Fourth Neuroscience Spring Conference

Translating neuroscience knowledge to clinical practice

London, March 13, 2020

Cutting Edge lecture

'Biomarkers for the diagnosis and monitoring of progression in Alzheimer's disease'

Dr Ivan Koychev, University of Oxford

Supported by the Gatsby Charitable Foundation and the Wellcome Trust

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Introduction

Alzheimer's disease (AD) is the most common type of neurodegenerative dementia, accounting for 50-70% of prevalent neurodegenerative dementia cases (Winblad et al., 2016). AD causes a progressive decline in cognitive function with the most typical initial symptom being short-term memory impairment.

AD neuropathology is characterised by:

- **neuronal loss** in specific brain regions – notably the medial temporal lobe structures and the temporo-parietal association cortices
- intraneuronal **neurofibrillary tangles** composed of aggregated and often truncated and hyperphosphorylated **tau protein**; and
- extracellular neuritic **plaques**, consisting of deposits of **β-amyloid** peptides (Blennow et al., 2006)

Blennow, K. et al. (2006) Alzheimer's disease. *Lancet* 368, 387-403.
Winblad, B. et al. (2016) Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol*. 15, 455-532.

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Introduction

Currently, **clinical diagnosis of AD** relies largely on documenting cognitive decline. This can be supplemented by additional parameters assessed through clinical investigations, such as blood tests and structural imaging. At the point of diagnosis, the disease has already caused severe brain damage.

Increasingly, and particularly with the prospect of disease modification, there has been a shift towards the use of **biomarkers** (Dubois et al., 2014) to **diagnose AD earlier** (pre-dementia stages) and **with more specificity**. Besides the clinical benefits of early and specific diagnosis, the use of biomarkers will enable the **monitoring of disease progression** and facilitate **clinical trials of novel candidate drugs**.

Dubois, B. et al. (2014). Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 13, 614-629.

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Intended Learning Outcomes

By completing this module, you will:

- ✓ **Review** up-to-date understanding of the role of neurofibrillary tangles and amyloid plaques in AD pathology
- ✓ **Understand** the terms *Alzheimer's Disease* and *Alzheimer's Dementia*
- ✓ **Identify** potential biomarkers for AD diagnosis and progression in four main areas:
  - ✓ Cognition
  - ✓ Neurodegeneration
  - ✓ Amyloid
  - ✓ Tau
- ✓ **Recognise** currently available biomarkers for AD and **categorise** potential future biomarkers as '*near future*' and '*distant future*'

Biomarkers for the diagnosis and monitoring of progression in Alzheimer's disease

The Gatsby/Wellcome Neuroscience Spring Conference

13th Mar 2020

Ivan Koychev

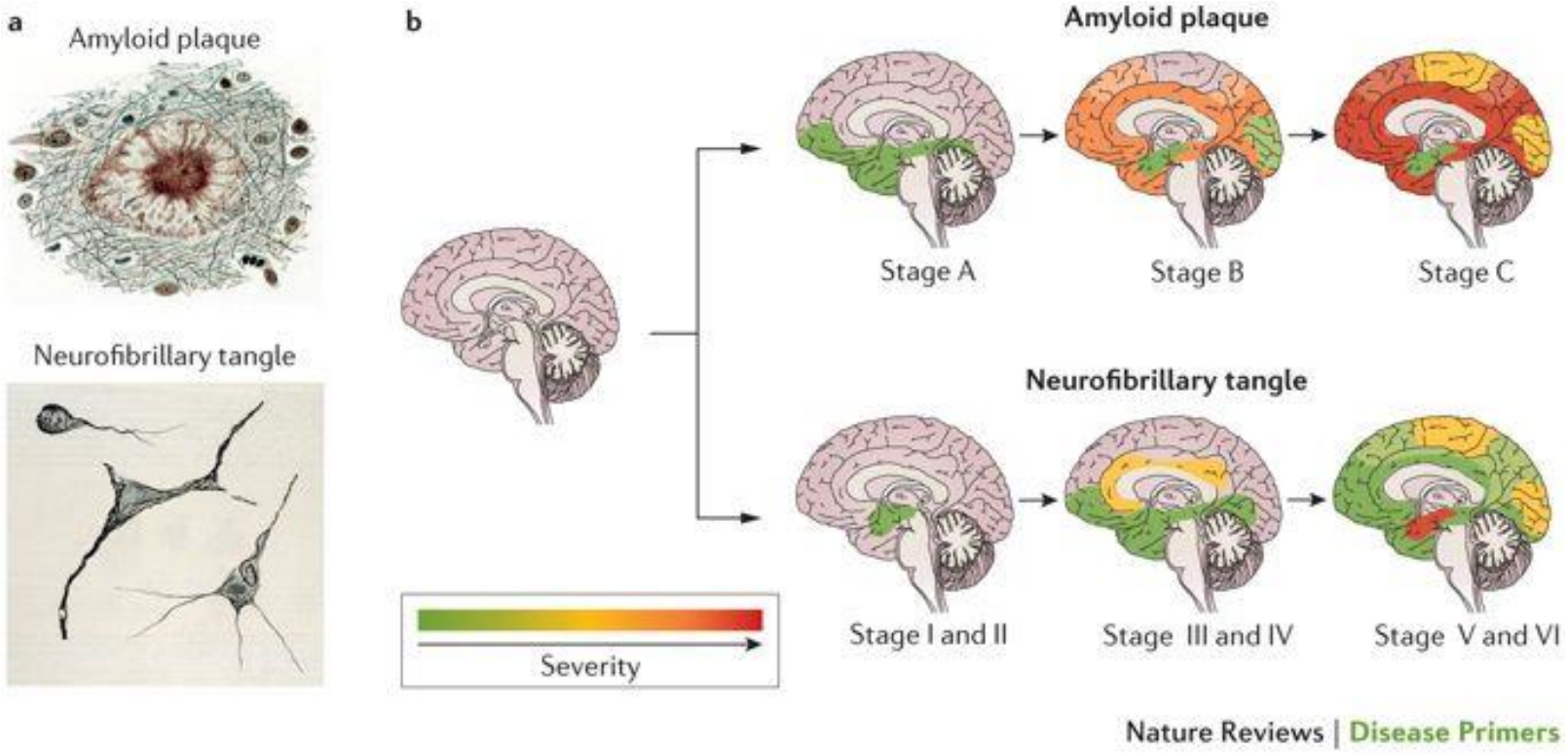
Senior Clinical Researcher I Consultant Neuropsychiatrist

University of Oxford I Oxford University Hospitals NHS Trust

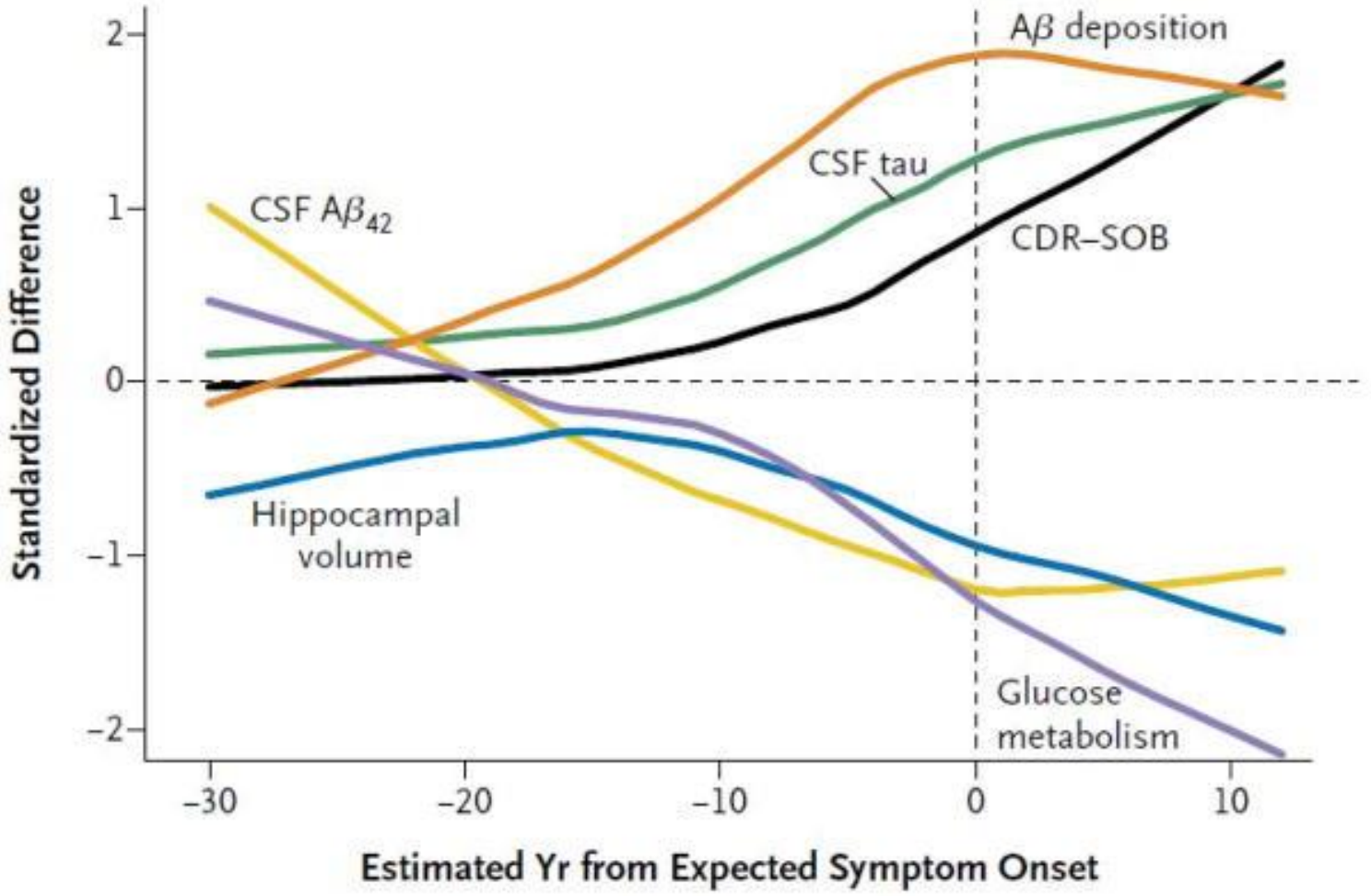
Disclosures

- NIHR trainee
- MRC grants: Deep and Frequent Phenotyping study, Dementias Platform UK, MRC-NIH Partnership in Neurodegeneration
- Academy of Medical Sciences Clinical Lecturer Starter Grant
- Oxford Alzheimer's Research UK
- Oxford University Clinical Graduate School
- Advisory Board Mantrah Ltd

