al, 2011, among others]
- Hippocampal volume loss may be better than cortical thickness reduction or global brain atrophy measures at predicting AD [Cuingnet, et al, 2011; Wolz, et al, 2011]
  - Still prediction accuracy 18 months before conversion was ~65% [Wolz, et al, 2011]
- Graded analyses?

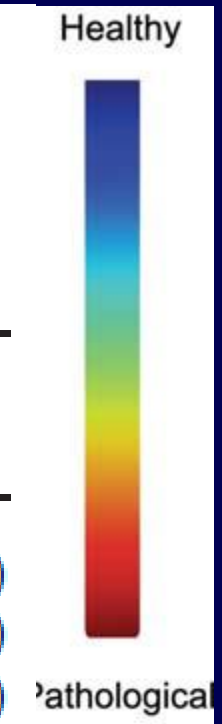
MR-based hippocampal grading yielded prediction accuracy up to 72.5% 7 years before conversion to AD
Grading was more efficient than hippocampal volume alone (64.6%)



HC gra

TABLE I. Demographic details of the AD patients and CN subjects of the ADNI database used as training dataset and of the stable CN and converter CN of the Bdx-3C dataset used as testing images

	Population size	% Male	Age (SD)	MMSE (SD)
CN (ADNI)	225	52%	76.0 (5.0)	29.1 (0.9)
AD (ADNI)	192	52%	75.6 (7.7)	22.8 (2.9)
Stable CN (Bdx-3C)	309	41%	72.7 (3.9)	28.4 (1.2)
Converter CN (Bdx-3C)	37	30%	75.4 (3.9)	27.9 (1.4)

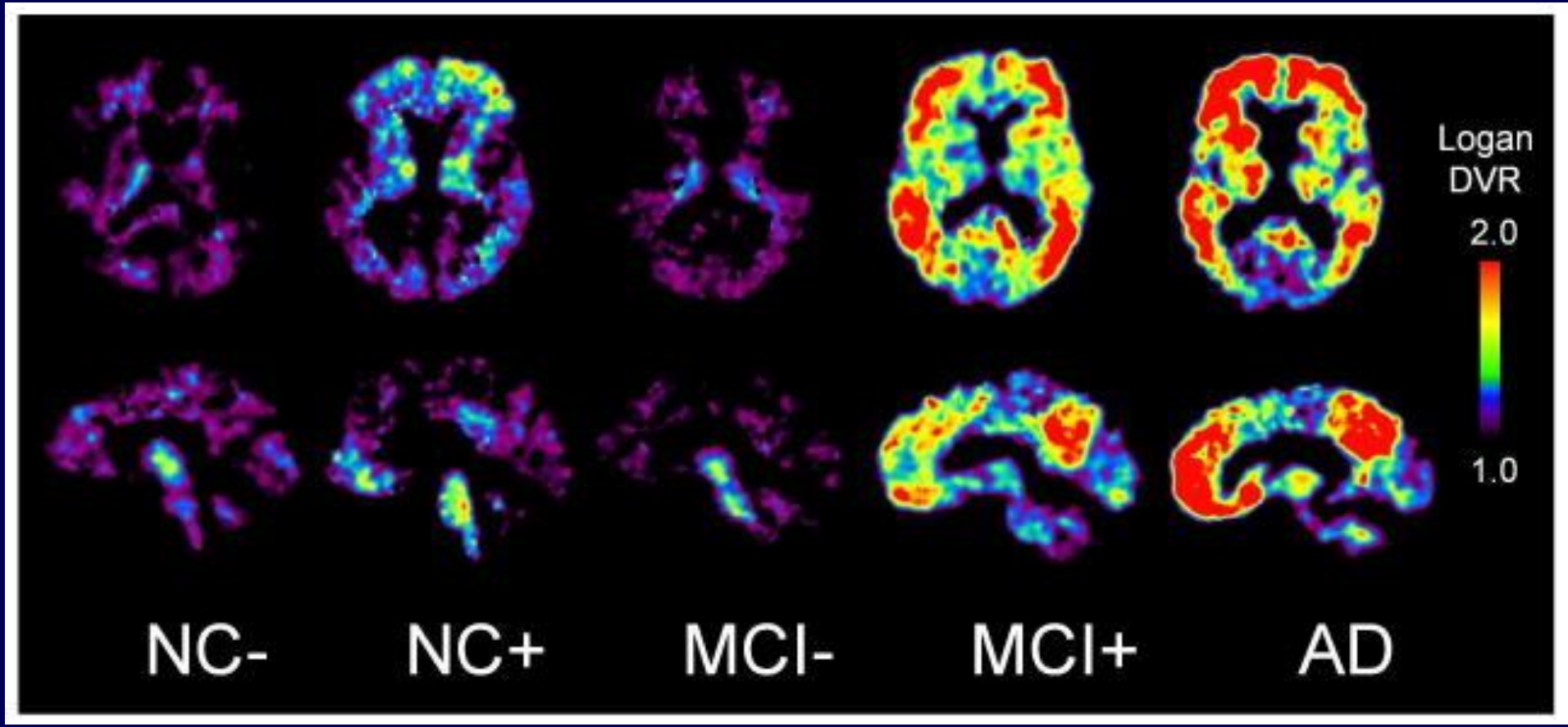


Coupe, et al, Human Brain Mapping, 2015

PET imaging

- Uses radiolabeled ligands to measure metabolic and neurochemical processes
- For dementia research: focus has been on FDG and Amyloid imaging
  - FDG = fluorodeoxyglucose; marker for brain metabolism
  - Amyloid tracers such as Pittsburgh compound B (PiB) and Florbetapir, which bind to fibrillar amyloid plaques

