SANDERS-BROWN CENTER ON AGING

alzheimer's association

GEC

UK UNIVERSITY OF KENTUCKY

Alzheimer's disease: diagnosis, treatment, and research advances

Greg Jicha, MD-PhD

Associate Professor of Neurology

Robert T. & Nyles Y. McCowan Endowed Chair in Alzheimer's Research

University of Kentucky

Overview of Multi-Part Series

- **Funded by OVAR-GEC (Arleen Johnson)**
- **Supported in part by:**
  - Sanders-Brown Center on Aging/UK ADC
  - Kentucky and Appalachia Public Health Training Center & KPHLI
  - Alzheimer Association of Greater Kentucky & Southern Indiana
  - Your local medical facility

Overview of Multi-Part Series

- **Quarterly CME/CNE/CE Programs focused on Aging and Dementia for Healthcare Professionals**
- **No fees required, but we appreciate advance registration**
- **Enduring materials in development**

Overview of Multi-Part Series

Year 1

- Alzheimer's Disease
- Non-AD dementias: DLB, FTD, VaD (1/13)
- Late stage and end-of-life care (4/13)
- Management of behavioral and psychiatric co-morbidities in dementia (6/13)

Year 2 in planning

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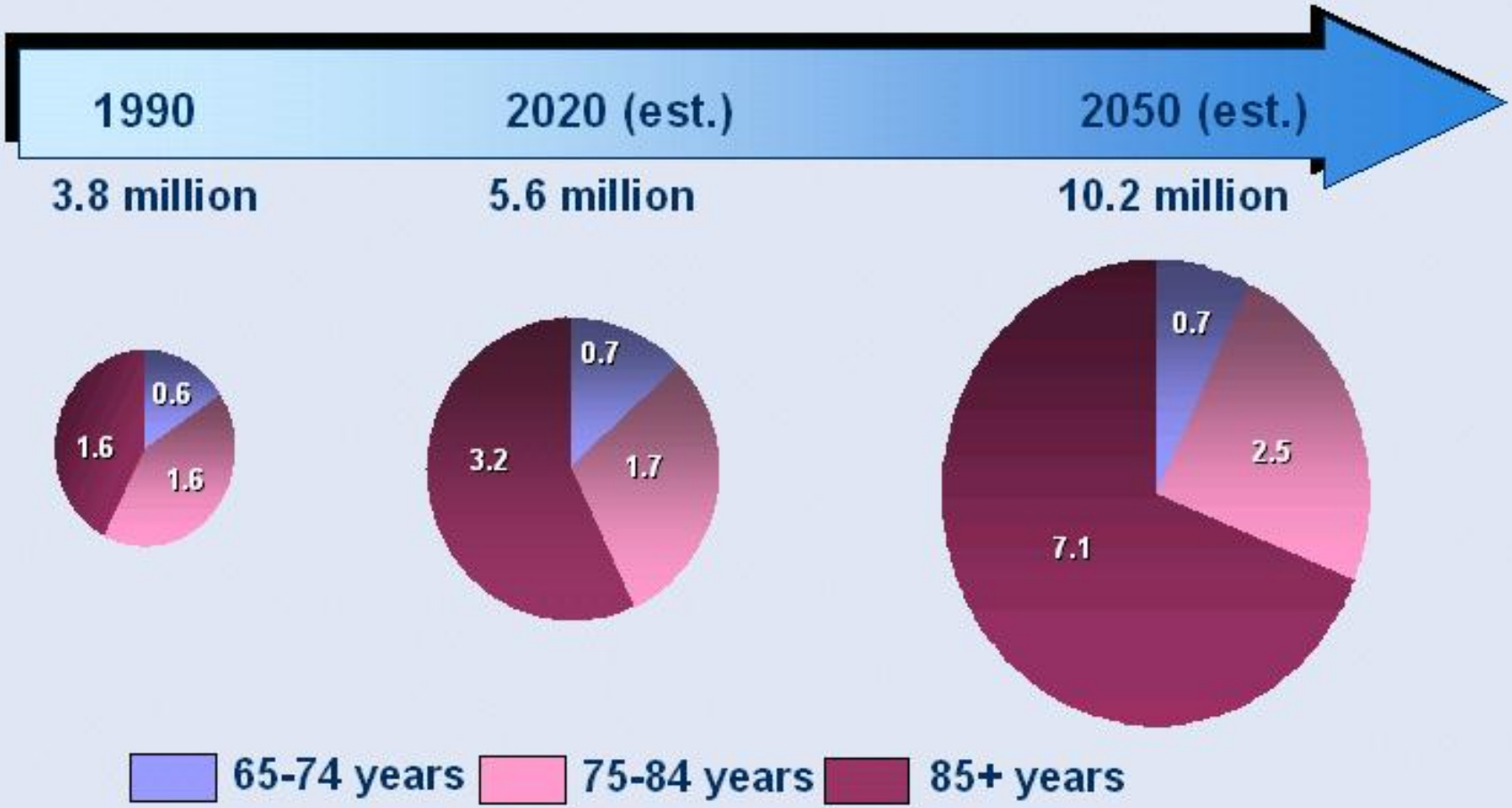
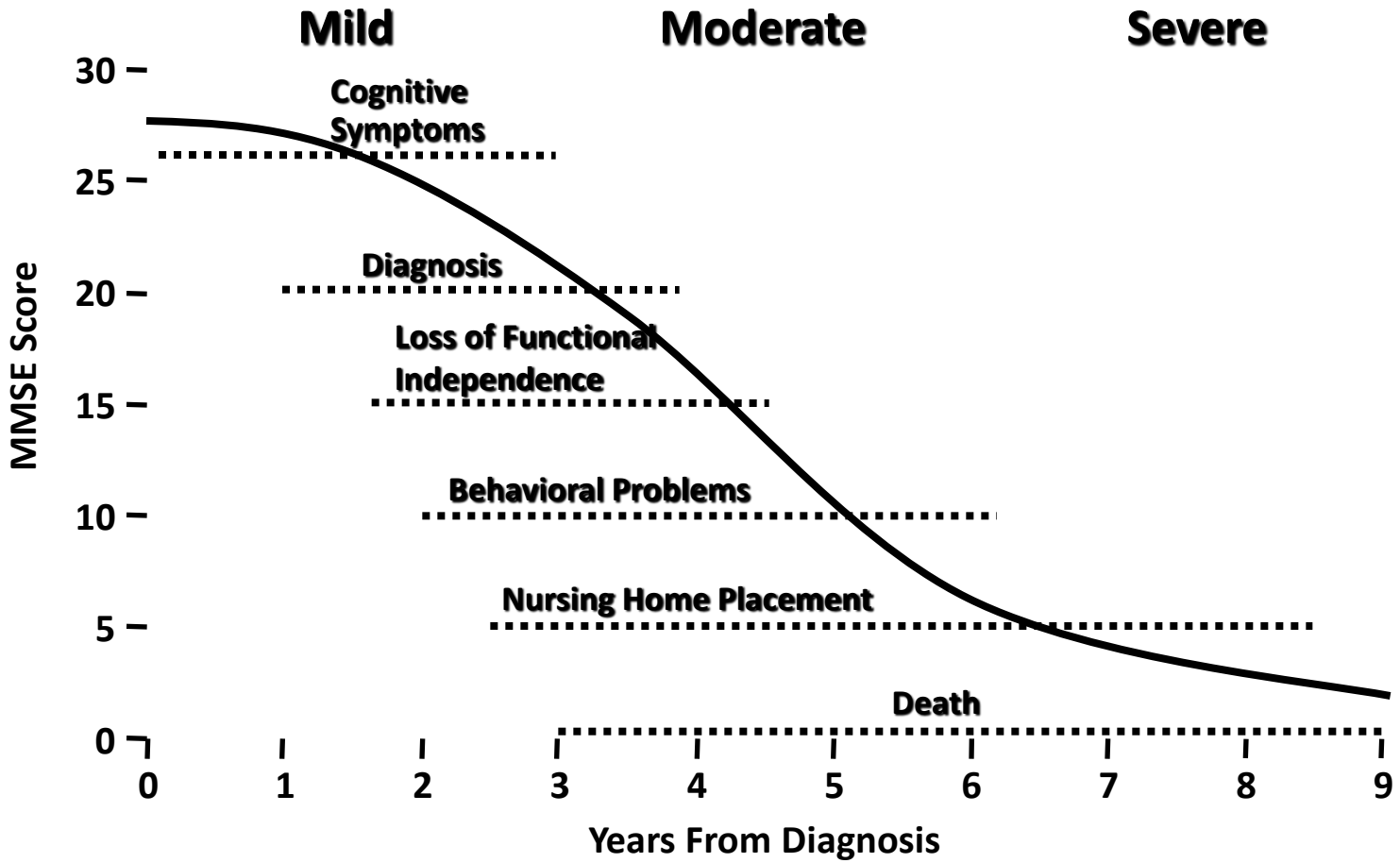
Alzheimer's Disease: An Impending Public Health Care Crisis

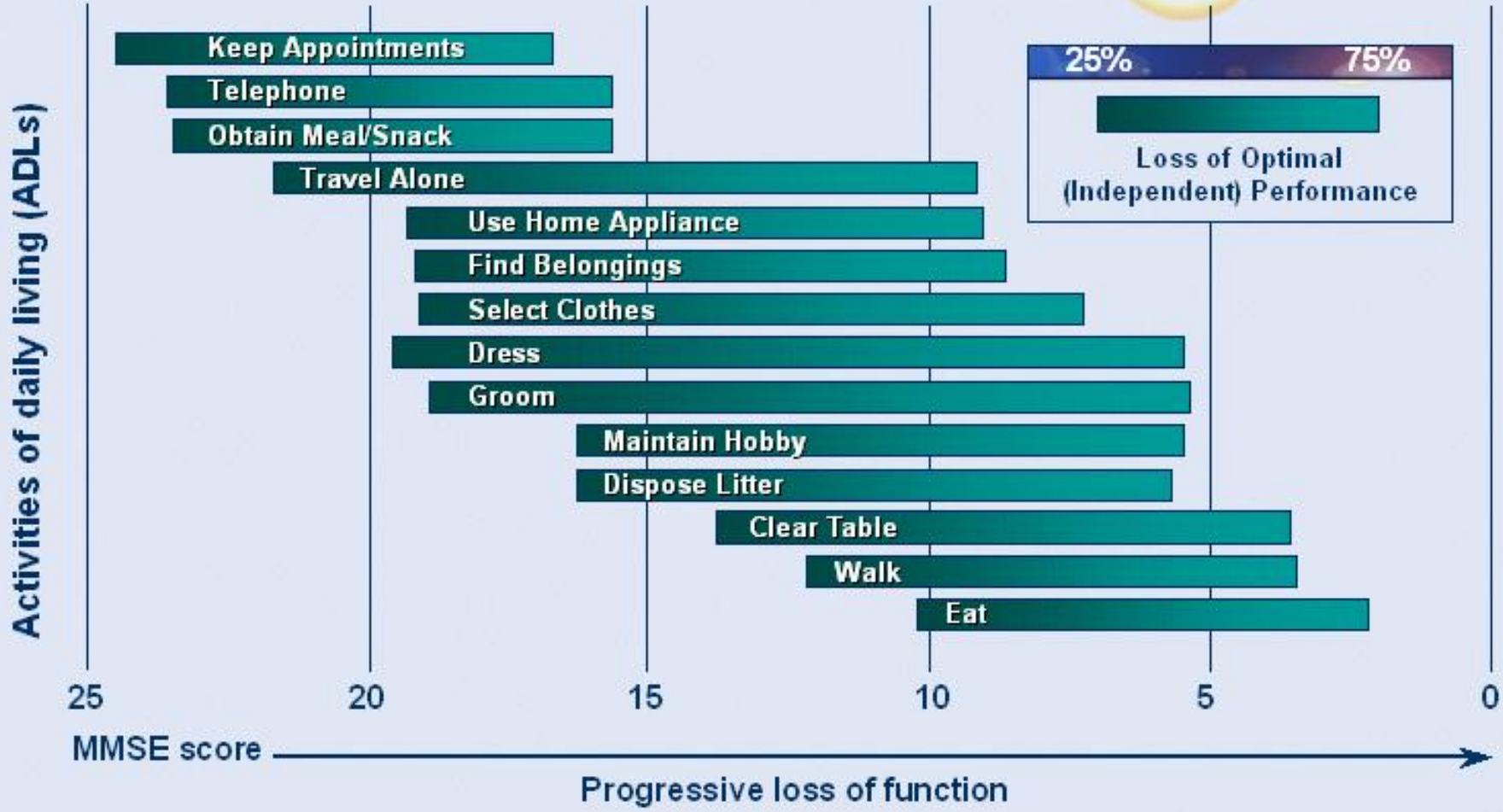


Evans. *Milbank* Q. 1990;68:267-289.

Clinical Disease Progression



MMSE Scores Correlate With Functional Ability



Adapted with permission from Galasko et al. *Eur J Neurol.* 1998;5:S9-S17.

Common Behaviors Associated with Alzheimer's Disease (M. Smart)

- Short term memory loss/repetition
- Lethargy/lack of initiative
- Emotional changes/mood swings/depression
- Agitation (anger, anxiety)
- Resistance to care
- Wandering/pacing
- Wanting to go home
- Shadowing
- Hallucinations, delusions, suspiciousness, paranoia
- Change in sleep patterns
- Rummaging, hoarding
- Loud verbal noises/yelling
- Abusive/combative behaviors