Microscopic pathology

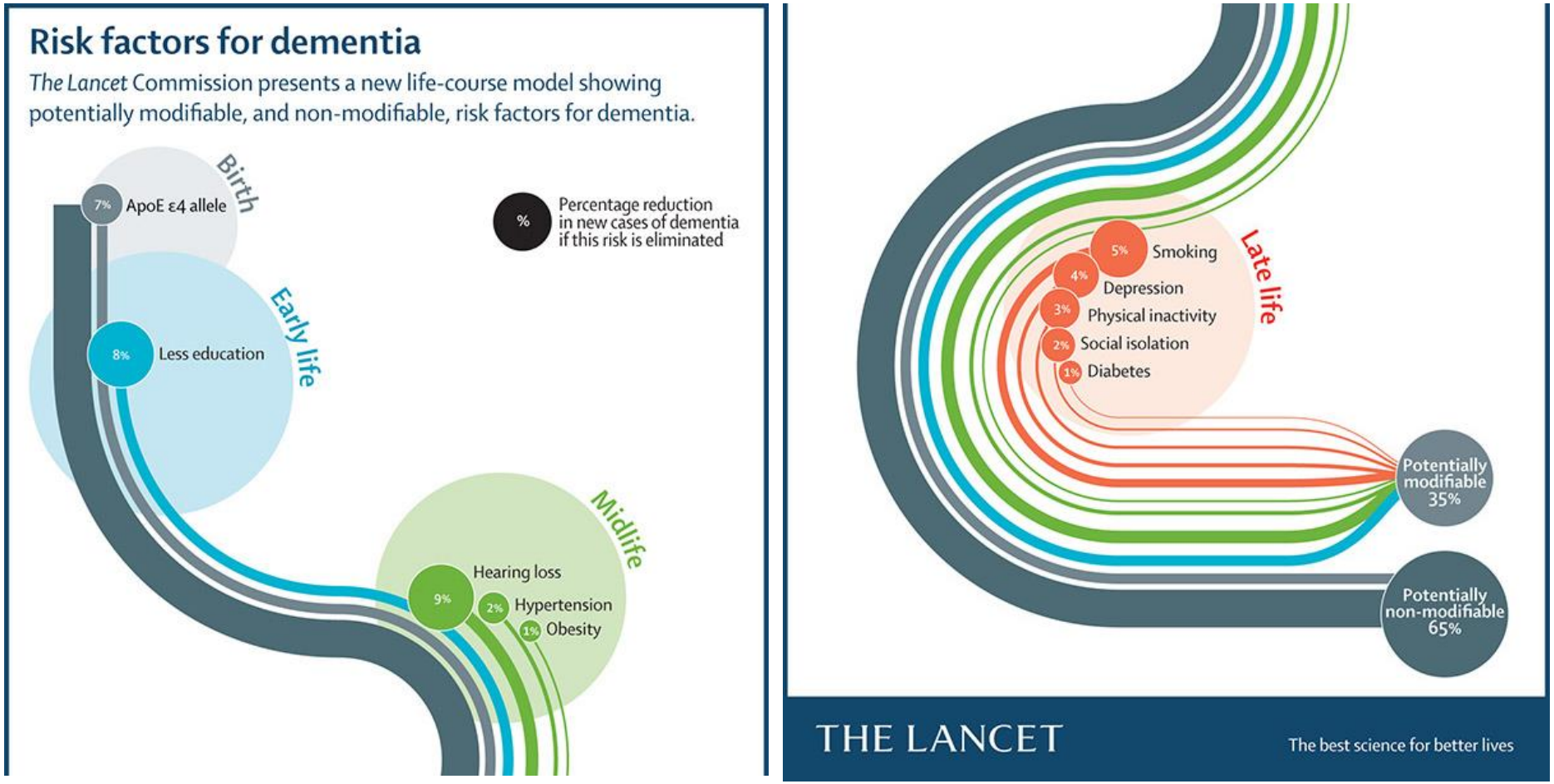


Biomarker temporal sequence



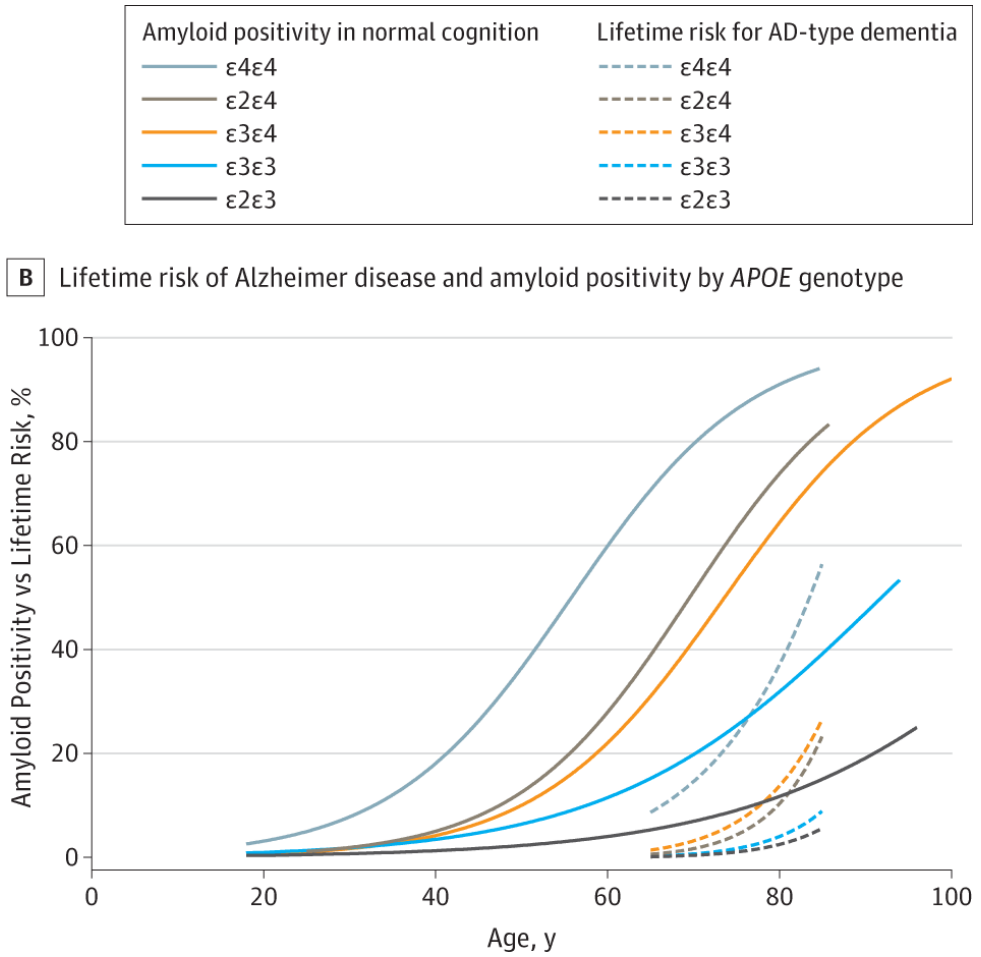
Jack et al. 2013 Lancet Neurology

Alzheimer's disease risk factors



Livingston et al. 2017 Lancet

APOE4 carriership effect



Jensen et al. JAMA 2015

Alzheimer's disease vs dementia

- Clinical criteria: Probable Alzheimer's dementia

Dementia + progressive + >2 cognitive domains

- Amyloid/Tau/Neurodegeneration framework: Alzheimer's disease

A+ *CSF ß-Amyloid <1025 pg/ml*

T+ *CSF p-Tau >24 pg/ml*

N+ *Schelten's score = 1 (<65 yrs)*
Schelten's score = 1.5 (65-75)
Schelten's score = 2 (>75 yrs)

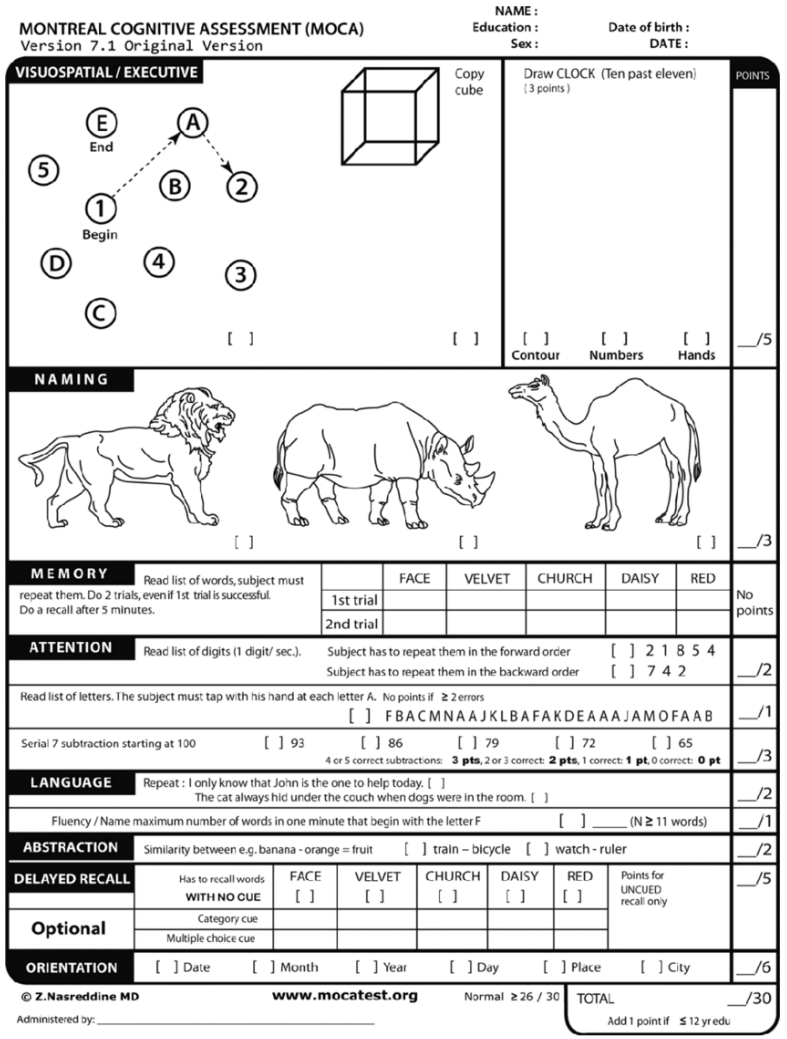
- Emergent Alzheimer's disease: Rapid amyloid/tau accumulation

ATN profiles	Biomarker category
A-T-(N-)	No pathology
A+T-(N-)	AD pathologic change
A+T-(N+)	AD pathologic change
A+T+(N-)	AD pathology
A-T+(N+)	Non-AD pathology
A-T-(N+)	Non-AD pathology
A-T+(N-)	Non-AD pathology

Biomarkers

- Main biomarkers
  - Cognition
  - Neurodegeneration
  - Amyloid
  - Tau
- Experimental biomarkers: ADLs, sleep, synaptic function
- Availability
  - Current
  - Near future
  - Distant future

Cognition: Current



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — Copy cube — Draw CLOCK (Ten past eleven) (3 points) — POINTS

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ] [ ] Contour [ ] Numbers [ ] Hands __/5

NAMING __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4. Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL __/5

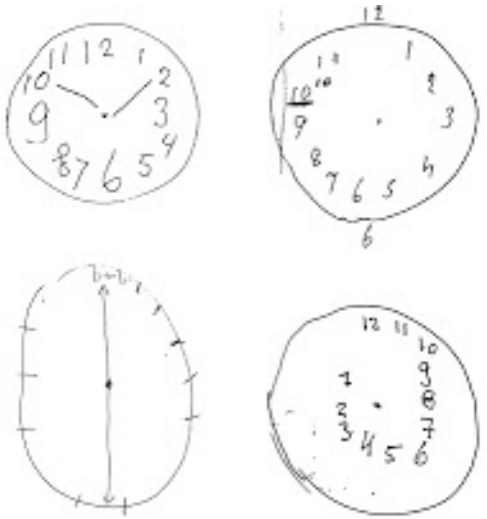
	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

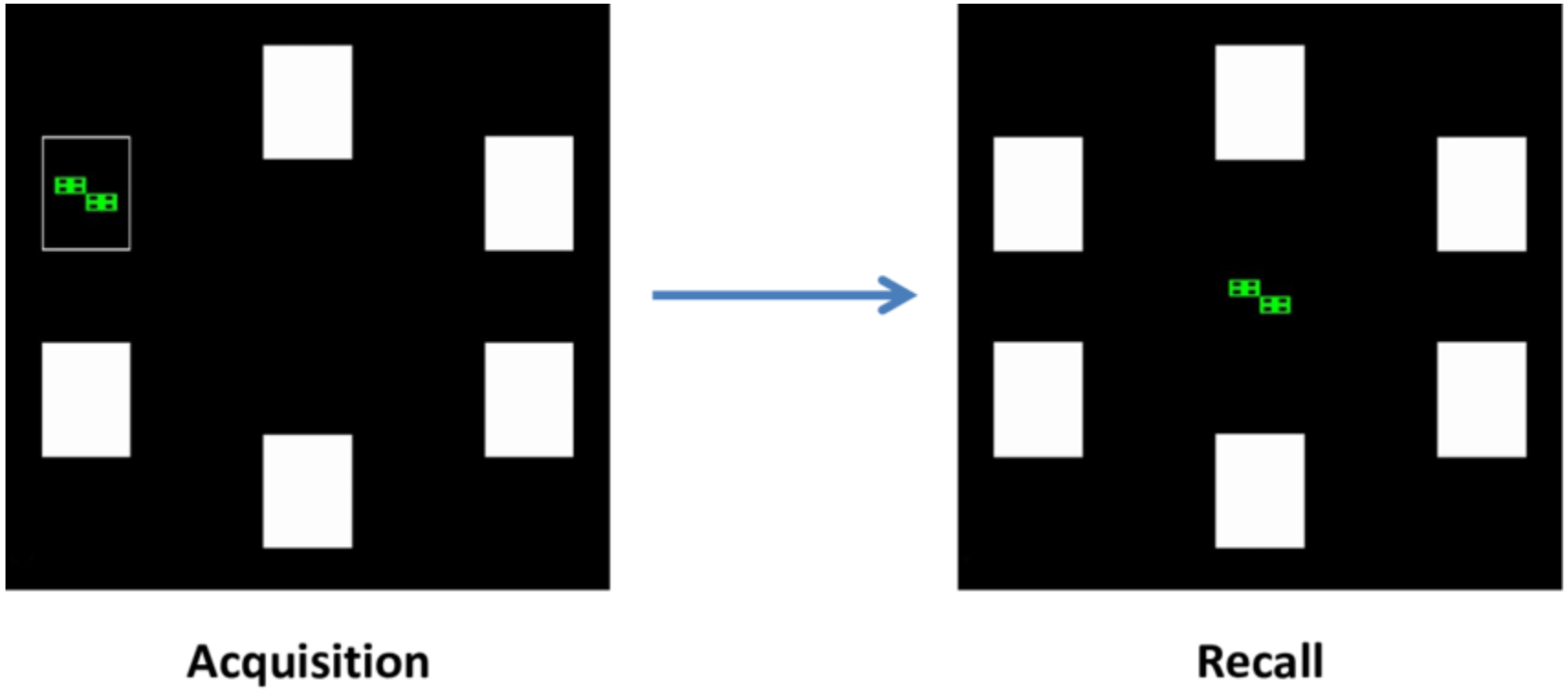
© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