Update on Amyloid Imaging: From Healthy Aging to Alzheimer's Disease



Wolk & Klunk, Curr Neurol Neurosci Rep, 2009

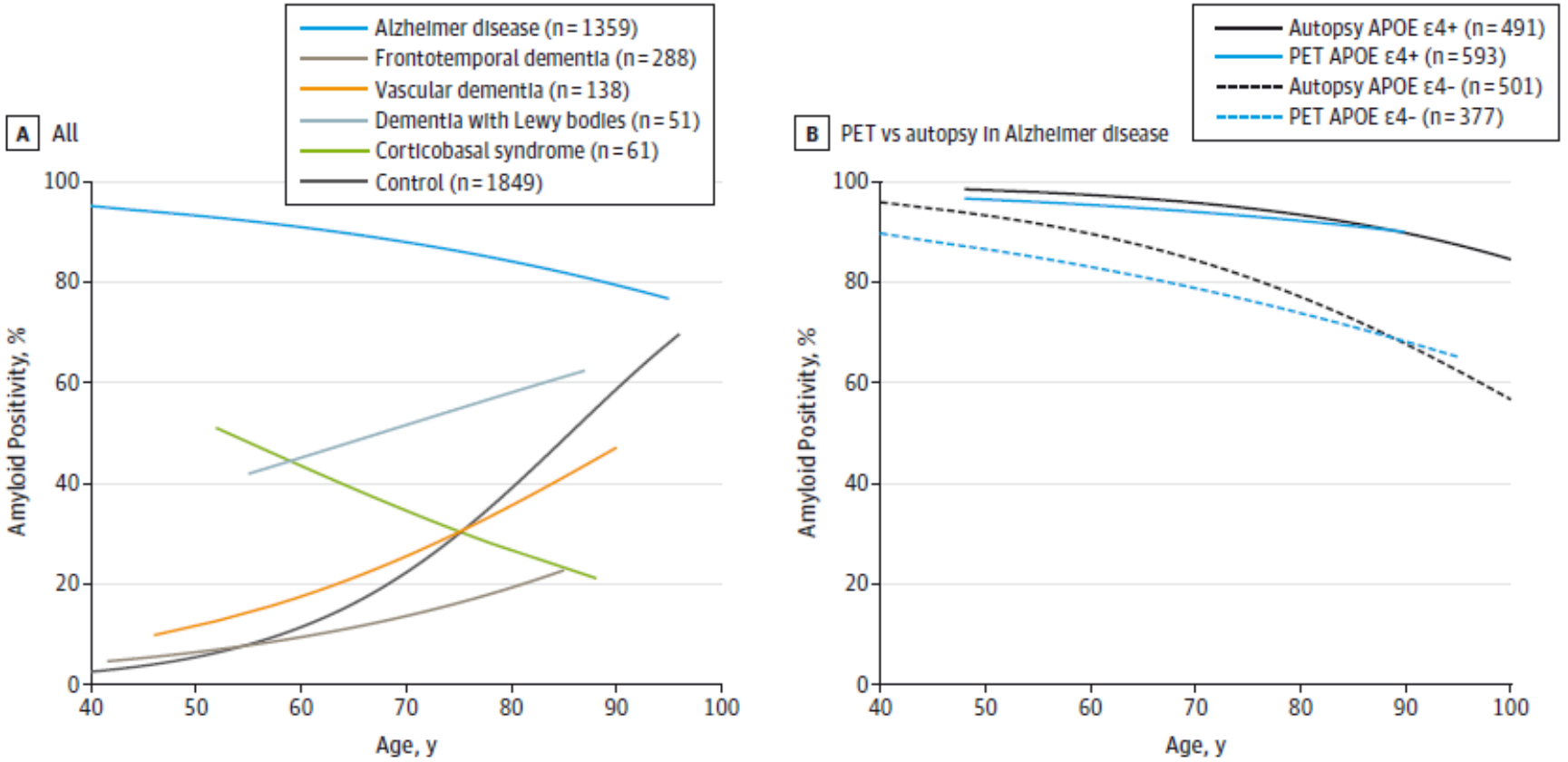
Is it always Alzheimer's disease?

Original Investigation

Prevalence of Amyloid PET Positivity in Dementia Syndromes A Meta-analysis

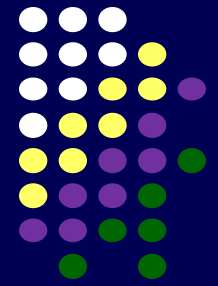
Rik Ossenkoppele, PhD; Willemijn J. Jansen, MSc; Gil D. Rabinovici, MD; Dirk L. Knol, PhD; Wiesje M. van der Flier, PhD; Bart N. M. van Berckel, MD, PhD; Philip Scheltens, MD, PhD; Pieter Jelle Visser, MD, PhD; and the Amyloid PET Study Group

Figure 2. Prevalence of Amyloid Positivity on PET According to Age for the Different Dementia Diagnostic Groups

