15th International Conference for Strategic Studies in Radiology Berlin/DE, August 24-26, 2023

Molecular Brain Imaging in Neurodegenerative Diseases: Exemplar for Biomarker Discovery and Clinical Translation

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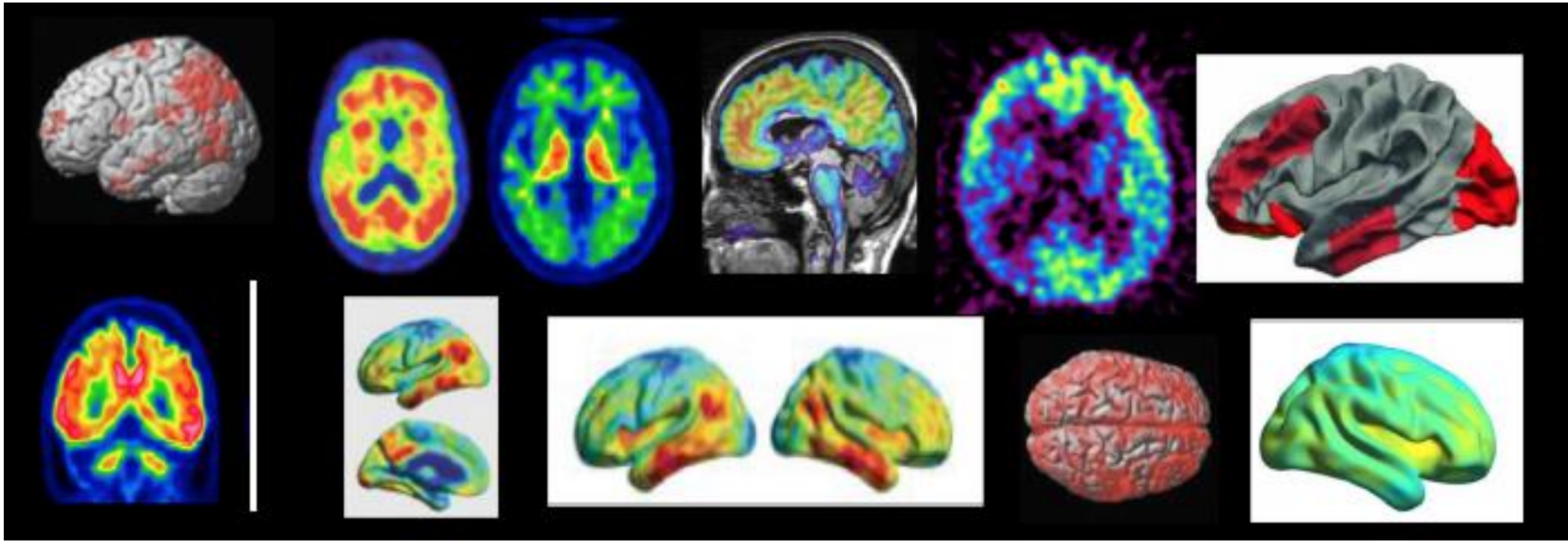
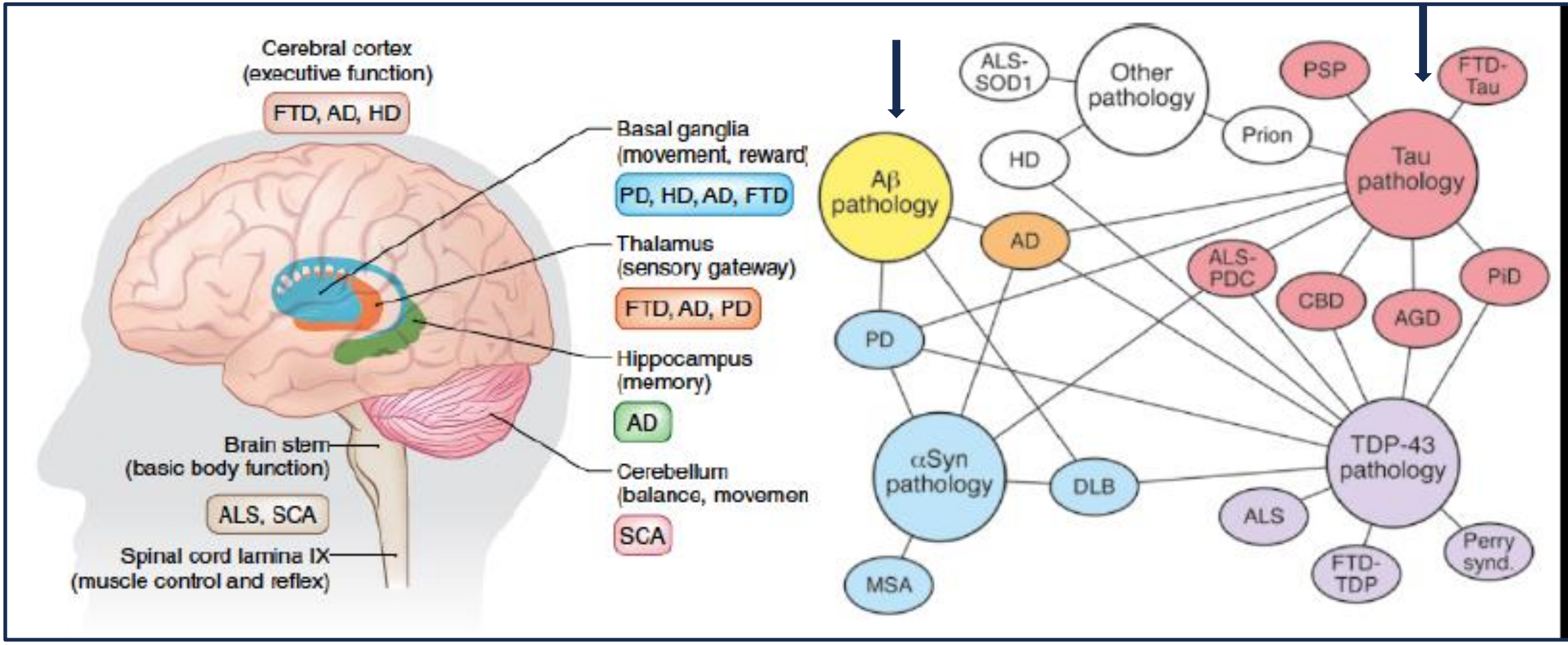
No disclosure

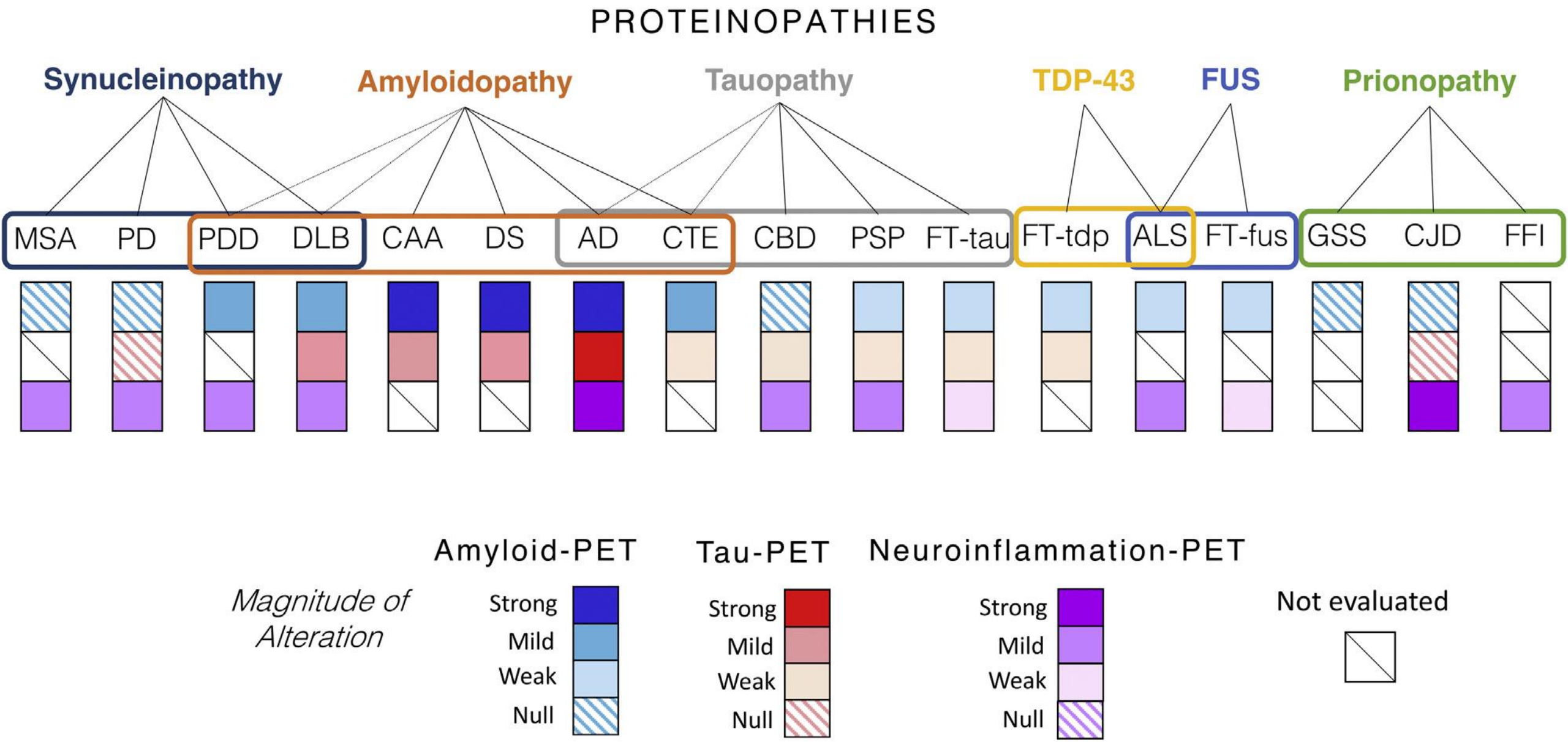
MOLECULAR BRAIN IMAGING is rapidly developing and providing new unique insights into pathophysiological mechanisms and development of diagnostic biomarkers with implication in drug treatments and clinical praxis.



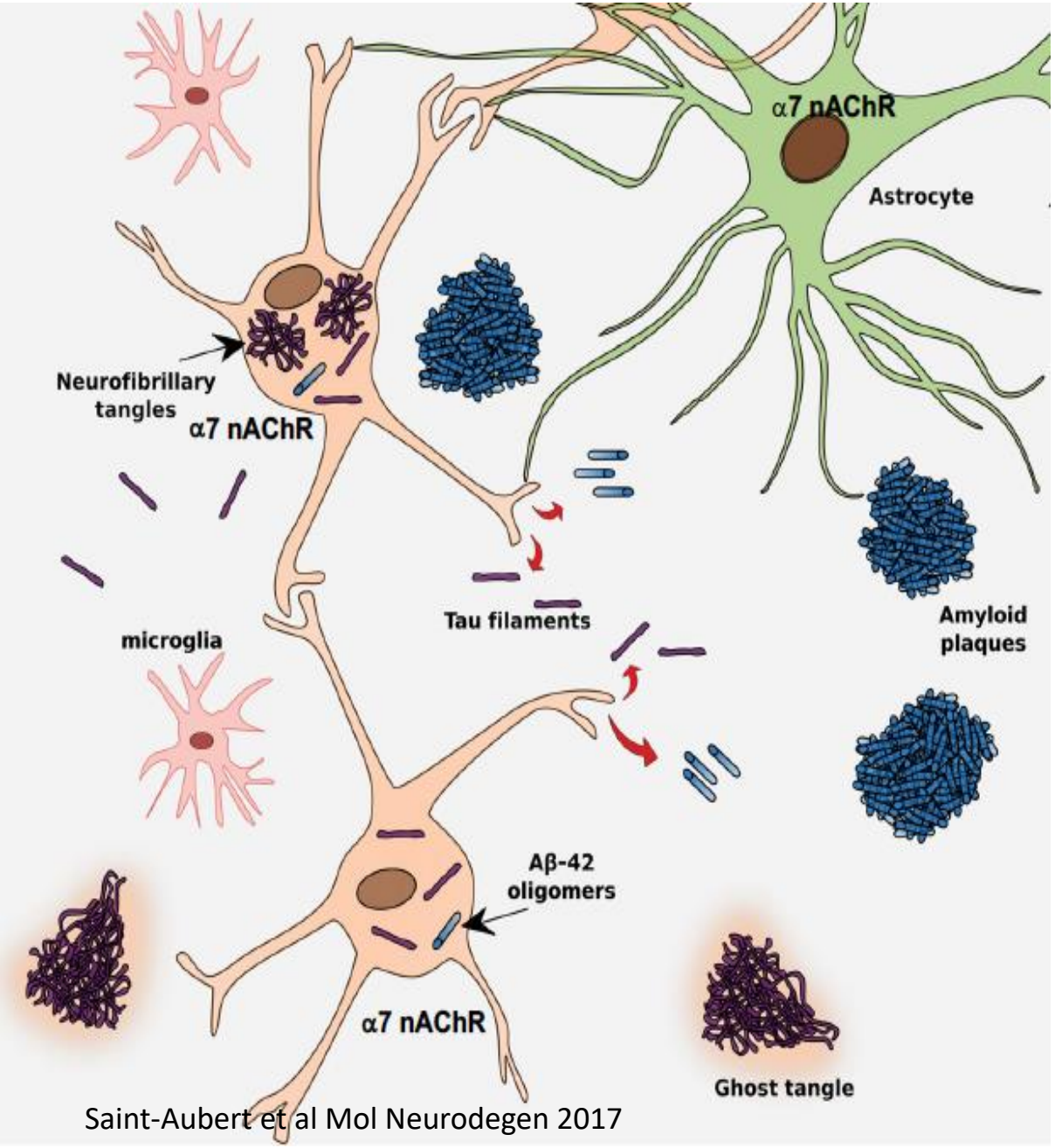
Neurodegenerative Disorders are Characterized by Different Proteinopathies



NEW IMAGING TECHNIQUES CREATE NEW POSSIBILTIES FOR EARLY DETECT AND TO DIAGNOSE DIFFERENT PROTEINOPATHIES

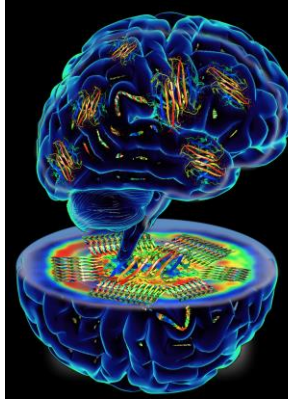


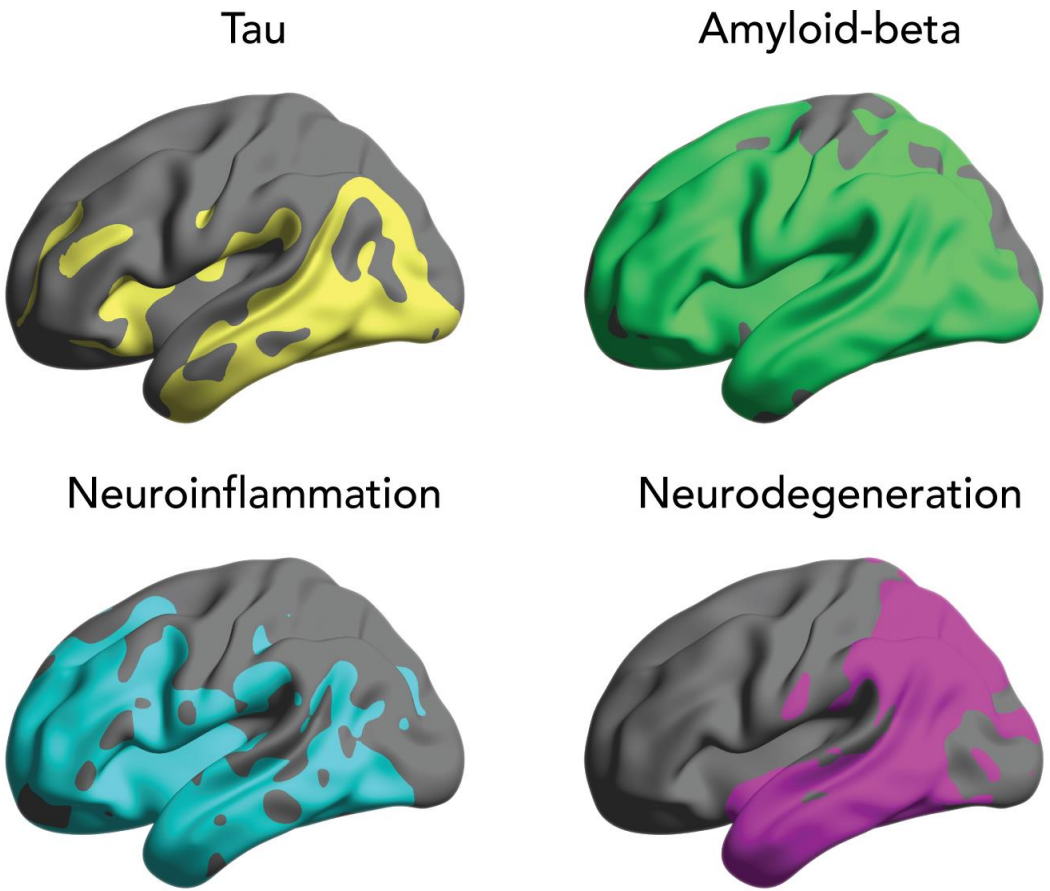
Perani et al. Alzheimer & Dementia 2019



Saint-Aubert et al Mol Neurodegen 2017

Alzheimer´s disease is characterized by complexed pathophysiological mechanisms that we need to further understand.

