새로운 진단기준

DUBOIS VS NIA-AA 진단기준

서울대학교 정신건강의학과
이동영

기존 진단기준의 특징

DSM-IV

- **Presence of both a memory disorder and impairment in at least one additional cognitive domain, both of which interfere with social function or activities of daily living(ADL)**
- **ADL impairment has come to define the threshold for the diagnosis of dementia beyond the identification of a cognitive abnormality**

NINCDS-ADRDA

- **Do not require evidence of interference with social or occupational functioning**
- **Definite diagnosis of AD is only made according to the NINCDS–ADRDA criteria (histopathological confirmation)**

DUBOIS GUIDELINE
REVISED NINCDS-ADRDA

Need to update the current research criteria

- Insufficient diagnostic specificity
- Improved recognition of non-AD dementia
- Improved identification of AD phenotype
- Need to test early intervention
- Problems with definition of MCI
- Unclear distinction between MCI & AD
- New biomarkers for AD

Overview of revised NINCDS-ADRDA

- Research criteria
  - Probable AD

- New lexicon of AD
  - Typical/ Atypical/ mixed AD
  - Prodromal AD/ AD dementia
  - Preclinical AD
  - MCI

Probable AD
core diagnostic criteria - I

A. **early and significant episodic memory impairment**

1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months
2. Objective evidence of significantly impaired episodic memory
3. The episodic memory impairment can be isolated or associated with other cognitive changes

Probable AD
core diagnostic criteria - II

B. Presence of medial temporal lobe atrophy

1. hippocampi, entorhinal cortex, amygdala evidenced on MRI

C. Abnormal cerebrospinal fluid biomarker

1. Low amyloid β1–42 concentrations, increased total tau/p-tau

D. Specific pattern on functional neuroimaging with PET

1. Reduced glucose metabolism in bilateral temporal parietal regions
2. Pittsburg compound B or FDDNP

E. Proven AD autosomal dominant mutation within the immediate family

New lexicon of AD - I

- **AD**
  - whole spectrum of the clinical phase
  - both the predementia and dementia
  - both specific memory changes and in-vivo markers
  - phenotype can be typical or atypical
  - Two stages
    - prodromal and dementia phase

New lexicon of AD - II

- **Prodromal AD** (predementia state of AD)
  - episodic memory loss, not sufficiently severe to affect IADL
  - biomarker evidence from CSF or imaging

- **AD dementia**
  - cognitive symptoms are severe to interfere with social functioning and IADL
  - changes in episodic memory + one(or more) other cognitive domain

New lexicon of AD - III

- **Typical AD**
  - m/c clinical phenotype of AD
  - progressive episodic memory deficit
  - supported by one or more in-vivo positive biomarkers
- **Atypical AD**
  - Less common clinical phenotype + AD pathology
  - non-fluent/logopenic aphasia, frontal variant of AD, PCA
  - supported by amyloidosis in brain or in CSF(Aβ, tau, p-tau)
- **Mixed AD**
  - Typical AD + CVD or LBD (clinical & imaging/biological evidence)

New lexicon of AD - IV

- **Preclinical states of AD**
  - asymptomatic at-risk state for AD
    - evidence of amyloidosis in the brain/ CSF
  - presymptomatic AD
    - individuals who will develop AD
    - autosomal dominant monogenic AD mutations

- **Alzheimer`s pathology**
  - senile neuritic plaques and neurofibrillary tangles
  - synaptic loss
  - vascular amyloid deposits within the cerebral cortex

New lexicon of AD - V

- **MCI**
  - absence of a significant effect on IADL
  - exclusion for individuals suspected
  - No meet new research criteria
  - Memory sx. (+) AD or biomarker(-)

New lexicon in the new research criteria framework

	AD diagnosis	Presence of impairment on specified memory tests	Evidence of biomarkers in vivo	Additional requirements
Prodromal AD	Yes	Required	Required	Absence of dementia
Preclinical AD				
Asymptomatic at risk for AD	No	Not present	Required	Absence of symptoms of AD
Presymptomatic AD	No	Not present	Not required	Absence of symptoms of AD and presence of monogenic AD mutation
Mild cognitive impairment	No	Not required	Not required	Absence of symptoms or biomarkers specific for AD