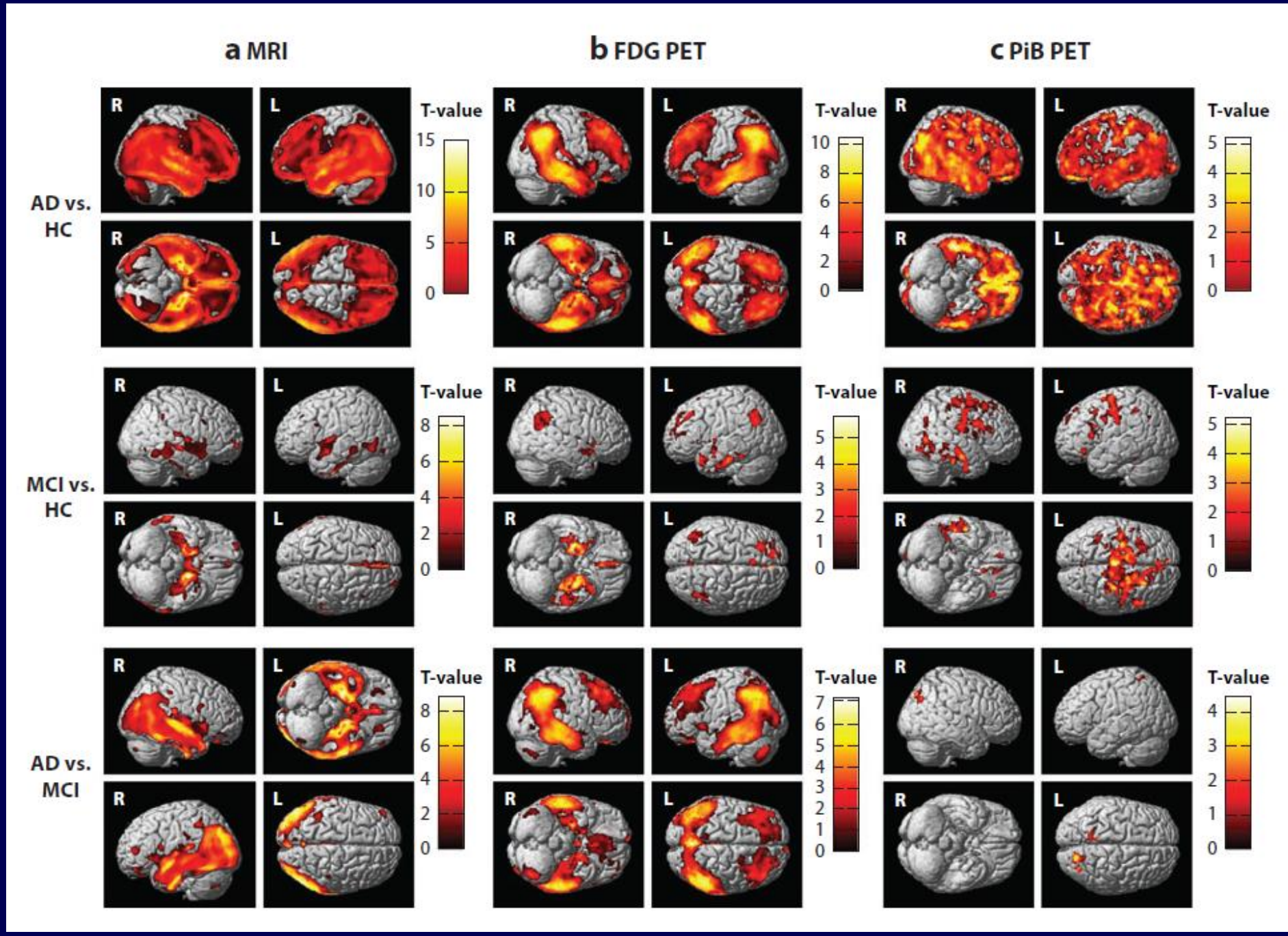


JAMA, 2015

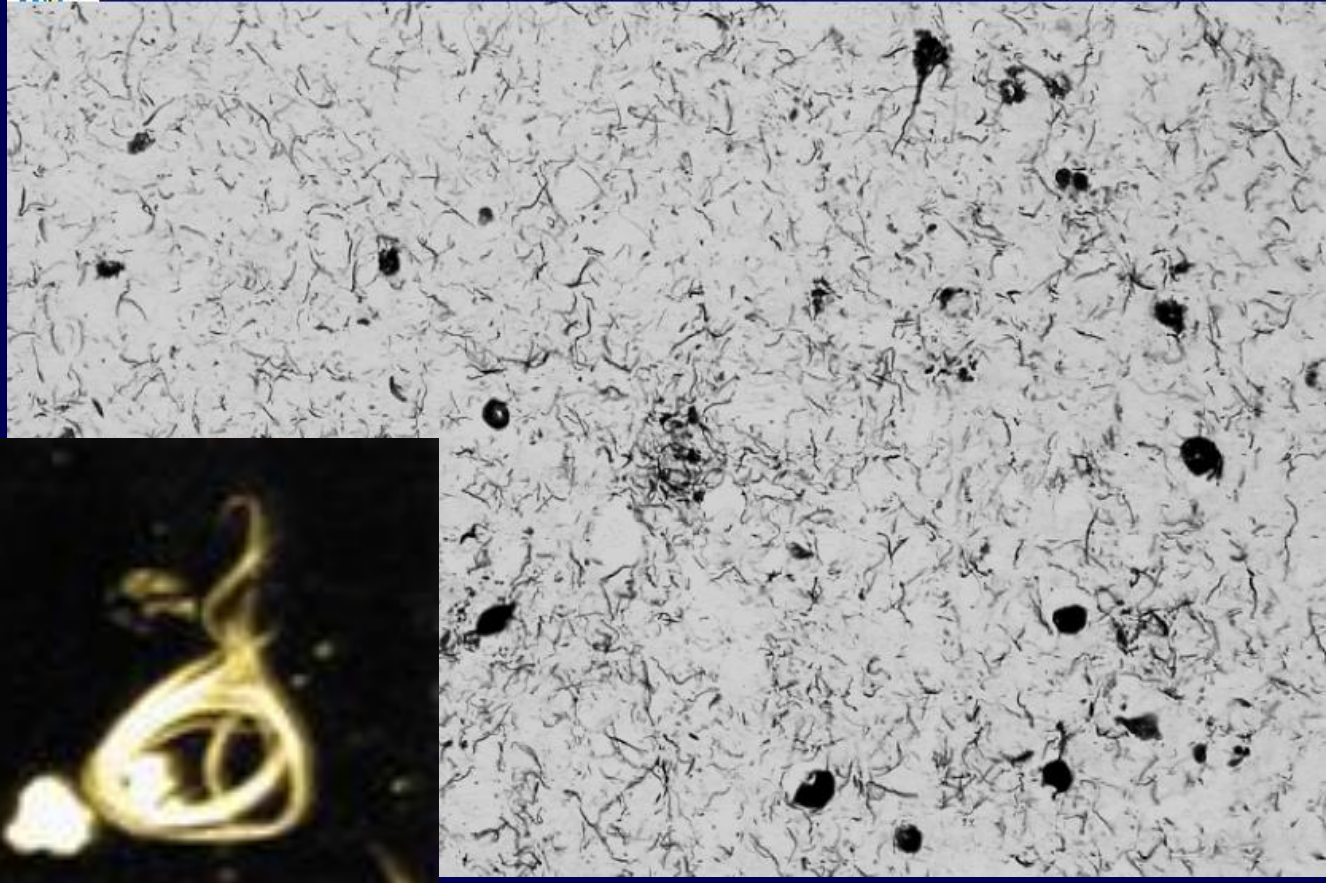
PET imaging in Normal Controls



- Approximately 25% to 30% of older adults with normal cognition are amyloid positive [Johnson et al. 2012, Mintun et al. 2006, Villemagne et al. 2008]
- Follow-up studies suggest they are more likely to progress to MCI or AD [Mintun et al. 2006, Villemagne et al. 2008]
