DSM-5 Renaming Dementia (?)

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Countdown to 2025
Progress on Ending Alzheimer's Disease
UC Irvine
September 20, 2013

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Disclosures

- Pfizer, Inc.: Chair DMC
- Janssen Alzheimer's Immunotherapy: Chair DMC
- GE Healthcare: Consultant
- Funding

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Neurocognitive Disorders Work Group

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Neurocognitive Disorders

Premises

A. New title
   - Replaces: delirium, dementia amnestic and geriatric cognitive disorders

B. Cognition
   - Core deficit in cognition
   - Decline from previous level of function

Neurocognitive Disorders

- Delirium
- Major Neurocognitive Disorder (NCD)
- Mild Neurocognitive Disorder (NCD)

Delirium

Delirium

- Disturbance of attention and awareness
- Change over a short period of time
- Includes disturbance in cognition
- Not better explained by preexisting condition
- Caused by physiological consequence of medical condition, substance use, or withdrawal

DSM-IV Definition

- "The essential feature of a delirium is a ***disturbance in consciousness*** that is accompanied by a change in cognition that cannot be better accounted for by a preexisting or evolving dementia."

Proposed Changes in DSM-5

Change	Current
A. *Disturbance in level of awareness* or arousal with reduced ability to direct, focus, sustain, and shift attention.	A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention

Addition

- Note : The following supportive features are commonly present in delirium but are not key diagnostic features: sleep-wake cycle disturbance, psychomotor disturbance, perceptual disturbances (e.g., hallucinations, illusions), emotional disturbances, delusions, labile affect, and EEG abnormalities (generalized slowing of background activity).

Neurocognitive Disorders

General Approach to NCD's

- Characterize the patient syndromically
  - Mild NCD
  - Major NCD
- Determine etiology of syndrome

Major Change

- Now including a pre-dementia condition termed “Mild Neurocognitive Disorder”
- DSM IV characterized mostly conditions at the dementia stage and their subtypes

Neurocognitive Disorders

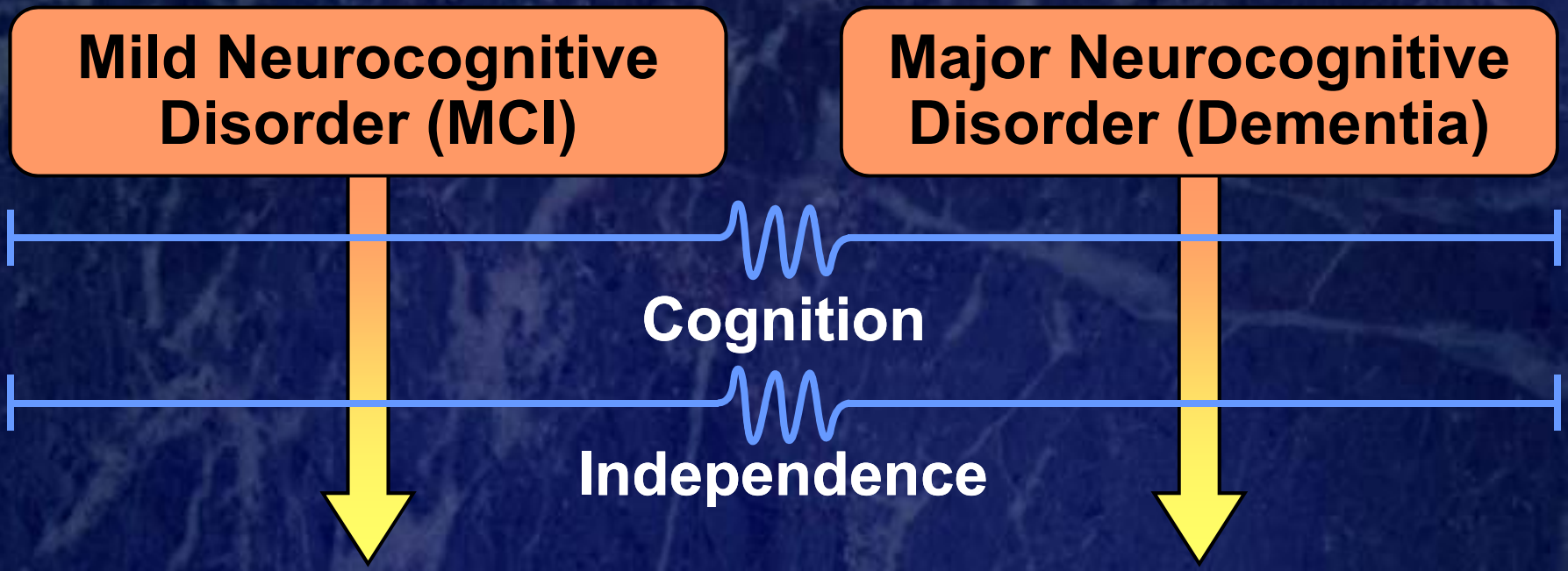
Major vs Mild

1. Severity
2. Independence
3. Usually a continuum with evolution
   Not always
4. Etiology

Neurocognitive Disorders

Domains

Domain	Tasks
Complex attention	Major: diminished, multiple stimuli Mild: takes longer
Executive abilities	Major: abandon complex activities Mild: ↑ effort, multi-tasking
Learning/memory	Major: repeat self in conversation Mild: recent events, occas repeat
Language	Major: anomia, paraphasias Mild: ↓ naming, word finding
Visuoconstruction Visuoperception	Major: not driving, ↓ navigation Mild: maps, effort
Social cognition	Major: insensitivity social contexts Mild: subtle personality, ↓ empathy



1. Cognitive decline
2. Single cognitive domain impaired (usually)
3. Preservation of independence

1. Cognitive decline
2. Significant cognitive impairment in one or more often multiple cognitive domains
3. Loss of independence

Major NCD
Dementia

A. Cognitive decline (1 or usually 2 cognitive domains)

   1. Report by patient, informant, clinician

      and

   2. Deficits on assessment

B. Interfere with independence assistance in IADL's

C. Not delirium

D. Not primarily attributable to another disorder

Mild NCD
MCI

Rationale

- Mild cognitive impairment
- Early recognition
- Intervention
- Clinical trials

Criteria

A. Cognitive decline
   1. Report by patient, informant, clinician
      and
   2. Mild cognitive deficits

B. Not interfere with independence greater effort
C. Not delirium
D. Not primarily attributable to other axis 1 disorder

NCD Etiologies

- Alzheimer's Disease
- Frontotemporal degen
- Lewy body disorders
- Vascular cognitive imp
- Traumatic brain injury
- Substance/medications
- HIV/AIDS
- Prion disorders
- Parkinson's disease
- Huntington disease
- Other medical issues
- Multiple causes

Alzheimer's Disease

General

1. Neurodegenerative disease
2. Gradual onset and decline
3. Typically includes a memory impairment
4. ? role of imaging and biomarkers

