Cognitive and Biomarker Profiles of Accurate and Inaccurate MCI Diagnosis: Implications for Outcomes and Treatment

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&

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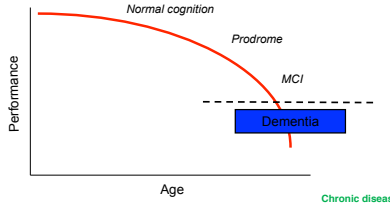
Introduction

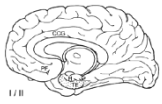
Neurodegenerative conditions of late life (e.g., AD, PD, DLB) involve slowly accruing neuron losses that evolve over some years before symptoms occur



Chronic disease model (Katzman 1976)

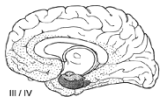
Neuropathologic Hallmarks Of AD: Evolution of Neurofibrillary Changes

Stages I / II (pre AD)



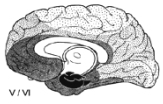
Neurofibrillary changes limited to entorhinal and transentorhinal (TE) regions

Stages III / IV (early AD)



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

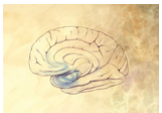
Stages V / VI (clinical AD)



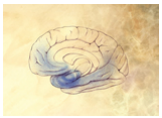
Cortical association areas severely involved; only primary sensory and motor areas spared

Braak & Braak

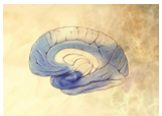
Cognitive Abilities Affected by AD



- Learning and Memory



- Language and Semantic Memory
- Executive Functions / Attention



- Visuospatial / Constructional Ability

Mild Cognitive Impairment

Suggested Criteria

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

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

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

Mild Cognitive Impairment

Table 1 *Clinical characterization of mild cognitive impairment (MCI)*

Definitions	Original Mayo Clinic [6]	Expanded/ Key Symposium [7, 8]	NIA-AA [16]	DSM-5 [15]
Criteria				
Self- or informant-reported memory complaint	x			
Self- or informant-reported cognitive complaint		x	x	x
Objective memory impairment	x			
Objective cognitive impairment		x	x	x
Essentially preserved general cognitive functioning	x			
Preserved independence in functional abilities	x	x	x	x
No dementia	x	x	x	x

Core clinical criteria according to major definitions are listed.
NIA-AA, National Institute on Aging-Alzheimer's Association workgroup; DSM-V, fifth edition of the Diagnostic and Statistical Manual of Mental Disorders; X: criterion required.

"The construct has evolved…but the core criteria have remained unchanged."

Petersen et al. (2014). *J Intern Med, 275*, 214-28.

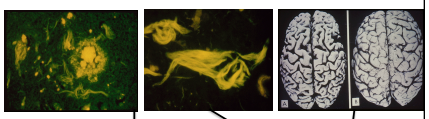
Mild Cognitive Impairment

Representative Example

- ✓ Memory complaint corroborated by informant
- ✓ One paragraph of *WMS-R* Logical Memory II
- ✓ MMSE ≥ 24 - 30
- ✓ Global Clinical Dementia Rating = 0.5
- ✓ Not demented: cognitive/functional abilities are preserved to an extent that they do not qualify for a diagnosis of dementia

Petersen et al. (2005). *NEJM, 352*, 2379-88.
Bateman et al. (2012). *NEJM, 367*, 795-804.
Alzheimer's Disease Neuroimaging Initiative (www.adni-info.org).

MCI Criteria Incorporating Biomarkers



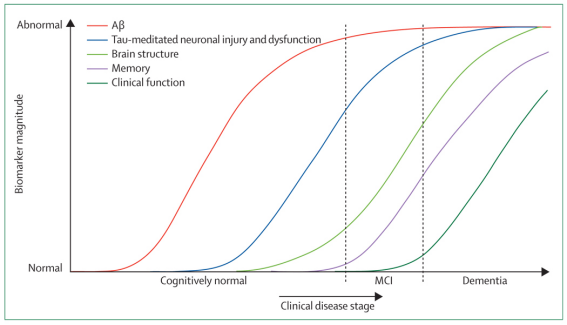
MCI criteria incorporating biomarkers

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

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.

Albert et al. (2011). *Alz & Dem.*

Proposed Staging Framework of the Cascade Of Events in Preclinical Alzheimer's Disease



Jack et al. (2010). *Lancet Neurol.*

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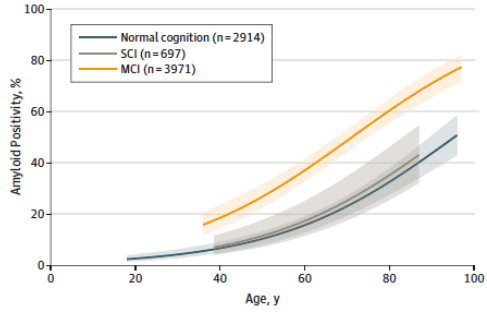


Jansen et al. (2015). *New Engl J Med.*

Preclinical Alzheimer's Disease Criteria Incorporating Biomarkers

Stage 1
Asymptomatic amyloidosis
-High PET amyloid tracer retention
-Low CSF $A\beta_{1-42}$

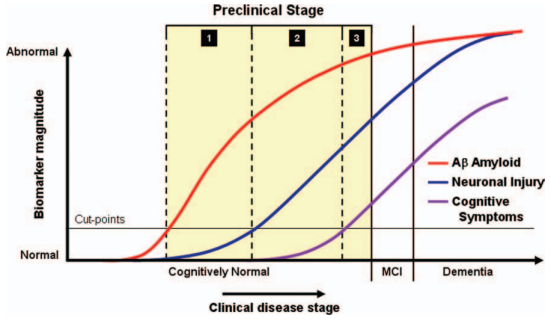
Stage 2
Amyloidosis + Neurodegeneration
-Neuronal dysfunction on FDG-PET/fMRI
-High CSF tau/p-tau
-Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
-Evidence of subtle change from baseline level of cognition
-Poor performance on more challenging cognitive tests
-Does not yet meet criteria for MCI

MCI → AD dementia

Sperling et al. (2011). *Alz & Dem.*

Preclinical Alzheimer's Disease Criteria Incorporating Biomarkers

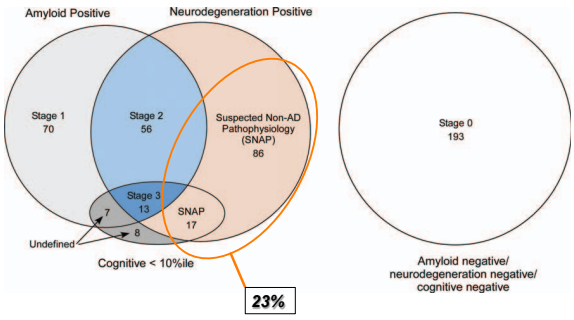


Jack et al. (2012). *Ann Neurol.*

Problems with the Temporal Sequence Of the Amyloid Cascade Model

- ✓ Preclinical axonal injury in preclinical fAD (Ryan et al 2013)
- ✓ Tau lesions in late-myelinating regions predate amyloid change (Braak et al 2011)
- ✓ Neurodegenerative biomarker positivity precedes Aβ
  - ✓ Metabolic abnormalities in ε4+ precede Aβ change (Reiman et al 2009)
  - ✓ Default network abnormalities in ε4+/PIB- subjects (Sheline et al 2010)
  - ✓ Aβ is not required to develop neurodegeneration in AD-affected regions in cognitively normal older adults (Wirth et al 2013)
  - ✓ Neurodegenerative biomarker positivity in the face of normal amyloid levels in 23% of Jack et al's (2012) own sample