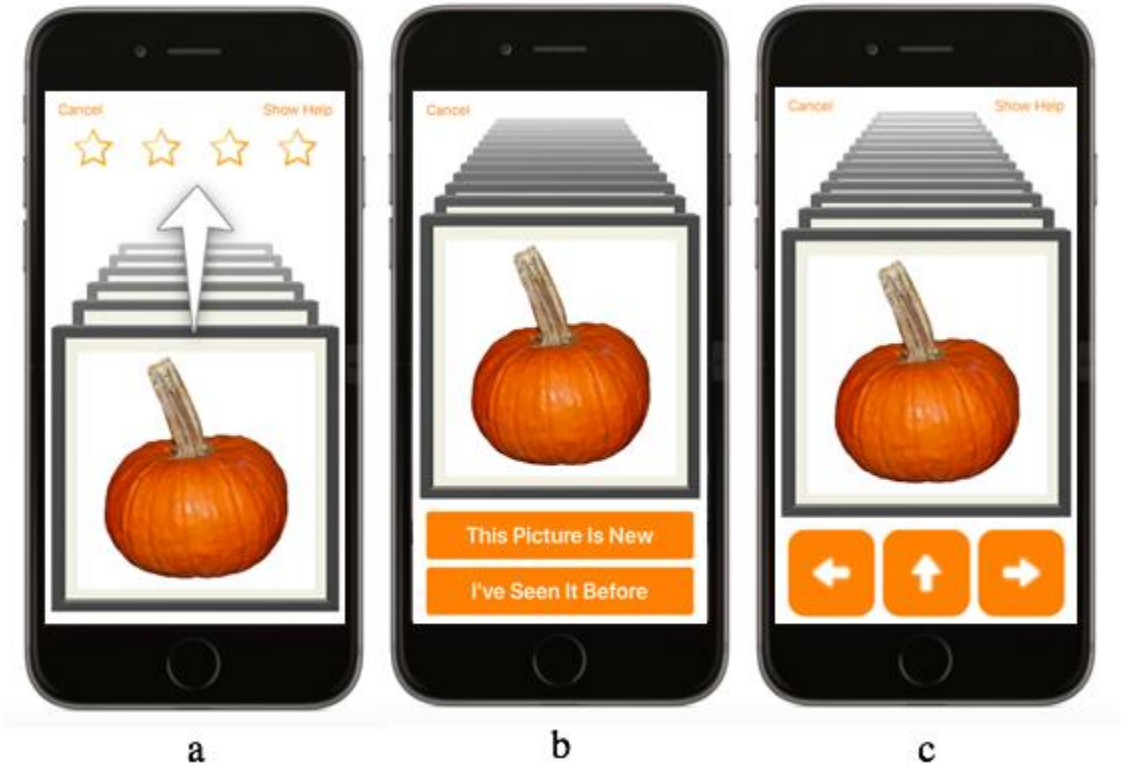
Administered by: _____

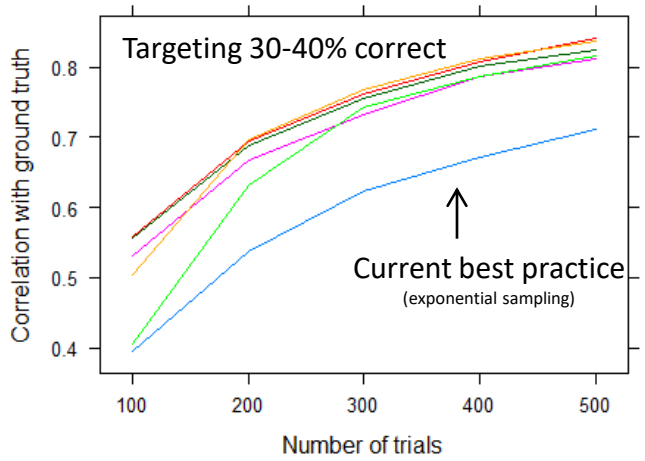


Cognition: Current/near future



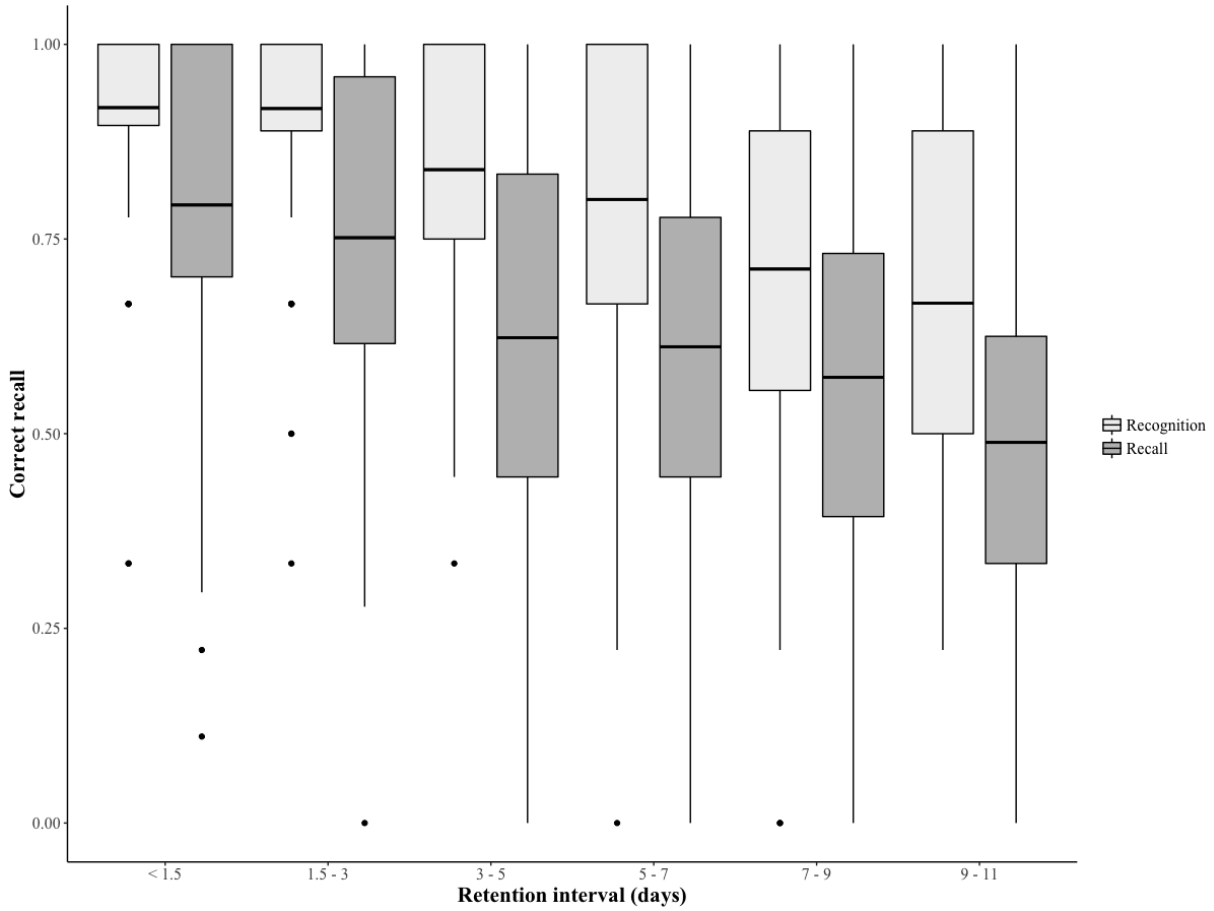
Cognition: Near future





Lancaster, Koychev et al. In press

Cognition: Near future

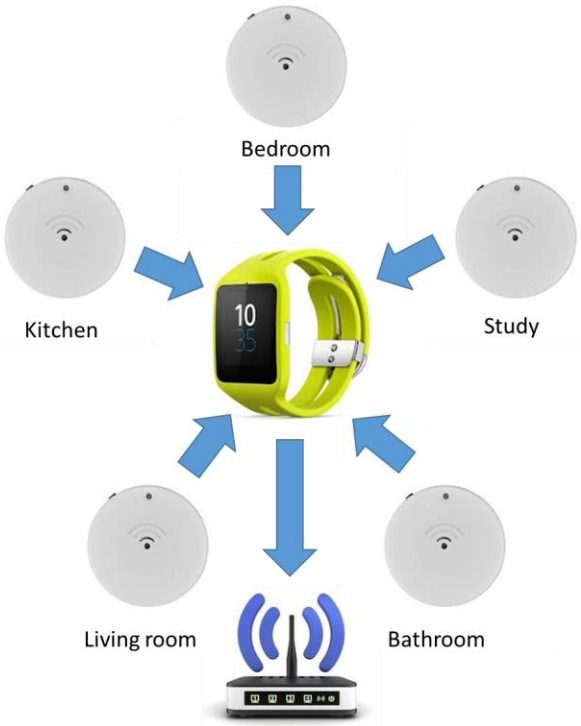


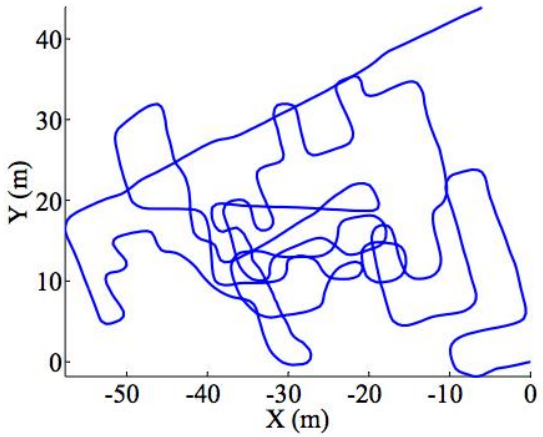
Lancaster, Koychev et al. In press

Cognition: (Not too) distant future

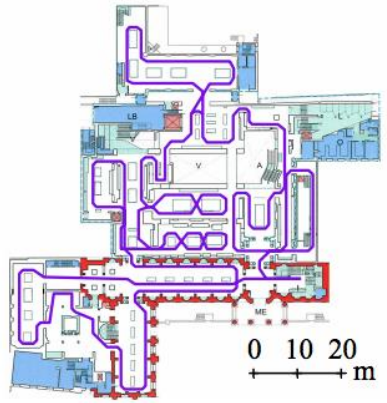
- Personal digital technology interaction
  - Adapted browsers
    - Typing speed
    - Speed of reading
  - Smartphone
    - Find correct words when texting
    - Time to find contact
    - Speech analysis (machine learning)
  - Internet of things
    - Pattern of use of technology around the house (machine learning)