Alzheimer's Disease

Major

1. Meets criteria for Major NCD

Mild

1. Meets criteria for Mild NCD

Probable and Possible AD

Alzheimer's Disease

Major Probable AD

1. Genetic mutation
2. All 3
   - Memory + other domain
   - Progressive
   - No additional contributions

Mild Probable AD

1. Genetic mutation

Mild Possible AD

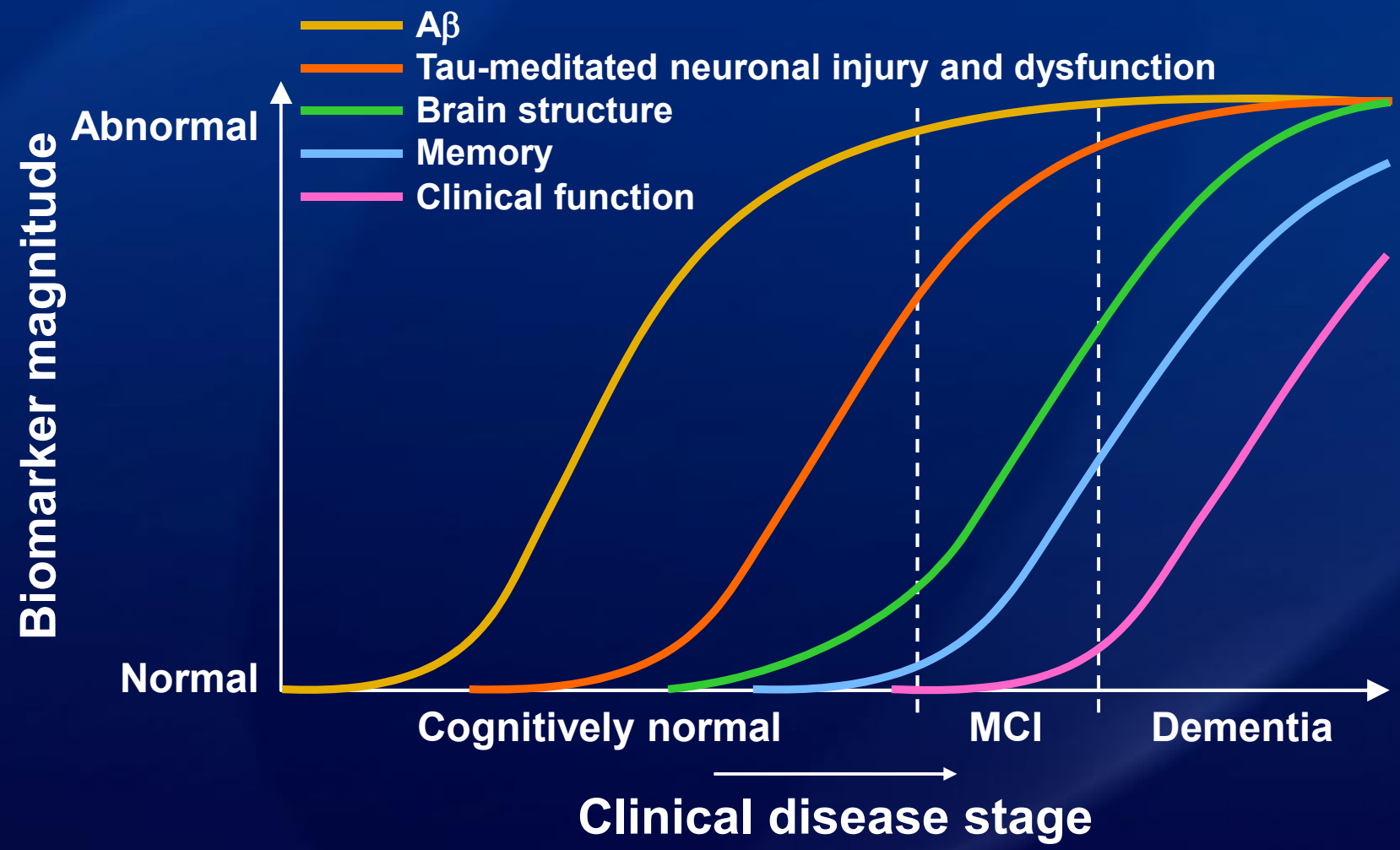
1. All 3
   - Memory disorder
   - Progressive
   - No additional contributions

Other Newish Criteria

- Alzheimer's Disease Spectrum
  NIA-AA

- Prodromal Alzheimer's Disease
  International Work Group

Hypothetical Model of Dynamic Biomarkers of the Alzheimer's Pathological Cascade



Jack et al: Lancet Neurol, 2010

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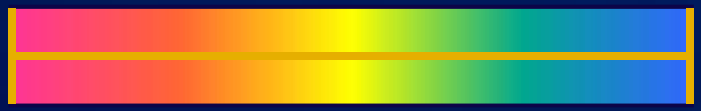
Alzheimer's Disease Spectrum

Preclinical AD

MCI Due to AD



Dementia Due to AD

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Dementia Due to AD

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
Probable AD dementia	Uninformative/ available	Conflicting/ indeterminant or unavailable	
Probable AD with evidence of path AD	Intermediate Highest	? Positive	Positive Positive
Possible AD dementia atypical with path	High consider secondary	Positive	Positive
Dementia unlikely AD	Lowest	Negative	Negative

McKhann et al: 2011

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MCI Due to AD

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI	Uninformative	Conflicting/ indeterminant or unavailable	
MCI due to AD – intermediate likelihood	Intermediate Intermediate	Positive Untested	Untested Positive
MCI due to AD – high likelihood	Highest	Positive	Positive
MCI – unlikely due to AD	Lowest	Negative	Negative

Albert et al: 2011

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Preclinical AD

Diagnostic category	Aβ (PET or CSF)	Neuronal injury	Clinical
Stage 1	Positive	Negative	Negative
Stage 2	Positive	Positive	Negative
Stage 3	Positive	Positive	Positive
Sage 0	Negative	Negative	Negative

Sperling et al: 2011

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Prodromal Alzheimer's Disease

- Episodic memory deficit
  - Supported by biomarkers
  - Essentially, amyloid by imaging or CSF

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Case Example

53 y/o woman

- 1 ½ yr history loss of self-confidence
- Not want to move
- Says “can’t think”
- Forgets rapidly in conversation
- Daughters have noticed x 1 yr
- Decreased reading comprehension
- Family human compass
- Sleep ok
- Concerned but not depressed

53 y/o woman

- Family history negative for dementia
- PMH: Good health, postpartum hemorrhage
- Med: supplements, Zoloft, ASA

53 y/o woman

- STMS: 37/38
- VIQ: 107, PIQ: 97
- Attention/Executive
  - Trails A and B: 50th %ile
  - Stroop: 50th %ile
- Language
  - Fluency: 90th %ile
  - BNT: 59/60