Dubois et al., 2010;9:1118-27 Lancet Neurol

Conclusions

- **Asymptomatic at-risk state for AD, presymptomatic AD**
  - Trials aimed at delaying onset of clinical signs
- **Prodromal AD**
  - Trials of drugs targeting progression to severe stages
- **Uniformity of definition**
  - Assist in constructing trial populations
  - Comparing results across trials

NIA-AA GUIDELINE

Introduction to the NIA-AA guideline
기존 진단의 한계점

- **NINCDS-ADRDA (1984 criteria)**
  - Clinico-pathological corrrespondence model
    - amyloid plaque without AD Sx.
    - AD pathology with atypical feature
  - MCI 개념의 출현(mid 1990s)
    - 기존의 개념으로는 pathology accumulation 설명 어려움
    - AD pathopysiological processes(AD-P)
    - AD clinical symptoms(AD-C)

Introduction to the NIA-AA guideline
새로운 진단기준에 추가된 요소

- **Revised NIA-AA**
  - Three phases
    - The dementia phase
    - The symptomatic, pre-dementia phase
    - The asymptomatic, preclinical phase of AD
  - AD biomarkers consensus
    - Close to AD pathologic criteria
    - AD specificity
      - Aβ accumulation
      - Neuronal degeneration or injury

Summary

- **Evidence for preclinical AD**
  - AD biomarkers
- **MCI stage criteria**
  - Conjunction of AD-P biomarker & clinical Dx
- **Revision of the criteria for dementia because of AD**
  - Expand of the 1984 criteria
  - Include biomarkers of AD

NIA-AA GUIDELINE
-DX OF DEMENTIA DUE TO AD-

The features of criteria required revision - I

- **AD histological pathology in broad clinical spectrum**
  - AD patho-physiological process
    - Antemortem biological changes
    - Postmortem neu-ropathological Dx.
- **Lack of distinguishing features of other dementia**
  - DLBD, bvFTD, VD, primary progressive aphasia
- **No inclusion of biomarkers**
  - MRI, PET, CSF assay

The features of criteria required revision - II

- **Memory impairment is always the primary cognitive deficit in AD**
  - Nonamnestic presentations in PCA
- **Lack of information about genetics of AD**
  - APP, presenilin 1 & 2
- **Proposed age cutoffs**
- **Extreme heterogeneity of the "Possible" AD**

Purpose of revised criteria of AD

- **Criteria for all-cause dementia**
- **Criteria for dementia caused by AD**
  - Probable AD dementia
  - Possible AD dementia
  - Probable or possible AD dementia with evidence of AD pathophysiological process
- **Flexible criteria**
  - For general healthcare providers
  - For specialized investigators
    - Available NP test, imaging, CSF measures

Criteria for all-cause dementia
core clinical criteria - I

1. **Interfere with the ability to function at work or at usual activities**
2. **Decline from previous levels**
3. **Not explained by delirium or major psychiatric disorder**
4. **Cognitive impairment**
    1. history-taking from pt. & knowledgeable informant
    2. objective cognitive assessment
5. **Minimum of two of the following domains**
    a. Impaired ability to acquire & remember new information
    b. Impaired reasoning & handling of complex task, poor judgement
    c. Impaired visuospatial abilities
    d. Impaired language function
    e. Changes in personality, behavior, or comportment

Proposed classification criteria for AD dementia

- **Probable AD dementia**
- **Possible AD dementia**

- **Probable or possible AD dementia with evidence of AD pathophysiological process**
  - for research

Probable AD dementia core clinical criteria - I

1. **Probable AD meets criteria for dementia**
   A. Insidious onset
   B. Clear-cut history of worsening of cognition
   C. Cognitive deficit are evident on history & exam
      a. Amnestic presentation
      b. Nonamnestic presentations
         - Language presentation
         - Visuospatial presentation
         - Executive dysfunction