Cognition: (Not too) distant future

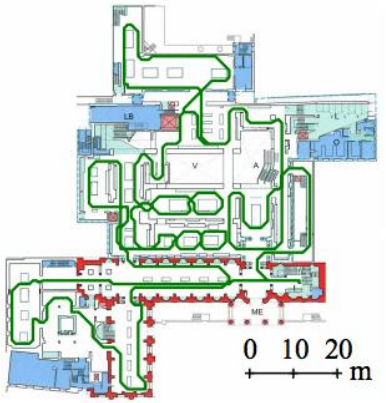




(a) Raw trajectory



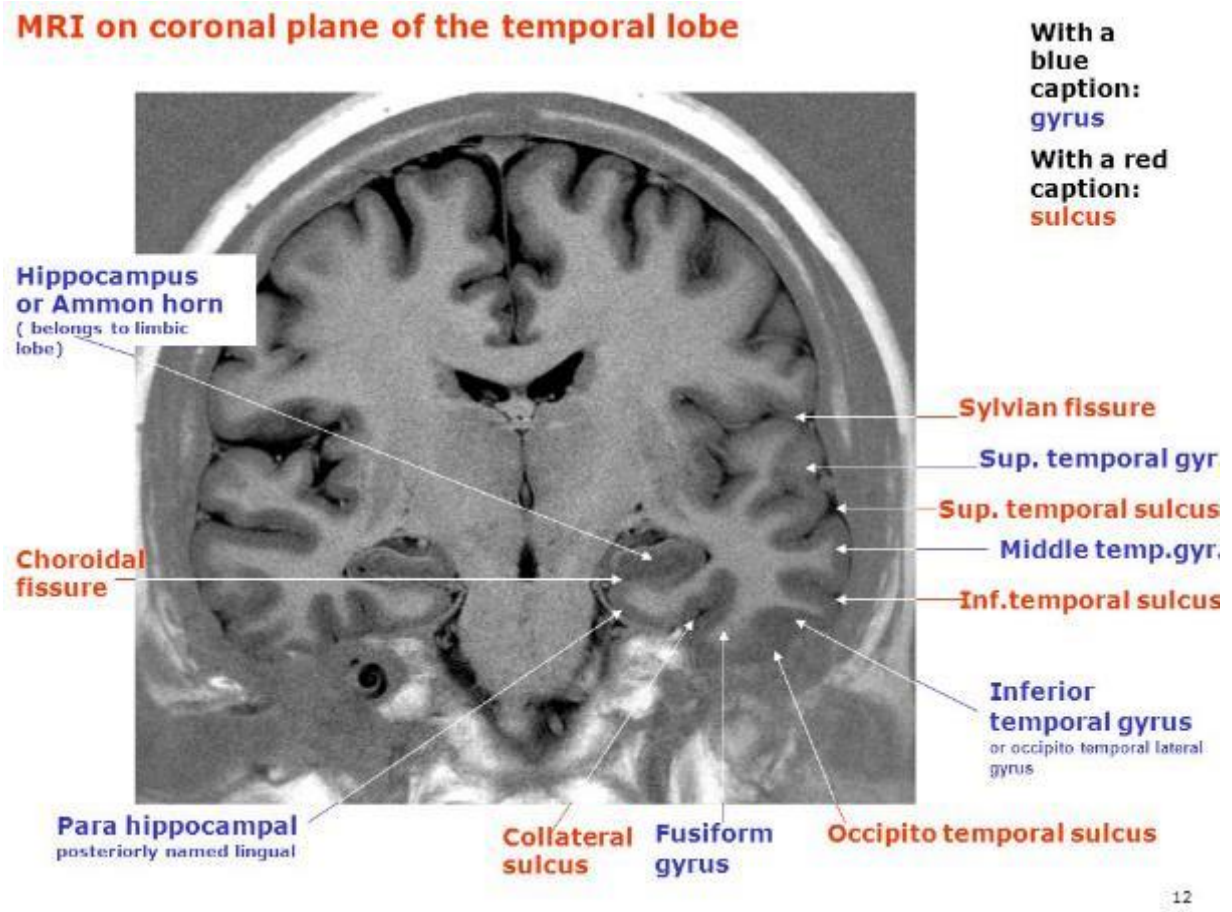
(b) Ground truth trajectory



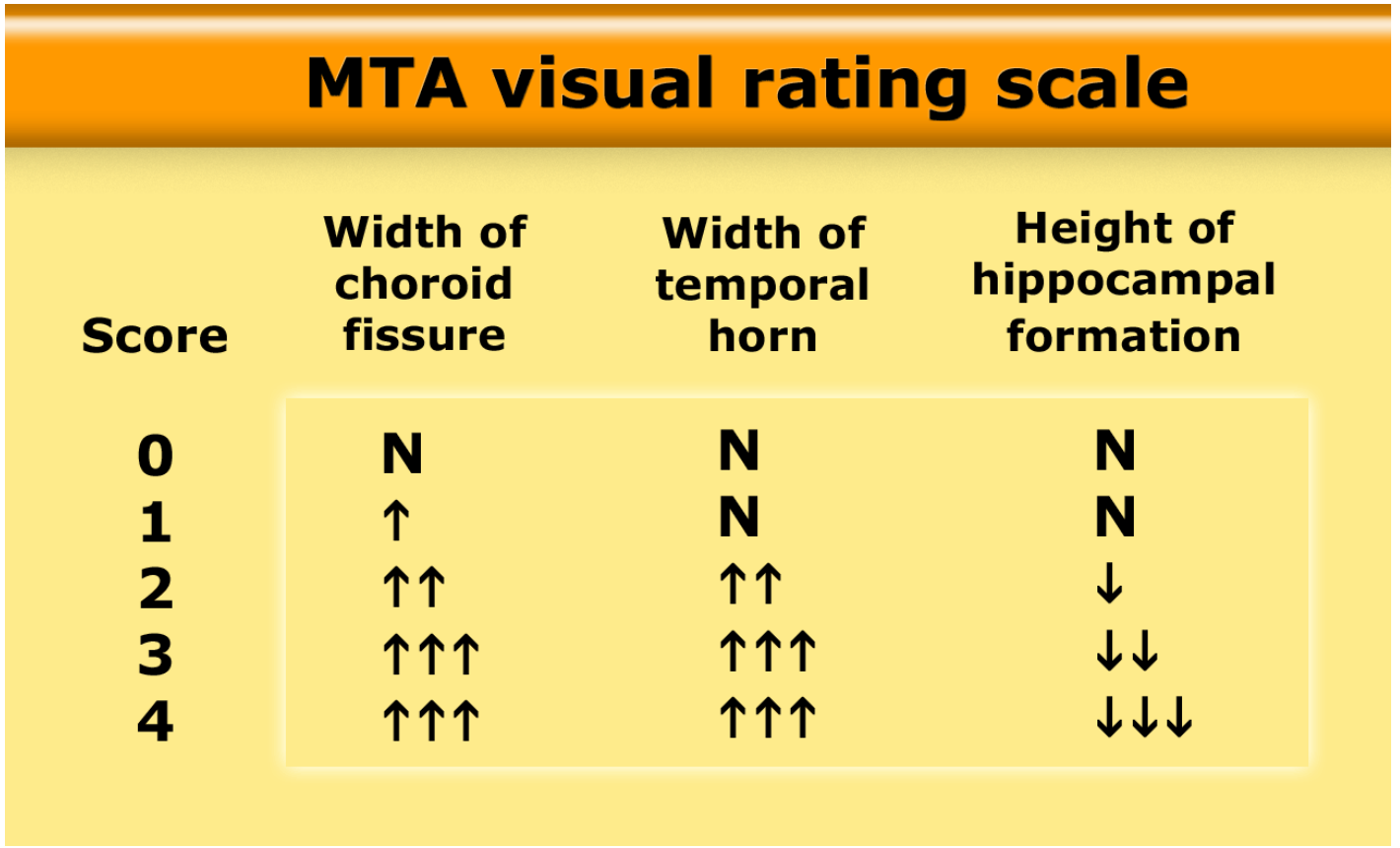
(c) Matched trajectory

Trigoni, Koychev et al. In prep

Neurodegeneration: Current



Neurodegeneration: Current



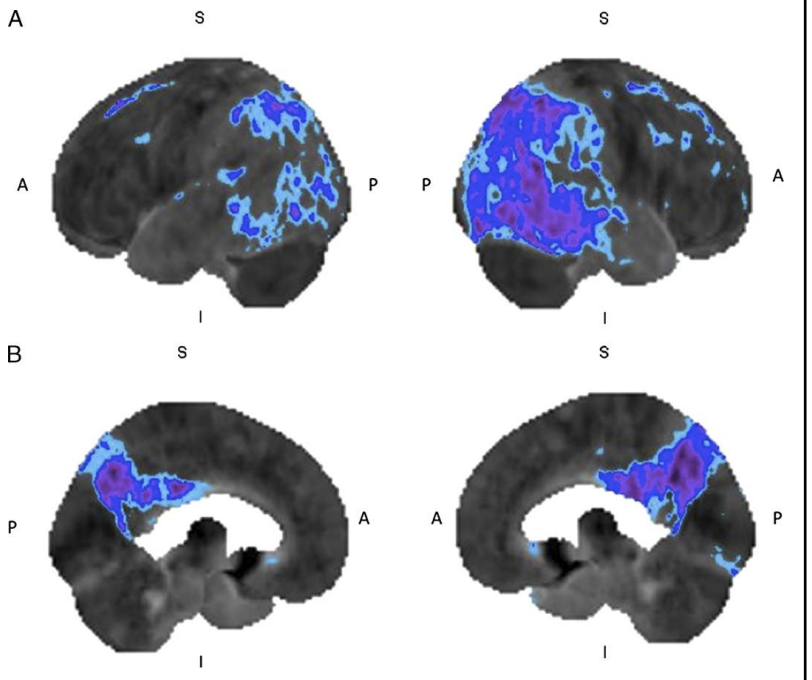
MTA visual rating scale

Score	Width of choroid fissure	Width of temporal horn	Height of hippocampal formation
0	N	N	N
1	↑	N	N
2	↑↑	↑↑	↓
3	↑↑↑	↑↑↑	↓↓
4	↑↑↑	↑↑↑	↓↓↓

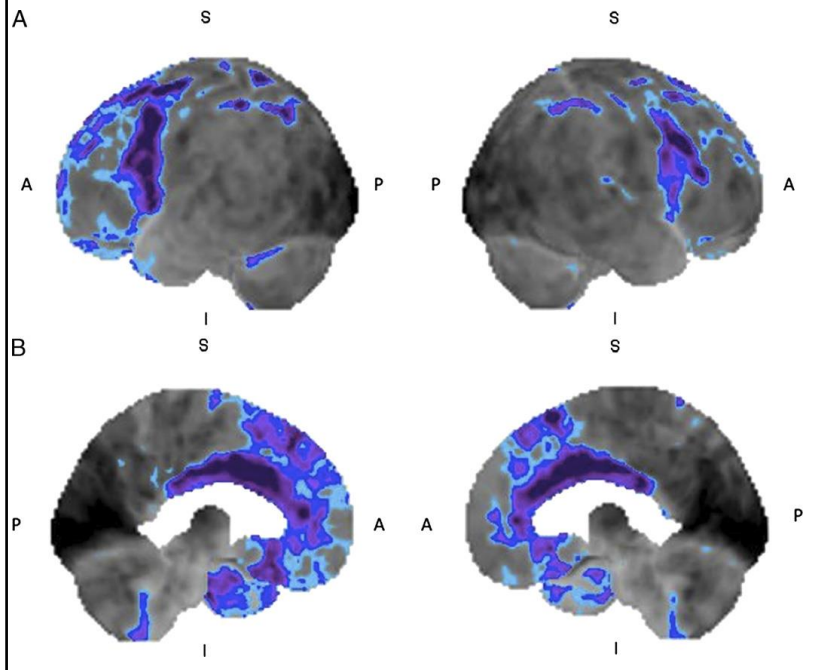
Radiopedia.org

Neurodegeneration: Current

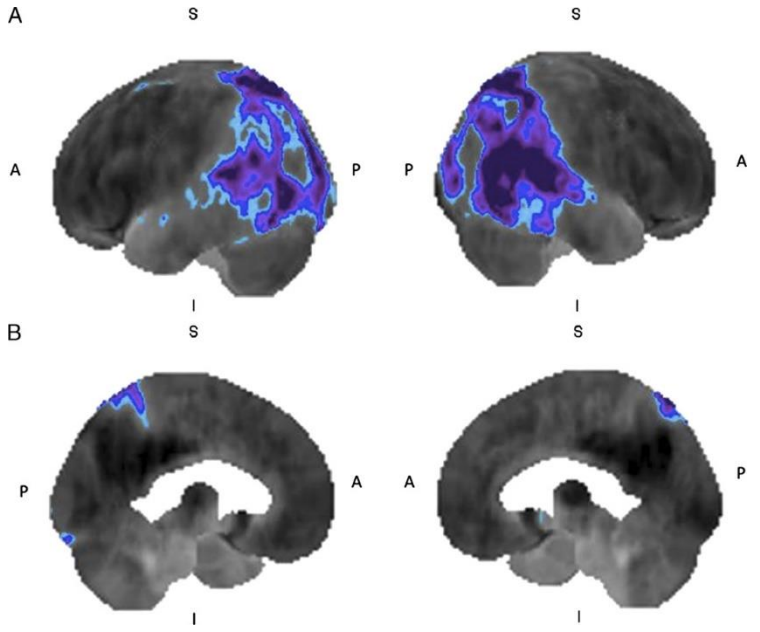
AD: posterior cingulate gyrus and parietal cortices extending to temporal



