Alzheimer’s disease: an update

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Disclosures

No relevant disclosures for this talk or mention of off-label content

Learning Objectives

- At the end of this talk, the attendees should be informed on the:
  - New diagnostic criteria for Alzheimer's disease dementia
  - New diagnostic methods
  - Current concepts on disease mechanisms
  - Current status of therapeutic approaches

New definitions

Alzheimer Disease: a new lexicon (Dubois et al, 2010)

- Alzheimer disease
  - Prodromal AD (“predementia” stage)
    - Hippocampal type episodic memory deficit, no dementia
    - supporting findings in CSF or neuroimaging
  - AD dementia
    - Typical AD
    - Atypical AD
    - Mixed AD
- Preclinical AD
  - Asymptomatic “at-risk”: amyloid PET, CSF
  - Presymptomatic: gene mutation carriers
  - Alzheimer-type pathology: NP, NFT, synaptic loss…

New diagnostic criteria: NIA-AA (McKhann et al, 2011)

Diagnosis of dementia

There are cognitive or behavioral symptoms that:

1. **Interfere with the ability to function at work or at usual activities; and**
2. **Represent a decline from previous levels of functioning and performing; and**
3. **Are not explained by delirium or major psychiatric disorder**

Diagnosis of dementia

4. Cognitive impairment is detected and diagnosed through a combination of

(1) history-taking from the patient and a knowledgeable informant and

(2) an objective cognitive assessment, a “bedside” mental status examination or neuropsychological testing.

Diagnosis of dementia

5. The cognitive or behavioral impairment involves a minimum of two of the following domains:

a. **Impaired ability to acquire and remember new information**—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.

b. **Impaired reasoning and handling of complex tasks, poor judgment**—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.

Diagnosis of dementia

c. **Impaired visuospatial abilities**—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.

d. **Impaired language functions** (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.

e. Changes in personality, behavior, or comportment— symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

Probable AD dementia

1. Meets criteria for dementia, and in addition, has the following characteristics:

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;

B. Clear-cut history of worsening of cognition by report or observation;

C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.

a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain

Probable AD dementia

b. Non-amnestic presentations:

Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.

Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.

Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

Probable AD Dementia

D. The diagnosis of probable AD dementia should not be applied when there is evidence of:

(a) Substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or

(b) core features of DLB other than dementia itself; or

(c) prominent features of behavioral variant frontotemporal dementia; or

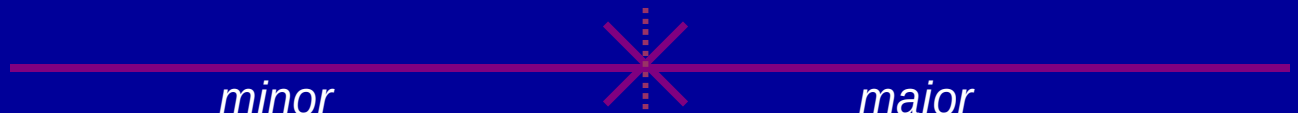
(d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or

(e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

New diagnostic criteria: DSM

DSM-5 (May 2013)

Minor Neurocognitive Disorder (MCI)
Major Neurocognitive Disorder (Dementia)



