

Mild Cognitive Impairment: The Current Status

Ronald C. Petersen, Ph.D., M.D.
Mayo Clinic College of Medicine
Rochester, MN

Updates on Dementia
Stanford University

June 4, 2008



Disclosures

- Elan Pharmaceuticals: Chair SMC
- GE Healthcare: Consultant



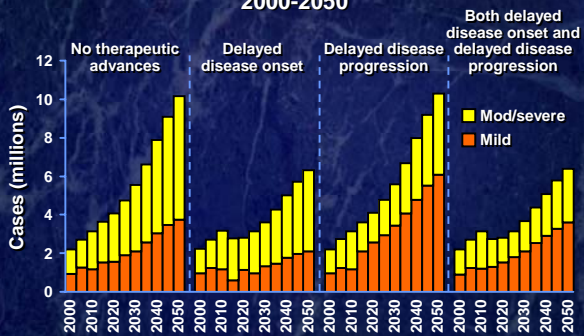
MILD COGNITIVE IMPAIRMENT

- Conceptual framework
- Epidemiology
- Clinical features
- Outcome
- Predictors
- Neuropathology
- Unresolved issues
- Clinical trials

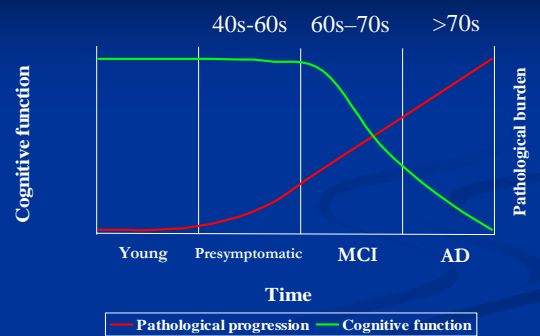
MILD COGNITIVE IMPAIRMENT

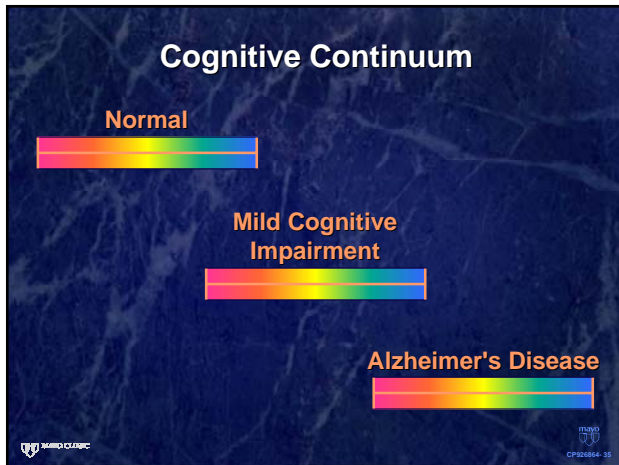
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Prevalence of Mild, Moderate/Severe and Total Cases of Alzheimer's Disease in the United States 2000-2050



Time Course: AD Pathology (in situ) & Clinical Expression





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Clinical Features

- ### MILD COGNITIVE IMPAIRMENT Original Criteria
- Memory complaint
 - Memory impaired for age
 - Normal general cognitive function
 - Normal activities of daily living
 - Not demented

Case

- ### 83 y/o Retired Priest
- Word finding difficulties
 - Mild memory concerns
 - ADL's preserved

83 Y/O PRIEST

• NEUROPSYCHOLOGY PROFILE

- VIQ 140
- PIQ 110
- FSIQ 129
- WORKING MEMORY 128
- VeMI 92
- ViMI 111

83 Y/O PRIEST

- LEARNING EFFIC 104
- DELAYED RECALL 71
- TRAILS A & B 50% ile
- BOSTON NAMING TEST 59/60
- FLUENCY 80% ile

34 months later

MILD COGNITIVE IMPAIRMENT Original Criteria

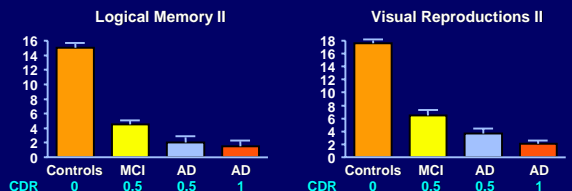
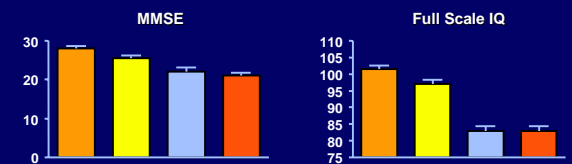
- Memory complaint
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ORIGINAL CRITERIA
Mild Cognitive Impairment
Clinical Characterization and Outcome

