Amnestic and Non-amnestic MCI Are Distinct Entities: Fact or Fiction?

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Disclosures: There is not a 1:1 correspondence between the slides in this presentation and those in the handout.

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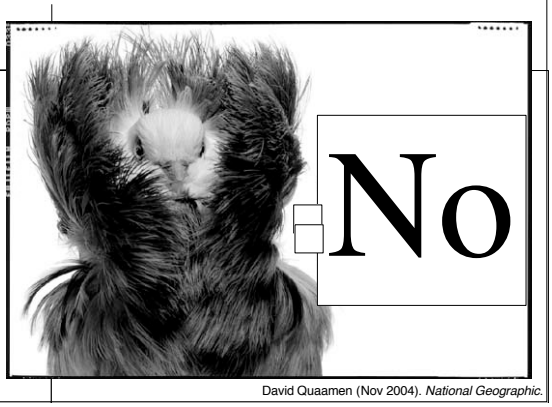
David Quaamen (Nov 2004). *National Geographic.*



David Quaamen (Nov 2004). *National Geographic.*

Amnestic and Non-amnestic MCI Are Distinct Entities: Fact or Fiction?

"Is MCI a clinical entity, a pathological entity, or both?...It might be most productive to keep these entities separate."

- Petersen et al. (2009). *Arch Neurol, 66, 1447-55.*

Heuristic Analogy

Cortical vs. Subcortical Dementia

- Reliance on profile analysis
  - Recall vs. recognition, letter vs. category fluency, etc.
- Experimental neuropsychological distinctions
  - Implicit vs. explicit memory, cortical disconnectivity, etc.
- Qualitative or process approach distinctions
  - Intrusion errors, naming errors, cognitive asymmetries
- Well-established brain-based distinctions (eg, AD vs. HD)

Recent ADNI Study

Variation of Historical Criteria

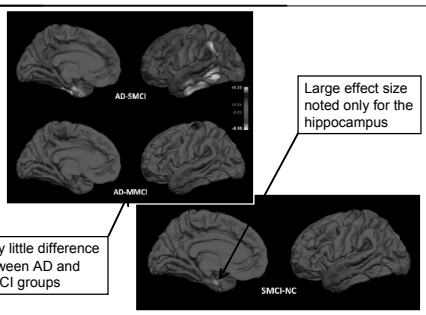
- Single Domain Amnestic MCI (SMCI; *n* = 79)
  - Delayed recall on one story (LM II) falls some unspecified level (ie, about 1.5 – 2 SDs) below education-corrected norms (Petersen et al. 2005, *NEJM*)
  - Global cognitive functioning (MMSE) intact (defined as ≥ 24/30)
  - CDR = 0.5

Variation of Typical Criteria

- Multiple Domain Amnestic MCI (MMCI; *n* = 96)
  - Fulfills criteria above for SMCI
  - Requires any other test to fall 2 SDs below normative sample (no age-, education-, sex- or ethnicity-based corrections to these data)

Fennema-Notestine et al. (2009). *Human Brain Mapping.*

Recent ADNI Study



Large effect size noted only for the hippocampus

Very little difference between AD and MMCI groups

Fennema-Notestine et al. (2009). *Human Brain Mapping.*

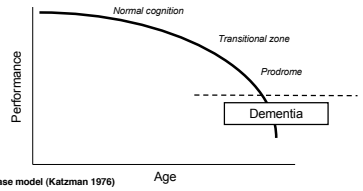
Assumptions

(aka Suspension of Disbelief)

- ✓ Validity of categorical approach
  - eg, Multi-domain MCI is not dementia?
- ✓ Studies adequately sample both cognitive *and* functional domains
- ✓ Brain-based distinctions are evident
  - Between MCI and dementia
  - Between MCI subtypes
  - Underlying pathologies support categorical approach

Introduction

- ✓ Neurodegenerative conditions of late life (e.g., AD, PD, DLB) involve slowly accruing neuron losses that evolve over some years before symptoms occur



Chronic disease model (Katzman 1976)

Definitions of Dementia

- ✓ NINCDS-ADRDA (McKhann et al. 1984)
  - Probable Alzheimer's disease
  - Possible Alzheimer's disease
  - Definite Alzheimer's disease
- ✓ Diagnostic and Statistical Manual of Mental Disorders (DSM-IV 1994)

Diagnosis of Dementia: Practice Recommendations

http://www.aan.com/professionals/practice/guidelines.cfm

- ✓ NINCDS-ADRDA and DSM criteria for AD are reliable and should be used routinely
- ✓ Structural neuroimaging initially is appropriate
  - ✓ To identify undetected pathology (neoplasms, hematomas, NPH)
- ✓ Depression is a common comorbidity in patients with dementia and should be screened for
- ✓ B_{12} deficiency and hypothyroidism are both common in the elderly and levels should be routinely assessed

Knopman et al. (2001). *Neurology, 56*, 1143-53.