53 y/o woman

- **Visuospatial**
  - Rey O copy: 50th %ile
  - JLO: 50th %ile
- **Memory**
  - Logical Memory: 17/10
  - Visual Reproductions: 64/21
  - AVLT: 7,6,11,10,8; DR 3

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MCI – unlikely due to AD	Lowest	Negative	Negative

Albert et al: 2011

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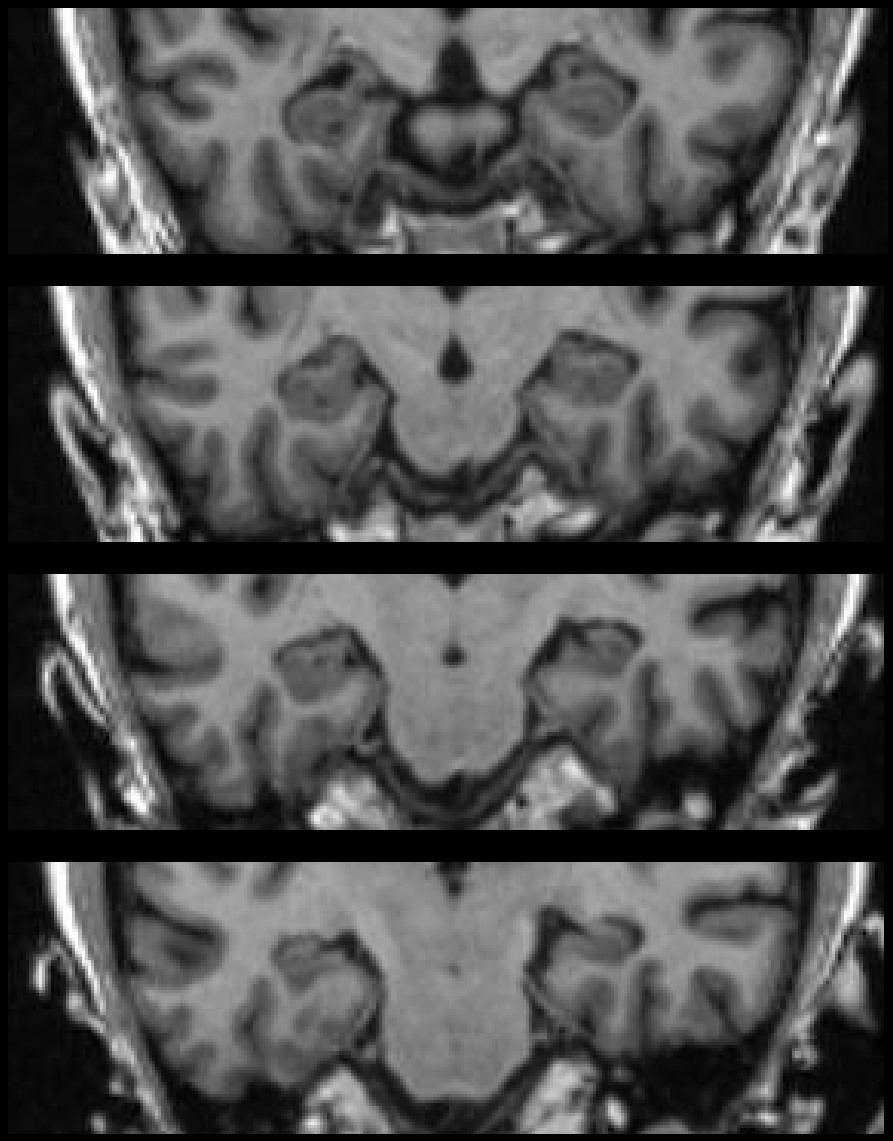
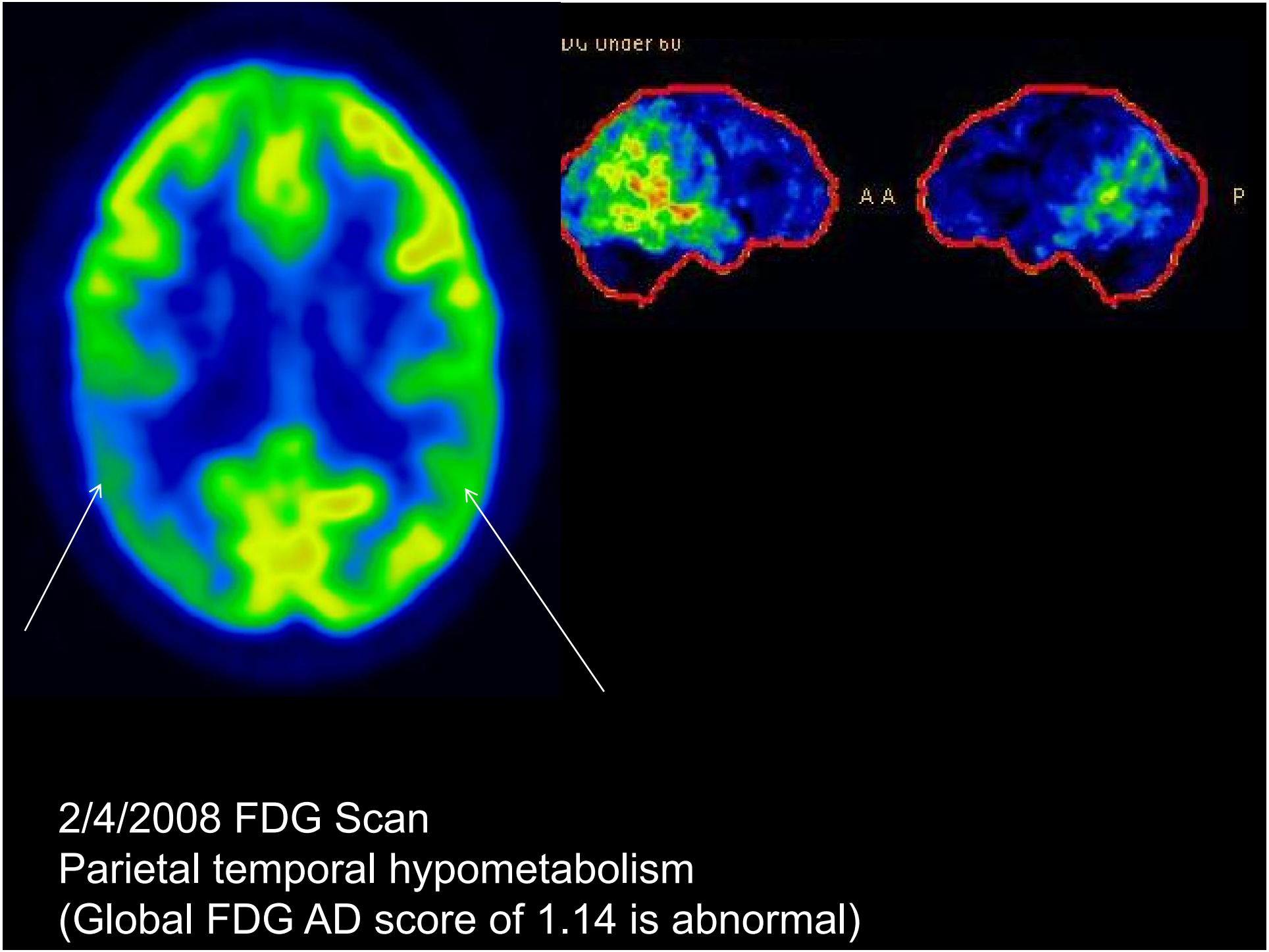
2008