Cognitive decline: -1 SD - -2 SD

Greater effort, compensatory strategies or adaptation may be required

Insufficient to interfere with independence

Substantial cognitive decline in one or more domains: < -2 SD

Compensation not possible

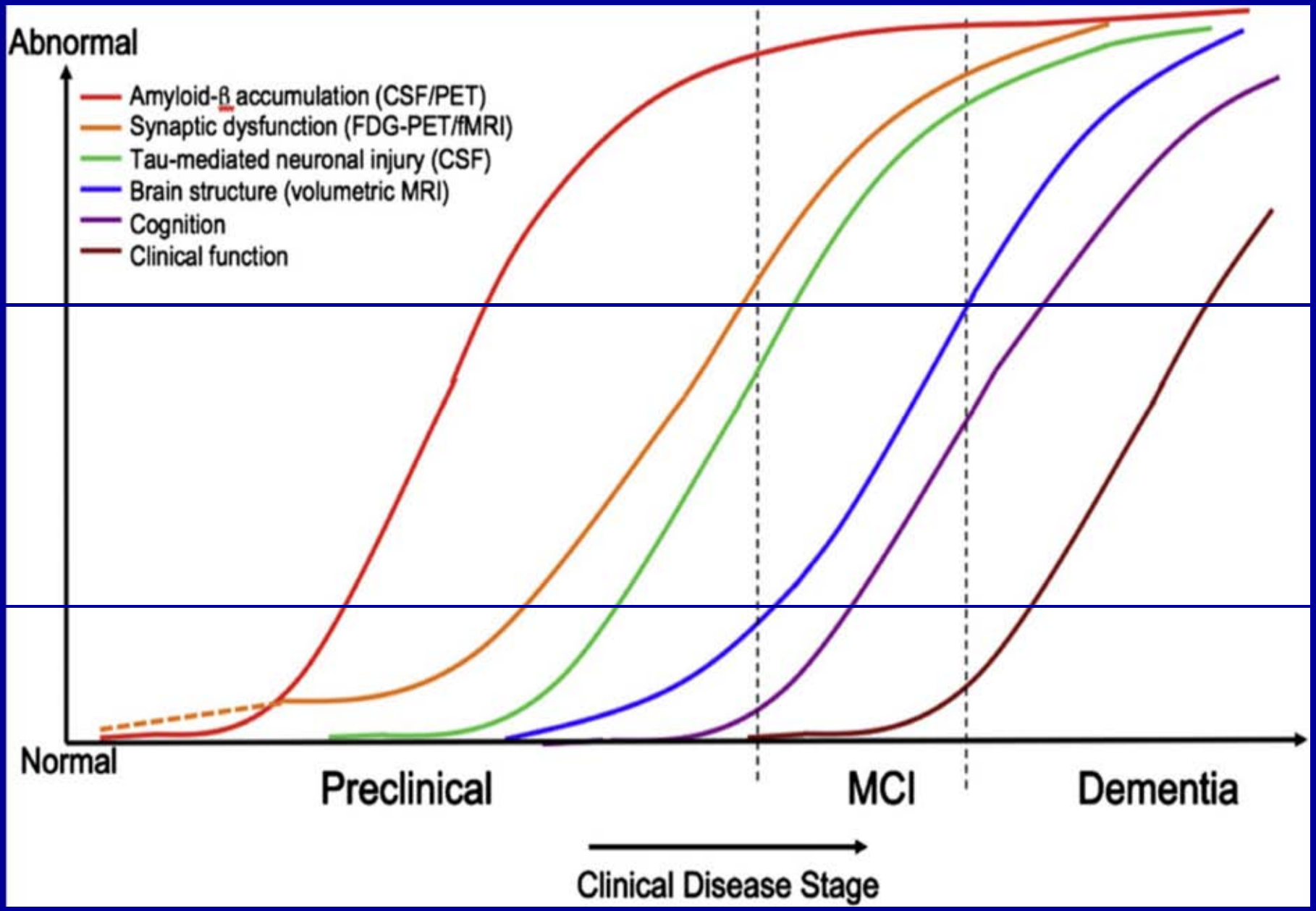
Sufficient to interfere with independence

Cognitive Domains

1. **Complex Attention**
   - sustained a., divided a., selective a., processing speed
2. **Executive Abilities**
   - planning, decision-making, working memory, responding to feedback/error correction, overriding habits, mental flexibility
3. **Learning and Memory**
   - immediate m., recent m. [incl. free recall, cued recall, and recognition m.]
4. **Language**
   - expressive language [including naming, fluency, grammar and syntax] and receptive language
5. **Visuoconstructional-perceptual ability**
   - construction, visual perception
6. **Social Cognition**
   - recognition of emotions, theory of mind, behavioral regulation

www.dsm5.org/ProposedRevisions

New mechanistic concept



Sperling, 2011

Clinical and biomarker changes in ad-AD (Bateman et al, NEJM, July 2012)

- 128 participants; age at baseline and age of disease onset in the parent to calculate the expected years from expected onset
- A-beta42 in CSF declines 25 years
- Amyloid deposition (PIB-PET) 15 years
- CSF tau increase, atrophy starts 15 years
- Cerebral hypometabolism, impaired episodic memory 10 years
- Global cognitive impiarment (MMSE; CDR) 5 years before expected symptom onset
- Criteria for dementia met 3 years after

New Genetic finding

(Jonsson et al, Nature, Aug 2012)