Diagnosis of Dementia: Recommendations For Future Research

http://www.aan.com/professionals/practice/guidelines.cfm

- ✓ Memory disorder should not be required of definition
  - ✓ **Not necessarily part of the initial presentation of VaD, DLB, & FTD**
- ✓ Explicit recognition of the pathologic overlap of AD, VaD, and DLB in the diagnostic criteria might lead to a more realistic approach to clinical diagnosis
- ✓ As we move into an era of earlier recognition of cognitive impairment, clarification of the distinctions between no cognitive impairment, mild cognitive impairment, and early dementia is needed

Knopman et al. (2001). *Neurology, 56*, 1143-53.

Diagnosis of Dementia: Recommendations For Future Research

http://www.aan.com/professionals/practice/guidelines.cfm

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Knopman et al. (2001). *Neurology, 56,* 1143-53.

Revising the NINCDS-ADRDA & DSM Criteria

A. General MCI criteria
1. Person is neither normal nor demented
2. Cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self/informant in conjunction with objective cognitive deficits
3. ADL are preserved and complex iADL are either intact or mildly impaired

B. Supportive features
1. Neuroimaging
2. Biomarkers
3. Genetics

Mild cognitive impairment is useful both clinically and as a research entity, and is a concept encompassing much more than a preclinical state of AD.

Winblad et al. (2004). *J Int Med, 256,* 240-6.

Revising the NINCDS-ADRDA & DSM Criteria

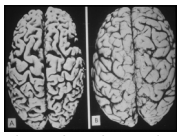
A. Core diagnostic criteria
1. Gradual and progressive change in memory (> 6 mos.)
2. Impaired episodic memory on objective testing
3. Episodic memory impairment can be isolated or not

B. Supportive features
1. Presence of MTL atrophy
2. Abnormal CSF biomarkers (low $A\beta_{1-42}$; increased tau)
3. Specific pattern on functional neuroimaging with PET
4. Proven AD autosomal dominant mutation within the immediate family

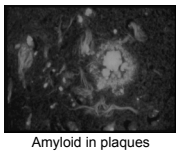
Criteria would eliminate MCI construct and its arbitrary binary outcome (eg, conversion vs. no conversion) in the clinical characterization process

Dubois et al. (2007). *Lancet Neurol, 6,* 734-746.

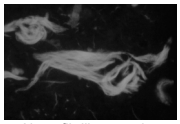
Neuropathologic Hallmarks Of AD



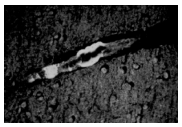
Brain atrophy and neuron loss



Amyloid in plaques



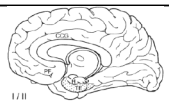
Neurofibrillary tangle



Cerebrovascular amyloid

Neuropathologic Hallmarks Of AD: Evolution of Neurofibrillary Changes

Stages I / II (pre AD)



Neurofibrillary changes limited to entorhinal and transentorhinal (TE) regions

Stages III / IV (early AD)

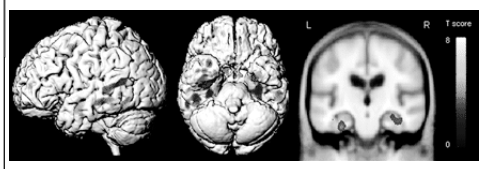
Severe involvement of TE regions; moderate changes in hippocampus; mild changes in some cortical association areas

Stages V / VI (clinical AD)

Cortical association areas severely involved; only primary sensory and motor areas spared

Braak & Braak

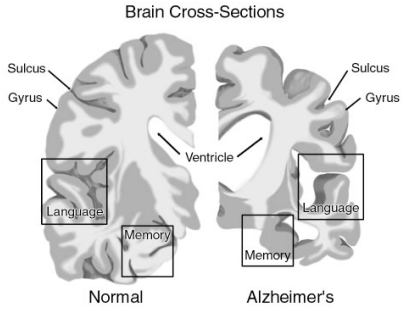
Neuropathologic Hallmarks Of AD:
Patterns of Gray Matter Loss Associated with High Tau Burden



