Triregionale SIN-SNO
Ivrea, 6-7 dicembre 2019

Aggiornamento sulle demenze: *clinica e diagnostica di laboratorio*

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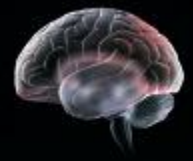
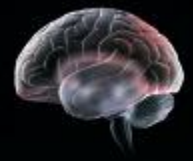
“What’s new in dementia?”

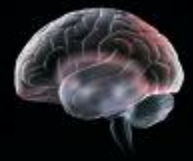
OUTLINE



- The AT(N) system: toward a biological definition of Alzhemer's disease
- Limbic-predominant age-related TDP-43 encephalopathy (LATE): a new type of dementia
- Are Anti-amyloid Therapies Still Worth Being Developed as Treatments for Alzheimer's Disease? The resuscitation of Aducanumab
- WHO: new guidelines to prevent cognitive decline and dementia

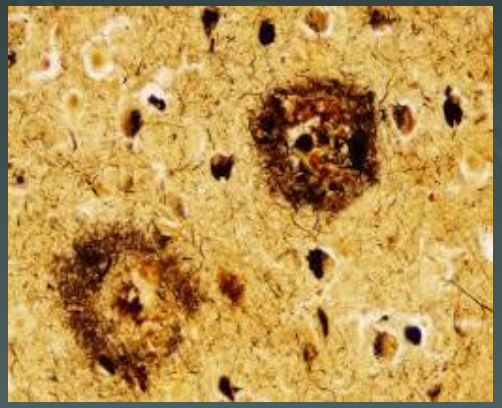


The AT(N) system: toward a biological definition of Alzhemer's disease



The AT(N) system: toward a biological definition of Alzhemer's disease

What's Alzheimer's disease?



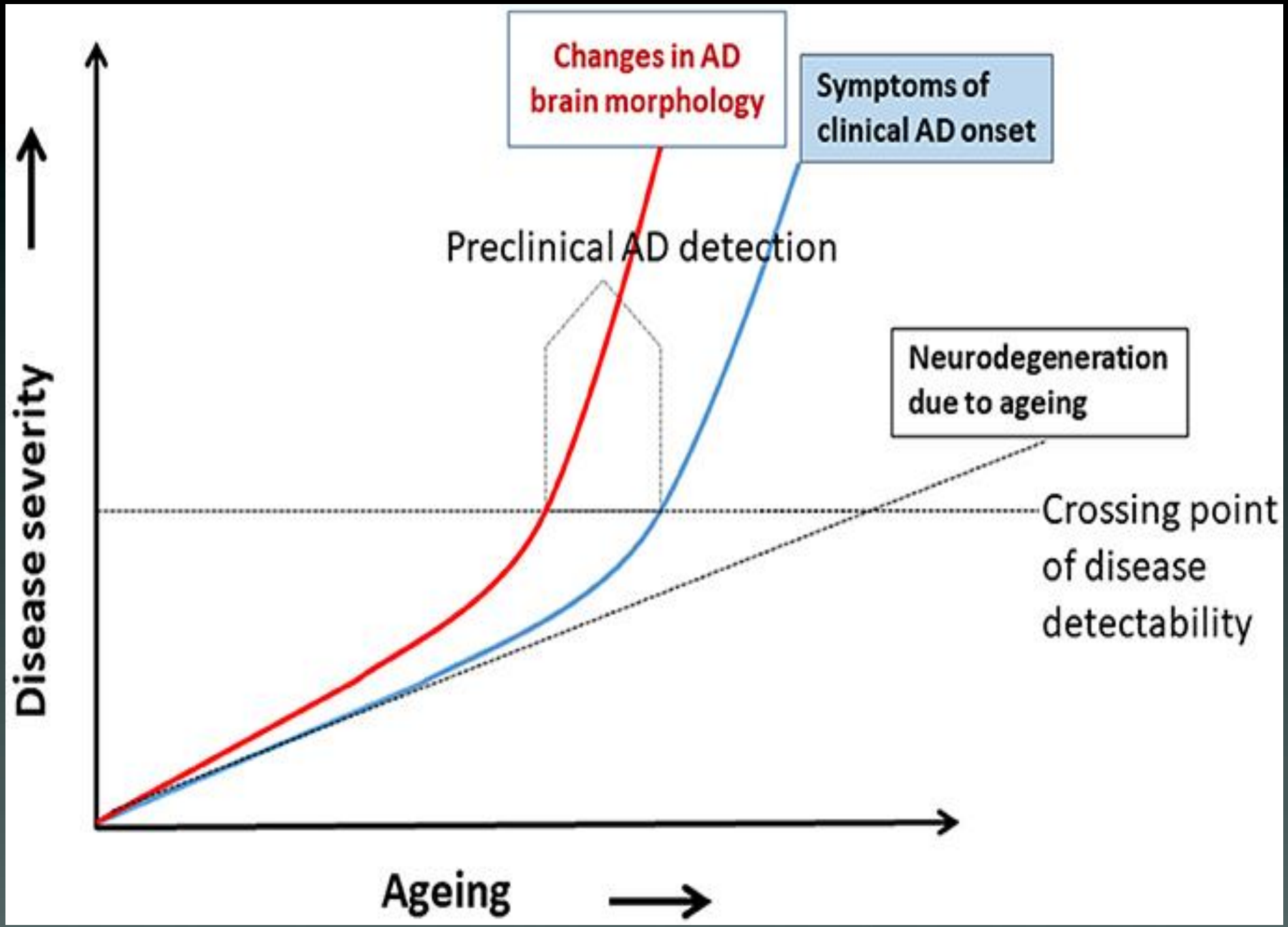
The term AD is often used to describe two very different entities:

- a prototypical clinical syndrome, mainly characterized by cognitive deficits, but without neuropathologic confirmation.
- a unique disease, showing at neuropathologic examination the presence of plaques and tangles, that is the leading cause of dementia.

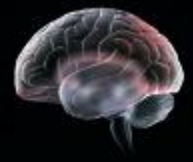
Major concerns

- It is now well established that the prototypical multidomain amnestic dementia historically used to define probable AD is neither sensitive nor specific for AD neuropathologic change: from 10% to 30% of individuals clinically diagnosed as AD dementia by experts do not display AD neuropathologic changes at autopsy.

- In addition, AD neuropathologic changes are often present without signs or symptoms, especially in older persons. Thirty to forty percent of cognitively unimpaired elderly persons have AD neuropathologic changes at autopsy.


Changes in AD brain morphology
Symptoms of clinical AD onset
Preclinical AD detection
Neurodegeneration due to ageing
Crossing point of disease detectability
Disease severity
Ageing

2011 NIA-AA criteria for AD



Preclinical

Mild Cognitive Impairment

Dementia

NIA-AA Criteria

Alzheimer's & Dementia, May 2011

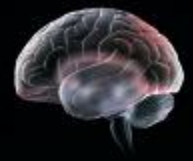
Updating NIA-AA guidelines

- Since the publication of the 2011 guidelines, data have continued to accumulate indicating that the cognitive decline in AD occurs continuously over a long period.

- Studies published since 2011 have reinforced the idea that certain imaging and CSF biomarkers are valid proxies for neuropathologic changes of AD.

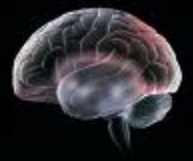
- Based on this background, NIA-AA leadership commissioned a work group whose charge was to examine the 2011 guidelines in the context of current scientific knowledge and if appropriate update them.

What's new in Alzheimer's disease



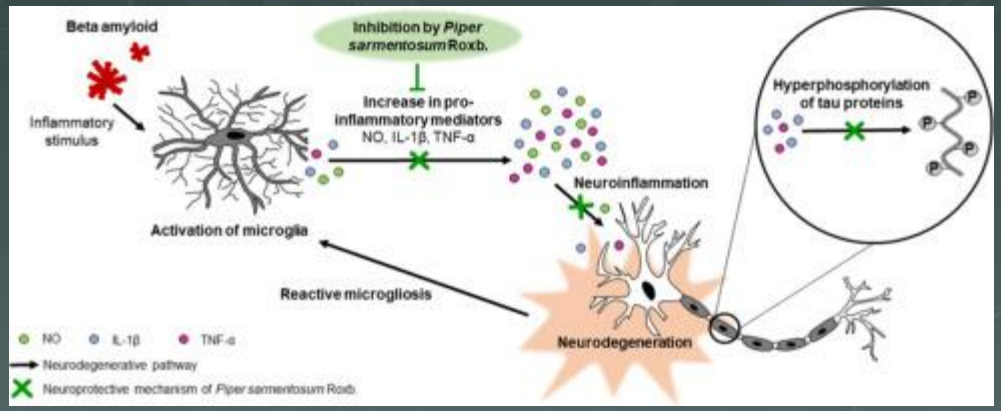
- The NIA-AA 2011 approach to incorporating biomarkers into models of AD began with patients' clinical symptoms, which appear relatively late in the disease, and worked backward to relate symptoms to biomarker findings.
- The Research Framework recommends a different approach where the neuropathologic changes detected by biomarkers define the disease.
- Defining AD by biomarkers indicative of neuropathologic change independent from clinical symptoms represents a profound shift in thinking.