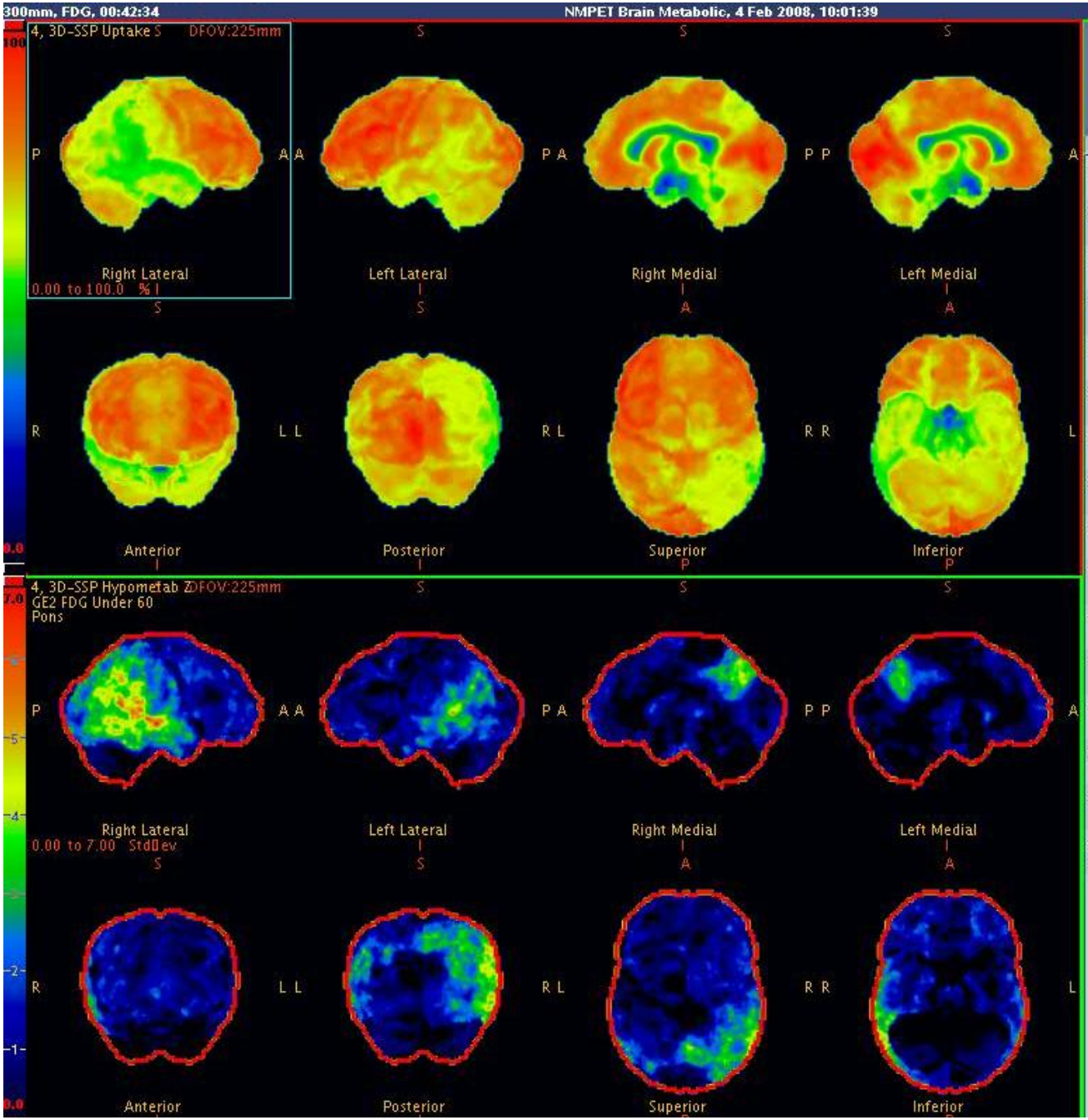


5/22/2008 MRI Scan
Hippvol in normal range (-0.31; greater than -0.7 is normal)

Mayo MCI Subject



2/4/2008 FDG Scan
Parietal temporal hypometabolism
(Global FDG AD score of 1.14 is abnormal)



3D-SSP Regional Hypometabolism (Z-Score)