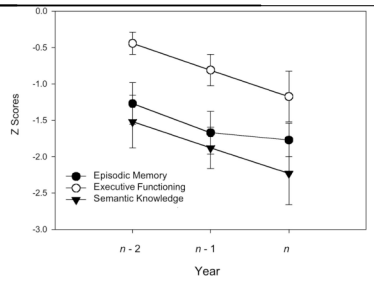
Braak stages 0 - IV

Whitwell et al. (2008). *Neurology.*

Gross Anatomic Changes In Alzheimer's Disease



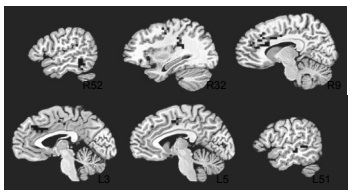
Profile of Cognitive Impairment in Prodromal AD



Mickes et al. (2007). *Neuropsychology.*

BOLD Response to Object Naming in AD Risk

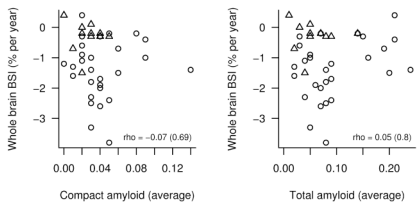
Non-demented APOE ε4 adults show increased frontal and posterior activity compared to ε3 adults



Warm colors: ε4 > ε3

Wierenga et al. (In Press). *NeuroImage.*

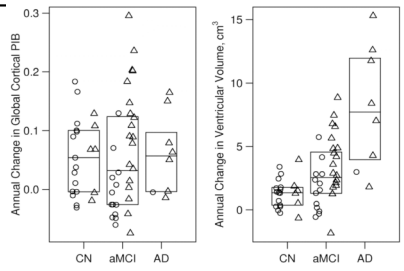
Neuropathologic Hallmarks Of AD:
β-Amyloid Not Associated with Brain Atrophy



"Rate of brain volume loss is not determined by the amount of insoluble Aβ in the gray matter."

Josephs et al. (2008). *Ann Neurol.*

PET Imaging: PIB



"Clinical symptoms are coupled to neurodegeneration not amyloid deposition."

Jack et al. *Brain* 2009 132:1355-1365.

PET Imaging: PIB

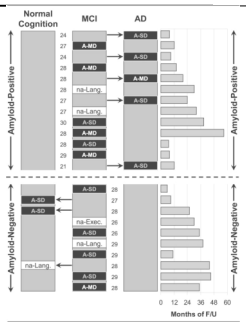
Table. Data by Amyloid Positivity Status

Characteristic	Amyloid-Positive (n=9)	Amyloid-Negative (n=29)	*P* Value[a]
Age, mean (SD), y	74.2 (5.4)	72.4 (8.0)	.65
Men, No. (%) of participants	4 (44)	9 (31)	.23
African American, No. (%) of participants	0	3 (10)	.57
Educational level, mean (SD)	14.3 (2.6)	14.9 (2.6)	.57
APOE ε4 allele positive, No. (%)	2 (22)	1 (4)	.13
GDS, mean (SD)	1.56 (2.3)	1.45 (1.6)	.77
IQ score (WTAR predicted), mean (SD)	108.2 (5.3)	108.1 (10.0)	.69
MMSE score, mean (SD)	28.9 (0.8)	28.5 (1.5)	.65
Clock drawing, mean (SD)	14.6 (0.5)	13.9 (2.0)	.57
Boston 12 score, mean (SD)	29.1 (1.2)	28.2 (1.9)	.22
Rey/Osterrieth Complex Figure score,[b] mean (SD)			
Copy	20.6 (2.4)	20.5 (1.5)	.78
Immediate	17.4 (3.1)	16.8 (3.6)	.92
Delayed	15.8 (3.7)	15.9 (4.0)	.66
Category fluency score, mean (SD)	20.2 (5.9)	20.1 (3.9)	.97
Letter fluency score, mean (SD)	40.7 (14.1)	43.2 (14.5)	.74
Word list delayed recall score,[b] mean (SD)	5.5 (1.1)	5.9 (1.5)	.02
Digit span forward score, mean (SD)	6.9 (0.9)	6.7 (1.3)	.65
Digit span backward score, mean (SD)	4.6 (1.5)	5.0 (1.3)	.57
Trail-making Test score, parts A and B, mean (SD)	3.1 (2.1)	2.3 (0.8)	.19
WAIS III Letter-number sequencing score, mean (SD)	8.9 (3.1)	10.0 (2.6)	.15
N-back task score, mean (SD)	37.0 (16.5)	31.6 (11.8)	.26
Stroop incongruent-neutral conditions, ms, mean (SD)	119.2 (47.2)	85.2 (64.0)	.13
Sensorimotor speed, ms, mean (SD)	257.0 (28.0)	269.3 (44.3)	.57
Conceptual comparison, ms, mean (SD)	785.3 (163.2)	745.1 (166.7)	.52
Perceptual comparison, ms, mean (SD)	781.5 (222.4)	749.3 (207.9)	.75
Hayling incongruent-congruent conditions, ms, mean (SD)	2043.3 (2695)	1681 (1740) med=1290	.89
Median	1010	1350	.89