Symptom diary…

Dementia Symptom Diary

DATE: _____

Name: _____

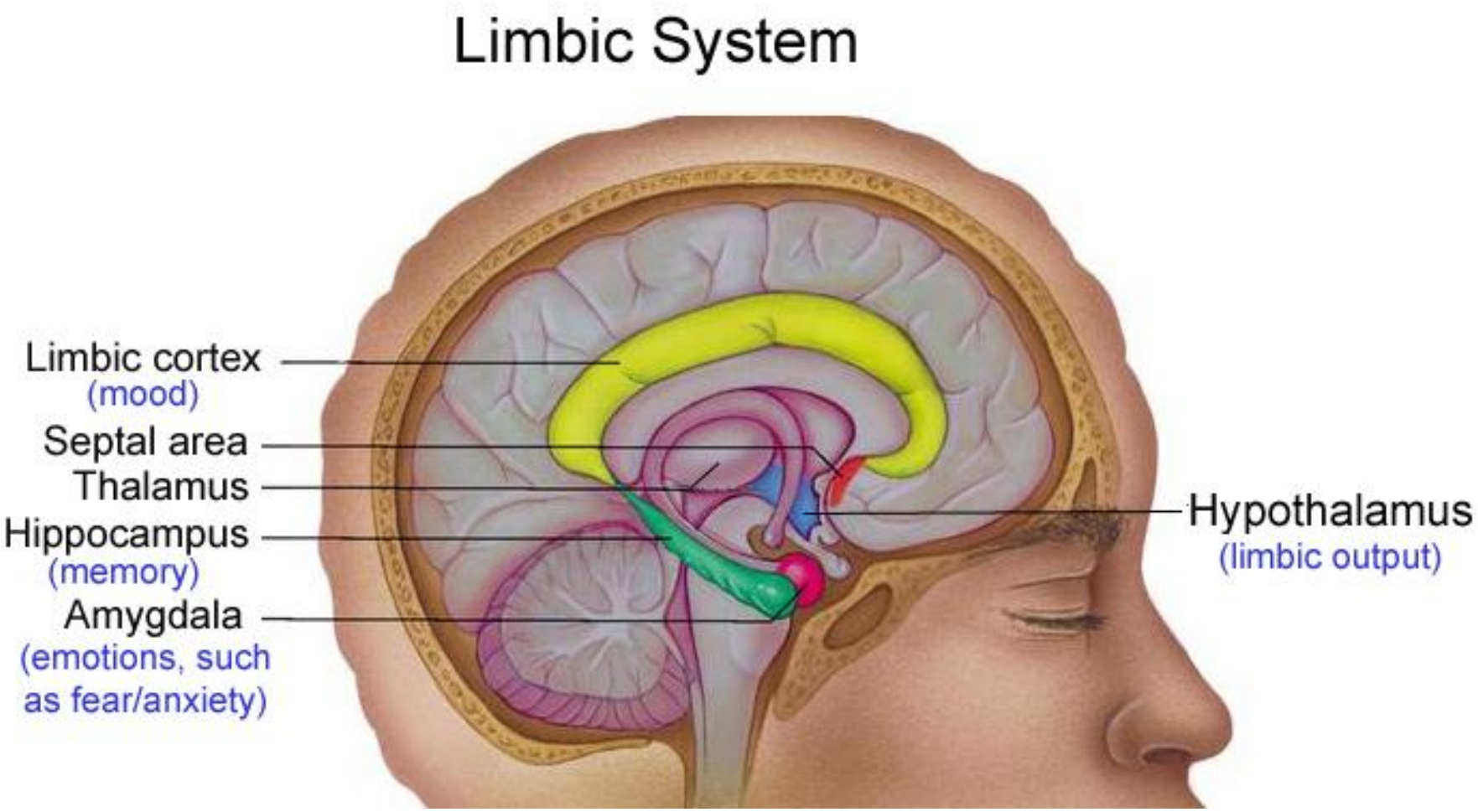
DOB: _____

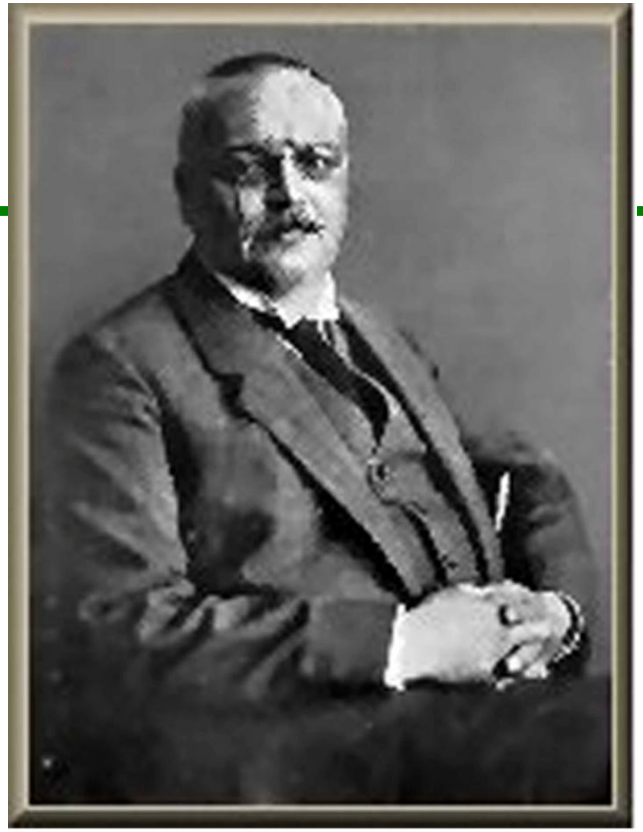
Symptom	Time started	Time ended	Triggers (what were they doing when symptom started?)	How bothersome is symptom to patient (rate on scale of 1 to 10)	How bothersome is symptom to caregiver (rate on scale of 1 to 10)	What makes symptom better?	What makes symptom worse?	Medication effects?

RATING SCALE: 1 to 10 for symptom severity with 1 being the least severe, and 10 being the most severe

*Use additional sheets as necessary to record all events of concern

Why is behavior a problem?





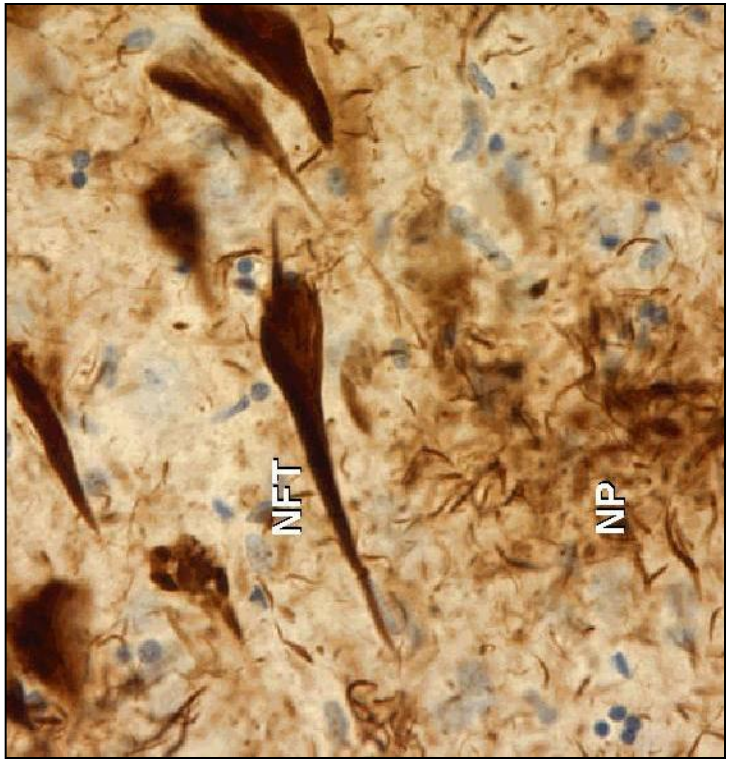
Alois Alzheimer 1864-1915

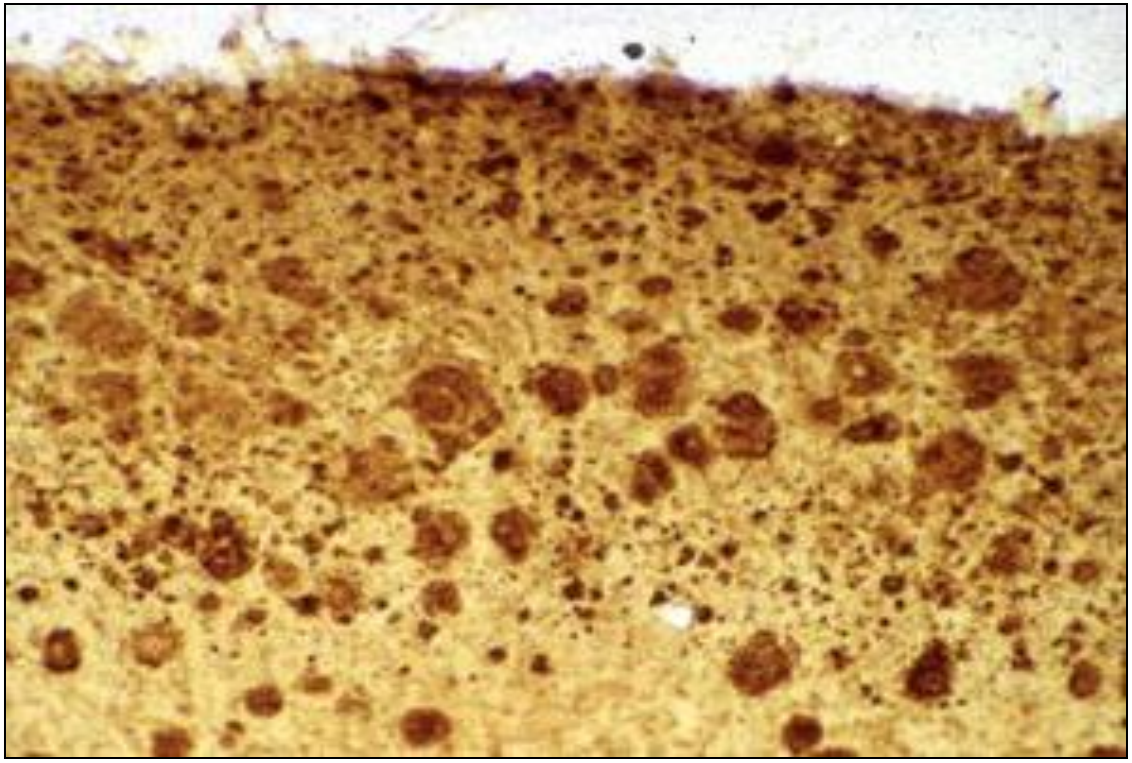
German neuropathologist & psychiatrist who described in 1906 the clinical and neuropathological features of a woman aged 51 years, with atrophied cerebral cortex, senile plaques and neurofibrillary tangles

History: Biology

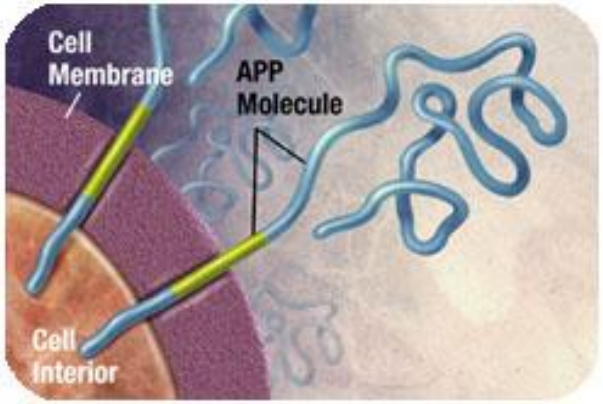
- 1906- first description of Auguste D. age 51
- 1976- cholinergic deficit in AD discovered
- 1984- β-amyloid discovered as key component of AD plaques
- 1986- tau protein discovered as key component of NFT

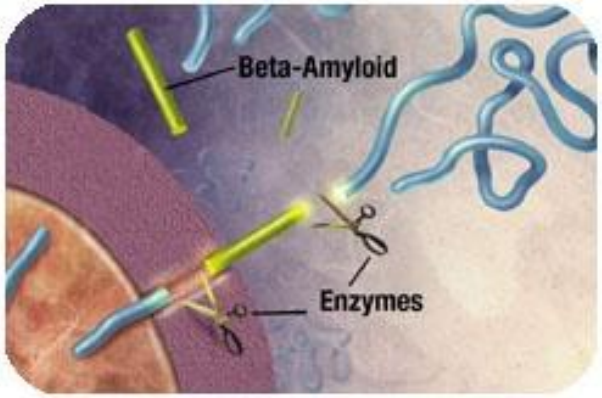
Alzheimer's disease pathology

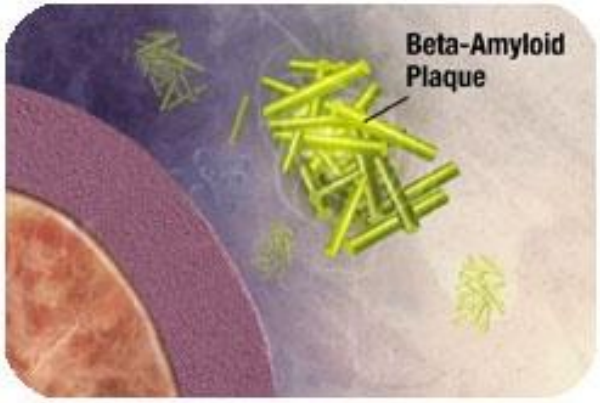




β amyloid is a key player in AD





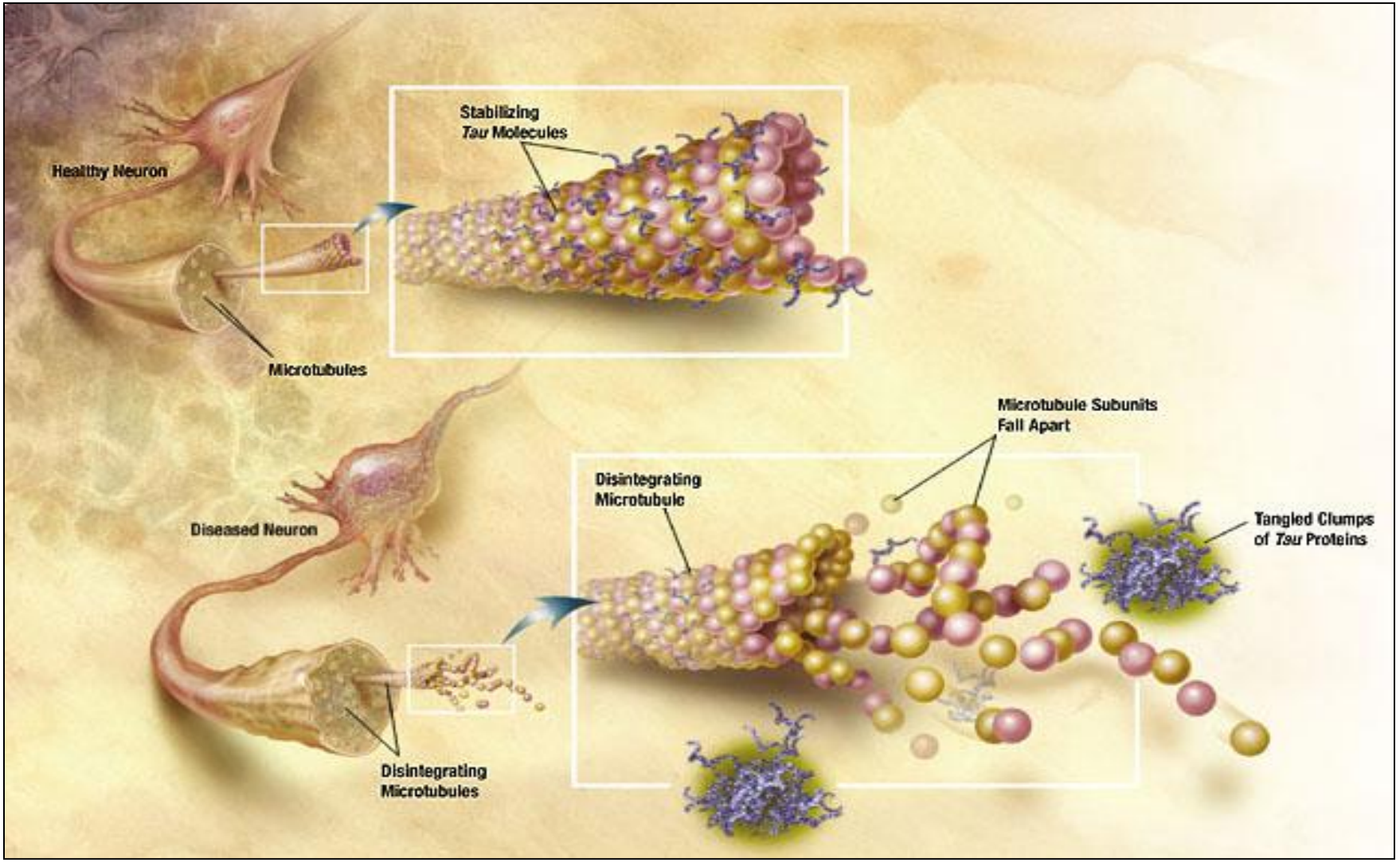


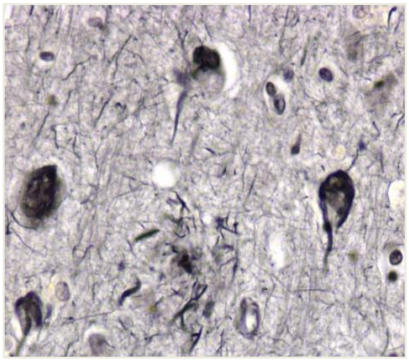
1) APP is a membrane-bound glycoprotein that may serve as a growth factor in injury and repair

2) APP is normally cleaved by α-secretase and β-secretase, but in AD, γ-secretase is active