- Coding variants in APP gene studied in whole genome data of 1795 Icelanders
- Those over 85 years with/without AD compared
- A coding mutation (A673T) in APP gene found which protects against AD and age-related cognitive decline
- This mutation results in 40% reduction in the formation of amyloidogenic peptides in vitro
- Rare mutation: 1 in 10 000 in North America
- Proof of principle that reducing beta-cleavage of APP may protect against AD

Amyloid Imaging

- 78 healthy subjects assessed with a cognitive battery and amyloid (florbetapir) PET (Sperling et al, 2013)
- Higher Florbetapir uptake correlated with lower immediate memory and delayed recall scores
- Higher amyloid burden is associated with lower memory performance among clinically normal older subjects.

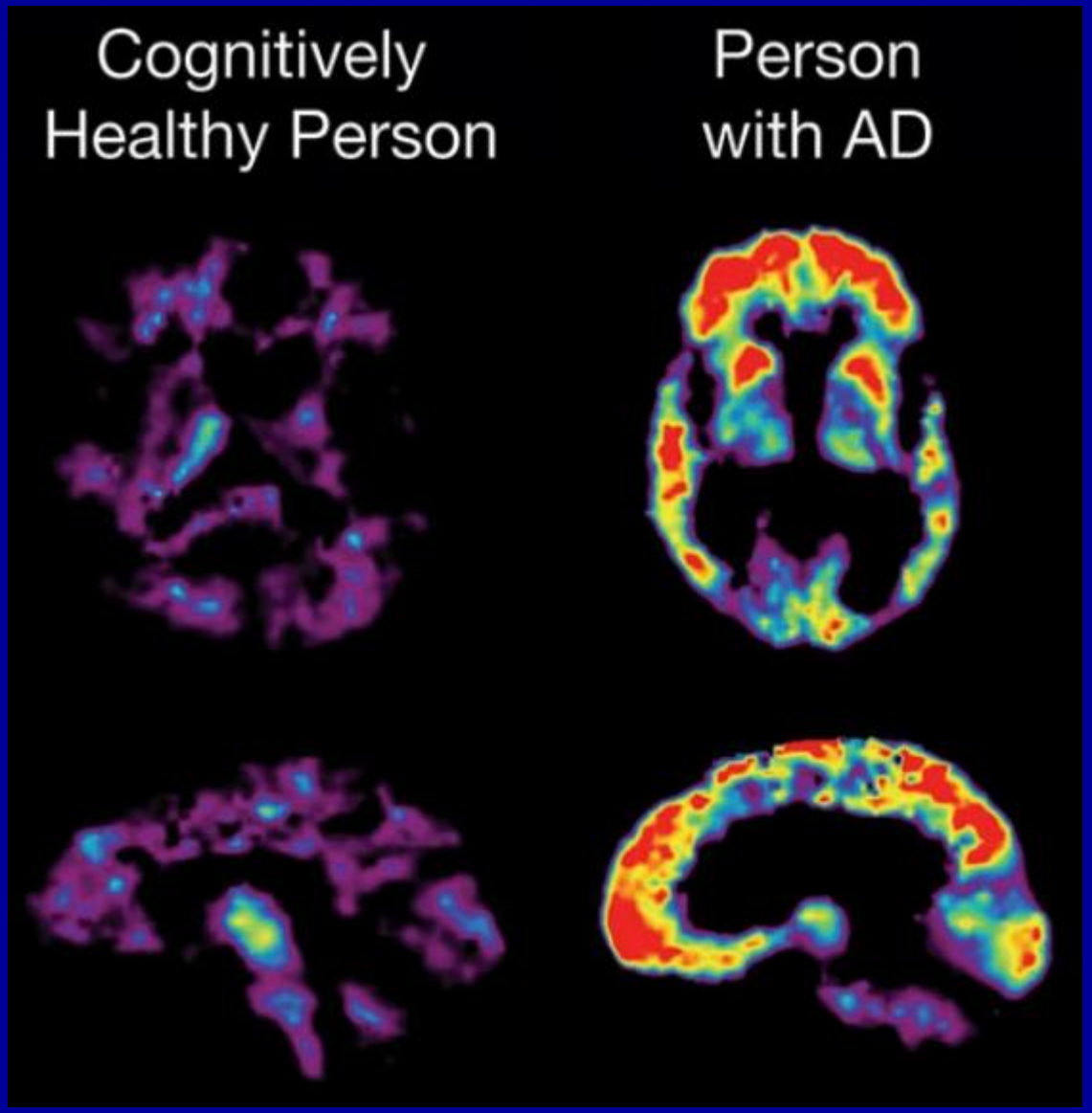
Biological markers and conversion to dementia (Prestia et al, 2013)