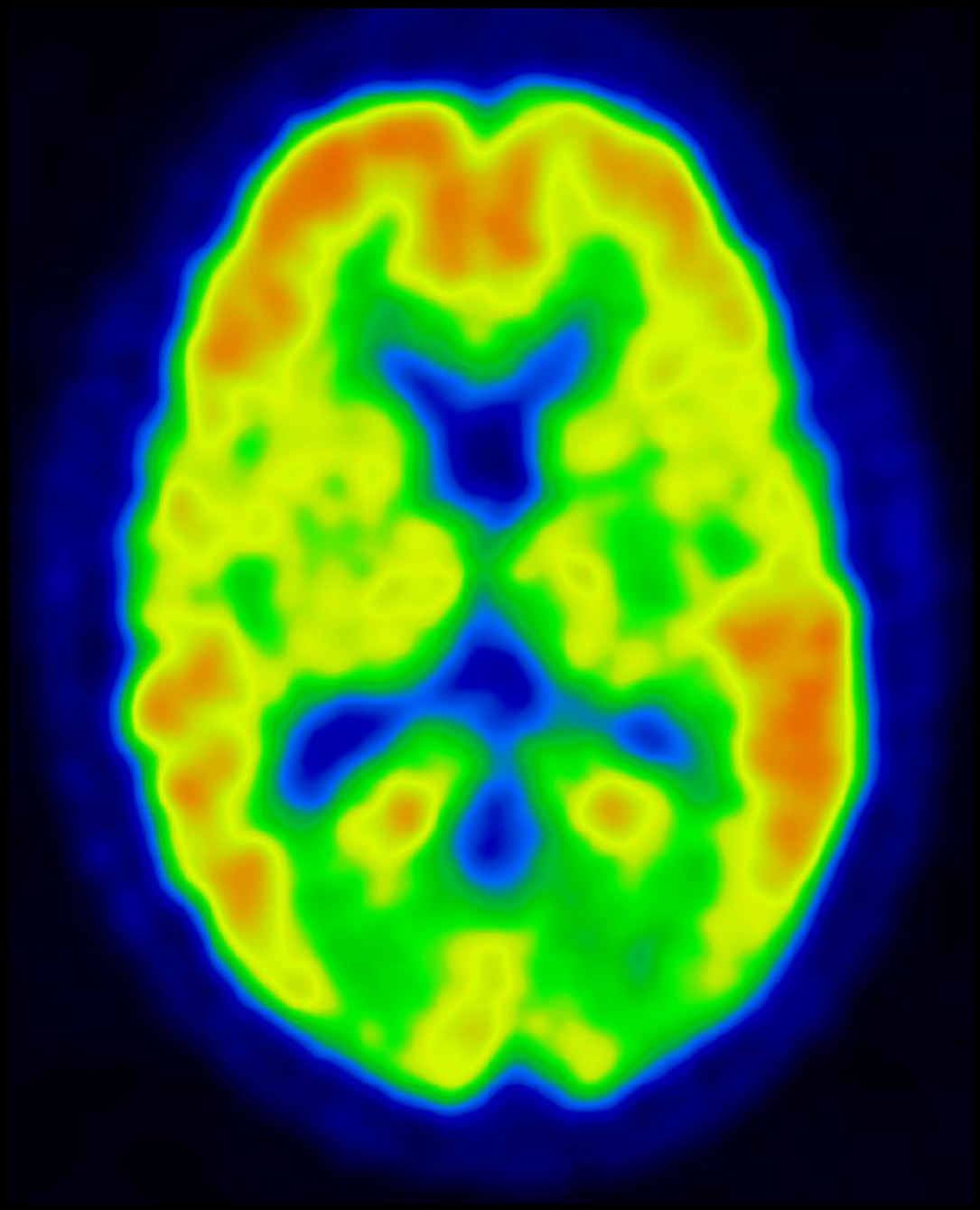
Normals File: GE2 FDG Under 60

Normalized By: Pons

Cortical Regions	R/L	Mean
Parietal Association	R	3.01
	L	1.51
Temporal Association	R	3.15
	L	1.82
Frontal Association	R	1.08
	L	0.75
Occipital Association	R	2.08
	L	0.95
Posterior Cingulate	R	1.14
	L	1.10
Anterior Cingulate	R	0.05
	L	-0.08
Medial Frontal	R	0.79
	L	0.64
Medial Parietal	R	2.80
	L	1.78
Sensorimotor	R	1.42
	L	0.34
Visual	R	1.21
	L	0.51
Caudate Nucleus	R	1.20
	L	1.41
Cerebellum	R	0.09
	L	0.20
Vermis	R	0.38
	L	-0.22
Pons		0.05
Average Association	R	2.02
	L	1.20
Averaged Cerebral		1.19
Global Average		0.93

2/4/2008 PIB Scan

Positive ; Ratio 2.5



MCI Due to AD

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MCI	Uninformative	Conflicting/indeterminant Untested	
MCI due to AD – intermediate likelihood	Intermediate Intermediate	Positive Untested	Untested Positive
MCI due to AD – high likelihood	Highest	Positive	Positive

Albert et al: 2011

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DSM-5

- Mild neurocognitive disorder
  Possible AD

Clinical Progression 2 yr later

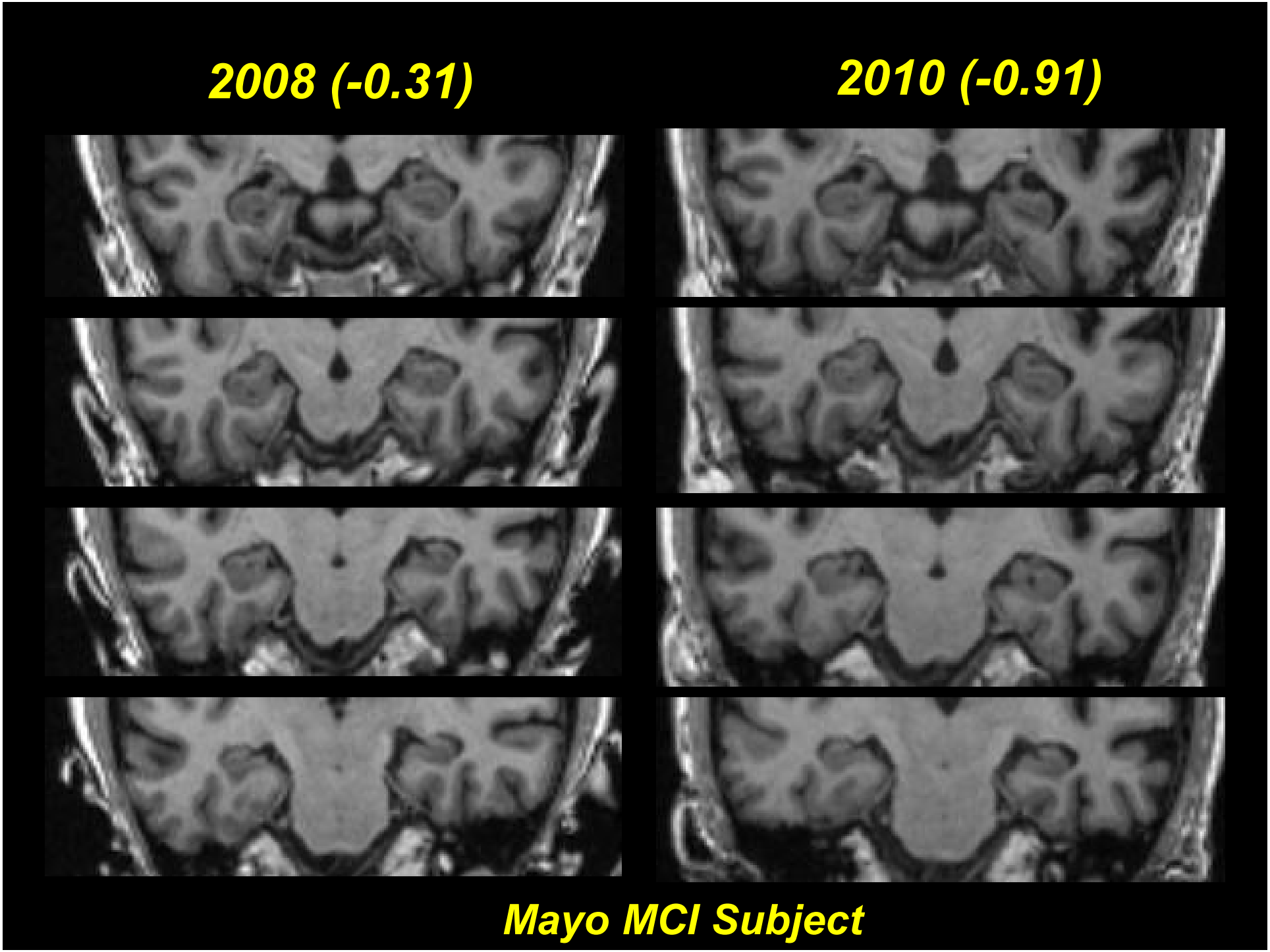
- Getting lost
- Frequent forgetting
- Not driving
- Despondent
- Needs assistance