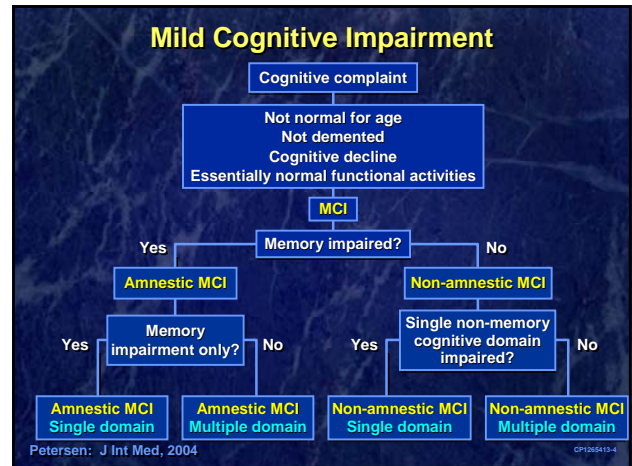
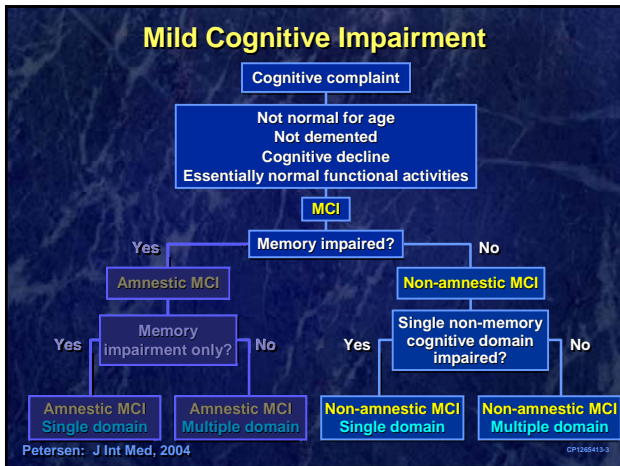
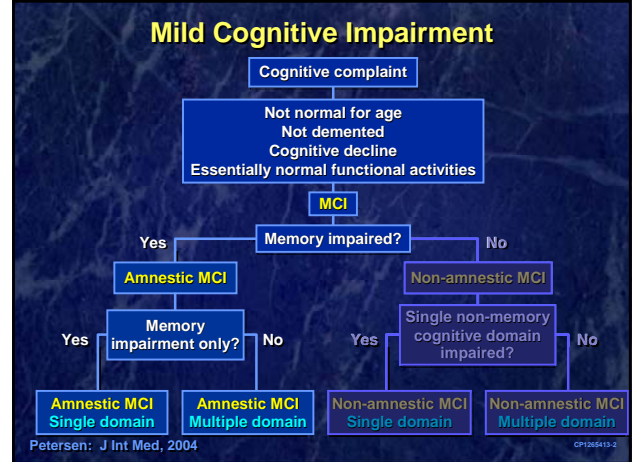
Ronald C. Petersen, PhD, MD; Glenn E. Smith, PhD; Stephen C. Waring, DVM, PhD; Robert J. Ivnik, PhD; Eric G. Tangalos, MD; Emre Kokmen, MD

Mild Cognitive Impairment Clinical Characterization and Outcome

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Eric G. Tangalos, MD; Emre Kokmen, MD



Current Classification Scheme for MCI



MCI Outcomes

		Etiology			
		Degen-erative	Vascular	Psychiatric	Med Cond
Clinical classification	Amnesic MCI	Single domain: AD		Depr	
	Multiple domain: AD, VCI, Depr				
Non-amnesic MCI	Single domain: FTD				
	Multiple domain: DLB, VCI				

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MCI Outcomes

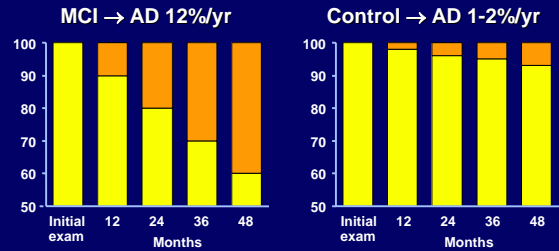
		Etiology			
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	Multiple domain: DLB, VCI				

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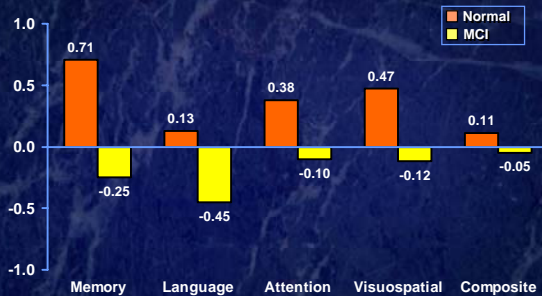
Mild Cognitive Impairment



Petersen RC et al: Arch Neurol 56:303-308, 1999

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MOANS Change Scores



MAYO CLINIC

CP127976-3

MCI Studies

Study	Number of Subjects	Age	MCI Prevalence	Progression Rate
Leipzig	980	75+	19.3%	8.7%
Italy	2830	65-84	16.1%	13.6%
India	960	67	15.0%	--
Vienna	581	75-76	24.0%	19.5%/10.7%
Cache County	206	65+	--	18.3%
Mayo	1969	70-89	16.3%	(10%)

MAYO CLINIC

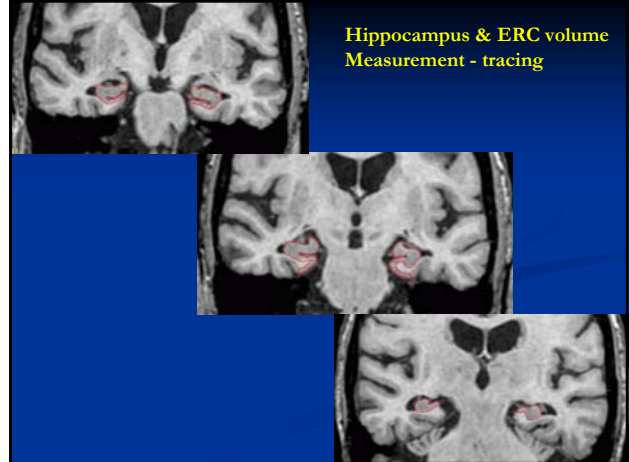
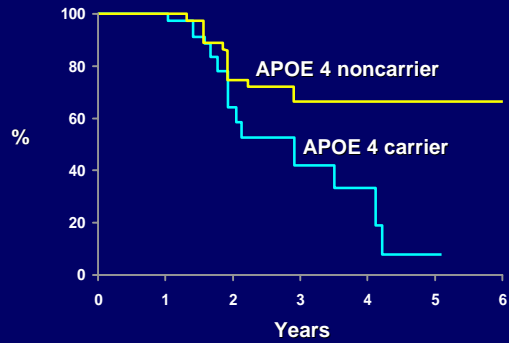
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MILD COGNITIVE IMPAIRMENT Predictors of Outcome

- Apo-E Status
+E4
- Clinical severity
- Hippocampal volumes
- ? FDG-PET
- ? CSF Biomarkers
- ? Amyloid imaging