Rethinking Alzheimer's disease

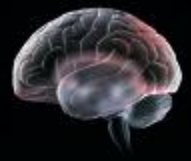


- We need to distinguish Alzheimer's unambiguously from other neurocognitive disorders.

- The biological definition explicitly specifies the attributes that together classify Alzheimer's as a unique disease entity: the intracerebral accumulation of abnormal Aβ and tau.



Rethinking Alzheimer's disease

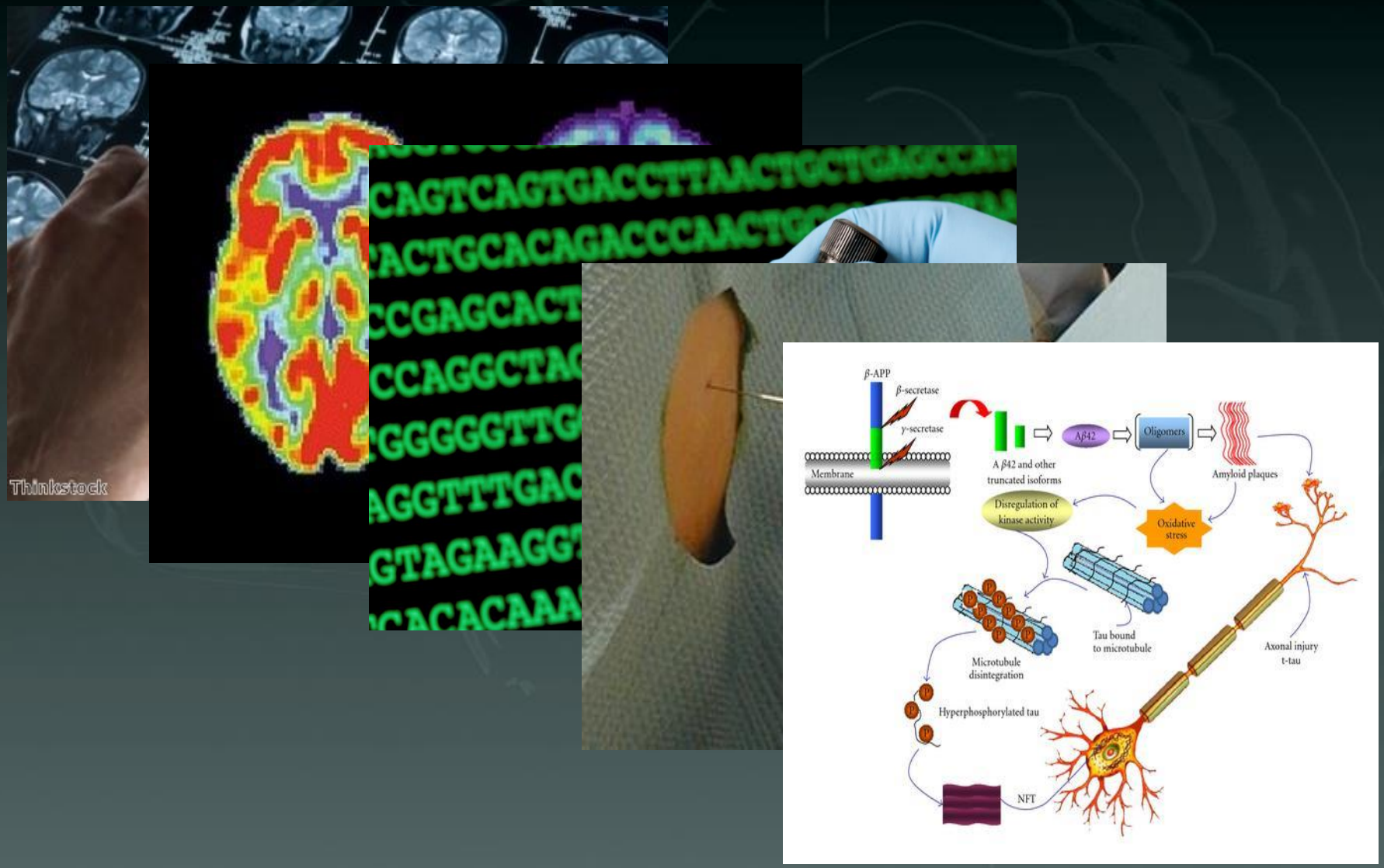


- Other areas of medicine have used this approach to define pathologic processes using biomarkers.

- For example, bone mineral density, hypertension, hyperlipidemia, and diabetes are defined by biomarkers.

- Interventions modulating these biomarkers have been shown to reduce the likelihood of developing fractures and myocardial and cerebral infarctions.

Biomarkers for Alzheimer's disease



"Imaging and CSF biomarkers are valid proxies for neuropathologic changes of AD"

- Imaging-to-autopsy comparison studies have established that amyloid positron emission tomography (PET) is a valid in vivo surrogate for Aβ deposits (in brain parenchyma/vessel walls).

- It is also now widely accepted that CSF Aβ42 is a valid indicator of the abnormal pathologic state associated with cerebral Aβ. An additional development has been the introduction of PET ligands for pathologic tau.

- By contrast, recent research has highlighted the fact that measures of neurodegeneration that are commonly used in AD research— MRI, FDG-PET, and CSF T-tau—are not specific for AD but rather are nonspecific indicators of damage that may derive from a variety of etiologies, for example, cerebrovascular injury.

ELSEVIER

CrossMark

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

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Abstract

In 2011, the National Institute on Aging and Alzheimer's Association created separate diagnostic recommendations for the preclinical, mild cognitive impairment, and dementia stages of Alzheimer's disease. Scientific progress in the interim led to an initiative by the National Institute on Aging and Alzheimer's Association to update and unify the 2011 guidelines. This unifying update is labeled a "research framework" because its intended use is for observational and interventional research, not routine clinical care. In the National Institute on Aging and Alzheimer's Association Research Framework, Alzheimer's disease (AD) is defined by its underlying pathologic processes that can be documented by postmortem examination or *in vivo* by biomarkers. The diagnosis is not based on the clinical consequences of the disease (i.e., symptoms/signs) in this research framework, which shifts the definition of AD in living people from a syndromal to a biological construct. The research framework focuses on the diagnosis of AD with biomarkers in living persons. Biomarkers are grouped into those of β amyloid deposition, pathologic tau, and neurodegeneration [AT(N)]. This

The authors' conflict of interest statements can be viewed online at https://doi.org/10.1016/j.jalz.2018.02.018.

[†]The listed National Institute on Aging program staff are acknowledged for their key contributions in leadership and scientific guidance on this project.

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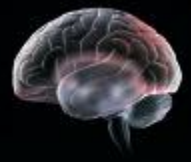
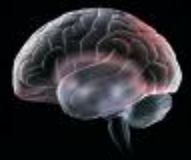
https://doi.org/10.1016/j.jalz.2018.02018

NIA-AA 2018 Research Framework



- Alzheimer's disease (AD) is defined by its underlying pathologic processes that can be documented by postmortem examination or in vivo by biomarkers.
- The definition of AD in living people shifts from a syndromal to a biological construct. The research framework focuses on the diagnosis of AD with biomarkers in living persons.
- Biomarkers are grouped into those of β amyloid deposition, pathologic tau, and neurodegeneration [AT(N)].