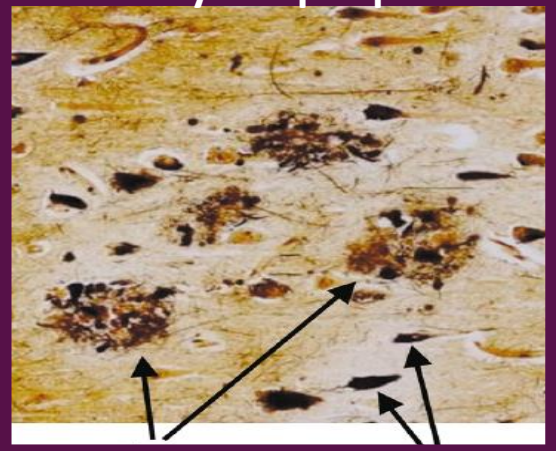




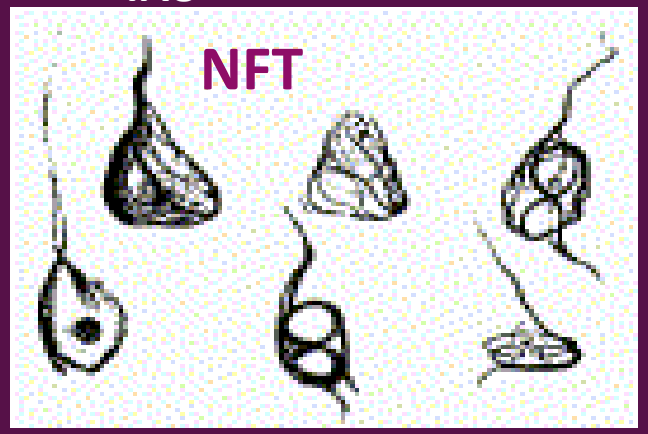
PET imaging can detect Alzheimer pathology in vivo !

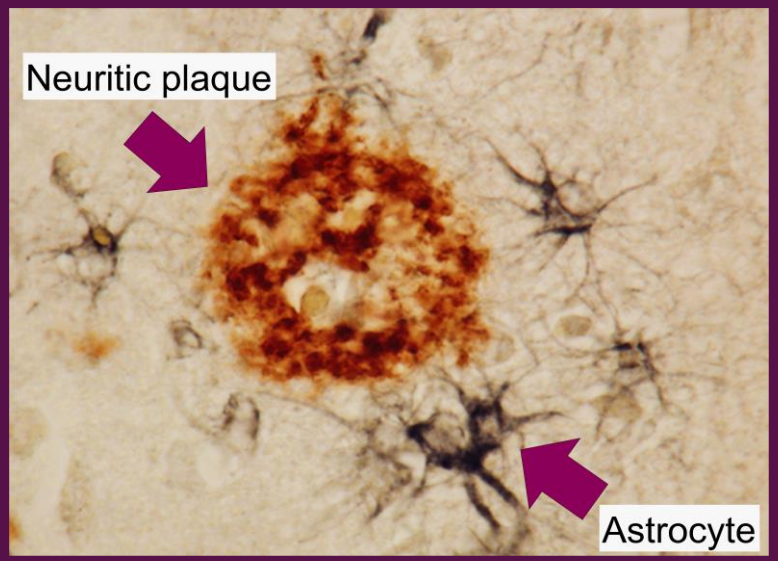
AD Pathology at autopsy

Amyloid plaques

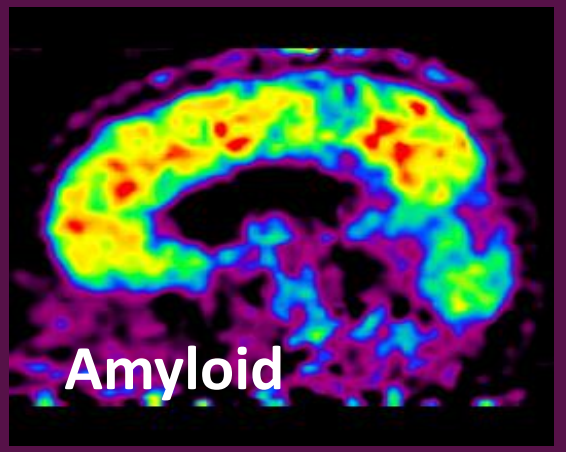


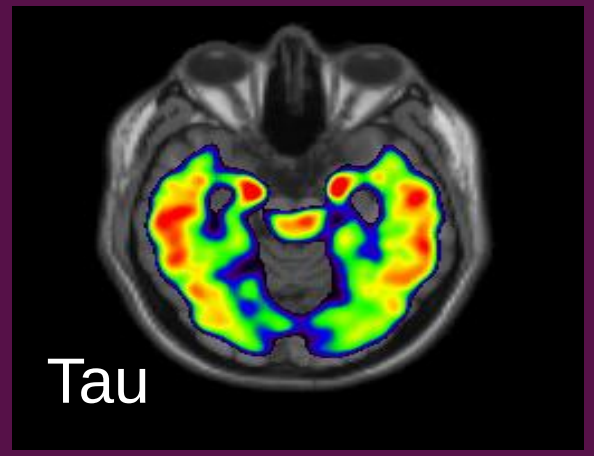
TAU

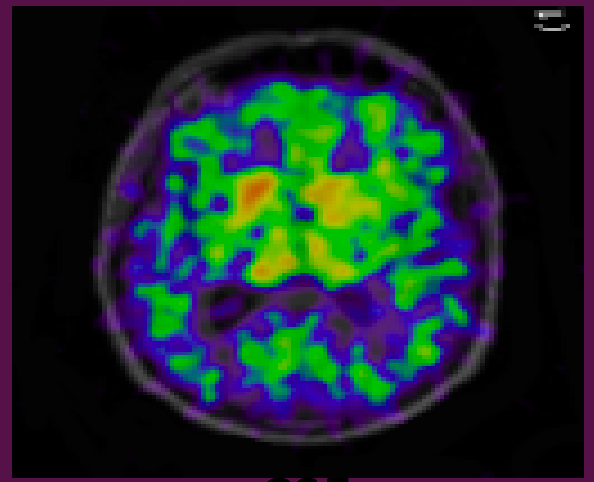




AD Pathology in vivo by PET







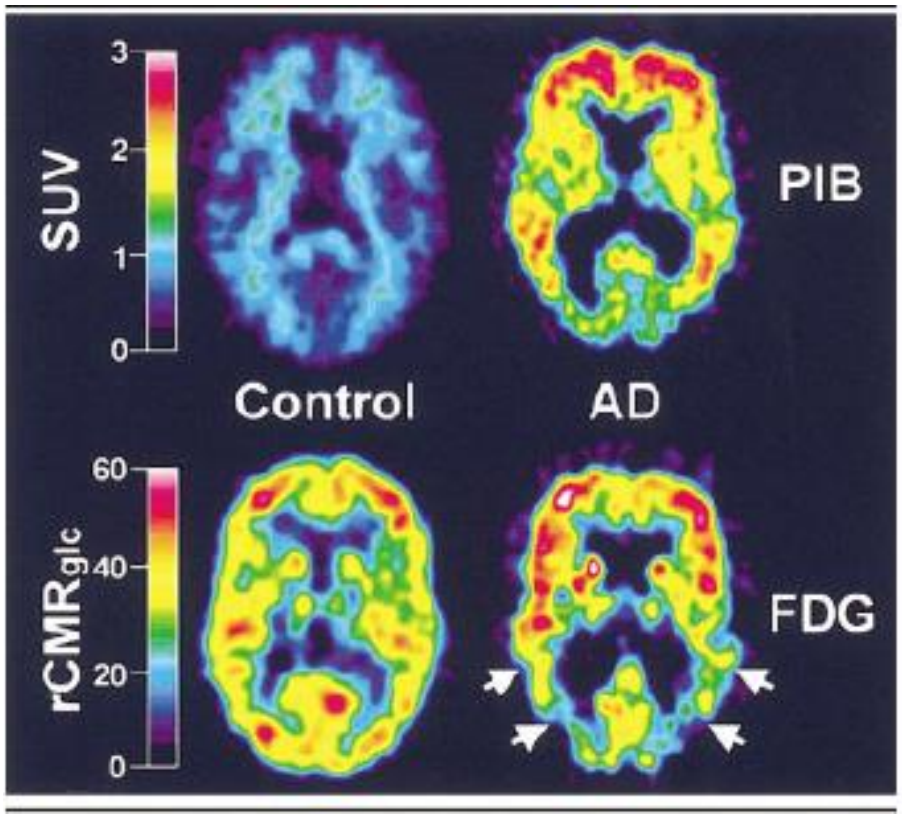
Astrocytes

Annals of Neurology Vol 55 No 3 March 2004

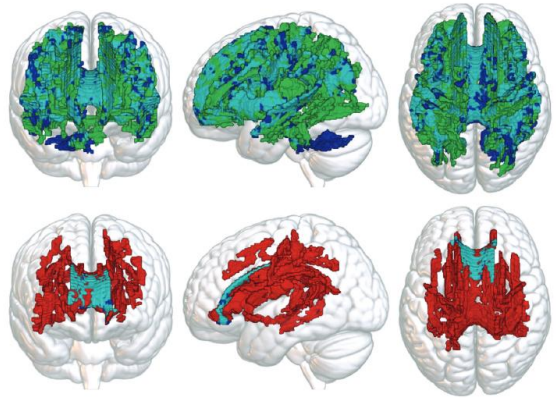
ORIGINAL ARTICLES

Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B

William E. Klunk, MD, PhD,[1] Henry Engler, MD,[2] Agneta Nordberg, MD, PhD,[3,4] Yanming Wang, PhD,[5] Gunnar Blomqvist, PhD,[2] Daniel P. Holt, BS,[5] Mats Bergström, PhD,[2] Irina Savitcheva, MD,[2] Guo-feng Huang, PhD,[5] Sergio Estrada, PhD,[2] Birgitta Ausén, MSCI,[4] Manik L. Debnath, MS,[1] Julien Barletta, BS,[6] Julie C. Price, PhD,[5] Johan Sandell, PhD,[2] Brian J. Lopresti, BS,[5] Anders Wall, PhD,[2] Pernilla Koivisto, PhD,[2] Gunnar Antoni, PhD,[2] Chester A. Mathis, PhD,[5] and Bengt Långström, PhD[2,6]



Annals of NEUROLOGY
An Official Journal of the American Neurological Association and The Child Neurology Society



EDITORIAL

The Proteomics of Positron Emission Tomography

Over the past decade, research into the biology of neurodegeneration has evolved from emphasizing dysfunction of neurotransmitter systems to include investigations of protein abnormalities. This is especially clear in the study of Alzheimer's disease (AD) in which the well-known findings concerning cholinergic dysfunction that led to the first specific therapies have been augmented by research suggesting key roles for amyloid and tau in the cause and pathogenesis of the disease. Indeed, the aggregation, altered processing, and abnormal folding of proteins that may disrupt neural function is now a widespread theme that echoes throughout the study of many neurodegenerative diseases.

The application of positron emission tomography (PET) to the study of AD parallels this shift in emphasis. Although most clinicians and scientists are familiar with the use of PET to measure fundamental physiological processes such as blood flow and glucose me-

In this issue of the *Annals*, Klunk and colleagues report the results of the next step in the evolution of PET in the application to AD: development of a radioligand targeted to the amyloid protein itself.[7] The compound, *N*-methyl-[^{11}C]-2-(4′-methylaminophenyl)-6-hydroxybenzothiasole (nicknamed PIB), is structurally related to the thioflavin-T molecule, a dye that has long been used to label amyloid in histological studies. Klunk and colleagues present a substantial amount of data that support the use of this compound as a marker of brain amyloid deposition. Previous work by this group demonstrated rapid blood–brain barrier permeability, with labeling of both amyloid angiopathy and plaques in transgenic mouse models of AD,[8] as well as in vitro binding to AD brain and synthetic amyloid fibrils but not to neurofibrillary tangles (NFTs).[9] The work reported here extends these observations to in vivo human studies

doi:10.1093/brain/awq349 Brain 2011: 134; 301–317 | 301

BRAIN
A JOURNAL OF NEUROLOGY

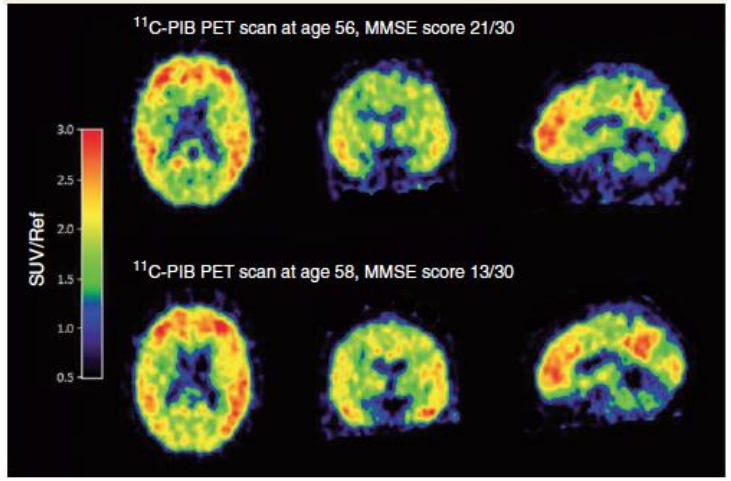
OCCASIONAL PAPER

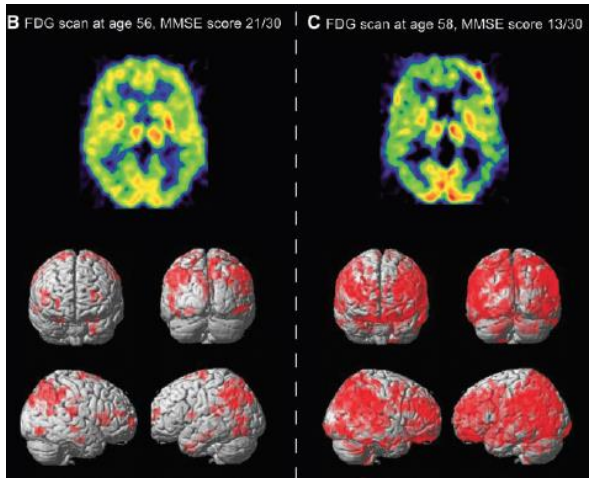
Positron emission tomography imaging and clinical progression in relation to molecular pathology in the first Pittsburgh Compound B positron emission tomography patient with Alzheimer's disease