MCI: Conversion to Dementia

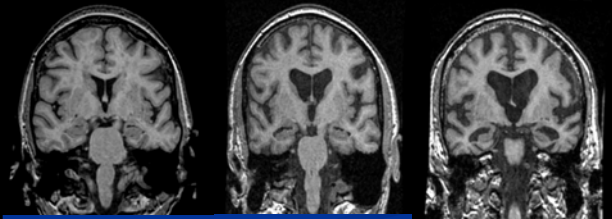


Atrophy and AD Stage

Control, 70 F

MCI, 72 F

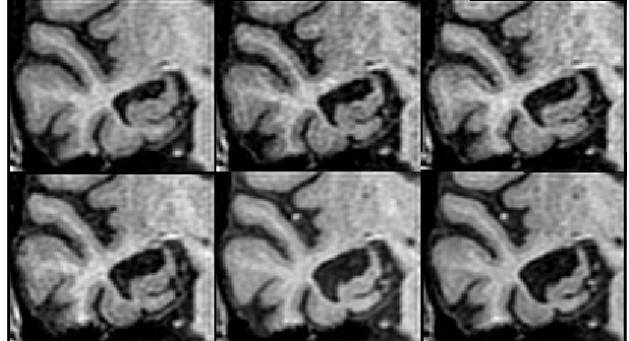
AD, 74 F



83 yo male
1993 MCI
MMSE=27

1996
MMSE=27

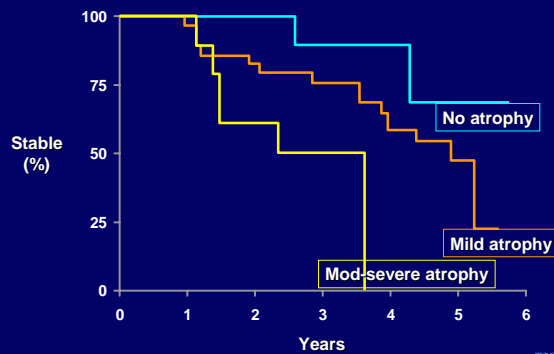
1997
MMSE=27



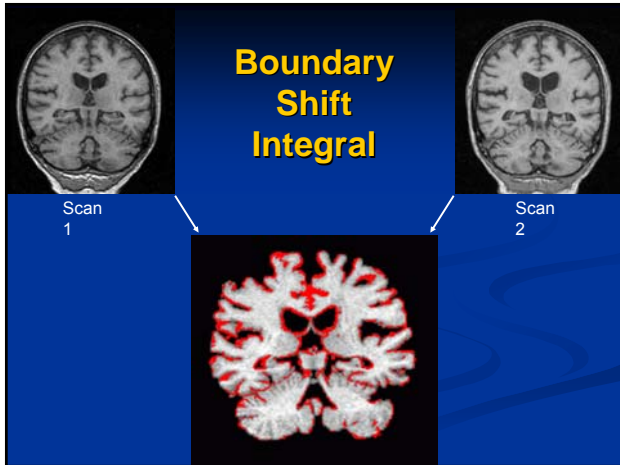
1999
MMSE=28

2001 converted to AD
MMSE=25

2003
MMSE=22

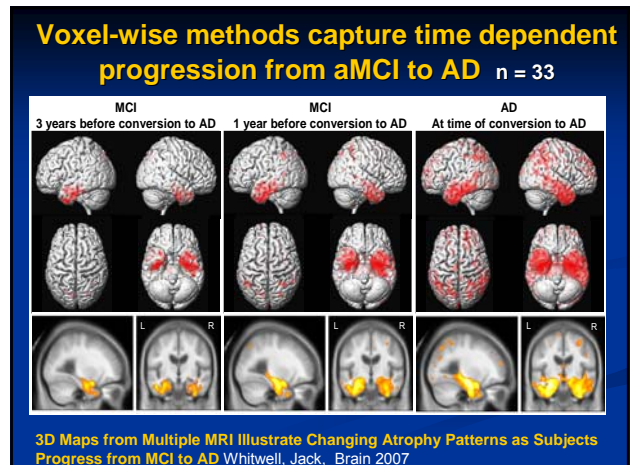
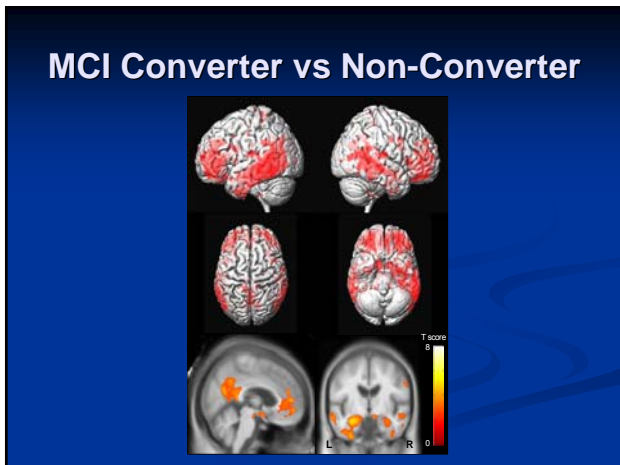
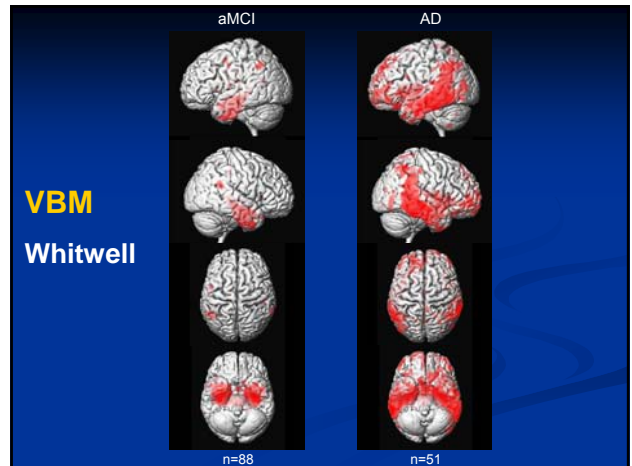
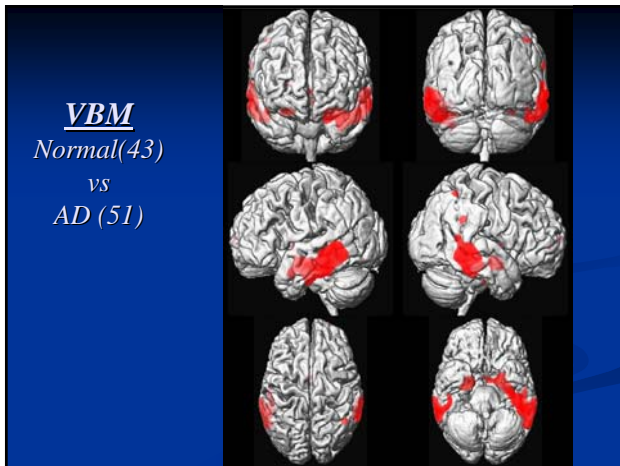