FTD: frontal and temporal cortices

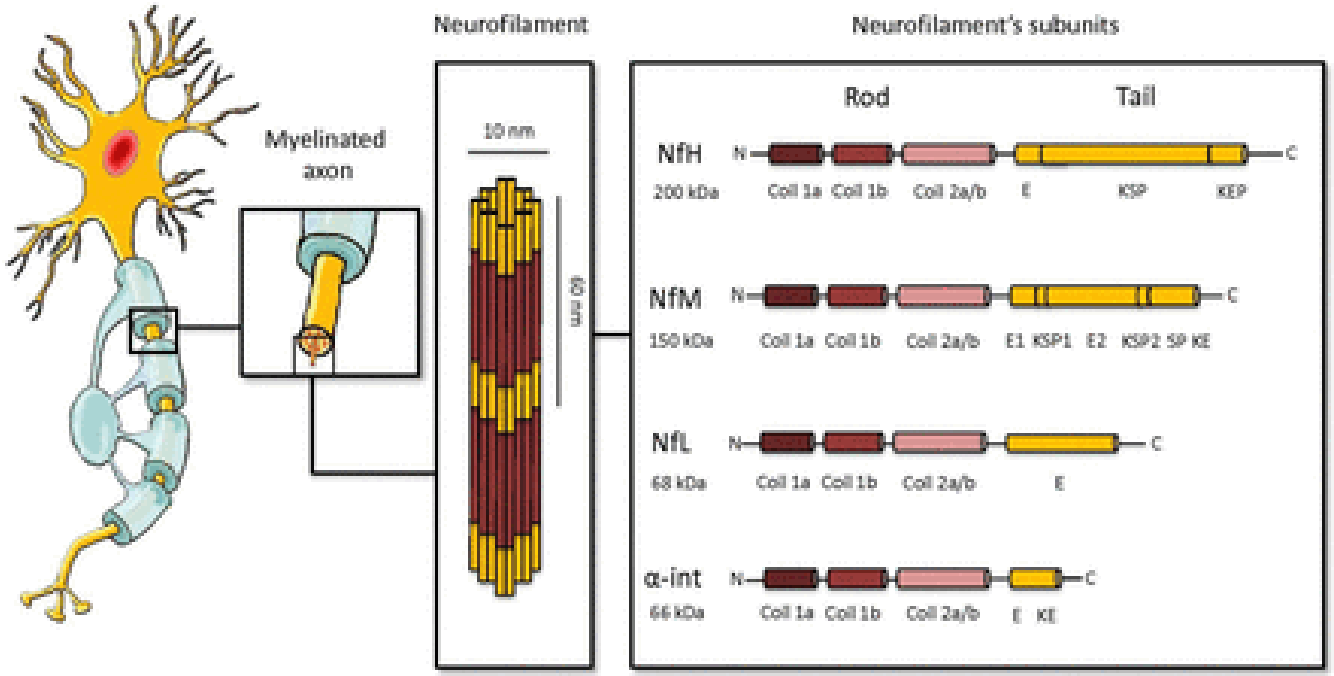


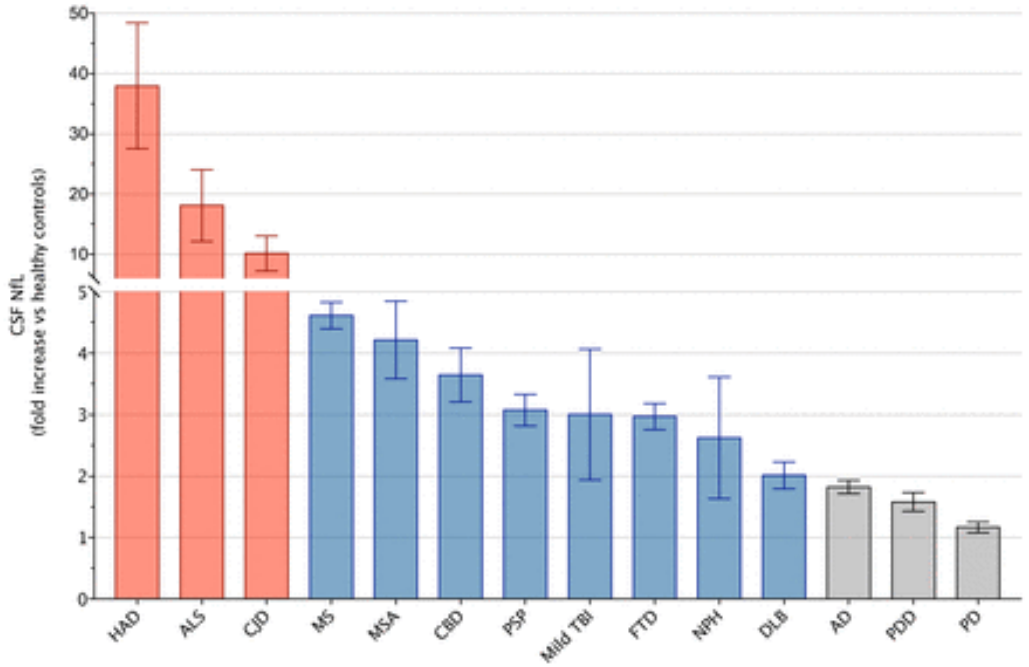
LBD: occipital + parietal



Marcus et al. Clin Nucl Med. 2014

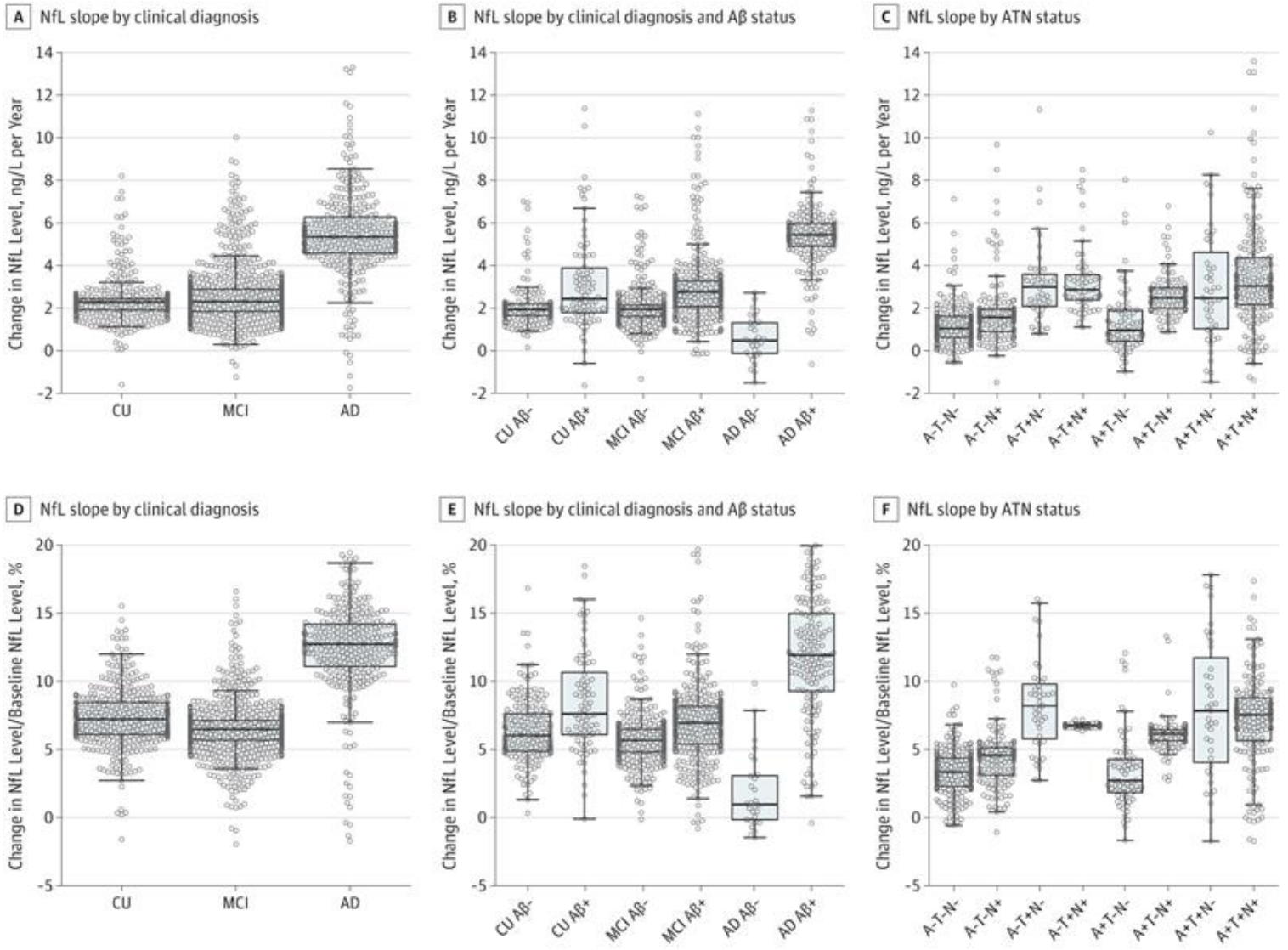
Neurodegeneration: Near future





Gaetani et al. Journal of Neurology, Neurosurgery & Psychiatry 2019

Neurodegeneration: Plasma NfL



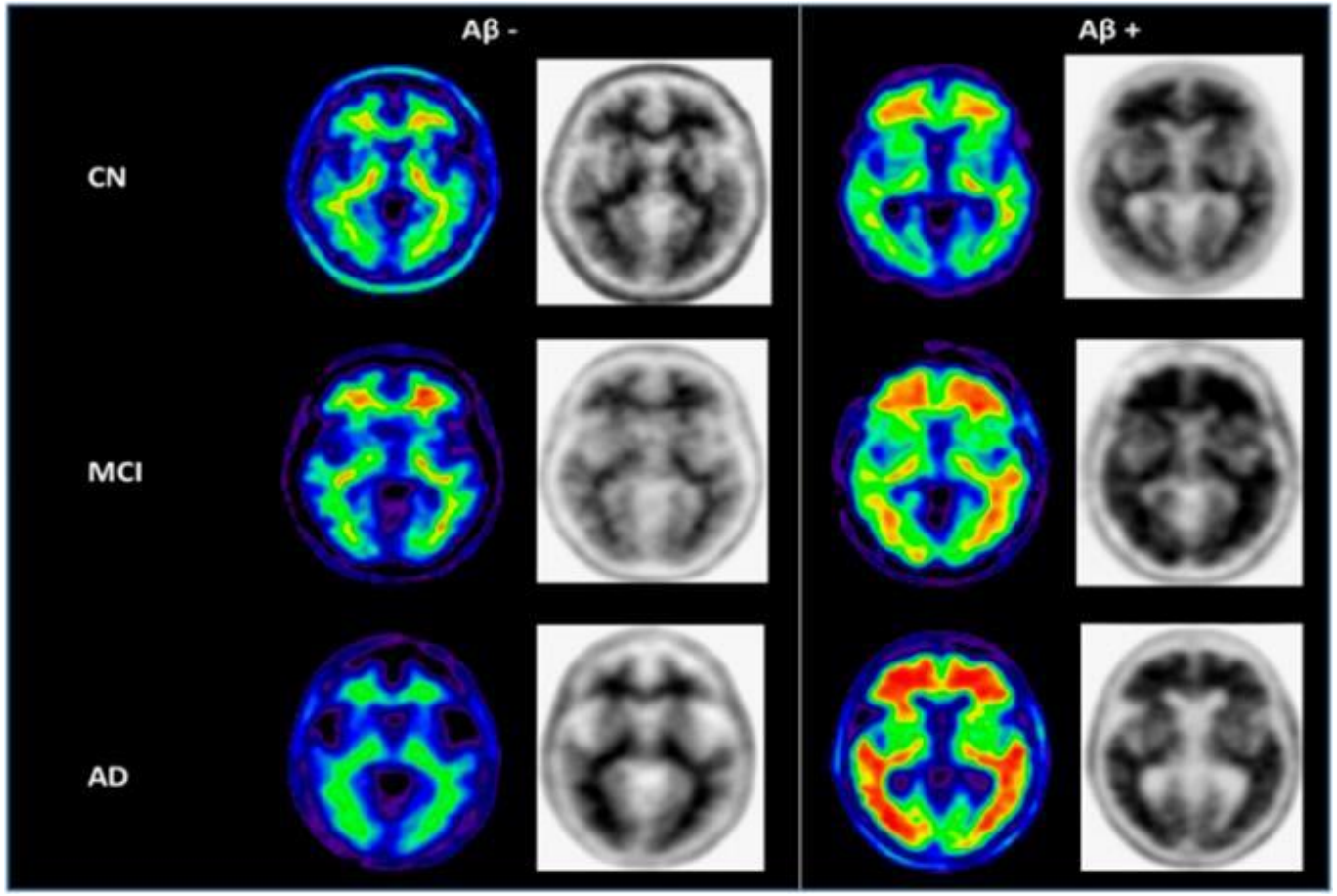
Mattsson et al.
JAMA Neurol. 2019

Amyloid and tau: Current

Diagnostic groups	Biomarker	AUC (95% CI)	Specificity (%)*
AD vs HC	AβX-42/X-40 ratio	0.95 (0.92–0.99)	93%
	Aβ1–42 (pg/mL)	0.93 (0.88–0.98)	90%
	T-tau/Aβ1–42 ratio	0.93 (0.89–0.97)	83%
AD vs DLB	AβX-42/X-40 ratio	0.73 (0.59–0.88)	47%
	T-tau/Aβ1–42 ratio	0.77 (0.66–0.88)	40%
AD vs bvFTD	T-tau/Aβ1–42 ratio	0.89 (0.85–0.94)	70%
	AβX-42/X-40 ratio	0.86 (0.77–0.94)	85%
AD vs PNFA	T-tau/Aβ1–42 ratio	0.67 (0.54–0.80)	24%

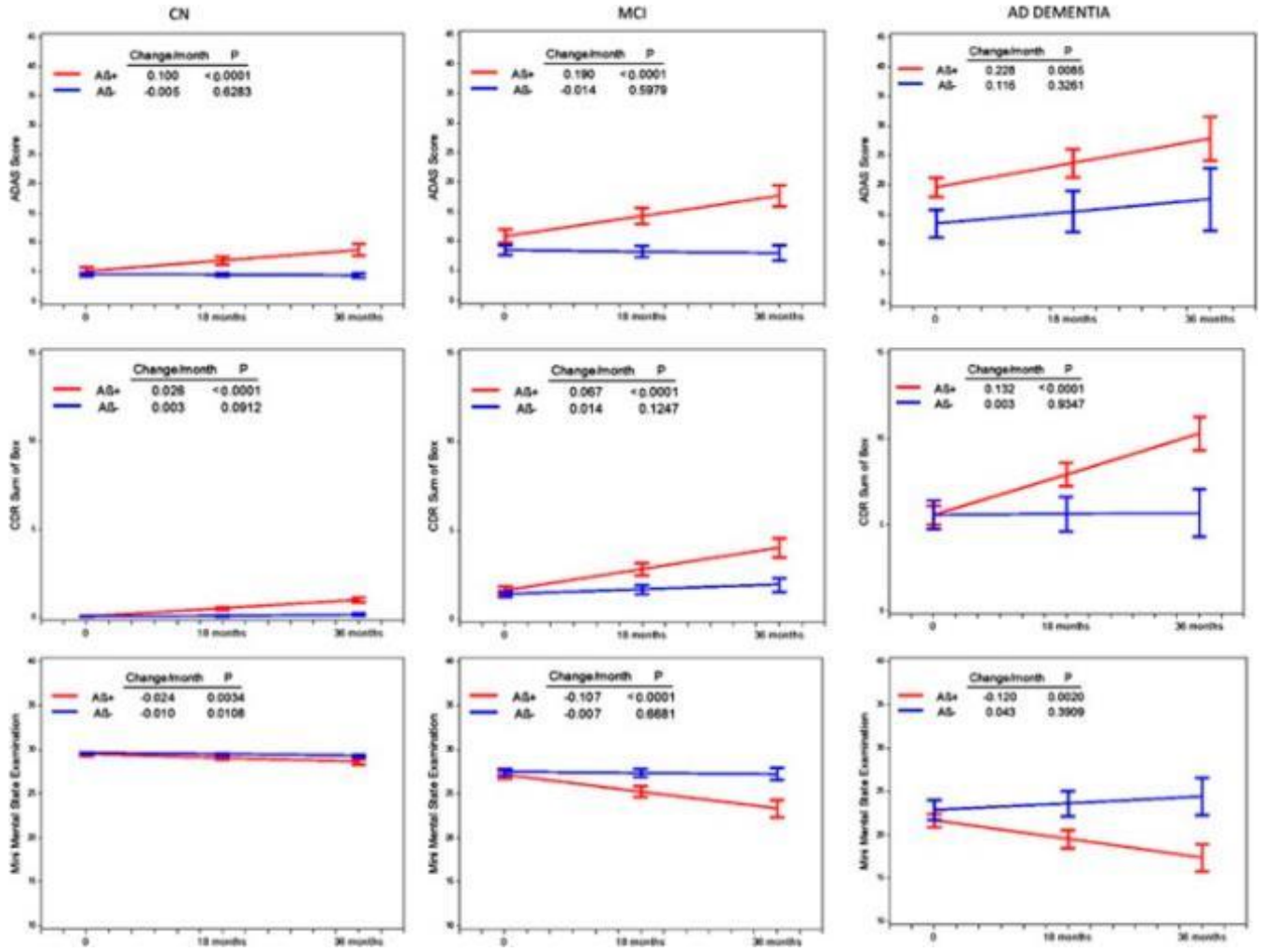
Paterson et al. Alzheimer's Research & Therapy 2018 10:32

Amyloid: Near future



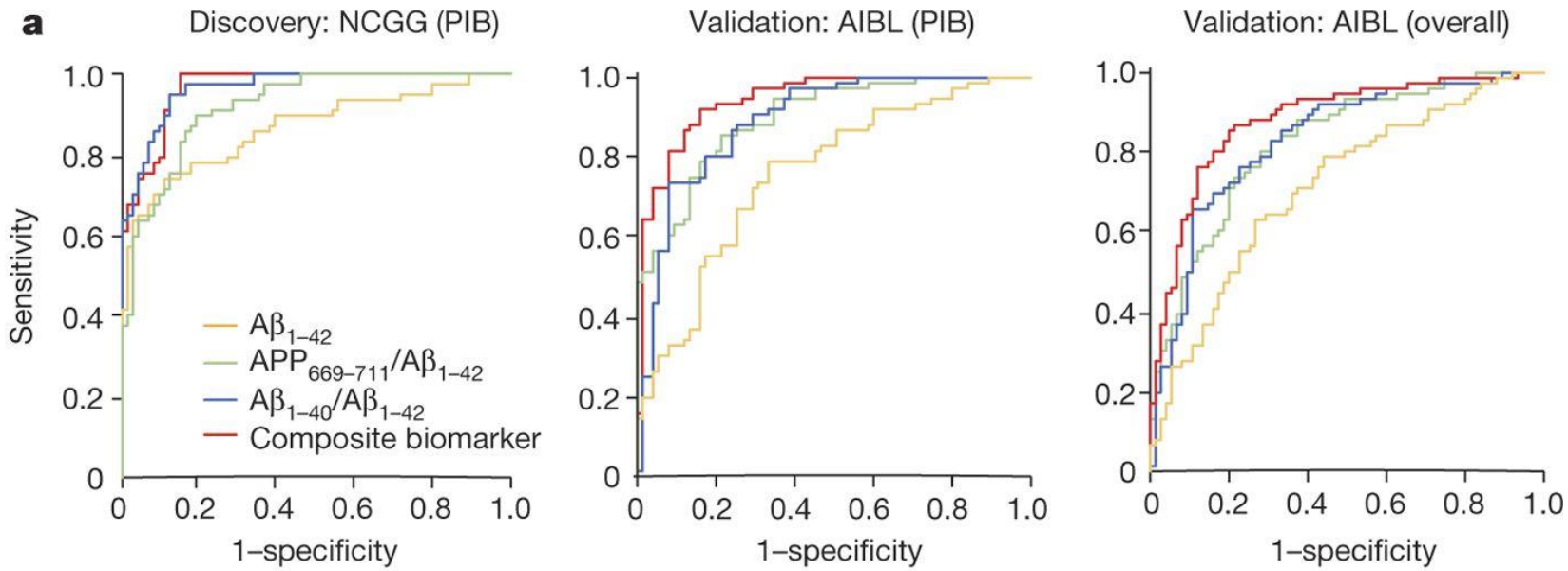
Doiswamy et al. Mol Psychiatry. 2014 Sep; 19(9): 1044–1051.

Amyloid: Near future



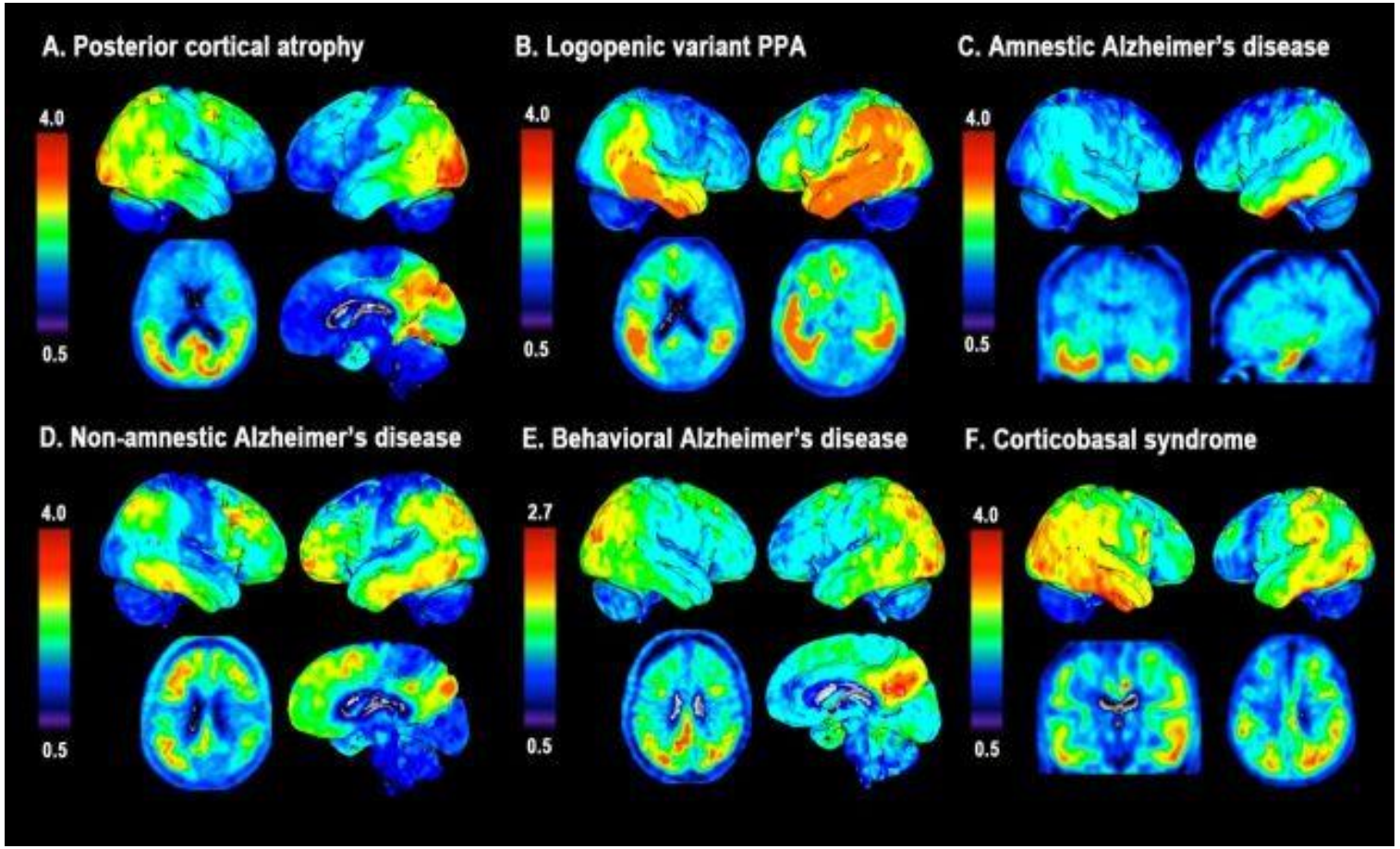
Doiswamy et al. Mol Psychiatry. 2014 Sep; 19(9): 1044–1051.