Ahmadul Kadir,[1,*] Amelia Marutle,[1,*] Daniel Gonzalez,[1] Michael Schöll,[1] Ove Almkvist,[1,2] Malahat Mousavi,[1] Tamanna Mustafiz,[1] Taher Darreh-Shori,[1] Inger Nennesmo[3] and Agneta Nordberg[1,2]

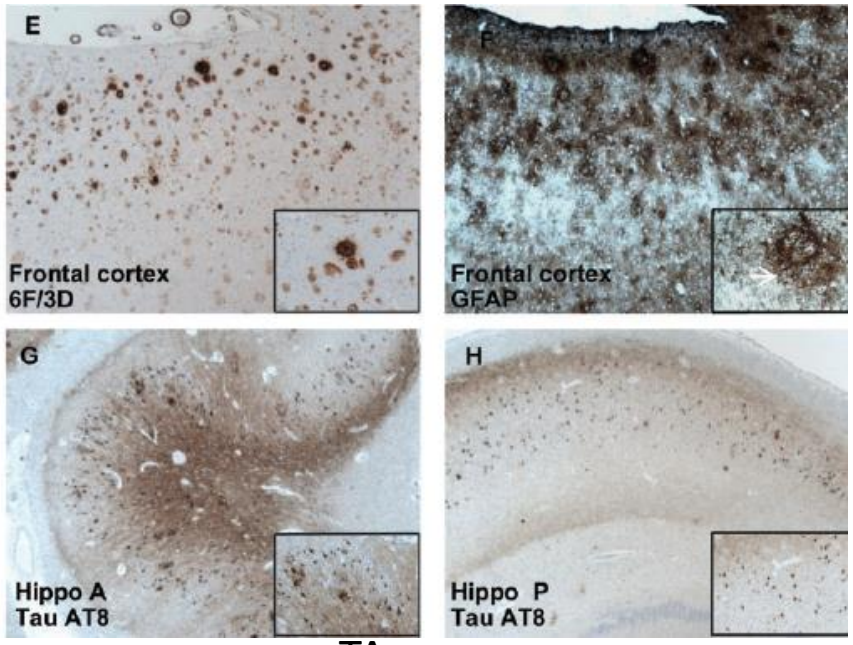
2 years follow-up

[11C]-PIB Amyloid → [18F] FDG uptake ↓



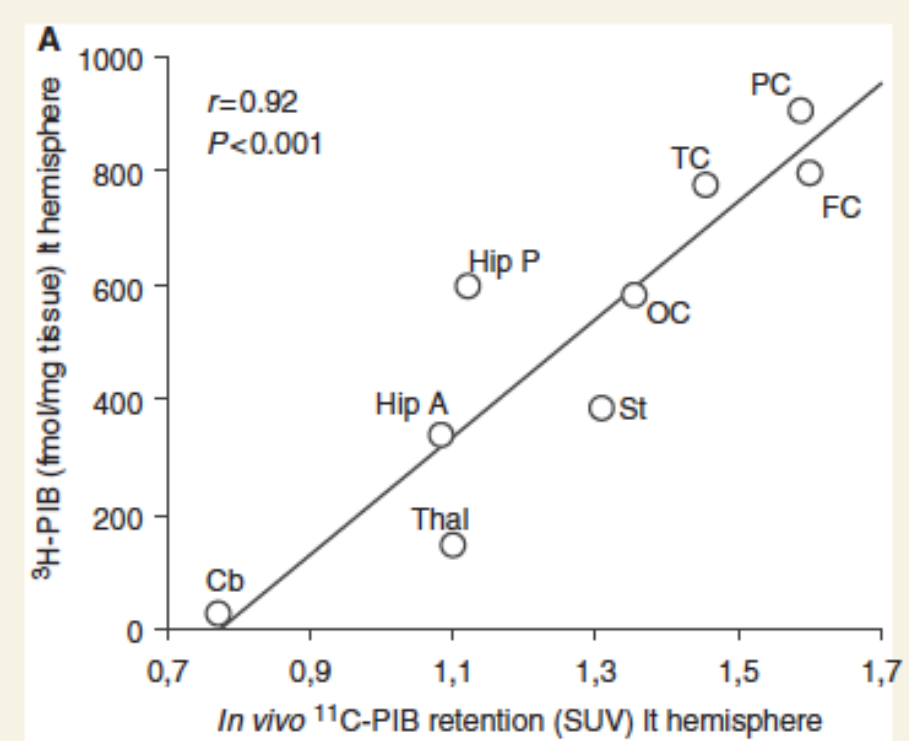


Amyloid plques GFAP



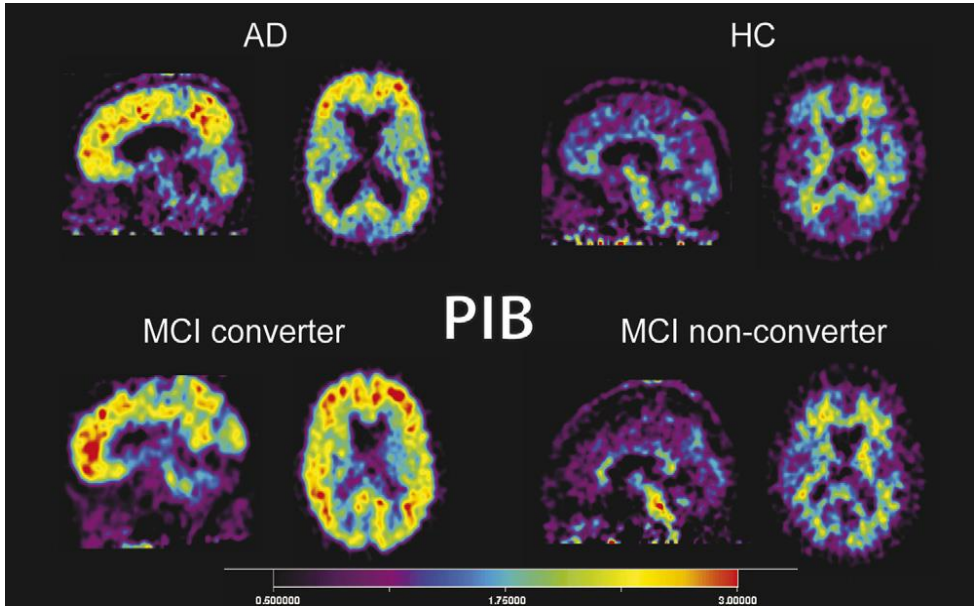
TAu

In vitro

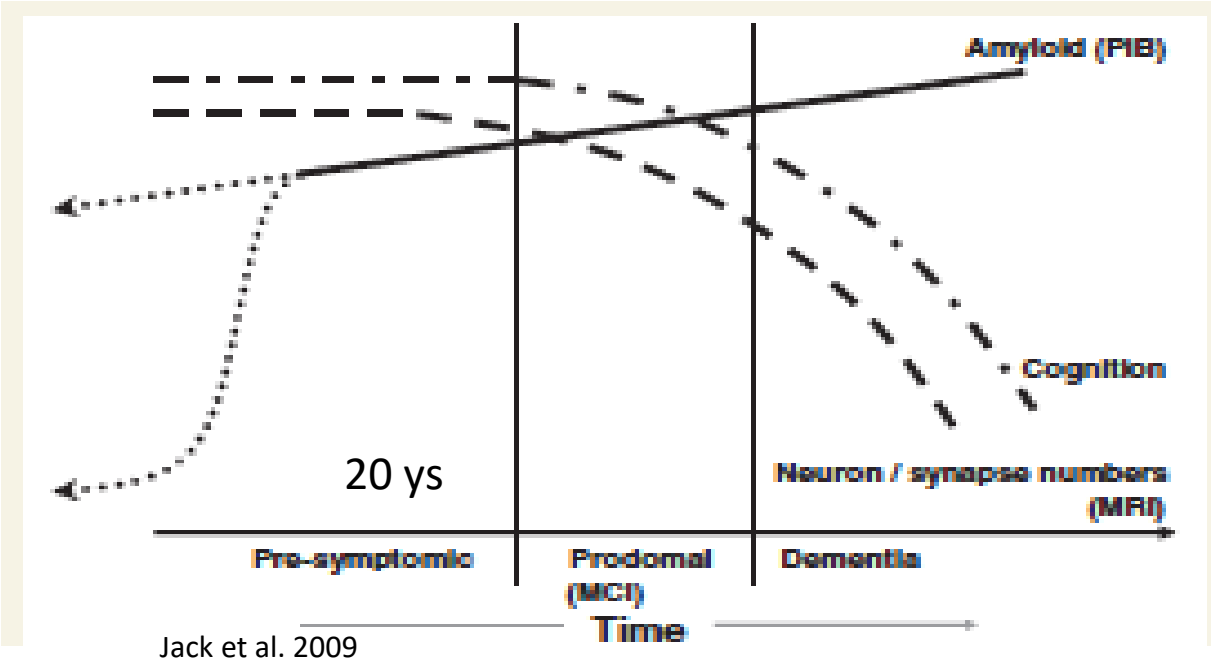


Positive Correlation Between In vivo/in vitro PIB Binding in Different Brain Regions

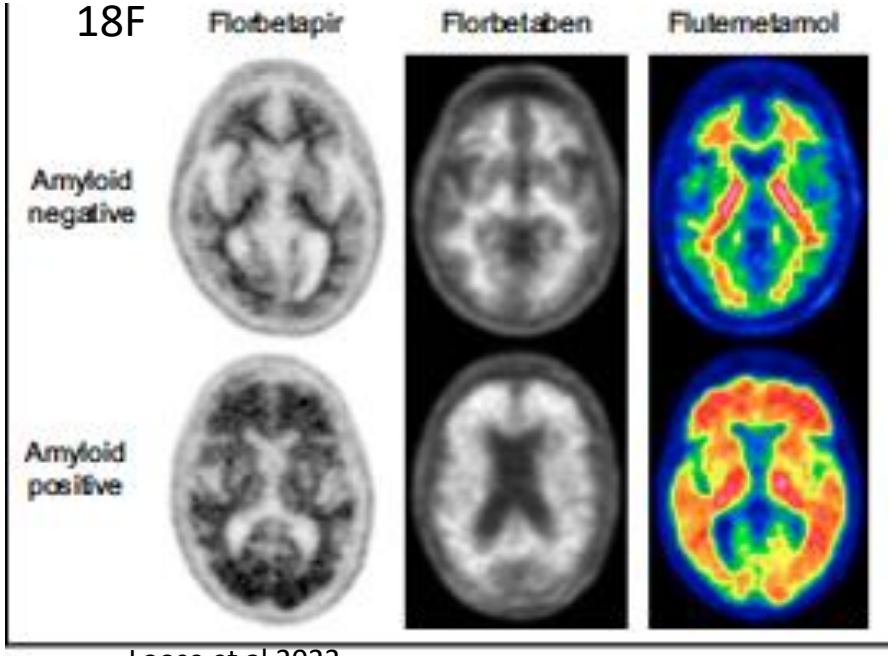
Amyloid 11C-PIB PET imaging in AD and MCI MCI=mild cognitiv impairment