Biomarkers in the AT(N) system



A: Aggregated Aβ or associated pathologic state

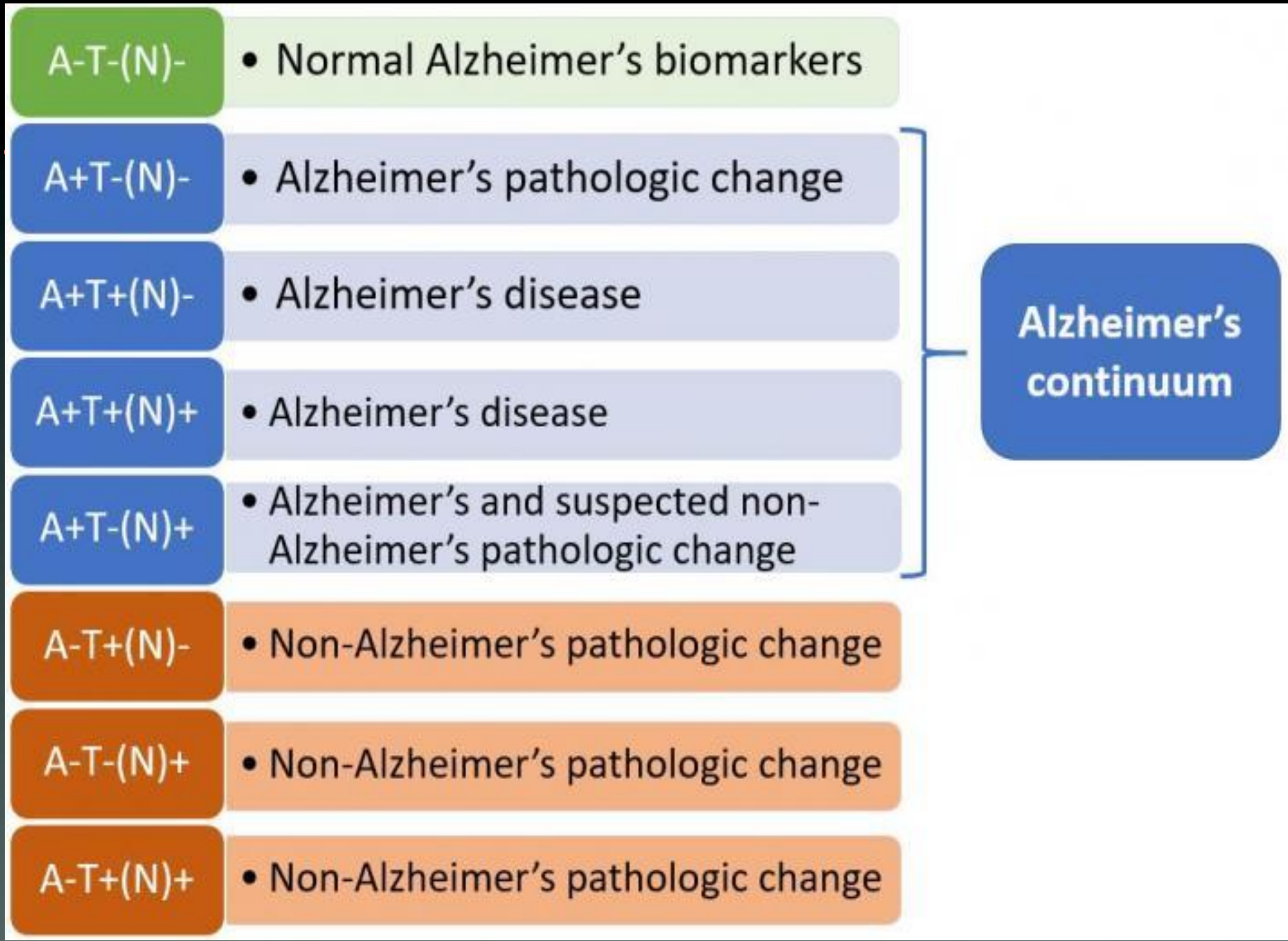
- Amyloid PET
- CSF Aβ42, or Aβ42/Aβ40 ratio

T: Aggregated tau (neurofibrillary tangles) or associated pathologic state

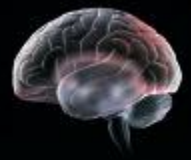
- CSF phosphorylated tau
- Tau PET

(N): Neurodegeneration or neuronal injury

- Anatomic MRI
- FDG PET
- CSF total tau

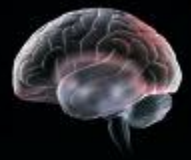

A-T-(N)-
• Normal Alzheimer's biomarkers
A+T-(N)-
• Alzheimer's pathologic change
A+T+(N)-
• Alzheimer's disease
A+T+(N)+
• Alzheimer's disease
A+T-(N)+
• Alzheimer's and suspected non-Alzheimer's pathologic change
Alzheimer's continuum
A-T+(N)-
• Non-Alzheimer's pathologic change
A-T-(N)+
• Non-Alzheimer's pathologic change
A-T+(N)+
• Non-Alzheimer's pathologic change

NIA-AA 2018 Research Framework



- It is premature and inappropriate to use this research framework in general medical practice.
- The committee recognized the research framework must function in two major contexts — observational cohort studies and interventional trials.
- However, the new NIA-AA Research Framework criteria offer a common structure and language to construct new Alzheimer's disease conceptual model.

Flexibility to incorporate new biomarkers



• The current form of the NIA-AA research framework is designed around biomarker technology that is presently available.

• TDP43 and α-synuclein proteinopathies, micro infarcts, hippocampal sclerosis, and argyrophilic grains can occur alone, or more frequently, along with AD pathologic changes; however, validated biomarkers are not presently available for them.

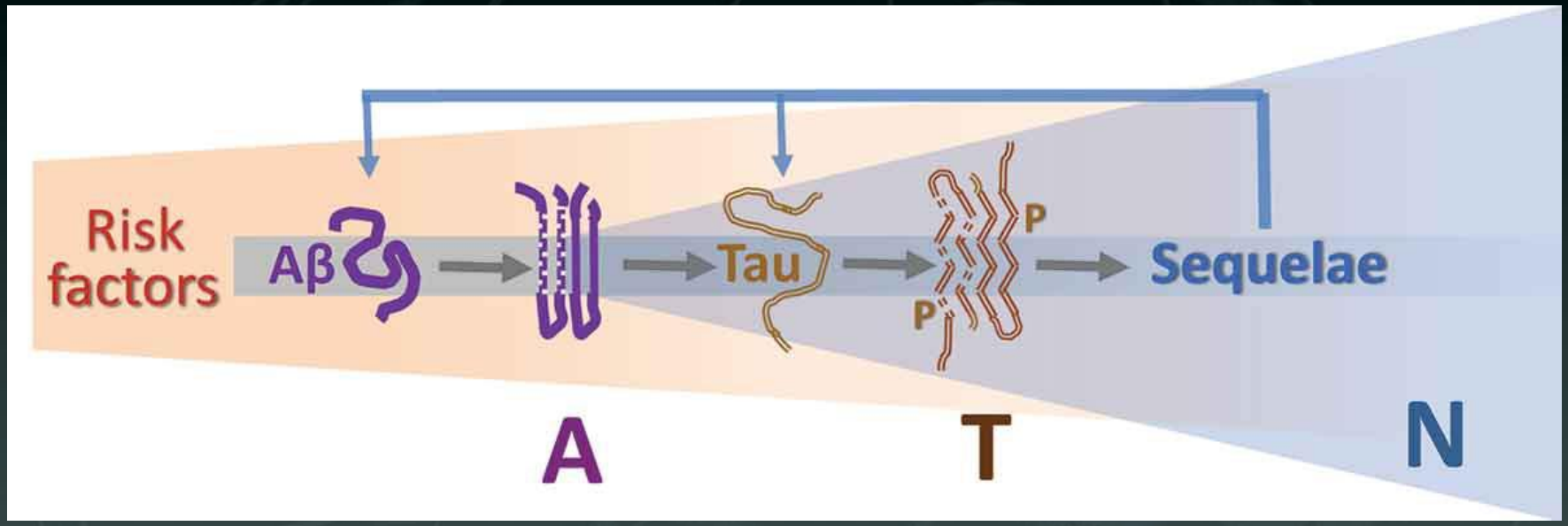
•The AT(N) biomarker scheme is expandable to incorporate new biomarkers. For example, a vascular biomarker group could be added, that is, ATV(N), when a clear definition of what constitutes V+ is developed.

ATN profiles among cognitively normal individuals and longitudinal cognitive outcomes.

Soldan A., et al. Neurology 2019, 92:1567-1579

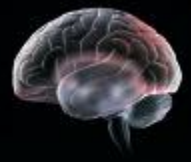
- OBJECTIVE: To examine the long-term cognitive trajectories of individuals with normal cognition at baseline and ATN profiles.
- METHODS: Pooling data across 4 cohort studies, 814 cognitively normal participants (mean baseline age = 59.6 years) were classified into 8 ATN groups. Cognitive performance was measured using a previously validated global factor score and with the Mini-Mental State Examination.
- RESULTS: Using different model formulations and cut points for determining biomarker abnormality, only the group with abnormal levels of amyloid, tau, and neurodegeneration (A+T+N+) showed consistently greater cognitive decline than the group with normal levels of all biomarkers (A-T-N-).
- CONCLUSION: The results are consistent with the hypothesis that both elevated brain amyloid and neurofibrillary tangles are necessary to observe accelerated neurodegeneration, which in turn leads to cognitive decline.

A causal upstream role for Aβ in the pathogenesis of AD



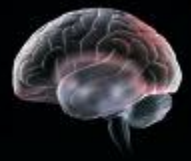
Although β-amyloidosis alone is insufficient to cause cognitive deterioration directly, it may be sufficient to cause downstream pathologic changes (i.e., tauopathy and neurodegeneration) that ultimately lead to cognitive deterioration.

What's new in dementia?



Limbic-predominant age-related TDP-43 encephalopathy (LATE): a new type of dementia

What's new in dementia?