Preclinical Alzheimer's Disease Criteria Incorporating Biomarkers



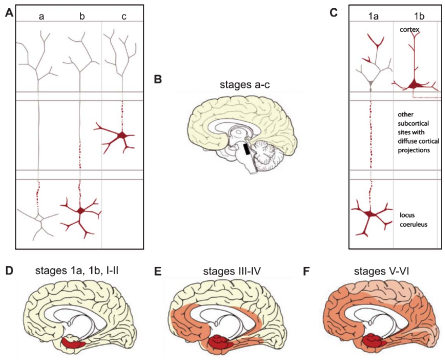
Jack et al. (2012). *Ann Neurol.*

Preclinical Alzheimer's Disease Criteria Incorporating Biomarkers

Approximately a quarter of our CN subjects (23%) were designated as SNAP. We believe that SNAP represents not a stage of preclinical AD, but rather a distinct biologically based category where amyloid biomarkers are normal but neuronal injury biomarkers are abnormal. We suspect, but cannot prove at this time, that such subjects represent the preclinical stage of non-AD pathophysiological processes. Most cases of dementia in elderly subjects are found at autopsy to have multiple pathologies that include AD; up to 1/3 are primarily attributable to pathologies other than AD, predominantly cerebrovascular disease and synucleinopathy.[57–62] It is therefore expected that preclinical forms of the non-AD pathologies must exist in elderly CN subjects recruited from a population-based sample. Subjects with predominantly cerebrovascular disease or synuclein pathologies but little or no AD pathology should present with a biomarker profile of normal amyloid PET and abnormalities on MRI and FDG.[63,64]

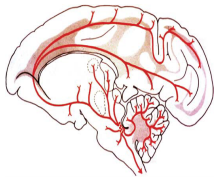
Jack et al. (2012). *Ann Neurol.*

Stages of AD-Associated Tau Pathology



Braak & del Tredici (2013). *J Alz Dis.*

Locus Coeruleus in Alzheimer's Disease



Efferent projections of the LC system in the monkey brain.

"In humans, it is pigmented [with neuromelanin], and its name means 'blue place'."

"A traditionally enigmatic reticular nucleus now seen as simultaneously influencing in almost all cortical areas of the brain."

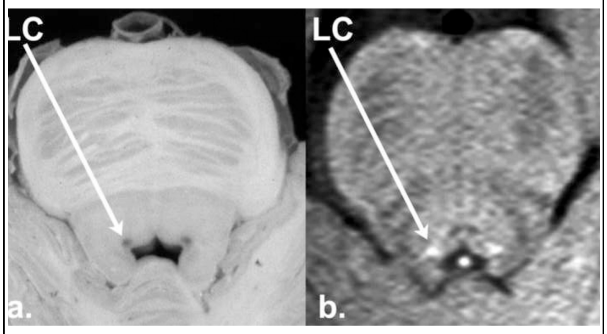
"The LC gives rise to a very large number of ascending noradrenergic axonal system that terminates diffusely over all cortical layers."

*"…three major ascending tracts – the central tegmental tract, dorsal longitudinal fasciculus, and medial forebrain bundle – **as well as vascular routes** to innervate the hypothalamus, thalamus, basal telencephalon, and entire isocortex."*

"Its stimulation inhibits spontaneous neuronal discharge nearly everywhere…a role of the LC is that it sets 'brain tone'…and by inhibiting background activity, the LC may depress irrelevant stimuli and allow relevant ones to stand out. Thus, by this route, norepinephrine may enhance the signal-to-noise ratio in brain."

Angevine & Cotman (1981). *Principles of Neuroanatomy.*

Locus Coeruleus in Alzheimer's Disease



Keren et al. (2009). *NeuroImage.*

Locus Coeruleus in Alzheimer's Disease

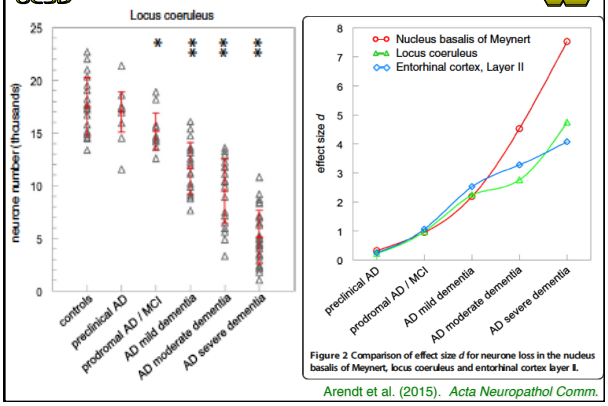
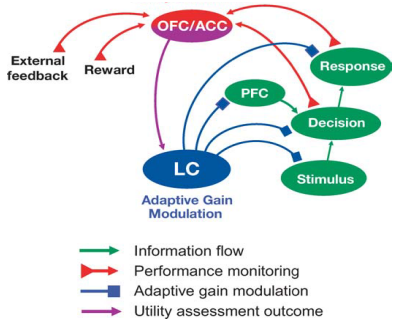


Figure 2 Comparison of effect size *d* for neurone loss in the nucleus basalis of Meynert, locus coeruleus and entorhinal cortex layer II.

Arendt et al. (2015). *Acta Neuropathol Comm.*

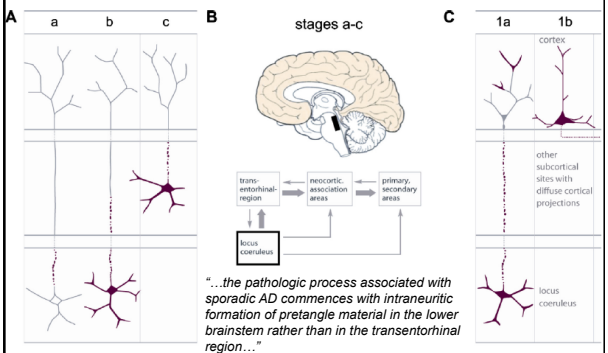
Locus Coeruleus in Alzheimer's Disease

Adaptive Gain Model of the LC-NE system.



Aston-Jones & Cohen (2005).

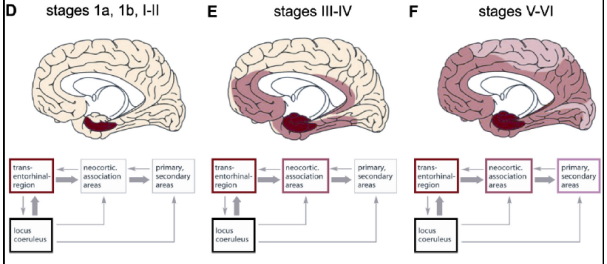
Stages of AD Tau Pathology



"…the pathologic process associated with sporadic AD commences with intraneuritic formation of pretangle material in the lower brainstem rather than in the transentorhinal region…"

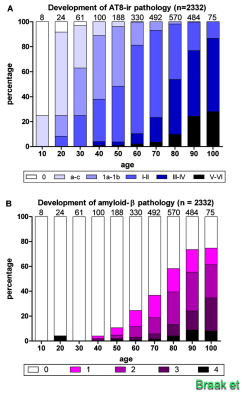
Braak et al. (2011). *J Neuropath Exp Neurol.*

Stages of AD Tau Pathology



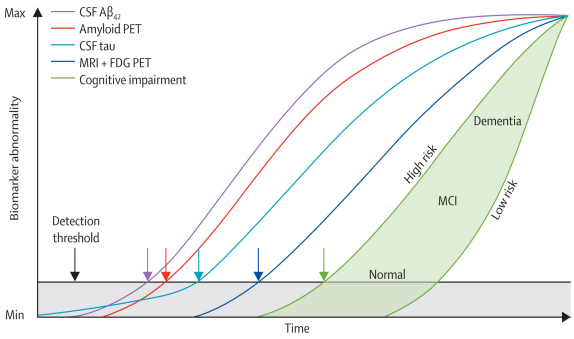
Braak et al. (2011). *J Neuropath Exp Neurol.*

Stages of AD-Associated Tau Pathology



Braak et al (2011). *J Neuropath Exp Path.*

Proposed Staging Framework of the Cascade Of Events in Preclinical Alzheimer's Disease



Jack et al. (2013). *Lancet Neurol.*

Cummings et al. Alzheimer's Research & Therapy 2014, 6:37
http://alzres.com/content/6/4/37

alzheimer's research&therapy

RESEARCH Open Access

Alzheimer's disease drug-development pipeline: few candidates, frequent failures

Jeffrey L Cummings[1*], Travis Morstorf[2] and Kate Zhong[1]

Abstract

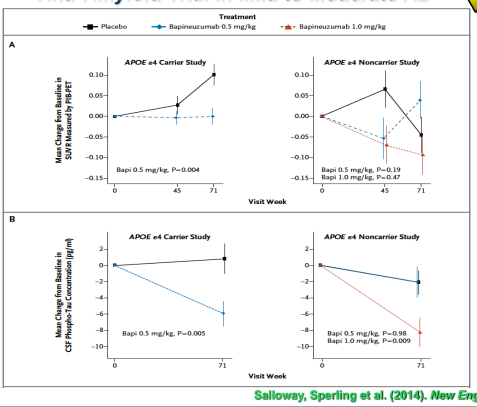
Introduction: Alzheimer's disease (AD) is increasing in frequency as the global population ages. Five drugs are approved for treatment of AD, including four cholinesterase inhibitors and an *N*-methyl-D-aspartate (NMDA)-receptor antagonist. We have an urgent need to find new therapies for AD.