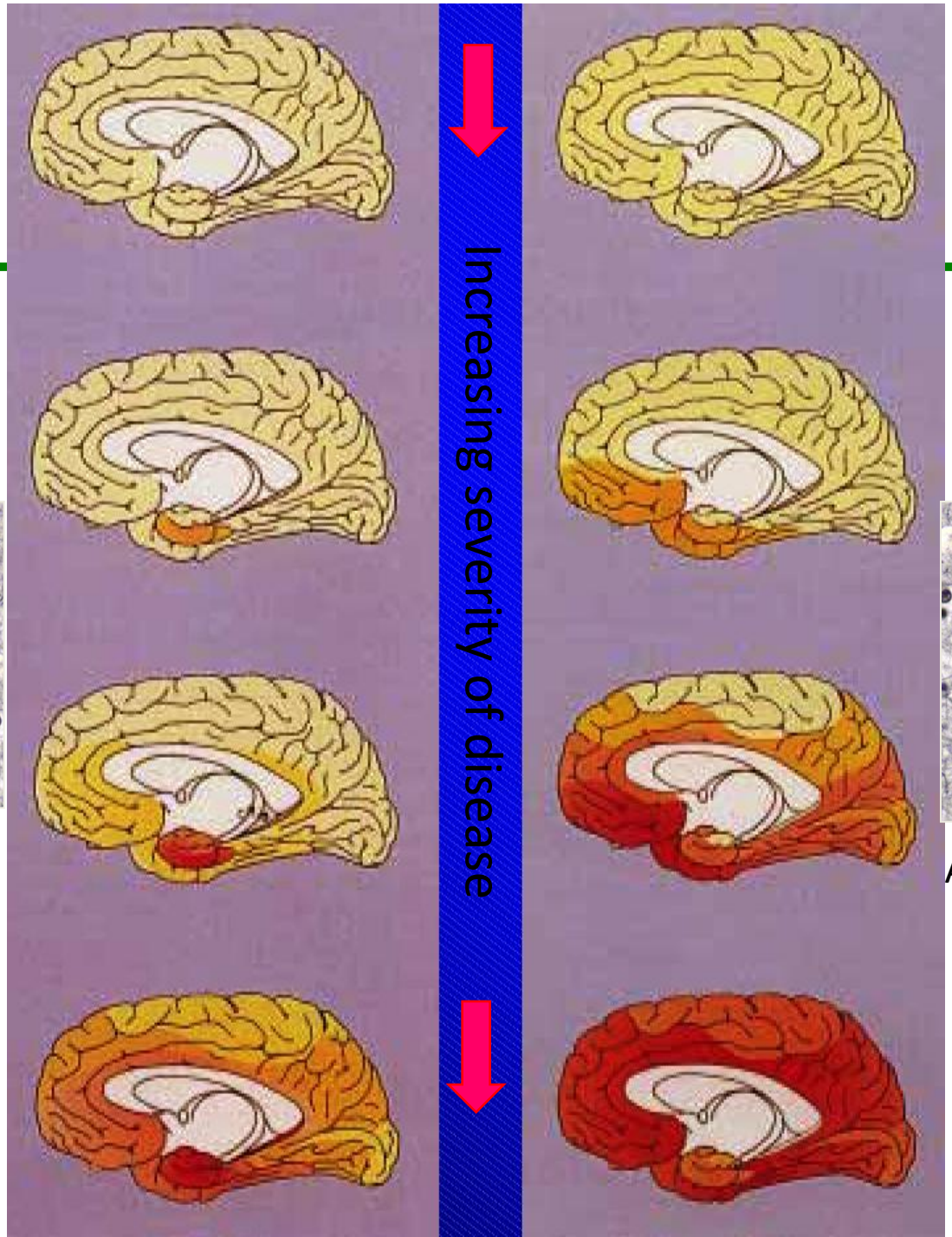
3) β-amyloid is toxic to cells and accumulates in brain tissue as amyloid plaques, a hallmark of the disease

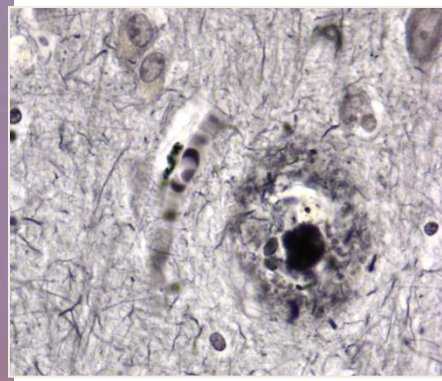
The role of the microtubule-associated protein tau in AD





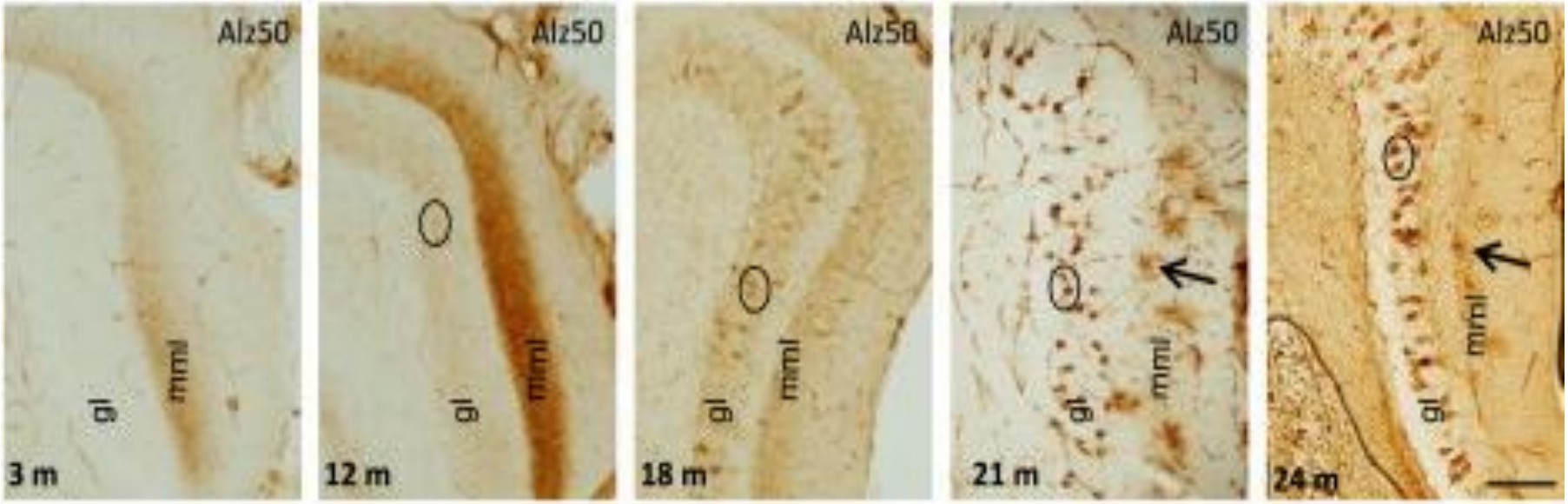
NFTs





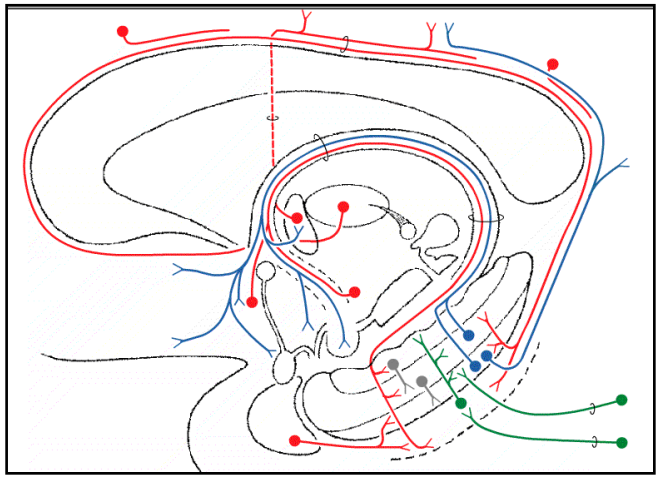
Amyloid plaques

Neurofibrillary degeneration spreads from nerve cell to nerve cell

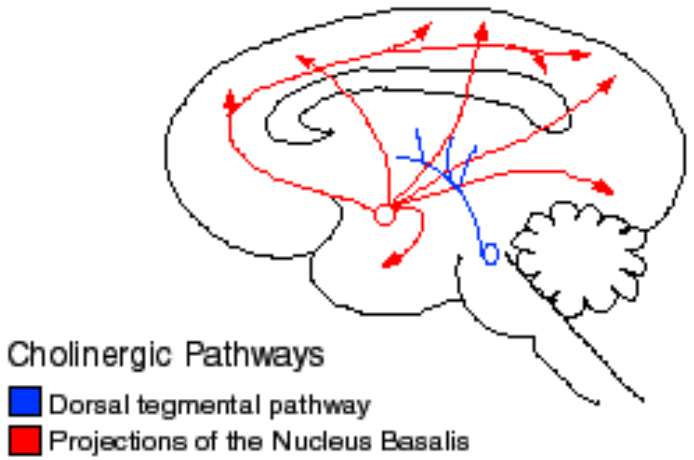


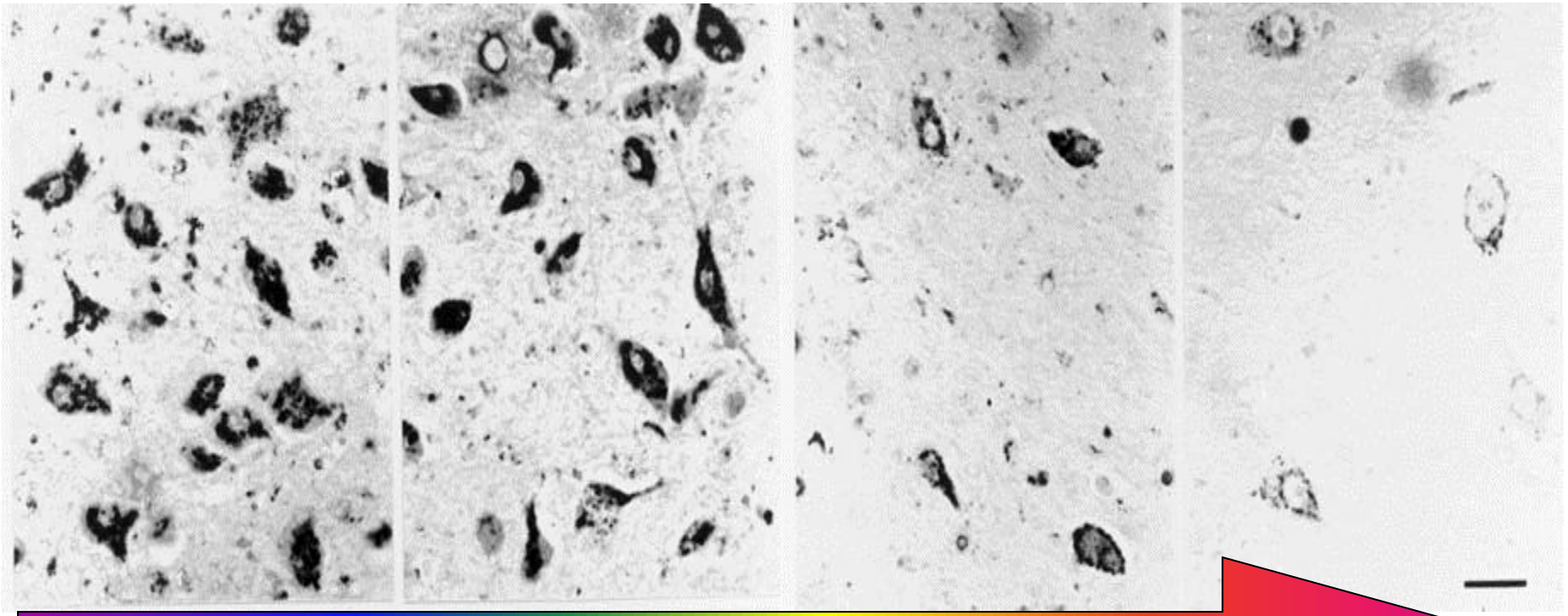
de Calignon et al., Neuron. 2012 Feb 23;73(4):685-97

Liu et al., PLoS One. 2012;7(2):e31302. Epub 2012 Feb 1

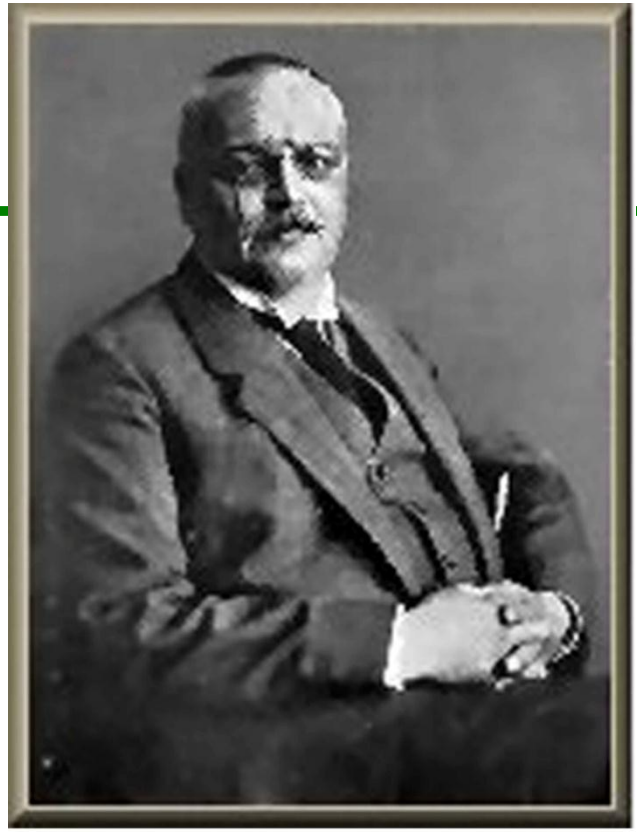


Cholinergic pathways





Increasing severity of disease

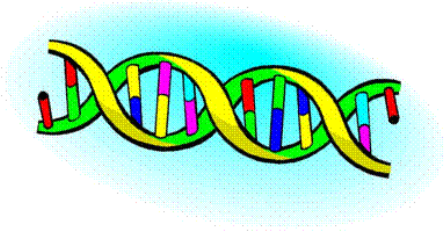


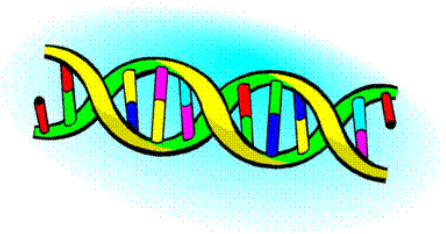
Alois Alzheimer 1864-1915

German neuropathologist & psychiatrist who described in 1906 the clinical and neuropathological features of a woman aged 51 years, with atrophied cerebral cortex, senile plaques and neurofibrillary tangles

History: Genetics

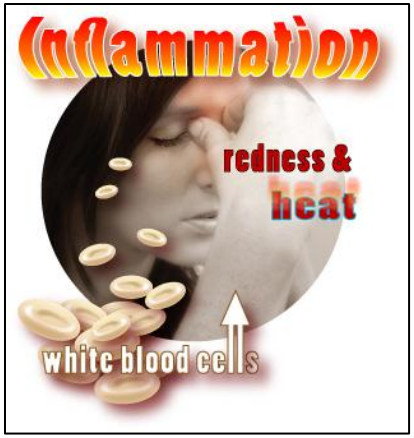
- 1906- first description of Auguste D. age 51
- 1991- APP (chr 21) linked to fAD
- 1992- ApoE (chr 19) linked to late onset sporadic AD
- 1995- PS 1 (chr 14) linked to fAD
- 1995-PS 2 (chr 1) linked to fAD
- 2008- AD Genetics Consortium identifies new risk factor genes

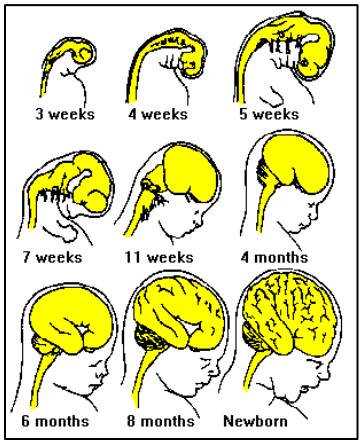


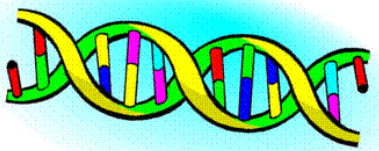


AD: Genetics

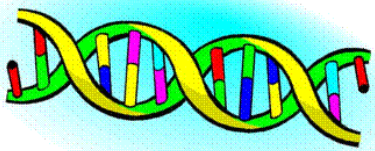
- **Cholesterol**
  - APOE, CLU, ABCA7, SORL1
- **Inflammation**
  - CR1, MS4A, CD33
- **Synapse function**
  - PICALM, BIN1, CD2AP
- **Brain development**
  - EPHA1