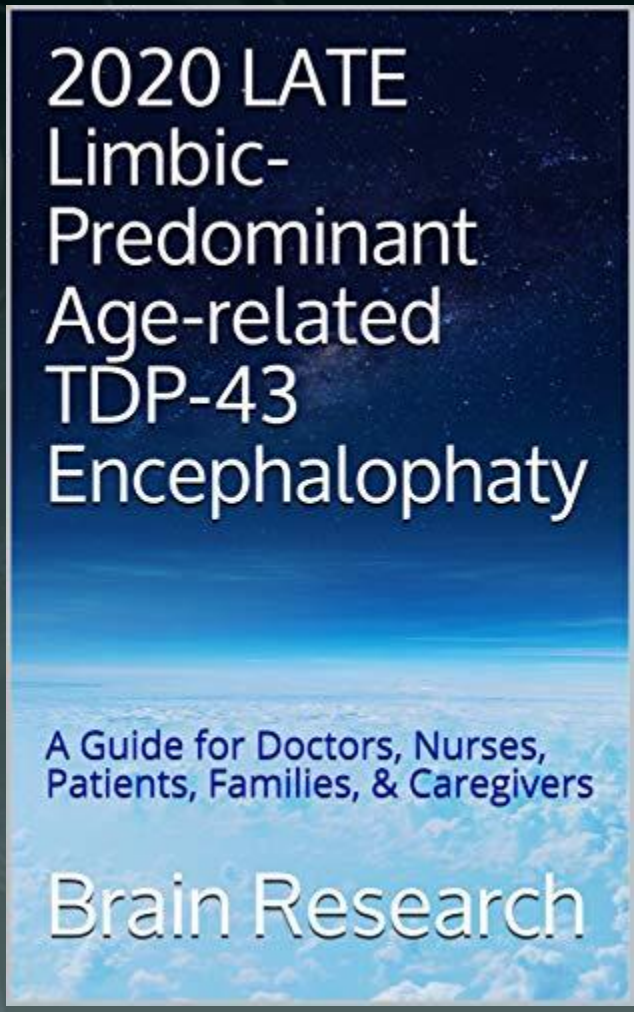
BRAIN

A JOURNAL OF NEUROLOGY

REVIEW

Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Peter T. Nelson, Dennis W. Dickson, John Q. Trojanowski, Clifford R. Jack Jr., Patricia A. Boyle, Konstantinos Arfanakis, Rosa Rademakers, Irina Alafuzoff, Johannes Attems, Carol Brayne, Ian T.S. Coyle-Gilchrist, Helena C. Chui, David W. Fardo, Margaret E. Flanagan, Glenda Halliday, Suvi R.K. Hokkanen, Sally Hunter, Gregory A. Jicha, Yuriko Katsumata, Claudia H. Kawas, C. Dirk Keene, Gabor G. Kovacs, Walter A. Kukull, Allan I. Levey, Nazanin Makkinejad, Thomas J. Montine, Shigeo Murayama, Melissa E. Murray, Sukriti Nag, Robert A. Rissman, William W. Seeley, Reisa A. Sperling, Charles L. White III, Lei Yu and Julie A. Schneider



What Does it Mean When What Looks Like Alzheimer's Isn't Alzheimer's?

What's LATE?

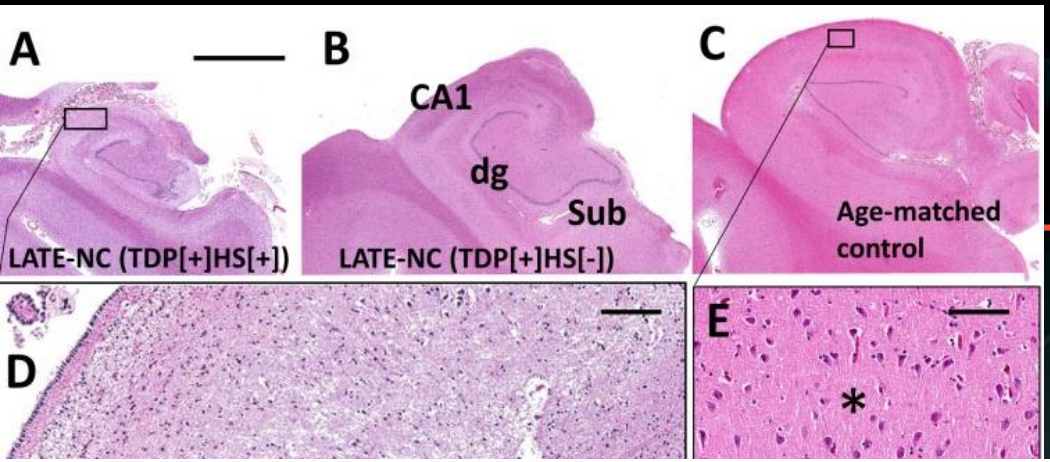
LATE neuropathological change (LATE-NC) is defined by a stereotypical TDP-43 proteinopathy in older adults, with or without coexisting hippocampal sclerosis pathology.

LATE-NC is a common TDP-43 proteinopathy, associated with an amnestic dementia syndrome that mimicked Alzheimer's-type dementia in retrospective autopsy studies.

LATE is distinguished from frontotemporal lobar degeneration with TDP-43 pathology based on its epidemiology (LATE generally affects older subjects), and relatively restricted neuroanatomical distribution of TDP-43 proteinopathy.

In community-based autopsy cohorts, 25% of brains had sufficient burden of LATE-NC to be associated with discernible cognitive impairment.

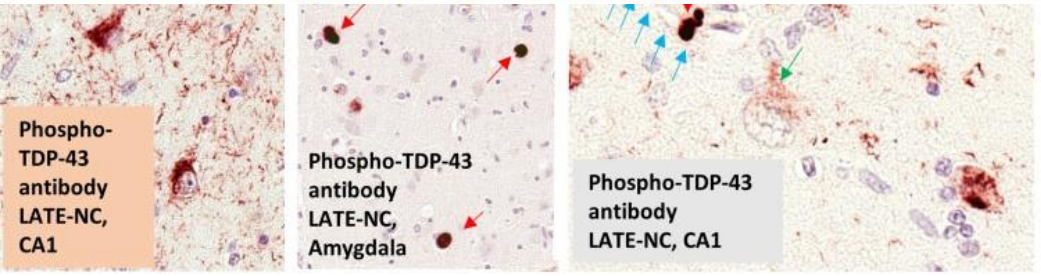
LATE neuropathological changes (LATE-NC).



(A–E) Coronally sectioned human hippocampi stained using haematoxylin and

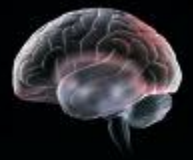
Simplified staging of TDP-43 proteinopathy* for routine LATE-NC diagnosis (consensus recommendation)		Josephs TDP-43 proteinopathy staging (KA Josephs et al, 2013)		Rush University TDP-43 proteinopathy staging (S Nag et al, 2017)	
0	None	0	None	0	None
1	Amygdala	1	Amygdala	1	Amygdala
2	Hippocampus	2	Entorhinal cortex, subiculum	2	Entorhinal cortex, CA1
		3	Dentate, Occipitotemporal cortex	3	Anterior temporal cortex
		4	Insula, Inf temporal cortex	4	Midtemporal and orbitofrontal cortex
		5	Inf olive, midbrain		
3	Middle frontal gyrus (MFG)	6	Basal ganglia, MFG	5	MFG

*-*Any* TDP-43 proteinopathy is seen in that anatomic region



to demonstrate the normal cellular architecture and intact eosinophilic neuropil (asterisk).

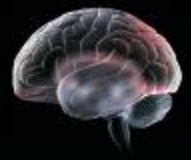
Genetics of LATE



The following five genes have been reported to harbour risk alleles associated with pathological manifestations we refer to as LATE-NC:

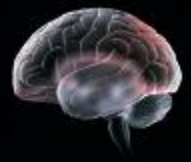
- granulin (GRN) on chromosome 17q,
- transmembrane protein 106B (TMEM106B) on chromosome 7p,
- ATP-binding cassette sub-family member 9 (ABCC9) on chromosome 12p,
- potassium channel subfamily M regulatory beta subunit 2 (KCNMB2) on chromosome 3q,
- apolipoprotein E (APOE) on chromosome 19q.