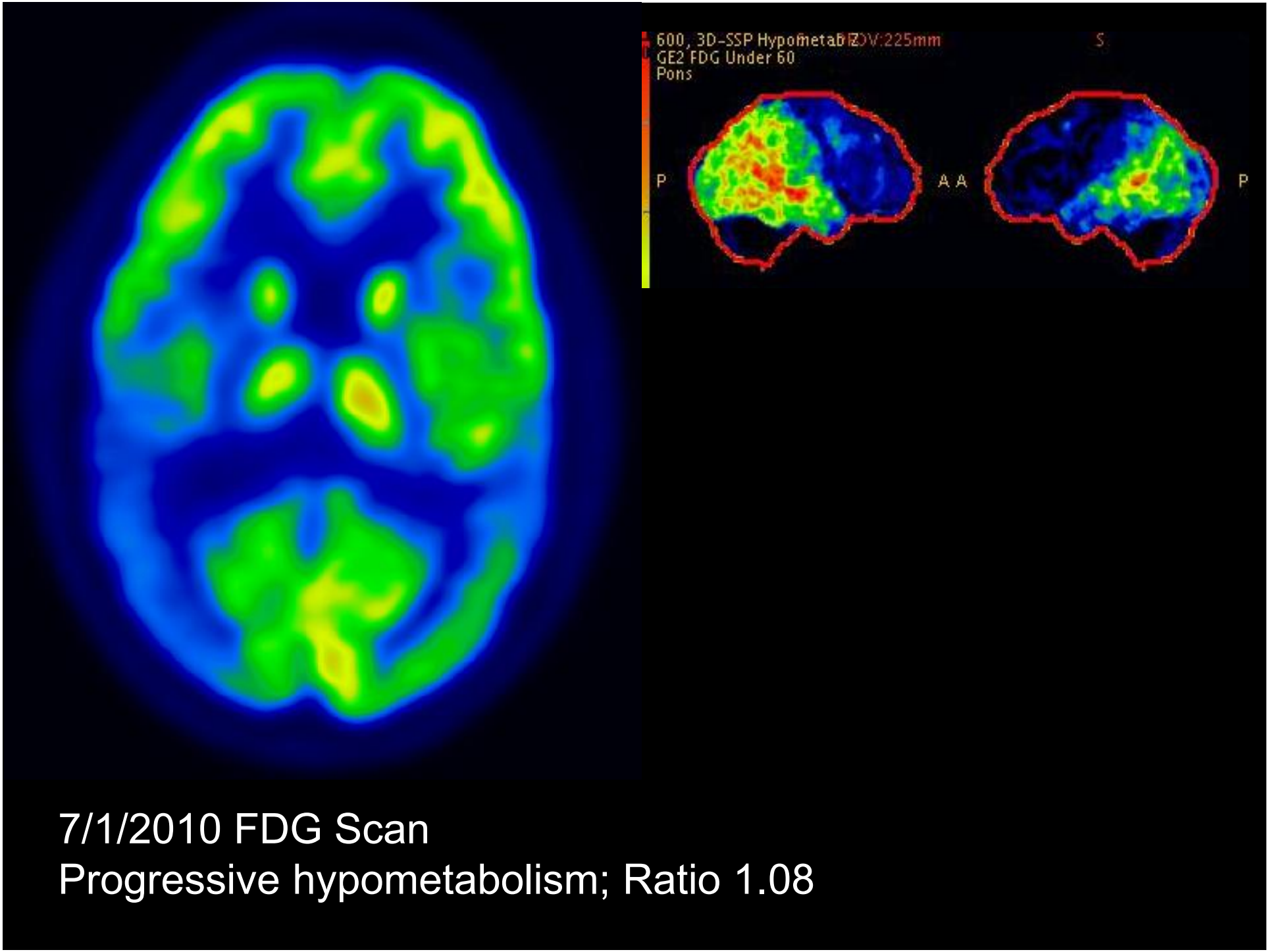
55 y/o woman

- STMS: 32/38
- VIQ: 107, PIQ: 97
- Attention/Executive
  - Trails A and B: 25th %ile
  - Stroop: 30th %ile
- Language
  - Fluency: 60th %ile
  - BNT: 50/60