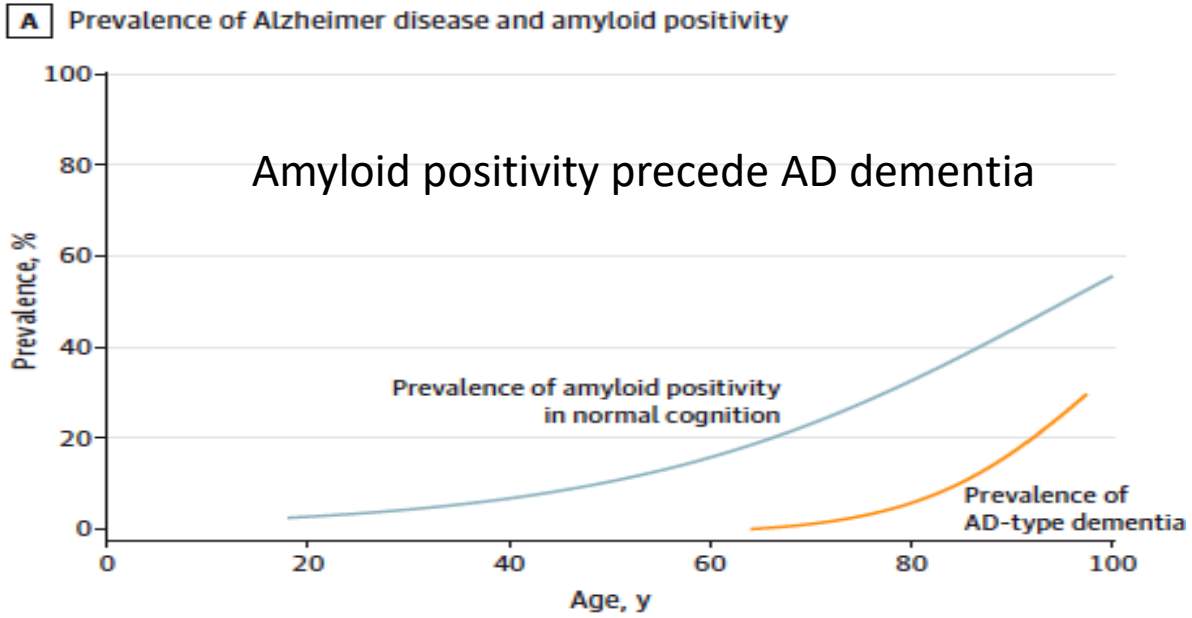
Forsberg et al. Neurobiol Aging 2008



Jack et al. 2009

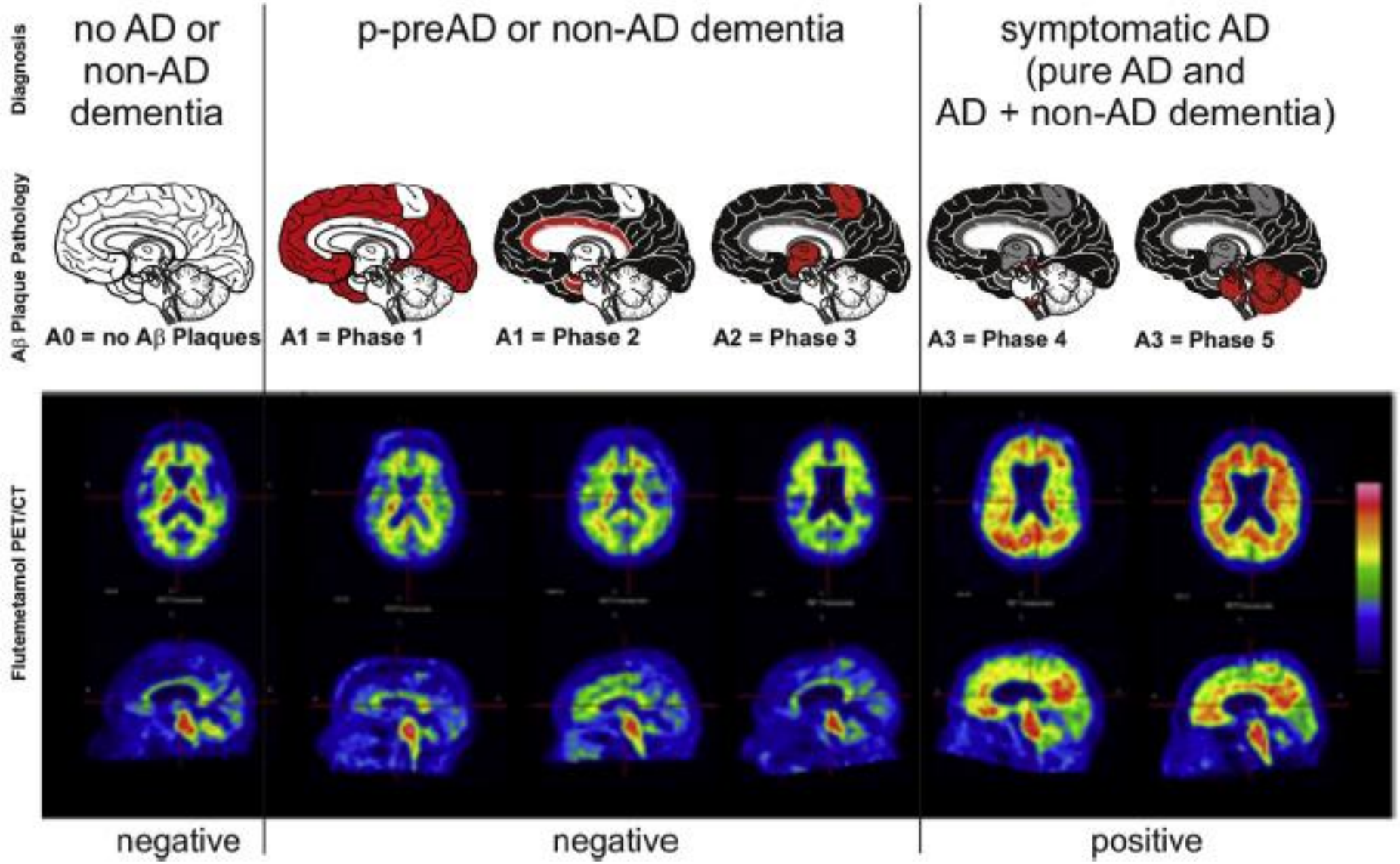


Loose et al 2023

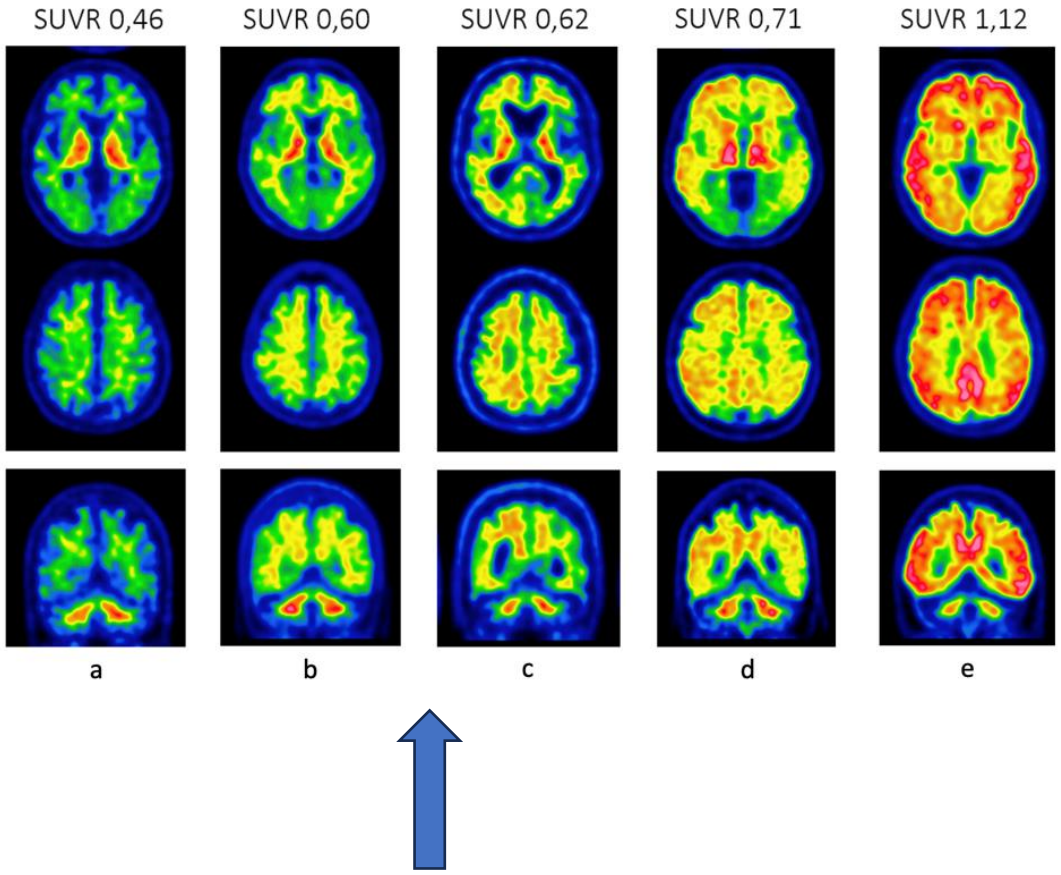


Jansen et al JAMA 2015

Pathology amyloid stages and corresponding Amyloid PET outcome



Practical experience of integrating visual and quantitative image interpretation in clinic
Examples of [^{18}F]Flutemetamol PET scans with different patterns of uptake



The Centiloid scale: quantitative amyloid plaque estimation allows earlier dection

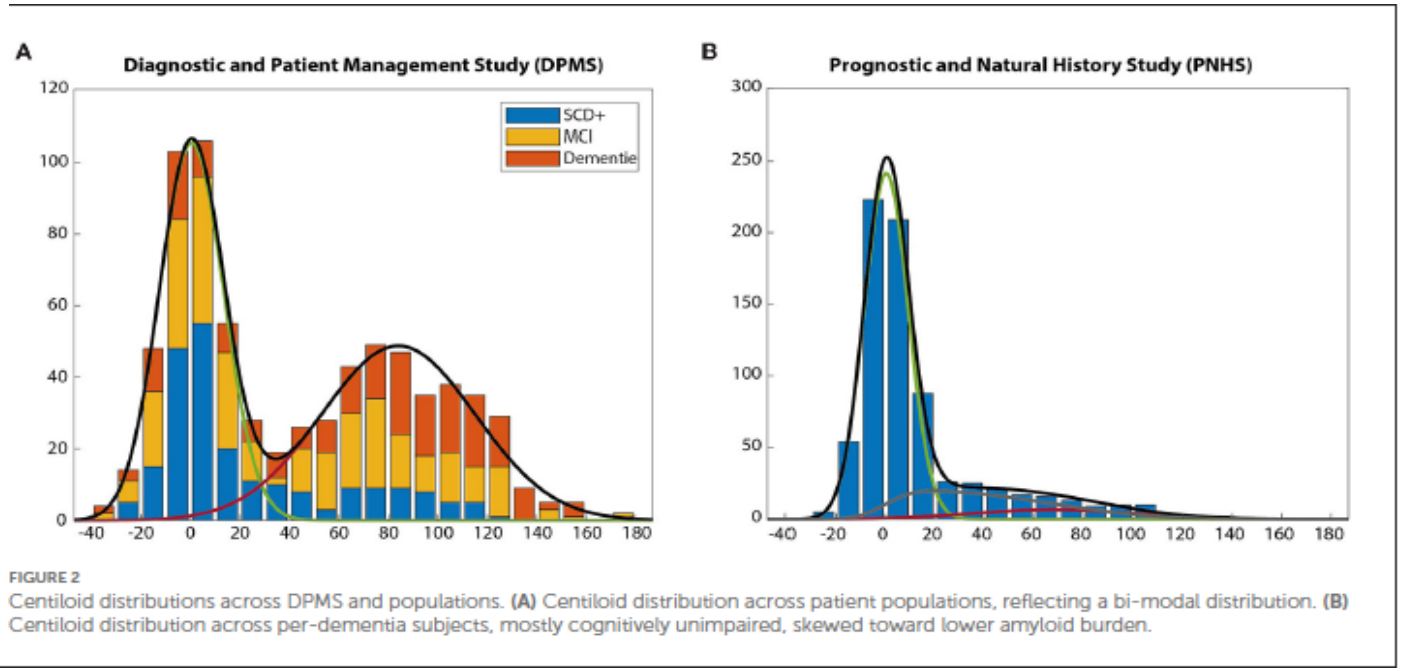


FIGURE 2
Centiloid distributions across DPMS and populations. **(A)** Centiloid distribution across patient populations, reflecting a bi-modal distribution. **(B)** Centiloid distribution across per-dementia subjects, mostly cognitively unimpaired, skewed toward lower amyloid burden.

Centiloid scale

Collij et al 2023

Blue= subjetive memory impairment
Yellow= mild cognitive impairment
Red= Alzheimer dementia

KAROLINSKA UNIVERSITY HOSPITAL

AMY Amyloid imaging to Alzheimer´s Diseas

IDEAS
Imaging Dementia—Evidence For Amyloid Scanning

The Imaging Dementia – Evidence for Amyloid Scanning (IDEAS) Study will determine the clinical usefulness and impact on patient-oriented outcomes of a brain positron emission tomography (PET) scan that detects amyloid plaques, a core feature of Alzheimer's disease, in patients with mild cognitive impairment (MCI) or dementia of uncertain cause.

A total of 18,488 Medicare beneficiaries meeting specific Appropriate Use Criteria (AUC) will be enrolled over 24 months at sites throughout the United States as part of the Centers for Medicare & Medicaid Services (CMS) Coverage with Evidence Development (CED) research program.

JAMA | Original Investigation

Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia

Gil D. Rabinovici, MD; Constantine Gatsonis, PhD; Charles Apgar, MBA; Kiran Chaudhary, MS; Ilana Gareen, PhD; Lucy Hanna, MS; James Hendrix, PhD; Bruce E. Hillner, MD; Cynthia Olson, MBA; Orit H. Lesman-Segev, MD; Justin Romanoff, MA; Barry A. Siegel, MD; Rachel A. Whitmer, PhD; Maria C. Carrillo, PhD

JAMA April 2, 2019 Volume 321, Number 13

- **Sample size 11,050 patients**

Patient management changed in 60 % of patients.
Most common change was in use of AD medications (Increased in Aβ PET+, decreased in Aβ PET-).
Diagnosis changed in 35.6% of patients.

- **Increase in diagnostic confidence.**
- **Decreased utilization of alternative diagnostics.**

AMYPAD
Amyloid imaging to prevent Alzheimer´s Disease

2016- 2021

900 memory clinic patients, 3100 preclinical or prodromal AD subjects, total 600

- Barcelonabeta Brain Research Center, Spain
- Centre Hospitalier Universitaire de Toulouse, France
- Karolinska Institutet, Sweden
- Stichting Katholieke Universiteit, NetherlandsStichting VUmc, Netherlands
- The University of Edinburgh, United Kingdom
- Université de Genève, Switzerland
- University College London, United Kingdom
- University Hospital of Cologne, Germany
- Alzheimer Europe

efpia imi innovative medicines initiative

- GE Healthcare Ltd, United Kingdom
- Janssen, Belgium
- Piramal Imaging Ltd, United Kingdom

Received: 16 September 2021 | Revised: 11 March 2022 | Accepted: 29 April 2022
DOI: 10.1002/alz.12696

FEATURED ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

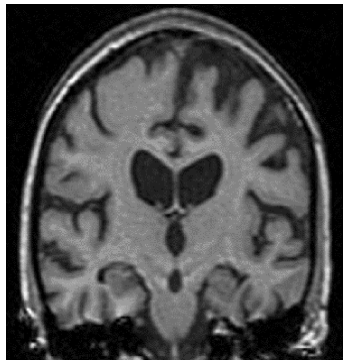
Description of a European memory clinic cohort undergoing amyloid-PET: The AMYPAD Diagnostic and Patient Management Study

Daniele Altomare[1,2] | Lyduine Collij[3] | Camilla Caprioglio[1,2] | Philip Scheltens[4] | Bart N.M. van Berckel[3] | Isadora Lopes Alves[3] | Johannes Berkhof[5] | Yvonne de Gier[3] | Valentina Garibotto[6,7] | Christian Moro[1,2] | Léa Poitrine[1,2] | Julien Delrieu[8,9] | Pierre Payoux[10,11] | Laure Saint-Aubert[10,12] | José Luis Molinuevo[13,14] | Oriol Grau-Rivera[13,15,16] | Juan-Domingo Gispert[13,15,17] | Carolina Minguillón[13,15,16] | Karine Fauria[13,16] | Marta Felez Sanchez[13] | Andreea Rădoi[13] | Alexander Drzezga[18,19,20] | Frank Jessen[21] | Claus Escher[21] | Philip Zeyen[21] | Agneta Nordberg[22,23] | Irina Savitcheva[24] | Vesna Jelic[25] | Zuzana Walker[26,27] | Ho-Yun Lee[27] | Lean Lee[26] | Jean-François Demonet[28] | Sonia Plaza Wuthrich[28] | Rossella Gismondi[29] | Gill Farrar[30] | Frederik Barkhof[3,31] | Andrew W. Stephens[29] | Giovanni B. Frisoni[1,2] | on behalf of the AMYPAD Consortium

Memory Assessment at Karolinska Hospital

KAROLINSKA UNIVERSITY HOSPITAL

Tertiary ,memory clinic



MRI/CT Structural investigation

Clinical examination

History Heredity

Functional analysis

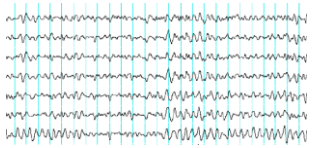
Neuropsychological tests

MMSE
MOCA
RUDAS

Speach assessments

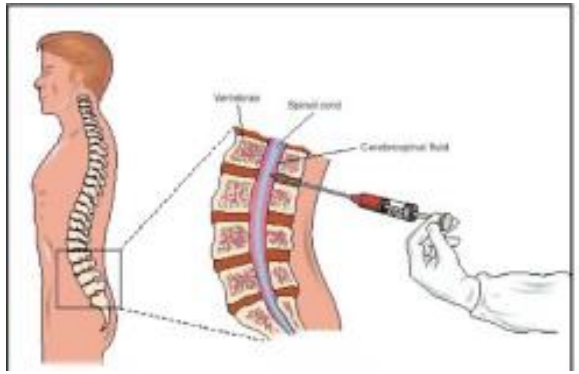
Optional

EEG



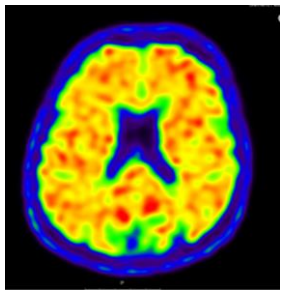
CSF

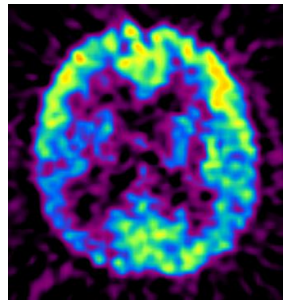
Aß42 Aß42/40
T-tau, p-tau NFL



blod/plasma

If the diagnosis still unclear? PET imaging is an option (18F-flutemetamol, 18F-FDG)





European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:1276–1286
https://doi.org/10.1007/s00259-019-04297-5