Note: "probable AD" by NINCDS-ADRDA(1984) meet current criteria

Probable AD dementia core clinical criteria – II

1. **Probable AD dementia with increased level of certainty**
    1. Probable AD dementia with documented decline
        - Active, evolving pathologic process
        - Not increase the certainty of AD pathophysiology
    2. Probable AD dementia in a carrier of a causative AD genetic mutation
        - *APP, PSEN1 or PSEN2*
        - Not Apo E ε4 allele

Possible AD dementia core clinical criteria

1. **Atypical course**
   - Sudden onset/ no progressive decline
2. **Etiologically mixed presentation**
   a. Concomitant CVD
   b. Features of Dementia with Lewy bodies
   c. Another neurological/medicla disease or medication use

Note: "possible AD" by NINCDS-ADRDA(1984) would not meet the current criteria

Probable AD dementia with evidence of AD pathophysiological process

- Biomarkers
  - Brain Aβ protein deposition
    - low CSF Aβ42
    - positive PET amyloid imaging
  - Downstream neuronal degeneration or injury
    - elevated CSF total & phosphorylated tau
    - decreased FDG uptake on PET in temporo-parietal cortex
    - atrophy on structural MRI in medial, basal, and lateral temporal lobe, and medial parietal cortex
  - Increase the certainty of AD pathophysiological process

Limitations of Biomarkers

- Several reasons
  1. The core clinical criteria : good Dx accuracy and utility
  2. More research need to ensure that criteria include biomarkers
  3. Limited standardization of biomarkers
  4. Limited to access in community settings

- Three circumstances
  - Investigational studies
  - clinical trials
  - optional clinical tool

Other criteria

- Possible AD dementia with evidence of the AD pathophysiological process
- Pathophysiologically proved AD dementia
- Dementia unlikely to be due to AD

NIA-AA GUIDELINE
-DX OF MCI DUE TO AD-

Introduction

- **Core clinical criteria**
  - Used in all clinical settings
  - w/o need of highly specialized test/procedures
- **Clinical research criteria**
  - Incorporate the use of biomarkers
  - For academic center & clinical trials
- **MCI due to AD**
  - Subset of CIND
  - Primary underlying pathophysiology is AD

Core clinical criteria

- **Concern regarding a change in cognition**
  - In comparison with the person`s previous level
- **Impairment in one or more cognitive domains**
  - Consider patient`s age & educational background
- **Preservation of independence in functional abilities**
  - Independent function, with minimal aids or assistance
- **Not demented**
  - no evidence of a significant impairment in social or occupational functioning
  - Serial evaluations are optimal

Cognitive assessment – formal test

- **Immediate & delayed recall**
  - Word-list learning test
    - Free and Cued Selective Reminding test, Rey Auditory Verbal Learning Test, California Verbal Learning Test
  - Other episodic memory measures
    - Logical Memory I and II / Visual Reproduction subtest of the Wechsler Memory Scale Revised
- **Other domain**
  - Executive function : Trail making test
  - Language : Boston naming test, letter and category fluency
  - Visuospatial skills: Figure copying
  - Attentional control: Digit span forward

Cognitive assessment – informal test

- Learn a street address and recall after interval
  - 서울시, 명동, 14번지, 한, 철수
- Name 3 object and recall
  - 나무, 자동차, 모자

- Limitation of informal test
  - Insensitive to subtle cognitive dysfunction during early MCI
  - Assessment of memory domain only

Research criteria

incorporating biomarkers

Table 2
Biomarkers under examination for AD

Biomarkers of Aβ deposition
CSF $A\beta_{42}$
PET amyloid imaging
Biomarkers of neuronal injury
CSF tau/phosphorylated-tau
Hippocampal volume or medial temporal atrophy by volumetric measures or visual rating
Rate of brain atrophy
FDG-PET imaging
SPECT perfusion imaging
Less well validated biomarkers: fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MR spectroscopy, diffusion tensor imaging, voxel-based and multivariate measures
Associated biochemical change
Inflammatory biomarkers (cytokines)
Oxidative stress (isoprostanes)
Other markers of synaptic damage and neurodegeneration such as cell death