AD: Genetics

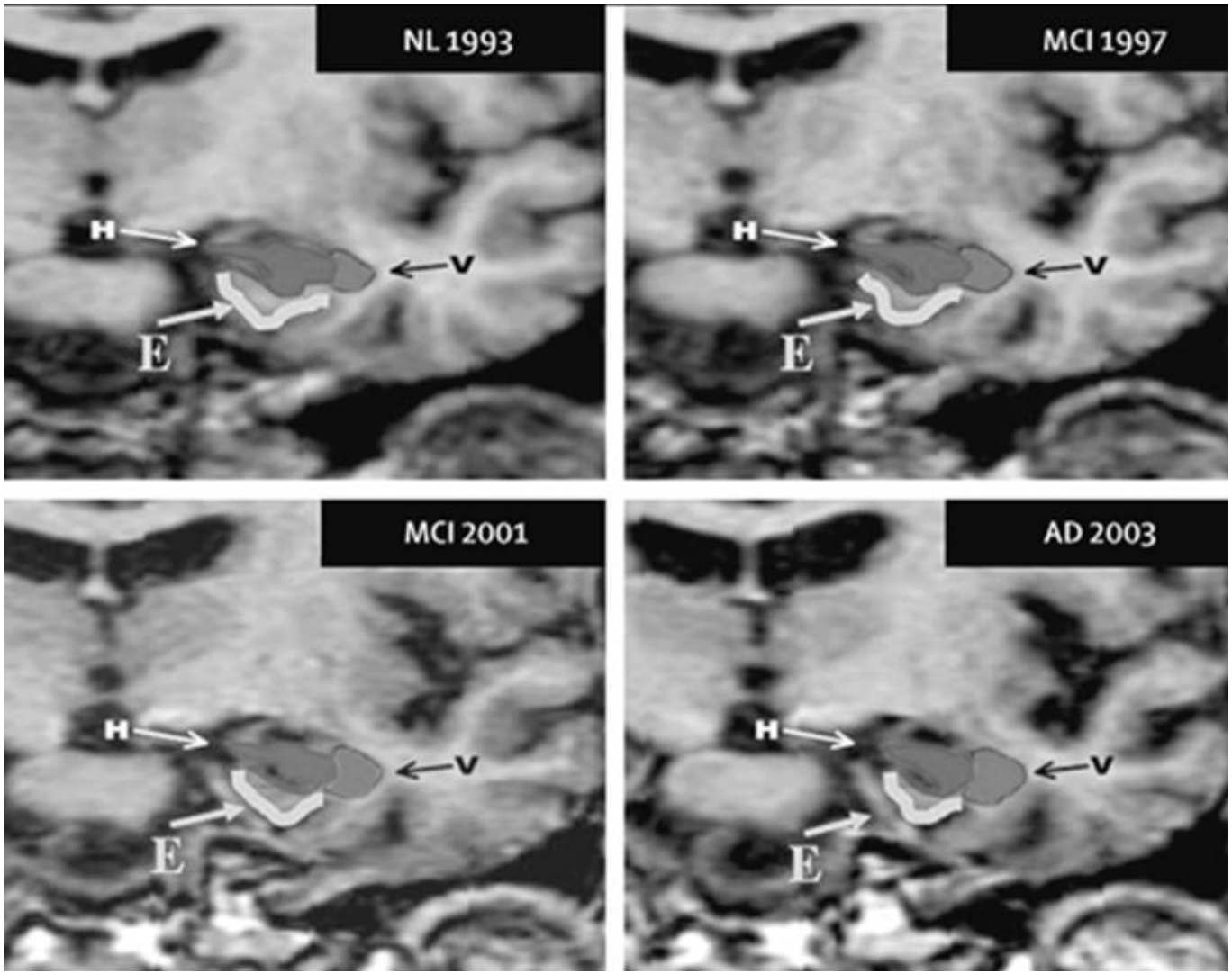


- **Autosomal dominant AD is very rare**
  - 500 families worldwide with onset in 40's
- **Genetic/Familial Risk is common**
  - Perhaps as high as 60% of the risk of AD
  - You can carry such mutations and never get AD
  - You can be free of all of these and still get AD
  - AMA/AAN practice parameter discourages genetic testing for AD except in suspected dominant AD
  - Emerging evidence for differential response to disease modifying agents may change this scenario
  - GINA may not protect your patients/clients

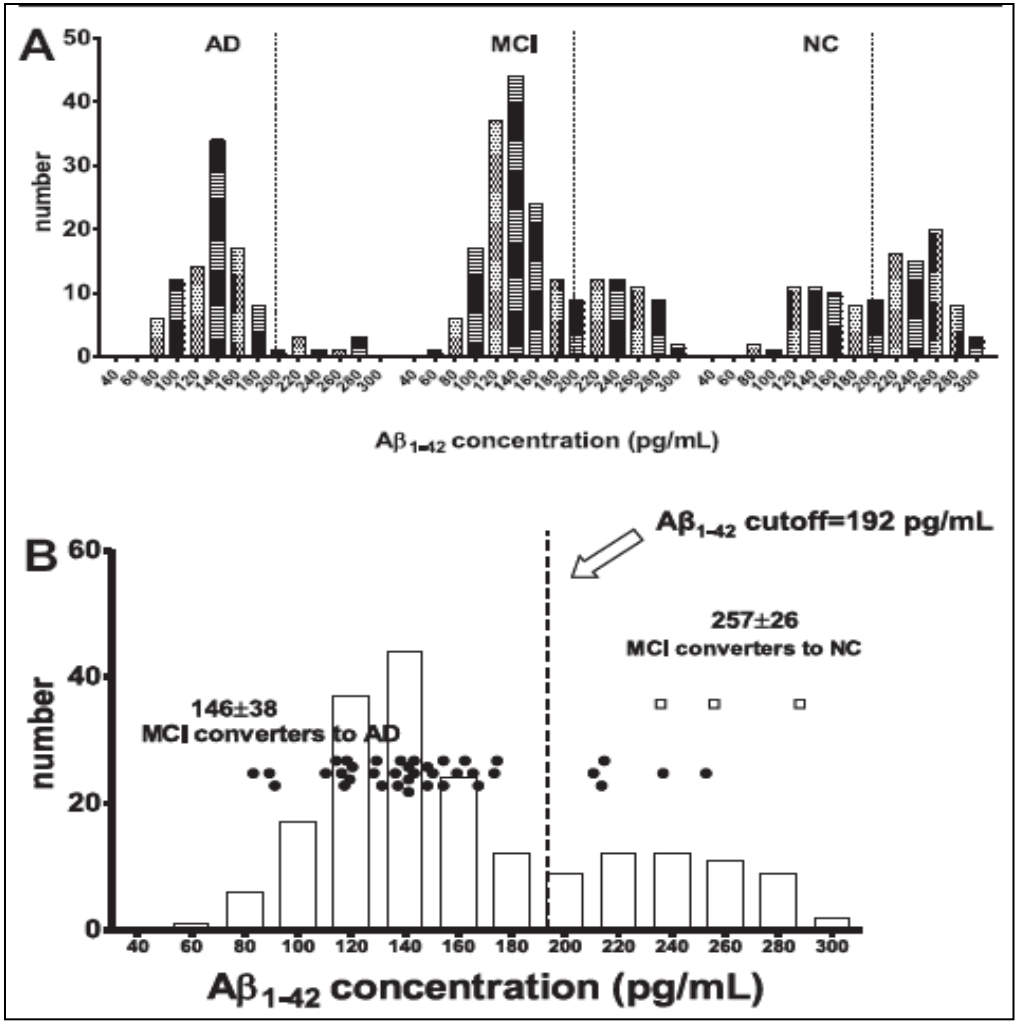
AD Biomarkers

- **Structural MRI**
  - Visualizes neuronal loss
- **CSF**
  - Measures b-amyloid and tau levels
- **FDG-PET**
  - Determines hypometabolism when brain structure is normal (AD vs. FTD approval)
- **Amyloid-PET**
  - Amyvid approved by FDA 4/12

Structural MRI can monitor progression of disease from normal ⇨ MCI ⇨ AD

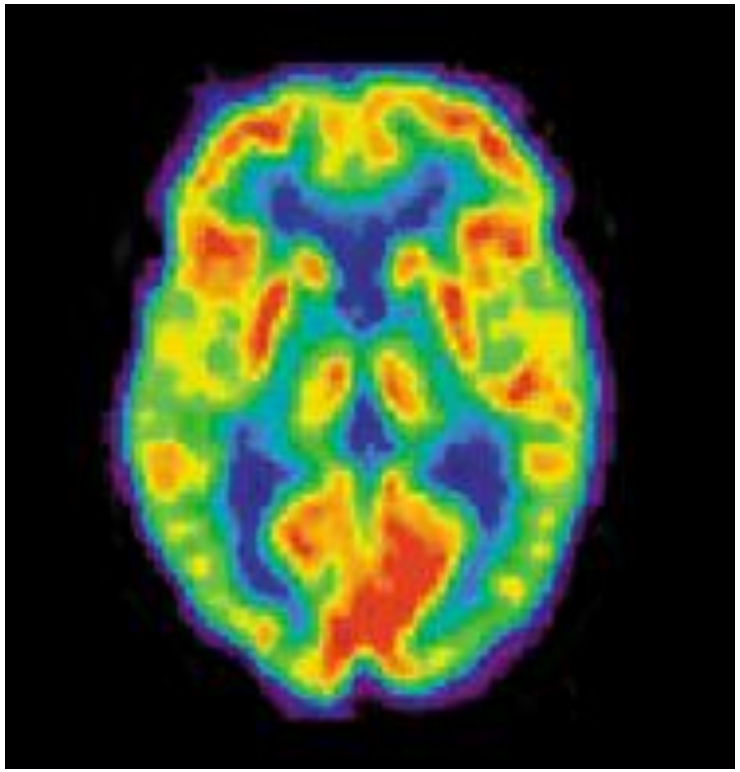


ADNI Data

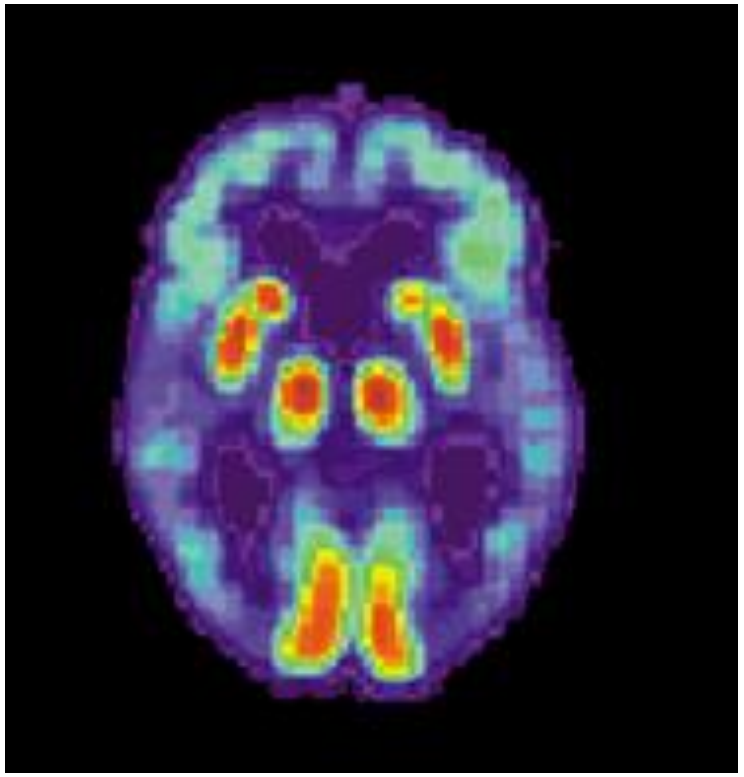


Shaw et al., Ann Neurol. 2009 Apr;65(4):403-13.

PET and AD: Hypometabolism



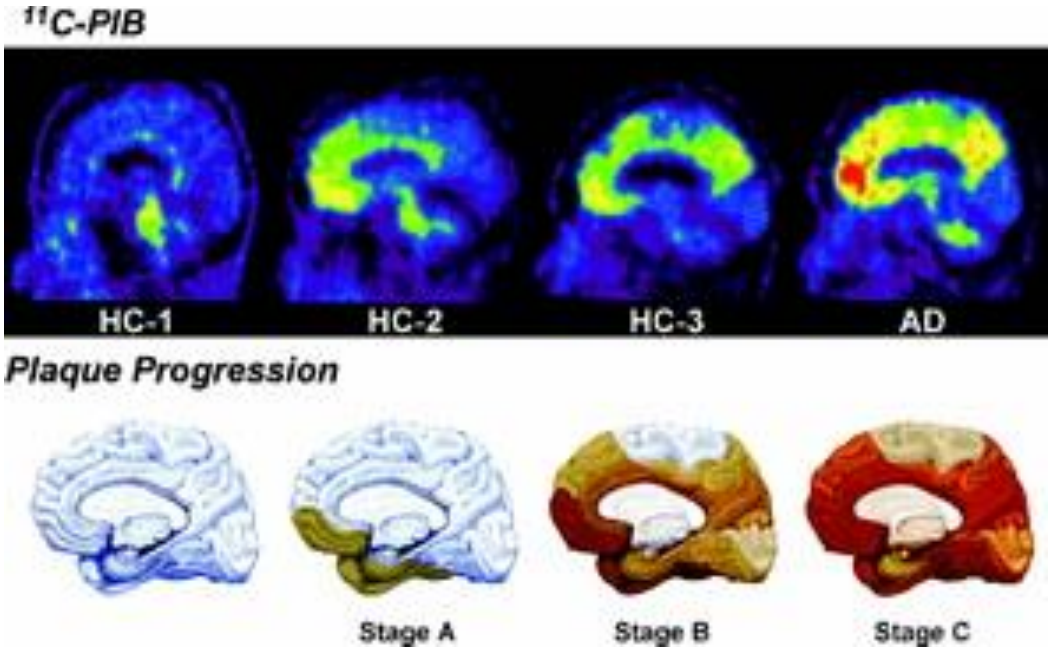
Normal

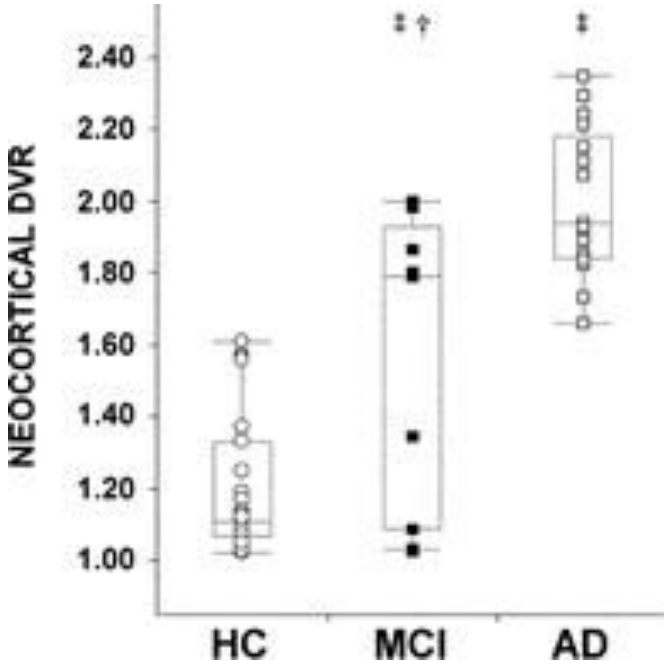


AD

ADEAR, 2003

In vivo imaging of amyloid deposition in normal controls and AD cases





[^{11}C]Pittsburgh Compound B (PIB), reflecting [beta]-amyloid (A[beta]) burden in the brain, in three asymptomatic healthy age-matched control subjects (HC 1 to 3) and one patient with Alzheimer disease

Rowe CC et al., Imaging beta-amyloid burden in aging and dementia. Neurology. 2007 May 15;68(20):1718-25.