Abbreviations: APOE ε4, apolipoprotein E ε4; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; WAIS III, Wechsler Adult Intelligence Scale III; WTAR, Wechsler Test of Adult Reading.
[a] Nonparametric tests were used for continuous variables, and the Fisher exact test was used for categorical variables.
[b] These tests were not administered to early participants, so the sample size is smaller (5 amyloid-positive and 23 amyloid-negative participants).

Aizenstein et al. 2008. *Arch Neurol.*

PET Imaging: PIB



Wolk et al. 2009. *Ann Neurol.*

Mild Cognitive Impairment

http://www.aan.com/professionals/practice/guidelines.cfm

Suggested Criteria

- ✓ Memory complaint, preferably corroborated by an informant
- ✓ Objective memory impairment
- ✓ Normal general cognitive function
- ✓ Intact activities of daily living
- ✓ Not demented

Petersen et al. (2001). *Neurology, 56,* 1133-42.

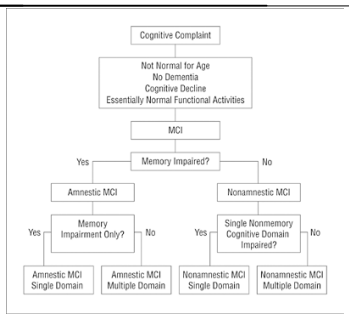
Mild Cognitive Impairment

Representative Example

- ✓ Memory complaint corroborated by informant
- ✓ One paragraph of *WMS-R* Logical Memory II
  - 0-7 years of education ≤ 2
  - 8-15 years of education ≤ 4
  - 16 or more years of education ≤ 8
- ✓ MMSE ≥ 24 - 30
- ✓ CDR = 0.5
- ✓ Not demented

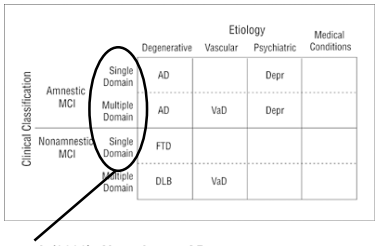
Petersen et al. (2005). *NEJM, 352,* 2379-88.

Subtypes of MCI



Petersen & Morris (2005). *Arch Neurol.*

Proposed Etiologies of Subtypes of MCI



Busse et al. (2006). *Neurology*. - AD was most common outcome in all but one MCI subtype.

Petersen & Morris (2005). *Arch Neurol.*

Cognitive Impairments in MCI

Table 3 *Distribution of 90 individuals with mild cognitive impairment (revised criteria)[6] by type of deficit*

Deficit	%
Memory only	30
Visuospatial only	11
Executive only	19
Memory and visuospatial	14
Memory and executive	7
Visuospatial and executive	9
Memory, visuospatial, and executive	10

"This illustrates that AD need not begin as a memory problem."