Amyloid: Distant future



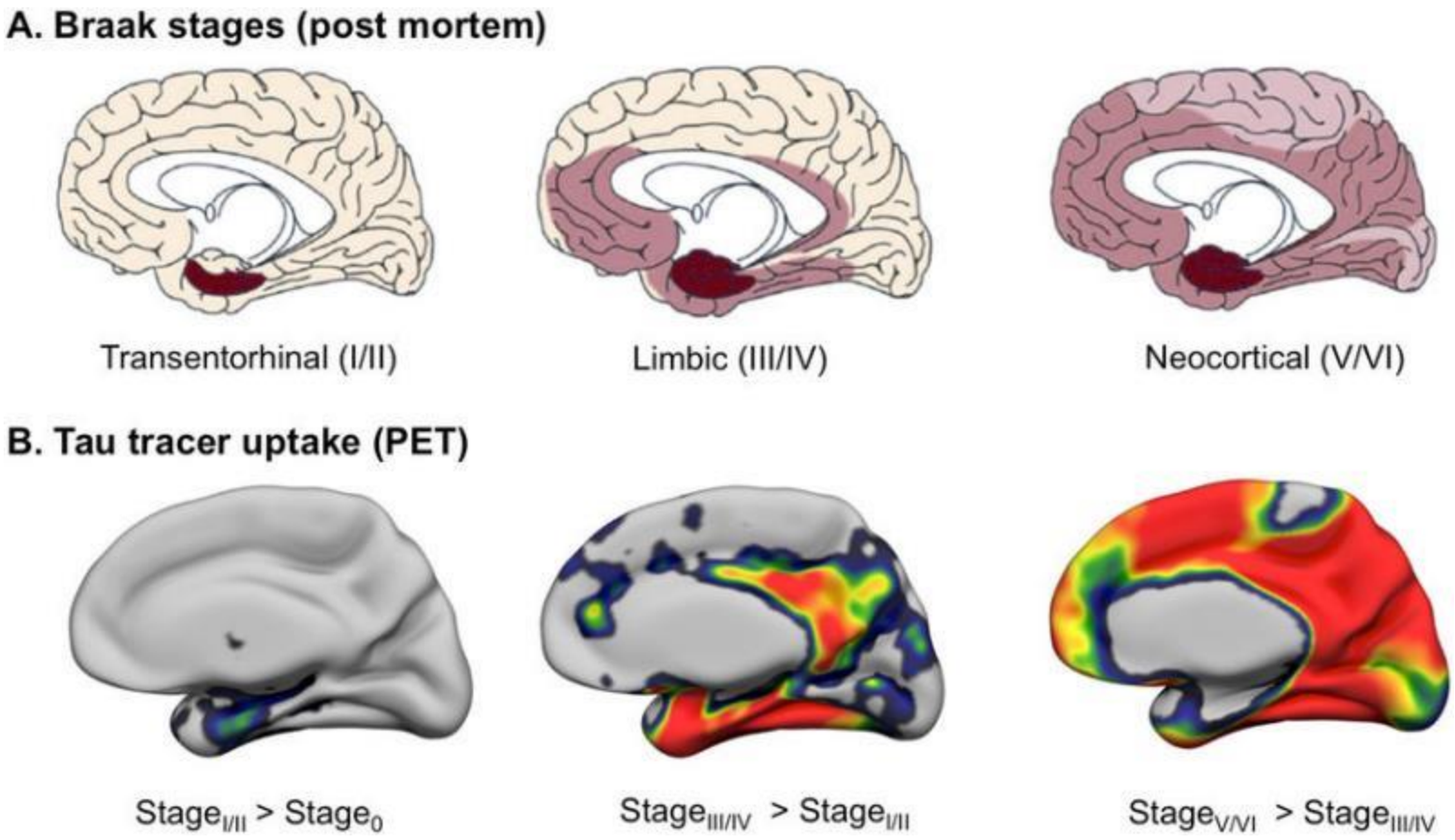
Nakamura et al. Nature 2018

Tau: Near future



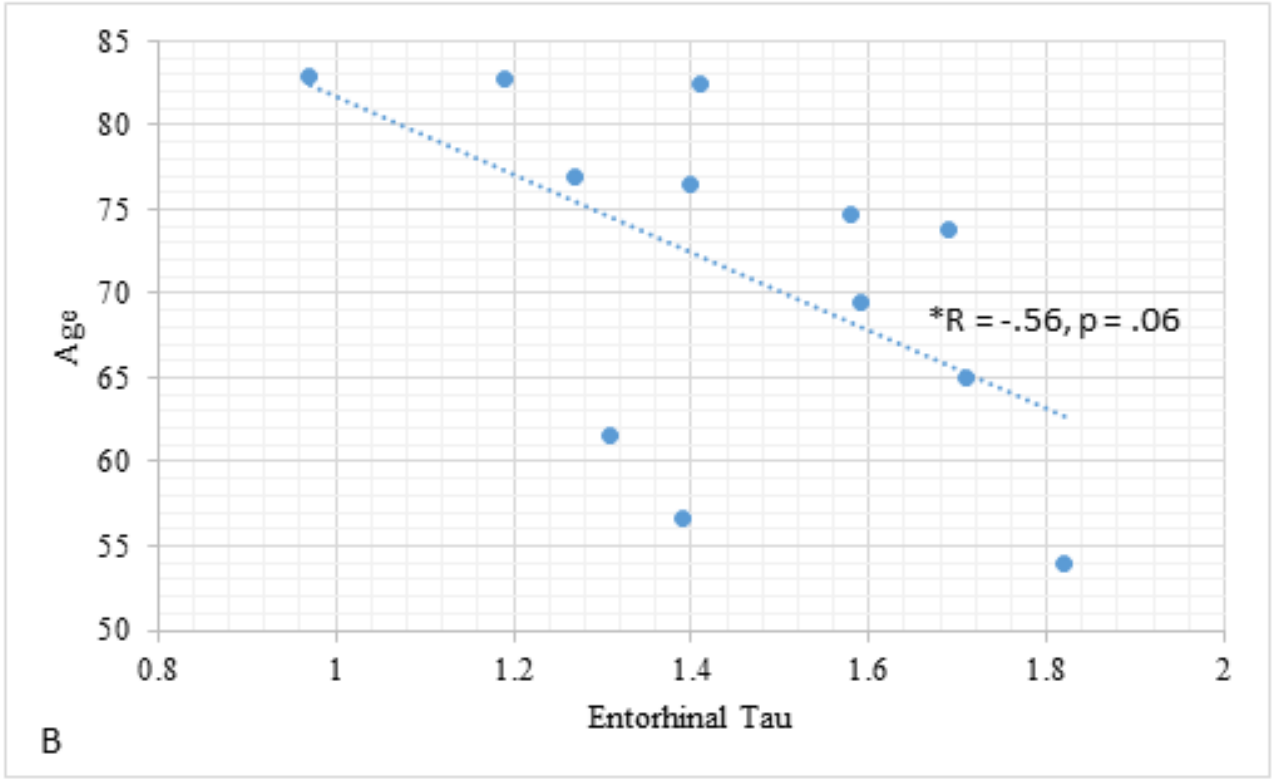
Ossenkoppele et al. Brain 2016

Tau: Near future



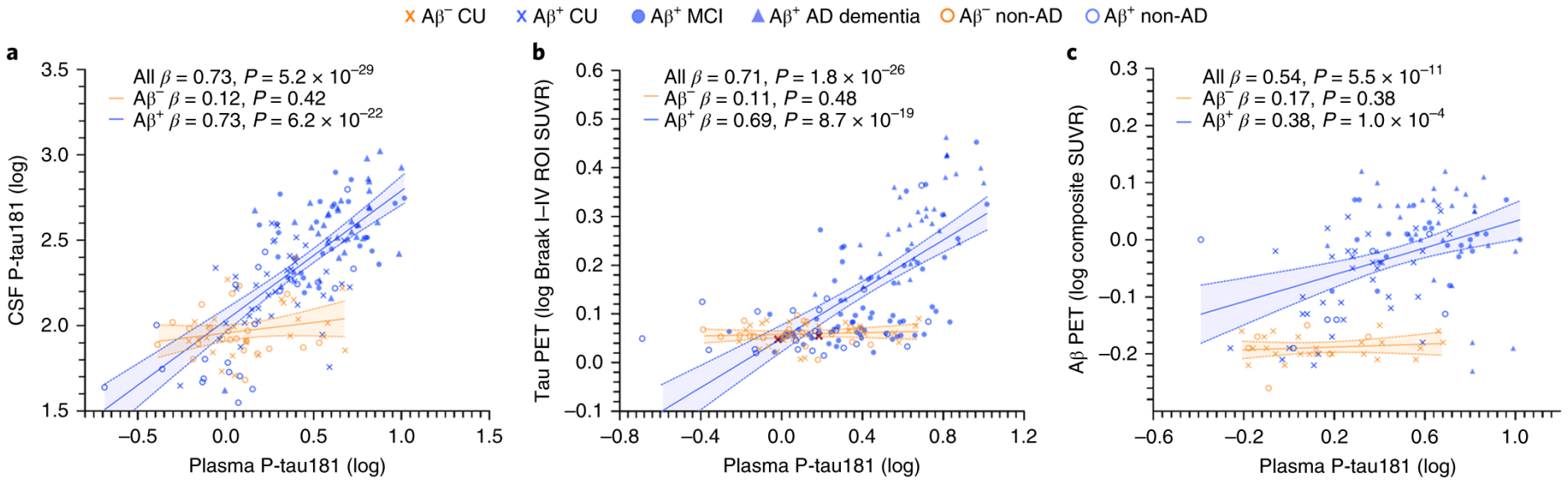
Schoell et al. Molecular and Cellular Neuroscience 2018