AD: Diagnosis

- **First start with a DSM-IV diagnosis of dementia:**
  - Functional decline
  - Represents a decline from previous levels of function
  - Not explained by delirium or psychiatric illness
  - Objective evidence for impairment
    - History from patient and informant
    - Bedside or formal mental status testing
  - Two or more cognitive domains affected
    - STM
    - reasoning/judgment/executive
    - Visuospatial
    - Language
    - behavior/personality

Reversible Causes of Dementia

- **V-subdural hematoma, stroke**
- **I-Syphilis, HIV, PML**
- **T-trauma, NPH, drugs**
- **A-SLE, Sjogren's, MS**
- **M-Thyroid, Wernicke's, Wilson's, SCD**
- **I-Vasculitis, Hashimoto's**
- **N-neoplasm, limbic encephalitis**
- **S-nonconvulsive status (EPC)**

The confound of delirium…

Dementia	vs	Delirium
• Level of consciousness-NL		• Altered consciousness
• Chronic (subacute)		• Acute/subacute
• Static		• Fluctuations

AD: Diagnosis (NINCDS-ADRDA)

- **Dementia by DSM-IV criteria**
- **Deficits in two or more areas of cognition**
- **Progressive worsening of memory and cognitive dysfunction**
- **Onset age 40-90**
- **Absence of other systemic/brain disorders**

New diagnostic criteria for AD 4/19/2011

"The NIA and the Alzheimer's Association hope that updating and revising the diagnostic criteria with the latest advances will accelerate the field in the direction of earlier detection and more effective treatment."

- William H. Thies, Ph.D., Alzheimer's Association Chief Medical and Scientific Officer

New diagnostic criteria for AD

- **Diagnostic criteria for Alzheimer's disease with dementia**
- **Diagnostic criteria for mild cognitive impairment (MCI) of the AD-type**
- **Diagnostic criteria for preclinical AD**

Diagnostic criteria for Probable Alzheimer's disease with dementia

- **Meets criteria for dementia**
- **Initial presentation is either:**
  - Amnestic
  - Non-amnestic: visuospatial, language, executive
- **Criteria should not be applied when:**
  - Substantial CVD by Hx of stroke or imaging
  - DLB, FTD, PPA, SD features
  - Other neurological or medical cause

Diagnostic criteria for Possible Alzheimer's disease with dementia

- **Atypical course**
  - Sudden onset
  - lack of documented decline by Hx or examination
- **Etiologically mixed presentation**
  - Comorbid:
    - CVD
    - DLB
    - or evidence for another neurological or medical disease or condition

AD dementia with evidence of the AD pathophysiological process

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (CSF tau, FDG-PET, structural MRI)
Probable AD dementia			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With three levels of evidence of AD pathophysiological process	Intermediate	Unavailable or indeterminate	Positive
	Intermediate	Positive	Unavailable or indeterminate
	High	Positive	Positive
Possible AD dementia (atypical clinical presentation)			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With evidence of AD pathophysiological process	High but does not rule out second etiology	Positive	Positive
Dementia-unlikely due to AD	Lowest	Negative	Negative

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, ^{18}fluorodeoxyglucose; MRI, magnetic resonance imaging.

AD Diagnosis Caveats

- **AD itself can be quite heterogeneous**
- **AD often coexists with other pathology**
- **MCI can revert to normal or remain stable for years**
- **Preclinical AD has not yet been fully explored**
  - We do not know if all biomarker positive subjects will progress to AD
  - Ethical implications in forewarning impending AD in someone who is completely normal and may remain so for 10-20 years or even forever

Diagnosis: Cognitive tests you can use in your practice!

- AD-8
- MMSE
- MOCA
- KSTMS (Kentucky version)
- MIS
- 3MS
- Animal naming

AD8 (screen tool)

1. Does your family member have problems with judgment (problems making decisions, bad financial decisions, problems with thinking, etc.)?
2. Does your family member show less interest in hobbies/activities?
3. Does your family member repeat the same things over and over (questions, stories, or statements)?
4. Does your family member have trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)?
5. Does your family member forget the correct month or year?
6. Does your family member have trouble handling complicated financial affairs (balancing checkbook, income taxes, paying bills, etc.)?
7. Does your family member have trouble remembering appointments?
8. Does your family member have daily problems with thinking or memory?

MMSE

Traditional test

- **Focus on orientation and other non-specific items**
- **Low sensitivity for early disease**
- **~ 10 minutes to administer**

The mini mental state examination

Orientation

Year, month, day, date. season	_____/5
Country, county, town, hospital, ward (clinic)	_____/5

Registration

Examiner names three objects (for example, apple, pen, and table)	
Patient asked to repeat objects, one point for each.	_____/3

Attention

Subtract 7 from 100 then repeat from result, stop after five subtractions. (Answers: 93, 86, 79, 72, 65)	
Alternatively if patient errs on subtraction get them to spell world backwards: D L R O W	
Score best performance on either task.	_____/5

Recall

Ask for the names of the objects learned earlier.	_____/3

Language

Name a pencil and a watch.	_____/2
Repeat: 'No ifs, and or buts.'	_____/1
Give a three stage command. Score one for each stage (for example, 'Take this piece of paper in your right hand, fold it in half and place it on the table.'	_____/3
Ask patient to read and obey a written command on a piece of paper stating: 'Close your eyes.'	_____/1
Ask patient to write a sentence. Score correct if it has a subject and a verb.	_____/1

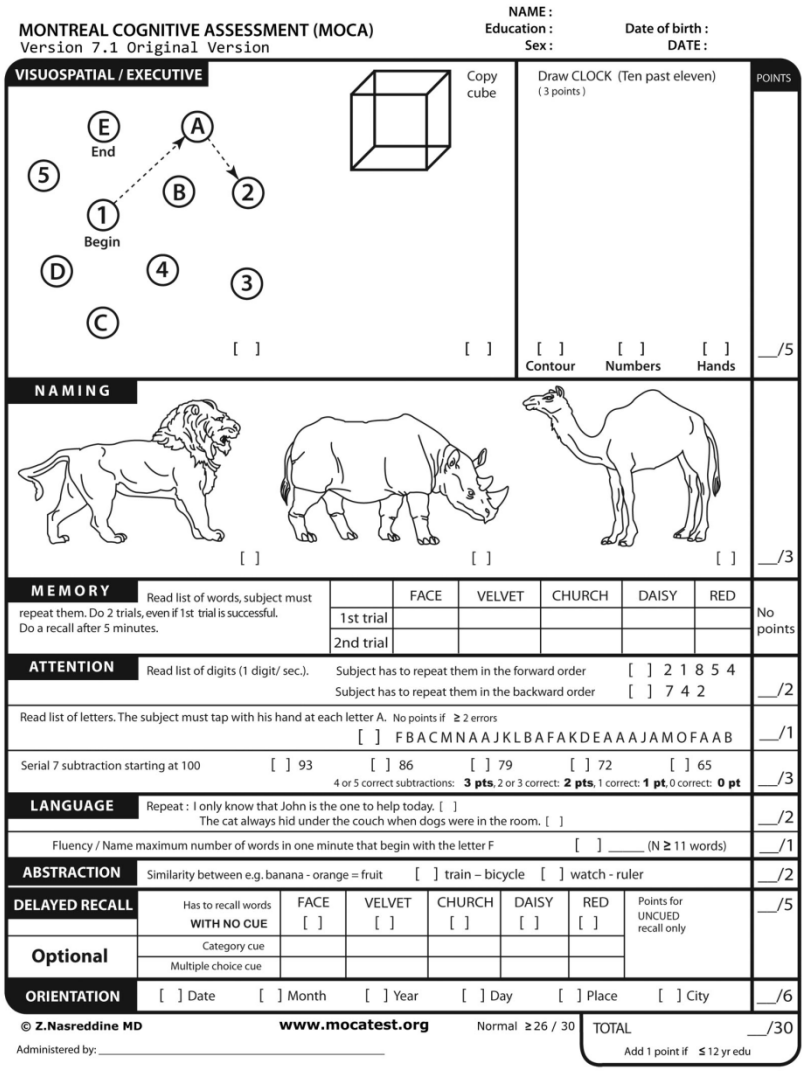
Copying

Ask patient to copy intersecting pentagons.	
Score as correct if they overlap and each has five sides.	_____/1

Total score: _____/30

MOCA

- Replacing the MMSE gradually
- Recommended by the Canadian Stroke Network for VCI/VaD
- Still lengthy, ~ 15 minutes to administer



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

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

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

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

NAMING __/3

[ ] [ ] [ ]

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

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

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

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

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

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

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

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

DELAYED RECALL

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

__/5

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

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

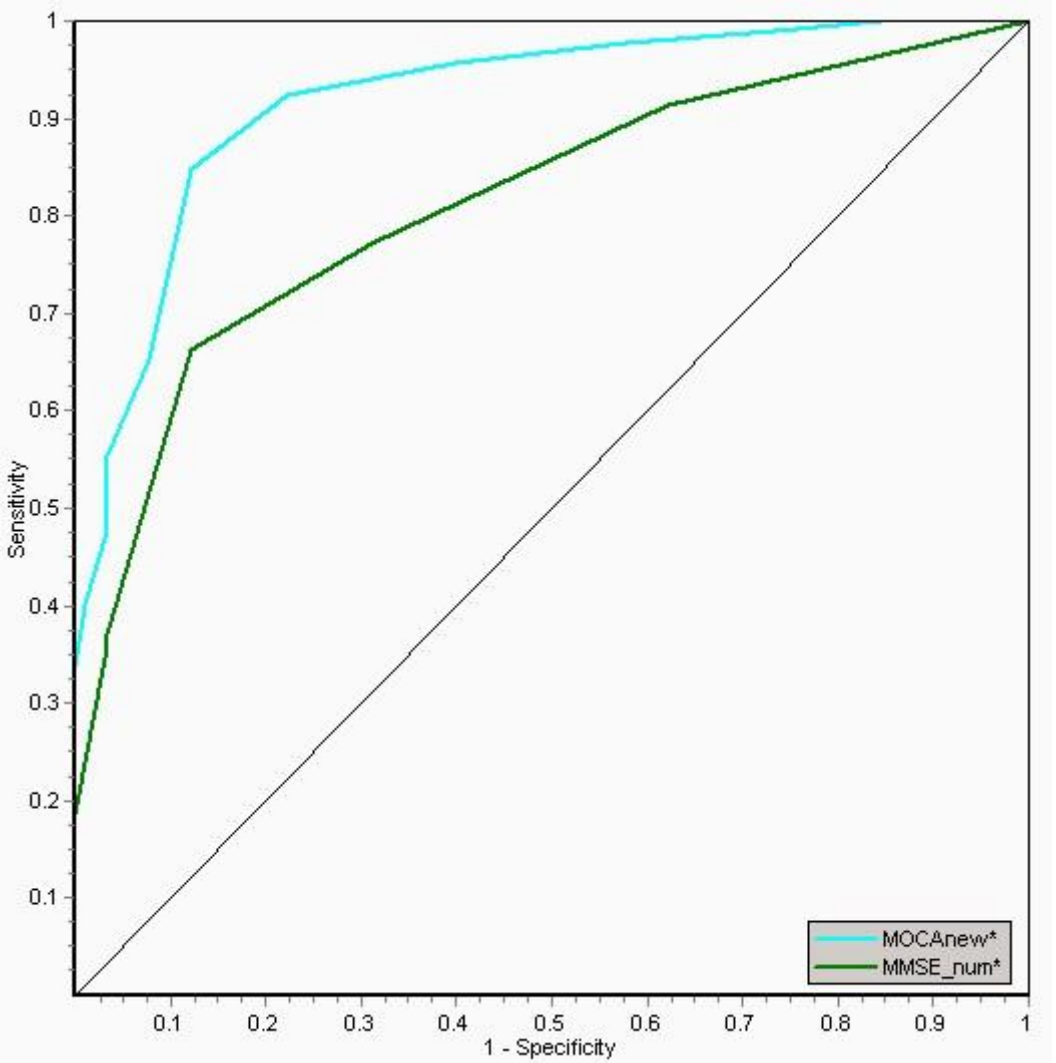
TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

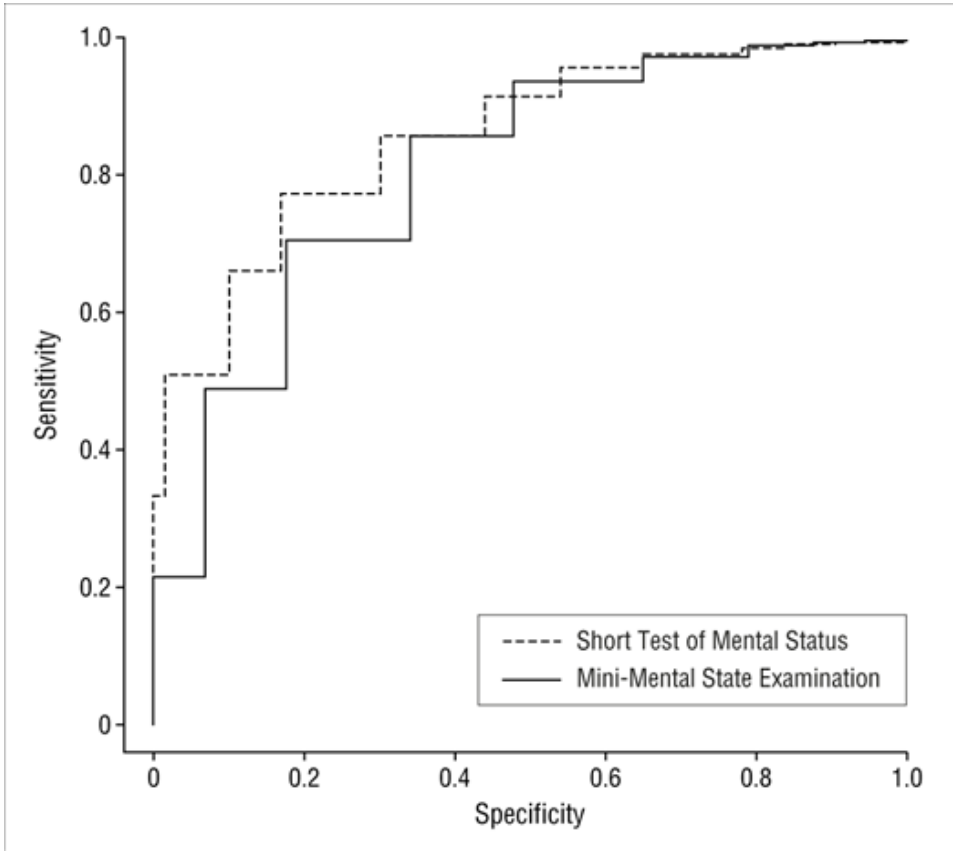
MMSE vs. MOCA

- **MMSE AUC**
  - 0.81
- **MOCA AUC**
  - 0.92

http://www.mocatest.org/normative_data.asp



Kokmen Short Test of Mental Status



MMSE AUC: 0.94
KSTMS AUC: 0.96

Subtest	Ideal Score
Orientation (Name, address, building, city, state, day [of the month or the week], month, year)	8
Attention (up to seven digits forward)	7
Learning (apple, Mr. Johnson, charity, tunnel) number of trials for acquisition _____	4
Calculation (5x13, 65-7, 58÷2, 29+11)	4
Abstraction (orange-banana, horse-dog, table-bookcase)	3
Construction (draw a clock showing quarter after eleven, copy a cube)	4
Information (president, first president, number of weeks/year, and definition of an island)	4
Recall	4
Total Score*	38 Total