Albert et al. 7(2011) 270-279 Alzheimer`s & Dementia

Research criteria

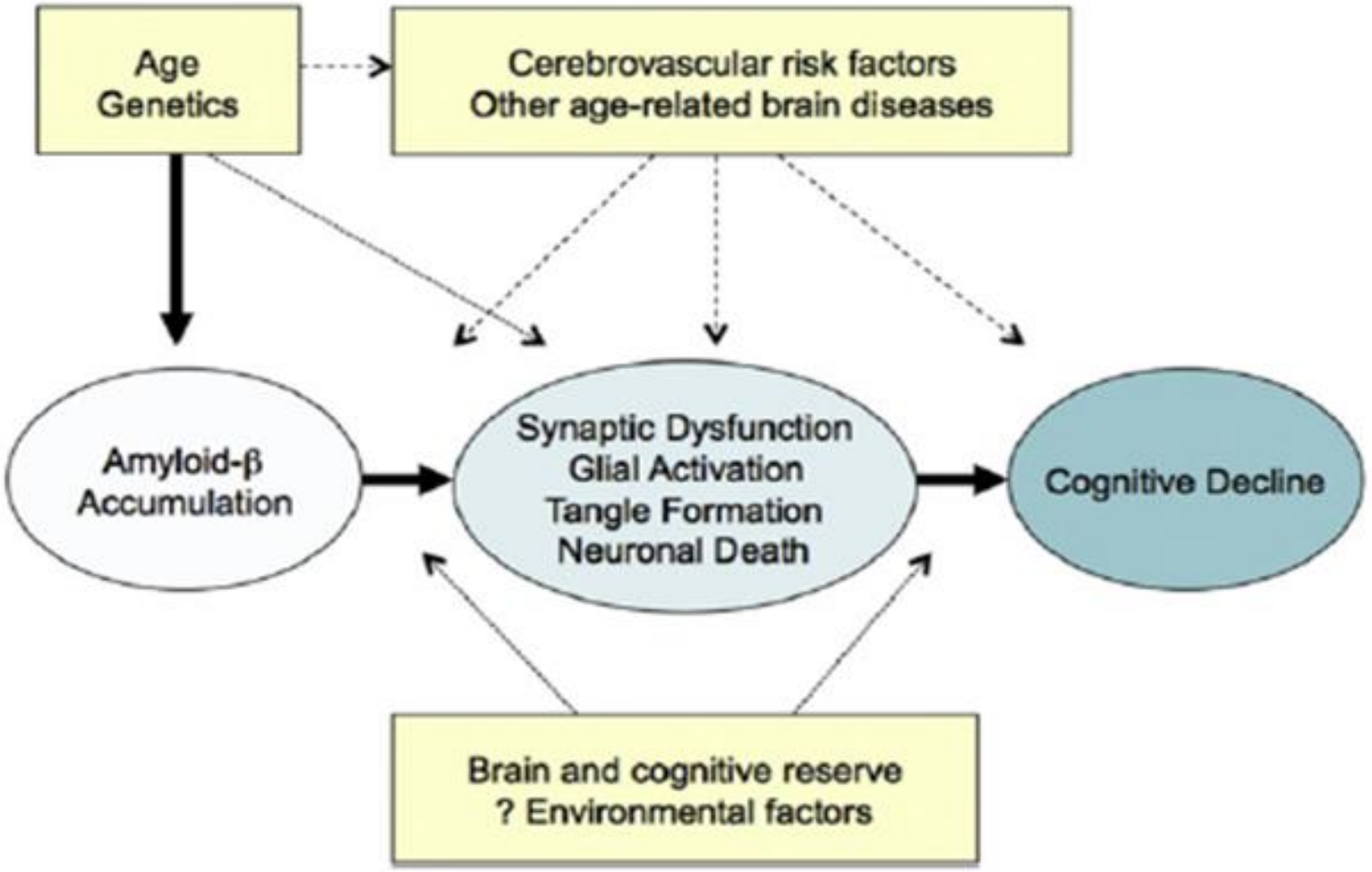
incorporating biomarkers

- **Limitation of current biomarkers for AD**
  - Difficult to understand the relative importance
  - Difficult to interpret conflict results
  - Dearth of truly predictive studies
  - Cannot define a specific cutoff
  - Timing of decline or progression

- **Application of biomarkers to the clinical research**
  - Different pathological protein targeted Tx.
  - Predict a higher rate of progression