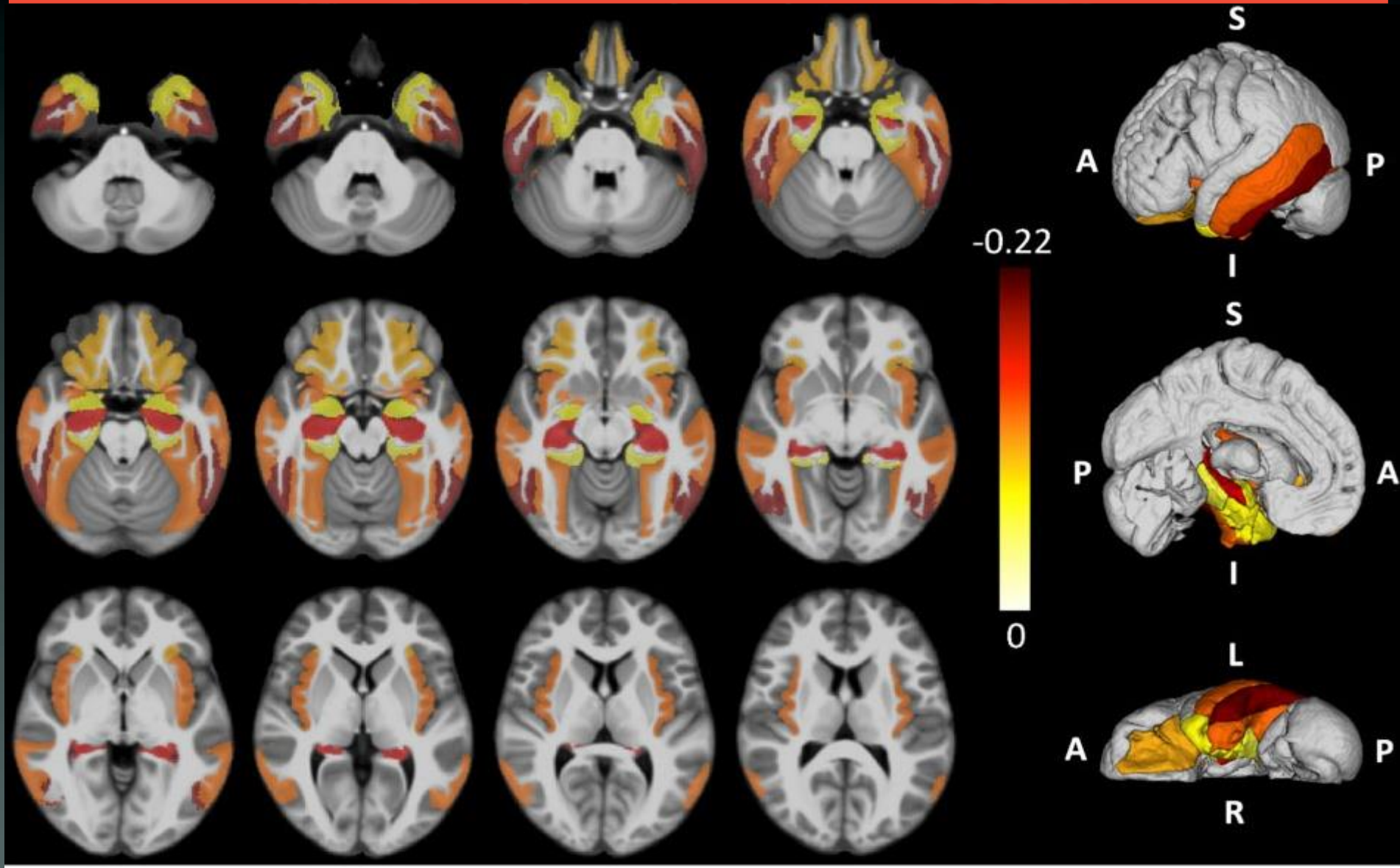
Clinical and neurocognitive features of LATE



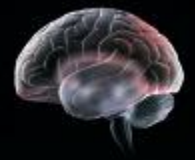
- The clinical course of subjects with autopsy-proven LATE-NC has been characterized as an amnestic cognitive syndrome that can evolve to incorporate multiple cognitive domains and ultimately to impair activities of daily living, i.e. the dementia syndrome.
- The cognitive impairment is greater than can be accounted for by Alzheimer Disease - NC or other pathologies.
- Neuropsychiatric disturbances have been reported in some subjects with LATE-NC, and a retrospective, cross-sectional, multicentre study found evidence of increased risk of ‘agitation/aggression’ symptoms in subjects with ADNC and comorbid TDP-43 proteinopathy in comparison to subjects with ADNC lackingTDP-43 proteinopathy

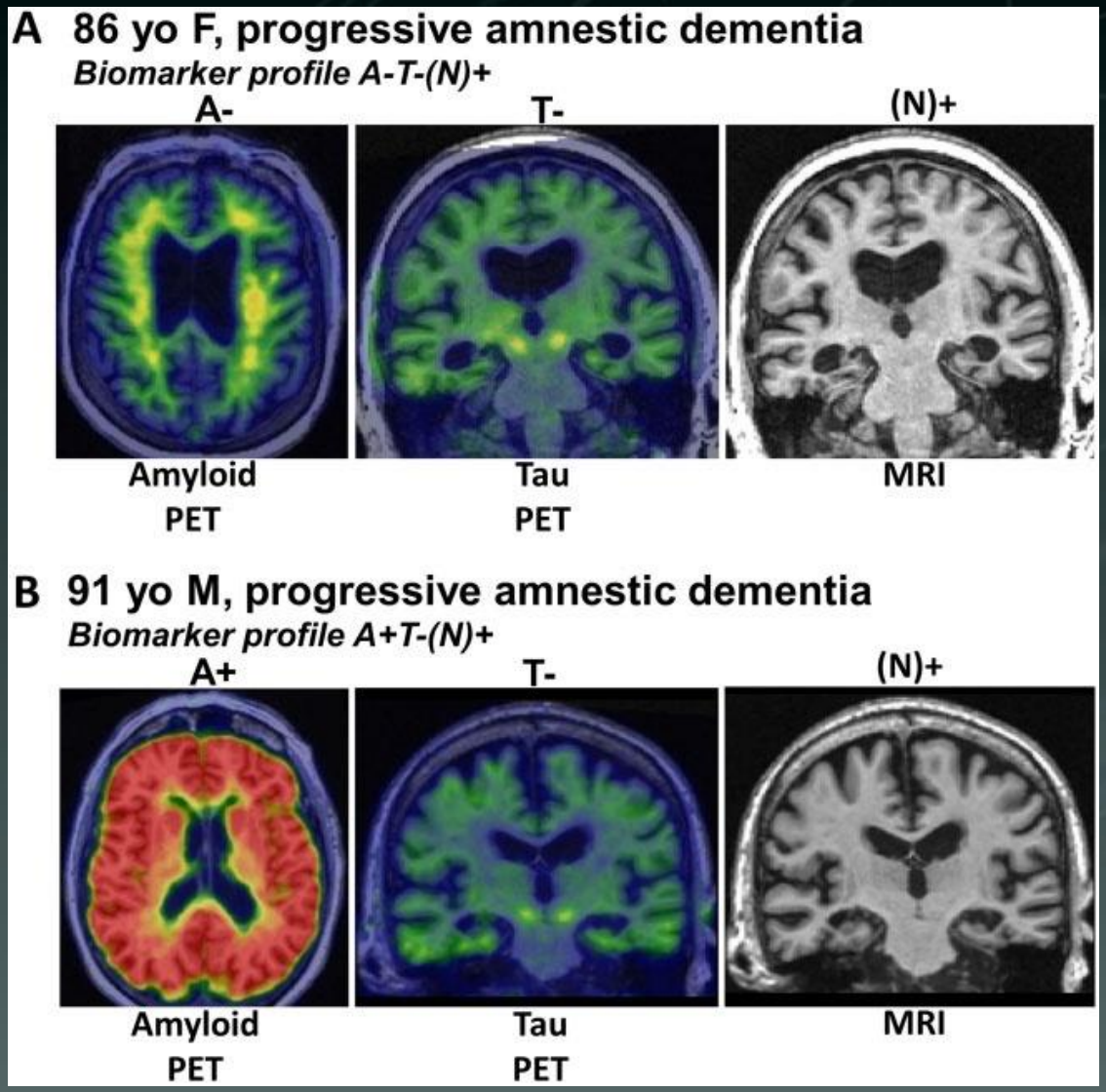
LATE: MRI studies





LATE: biomarkers

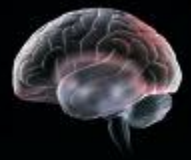




There is no molecule-specific biomarker for LATE.

This is an important area of need for use in clinical trials (including as a potential exclusion criterion for Alzheimer's disease clinical trials) and longitudinal studies of the clinical and pathological progression of LATE.

LATE: future directions

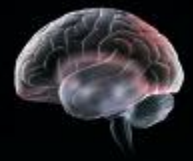


Animal models and basic science research into LATE are imperative, with the caveat that the aged human brain is challenging to model accurately.

Development of specific LATE biomarker(s) should be a high scientific priority. Developing biomarkers or other criteria to identify subjects with LATE would augment observational studies that seek to unravel the natural history of LATE, and its coevolution with other ageing related diseases.

Additional epidemiological, clinical, neuroimaging, and genetic studies will be important to better characterize the public health impact and clinical phenotypes for LATE.

What's new in Alzheimer's disease



Are Anti-amyloid Therapies Still Worth Being Developed as Treatments for Alzheimer's Disease? The resuscitation of *Aducanumab*

"Will We Ever Cure Alzheimer's?"

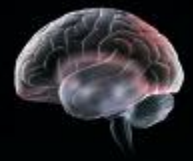
March 22, 2019

Latest Experimental Alzheimer's Drug Fails Testing

Drugmakers Biogen and Eisai ended studies of treatment, deeming it unlikely to benefit patients in latest research setback

The search for new Alzheimer's disease treatments hit another big setback on Thursday when drugmakers Biogen Inc. and Eisai Co. said they would terminate two late-stage studies of an experimental drug after determining it would likely fail to help patients.