Methods: We examined Clinicaltrials.gov, a public website that records ongoing clinical trials. We examined the decade of 2002 to 2012, to better understand AD-drug development. We reviewed trials by sponsor, sites, drug mechanism of action, duration, number of patients required, and rate of success in terms of advancement from one phase to the next. We also reviewed the current AD therapy pipeline.

Results: During the 2002 to 2012 observation period, 413 AD trials were performed: 124 Phase 1 trials, 206 Phase 2 trials, and 83 Phase 3 trials. Seventy-eight percent were sponsored by pharmaceutical companies. The United States of America (U.S.) remains the single world region with the greatest number of trials; cumulatively, more non-U.S. than U.S. trials are performed. The largest number of registered trials addressed symptomatic agents aimed at improving cognition (36.6%), followed by trials of disease-modifying small molecules (35.1%) and trials of disease-modifying immunotherapies (18%). The mean length of trials increases from Phase 2 to Phase 3, and the number of participants in trials increases between Phase 2 and Phase 3. Trials of disease-modifying agents are larger and longer than those for symptomatic agents. A very high attrition rate was found, with an overall success rate during the 2002 to 2012 period of 0.4% (99.6% failure).

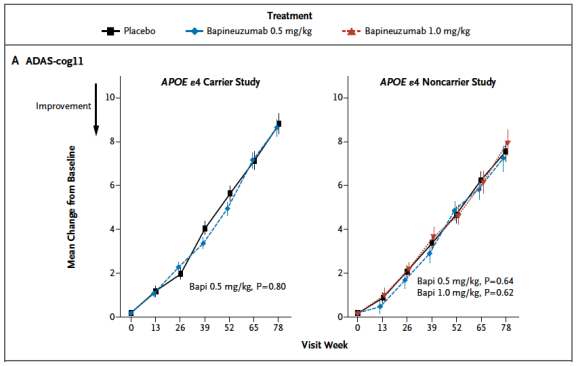
Conclusions: The Clinicaltrials.gov database demonstrates that relatively few clinical trials are undertaken for AD therapeutics, considering the magnitude of the problem. The success rate for advancing from one phase to another is low, and the number of compounds progressing to regulatory review is among the lowest found in any therapeutic area. The AD drug-development ecosystem requires support.

Anti-Amyloid Trial in Mild to Moderate AD



Salloway, Sperling et al. (2014). *New Engl J Med.*

Anti-Amyloid Trial in Mild to Moderate AD



Salloway, Sperling et al. (2014). *New Engl J Med.*

Anti-Amyloid Trial in Mild to Moderate AD

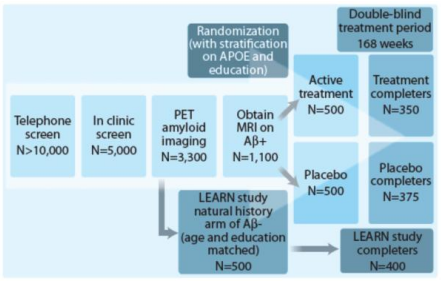
"Amyloid accumulation probably starts many years before the onset of symptoms, and initiation of anti-amyloid treatment only after dementia develops may be too late to affect the course of the disease."

Salloway, Sperling et al. (2014). *New Engl J Med.*

"In spite of evidence of target engagement by bapineuzumab, no clinical benefit was evident…these finding raise questions about whether bapineuzumab was initiated early enough to affect the disease course, the exposure was sufficient, or the most pathologic Aβ species were targeted."

Liu et al. (2015). *Neurology.*

The A4 Study: Anti-Amyloid Treatment In Asymptomatic Alzheimer's Disease



Secondary prevention trial with solanezumab

Sperling et al. (2014). *Sci Translation Med.*

Comment: Yet another "disconnect" between amyloid and Alzheimer disease?

Amyloid plaque pathology is a defining characteristic of Alzheimer disease (AD), and the amyloid cascade hypothesis remains a central focus of AD research. Yet at least a dozen treatment trials have achieved target engagement by reducing fibrillar amyloid or its production, but have shown no clinical benefit. The article by Liu et al.[1] shows that the monoclonal anti-Aβ antibody bapineuzumab diminished binding of ^{11}C–Pittsburgh compound B (PiB) in mild to moderate AD dementia, most notably in persons with *APOE* ε4.

The phase III bapineuzumab trials, however, failed to show treatment-related attenuation of cognitive or functional decline. The article by Liu et al. does not discuss that disconnect, perhaps because it is now all too familiar. The rationale usually offered for it is that the intervention was offered too late in the AD pathogenetic cascade.

Speculation is growing, however, regarding another explanation: that fibrillar amyloid (the target of PiB) does not cause the symptoms of AD dementia. Newer trials are testing whether anti-amyloid treatments can attenuate the progress of preclinical AD, either in cognitively normal elders with evidence of cerebral amyloidosis[2] or in those who harbor a pathogenetic *PSEN1* mutation.[3] Contemplation of the eventual results of these trials raises a serious question: just what would constitute compelling evidence that anti-amyloid treatments cannot stop the evolution of the AD pathogenic cascade? Indeed, a null result from the *PSEN1* trial would place the severest strain on the entire amyloid cascade hypothesis. The pharmaceutical industry has by now invested several billion dollars in anti-amyloid therapeutics. Karl Popper taught us that scientific discovery requires falsifiable hypotheses. Should we not be asking what could convince us that the anti-amyloid treatment emperor may have no clothes?[4]

Breitner (2015). *Neurology.*

Brain Injury Biomarkers Are Not Dependent on β-Amyloid in Normal Elderly

David S. Knopman, MD,[1,2] Clifford R. Jack,Jr, MD,[2,3] Heather J. Wiste, BA,[4]
Stephen D. Weigand, MS,[4] Prashanthi Vemuri, PhD,[1] Val J. Lowe, MD,[3]
Kejal Kantarci, MD,[3] Jeffrey L. Gunter, PhD,[3] Matthew L. Senjem, MS,[3]
Michelle M. Mielke, PhD,[5] Rosebud O. Roberts, MBBCh,[5] Bradley F. Boeve, MD,[1,2]
and Ronald C. Petersen, MD, PhD[1,2,5]

Objective: The new criteria for preclinical Alzheimer disease (AD) proposed 3 stages: abnormal levels of β-amyloid (stage 1), stage 1 plus evidence of brain injury (stage 2), and stage 2 plus subtle cognitive changes (stage 3). However, a large group of subjects with normal β-amyloid biomarkers have evidence of brain injury; we labeled them as the "suspected non-Alzheimer pathophysiology" (sNAP) group. The characteristics of the sNAP group are poorly understood.
Methods: Using the preclinical AD classification, 430 cognitively normal subjects from the Mayo Clinic Study of Aging who underwent brain magnetic resonance (MR), ^{18}fluorodeoxyglucose (FDG), and Pittsburgh compound B positron emission tomography (PET) were evaluated for FDG PET regional volumetrics, MR regional brain volumetrics, white matter hyperintensity volume, and number of infarcts. We examined cross-sectional associations across AD preclinical stages, those with all biomarkers normal, and the sNAP group.
Results: The sNAP group had a lower proportion (14%) with apolipoprotein E ε4 genotype than the preclinical AD stages 2 + 3. The sNAP group did not show any group differences compared to stages 2 + 3 of the preclinical AD group on measures of FDG PET regional hypometabolism, MR regional brain volume loss, cerebrovascular imaging lesions, vascular risk factors, imaging changes associated with α-synudeinopathy, or physical findings of parkinsonism.
Interpretation: Cognitively normal persons with brain injury biomarker abnormalities, with or without abnormal levels of β-amyloid, were indistinguishable on a variety of imaging markers, clinical features, and risk factors. The initial appearance of brain injury biomarkers that occurs in cognitively normal persons with preclinical AD may not depend on β-amyloidosis.