- Cognitive reserve has been shown to independently modulate the relationship between amyloid accumulation and cognition in healthy older adults [Rentz et al. 2010] as well as in patients with MCI and AD [Kemppainen et al. 2008, Vemuri et al. 2011]



From Riscacher & Saykin, Ann Rev Clin Psychol, 2013

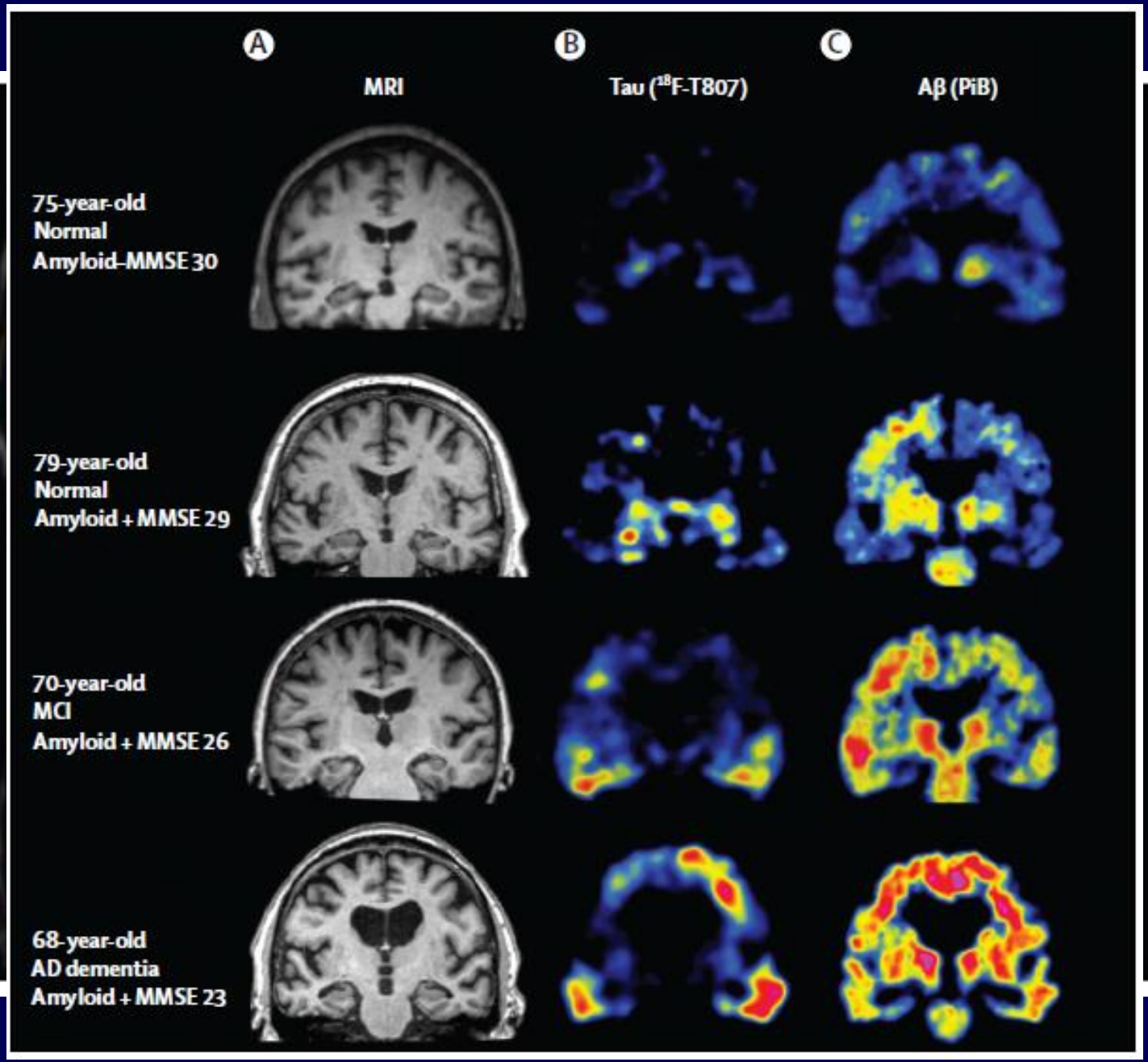


WHAT ABOUT TAU?