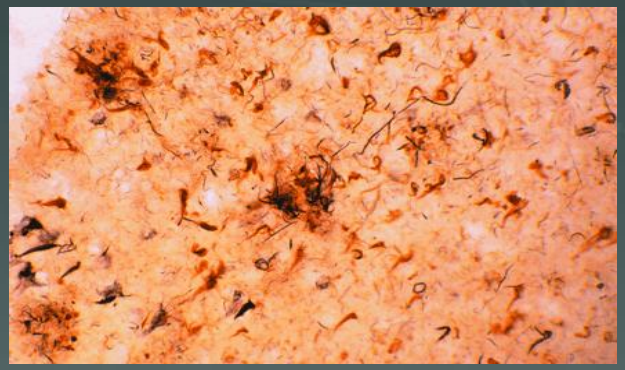
Rethinking Aβ-centric therapies

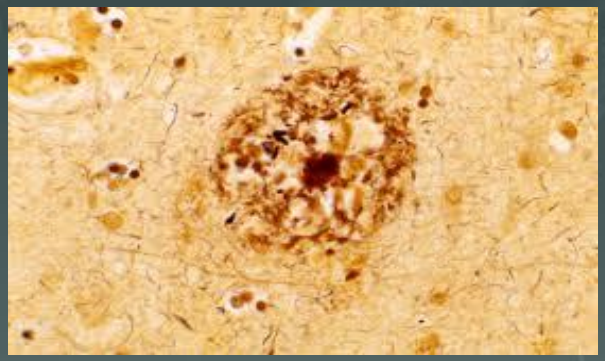


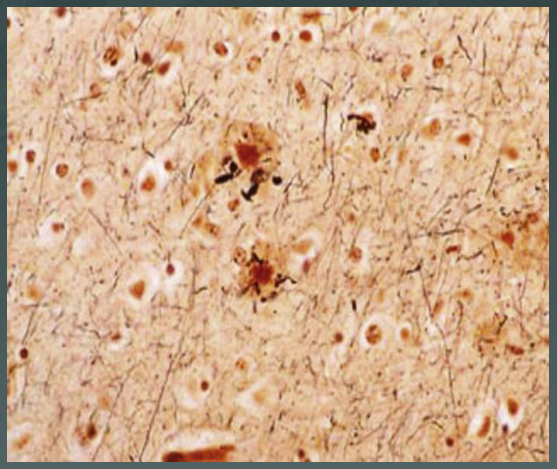
- The bulk of AD research during the last twenty-five years has been Aβ-centric based on a strong faith in the Amyloid Cascade Hypothesis which is not supported by the data on humans.
- The main function of APP is probably synaptic formation and repair. APP expression is rapidly upregulated during neural stress.
- Aβ, though amyloidogenic, is a normal metabolite of APP. An imbalance between the rate of production and clearance of Aβ leads to its deposition as amyloid plaques.
- The bulk of the studies suggest that soluble/oligomeric Aβ as the main neurotoxic state of the peptide. Aggregation of Aβ into fibrils could be a neuroprotective response.

Anti-amyloid therapies for AD

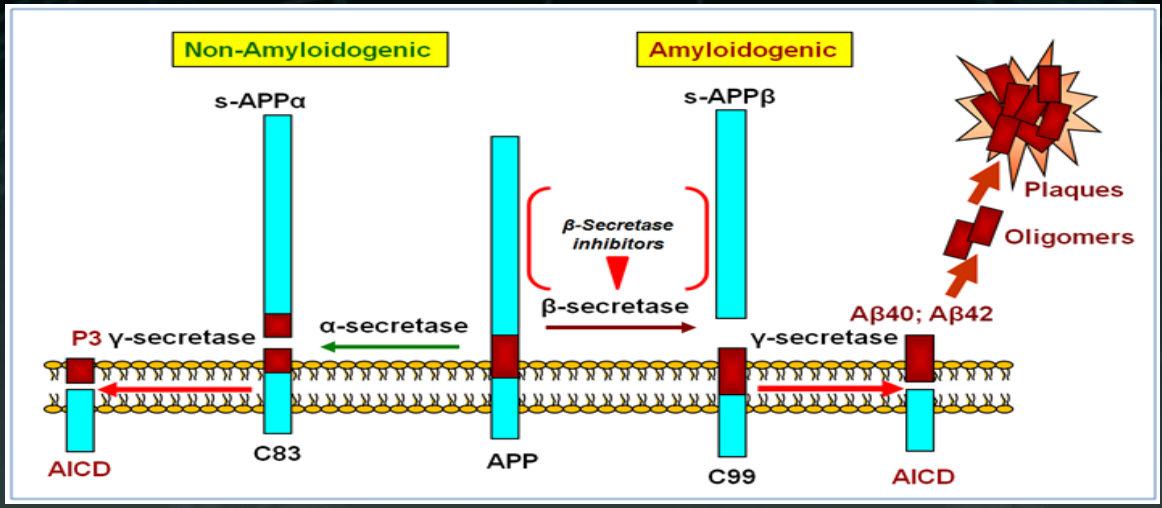
- Inhibition of peptide synthesis
- Active immunization
- Passive immunization







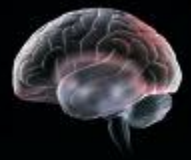
Inhibition of peptide synthesis



• Many small molecules specific inhibitors of gamma-secretases were developed and several clinical trials have been launched. Unfortunately, tarenflurbil and semagacestat, the first gamma-secretase inhibitors tested in clinical trials, failed in phase III at demonstrating any therapeutic efficacy.

• To date, seventeen BACE1 inhibitors have failed in double-blind, placebo-controlled clinical trials in patients with mild-to-moderate or prodromal AD, or in cognitively normal subjects at risk of developing AD.

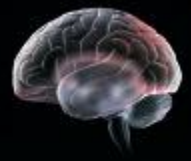
Passive immunization



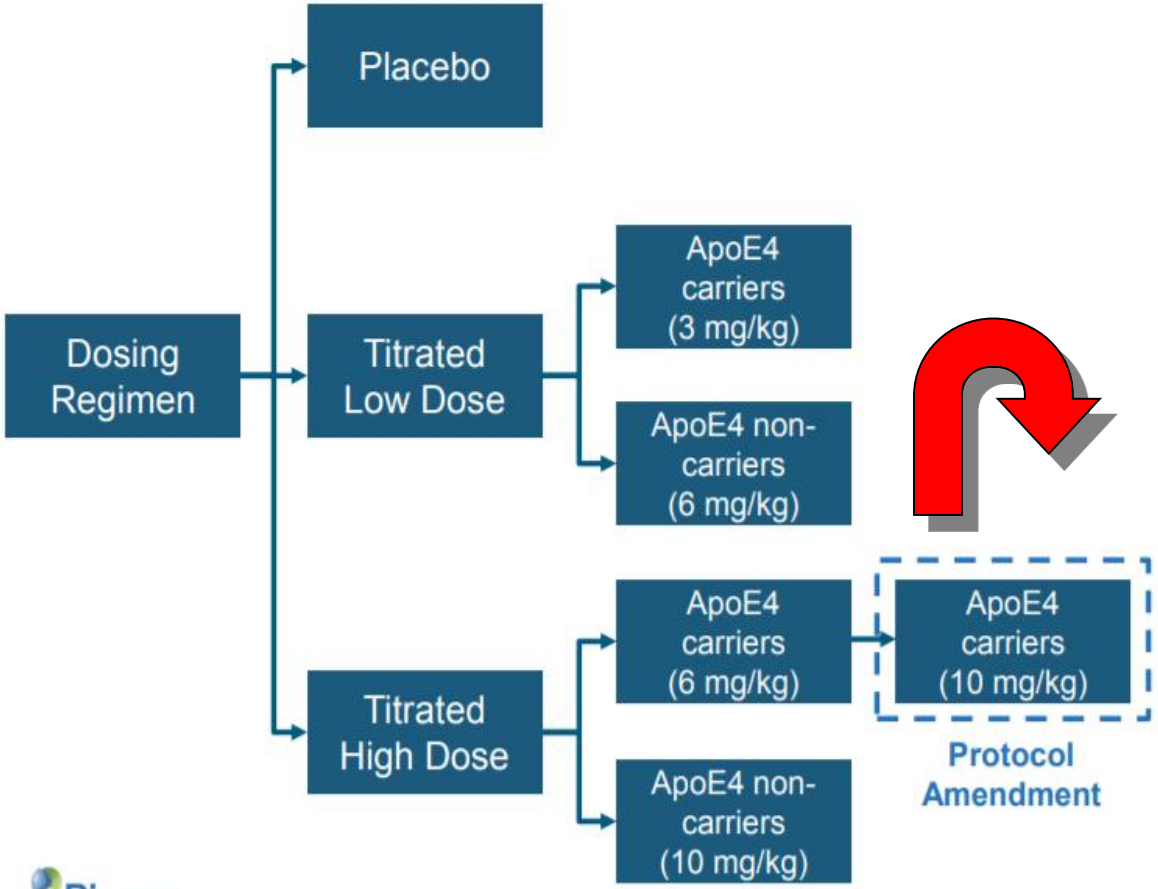
• Phase 3 clinical trials of bapineuzumab and solanezumab, antibodies targeted at amyloid-beta (Aβ) removal, have failed to meet their primary endpoints. Neither drug improves clinical outcomes in patients with late onset AD, joining a long list of unsuccessful attempts to treat AD with anti-amyloid therapies.

• New passive anti-Aβ immunotherapies (gantenerumab and crenezumab) are being tested in prodromal Alzheimer's disease patients, in presymptomatic individuals with Alzheimer's disease-related mutations, or in asymptomatic individuals at risk of developing Alzheimer's disease to definitely test the Aβ cascade hypothesis of Alzheimer's disease.