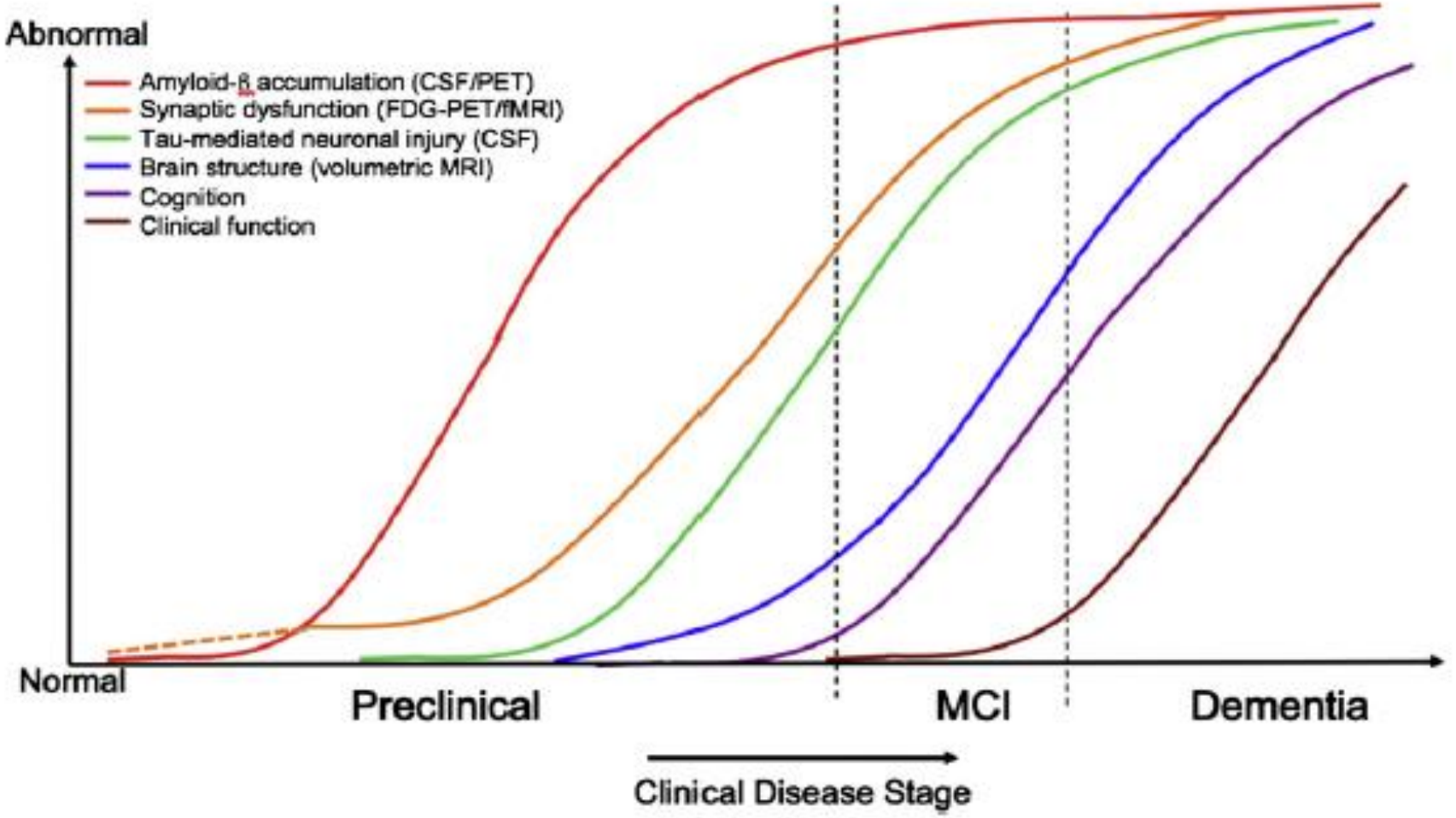
NIA-AA GUIDELINE DEFINING THE PRECLINICAL STAGES OF AD