Tang-Wai et al., *Arch Neurol.* 2003;60(12):1777-1781

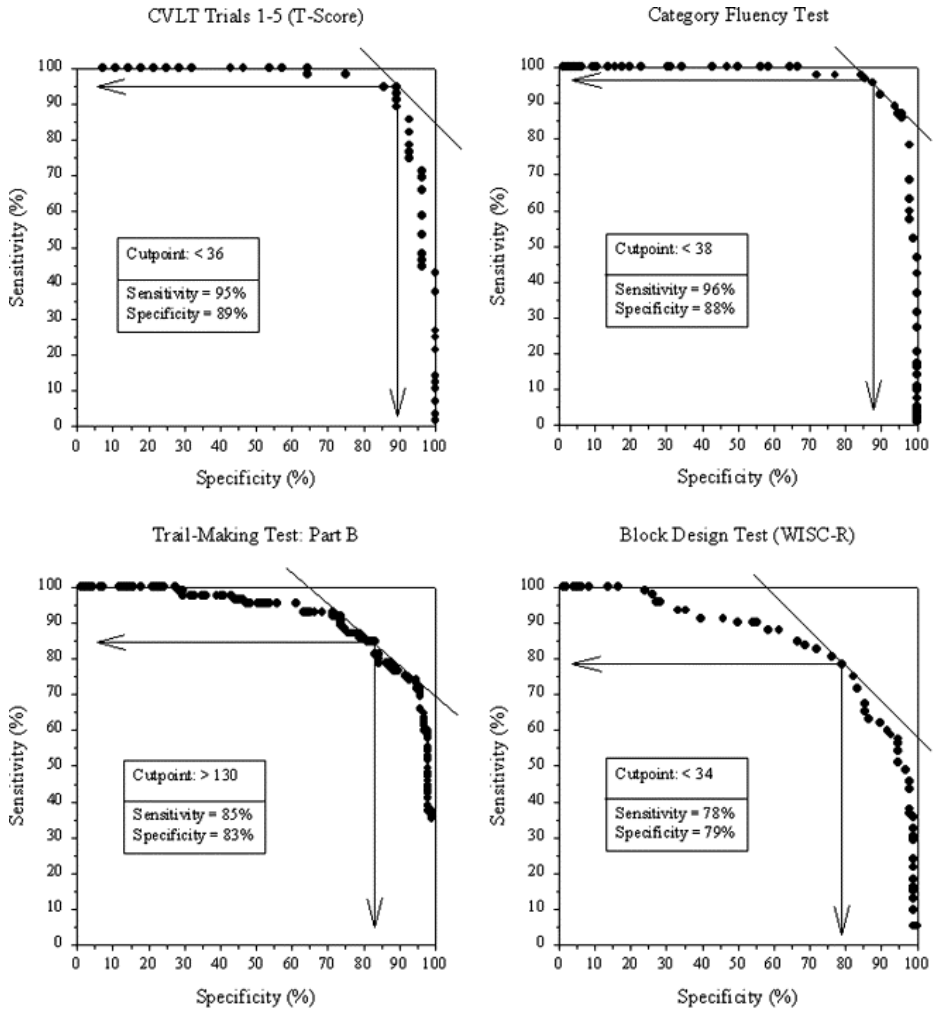
KSTMS: Kentucky Version

Subtest	**Ideal Score**
Orientation **(building, Floor, city, state, day of the month, day of the week, month, year)**	**8**
Attention **(up to seven digits forward)**	**7**
Learning **(apple, Mr. Johnson, charity, tunnel)** **number of trials for acquisition _____**	**4**
Calculation **simple money problems (cup of coffee is 0.65 and you pay with a dollar, what is your change? How many quarters in $2.75?**	**4**
Abstraction **(difference between sugar-vinegar & lie-mistake)**	**3**
Construction **(draw a clock showing eleven ten,** **copy a cube)**	**4**
Information **(president, first president, price of gas, and other episodic event from recent media)**	**4**
Recall (free and cued)	**4**
Total Score*	**38** **Total**

Subtest	Ideal Score
Orientation (Name, address, building, city, state, day [of the month or the week], month, year)	8
Attention (up to seven digits forward)	7
Learning (apple, Mr. Johnson, charity, tunnel) number of trials for acquisition _____	4
Calculation (5x13, 65-7, 58÷2, 29+11)	4
Abstraction (orange-banana, horse-dog, table-bookcase)	3
Construction (draw a clock showing quarter after eleven, copy a cube)	4
Information (president, first president, number of weeks/year, and definition of an island)	4
Recall	4
Total Score*	38 Total

Animal naming

- **Quick 60 second test**
- **General rule of thumb**
  - # words should exceed years of education
- **Continuous variable to track progression over time**



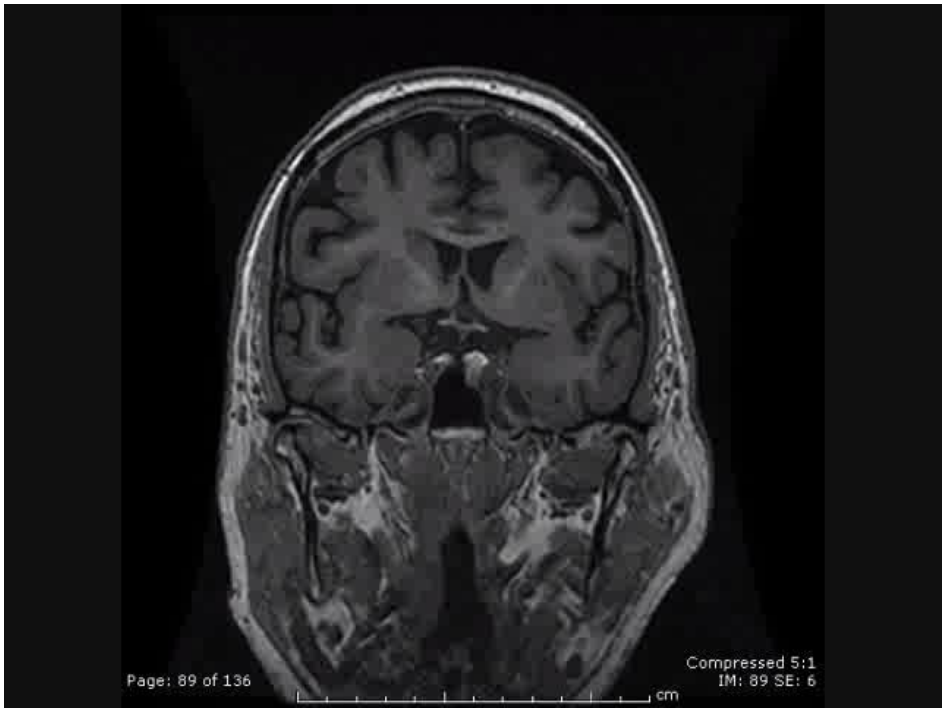
Salmon, D. 2008 Handbook of Clinical Neurology Volume 88, Pages 113–135

Diagnosis: You can interpret and use MRI in your practice!

- **Five point scale (0 to 4)**
- **Rates the size of three medial temporal structures**
  - Hippocampus
  - Entorhinal cortex
  - Perirhinal cortex
- **Developed based on Scheltens et al. *J. Neurol* 1995**

Visual Rating System (VRS)

- **MRI Characteristics**
  - **T2 weighted 3D Echo sequence such as MP-RAGE or similar in the CORONAL PLANE**

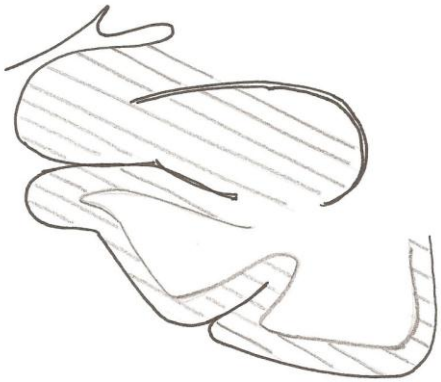


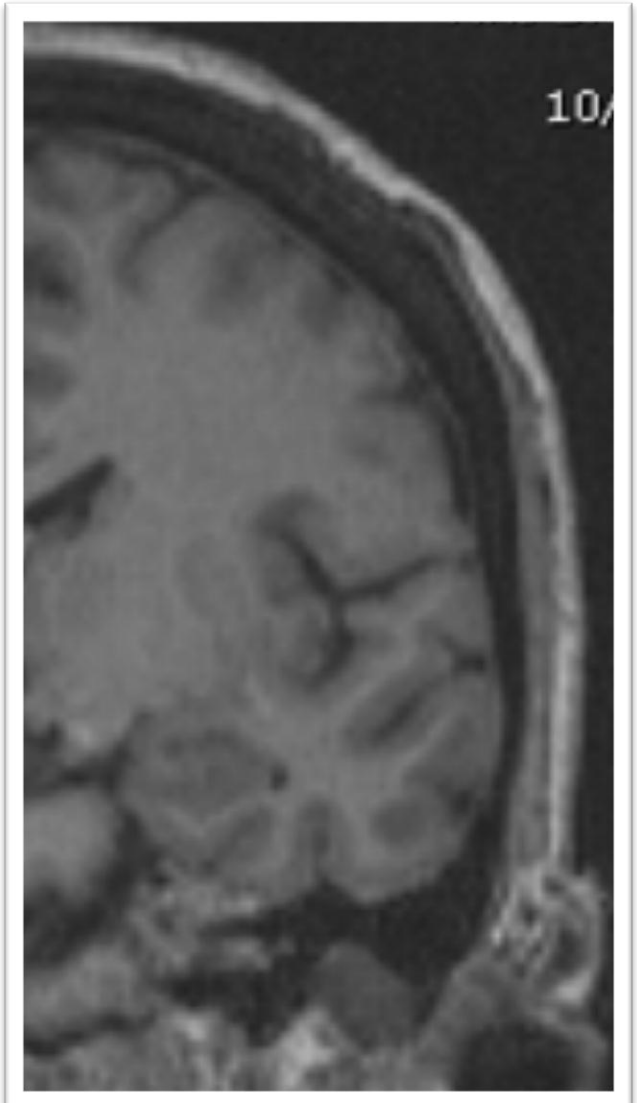
Visual Rating System (VRS)

ENTORHINAL CORTEX

RATING = 0 NO ATROPHY

- NORMAL THICKNESS
- NO WIDENING OF COLLATERAL SULCUS

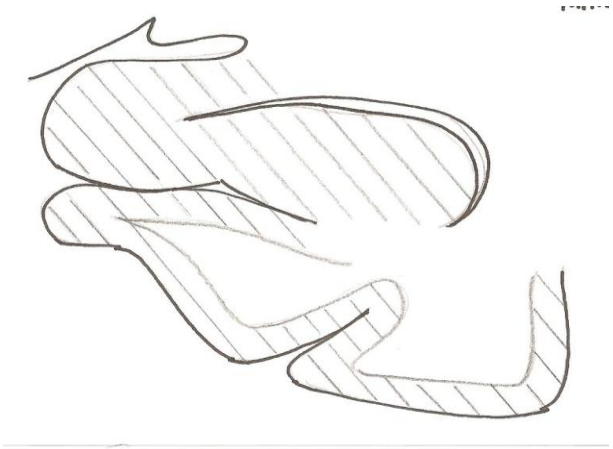


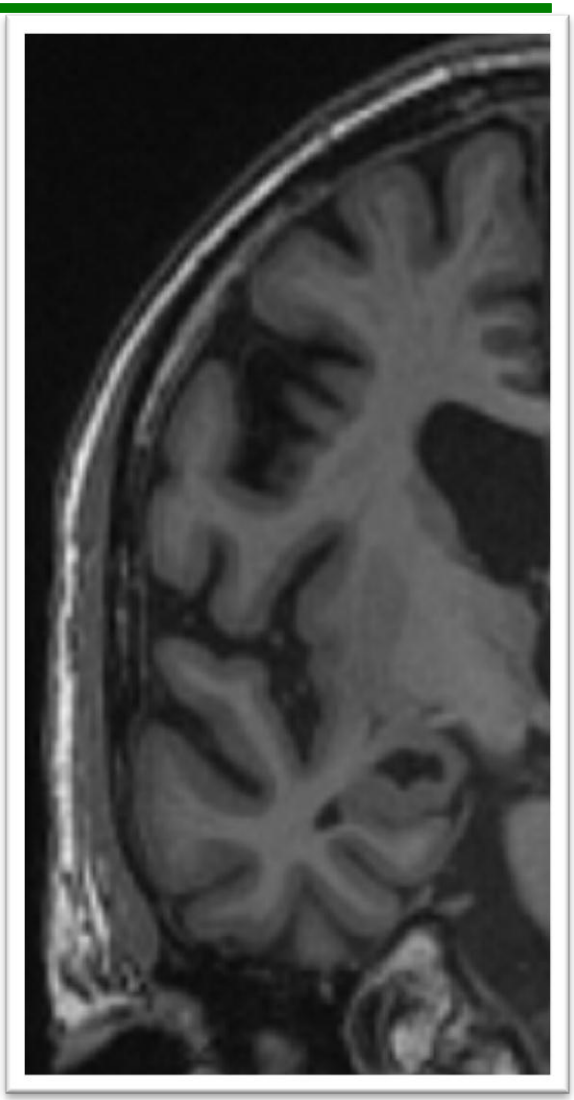


Visual Rating System (VRS)

RATING = 1
MINIMAL ATROPHY
ENTORHINAL CORTEX

1. **SLIGHT DECREASE IN THICKNESS**
   OR
2. **MINIMAL COLLATERAL SULCUS WIDENING**
   OR
3. **BOTH**





Visual Rating System (VRS)

ENTORHINAL CORTEX

RATING = 2 MILD ATROPHY

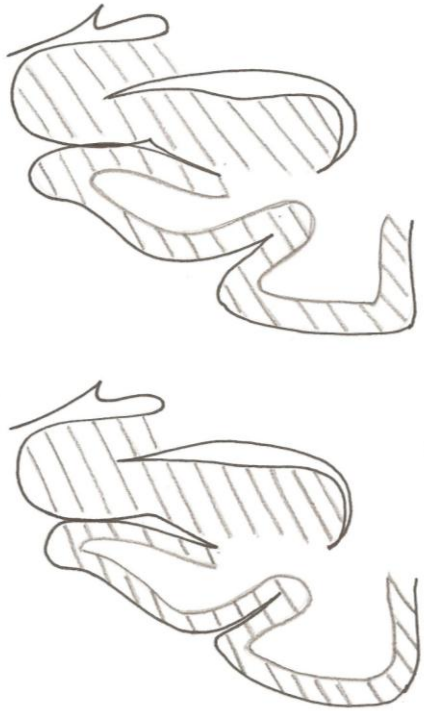
1. MILD DECREASE IN THICKNESS

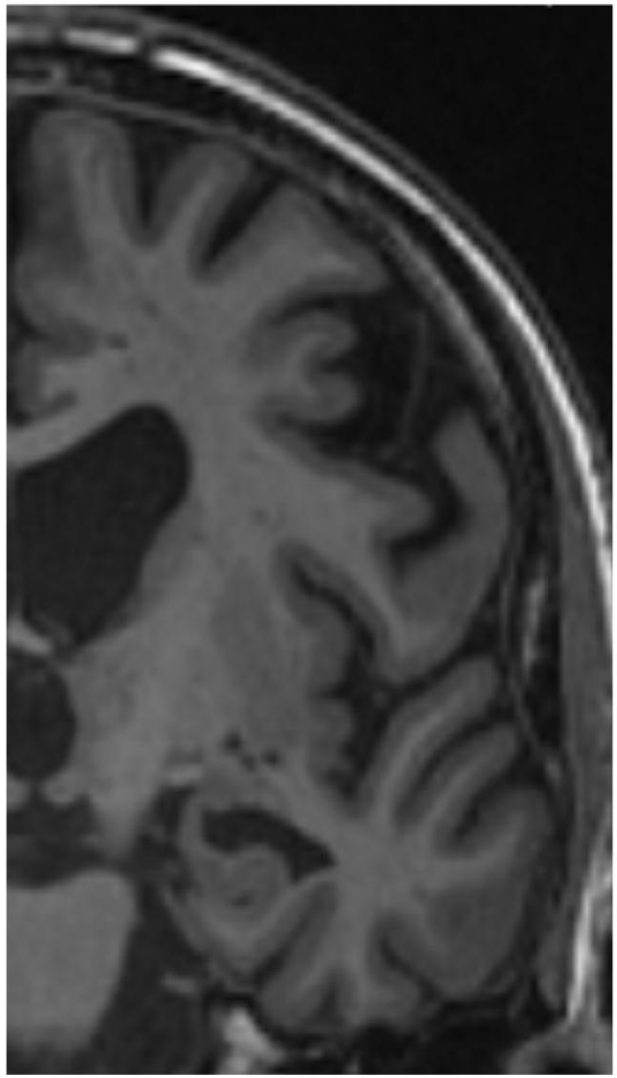
OR

2. MILD WIDENING OF COLLATERAL SULCUS

OR

3. BOTH





Visual Rating System (VRS)