Aducanumab: Alzheimer's drug resurrected!



EMERGE and ENGAGE dosing regimens



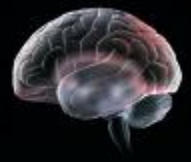
EMERGE/ENGAGE Overview

- Two identically designed Phase 3 studies
- Enrolled patients with mild cognitive impairment due to Alzheimer's disease (AD) and mild AD dementia
- All patients screened with PET* for elevated brain amyloid beta levels
- ~ 2/3 of patients were ApoE4 carriers in each study, well balanced across arms
- Primary endpoint: CDR-SB# at 18 months
- All treatment arms included titration

Biogen

* PET = positron emission tomography
# CDR-SB = Clinical Dementia Rating-Sum of Boxes

Aducanumab: Alzheimer's drug resurrected!



Primary endpoint of EMERGE (larger dataset)

	ITT Population		OTC Population	
	% Reduction vs. Placebo[a] p-value		% Reduction vs. Placebo[a] p-value	
	Low dose (N=543)	High dose (N=547)	Low dose (N=329)	High dose (N=340)
CDR-SB	**-14%** 0.117	**-23%** 0.010	**-16%** 0.134	**-23%** 0.031

[a]: difference in change from baseline vs. placebo at Week 78. Negative percentage means less decline in the treated arm.

N: numbers of randomized and dosed subjects that were included in the analysis. Placebo = 548 (ITT) and 313 (OTC).

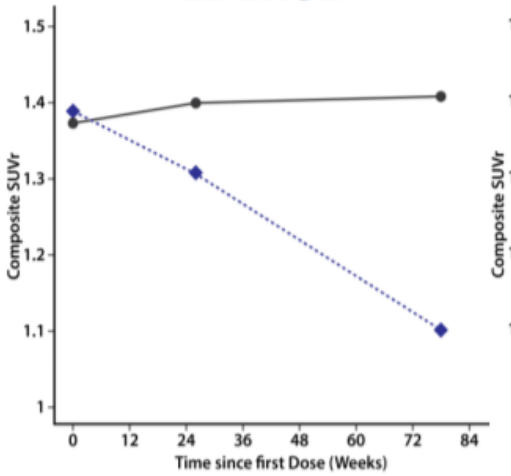
Biogen

Aducanumab

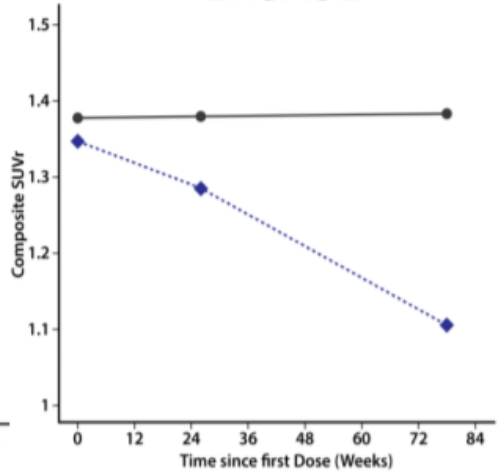
ENGAGE consistent with EMERGE in subset of patients with sufficient exposure to 10 mg/kg aducanumab

Amyloid PET

EMERGE

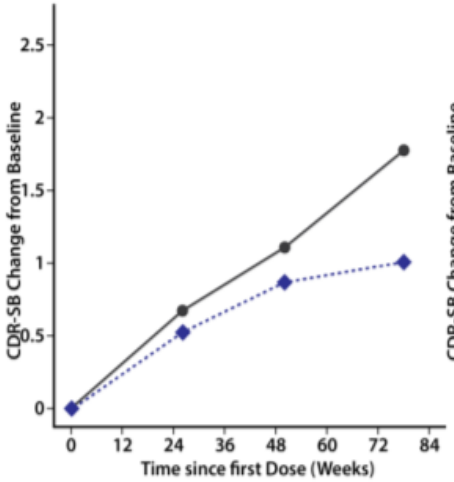


ENGAGE

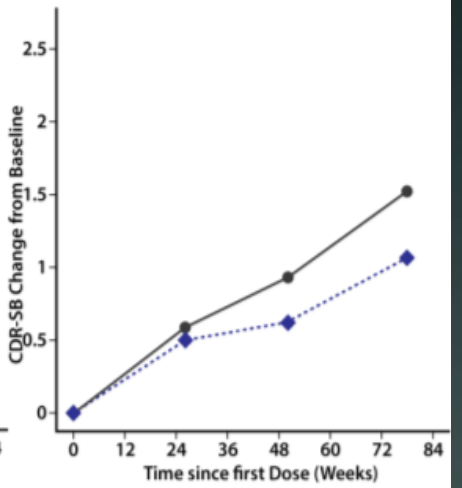


CDR-SB

EMERGE



ENGAGE



	Amyloid PET EMERGE			Amyloid PET ENGAGE			CDR-SB EMERGE				CDR-SB ENGAGE			
	Wk 0	Wk 26	Wk 78	Wk 0	Wk 26	Wk 78	Wk 0	Wk 26	Wk 50	Wk 78	Wk 0	Wk 26	Wk 50	Wk 78
PBO	157	128	90	157	128	90	546	532	437	297	545	522	460	336
ADU	55	46	43	55	46	43	147	146	146	127	116	116	114	97

Placebo

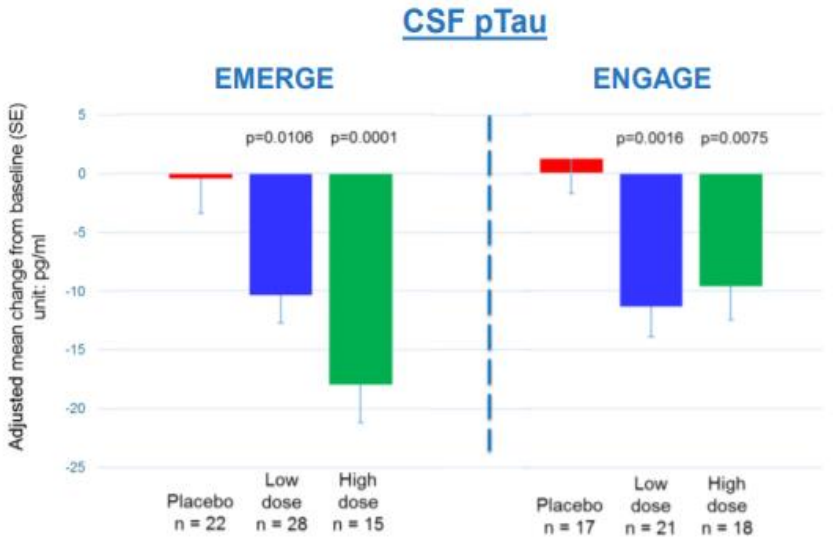
≥ 10 uninterrupted 10 mg/kg dosing intervals at steady-state

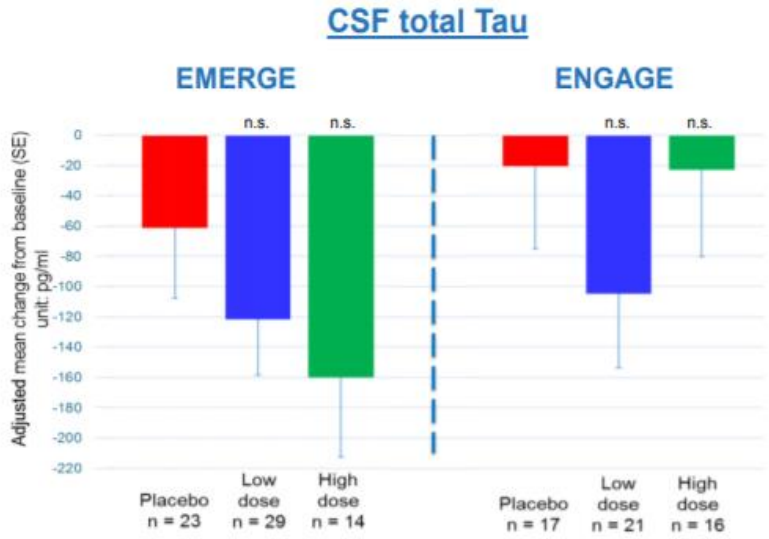
Biogen

PBO = placebo; ADU = aducanumab

Aducanumab

CSF biomarkers of tau pathology and neurodegeneration in AD are reduced in aducanumab-treated subjects

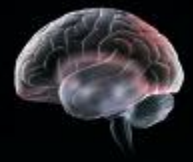




CSF pTau and CSF total Tau measured at 18 months (data analyzed using ANCOVA); n.s. = not significant