ANN NEUROL 2013;73:472–480

Brain Injury Biomarkers Are Not Dependent on β-Amyloid in Normal Elderly

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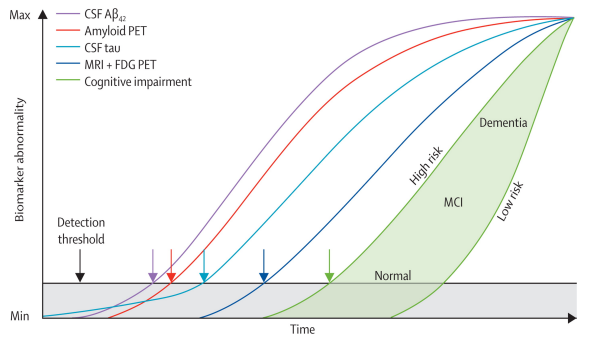
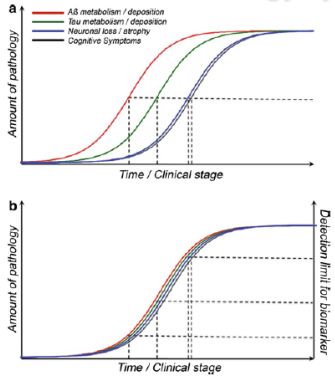
Proposed Staging Framework of the Cascade Of Events in Preclinical Alzheimer's Disease



Jack et al. (2013). *Lancet Neurol.*

Amyloid and Tau Pathology by Age



Braak et al. (2013). *Acta Neuropathol.*

Comparisons of Biomarkers and Cognitive Measures in Predicting Progression to Alzheimer's Disease

Table 5. Clustered Logistic Regression Models of Conversion During 2 Years

Variable	OR (95% CI)	Δ R^2	*P* Value
Demographic characteristics and *APOE* (χ^2 = 14.17/ *P* < .001; AUC = 0.61)			
APOE	2.51 (1.55-4.09)	.06	<.001
Cognitive markers (χ^2 = 106.15/ *P* < .001; AUC = 0.80)			
ADAS memory	1.07 (1.01-1.14)	.18	<.001
Logical Memory delay	1.01 (0.96-1.06)	.06	<.001
Clock Drawing test	0.95 (0.85-1.07)	.05	<.001
AVLT delay	0.80 (0.70-0.91)	.04	<.001
Trails A	0.99 (0.98-0.99)	.03	<.001
Brain volumetric measures (χ^2 = 50.15/ *P* < .001; R^2 = 0.27; AUC = 0.77)			
Left middle temporal lobe	0.02 (0.01-0.09)	.18	<.001
Left hippocampus	0.022 (0.006-0.087)	.09	<.001
CSF biomarkers (χ^2 = 12.36/ *P* < .001; AUC = 0.64)			
Tau/Aβ1-42 ratio	0.03 (0.03-0.22)	.11	<.001
"Winners" model, ie, including only previous significant measures (χ^2 = 39.49/ *P* < .001; AUC = 0.80)			
Logical Memory delayed total	0.80 (0.67-0.95)	.18	<.001
Left middle temporal lobe thickness	0.04 (0.01-0.27)	.10	<.001
AVLT delayed	0.77 (0.64-0.92)	.06	.02

Abbreviations: ADAS, Alzheimer Disease Assessment Scale; *APOE*, apolipoprotein; AUC, area under the curve; AVLT, Auditory Verbal Learning Test; CI, confidence interval; CSF, cerebrospinal fluid; OR, odds ratio.

Gomar et al. (2011). *Arch Gen Psychiatry.*

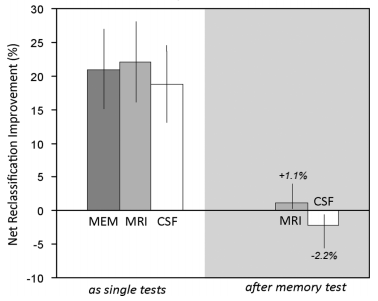
Comparisons of Biomarkers and Cognitive Measures in Predicting Progression to Alzheimer's Disease

Table 2 Normal, MCI, and AD subjects with available data for all measures of interest and ROC analysis results

		Neuroimaging		CSF biomarkers					
	Genetic: APOE ε4	FDG-PET	Hippocampal volume	$A\beta_{1-42}$	$p\text{-tau}_{181p}$	t-tau	$p\text{-tau}_{181p}/A\beta_{1-42}$	$t\text{-tau}/A\beta_{1-42}$	Memory: AVLT
Sample sizes[a]									
AD	193	97	146	102	102	100	102	100	193
MCI	85	85	85	85	84	83	83	83	85
Normal	227	102	198	114	114	114	114	114	229
ROC curve analyses (AD and normal)[b]									
ROC AUC		0.88	0.89	0.81	0.80	0.80	0.84	0.85	0.95
Threshold value		1.21	3,260.40	165.50	26.10	86.80	0.14	0.46	33.50
Sensitivity, %		82	79	82	80	71	87	85	93
Specificity, %		70	82	70	70	77	70	78	88
Overall accuracy, %		76	81	76	75	74	78	81	90
Positive/negative predictive value (MCI), %									
Positive predictive value	40	41	41	38	42	42	42	39	41
Negative predictive value	74	79	78	76	83	73	87	76	88

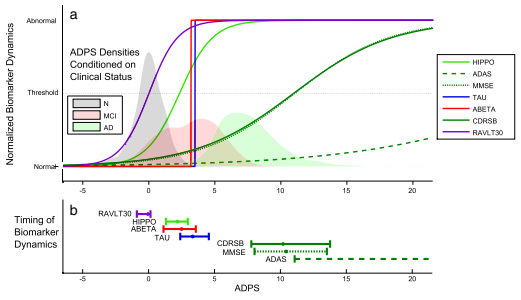
Landau et al. (2010). *Neurology.*

Comparisons of Biomarkers and Cognitive Measures in Predicting Progression to Alzheimer's Disease



Richard, Schmand, et al. (2013). *BMJ Open.*

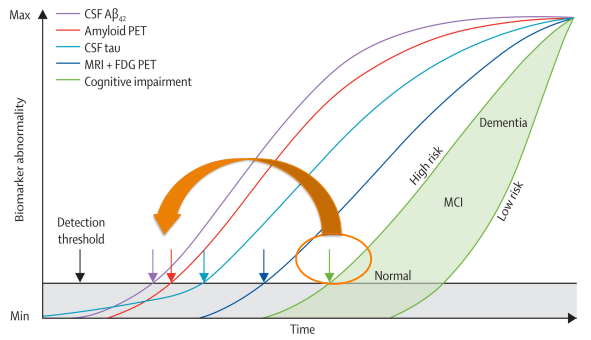
Comparisons of Biomarkers and Cognitive Measures in Predicting Progression to Alzheimer's Disease



ADPS – Alzheimer's Disease Progression Score

Jedynak et al. (2012). *NeuroImage.*

Proposed Staging Framework of the Cascade Of Events in Preclinical Alzheimer's Disease



Jack et al. (2013). *Lancet Neurol.*

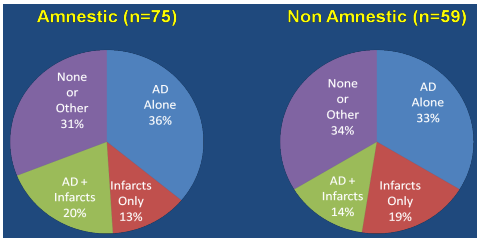
Underlying Neuropathology in MCI

Group	Mean rate of Amyloid Positivity	P-Value
Amnestic MCI	58%	*p* = .03 vs. Non-Amn MCI
Non-Amn MCI	47%	*p* = .03 vs. NC
Normal Cognition	32%	

Both amnestic and nonamnestic MCI are associated with amyloid positivity, and a substantial number of MCI are *not* amyloid positive.