ENTORHINAL CORTEX

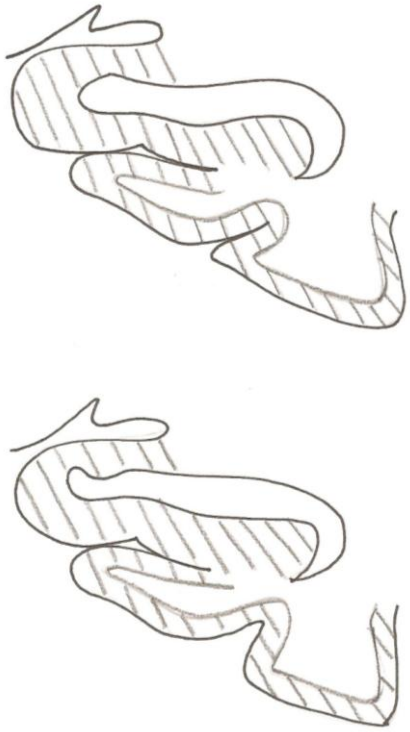
RATING = 3

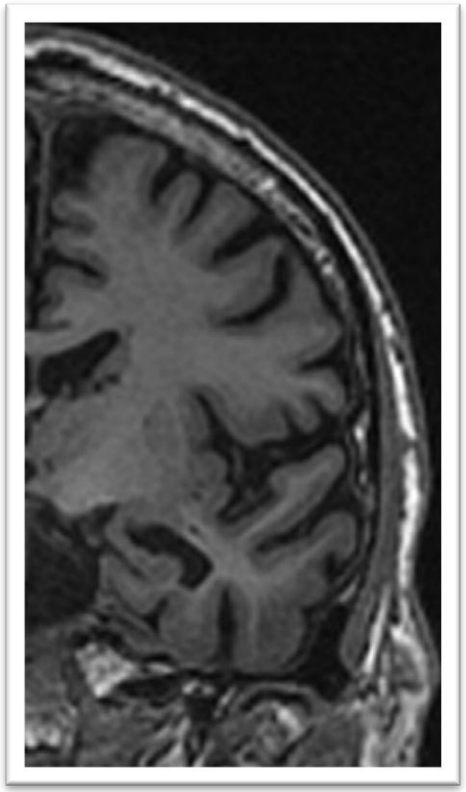
MODERATE ATROPHY

1. **MODERATE DECREASE IN THICKNESS (EVEN IN THE ABSENCE OF WIDENING OF COLLATERAL SULCUS)**

OR

2. **BOTH MODERATE DECREASE IN THICKNESS AND WIDENING OF COLLATERAL SULCUS**





Visual Rating System (VRS)

ENTORHINAL CORTEX

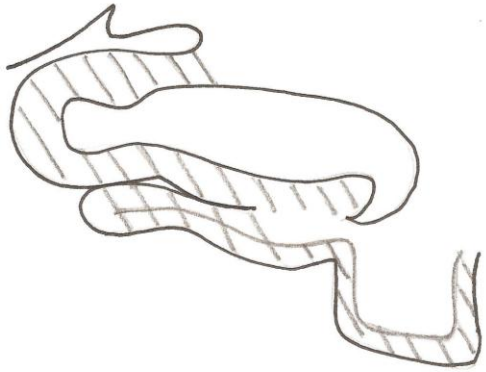
RATING = 4

SEVERE ATROPHY

1. **SEVERE DECREASE IN THICKNESS (EVEN IN THE ABSENCE OF WIDENING OF COLLATERAL SULCUS)**

   OR

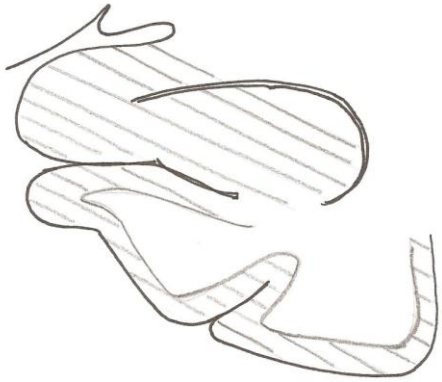
2. **BOTH SEVERE DECREASE IN THICKNESS AND WIDENING OF COLLATERAL SULCUS**

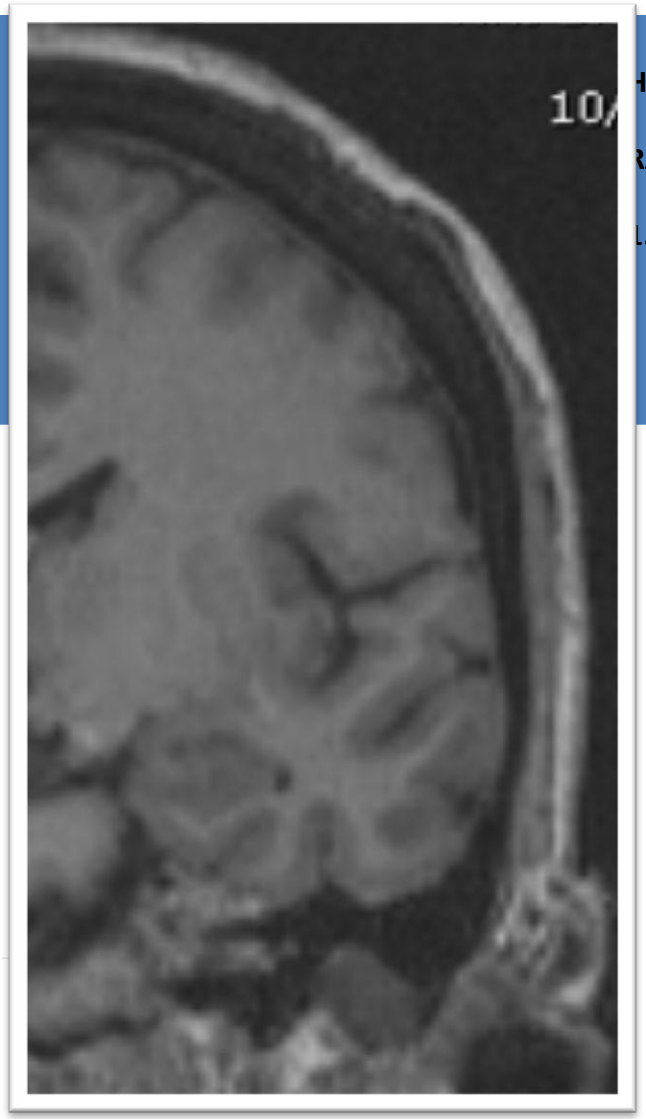


HIPPOCAMPUS

RATING = 0 NO ATROPHY

1. NORMAL THICKNESS

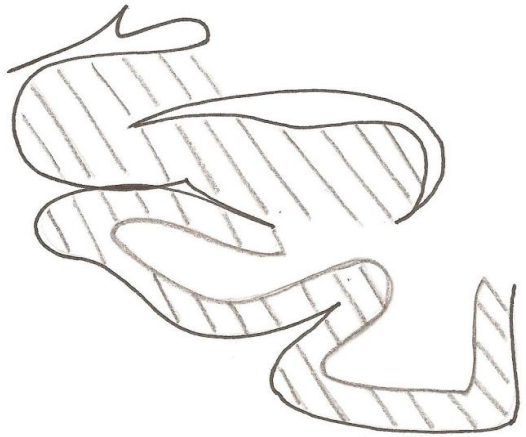




HIPPOCAMPUS

RATING = 2 MILD ATROPHY

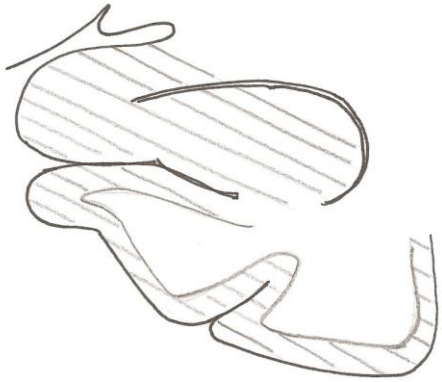
1. MILD DECREASE IN THICKNESS (Between 25 and 50 % decrease)



HIPPOCAMPUS

RATING = 0 NO ATROPHY

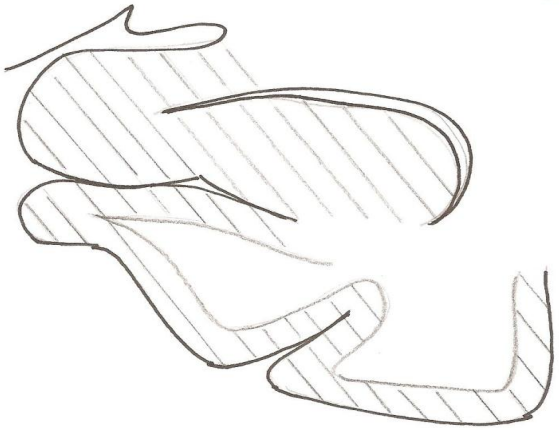
1. **NORMAL THICKNESS**

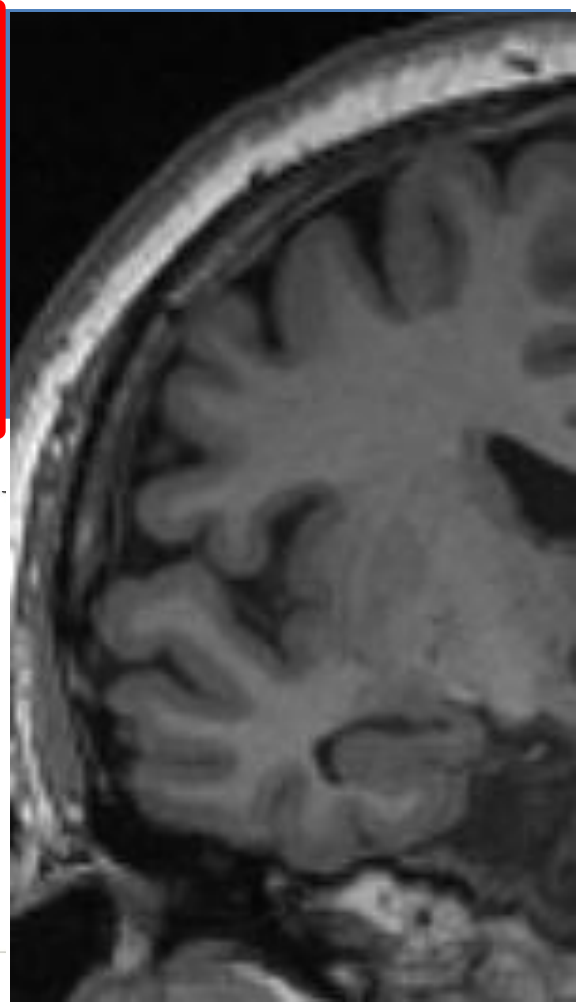


HIPPOCAMPUS

RATING = 1 MINIMAL ATROPHY

1. **SLIGHT DECREASE IN THICKNESS (Less than 25% decrease)**

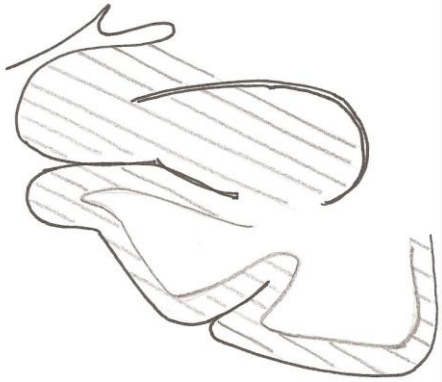


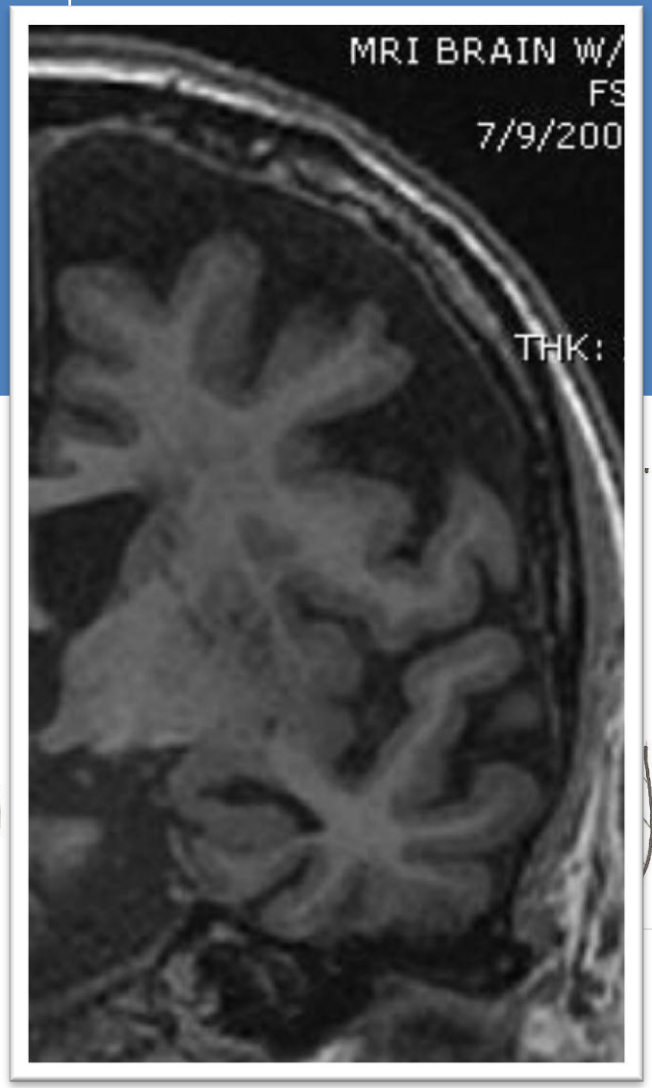


HIPPOCAMPUS

RATING = 0 NO ATROPHY

1. **NORMAL THICKNESS**

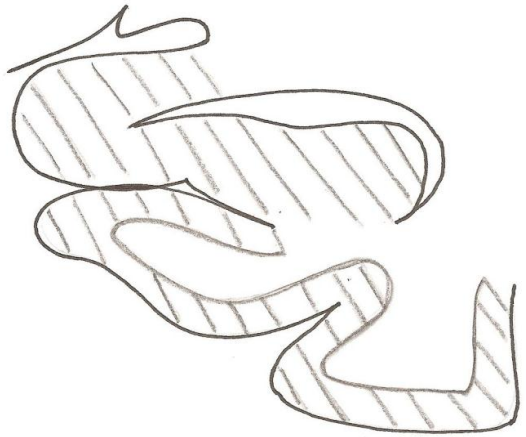




HIPPOCAMPUS

RATING = 2 MILD ATROPHY

1. **MILD DECREASE IN THICKNESS (Between 25 and 50 % decrease)**



HIPPOCAMPUS

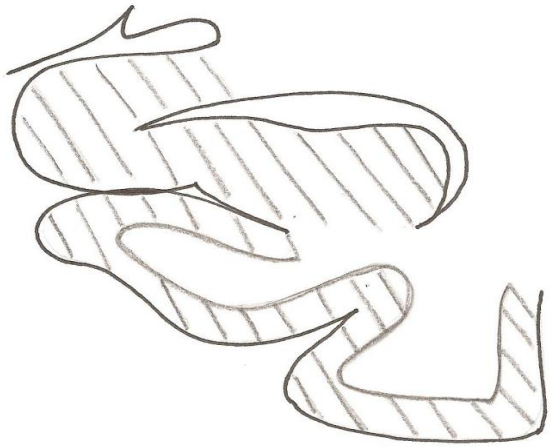
RATING = 2 MILD ATROPHY

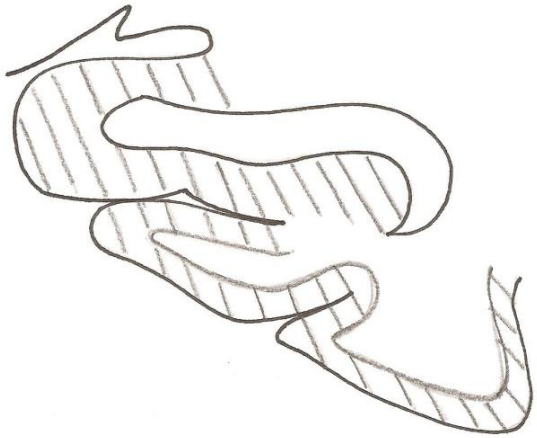
1. **MILD DECREASE IN THICKNESS (Between 25 and 50 % decrease)**