- 73 patients with MCI; CSF A?1-42, cortical metabolism (FDG-PET) and hippocampal volume assessed
- Patients divided into 5 groups: 1) A?1-42?FDG-PET?Hippo?2) A?1-42+ FDG-PET?Hippo?3) A?1-42 + FDG-PET + Hippo?4) A?1-42 + FDG-PET+ Hippo+, and 5) any other combination.
- **In** follow-up, 29 progressed to dementia. Incident dementia increased with greater biological severity in groups 1 to 5 from 4% to 27%, 64%, and 100%; and occurred increasingly earlier.
- “The core biomarker pattern is in line with the current pathophysiologic model of AD. Fully normal and fully abnormal pattern is associated with exceptional and universal development of dementia”.

Progression of tau pathology in AD

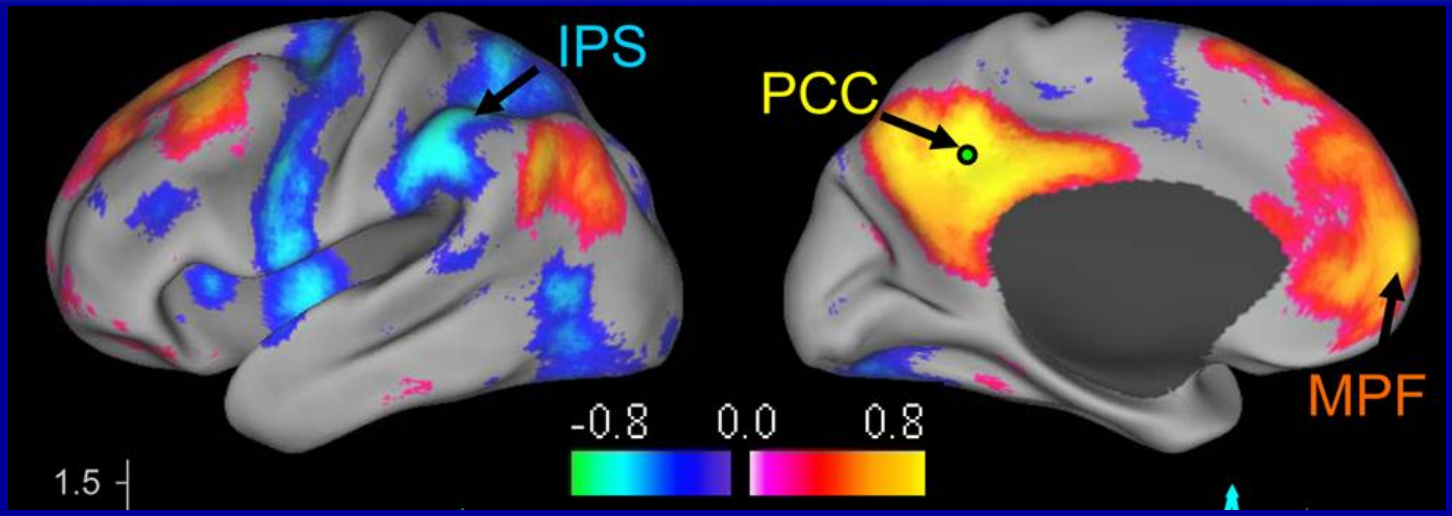
- Tauopathy in AD starts in entorhinal cortex (EC). A transgenic mouse differentially expressing pathological human tau in the EC studied
- Pathology propagates from the EC supporting a trans-synaptic spread along anatomically connected networks, between connected and vulnerable neurons (Liu et al, 2012);
- A sequence of progressive misfolding of tau proteins, circuit-based transfer to new cell populations, and deafferentation induced degeneration are part of tau-induced neurodegeneration (de Calignon et al, 2012).