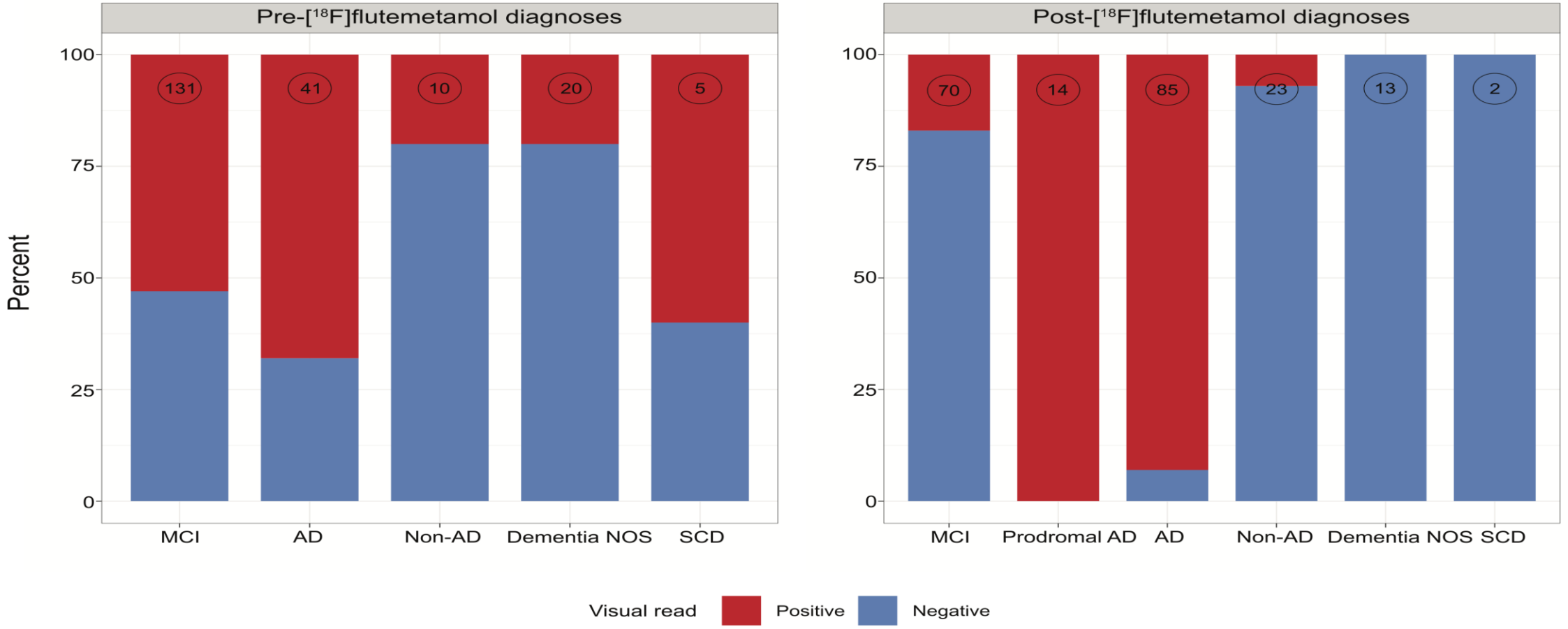
ORIGINAL ARTICLE

Clinical impact of [^{18}F]flutemetamol PET among memory clinic patients with an unclear diagnosis

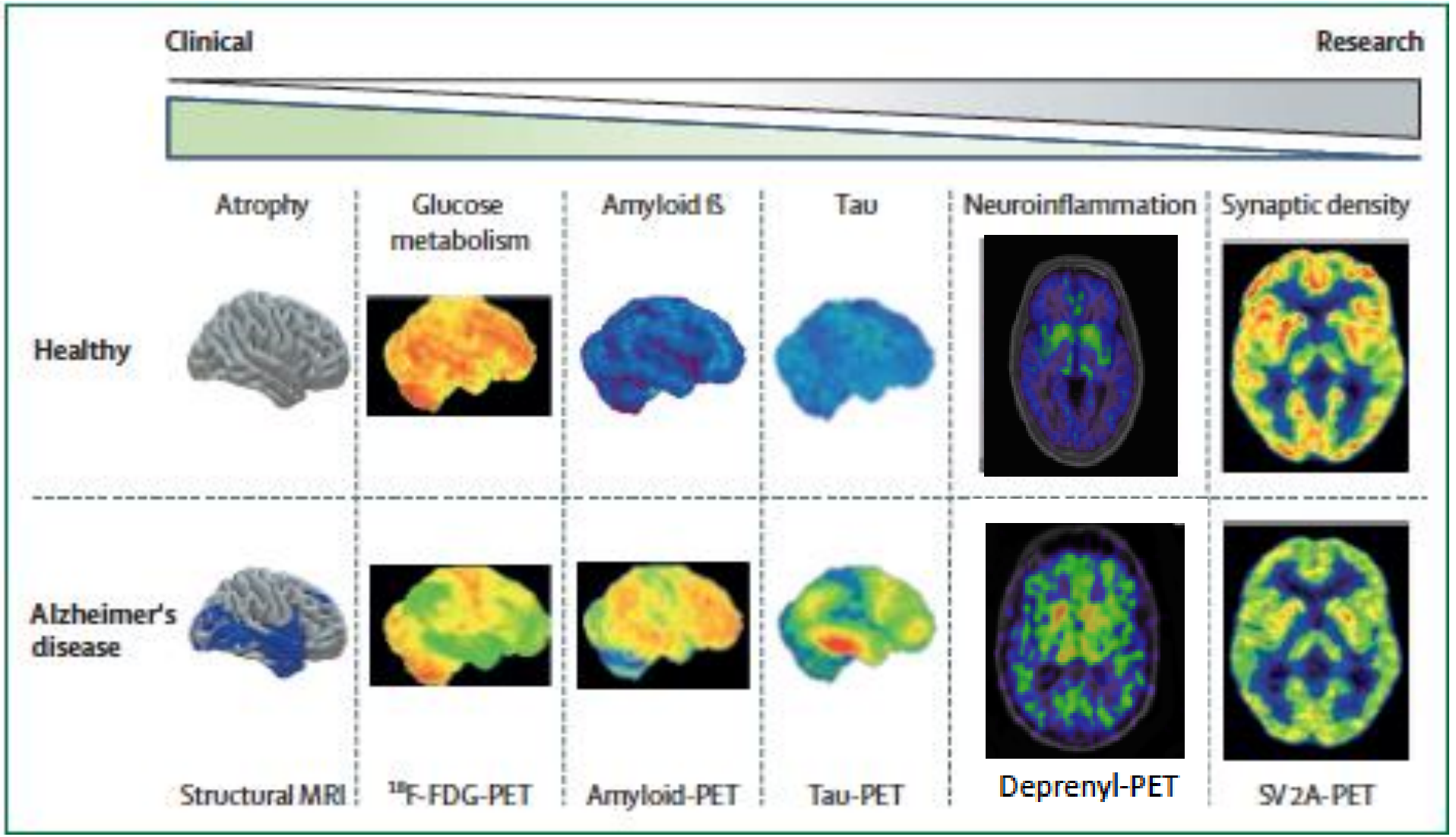
Antoine Leuzy[1] · Irina Savitcheva[2] · Konstantinos Chiotis[1] · Johan Lilja[3,4] · Pia Andersen[5] · Nenad Bogdanovic[5] · Vesna Jelic[1,5] · Agneta Nordberg[1,5]

Change in diagnosis 44 % of cases
N=207 patients

Increase in AD drug treatment 218% in prodromal AD, AD

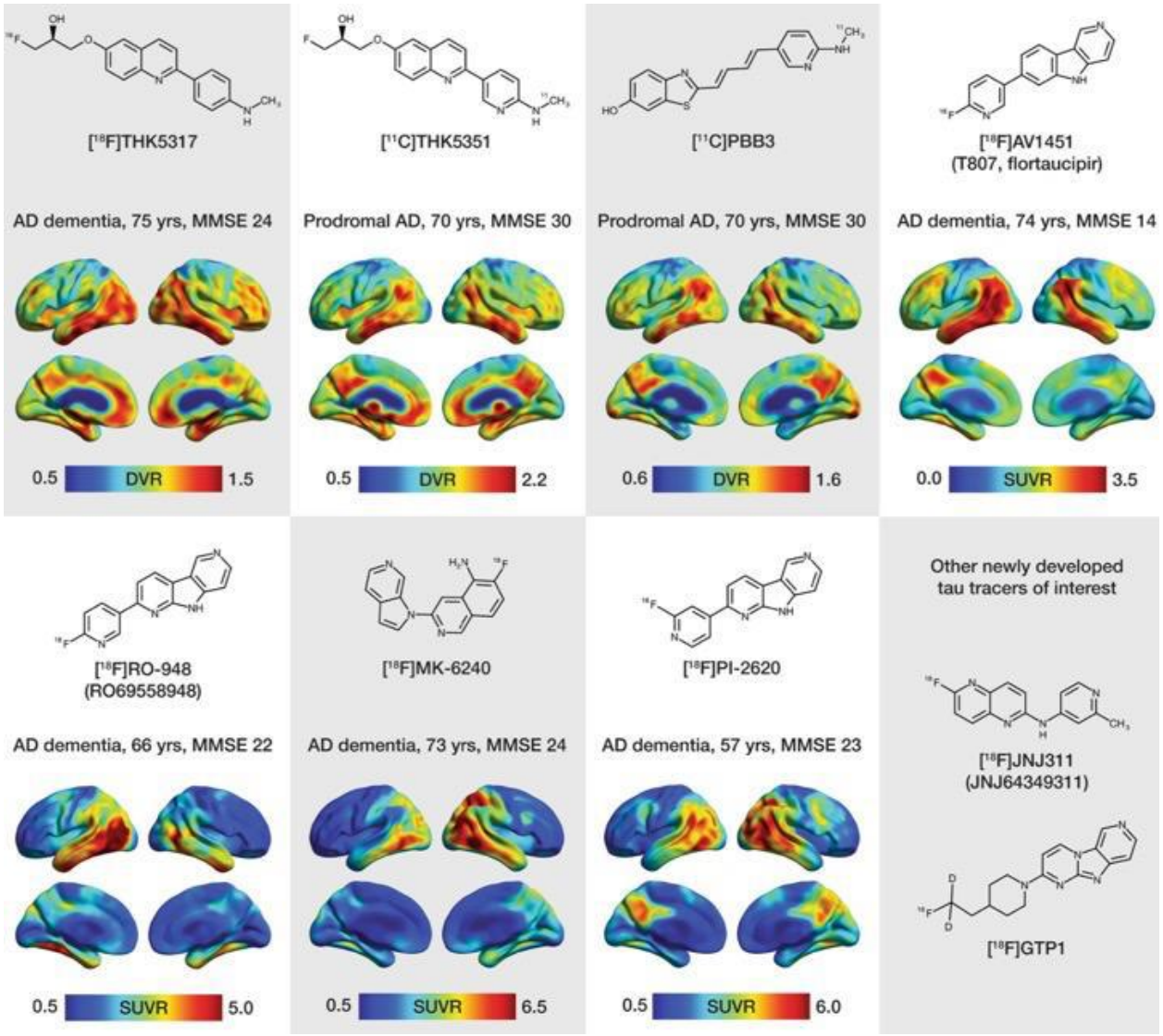


MOLECULAR imaging of pathological hallmarks in Alzheimer´s disease



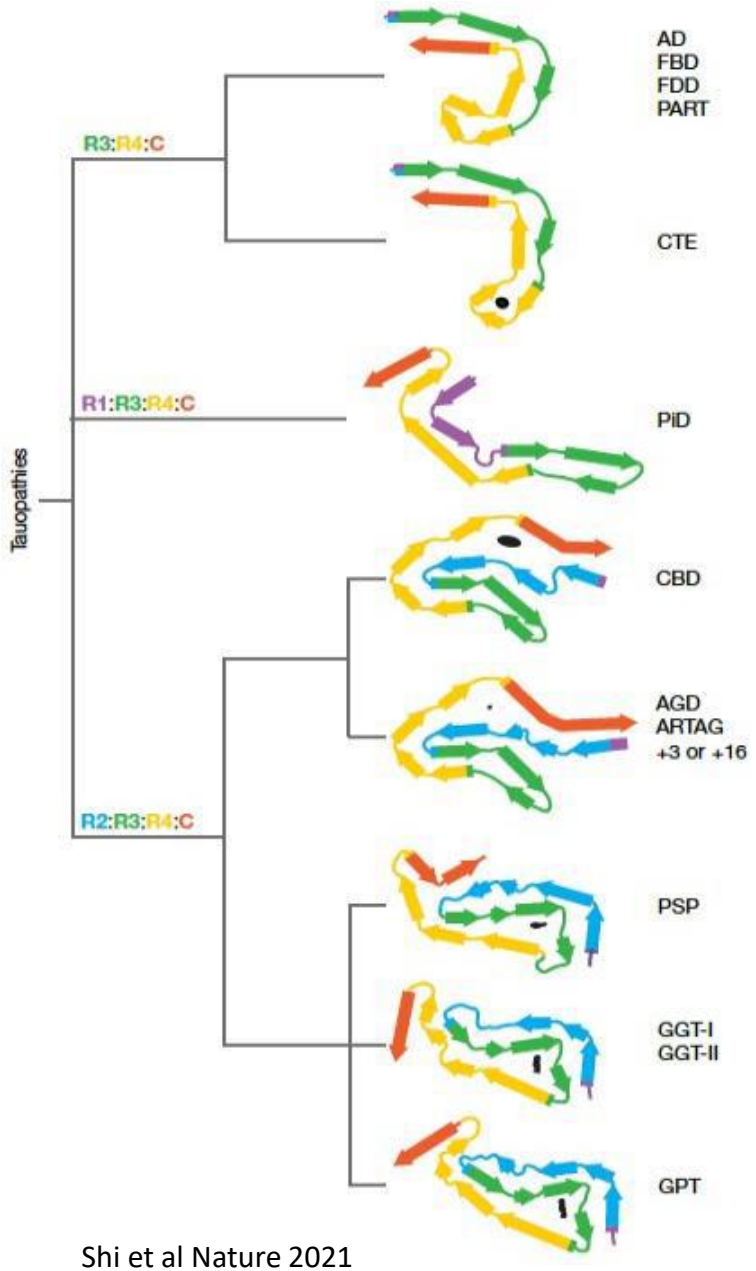
Modified from Chetelat et al. 2021

First and second generation Tau PET tracers



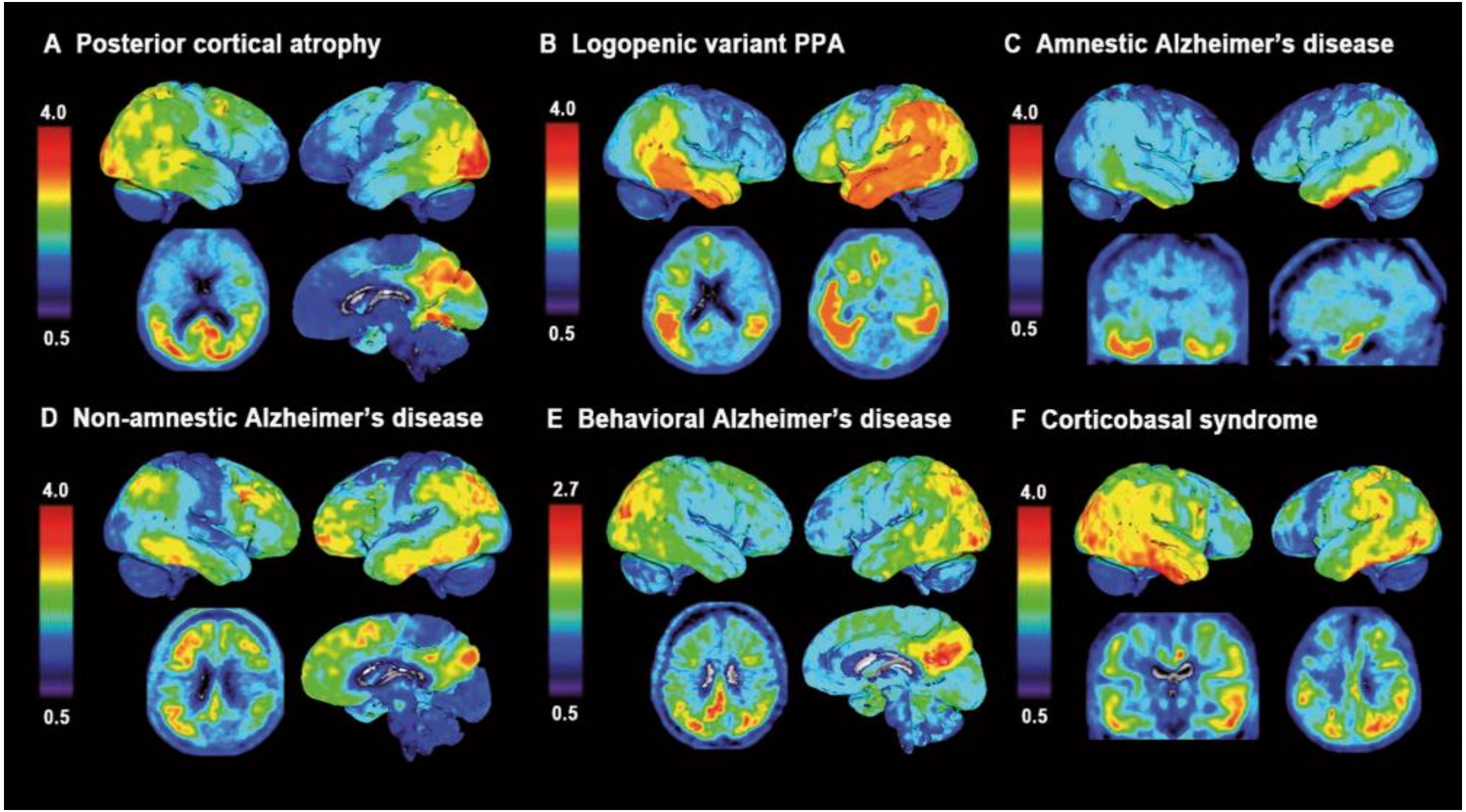
Leuzy , Chiotis et al Molecular Psychiatry 2019