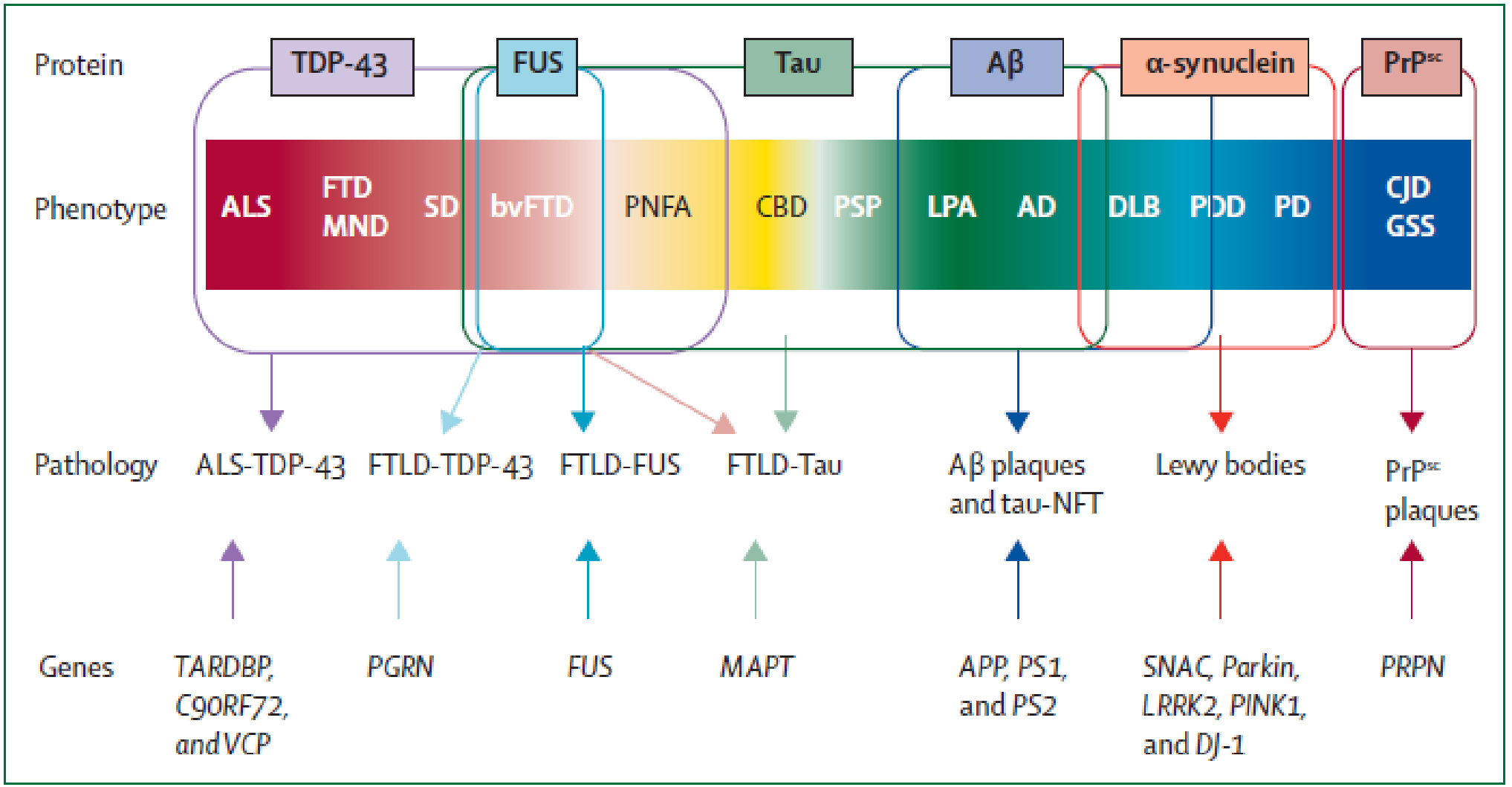
Tau Imaging

- Many challenges to tau imaging, for example:
  - Intracellular
  - Six tau isoforms with different structures
  - In AD, tau aggregates are coexistent with beta amyloid
  - In AD, tau is in lower concentrations than beta amyloid
- Must have high selectivity for tau over Aβ
- High binding affinity
- Low non-specific binding
- Ability to cross the BBB, long half-life, not metabolized

Villemagne, et al, Lancet Neurology, 2015



Villemagne, et al, Lancet Neurology, 2015



Short 0N3R isoform	Myotonic dystrophy	Neurofibrillary tangles	NA

Adapted from Villemagne et al,[19] by permission of Future Medicine. 3R–three repeat. 4R–four repeat. NA–data not available. Short 0N3R–the shortest isoform of fetal tau (where N denotes the number of N-terminal inserts and R the number of microtubule-binding domains). *Tau conformation at much lower prevalence.

Table: **Morphological and ultrastructural conformations of tau isoforms in tauopathies**

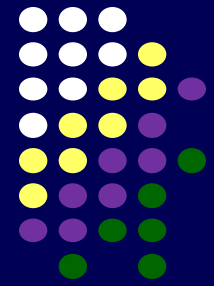
WHY SO EXCITING?