New diagnostic methods



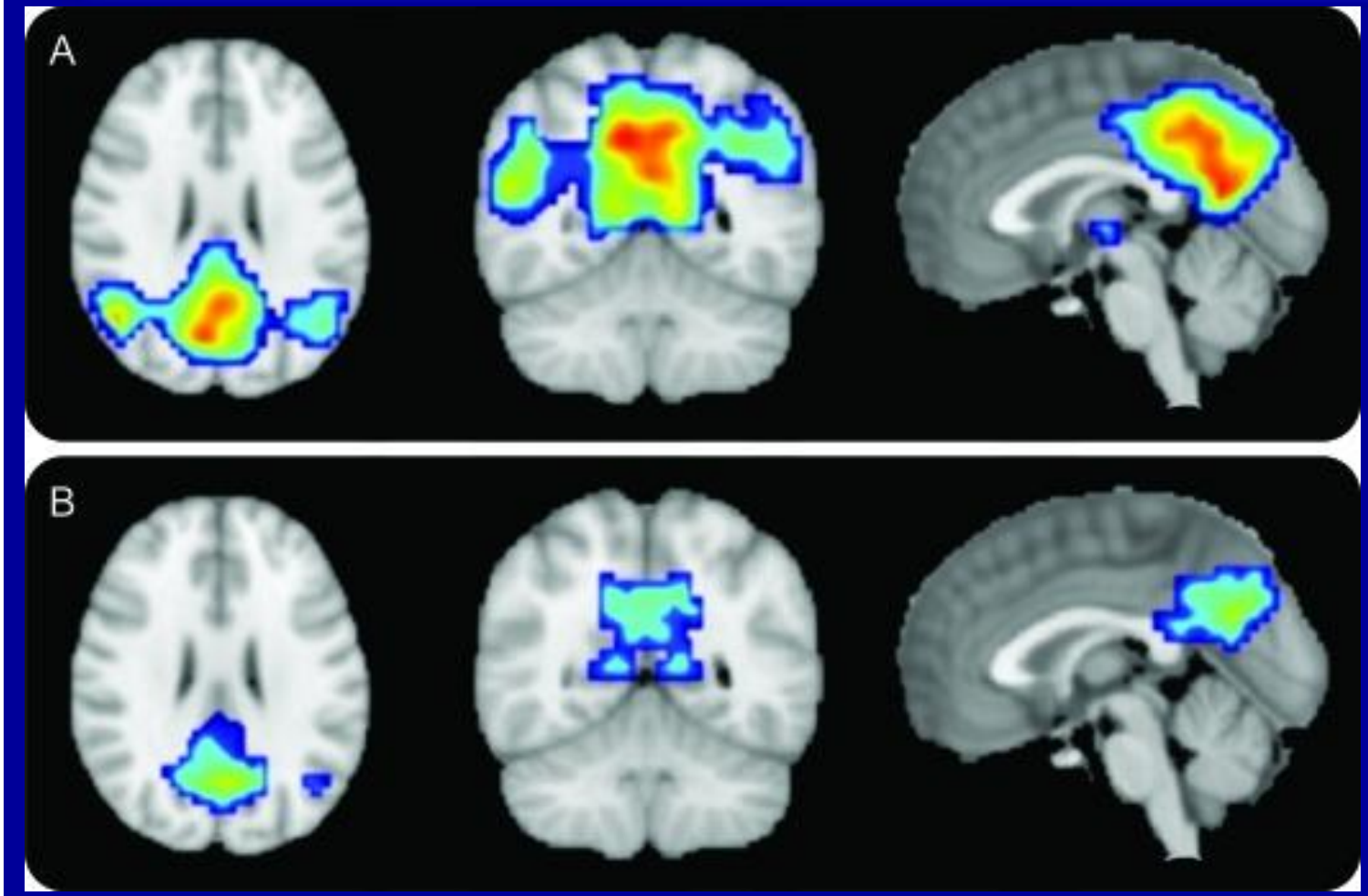
Florbetapir imaging for amyloid accumulation

fMRI in normals: default mode



- Brain is active at rest (DEFAULT MODE)
- Task free fMRI: low frequency coherent voxels (connectivity analysis)
- In MCI and AD progressive deterioration of DM activity (Rombouts et al. 2005, Human Brain Mapp)

Baseline DMN -MCI



Not-converted to AD

Converted to AD

Petrella et al, 2011, Neurology.