Jansen et al. (2015). *New Engl J Med.*

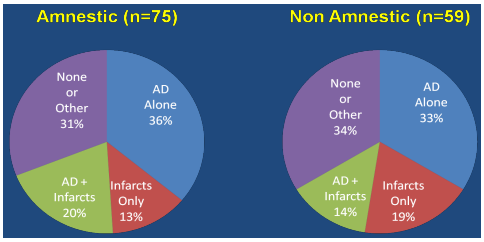
Underlying Neuropathology in MCI



Not much difference in underlying neuropathologies
- 'pure' AD pathology common to both MCI subtypes
- other pathologies common to both subtypes as well

Schneider et al. (2009). *Ann Neurol.*

Underlying Neuropathology in MCI



Current nosology for MCI is not doing a very good job of characterizing the underlying neuropathology

Schneider et al. (2009). *Ann Neurol.*

Improving Definitions

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
  - eg, original ADNI not well suited to assess MCI subtypes
- Lack of consensus on uniform set of criteria
- Disparate means by which MCI is diagnosed
  - reliance on few measures and clinical judgment

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)

Defining the Cognitive Impairment of MCI

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

- ✓ Multiple measures 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 one measure (median=4/40; Heaton et al. 1999, 2004)
  - ✓ 26% of the older adults in the *standardization* sample for the WMS-III obtained one or more impaired memory score (>1.5 SDs; Brooks et al 2007)
- ✓ More than 20% of healthy older adults obtain 1 impaired score in 2 different domains but far fewer (< 5%) earn 2 or more impaired scores in the same domain (Palmer et al. 1998)
- ✓ A cutoff score of 1 SD provides the best sensitivity and specificity (Busse et al. 2006; Heaton et al. 1999, 2004)
  - ✓ More strict (1.5 or 2 SD) cutoffs trade modest gains in specificity for larger losses in sensitivity (Taylor & Heaton 2001).

Jak et al. (2009). *Am J Geriatr Psychiatry.*

Defining the Cognitive Impairment of MCI

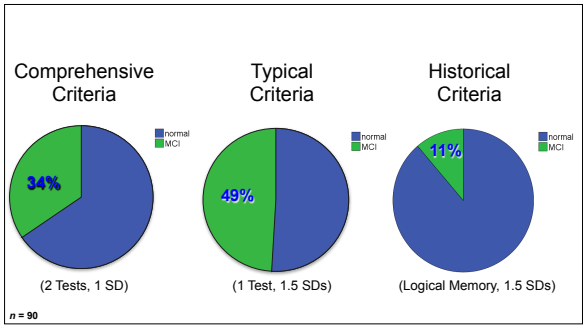
Historical Criteria (Petersen et al. 1999)
Memory on one test (eg, Story A LM II) falls 1.5 SD below published norms
Global cognitive functioning (MMSE) intact (defined as ≥ 24/30); CDR = 0.5

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.

Defining the Cognitive Impairment of MCI



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

Difficulties With Typical MCI Diagnostic Criteria

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.
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doi:10.1017/S1355617709990638

MCI SERIES

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

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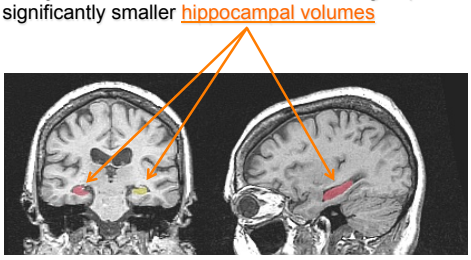
(Received December 3, 2008; Final Revision February 9, 2009; Accepted February 10, 2009)

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

Brain-Based Empirical Support for Comprehensive Criteria

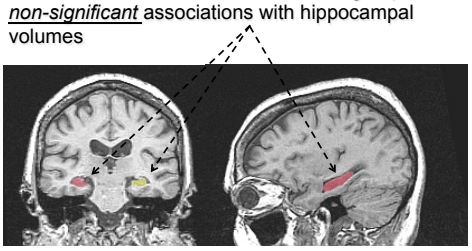
Comprehensive Criteria: Amnestic MCI group had significantly smaller hippocampal volumes



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

Brain-Based Empirical Support for Comprehensive Criteria

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



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

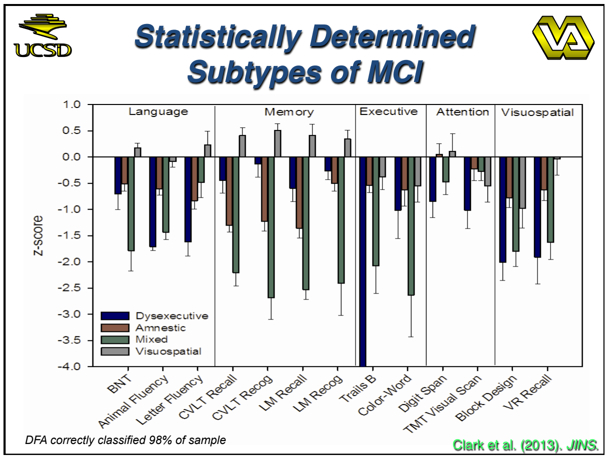
Statistically Determined Subtypes of MCI

Evidence for Distinct Cognitive or Biomarker Phenotypes of MCI Derived from Cluster Analysis

Cluster analysis groups individuals on the basis of their test scores or biomarkers that is not based on (or biased by) artificial cutoffs or long-term trajectories.

Individuals are separated into groups such that those within a group are as similar to each other as possible and groups are as different from each other as possible.

Because cluster analysis is a descriptive approach, discriminant function analyses (DFA) are used to quantitatively demonstrate the ability of the neuropsychological measures to discriminate the clustered subgroups.


UCSD
Statistically Determined
Subtypes of MCI
z-score
1.0
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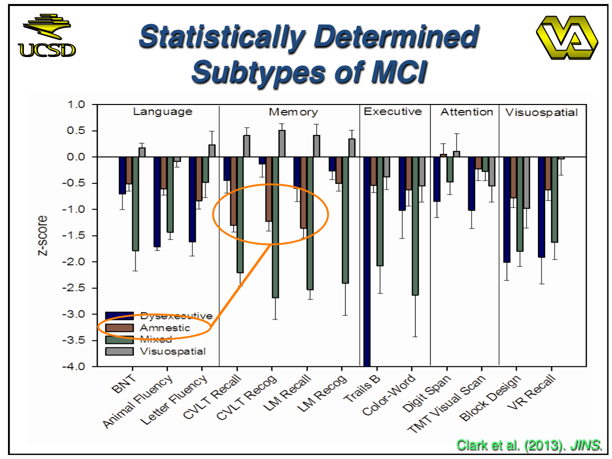
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
Language
Memory
Executive
Attention
Visuospatial
Dysexecutive
Amnestic
Mixed
Visuospatial
BNT
Animal Fluency
Letter Fluency
CVLT Recall
CVLT Recog
LM Recall
LM Recog
Trails B
Color-Word
Digit Span
TMT Visual Scan
Block Design
VR Recall
DFA correctly classified 98% of sample
Clark et al. (2013). JINS.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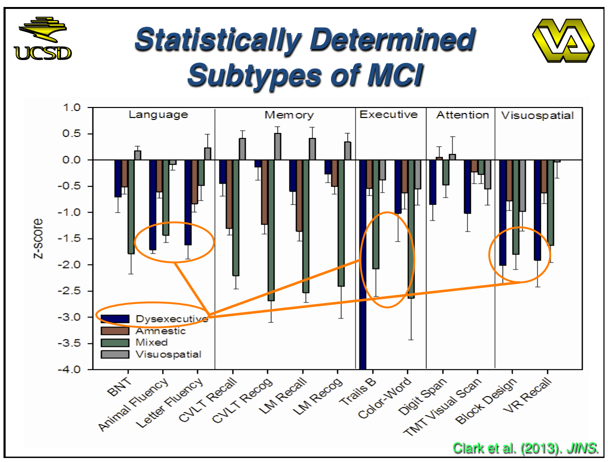
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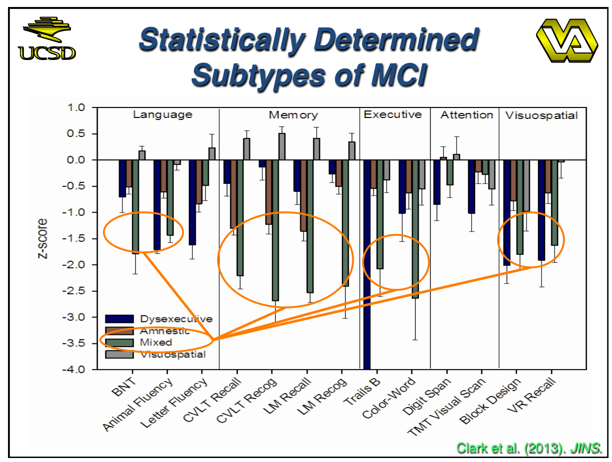
Clark et al. (2013). JINS.