Other ideas for early detection

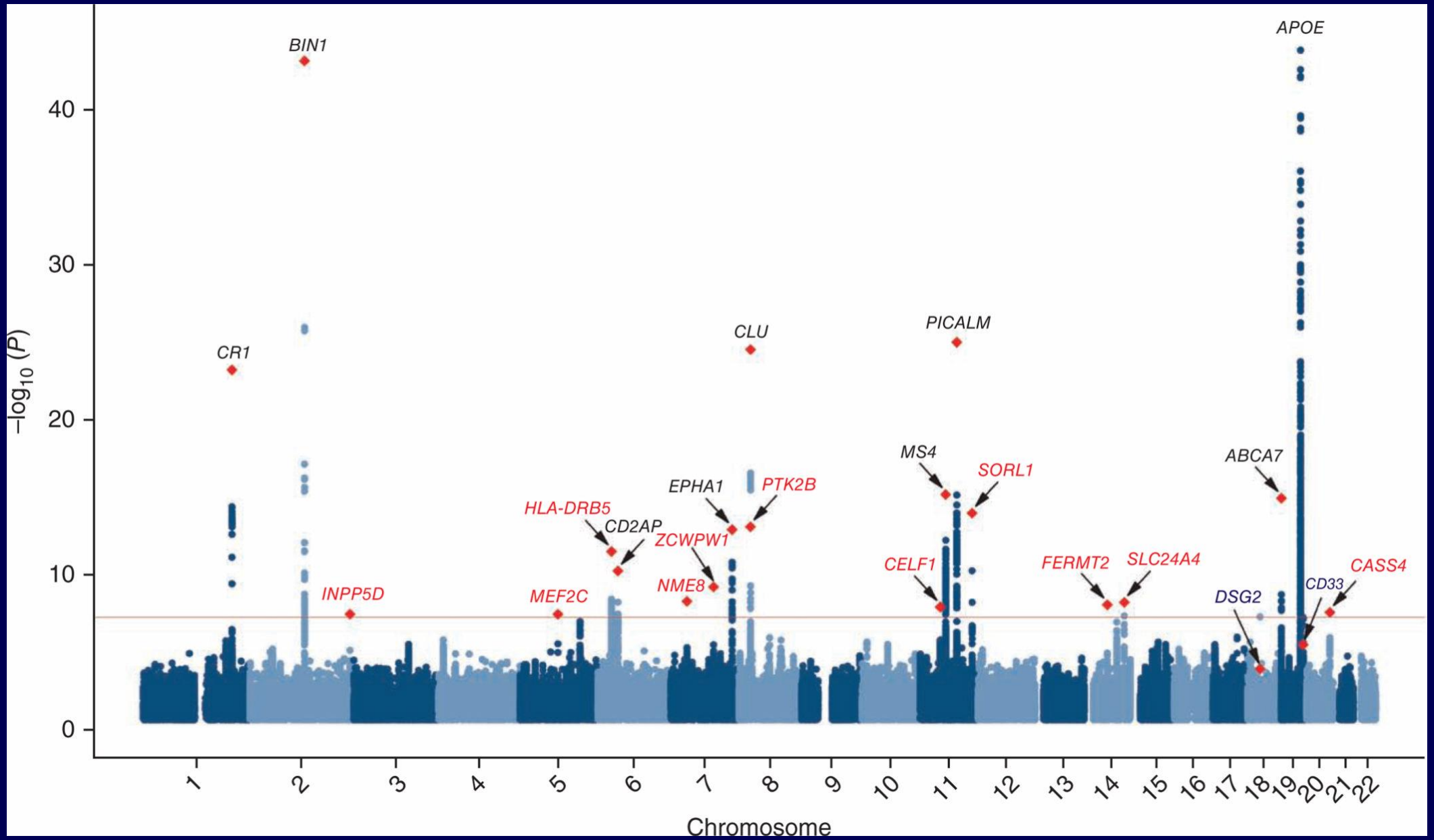
- EEG[1]
  - Can detect dementia early and has been able to differentiate AD from other dementia types
  - Non-invasive, can be inexpensive
- Retinal Oximetry[2]
  - Detects changes in retinal oxygen metabolism
  - Able to distinguish mild/mod AD from HC
- Odor detection[3]
  - Lower detection ability in patients with AD
- Genome Wide Association Studies

Recent reviews: 1. Al-Qazzaz, et al, Scientific World Jl, 2015; 2. Einarsdottir, et al, J of Alz Dis, 2015 (epub); 3. Joussain, et al, J of Alz Dis, 2015 (epub)

Genome-Wide Association Studies



- To better understand the molecular drivers of disease to increase the range of therapeutic targets
- Involves rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease
- If certain genetic variations are found to be significantly more frequent in people with a disease compared to people without disease, the variations are said to be "associated" with the disease.
- However, the associated variants themselves may not directly cause the disease. They may just be "tagging along" with the actual causal variants.
- Genetic risk loci have been found that add to our knowledge of AD



Lambert JC, et al. Nat Genet. 2013 Dec;45(12):1452-8.