Tau: Near future



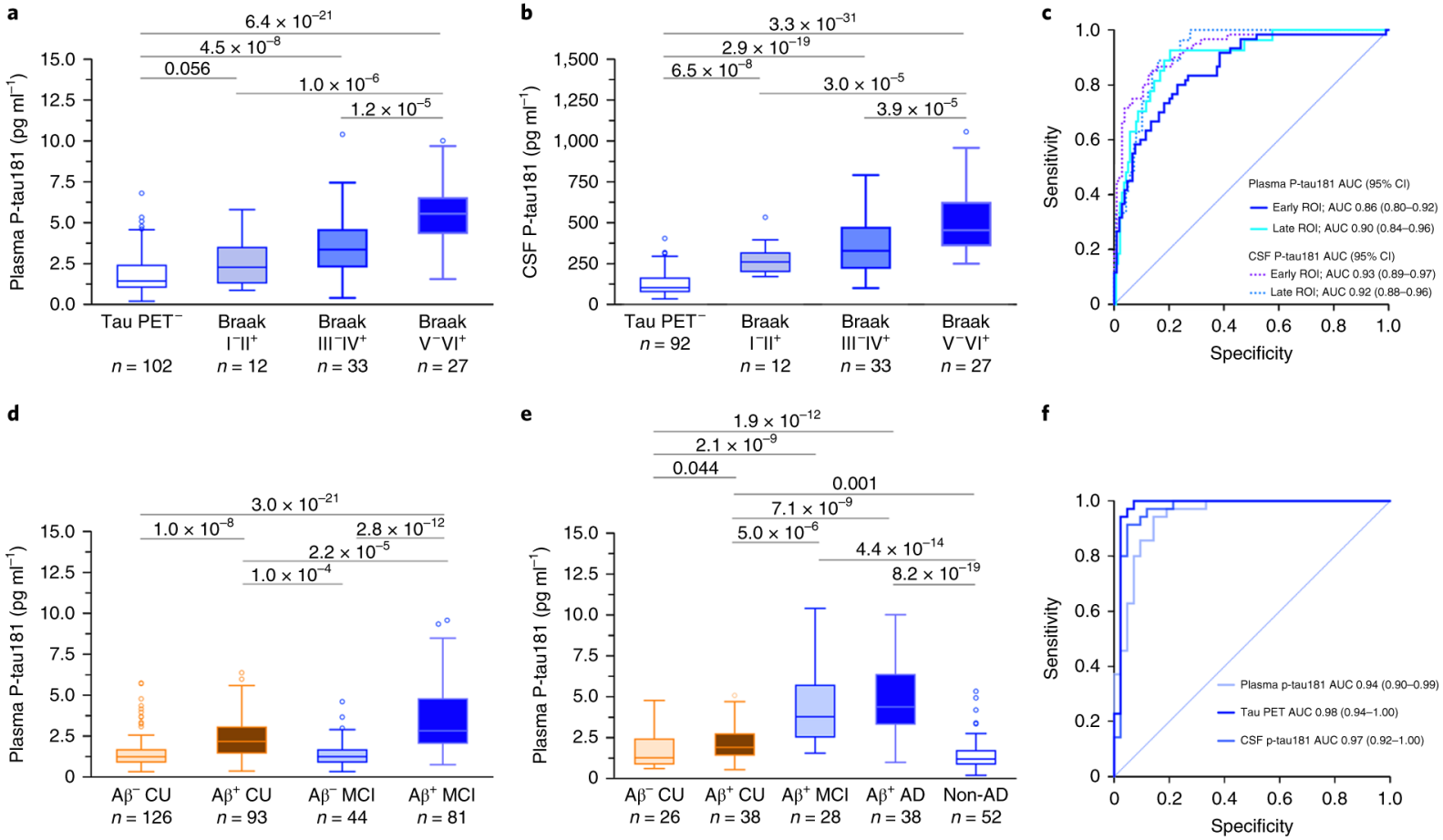
Koychev et al. 2018 JAD

Tau: Distant future



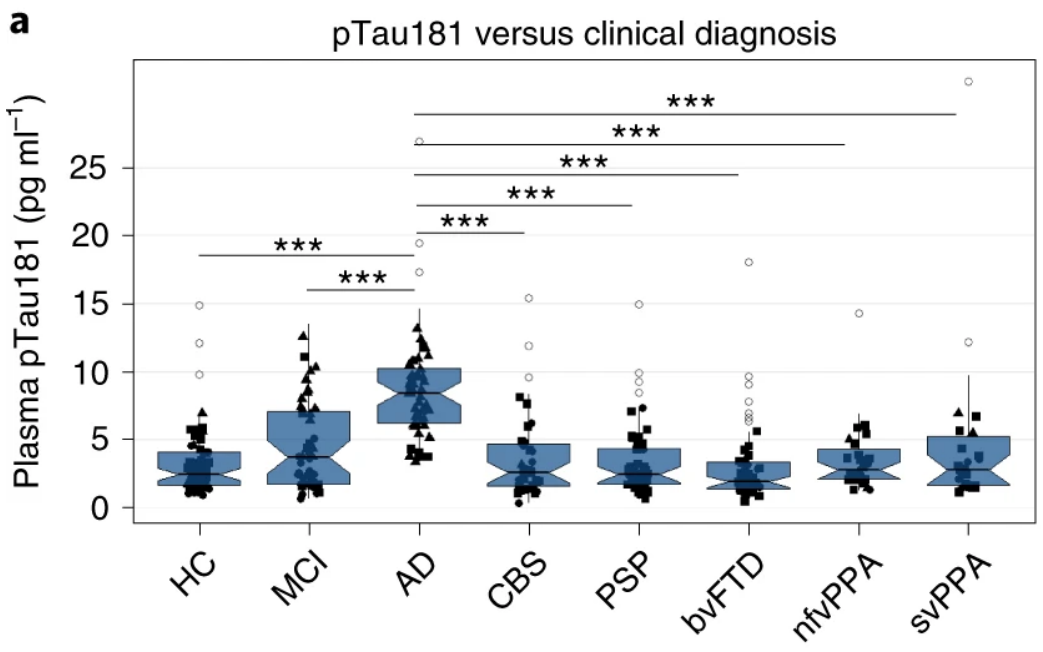
Janelidze et al. Nature Medicine 2020

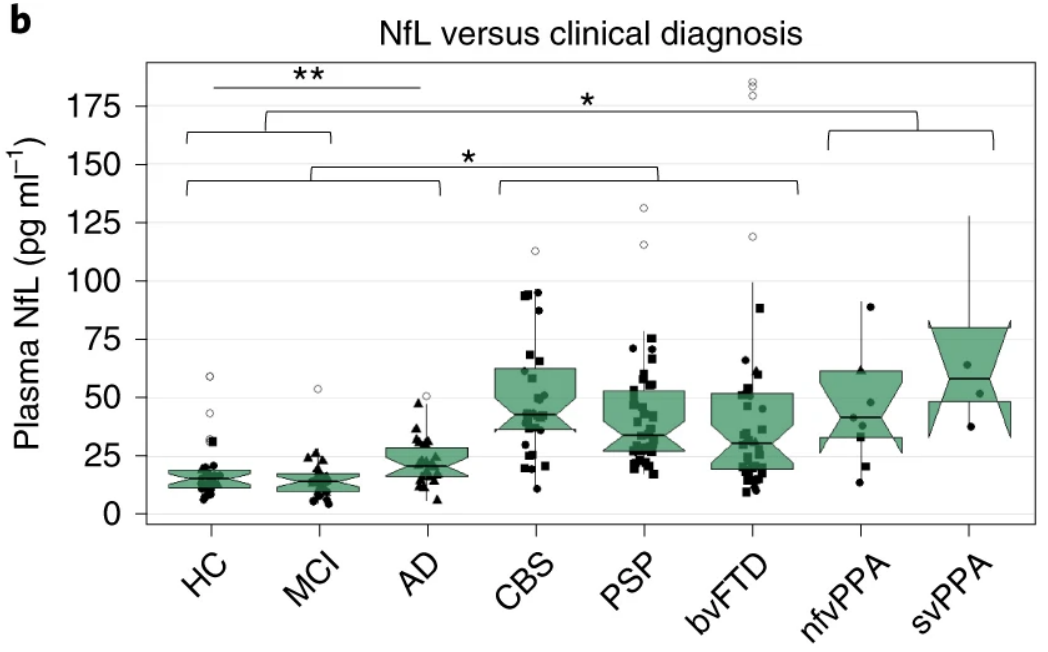
Tau: Distant future



Janelidze et al. Nature Medicine 2020

Tau: Distant future

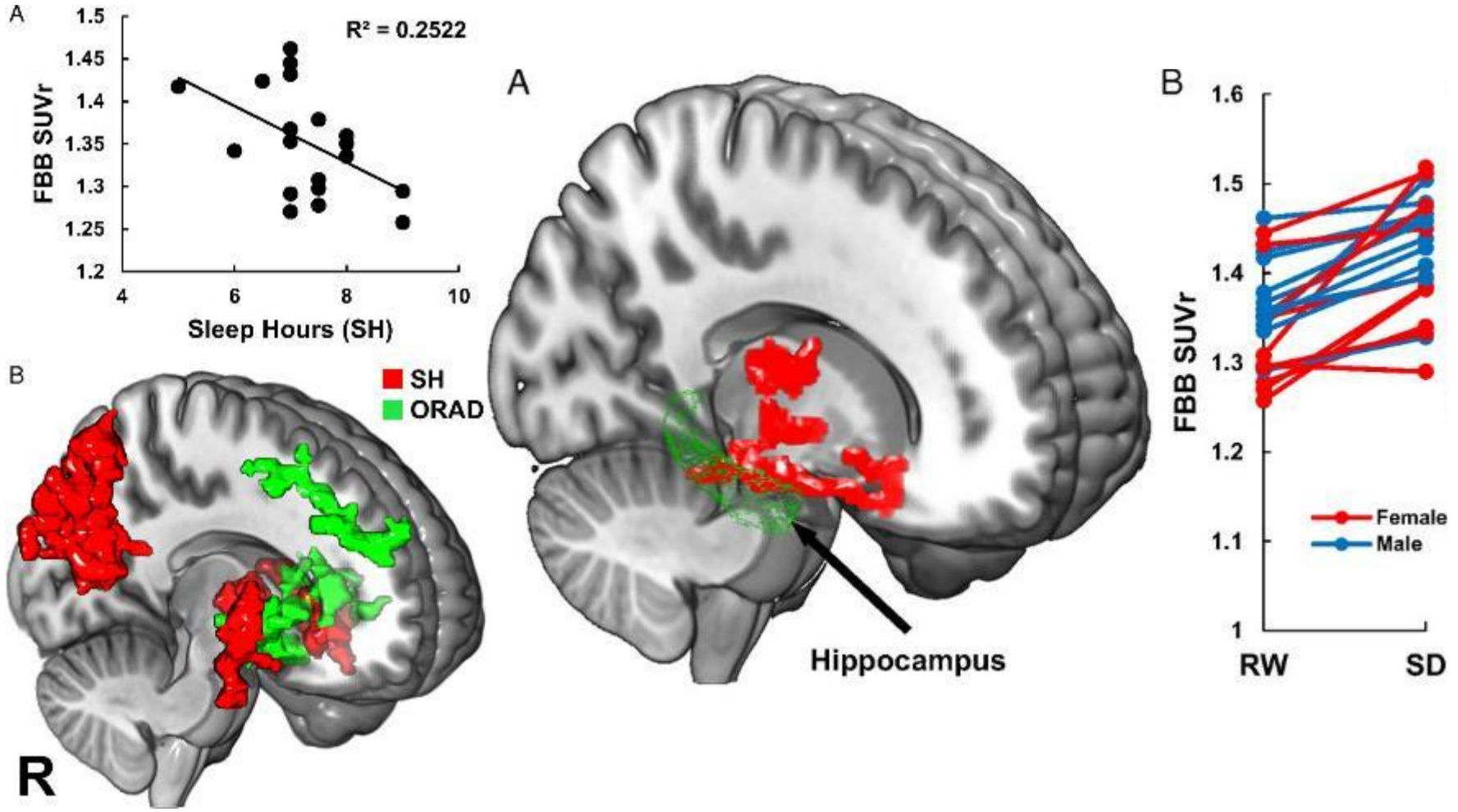




Janelidze et al. Nature Medicine 2020

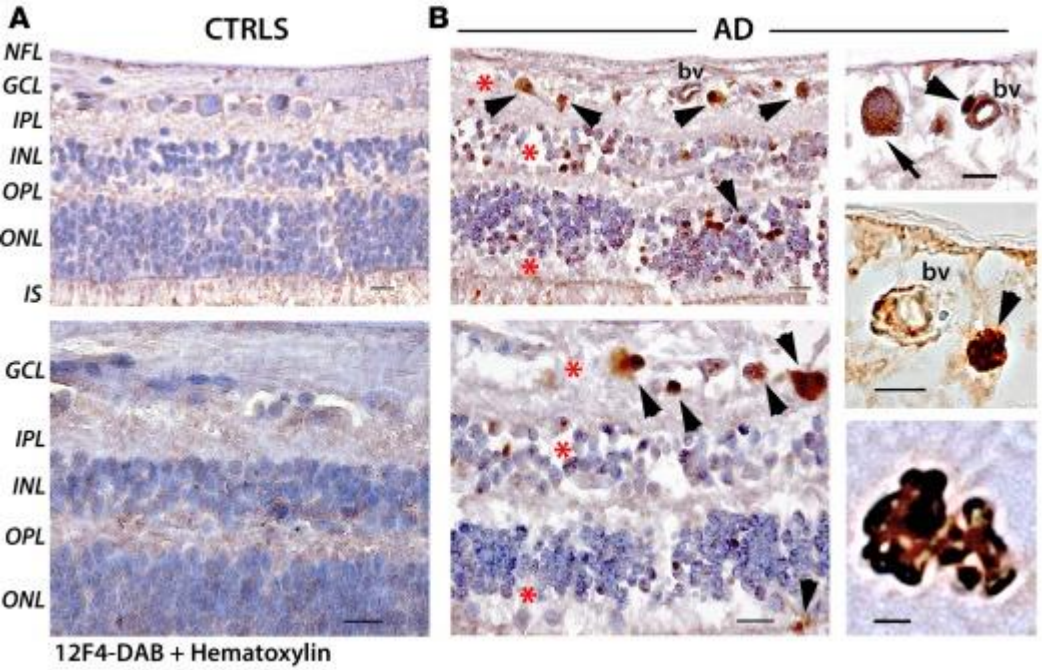
Experimental biomarkers

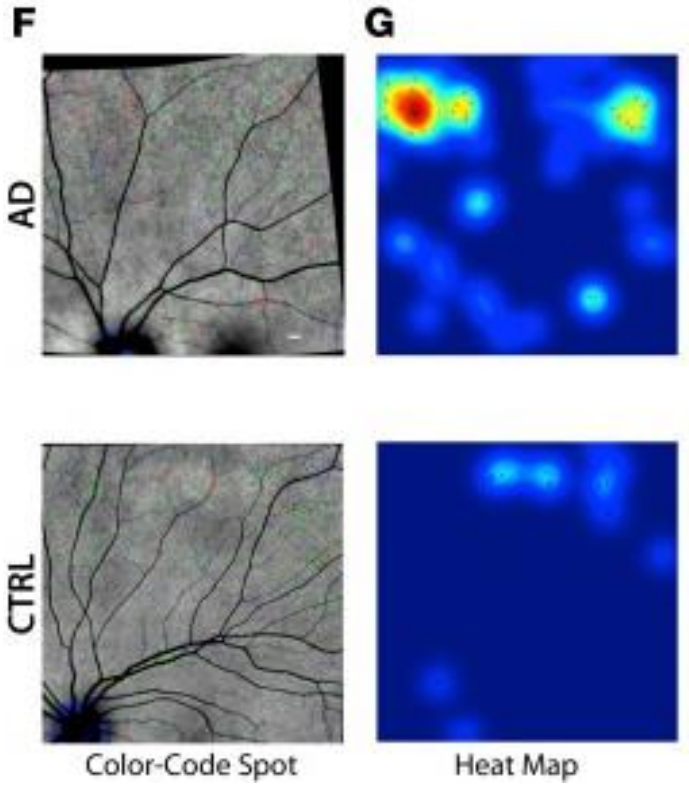
Experimental biomarkers: Sleep

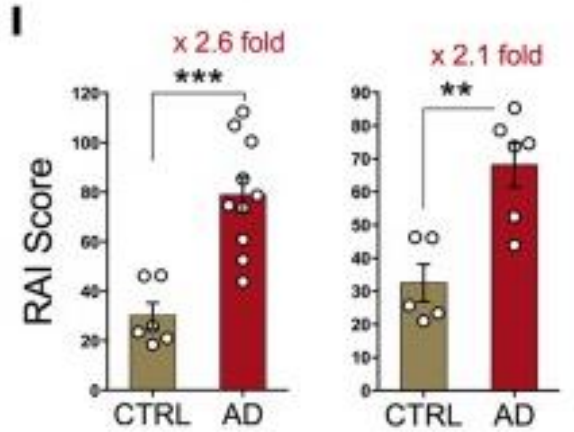


Shokri-Kojori et al. PNAS 2018

Experimental biomarkers: Retinal imaging

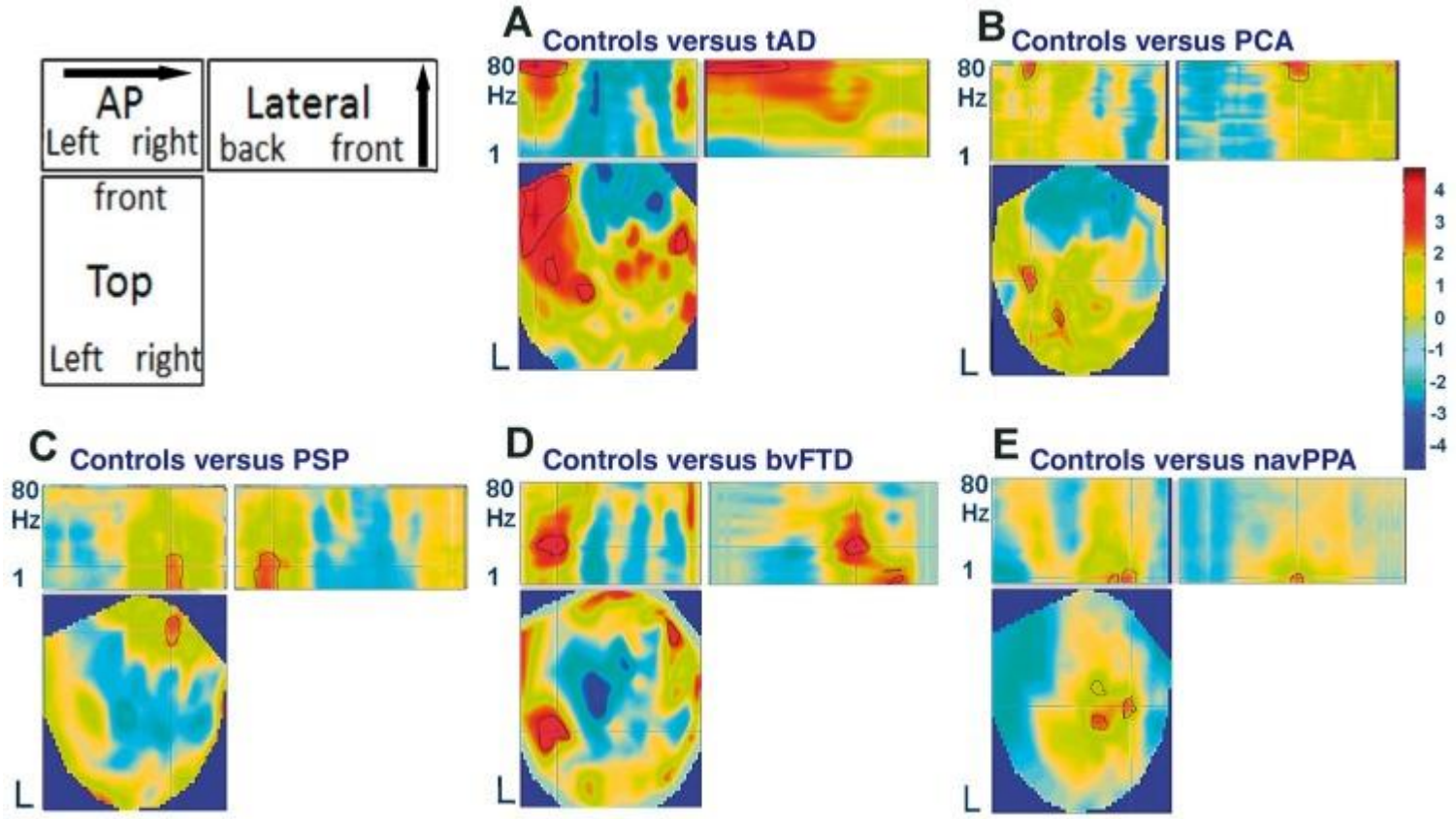






Koronyo et al. JCI Insight. 2017