Storandt et al. (2006). *Neurology.*

Review of Cognitive Declines in Preclinical AD

Neuropsychological studies	Percent of studies significant
General cognitive	38%
Attention	71%
Processing speed	43%
Verbal learning	57%
Verbal memory	50%
Visual learning	29%
Visual memory	28%
Working memory	12%
Language	33%
Motor speed	17%
Executive functioning	44%
Visuospatial	26%
Praxis	17%
Olfactory	100%

Twamley, Ropacki, & Bondi (2006) *J Int Neuropsych Soc.*

Difficulties With MCI Diagnosis

- ✓ Defining objective memory impairment
  - ✓ Increasing threshold from -1 to -1.5 SD reduced diagnosis by half in MCI subjects (Ganguli et al 2004, *Neurology*)
  - ✓ -1 SD (not -1.5 SD) had highest predictive power for AD and for normative studies' suggested cutoffs (Busse et al 2006; Heaton et al 2005)
  - ✓ No cutoff: clinical decision based on memory impairment "out of proportion to their other cognitive domains" (Jicha et al. 2006)
    - ✓ Rests on assumption that an individual's abilities are roughly equal across cog domains (WAIS-III IQ–WMS-III delay = 18-32%; IQ–CVLT LDFR = 18%; IQ–Rey-O delay = 0%)
- ✓ Defining and measuring functional impairment
  - ✓ Performance-based assessment of complex instrumental ADLs (e.g., medication scheduling test: Carlson et al 2005, *JAGS*)
  - ✓ CDR ratings of ADL somewhat ignored in scoring

Difficulties With MCI Diagnosis

Quantification of Five Neuropsychological Approaches to Defining Mild Cognitive Impairment

Amy J. Jak, Ph.D., Mark W. Bondi, Ph.D., Lisa Delano-Wood, Ph.D., Christina Wierenga, Ph.D., Jody Corey-Bloom, M.D., Ph.D., David P. Salmon, Ph.D., Dean C. Delis, Ph.D.

(Am J Geriatr Psychiatry 2009; 17:368–375)

Jak et al. (2009). *Am J Geriatr Psychiatry, 17*, 368-75.

Difficulties With MCI Diagnosis

Comprehensive Neuropsychological Criteria – developed in light of multiple pieces of evidence that reflect the difficulty of interpreting an isolated impaired score

- ✓ Multiple measures tend to provide a more reliable estimate of a cognitive construct than a single measure (Anastasi & Urbina, 1997)
- ✓ Majority of neurologically normal adults will score in the impaired range on at least 1 measure (median=4/40; Heaton et al. 1999, 2004)
- ✓ Findings show that a cutoff score of 1 SD provides the best sensitivity and specificity (Busse et al. 2006; Heaton et al. 1999, 2004)
- ✓ A sizeable minority of healthy older adults (> 20%) obtain 1 impaired score in 2 different domains but fewer (< 5%) earn 2 or more impaired scores in the same domain (Palmer et al. 1998)

Jak et al. (2009). *Am J Geriatr Psychiatry, 17*, 368-75.

Difficulties With MCI Diagnosis

Defining the cognitive impairment of MCI

Historical Criteria (Petersen et al. 1999)

Memory on one test (eg, Story A LM II) falls 1.5 SD below published norms

Global cognitive functioning (MMSE) intact (defined as ≥ 24/30); CDR = 0.5

Typical Criteria (Petersen & Morris 2005)

Requires only one test within a cognitive domain falls 1.5 SD below norms

Comprehensive Neuropsychological Criteria (Jak et al. 2009)

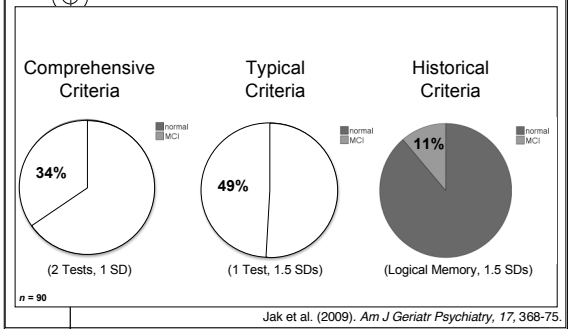
Requires 2 tests in a domain to fall 1.0 SD below norms; performance-based complex iADL intact (*T*-score ≥ 40)

Neuropsychologically-derived operational definition of MCI subtypes:

Memory (6), exec. function (6), attention (3), visuospatial (3), language (3)

Jak et al. (2009). *Am J Geriatr Psychiatry, 17*, 368-75.

Difficulties With MCI Diagnosis



Jak et al. (2009). *Am J Geriatr Psychiatry, 17*, 368-75.