Cryo-EM tau fibril structures for 3R,3/4R, 4R tauopathies



Shi et al Nature 2021

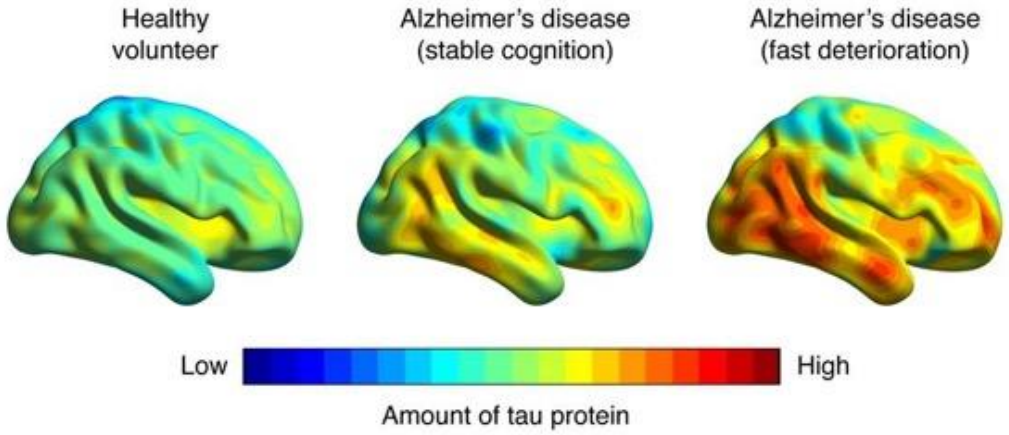
Different AD phenotypes with different regional Tau deposition



[^{18}F]-Flortaucipir PET

Ossenkoppele et al.Brain 2016

TAU PET imaging can better predict cognitive decline than CSF biomarkers or FDG-PET



Chiotis et al. 2021

www.nature.com/mp

Molecular Psychiatry 2021

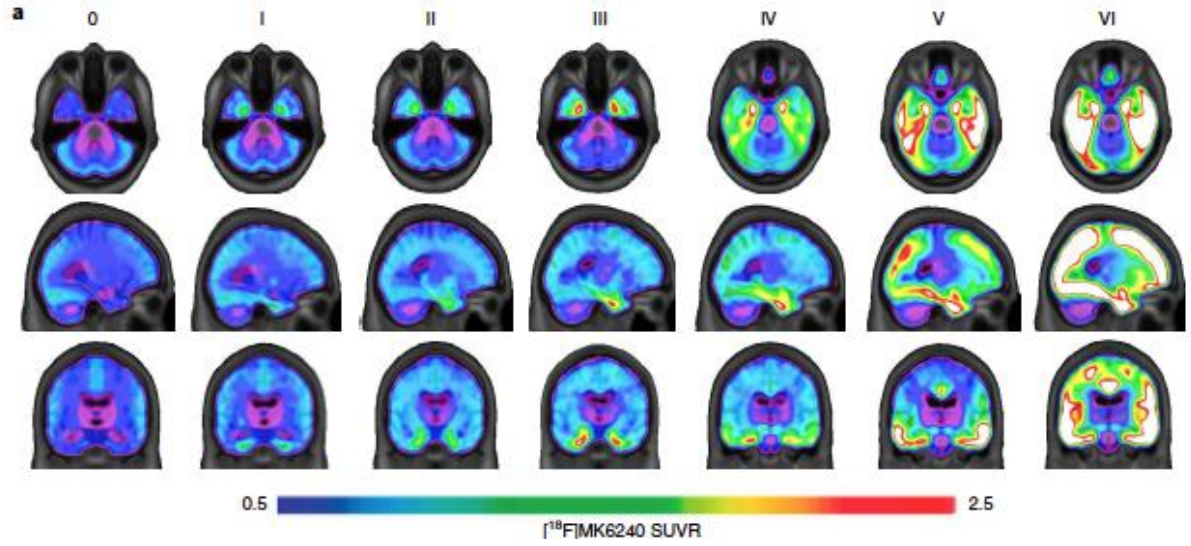
ARTICLE OPEN

Check for updates

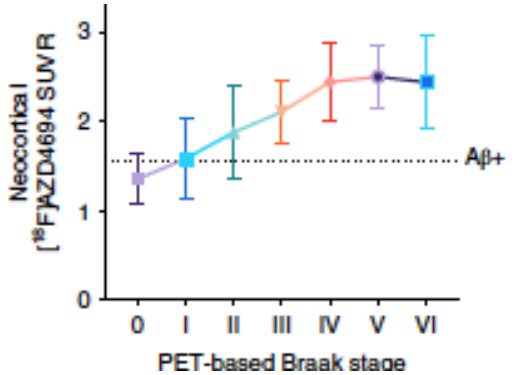
Alzheimer's disease profiled by fluid and imaging markers: tau PET best predicts cognitive decline

Marco Bucci[1], Konstantinos Chiotis[1,2] and Agneta Nordberg[1,3]✉ for the Alzheimer's Disease Neuroimaging Initiative

Biomarker modelling of AD using PET-based Braak staging with tau PET ligand 18F-MK-6240

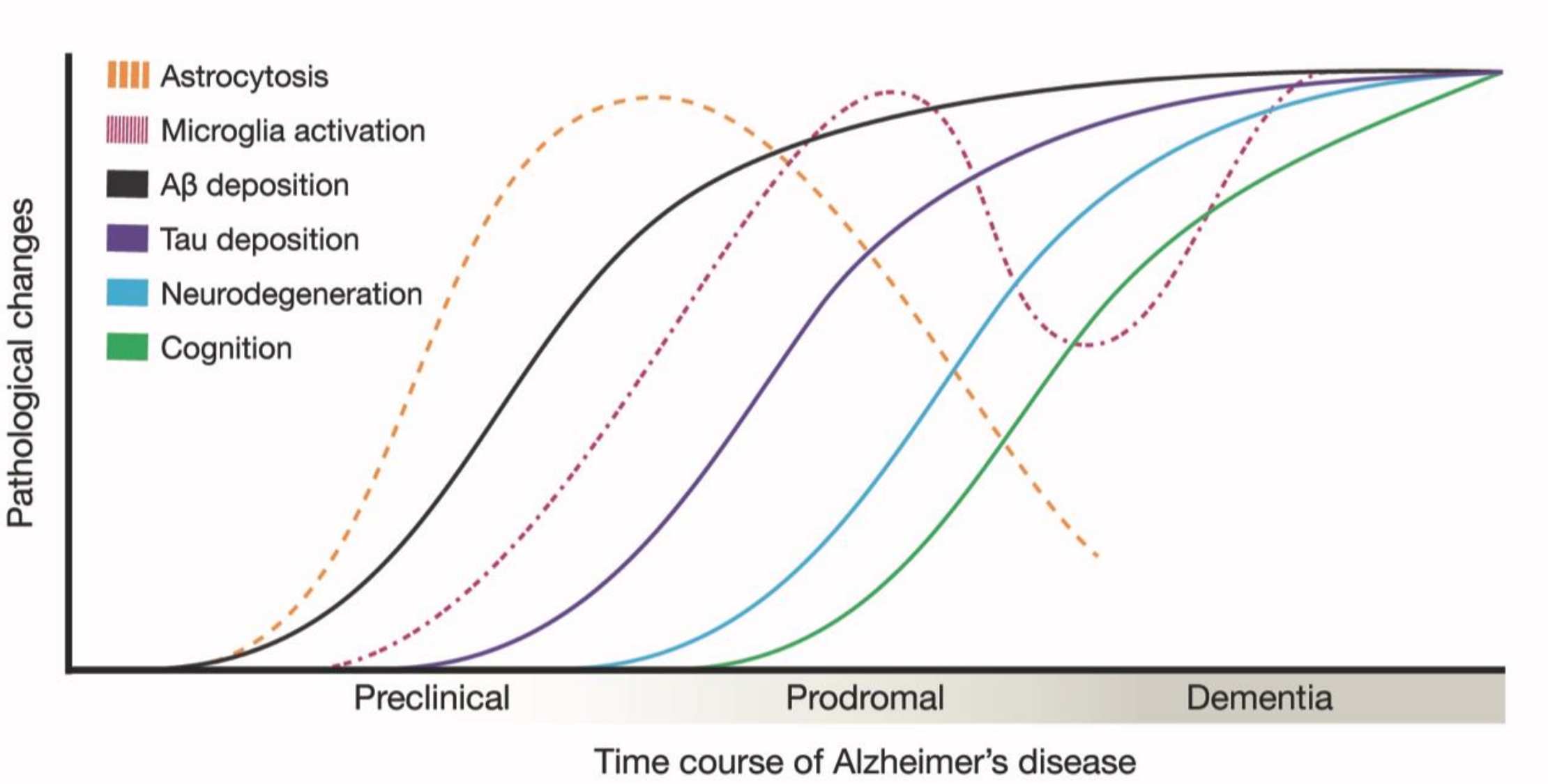


Therrialut et al. 2022



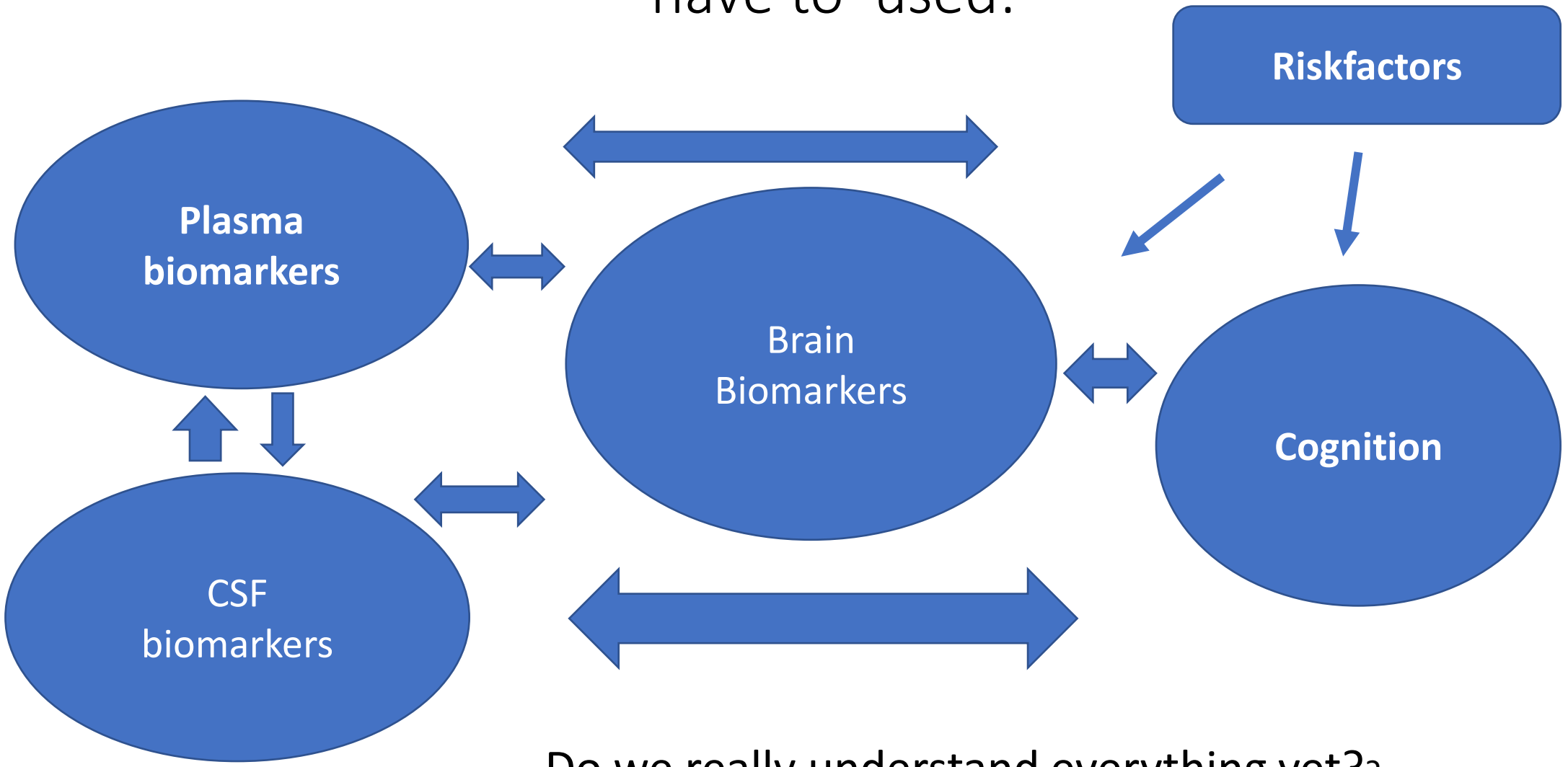
Amyloid PET

What multi-tracer PET molecular imaging might tell us…….