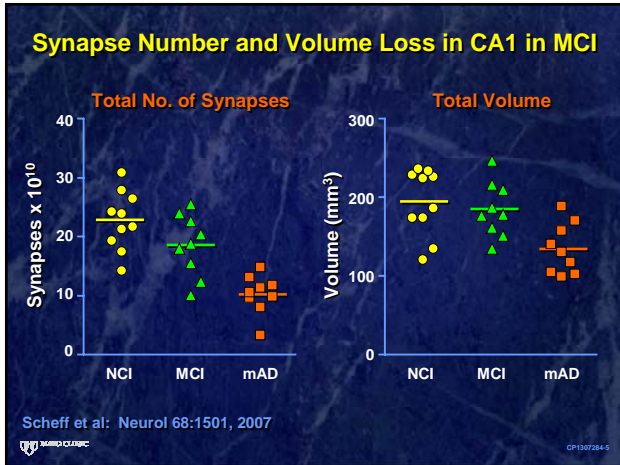
Boundary Shift Integral



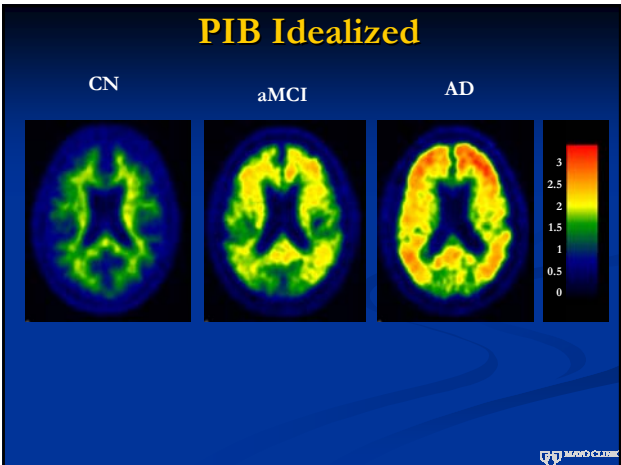
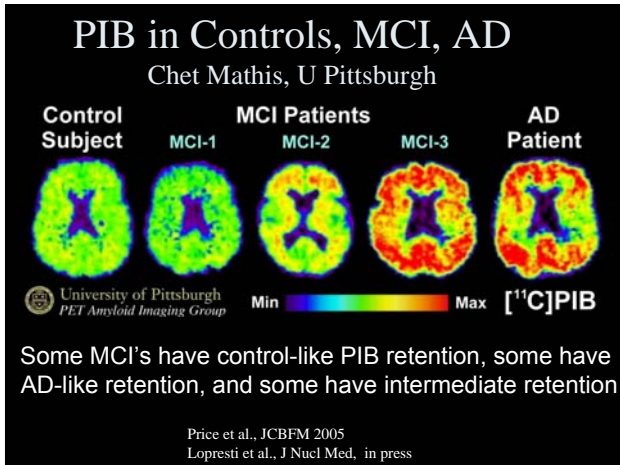
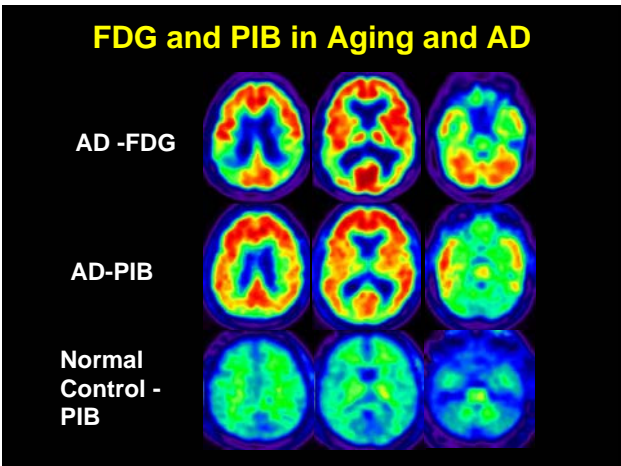
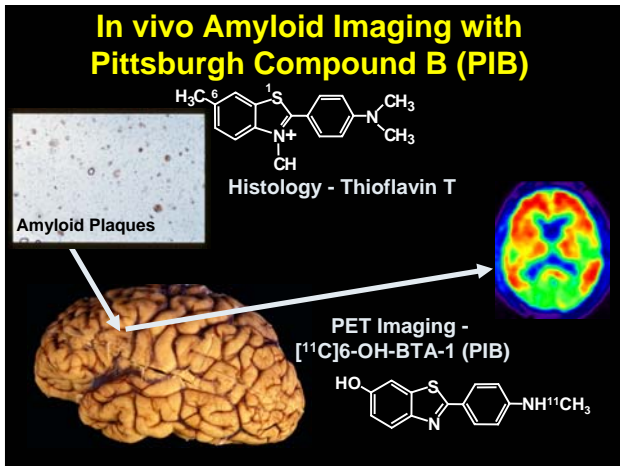
New Neuroimaging Research