UCSD
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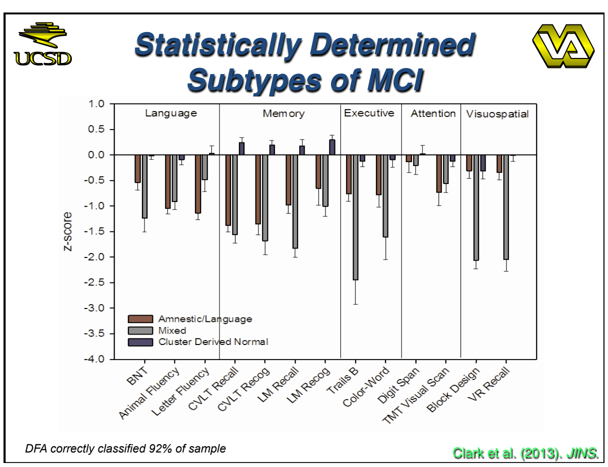
Clark et al. (2013). JINS.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-2.5
-3.0
-3.5
-4.0
Language
Memory
Executive
Attention
Visuospatial
Amnestic/Language
Mixed
Cluster Derived Normal
BNT
Animal Fluency
Letter Fluency
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CVLT Recog
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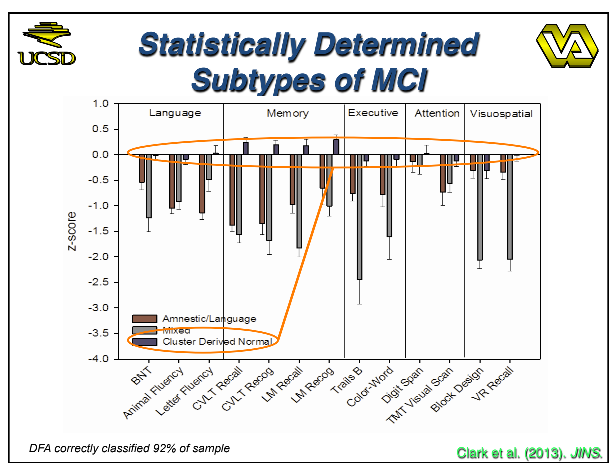
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DFA correctly classified 92% of sample
Clark et al. (2013). JINS.

Statistically Determined Subtypes of MCI

- ✓ Cluster analyses revealed different MCI subtypes depending on the MCI definition used
  - Both schemes revealed *Amnestic* and *Mixed* subtypes
  - *Mixed* subtype more severely impaired in both schemes (episodic/semantic memory impaired, executive dysfunc)
  - Nearly half cognitively normal via conventional scheme; dx susceptible to false positive diagnostic errors
- ✓ *Amnestic / Non-Amnestic* dichotomy summarily combines all non-memory deficits and obscures important profile differences; does not adequately capture the heterogeneity of MCI.

Clark et al. (2013). *JINS.*

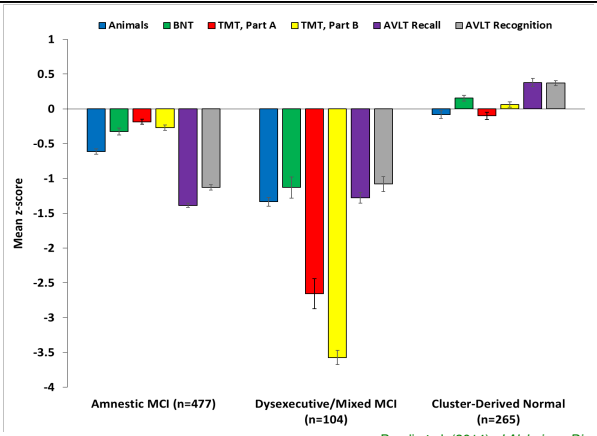
Cluster Analyses of MCI participants by Conventional ADNI Diagnostic Criteria and Neuropsychological Criteria

Bondi et al. (2014). *J Alzheimer Dis.*

Cluster Analysis: ADNI Criteria

- 846 MCI participants based on ADNI criteria (304 Normal)
- Six measures:
  - Animal Fluency & Boston Naming Test
  - Trail Making Test, Parts A & B
  - Rey Auditory Verbal Learning Test – Recall & Recognition
- Cluster analysis of z-scores identified 3 groups:
  - **Amnestic MCI (n = 477)**
  - **Dysexecutive MCI (n = 104)**
  - **Cluster-Derived Normal (n = 265)**

Bondi et al. (2014). *J Alzheimer Dis.*

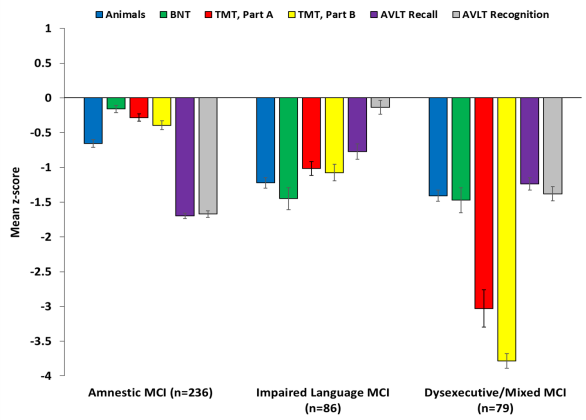


Bondi et al. (2014). *J Alzheimer Dis.*

Cluster Analysis: Neuropsychological Criteria

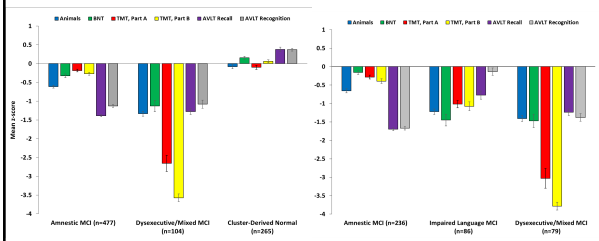
- 401 MCI participants based on NP criteria
- Cluster analysis of z-scores identified 3 groups:
  - **Amnestic MCI (n = 236)**
  - **Impaired Language MCI (n = 86)**
  - **Dysexecutive/Mixed MCI (n = 79)**