Gene	Location	SNP	Risk allele frequency controls	OR (95% CI)	Population-attributable fraction (%)	Potential functional variant
APOE (apolipoprotein E)	19q13.32	ε4	0.16	3.78 (2.60–5.48)	30.8[a]	ε4
SORL1 (sortilin-related receptor-1)	11q24.1	rs11218343-T	0.96	1.30 (1.22–1.39)	0.91[b]	Common and rare pathogenic variants[34,35]
BIN1 (bridging integrator 1)	2q14.3	rs6733839-T	0.41	1.22 (1.18–1.25)	8.2[a]	rs59335482, 3 bp insertion[40]
CR1 (complement component (3b/4b) receptor 1)	1q32.2	rs6656401-A	0.20	1.18 (1.14–1.22)	3.5[a]	Intragenic CNV resulting in different CR1 isoforms[41]
CLU (clusterin)	8p21.1	rs9331896-T	0.62	1.16 (1.12–1.19)	5.1[b]	Rare coding and common regulatory variants[30,31]
PICALM (phosphatidylinositol-binding clathrin assembly protein)	11q14.2	rs10792832-G	0.64	1.15 (1.12–1.18)	4.5[b]	—
ABCA7 (ATP-binding cassette transporter A)	19p13.3	rs4147929-A	0.19	1.15 (1.11–1.19)	2.8[a]	Loss-of-function variants[37,38]
FERMT2 (fermitin family member 2)	14q22.1	rs17125944-C	0.09	1.14 (1.09–1.19)	1.2[a]	—
CASS4 (Cas scaffolding protein family member 4)	20q13.31	rs7274581-T	0.92	1.14 (1.09–1.19)	1.0[b]	—
MS4A6A locus (membrane-spanning 4-domains, subfamily A)	11q12.2	rs983392-A	0.60	1.11 (1.09–1.15)	3.8[b]	—
EPHA1 (EPH receptor A1)	7q35	rs11771145-G	0.66	1.11 (1.08–1.14)	3.3[b]	—
HLA-DRB5,HLA-DRB1 locus (major histocompatibility complex, class II, DR beta 5/beta 1)	6p21.32	rs9271192-C	0.28	1.11 (1.08–1.18)	3.0[a]	—
PTK2B (protein tyrosine kinase 2 beta)	8p21.2	rs28834970-C	0.37	1.10 (1.08–1.13)	3.6[a]	—
CD2AP (CD2-associated protein)	6p12.3	rs10948363-G	0.27	1.10 (1.07–1.13)	2.6[a]	—
ZCWPW1 locus (zinc finger, CW type with PWWP domain 1)	7q22.1	rs1476679-T	0.71	1.10 (1.06–1.12)	2.5[b]	—
SLC24A4/RIN3 locus (solute carrier family 24/Ras and Rab interactor 3)	14q32.12	rs10498633-G	0.78	1.10 (1.06–1.14)	1.9[b]	—
INPP5D (inositol polyphosphate-5-phosphatase)	2q37.1	rs35349669-T	0.49	1.08 (1.05–1.11)	3.8[a]	—
MEF2C (myocyte enhancer factor 2C)	5q14.3	rs190982-A	0.59	1.08 (1.05–1.11)	2.8[b]	—
NME8 locus (NME/NM23 family member 8)	7p14.1	rs2718058-A	0.63	1.08 (1.05–1.11)	2.5[b]	—
CELF1 locus (CUGBP, Elav-like family member 1)	11p11.2	rs10838725-C	0.32	1.08 (1.05–1.11)	2.5[a]	—
CD33 (CD33 molecule)	19q13.41	rs3865444-C	0.69	1.06 (1.04–1.1)	1.8[b]	rs12459419 located in a putative SRSF2 splice site of exon 2, leading to alternative splicing of the IgV domain[44]

Have we missed the boat?

ROLE FOR NEUROPSYCHOLOGY

Mr. Jones

Name: [redacted]
DOB: [redacted]/19
Occupation: re

ESTIMATE (

WRAT
-1 SD:
Barona: 117.0

VERBAL MEMORY

WMS-IV LM - Version A/B

	Raw	*SS*	*%ile*
LM I Recall (53)	15	7	16th
LM II Recall (39)	0	3	1st
LM II Recog (23)	11	x	3-9th

CVLT -II-short	*Raw*	*Standard*
Total 1-4 (36)	9	
Trial 1	0	-3.5
Trial 4	4	-2
SD Free Recall	0	-2.5
LD Free Recall	0	-1.5
LD Cued Recall	0	-2.5
Repetitions	0	-0.5
Free Recall Intrusions	11	5
Cued Intrusions	0	-0.5
Recognition Hits	x	x
False Positives	x	x
0/2/3/4		

VISUAL MEMORY

WMS-IV VR	*Raw*	*SS*	*%*
VR I Recall	18	8	25th
VR II Recall	0	4	3rd
VR II Recognition	x	x	x

BVMT	*Raw*	*z*	*%*
Total	6	-2.4	<1st
Delayed	0	<-3	<1st
2/2/2			

ABSTRACTION	*Raw*	*SS*	*%*
Similarities	19	9	37th
Matrix Reasoning	x	x	x

VISUO-SPATIAL	*Raw*	*SS*	*%ile*
Block Design	24	11	63rd
VR II Copy	42	x	51-75th

Target Cancellation – time: 220" errors: 1 omission

ATTENTION/CONCENTRATION

Digit Span	*Span*	*Raw*	*SS*	*%ile*
Digits Forward	7	11	1.3	
Digits Reverse	4	7	-0.1	
Digits Sequence	0/5	0/7		
Digit Span Total		18/25	8/12	25th/74th

Trailmaking Test	*Sec*	*z*	*%ile*
Part A (Errors= 0)	36	0.95	84th
Part B (Errors= 2)	dc		<1st

LANGUAGE	*Raw*	*z*	*%ile*
BNT	49	-0.26	40th
FAS	32	-0.4	35th
Animal Naming	11	-1.2	12th
Writing	2		