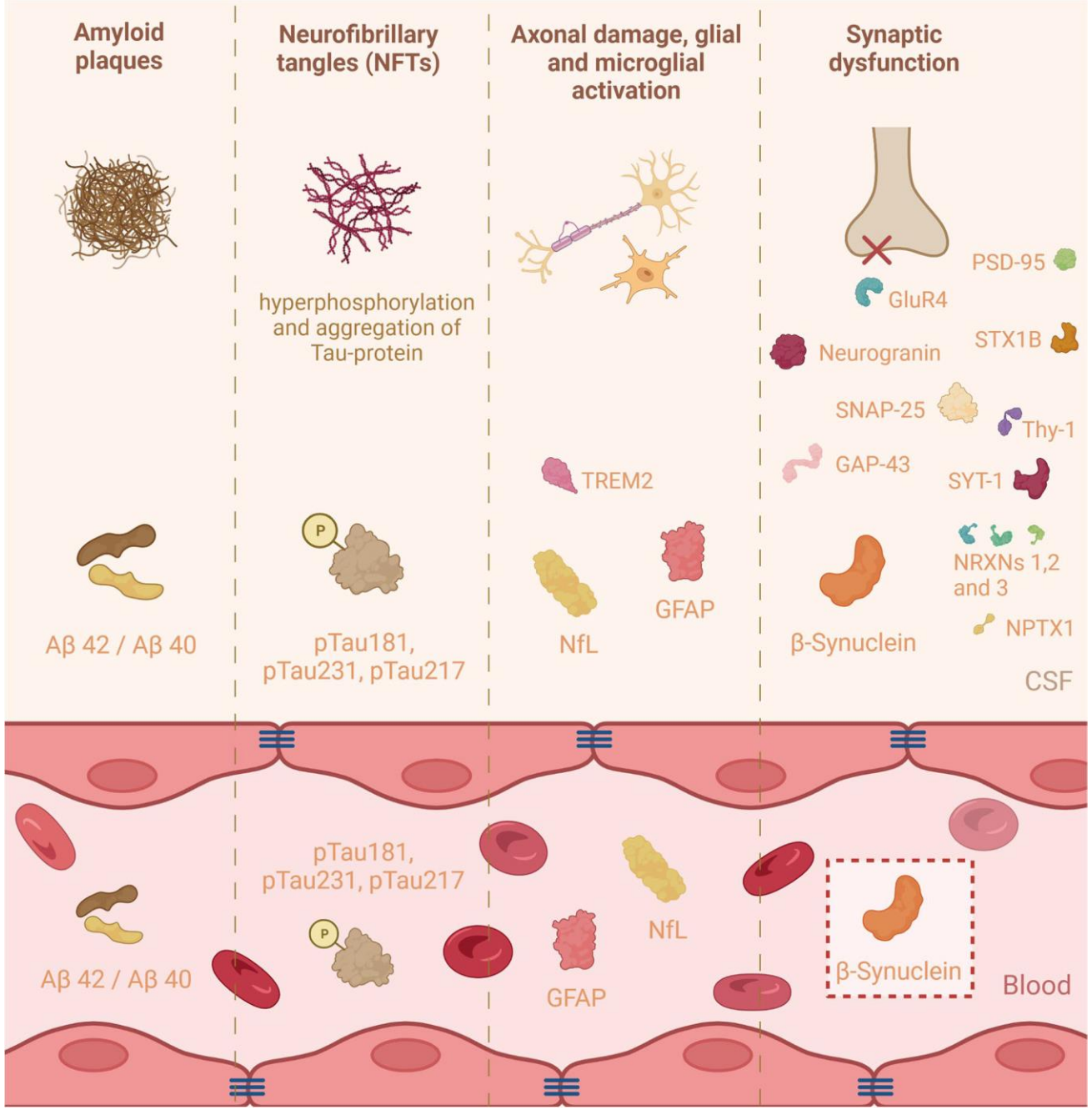


MOLECULAR IMAGING is rapidly developing and is now also coming into clinical praxis

To unravel the AD continuum different type of biomarkers have to used:



Do we really understand everything yet?



Mohaupt et al.2022

Are the various biomarkers comparable?

Imaging and fluid biomarkers

Brain

- Amyloid PET
- Tau Pet
- Astrocyte PET
- FDG PET

CSF

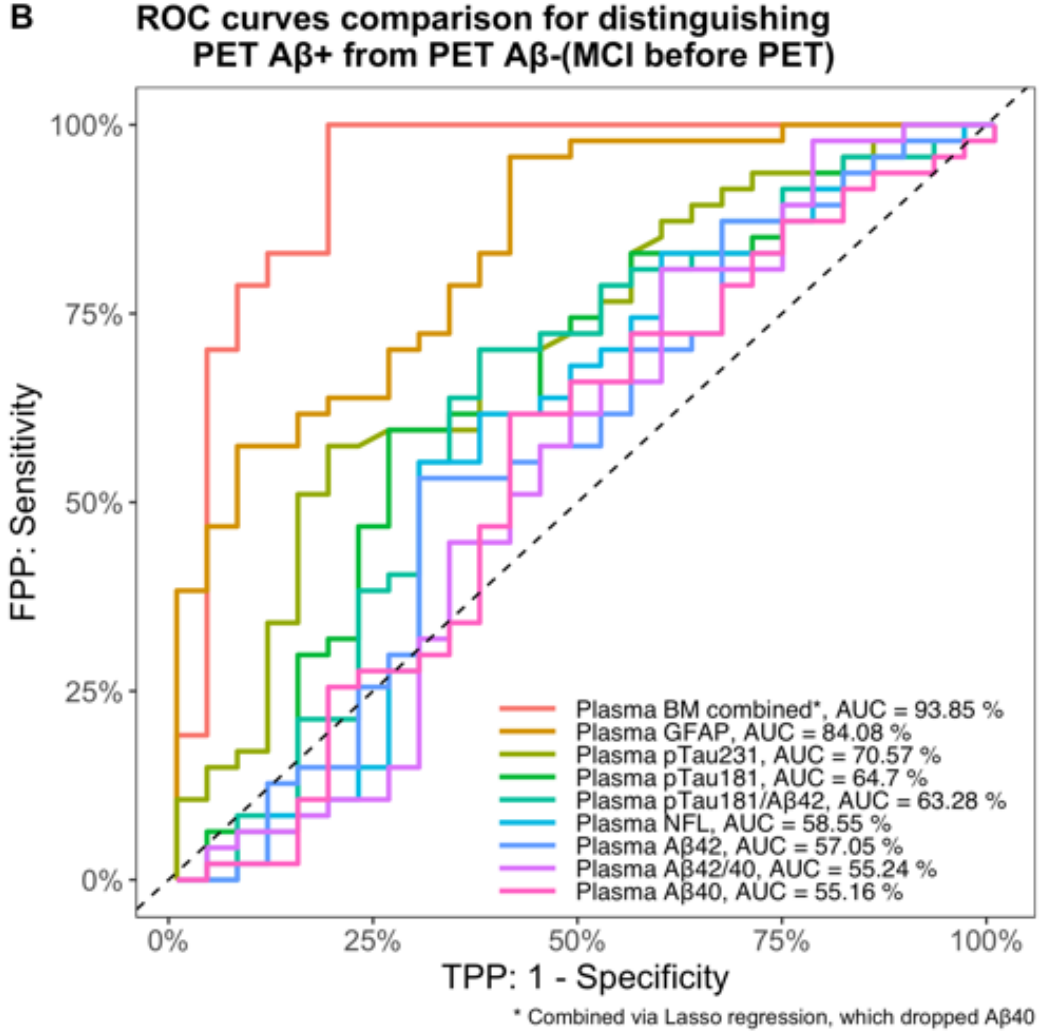
- Aß 42
- Aß42/40
- pTau
- t-Tau
- NFL
- ß-Synuclein

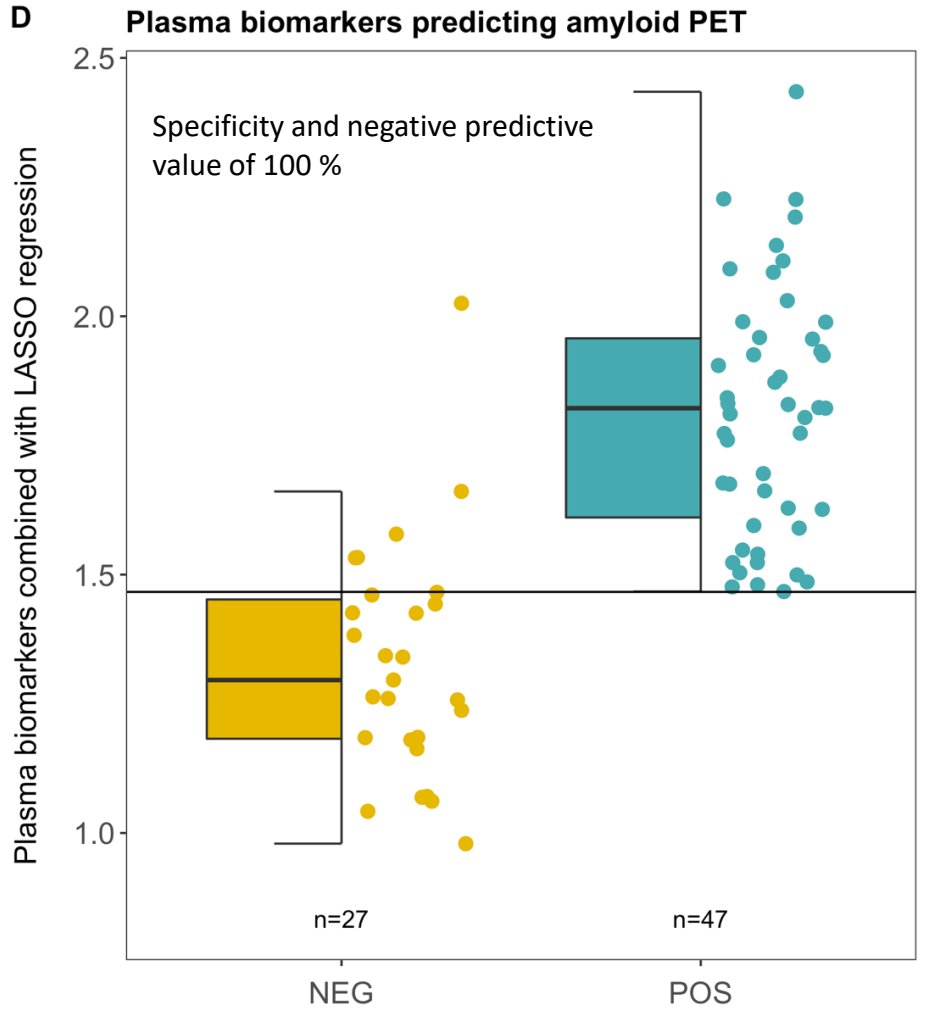
Plasma biomarkers

- Aß 42/40
- p-Tau 181, p-Tau 231, p-Tau 217
- GFAP
- NFL
- ß-Synuclein

Using plasma biomarkers before knowledge of amyloid PET data

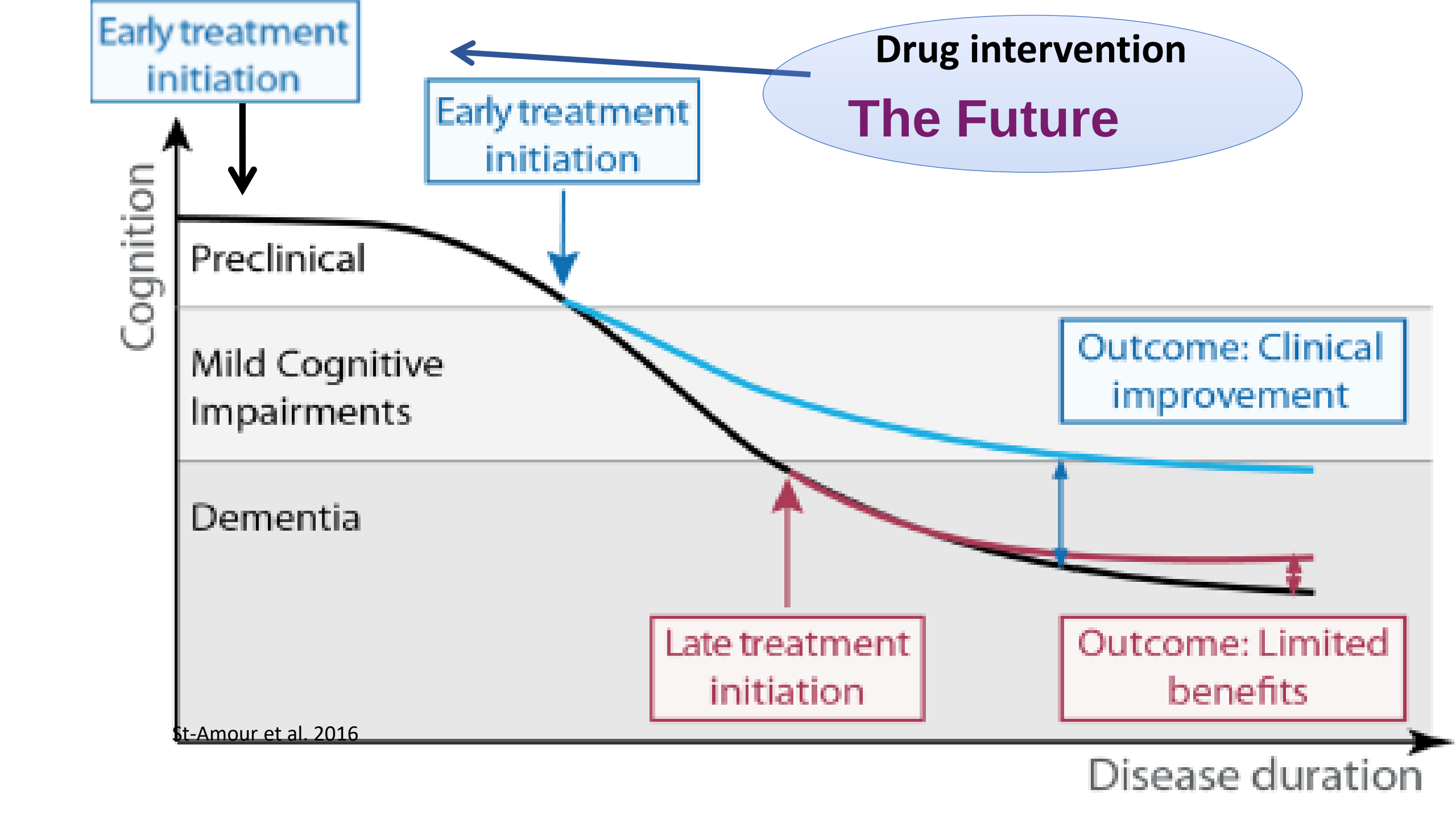
Clinical patient cohort Karolinska n=126





Plasma biomarkers combined result in superior AUC to plasma biomarkers alone.
Plasma GFAP and Plasma pTau231 important contributors to the pooled variables.

Bucci, Bluma et al. Translational Psychiatry 2023



St-Amour et al. 2016

New amyloid immunization therapy in Alzheimer´s disease

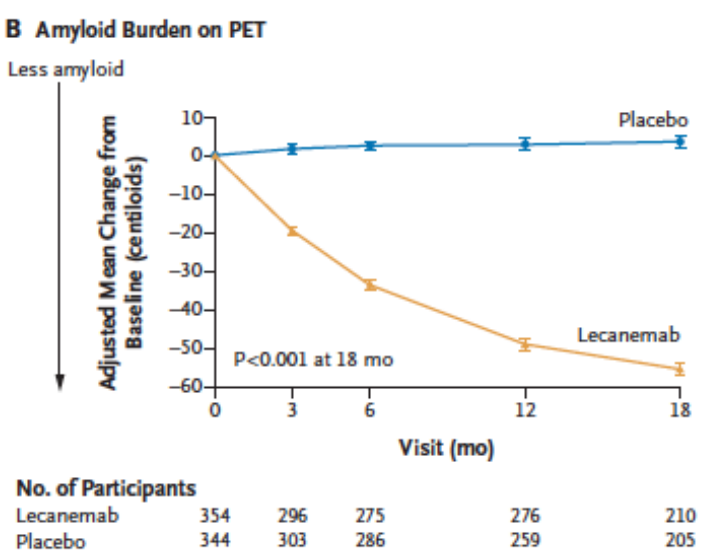
The NEW ENGLAND JOURNAL of MEDICINE

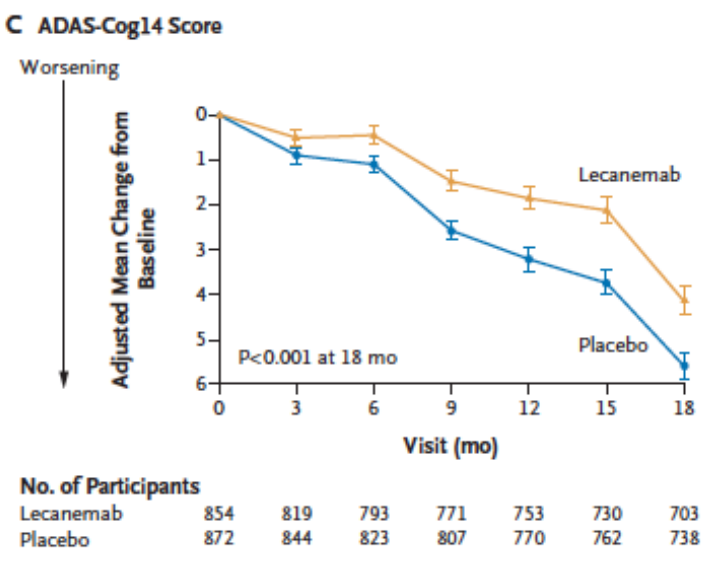
ORIGINAL ARTICLE

Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Sw... nan, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reydermar... Catayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