Difficulties With MCI Diagnosis

Typical Criteria (ie, MCI diagnosis based on 1 test)

Amnestic MCI → *56% less impaired*; 25% unchanged; 19% more impaired

2-3 yrs

Non-Amn MCI → *47% less impaired*; 24% unchanged; 29% more impaired

Comprehensive Criteria (ie, MCI dx based on 2+ tests)

Amnestic MCI → *0% less impaired*; 50% unchanged; 50% more impaired

2-3 yrs

Non-Amn MCI → *18% less impaired*; 55% unchanged; 27% more impaired

Loewenstein et al. (2009). *Dem Geriatr Cog Dis.*

Brain-Based Empirical Support for Comprehensive Criteria

Journal of the International Neuropsychological Society (2009), **15**, 890–897.

doi:10.1017/S1355617709090638

MCI SERIES

Profile of hippocampal volumes and stroke risk varies by neuropsychological definition of mild cognitive impairment

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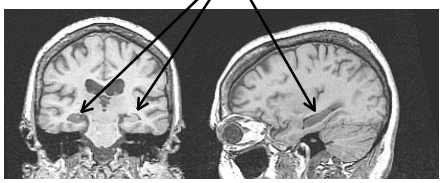
(RECEIVED December 3, 2008; FINAL REVISION February 9, 2009; ACCEPTED February 10, 2009)

Jak et al. (2009). *J Int Neuropsychol Soc.*

Brain-Based Empirical Support for Comprehensive Criteria

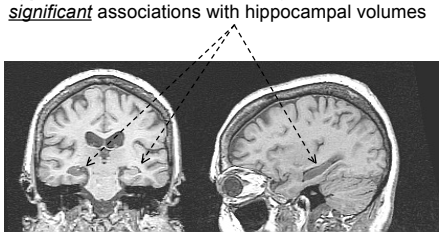
Comprehensive Criteria: Amnestic MCI group had significantly smaller hippocampal volumes



Jak et al. (2009). *J Int Neuropsychol Soc.*

Brain-Based Empirical Support for Comprehensive Criteria

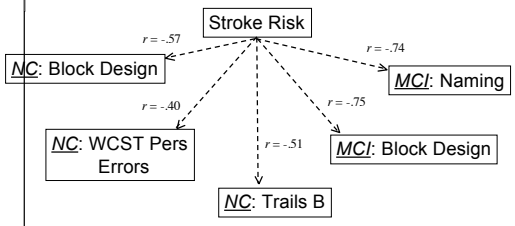
Typical Criteria: Amnestic MCI group had *non-significant* associations with hippocampal volumes



Jak et al. (2009). *J Int Neuropsychol Soc.*

Brain-Based Empirical Support for Comprehensive Criteria

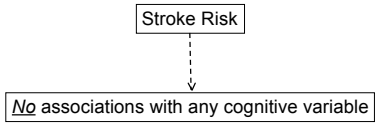
Comprehensive Criteria



Jak et al. (2009). *J Int Neuropsychol Soc.*

Brain-Based Empirical Support for Comprehensive Criteria

Typical Criteria



Jak et al. (2009). *J Int Neuropsychol Soc.*

Diffusion Tensor Imaging in MCI

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Stroke risk modifies regional white matter differences in mild cognitive impairment

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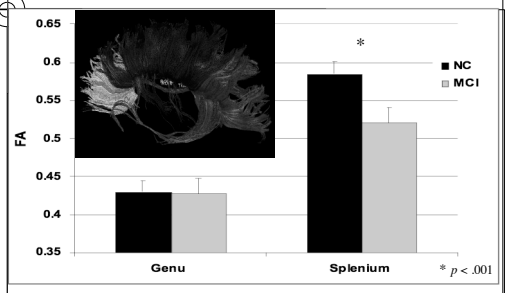
Diffusion Tensor Imaging in MCI



Delano-Wood et al. (2008). *Neurobiol Aging.*

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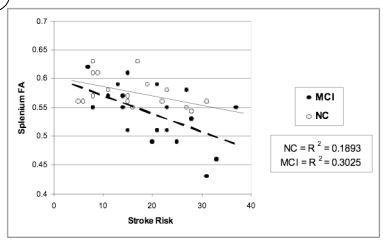

Posterior white matter pathology may contribute to the development of MCI-related cognitive changes

Delano-Wood et al. (2008). *Neurobiol Aging.*

Brain-Based Empirical Support for Comprehensive Criteria

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Brain substrates of learning and retention in mild cognitive impairment diagnosis and progression to Alzheimer's disease

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Chang et al. (2009). *Neuropsychologia.*