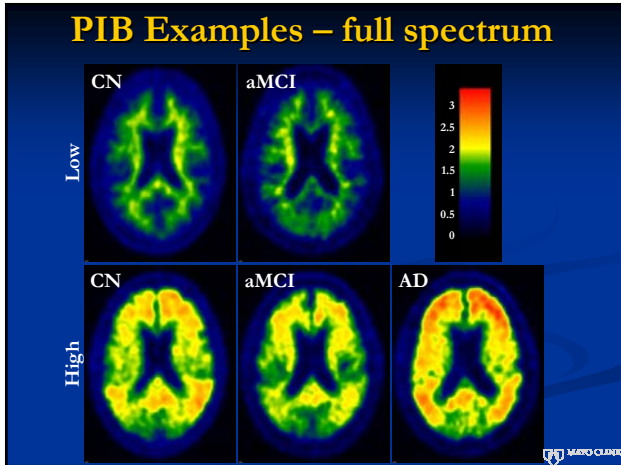
Voxel-based Morphometry



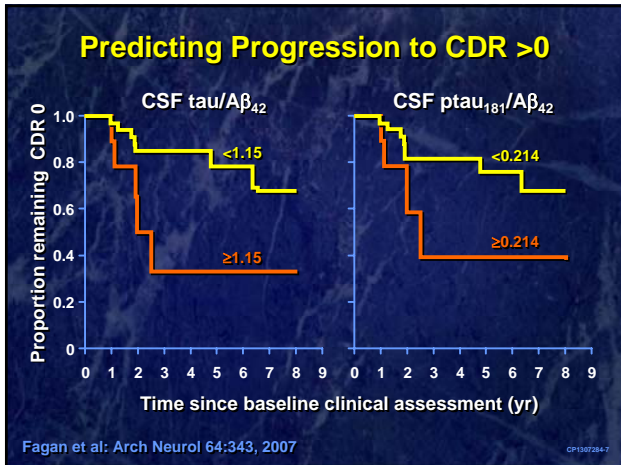
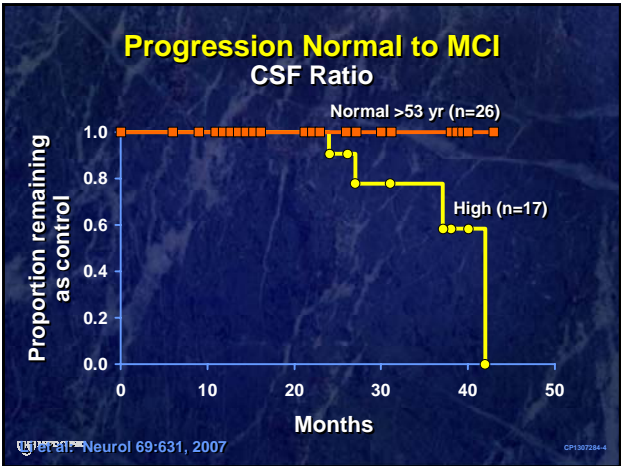
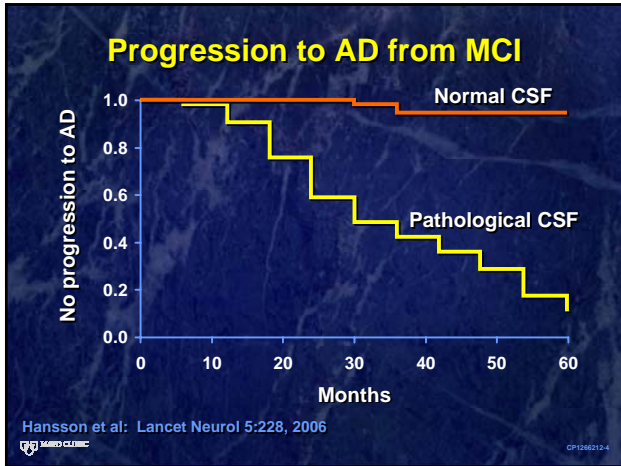


Molecular Neuroimaging





Cerebrospinal Fluid



Alzheimer's Disease Neuroimaging Initiative ADNI

ADNI

- Observational study of imaging and biomarkers
- Normals = 200
- MCI = 400
- AD = 200
- MRI, FDG PET, PiB, CSF, biomarkers
- 3 years

UMIN CLINICAL

ADNI Demographics

	Normal controls (n=229)	MCI (n=398)	AD (n=192)	P
Age, mean (SD)	76.4 (5.0)	75.3 (7.5)	75.8 (7.4)	0.15
Female (%)	48.0	35.4	47.4	0.002
Years of education, mean (SD)	15.6 (3.1)	16.0 (2.9)	14.7 (3.1)	<0.001
Apolipoprotein E e4: Positive (%)	26.6	53.5	65.6	<0.001

UMIN CLINICAL

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ADNI Cognitive Function

	Normal (n=229)	MCI (n=398)	AD (n=192)
Estimated premorbid verbal IQ	119.8 (9.0)	116.2 (9.7)	113.6 (9.9)
Memory			
Auditory verbal learning			
Trials 1-5 correct	43.3 (9.09)	30.7 (9.03)	23.2 (7.70)
Delayed recall (%)	65.8 (27.6)	32.1 (31.4)	11.3 (21.9)
Language			
Boston Naming	27.9 (2.3)	25.5 (4.1)	22.3 (6.2)
Category fluency total	34.6 (8.1)	26.7 (7.5)	20.3 (7.5)
Executive function			
Trail A time	36.5 (13.2)	44.8 (22.8)	68.2 (36.8)
Trail B time	89.2 (44.3)	130.5 (73.5)	199.6 (86.8)
Digit symbol correct	45.7 (10.2)	36.9 (11.1)	26.7 (12.9)
Visuospatial ability			
Clock draw: Copy	4.86 (0.43)	4.65 (0.68)	4.31 (1.00)
Attention			
Digit span: Forward	8.78 (1.99)	8.22 (2.01)	7.54 (1.94)
Digit span: Backward	7.21 (2.16)	6.17 (2.2)	4.96 (1.83)