2022, at NEJM.org. DOI: 10.1056/NEJMoa2212948

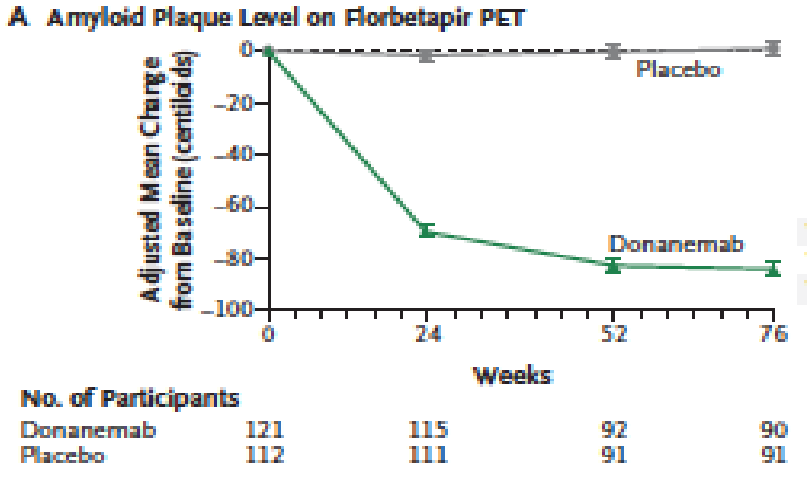


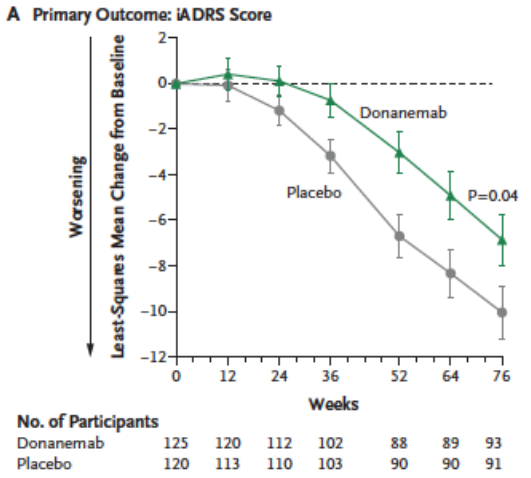


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MAY 6, 2021 VOL. 384 NO. 18

Donanemab in Early Alzheimer's Disease

Mark A. Mintun, M.D., Albert C. Lo, M.D., Ph.D., Cynthia Duggan Evans, Ph.D., Alette M. Wessels, Ph.D., Paul A. Ardayfio, Ph.D., Scott W. Andersen, M.S., Sergey Shcherbinin, Ph.D., JonDavid Sparks, Ph.D., John R. Sims, M.D., Miroslaw Brys, M.D., Ph.D., Liana G. Apostolova, M.D., Stephen P. Salloway, M.D., and Daniel M. Skovronsky, M.D., Ph.D.





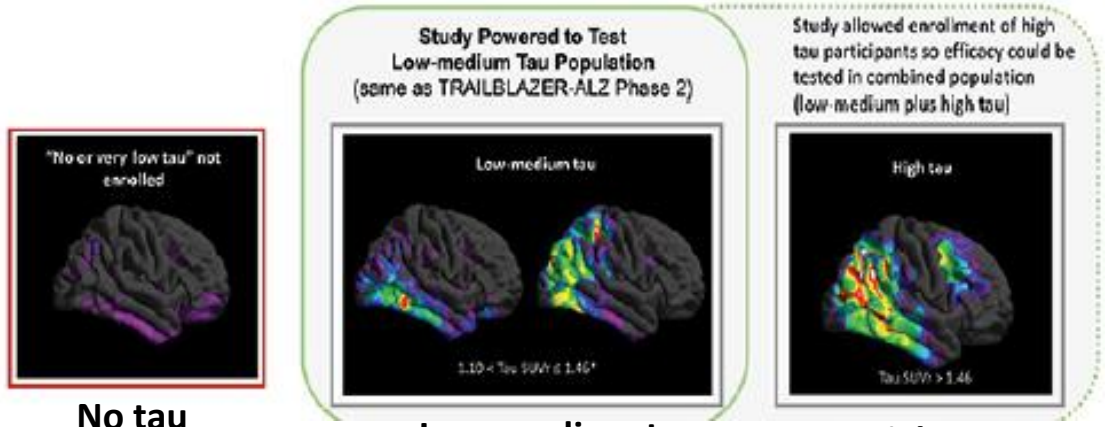
JAMA. doi:10.1001/jama.2023.13239
Published online July 17, 2023.

JAMA | Original Investigation

Donanemab in Early Symptomatic Alzheimer Disease
The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

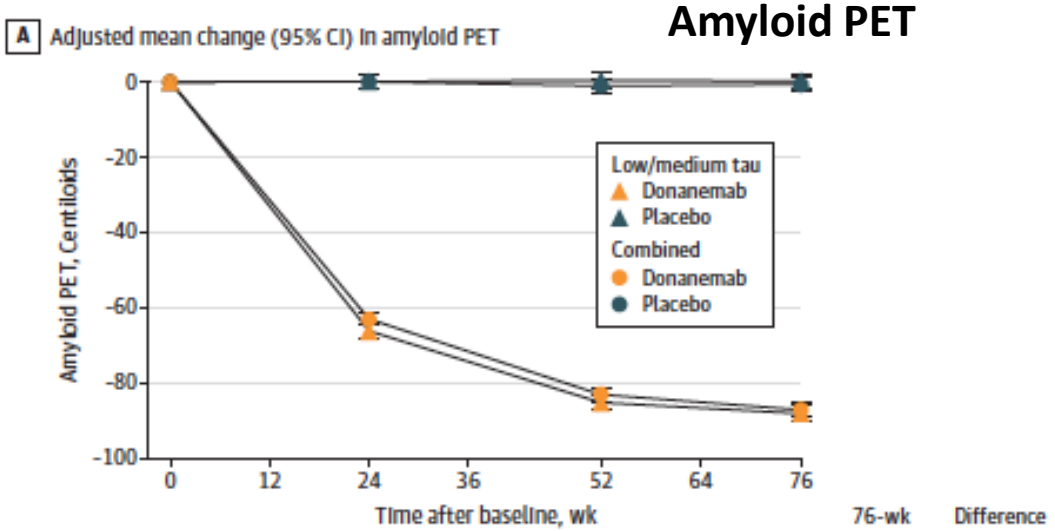
John R. Sims, MD; Jennifer A. Zimmer, MD; Cynthia D. Evans, PhD; Ming Lu, MD, MS, MPH; Paul Ardayfio, PhD; JonDavid Sparks, PhD; Alette M. Wessels, PhD; Sergey Shcherbinin, PhD; Hong Wang, PhD; Emel Serap Monkul Nery, MD; Emily C. Collins, PhD; Paul Solomon, PhD; Stephen Salloway, MD; Liana G. Apostolova, MD; Oskar Hansson, MD, PhD; Craig Ritchie, MD, PhD; Dawn A. Brooks, PhD; Mark Mintun, MD; Daniel M. Skovronsky, MD, PhD; for the TRAILBLAZER-ALZ 2 Investigators

TAU PET prior treatment



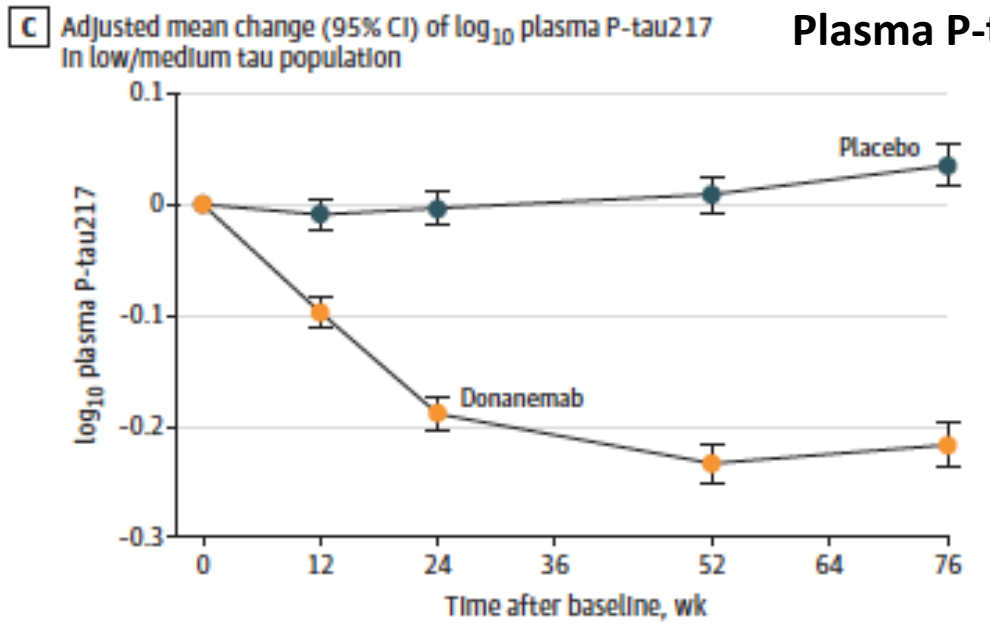
No tau | Low-medium tau | High tau

Amyloid PET



No. of participants					76-wk value, Centiloids	Difference from baseline %
Low/medium tau						
Donanemab	525	521	463	433	-88.0	-85.5
Placebo	556	552	498	470	0.2	0.2
Combined						
Donanemab	765	760	670	614	-87.0	-83.7
Placebo	812	805	729	690	-0.7	-0.7

Plasma P-tau217



No. of participants					
Placebo	537	517	511	449	429
Donanemab	522	493	464	410	395

⟹ **No effect of donanemab treatment on Tau PET (18F-flortaucipir)**

Can We Use Blood Biomarkers as Entry Criteria and for Monitoring Drug Treatment Effects in Clinical Trials? A Report from the EU/US CTAD Task Force

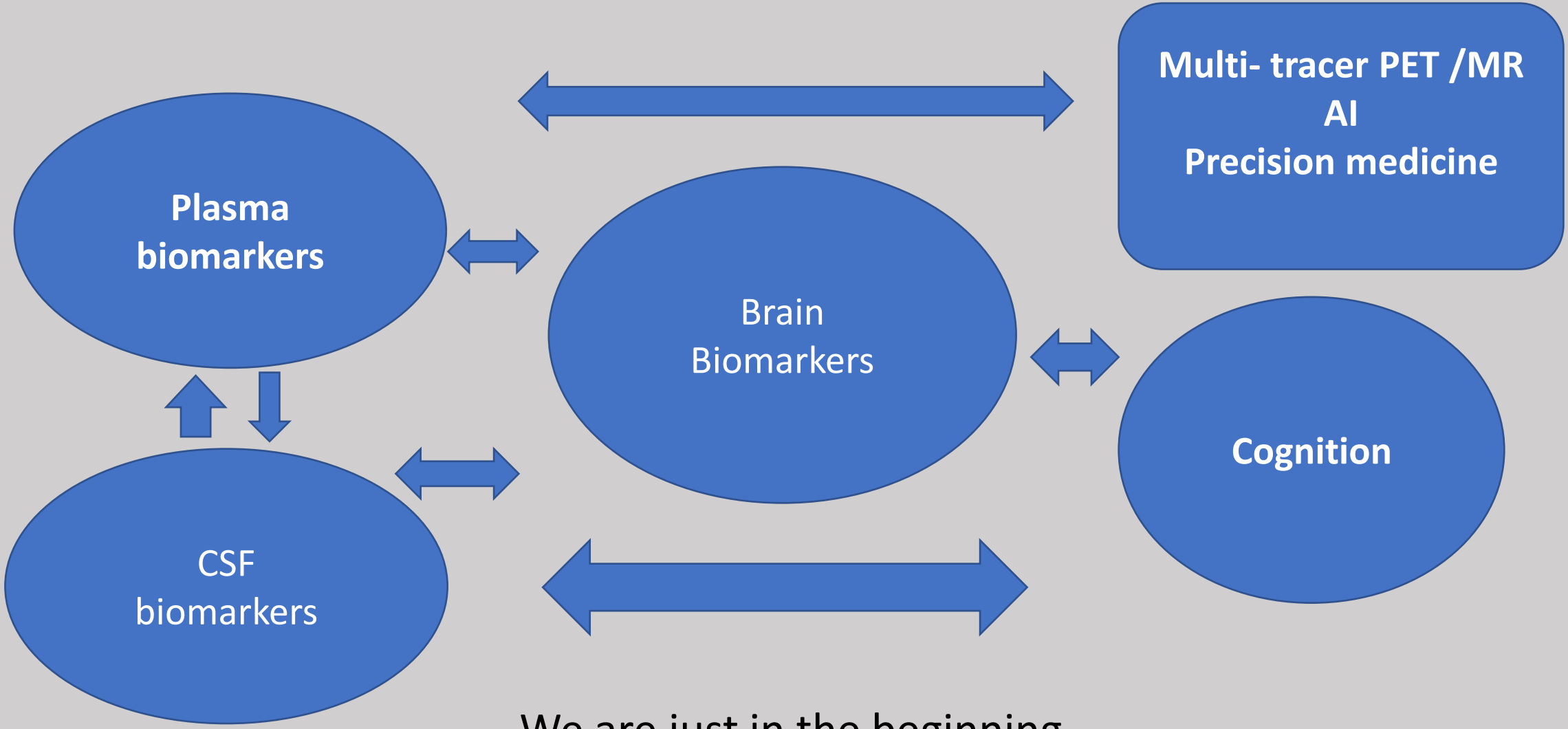
D. Angioni1, O. Hansson2, R.J. Bateman3, C. Rabe4, M. Toloue5, J.B. Braunstein6, S. Agus7, J.R. Sims8, T. Bittner4, M.C. Carrillo9, H. Fillit10, C.L. Masters11, S. Salloway12, P. Aisen13, M. Weiner14, B. Vellas1-15, S. Gauthier16 and the EU/US/CTAD Task force

Table 1. Some examples of BBMs use in clinical trials as entry criteria

PRE-SCREENING						
Study	**Clinicaltrial.gov Identifier**	**Phase**	**Population**	**Drug**	**BBM**	**Confirmatory Exam**
AUTONOMY	NCT04619420	II	Early symptomatic AD	JNJ-63733657	p-tau217	Tau PET
INVOKE-2	NCT04592874	II	Early symptomatic AD	AL002	PrecivityAD™ (algorithm derived from Aβ 42/40, ApoE and Age)	Amyloid PET or CSF
PROSPECT-ALZ	NCT05063539	II	Early symptomatic AD	LY3372689	p-tau217	Amyloid PET Tau PET
TRAILBLAZER-ALZ 2	NCT04437511	III	Early symptomatic AD	Donanemab	p-tau181	Amyloid PET Tau PET
AHEAD 3-45	NCT04468659	III	Preclinical AD	Lecanemab	Aβ42/40 ratio	Amyloid PET
SKYLINE	NCT05256134	III	Preclinical AD	Gantenerumab	p-tau181 and ApoE	Amyloid PET or CSF
SCREENING						
Study	**Clinicaltrial.gov Identifier**	**Phase**	**Population**	**Drug**	**BBM**	
TRAILBLAZER-ALZ 3	NCT05026866	III	Preclinical AD	Donanemab	p-tau217	

JPAD 2023

Molecular brain imaging a promising future key-player for biomarker discovery and clinical translation in neurogenereative diseases



We are just in the beginning……