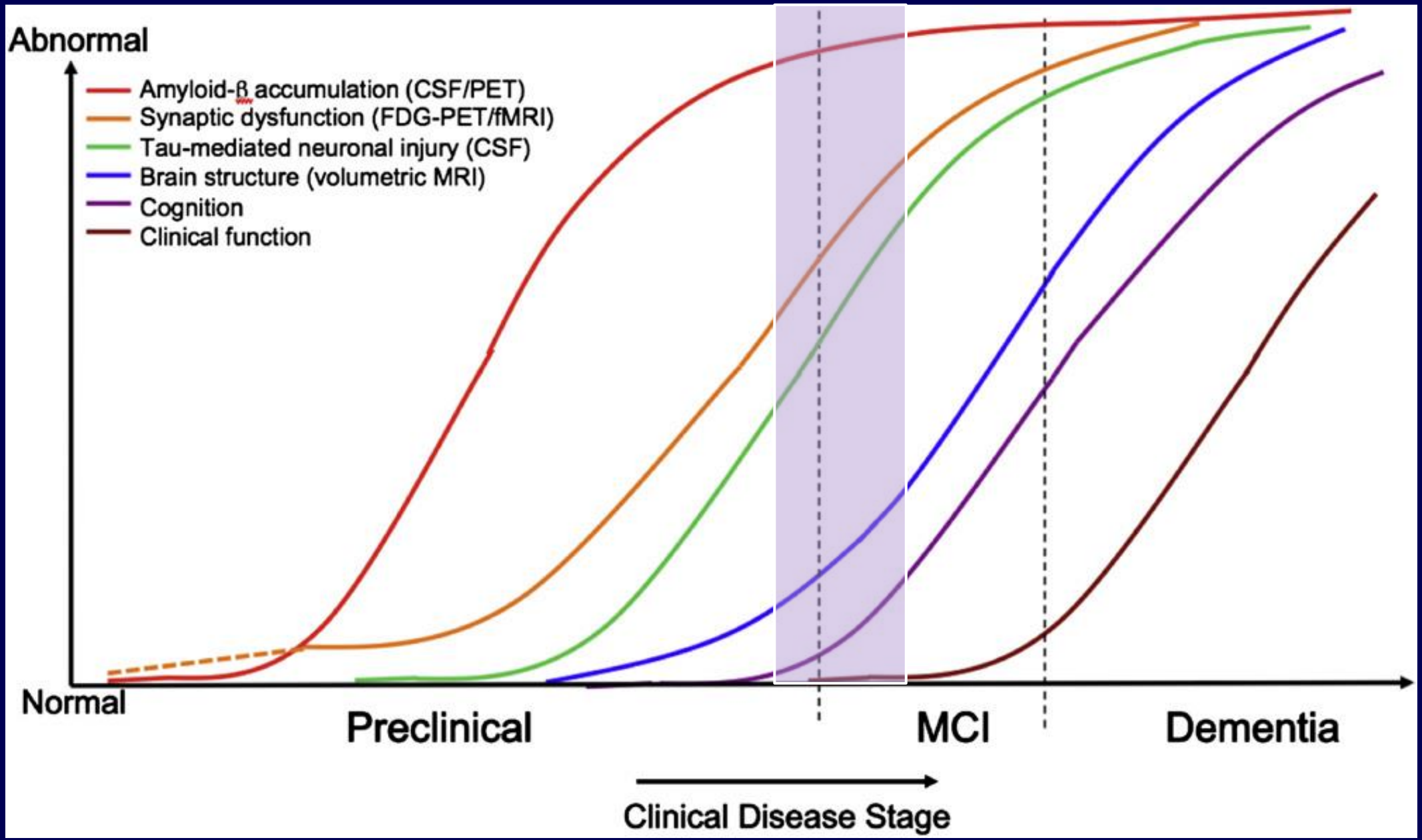
FUNCTIONAL SCALES

OARS Instrumental ADL (patient)	10/14
OARS Instrumental ADL (collateral)	8 /14
OARS Physical ADL (patient)	14 /14
OARS Physical ADL (collateral)	14 /14

MOOD

GDS 00 /30

EFFORT	*Raw*	*Effort*
Dot counting	21	Y
Reliable Digit Span	11	Y
CVLT Forced Choice	6/9	N

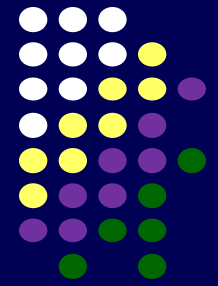


Sperling, et al., 2011 – adapted from Jack, et al., 2010

The good, the bad, and the ugly . . .

ETHICS OF EARLY DETECTION

Clinical (neuro) Psychologists



- Uncertainty/Not knowing
- Treatment might extend current quality of function
- Ruling out reversible causes or contributors
- Inducing behavioral change: carpe diem, better control of health/chronic conditions
- Time to plan for the future, make wishes known
- No effective treatments, no cures
- Participate in Clinical Trials and research
- Casts a pall over all
- Long-term care or life insurance denials
- Stress, anxiety, depression – suicide

Robin Williams's Widow Points to Dementia as a Suicide Cause

By DAVE ITZKOFF and BENEDICT CAREY NOV. 3, 2015

For the first time in more than a year, the widow of the actor Robin Williams is speaking publicly about the circumstances that preceded Mr. Williams's death, and sharing details about a disease he had when he died.

In interviews with People magazine and with ABC News, the widow, Susan Schneider Williams, laid the blame for her husband's suicide in 2014 not on depression

Susan Schneider Williams and Robin Williams at an awards show in New York in April 2013.
Charles Sykes/Associated Press

AD 2025:
The Treatment Horizon

- **Earlier recognition of Alzheimer's disease**
- Disease-modifying therapy
- Combination disease-modifying and symptomatic therapy
- Integration of biomarkers into clinical practice
  - Spinal fluid
  - Blood
  - Imaging
  - Genetics as well
- Many unanswered questions regarding risk/cause

PREVENTION = HEALTHY AGING

Dementia affects everyone

Further question/comments: etritt@uw.edu