Bondi et al. (2014). *J Alzheimer Dis.*



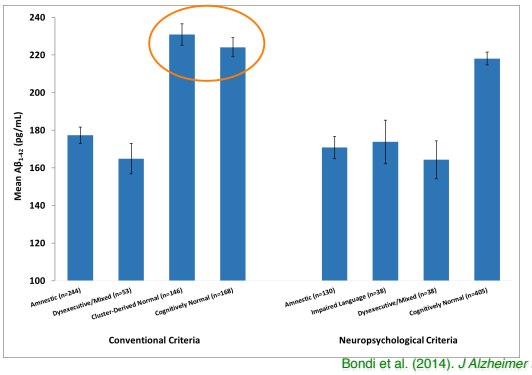
Bondi et al. (2014). *J Alzheimer Dis.*

Conventional *Neuropsychological*



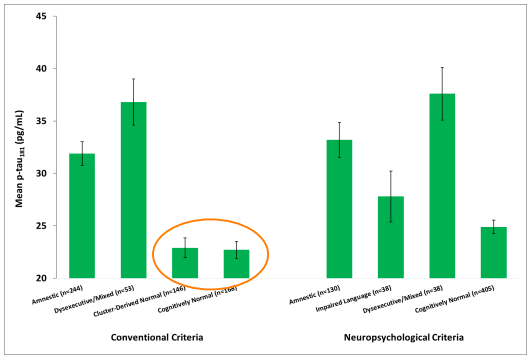
Bondi et al. (2014). *J Alzheimer Dis.*

CSF: $A\beta_{1\text{-}42}$



Bondi et al. (2014). *J Alzheimer Dis.*

CSF: p-Tau



Bondi et al. (2014). *J Alzheimer Dis.*

Comparison of Progression Rates

	MCI based on ADNI criteria	MCI based on Neuropsychological Criteria
Progression to dementia	**239 (28%)**	**179 (45%)**
Reversion to normalcy	**33 (4%)**	**2 (0.5%)**
No change	574 (68%)	220 (55%)
Total	846 (100%)	401 (100%)

Bondi et al. (2014). *J Alzheimer Dis.*

Summary of Findings

- Conventional MCI diagnosis produced a cognitively normal subtype (fully $^1/_3$ of the ADNI MCI sample)
  - Fewer APOE ε4 carriers
  - Normal levels of CSF $A\beta_{1\text{-}42}$ and P-tau biomarkers
  - Fewer who progressed to dementia (4-5 fold less than impaired types)
  - Were as likely to revert as to progress
- Neuropsychological method produced three distinct cognitive phenotypes of MCI
  - CSF AD biomarker associations
  - More stable diagnoses with negligible reversion
  - Greater percentages who progress to dementia
  - No *Cluster-Derived Normal* subtype
- Conventional criteria susceptible to *false positive* diagnostic errors due to its under-reliance on NP performance and over-reliance on
  - Single impaired test scores
  - Rating scales (CDR) and screening measures (MMSE)
  - Subjective ratings of memory complaints

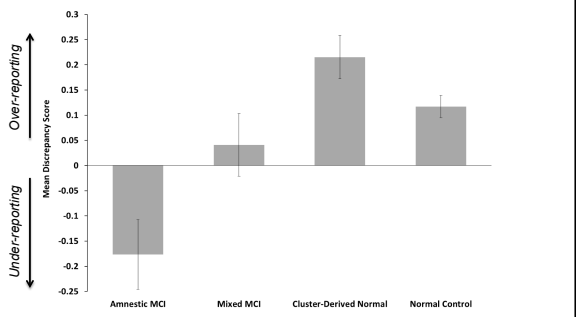
Bondi et al. (2014). *J Alzheimer Dis.*

Conclusions

- Susceptibility of conventional criteria for MCI to false positive errors could have unfortunate consequences
  - prior MCI studies may be diluting important biomarker relationships
- Using an actuarial neuropsychological method to
  - circumvent interpreting an isolated impaired score
  - understand the base rates of 'impaired' low scores
  - apply cutoffs that optimize classification rates
  - assign less weight to subjective ratings of cognitive impairment

  will reduce the potential for false positive errors.

Subjective Cognitive Complaints: Test of Everyday Cognition (ECog)

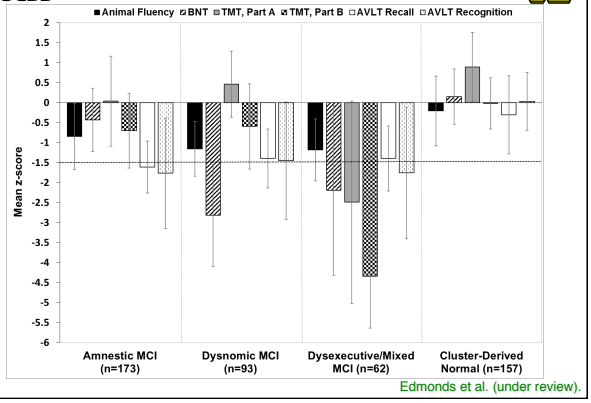


Edmonds et al. (2014). *J Int Neuropsychol Soc.*

Future Directions

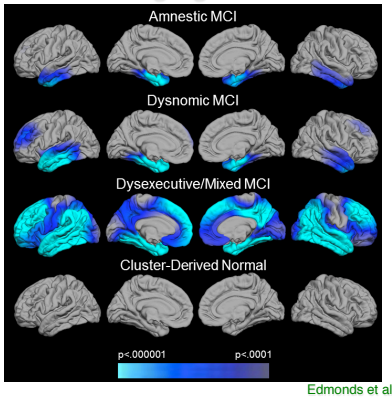
- Compare neuroimaging substrates of the cluster phenotypes of MCI
- Examine for *false negative* diagnoses in ADNI
- Add a 4th domain of visuospatial skills
- Compare the 2-test per domain method to a broader battery with 3 tests per domain
- Expand methodology to examine preclinical AD

Neuroimaging Substrates



Edmonds et al. (under review).

Neuroimaging Substrates



Edmonds et al. (under review).

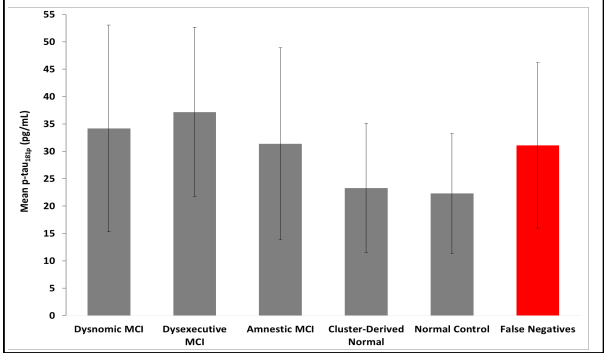
Comparison of Diagnostic Methods: The Possibility of False Negative Diagnoses

All NC and MCI subjects in ADNI database (with the 6 neuropsychological variables)

	Neuropsychological Criteria		
	MCI	**Normal**	Total
ADNI Criteria **MCI**	**388**	**472**	**860**
Normal	**37**	**483**	520
Total	**425**	955	1,380

Comparison of Diagnostic Methods: The Possibility of False Negative Diagnoses

CSF P-tau



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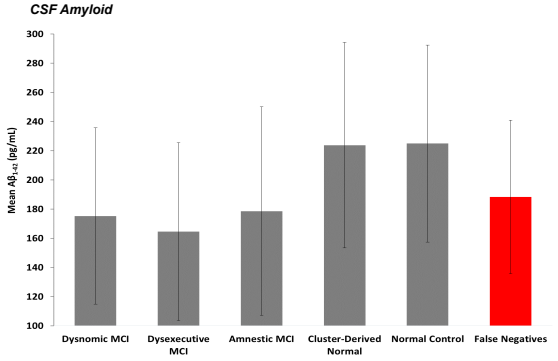


Expand Diagnostic Methods to Operationalize Preclinical Alzheimer's Disease

Stage 1
Asymptomatic amyloidosis
-High PET amyloid tracer retention
-Low CSF $A\beta_{1-42}$

Stage 2
Amyloidosis + Neurodegeneration
-Neuronal dysfunction on FDG-PET/fMRI
-High CSF tau/p-tau
-Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
-Evidence of subtle change from baseline level of cognition
-Poor performance on more challenging cognitive tests
-Does not yet meet criteria for MCI