UMIN CLINICAL

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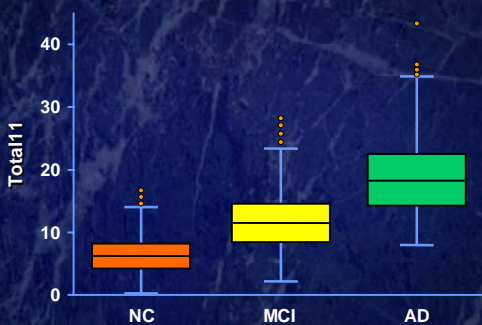
ADNI Cognitive Function

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Visuospatial ability			
Clock draw: Copy	4.86 (0.43)	4.65 (0.68)	4.31 (1.00)
Attention			
Digit span: Forward	8.78 (1.99)	8.22 (2.01)	7.54 (1.94)
Digit span: Backward	7.21 (2.16)	6.17 (2.2)	4.96 (1.83)

UMIN CLINICAL

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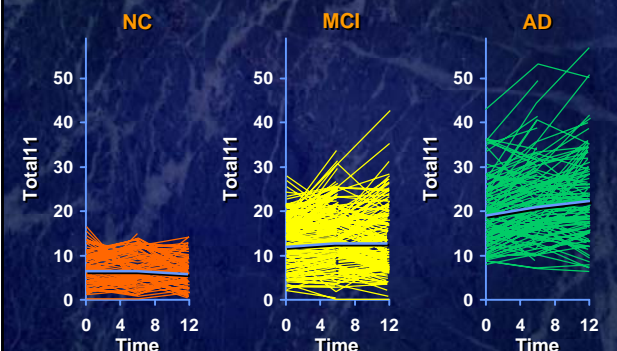
ADAS-Cog Baseline



UMIN CLINICAL

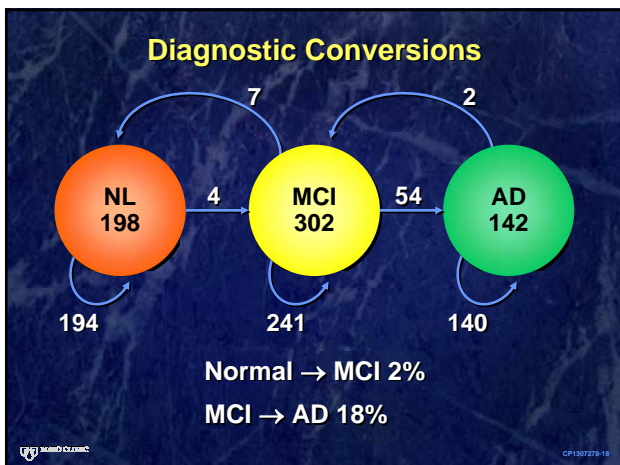
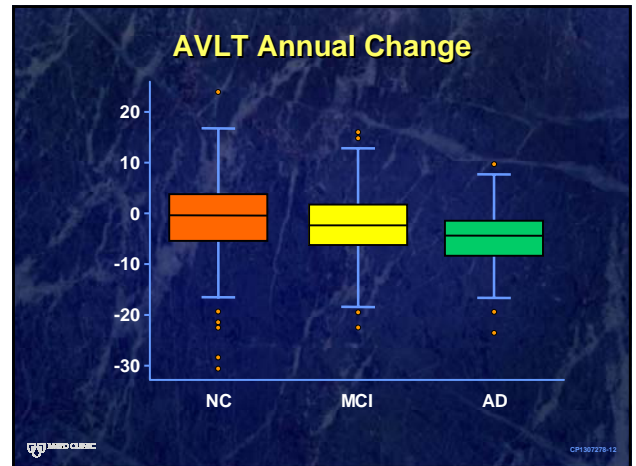
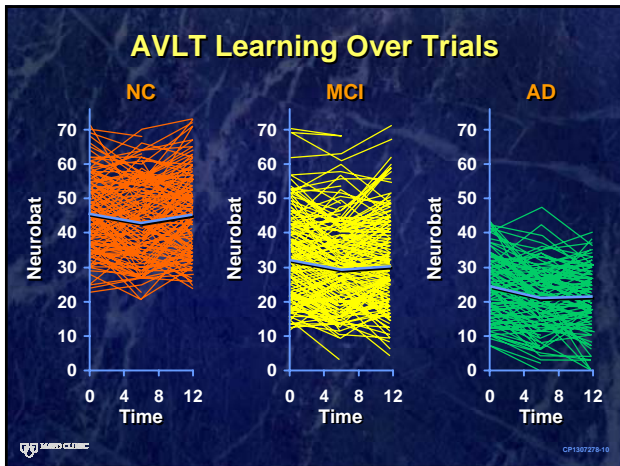
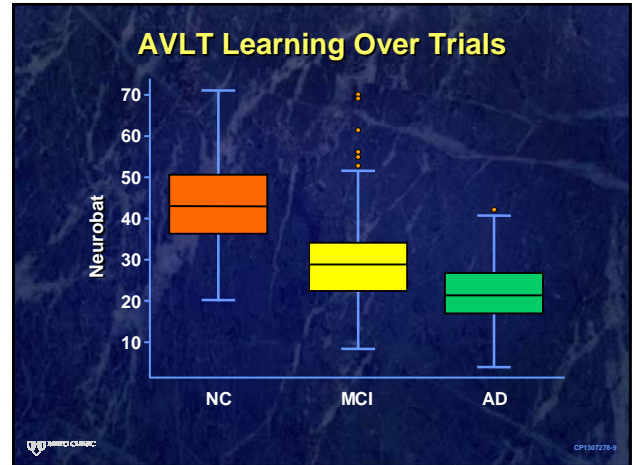
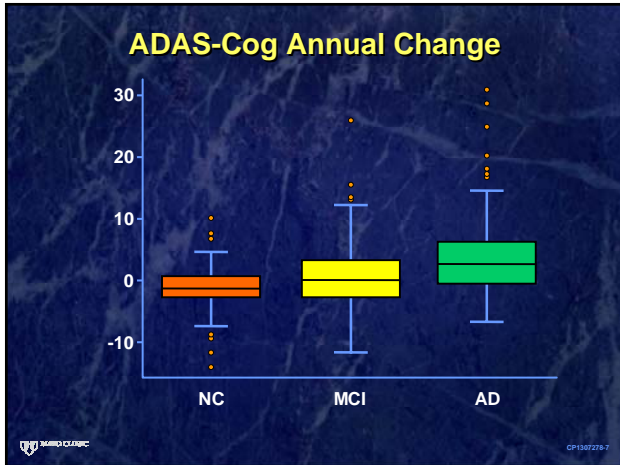
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ADAS-Cog