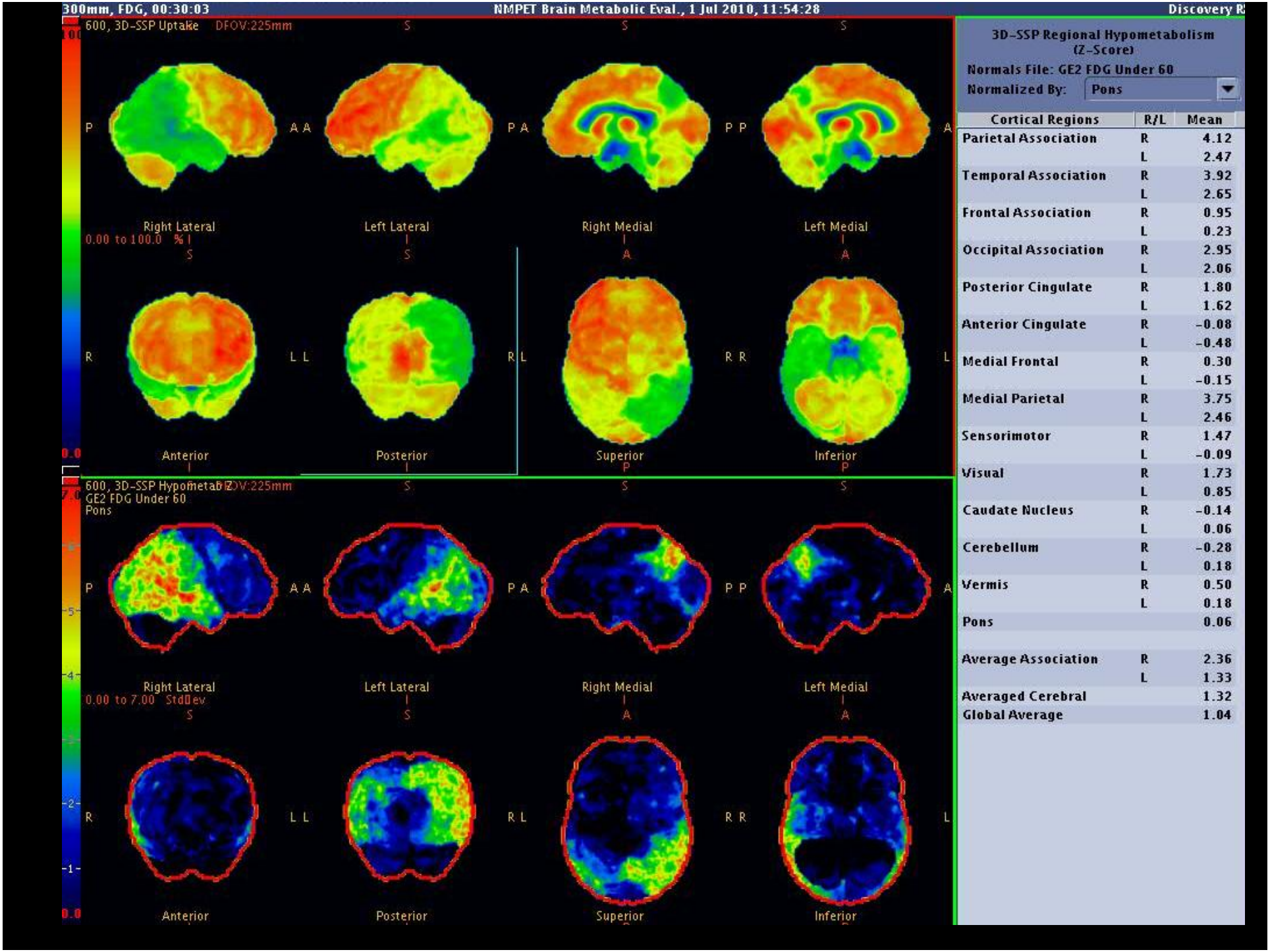
55 y/o woman

- **Visuospatial**
  - Rey O copy: 30th %ile
  - JLO: 25th %ile
- **Memory**
  - Logical Memory: 12/5
  - Visual Reproductions: 32/15
  - AVLT: 3,4,3,5,4; DR 0


2008 (-0.31)
2010 (-0.91)
Mayo MCI Subject

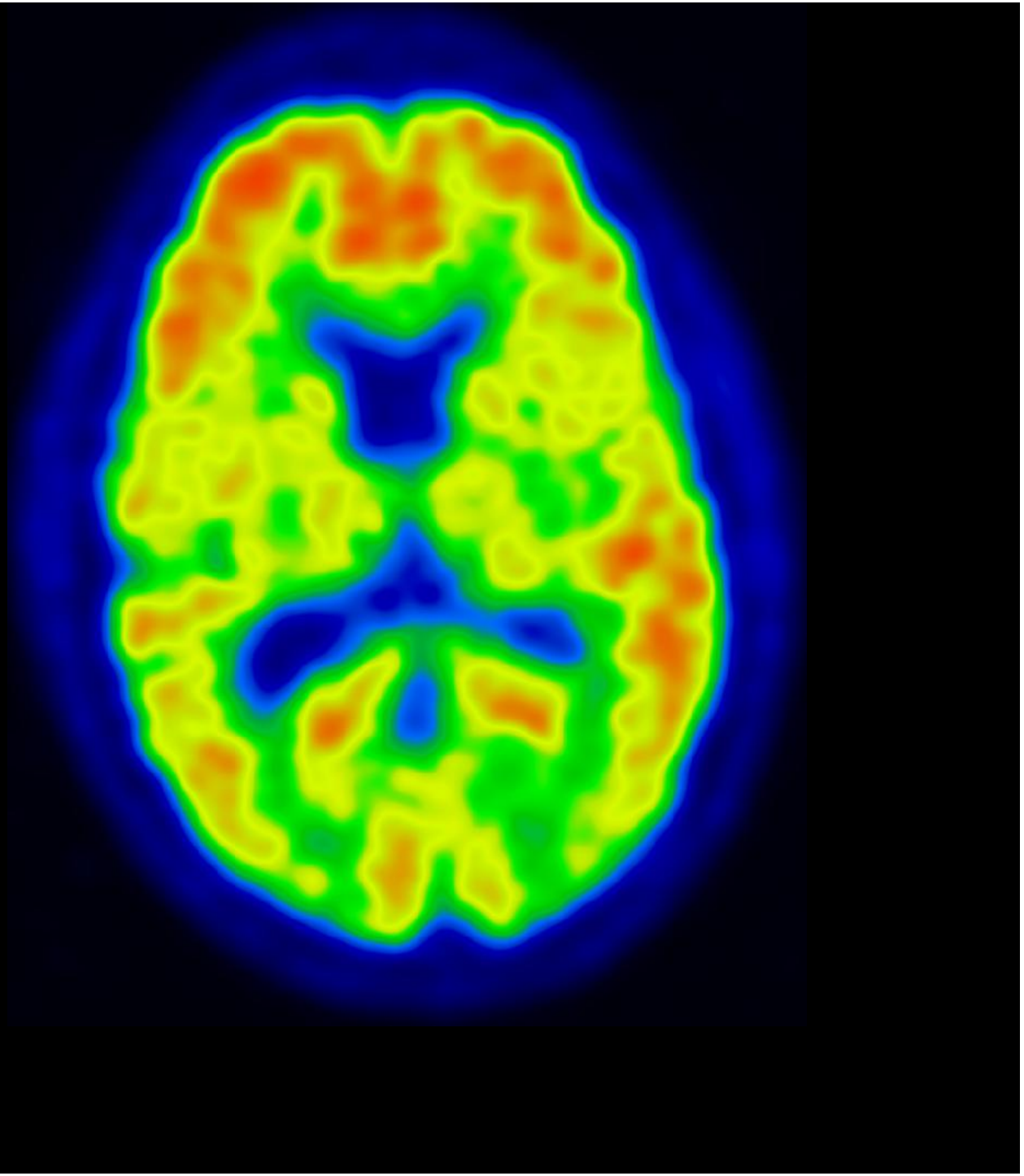


7/1/2010 FDG Scan
Progressive hypometabolism; Ratio 1.08



Cortical Regions	R/L	Mean
Parietal Association	R	4.12
	L	2.47
Temporal Association	R	3.92
	L	2.65
Frontal Association	R	0.95
	L	0.23
Occipital Association	R	2.95
	L	2.06
Posterior Cingulate	R	1.80
	L	1.62
Anterior Cingulate	R	-0.08
	L	-0.48
Medial Frontal	R	0.30
	L	-0.15
Medial Parietal	R	3.75
	L	2.46
Sensorimotor	R	1.47
	L	-0.09
Visual	R	1.73
	L	0.85
Caudate Nucleus	R	-0.14
	L	0.06
Cerebellum	R	-0.28
	L	0.18
Vermis	R	0.50
	L	0.18
Pons		0.06
Average Association	R	2.36
	L	1.33
Averaged Cerebral		1.32
Global Average		1.04