Brain-Based Empirical Support for Comprehensive Criteria

- ✓ Studies of MCI have relied almost exclusively on delayed recall or retention measures in diagnosis (Arnaiz & Almkvist, 2003)
- ✓ More recent conceptualizations of MCI continue to rely on the retention deficit in classifying 'amnestic' and 'non-amnestic' subtypes
- ✓ Such practices negate a large body of evidence that preclinical AD is also characterized by an encoding or learning deficit (Weingartner et al. 1981; Greene et al. 1996; Grober & Kawas, 1997; Bondi et al. 1999)
- ✓ Thus, sole reliance on delayed recall measures in amnestic MCI diagnosis may miss an important subgroup at risk for developing AD

Chang et al. (2009). *Neuropsychologia.*

Cox Models of Baseline Factors Predictive of Progression to AD

Baseline Variable	Risk Ratio	95% CI
1st Model - *Learning* (Overall $\chi^2 = 24.1$, $p < .001$)		
APOE ε4 Carrier	7.65	0.87 - 67.4
List A Total Learning	5.18	1.55 - 17.3
2nd Model - *Memory* (Overall $\chi^2 = 26.2$, $p < .001$)		
APOE ε4 Carrier	6.19	0.60 - 63.9
Long Delay Free Recall	3.37	1.15 - 9.88
Cued Recall Intrusions	2.90	1.10 - 7.64

Bondi et al. (1999). *Psychology & Aging, 14,* 295-303.

Brain-Based Empirical Support for Comprehensive Criteria

Amnestic MCI classified 607 ADNI subjects into one of 4 subgroups based on their MOANS (Ivnik et al. 1992) age-corrected scores on learning and retention indices of the *Rey Auditory Verbal Learning Test*

MCI Subtypes

HL-LR = High Learning / Low Retention

LL-HR = Low Learning / High Retention

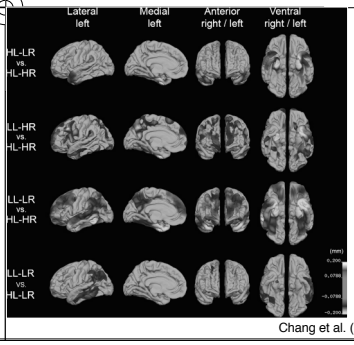
LL-LR = Low Learning / Low Retention

Normal Control

HL-HR = High Learning / High Retention

Chang et al. (2009). *Neuropsychologia.*

Brain-Based Empirical Support for Comprehensive Criteria



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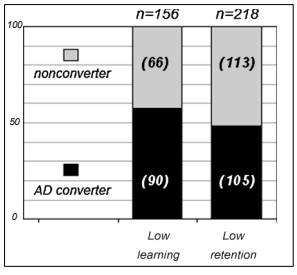
Chang et al. (2009). *Neuropsychologia.*

Brain-Based Empirical Support for Comprehensive Criteria



Chang et al. (2009). *Neuropsychologia.*

Brain-Based Empirical Support for Comprehensive Criteria

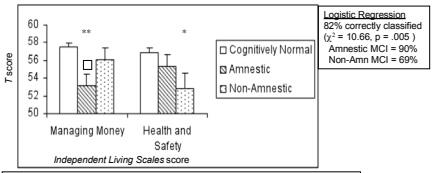
- ✓ The conventional practice of relying solely on delayed recall or retention measures in studies of amnestic MCI misses an important subset of older adults at risk of developing AD
- ✓ Results highlight the utility of including learning measures when making a diagnosis of MCI and for predicting clinical outcome

Chang et al. (2009). *Neuropsychologia.*

Difficulties With MCI Diagnosis

- ✓ Defining objective memory impairment
  - ✓ Increasing threshold for memory impairment from -1 to -1.5 SD reduced diagnosis by half in MCI subjects (Ganguli et al 2004, *Neurology*)
  - ✓ -1 SD (not -1.5 SD) had highest predictive power for AD and for normative studies' suggested cutoffs (Busse et al 2006; Heaton et al 2005)
  - ✓ No cutoff: clinical decision based on memory impairment "out of proportion to their other cognitive domains" (Jicha et al. 2006)
    - ✓ Rests on assumption that an individual's abilities are roughly equal across cog domains (WAIS-III IQ–WMS-III delay = 18-32%; IQ–CVLT LDFR = 18%; IQ–Rey-O delay = 0%)
- ✓ Defining and measuring functional impairment
  - ✓ Performance-based assessment of complex instrumental ADLs (e.g., medication scheduling test: Carlson et al 2005, *JAGS*)
  - ✓ CDR ratings of ADL somewhat ignored in scoring