UMIN CLINICAL

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Amnesic MCI Baseline Data

	ADCS	ADNI	UDS	MCSA
No.	259	398	2,128	241
Age	72.9 (7.6)	75.3 (7.5)	76.1 (9.6)	82.0 (5.2)
Educ	14.7 (3.1)	16.0 (2.9)	14.5 (3.5)	13.1 (3.5)
MMSE	27.3 (1.8)	27.0 (1.8)	26.9 (2.7)	25.4 (2.5)
CDR, SoB	1.9 (0.8)	1.6 (0.9)	1.4 (1.2)	0.9 (1.0)
ADAS-Cog	11.0 (4.2)	11.5 (4.4)	-	-

Amnesic MCI First 12-Month Change

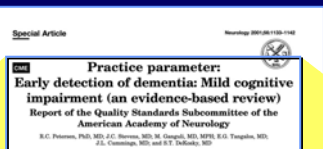
	ADCS	ADNI	UDS	MCSA
MMSE	-0.3 (2.3)	-1.0 (2.0)	-0.6 (2.8)	-0.1 (3.1)
CDR, SoB	+0.4 (1.3)	+0.7 (1.3)	+0.5 (1.4)	+0.4 (1.1)
ADA-Cog	+0.6 (4.1)	+1.0 (4.5)	—	—

MMSC

CP126920-1

Breadth of MCI Research

- Epidemiology
- Clinical
- Imaging
- Biomarkers
- Mechanism of disease
- Neuropathology
- Clinical trials



Practice Parameter: Early Detection of Dementia: Mild Cognitive Impairment (an Evidence-Based Review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

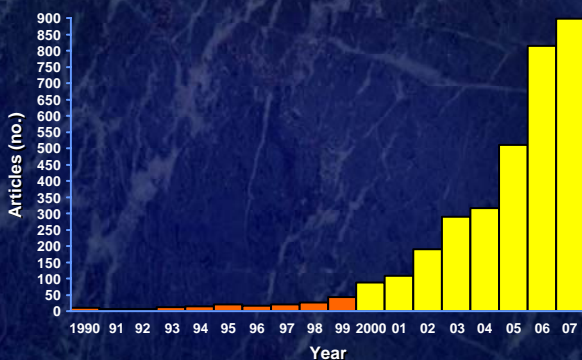
Ronald C. Petersen, PhD, MD; J. C. Stevens, MD; M. Ganguli, MD, MPH; E. G. Tangalos, MD; J. L. Cummings, MD; and S. T. DeKosky, MD

CP118052-8

AAN PRACTICE PARAMETER DETECTION SUMMARY RECOMMENDATIONS

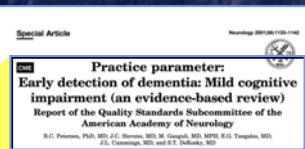
- **GUIDELINE**
 - PATIENTS WITH A MILD COGNITIVE IMPAIRMENT SHOULD BE **RECOGNIZED AND MONITORED** FOR A COGNITIVE AND FUNCTIONAL DECLINE DUE TO THEIR INCREASED RISK FOR SUBSEQUENT DEMENTIA

Publications on MCI



MMSC

CP126923-4



Practice Parameter: Early Detection of Dementia: Mild Cognitive Impairment (an Evidence-Based Review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

Ronald C. Petersen, PhD, MD; J. C. Stevens, MD; M. Ganguli, MD, MPH; E. G. Tangalos, MD; J. L. Cummings, MD; and S. T. DeKosky, MD

CP118052-8

Mild Cognitive Impairment Should Be Considered for DSM-V

Ronald C. Petersen, PhD, MD, and John O'Brien, DM

ABSTRACT

Mild cognitive impairment is a topic of great activity from both clinical and research perspectives. It represents a transitional state between the cognitive changes of aging and the earliest clinical manifestations of dementia. We present a case for its inclusion in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed; DSM-V) based on clinical, outcome, epidemiological, neuroimaging, and pathophysiological data. The strongest case for inclusion can be made for the amnesic subtype, which is likely a clinical precursor of Alzheimer's disease. Arguments are presented as to why mild cognitive impairment can be considered as an entity distinct from normal aging and from clinically probable Alzheimer's disease and why it deserves consideration as a separate construct. In many respects, mild cognitive impairment fulfills criteria for inclusion more adequately than many other conditions currently codified in DSM-IV. Future research directions to help clarify some of the remaining uncertainties are proposed. *J Geriatr Psychiatry Neurol* 2006;19:147-154

Keywords: mild cognitive impairment; Alzheimer's disease; dementia; DSM-V

Petersen and O'Brien: *J Geriatr Psych and Neurol* 19:147, 2006



CP1266212-9

So, is MCI too late?



EDITORIAL

Is amnesic mild cognitive impairment always AD?

William Jagust, MD

Address correspondence and reprint requests to Dr. William Jagust, Division of Geriatrics, University of California, Berkeley, CA 94720-3280; jagust@berkeley.edu

Neurology 2008;70:502-503

It has long been recognized that Alzheimer disease (AD), by nature a slowly progressive degenerative illness, must pass through a prodromal period during which symptoms are mild or barely detectable despite active disease. Prompted by its ties to the molecular pathogenesis of AD that offer hope for treatment, techniques like neurophysiology and brain imaging have been refined to detect evidence of AD in mildly affected individuals in order to identify those who might benefit most from early intervention. This approach has culminated in the identification and definition of the syndrome of mild cognitive impairment (MCI).^{1,2} MCI has further been divided into amnesic (amnestic) MCI, generally believed to represent preclinical AD, and non-amnesic MCI, which is thought to represent a spectrum of conditions including MCI, DLB, and PSP.