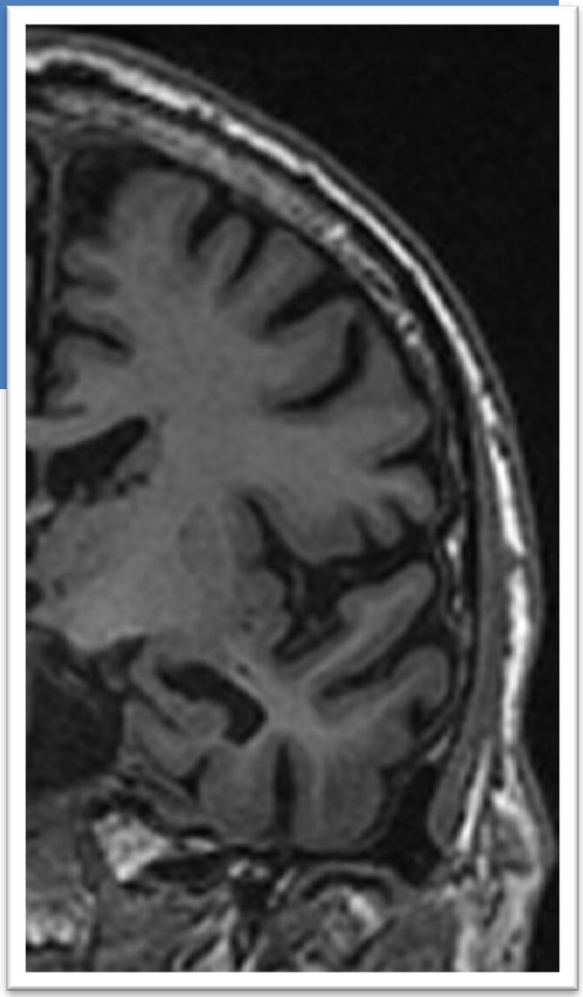
HIPPOCAMPUS

RATING = 3 MODERATE ATROPHY

1. **MODERATE DECREASE IN THICKNESS (Between 50 and 75 % decrease)**





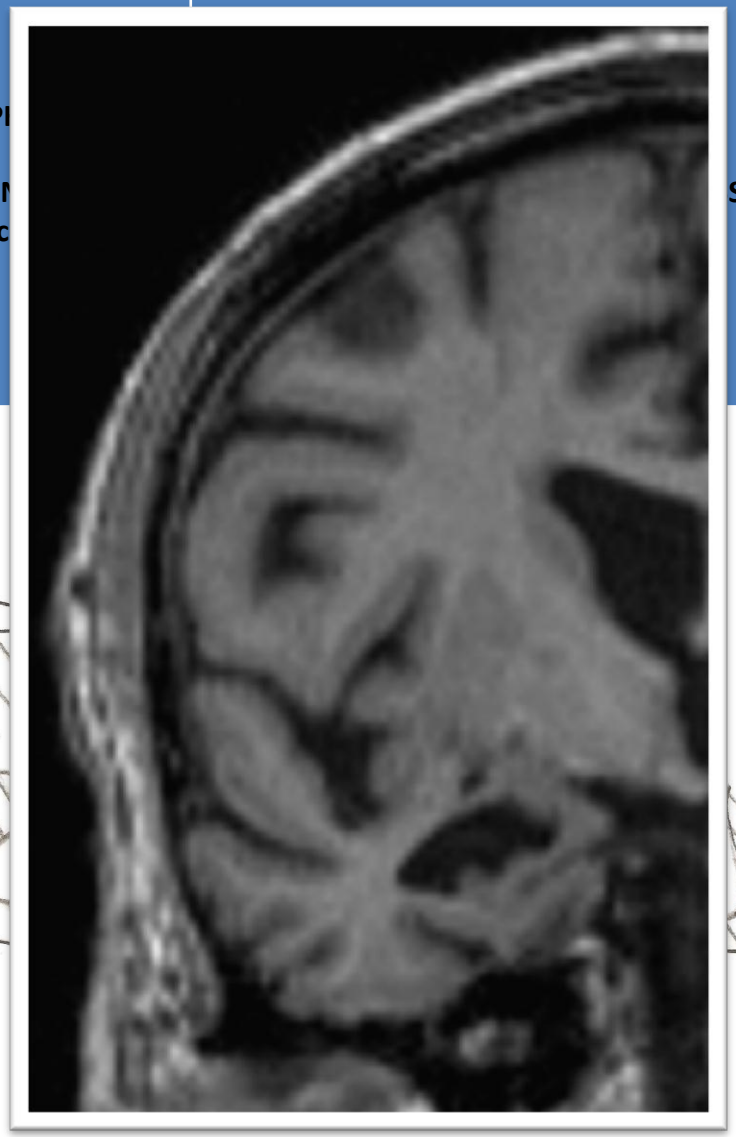


HIPPOCAMPUS

RATING = 2 MILD ATROPI

1. **MILD DECREASE IN THICKN**
   (Between 25 and 50 % dec

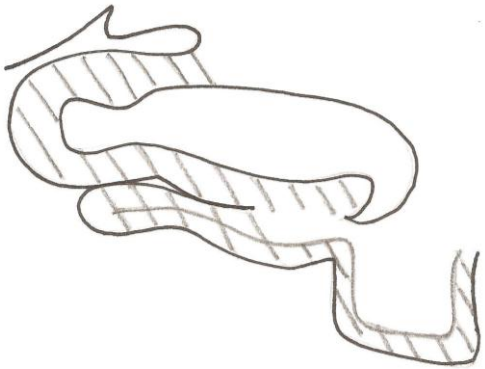
S



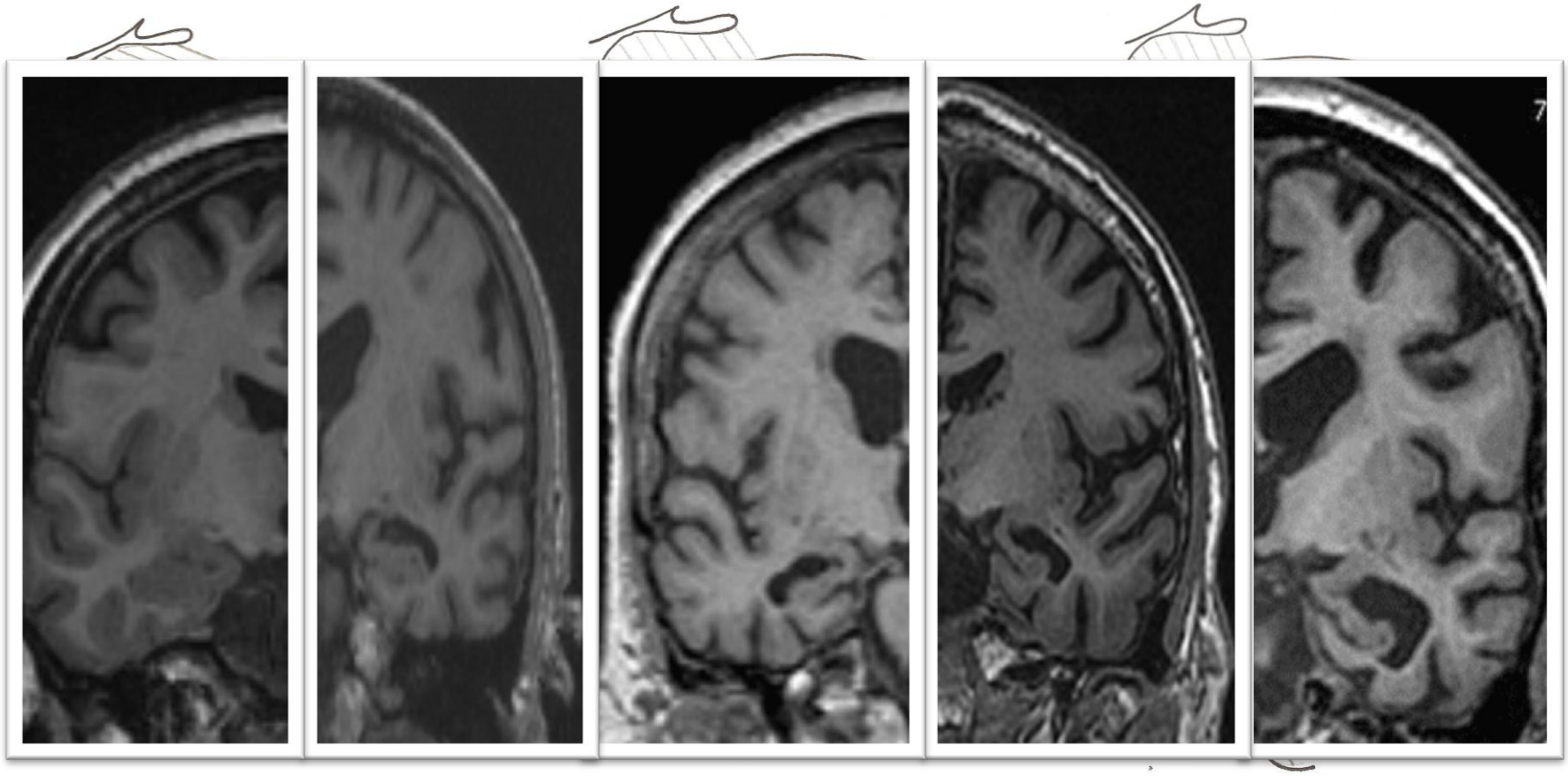
HIPPOCAMPUS

RATING = 4 SEVERE ATROPHY

1. **SEVERE DECREASE IN THICKNESS**
   (More than 75% decrease)



RATING = 0 NO ATROPHY	RATING = 1 MINIMAL ATROPHY	RATING = 2 MILD ATROPHY
1. NO WIDENING OF LOTS LOTS: Lateral Occipitotemporal	1. MINIMAL WIDENING OF LOTS	1. MILD WIDENING OF LOTS

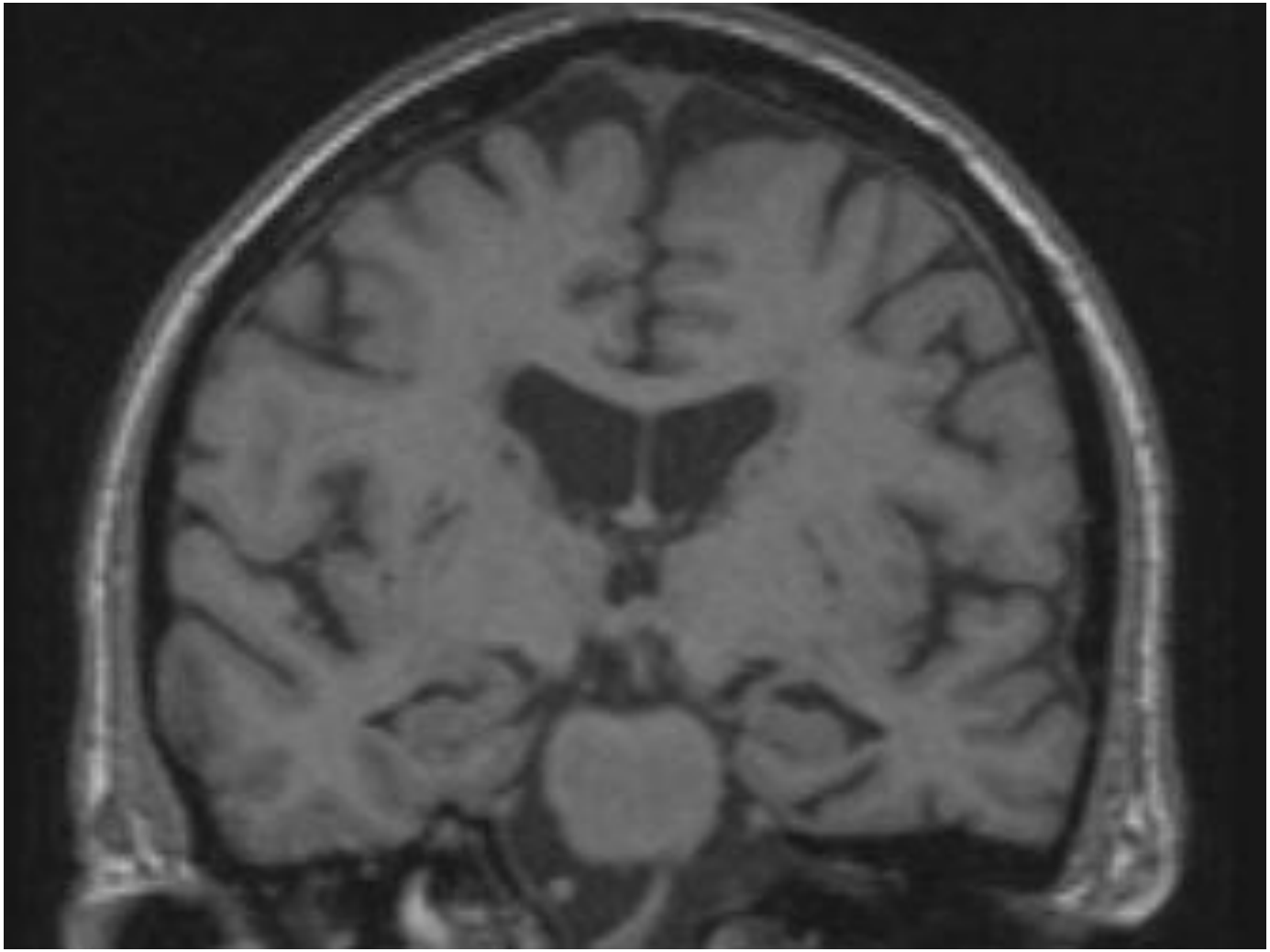


Visual Rating System (VRS)

Mr. ER is a 78 yo male evaluated for the first time in 2005 at the Wien Center. He presented with mild cognitive deficits predominantly in short term memory and word finding difficulties. He also had mild symptoms of depression that required the use of an antidepressant.

	MMSE	BNCG	D Recall	FAQ	PSMS
1/12/2005	27	53/60	10/15	2/36	0/24

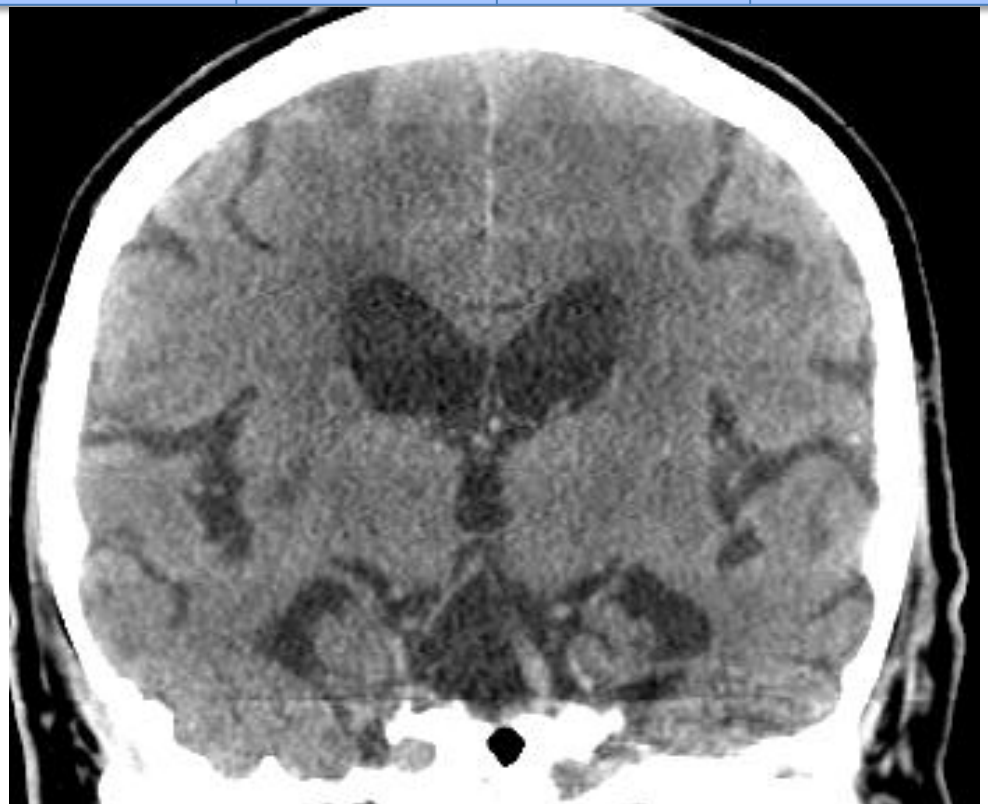
Visual Rating System (VRS)



January 2005

Visual Rating System (VRS)

	MMSE	BNCG	DR	FAQ	PSMS
1/12/2005	27	53/60	10/15	2/36	0/24
9/27/2011	17	30/60	0/15	31/36	15/24



February 2011

More to come…