A blood based miRNA test for AD (Leidinger et al 2013)

- Next-generation sequencing of miRNAs from blood samples of 48 AD patients and 22 controls
- A total of 140 unique mature miRNAs with significantly changed expression levels.
- A panel of 12 miRNAs selected for further analysis on a larger cohort of 202 samples, comprising AD patients, healthy controls and patients with other CNS illnesses.
- Using this 12-miRNA signature, AD and controls differentiated with an accuracy of 93%, a specificity of 95% and a sensitivity of 92%.
- Differentiation of AD from other neurological diseases with accuracies between 74% and 78%.

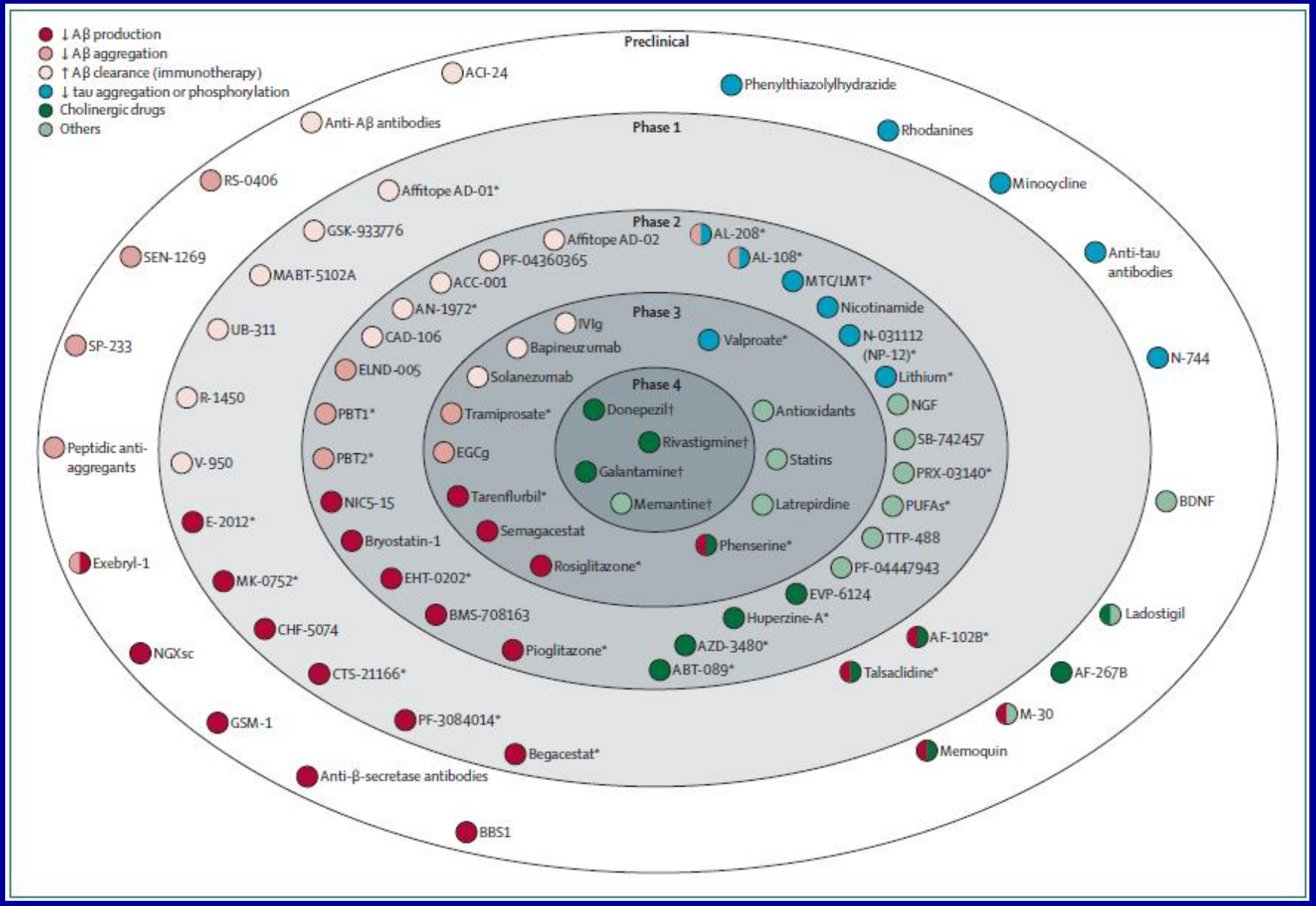
New epidemiological findings

New epidemiological findings

- Higher adherence to Mediterranian diet associated with lower likelihood of incident cognitive impairment (Tsivgoulis et al, 2013)
- Anti-HT (diuretic, ARB, and ACE-I) use, in addition to and/or independently of mean systolic blood pressure, associated with reduced risk of AD dementia (Yasar et al, 2013)
- The risk of cancer in patients with AD dementia was halved, and the risk of AD dementia in patients with cancer was 35% reduced (Musicco et al, 2013)