MCI → AD dementia

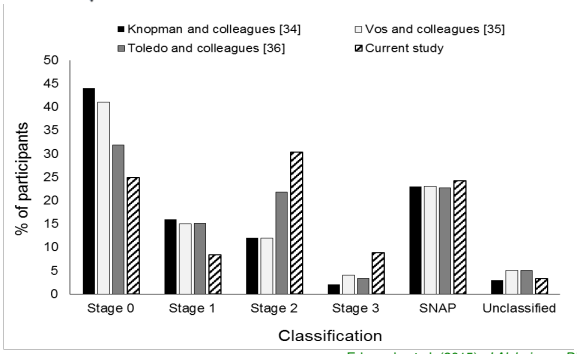
Sperling et al. (2011). *Alz & Dem.*

Expand Diagnostic Methods to Operationalize Preclinical Alzheimer's Disease

	Mild Cognitive Impairment	Subtle Cognitive Decline
Neuropsychological Testing:	Impaired score (>1 SD below age-corrected normative mean) on two measures in the **same** cognitive domain; **or** impaired score in each of the three cognitive domains sampled	Impaired score (>1 SD below age-corrected normative mean) on two measures in **different** cognitive domains
Functional Abilities:	Functional Assessment Questionnaire score: **≥9**	Functional Assessment Questionnaire score: **6-8**

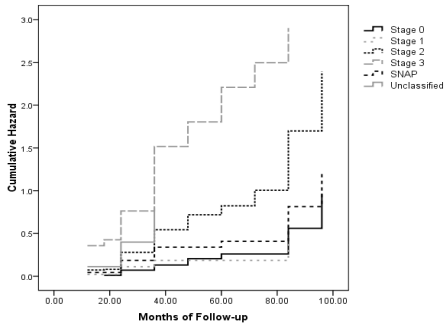
Edmonds et al. (2015). *J Alzheimers Dis.*

Expand Diagnostic Methods to Operationalize Preclinical Alzheimer's Disease



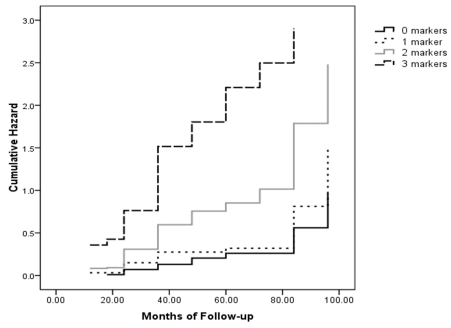
Edmonds et al. (2015). *J Alzheimers Dis.*

Expand Diagnostic Methods to Operationalize Preclinical Alzheimer's Disease



Edmonds et al. (2015). *J Alzheimers Dis.*

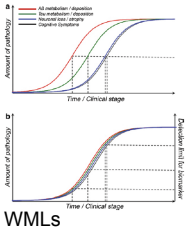
Expand Diagnostic Methods to Operationalize Preclinical Alzheimer's Disease



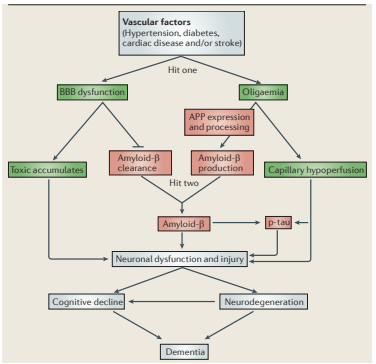
Edmonds et al. (2015). *J Alzheimers Dis.*

Need for Better Recognition of Multiple Pathologies in Biomarker Studies

- ✓ *Cerebrovascular disorders common in AD:*
  - Infarction
  - Atherosclerosis
  - Cerebral amyloid angiopathy
  - Subcortical small vessel disease / WMLs
- ✓ Detecting occult cerebrovascular dysfunction prior to observed lesions would represent a major advancement in preclinical AD detection



The Two-Hit Vascular Hypothesis For Alzheimer's Disease



Zlokovic (2011). *Nat Rev Neurosci.*

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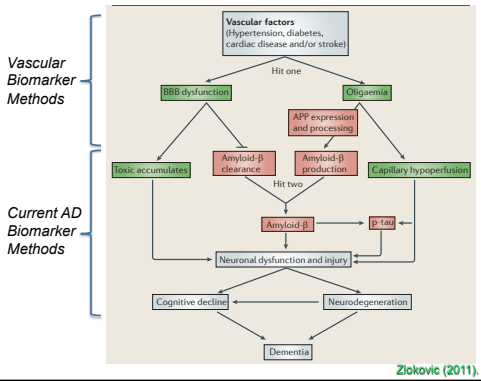

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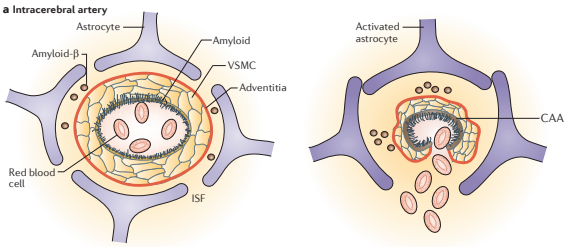

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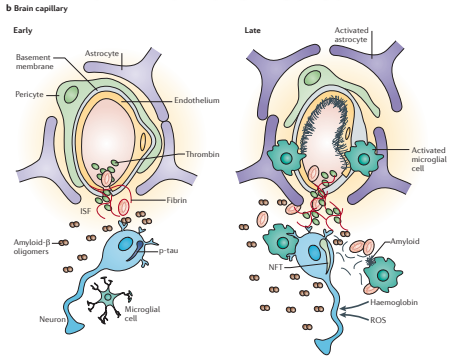
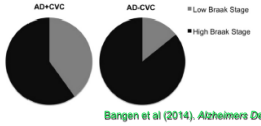


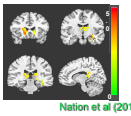
Zlokovic (2011). *Nat Rev Neurosci.*

Appreciating the Vascular Contributions To AD Neurodegeneration



Bangen et al (2014). *Alzheimers Dement.*

Elevated CVR in AD

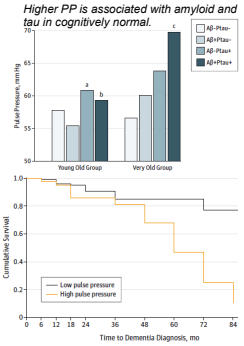


Nation et al (2013). *J Alz Dis.*

Higher MAP is associated with lower CBF in persons without dementia.

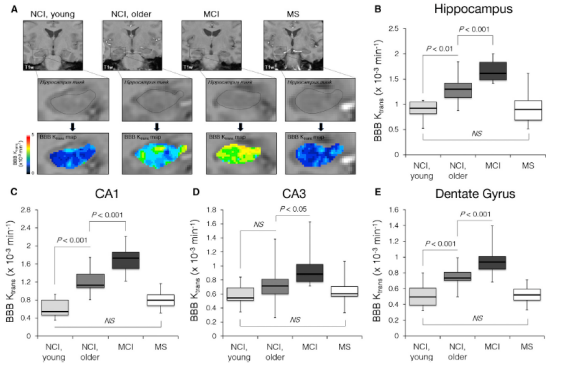
Clark et al (2015). *Alz Res Ther.*

Higher PP is associated with amyloid and tau in cognitively normal.



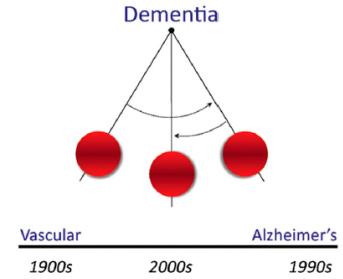
Nation et al (2015). *JAMA Neurology.*

BBB Breakdown in Normal Aging and MCI



Montagne et al. (2015). *Neuron.*

Appreciating the Combination of Vascular and AD Pathologies



Iadecola (2013). *Neuron.*

Summary: Improving Prediction of Outcomes

- Cognitive markers remain either comparable or better predictors of progression than biomarkers
- Neuropsychological approaches to MCI and Preclinical AD diagnosis provide a more thorough sampling of cognitive domains and ultimately a more complete accounting of the validity and reliability of diagnoses
- Need for better integration of multiple markers and better recognition of multiple pathologies
  - e.g., Cognition + AD Biomarkers + Vascular Biomarkers

Thank You