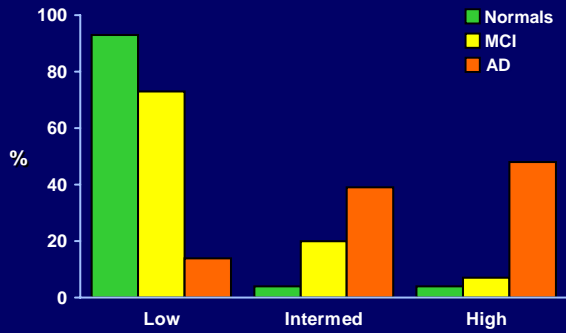
By using a whole-brain, voxel-based approach to MRI data analysis, the authors were able to show that patients with amCI who progressed to AD in a short period of time (average of 18 months) demonstrated widespread cortical atrophy at baseline compared to controls in many areas of association and limbic cortex known to be affected by AD. In contrast, patients with amCI who were stable over a long time period (almost 4 years) showed no such atrophy. These results directly and incisively address a number of key controversies in the MCI arena.

Jagust: *Neurology* 70:502-2008



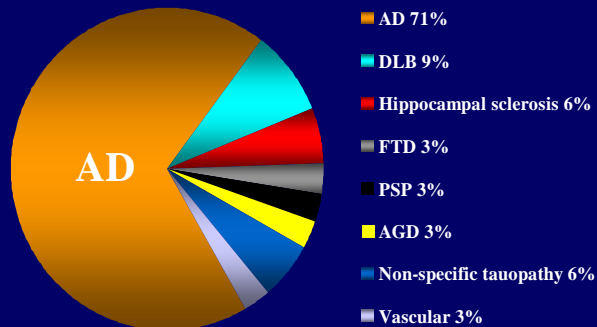
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NIA-REAGAN



CP1183543-12

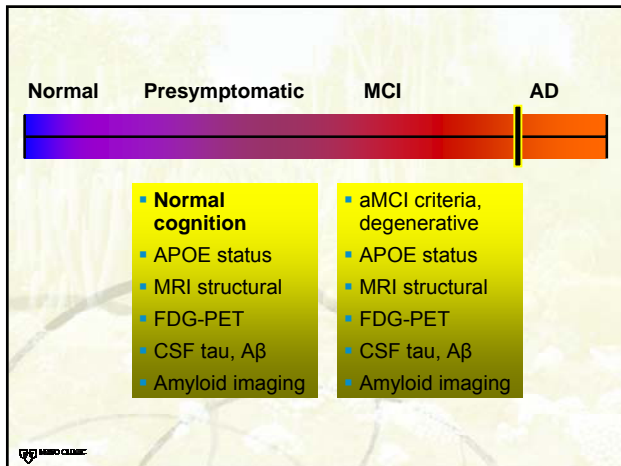
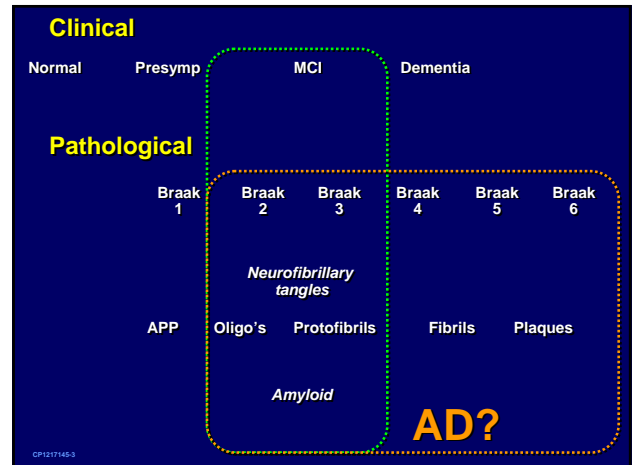
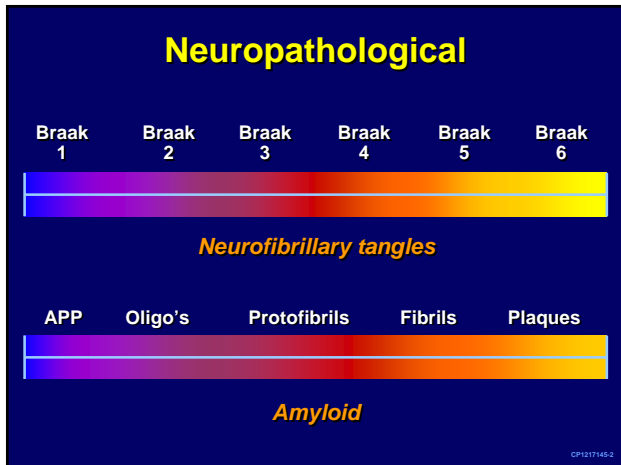
Pathological Outcome of MCI



Clinical



CP1217145-1



- ## MCI SUMMARY
- **USEFUL CONCEPT**
 - **CRITERIA AVAILABLE**
 - CLINICIAN INVOLVED
 - ALGORITHM
 - **OUTCOME DEPENDENT**
 - **NEUROPATH TRANSITIONAL**
 - **CLINICAL TRIALS FEASIBLE**

- ## MAYO ALZHEIMER'S DISEASE RESEARCH CENTER
- | | |
|---|---|
| <ul style="list-style-type: none"> • Rochester <ul style="list-style-type: none"> – Brad Boeve – David Knopman – Eric Tangalos – Joe Parisi – Cliff Jack – Walter Rocca – Bob Ivnik – Glenn Smith – Rosebud Roberts – Shane Pankratz – Yonas Geda | <ul style="list-style-type: none"> • Jacksonville <ul style="list-style-type: none"> – Steve Younkin – Dennis Dickson – Neill Graff-Radford – Shu-Hui Yen – Todd Golde – Mike Hutton – John Lucas – Tanis Ferman – Floyd Willis |
|---|---|
- mayo