New treatment approaches

Drug development in AD



Mangialasche et al 2010

New failures

- **BAPINEUZUMAB**
- **SOLANEZUMAB (?)**
- **GAMMAGARD (IVIG)**
- **Ongoing:**
  - **Other passive and active immunizations**

Alzheimer's Prevention Trials at a Glance

Trial	Participants	Treatment	Outcome Measures
API: Alzheimer's Prevention Initiative	300 members of Colombian families, including 100 carriers of a mutated *PSEN1* gene	Crenezumab (Genentech)	Primary: Cognitive. Secondary: Biomarkers, including brain scans to measure amyloid accumulation and brain atrophy
DIAN: Dominantly Inherited Alzheimer Network	240 members of families with early-onset Alzheimer's; 60 have a mutation in one of three genes	Three anti-amyloid therapies to be determined	An initial phase will use biomarkers to identify the most promising drug candidate for a follow-up phase to examine cognitive effects
A4: Anti-Amyloid Treatment of Asymptomatic Alzheimer's	1500 healthy seniors, including 500 with amyloid-positive brain scans	One anti-amyloid therapy to be determined	Primary: Cognitive Secondary: Biomarkers

NEW FINDINGS

- Bexarotene, a drug for skin cancer, induces rapid reduction in the amount of soluble amyloid, formed amyloid plaques and associated behavioral changes in AD mouse models (Cramer et al, Science, 2012);
  - not replicated in several follow-up studies (Nature, May 2013)
- EpoD, another anti-cancer agent at Phase II, stabilizes microtubules, reduces formed tangles, improves deficits in learning and memory tests (Zhang et al, J Neuroscience, 2012)

Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease

Susan D Rountree[1], Wenyaw Chan[2], Valory N Pavlik[3], Eveleen J Darby[1], Samina Siddiqui[4] and Rachelle S Doody[1]

Relationship between persistency index and outcome measures (mixed effects regression analysis)

Outcome(s) with adjustment[a]	Beta coefficient[b] (standard error)			
	Intercept	Time, years	Persistency index	Persistency index × time
MMSE	3.89 (2.001)	−2.58 (0.13)[c]	−1.09 (0.77)	1.02 (0.23)[c]
ADAS-Cog[d]	55.45 (5.65)[c]	3.68 (0.66)[c]	−3.75 (2.09)	2.74 (1.32)[e]
BPMSE	10.46 (3.47)[e]	−2.55 (0.25)[c]	−1.76 (1.90)	1.00 (0.52)
PSMS	10.03 (1.85)[c]	1.68 (0.12)[c]	−0.09 (0.66)	−0.43 (0.21)[f]
IADL	18.63 (2.54)[c]	2.36 (0.17)[c]	4.19 (0.91)[c]	−1.42 (0.29)[c]
CDR-SB	11.43 (1.43)[c]	1.67 (0.09)[c]	1.42 (0.54)[e]	−0.61 (0.17)[g]