Biogen

Aducanumab



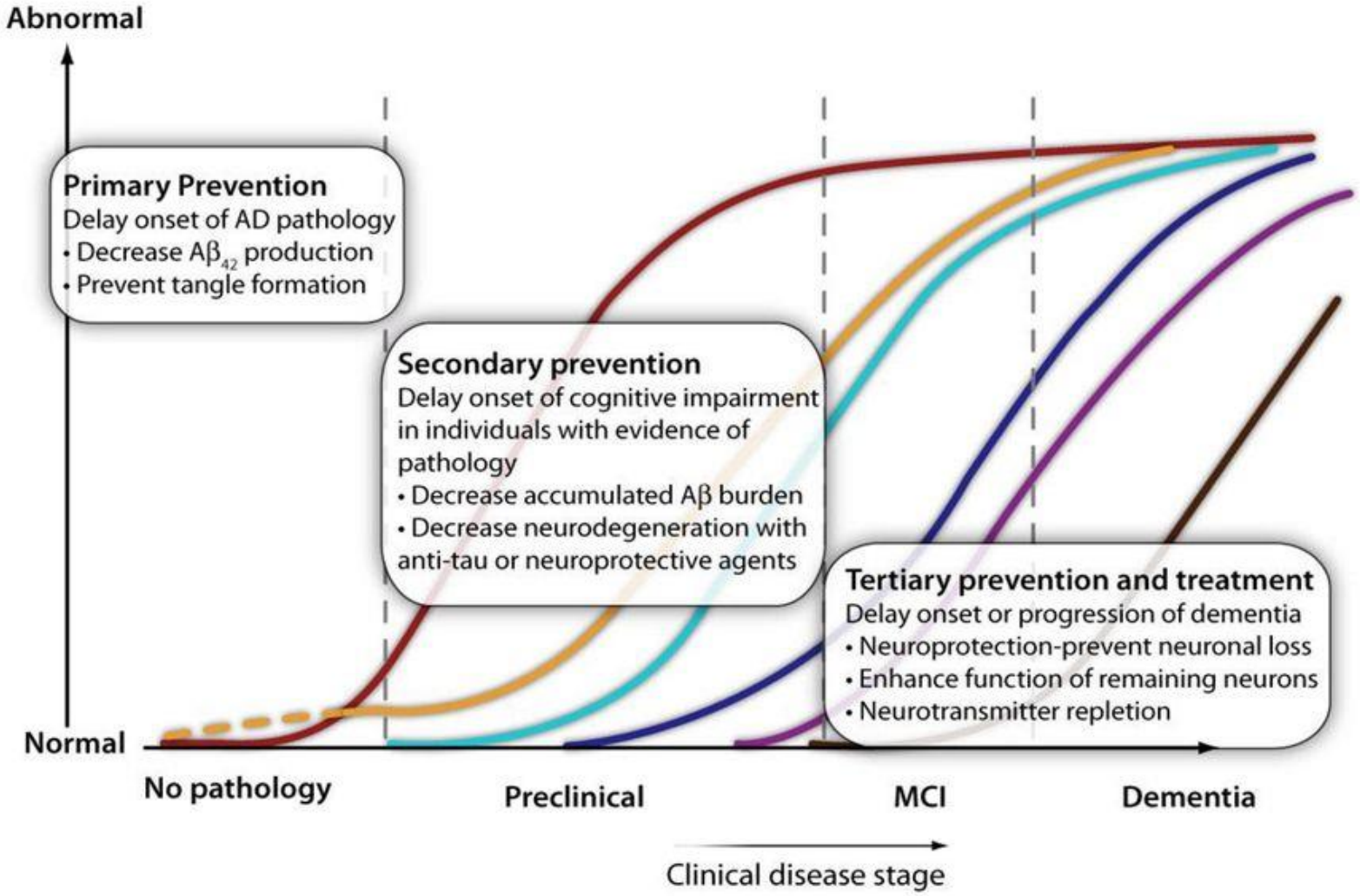
- “Data dredging or a 50 billion dollar drug?”

- “Is Biogen’s Aducanumab for Alzheimer’s the Holy Grail or Cold Fusion?”

What's new in dementia?

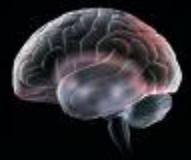
WHO new guidelines to prevent dementia

Testing the Right Target and the Right Drug at the Right Stage of Alzheimer's Disease



Sperling RA, Jack CR, Aisen P *Sci Transl Med* 2011

What's new in dementia?



- The *WHO Guidelines on risk reduction of cognitive decline and dementia* provide evidence-based recommendations on lifestyle behaviours and interventions to delay or prevent cognitive decline and dementia.

- The increasing numbers of people with dementia, its significant social and economic impact and lack of curative treatment, make it imperative for countries to focus on reducing modifiable.

- These WHO Guidelines are an important tool for health care providers as well as governments, policy-makers and other stakeholders to strengthen their response to the dementia challenge.

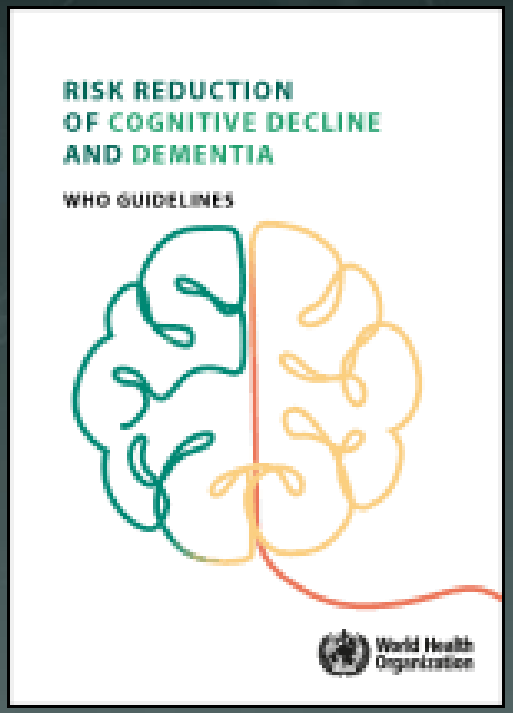
RISK REDUCTION OF COGNITIVE DECLINE AND DEMENTIA

WHO GUIDELINES

EVIDENCE PROFILES

- Physical activity interventions
- Tobacco cessation interventions
- Nutritional interventions
- Interventions for alcohol use disorder
- Cognitive interventions
- Social activity
- Weight management
- Management of hypertension
- Management of diabetes
- Management of dyslipidaemia
- Management of depression
- Management of hearing loss

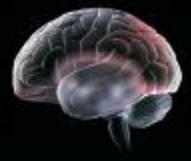
World Health Organization



Physical activity: research evidence

- Physical activity has rather consistently reported small but beneficial effects on cognition. There is enough low to moderate quality evidence supporting these effects. It is important to consider that in order to achieve maximum benefit, it is crucial to start such interventions in at-risk people. Earlier, the better.
- Even in MCI populations, low evidence suggests cognitive benefits of physical exercise.
- The effect of these interventions seems to be mostly due to aerobic exercise.

WHO GUIDELINES FOR RISK REDUCTION OF COGNITIVE DECLINE AND DEMENTIA: SUMMARY



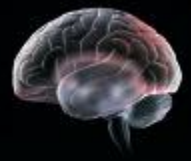
INTERVENTION	QUALITY OF EVIDENCE	RECOMMENDATION STRENGTH
Physical activity	Moderate	Strong
Physical activity with mild cognitive impairment	Low	Conditional
Tobacco cessation	Low	Strong
Nutrition: Mediterranean diet	Moderate	Conditional
Nutrition: WHO dietary recommendations	Low to high	Conditional
Nutrition: No vitamin supplementation, MUFA	Moderate	Strong
Reduce/cease harmful drinking of alcohol	Moderate	Conditional
Cognitive interventions (training)	Very low to low	Conditional
Social activity	Insufficient evidence	Support for health and well-being
Weight Management	Low to moderate	Conditional
Hypertension management, WHO guidelines	Low to high	Strong
Hypertension management, reduce risk	Very low	Conditional
Management of Diabetes Mellitus, WHO guidelines	Very low to moderate	Strong
Management of Diabetes Mellitus, reduce risk	Very low	Conditional
Management of Dyslipidaemia (high cholesterol)	Low	Conditional
Management of Depression	Insufficient evidence	Provide treatment for those meeting WHO guidelines
Management of hearing loss	Insufficient evidence	Provide screening, intervention according to WHO guidelines

Take-Home messages - I

- The NIA-AA research framework defines AD biologically, by neuropathologic change or biomarkers, and treats cognitive impairment as a symptom/sign of the disease rather than the definition of the disease. This approach should enhance efforts to understand both the biology of AD and the multifactorial etiology of dementia.

- Limbic-predominant age-related TDP-43 encephalopathy, is a proposed diagnosis for a new form of dementia, defined by a buildup of misfolded TDP-43 protein in the brain, especially the limbic system, typically in patients over 85 years. LATE is suspected to be present in about a quarter of people over 85, and is often comorbid with other forms of dementia.

Take Home Messages - II



• One month ago, Biogen stunned the Alzheimer's field by announcing that aducanumab - presumed dead last March - appears to have worked in one of its two Phase 3 trials. Based on the results of a new analysis, and interactions with the FDA, Biogen will file for regulatory approval in early 2020.

• According to new guidelines issued by the WHO, people can reduce their risk of dementia by getting regular exercise, not smoking, avoiding harmful use of alcohol, controlling their weight, eating a healthy diet, and maintaining healthy blood pressure, cholesterol and blood sugar levels.


Thank you for your attention