Hypothetical model of AD pathology



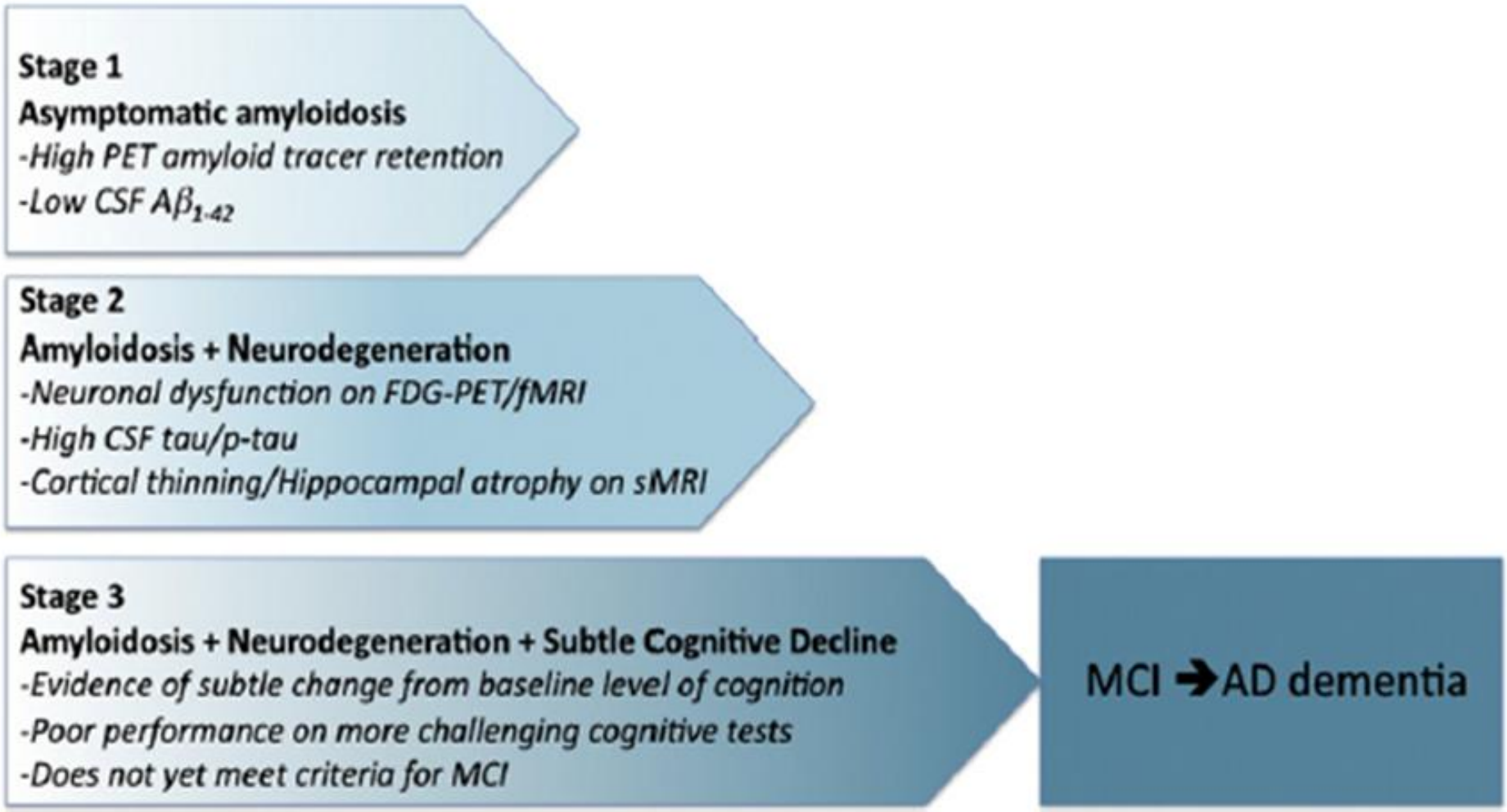
Sperling et al., 7(2011) 280-292 Alzheimer`s & dementia

Hypothetical model of biomarkers of AD



Sperling et al., 7(2011) 280-292 Alzheimer`s & dementia

Operational research framework for staging preclinical AD



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