Performance-Based Complex Instrumental ADL Performance by MCI Subtype



Logistic Regression
82% correctly classified
(χ^2 = 10.66, p = .005)
Amnestic MCI = 90%
Non-Amn MCI = 69%

** p < .01 - Amnestic MCI group performed significantly worse than the NC group
* p < .05 - Non-Amnestic MCI group performed significantly worse than the NC group

Performance-based IADL assessment may have utility in distinguishing MCI subtypes

Bangen et al. (in press). *J Int Neuropsychol Soc.*

Difficulties With MCI Diagnosis

CDR Box Scores	Memory	0.5
	Orientation	0.5
	Judgement / Problem Solving	0.5
	Community Affairs	1
	Home and Hobbies	1
	Personal Care	0
	Overall CDR	0.5

- ✓ Higher percentage identified as MCI with CDR than with neuropsychological criteria
  - ✓ A higher percentage of NP-defined MCI progressed to dementia
- ✓ CDR more sensitive to demographic and clinical factors leading to more 'false positives'
  - ✓ Identification of CDR 0.5 as AD or prodrome is not advisable

Saxton et al. (2009). *JNNP.*

Difficulties With MCI Diagnosis

CDR Box Scores
- Memory
- Orientation
- Judgment / Problem Solving
- Community Affairs
- Home and Hobbies
- Personal Care

ADL

CDR = 0.5

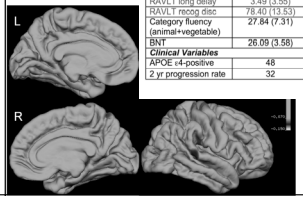
Intact ADL: ADL = 0 or ADL = 0.5 (on 1 scale only) and Personal Care = 0

Impaired ADL: ADL = 0.5 (on 2 or more scales) or ADL = 1 (on any scale)

Chang et al. (in preparation).

Difficulties With MCI Diagnosis

Neuropsychological Variables	***Intact ADL*** (*n* = 179)	***Impaired ADL*** (*n* = 104)	*p*-value
MMSE	27.25 (1.76)	27.34 (1.58)	.69
Digit Symbol	39.82 (10.11)	37.47 (10.97)	.07
Digit Span forward	8.46 (2.01)	8.13 (1.99)	.18
Digit Span Backward	6.45 (2.04)	5.98 (1.99)	.06
Trails A (sec)	40.18 (16.27)	43.44 (24.08)	.18
Trails B (sec)	112.26 (59.14)	129.16 (72.31)	.03
LM I	7.64 (2.98)	7.24 (3.06)	.28
LM II	4.09 (2.67)	3.90 (2.69)	.57
LM saving (%)	51% (28)	59% (56)	.15
RAVLT 1-5 total	32.36 (9.75)	30.53 (7.92)	.10
RAVLT short delay	4.41 (3.36)	3.45 (2.85)	.02
RAVLT long delay	3.49 (3.55)	2.50 (3.02)	.02
RAVLT recog disc	78.40 (13.53)	72.53 (16.77)	.001
Category fluency (animal+vegetable)	27.84 (7.31)	26.58 (7.17)	.16
BNT	26.09 (3.58)	25.77 (3.92)	.48
Clinical Variables			
APOE ε4-positive	48	62	.014
2 yr progression rate	32	47	.017



Chang et al. (in preparation).

Summary

- ✓ Despite increasing sophistication in genetics, imaging and biomarkers, concomitant sophistication in profiling cognition in MCI is lacking
  - ✓ Push for cognitive screening diminishes sensitivity
  - ✓ Push for fewer measures diminishes reliability
    - e.g., original ADNI not well suited to assess MCI subtypes
- ✓ Important role for examining combined risks
  - ✓ MCI + APOE ε4 (Petersen et al. 2005)
  - ✓ MCI + Stroke risk (Jak et al. 2009; Delano-Wood et al. 2008)
  - ✓ MCI + PIB-positivity (Wolk et al. 2009)

Summary

- ✓ Comprehensive neuropsychological approaches to MCI diagnosis will provide for a more thorough sampling of cognitive domains and ultimately a more complete accounting of the validity of MCI subtypes
  - ✓ Empirically derived cutoffs
  - ✓ Consistent use of normative reference standards
  - ✓ Performance-based ADL assessments
  - ✓ Less reliance on cognitive screening measures
  - ✓ Less reliance on self- or informant-based reporting

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