7/1/2010 PIB Scan
Progressive
Ratio 2.7



Dementia Due to AD

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McKhann et al: 2011

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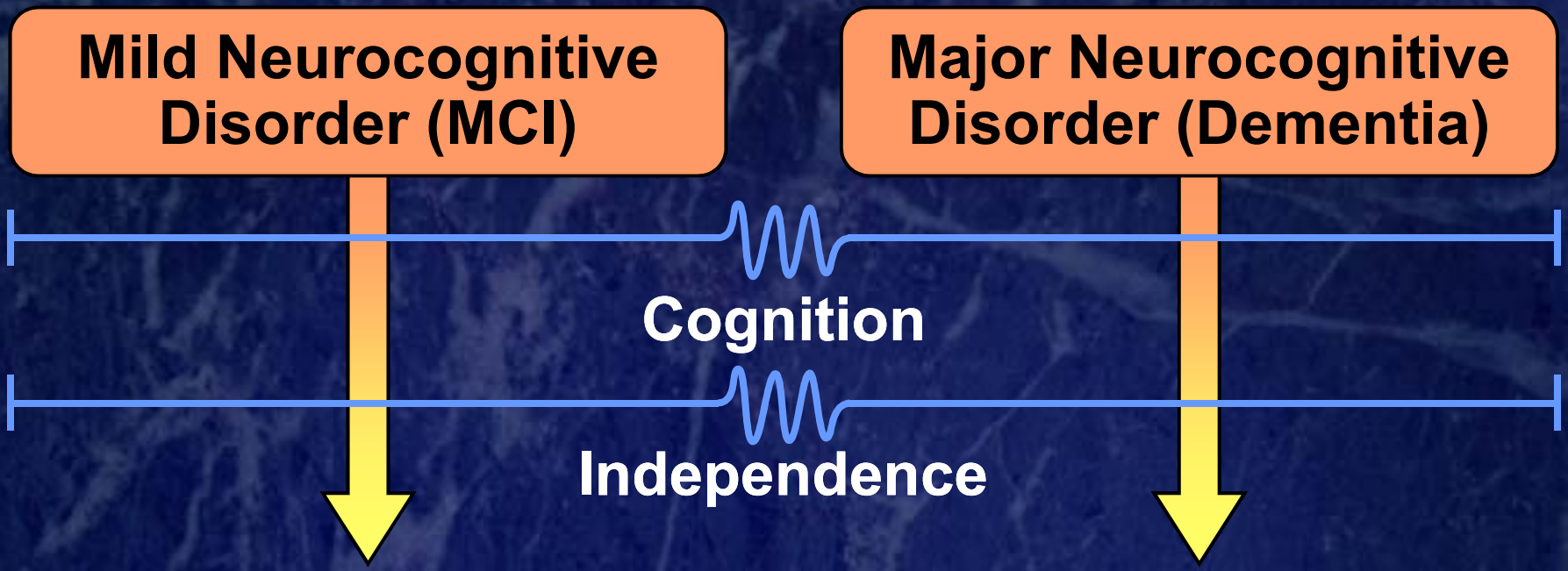
DSM-5

- Major neurocognitive disorder
  Probable AD



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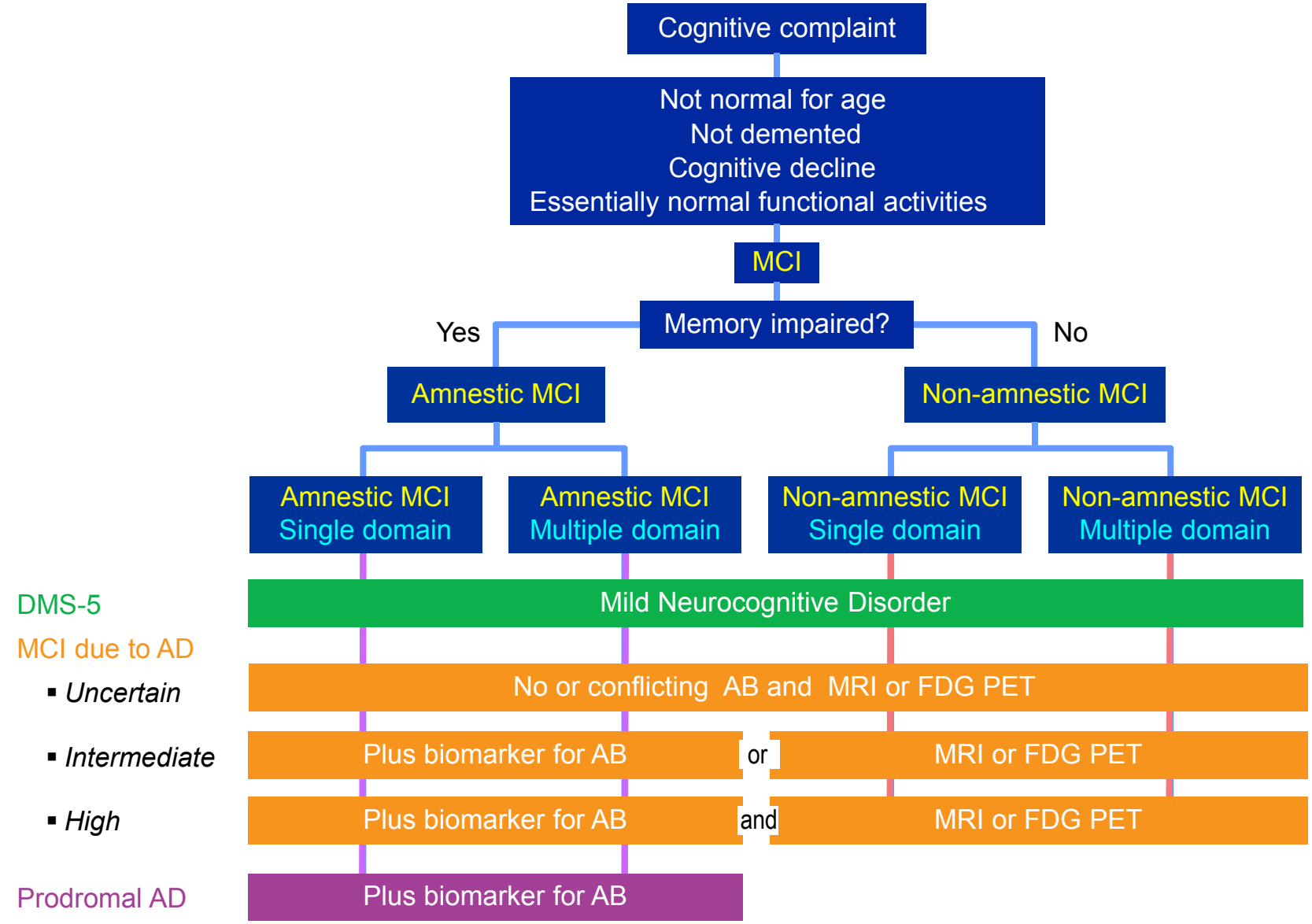

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Summary

- DSM-5
  - New terminology, but no conceptual deviations
  - MCI due to AD and Dementia due to AD can be subsumed
  - Adoption of terminology, e.g., Major NCD vs. Dementia to be determined