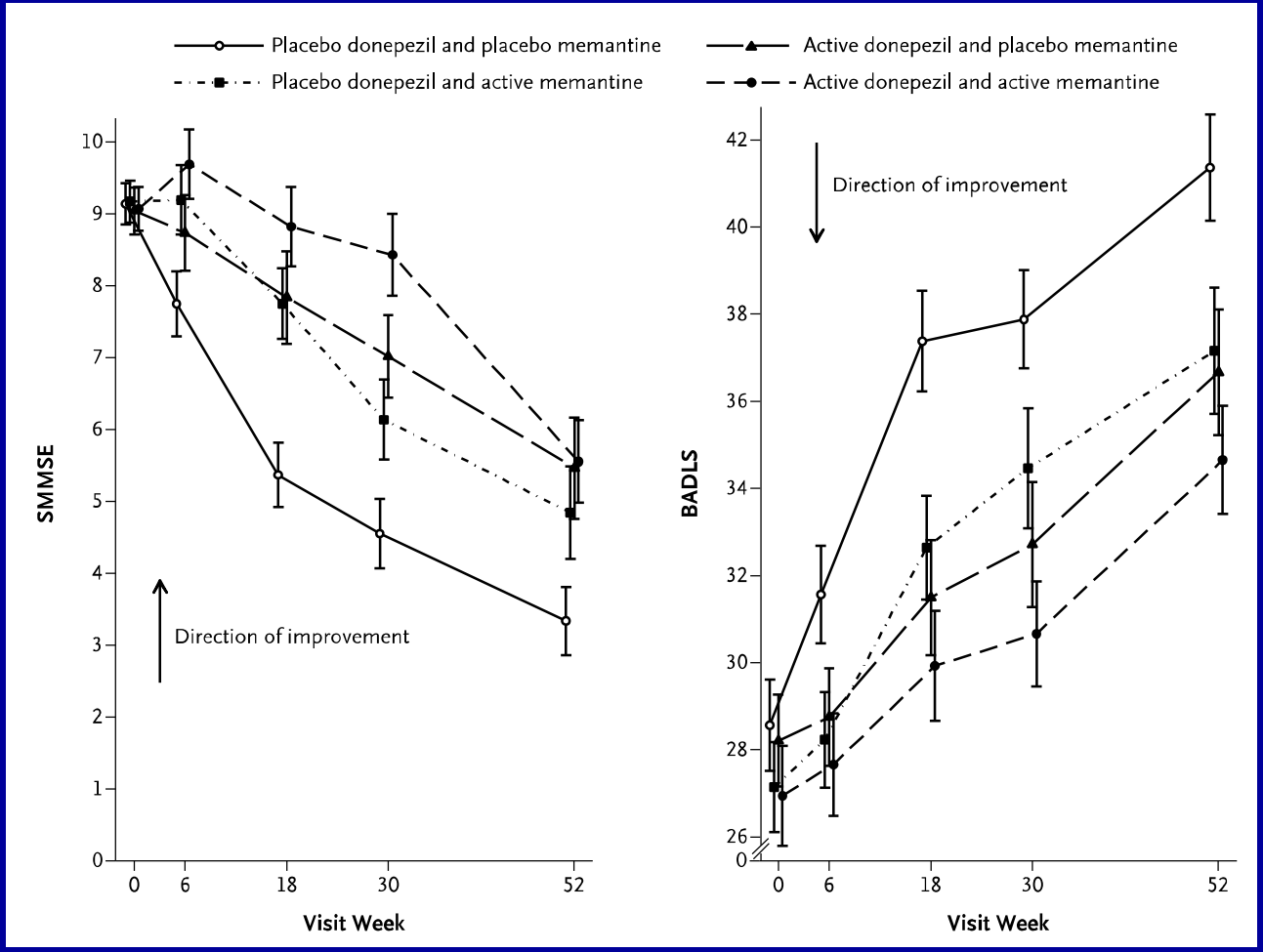
Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease (Howard R et al; NEJM, 2012)

• 295 patients treated with donepezil for at least 3 months, with moderate or severe AD (5 to 13 on the MSE), assigned to continue donepezil, discontinue donepezil, discontinue donepezil and start memantine, or continue donepezil and start memantine, for 52 weeks.

• Patients who continued donepezil, compared to those who discontinued, had 1.9 points higher score on MMSE and 3.0 points lower score on BADLS ($P<0.001$ for both). Patients who received memantine, compared to placebo, had a 1.2 points higher score on MMSE ($P<0.001$) and 1.5 points lower on BADLS ($P = 0.02$). The efficacy of donepezil and of memantine did not differ significantly in the presence or absence of the other.

• In patients with moderate or severe AD, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference with significant functional benefits over 12 months.

Combination in moderate to severe Alzheimer‘s disease



Howard et al., N Engl J Med, 2012

Conclusions

- New definitions, new diagnostic criteria for AD and AD dementia
- Role of early amyloid deposition more and more emphasized
- Amyloid-based treatments in more advanced stages failed
- Studies in very early AD cases on-going

References

- Dubois et al, Lancet Neurology; 2010
- McKhann et al, Alzheimers Dementia; 2011
- DSM-5, 2013
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- Bateman et al, NEJM, 2012
- Petrella et al, Neurology, 2011
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- Howard et al, NEJM, 2012