Experimental biomarkers: Synaptic function

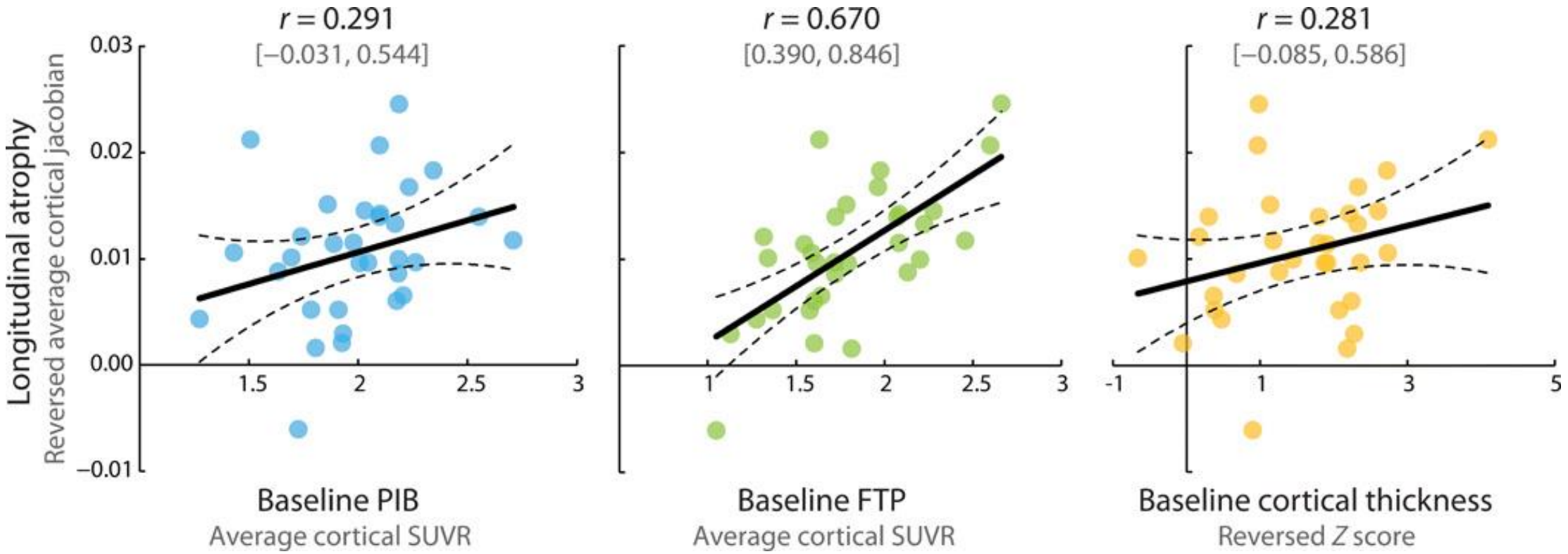


Sami S et al. Brain. 2018

So what?

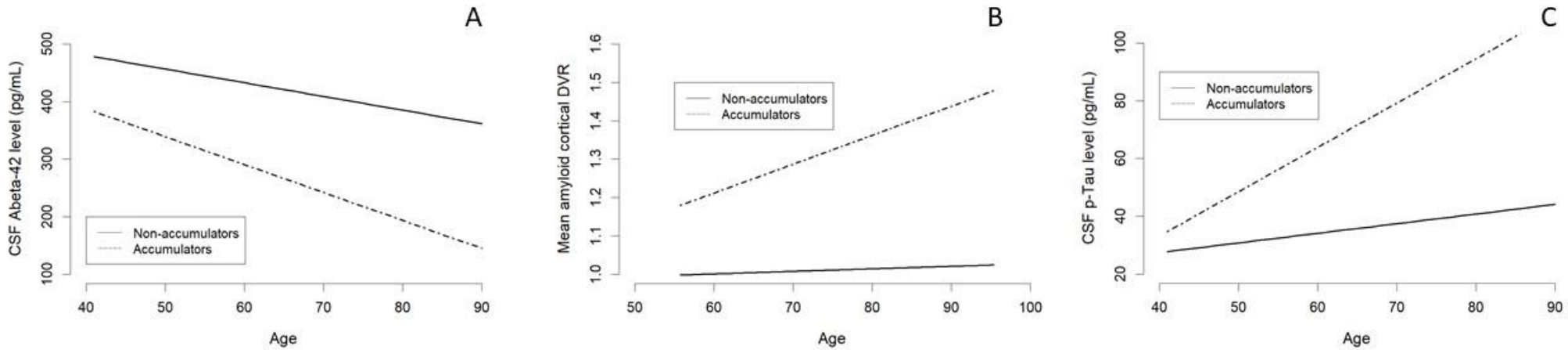
- Differential diagnosis
- Neurodegeneration prediction
- Preclinical diagnosis
  - Preclinical AD diagnosis -> ATN status
  - Emergent AD identification
- Preclinical disease tracking -> modification trials

Neurodegeneration prediction



La Joie et al. 2020 Science Translational Medicine

Emergent AD: Rapid accumulators



Koychev, Vaci et al. In press

Emergent AD: Switch-on time point

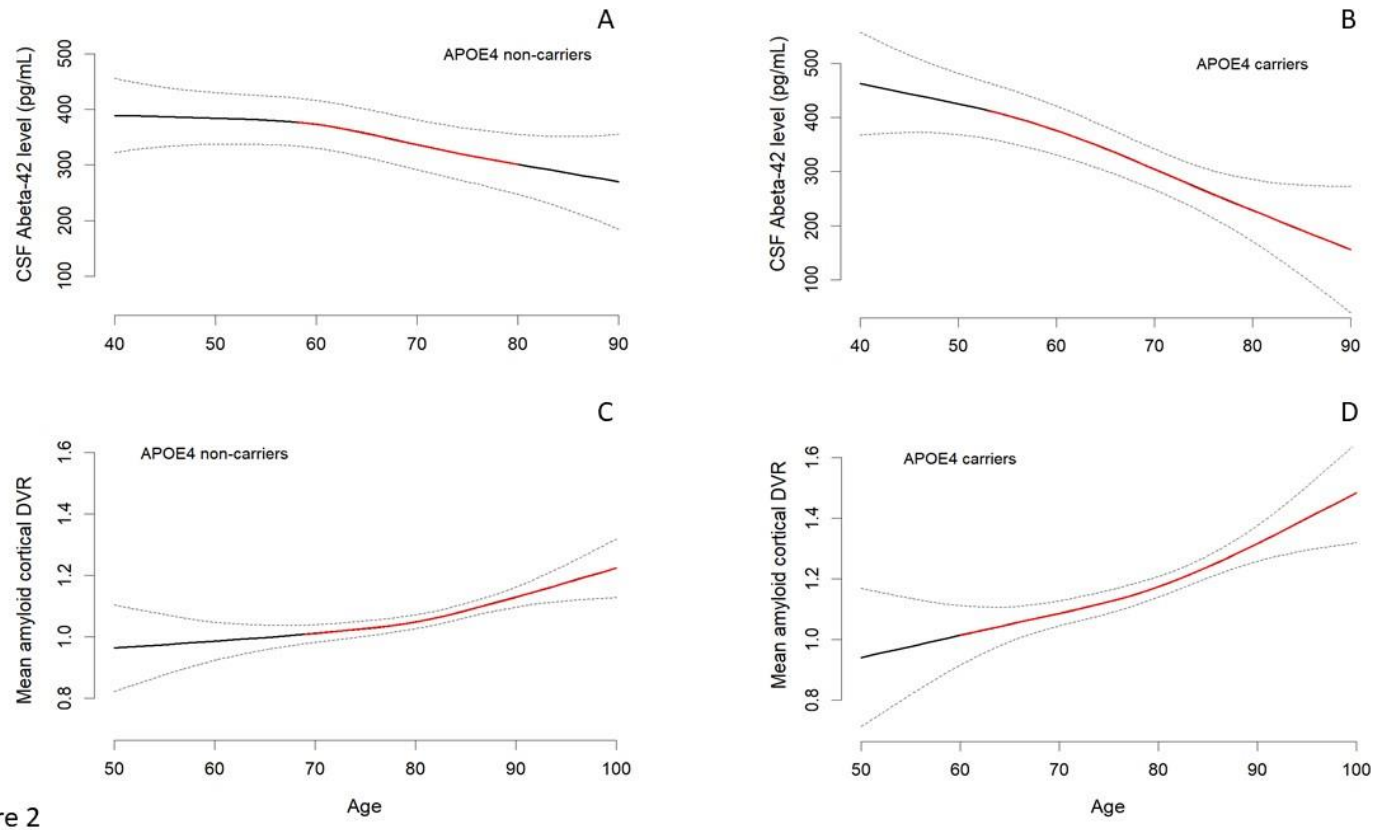
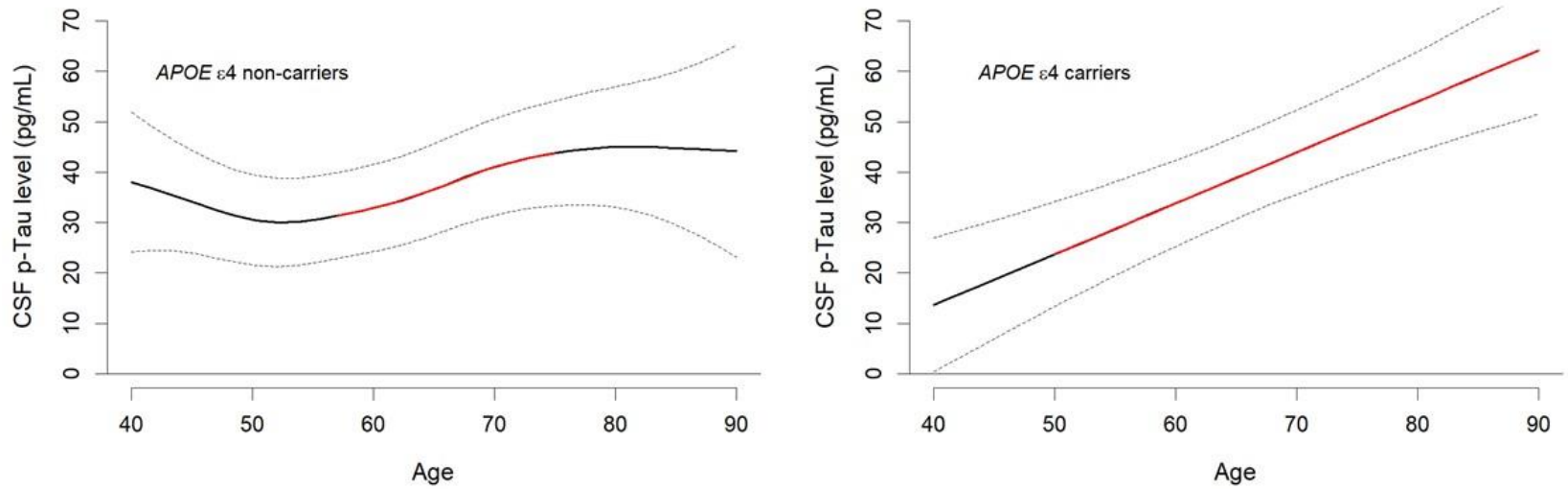


Figure 2

Koychev, Vaci et al. In press

Emergent AD: Switch-on time point



Koychev, Vaci et al. In press

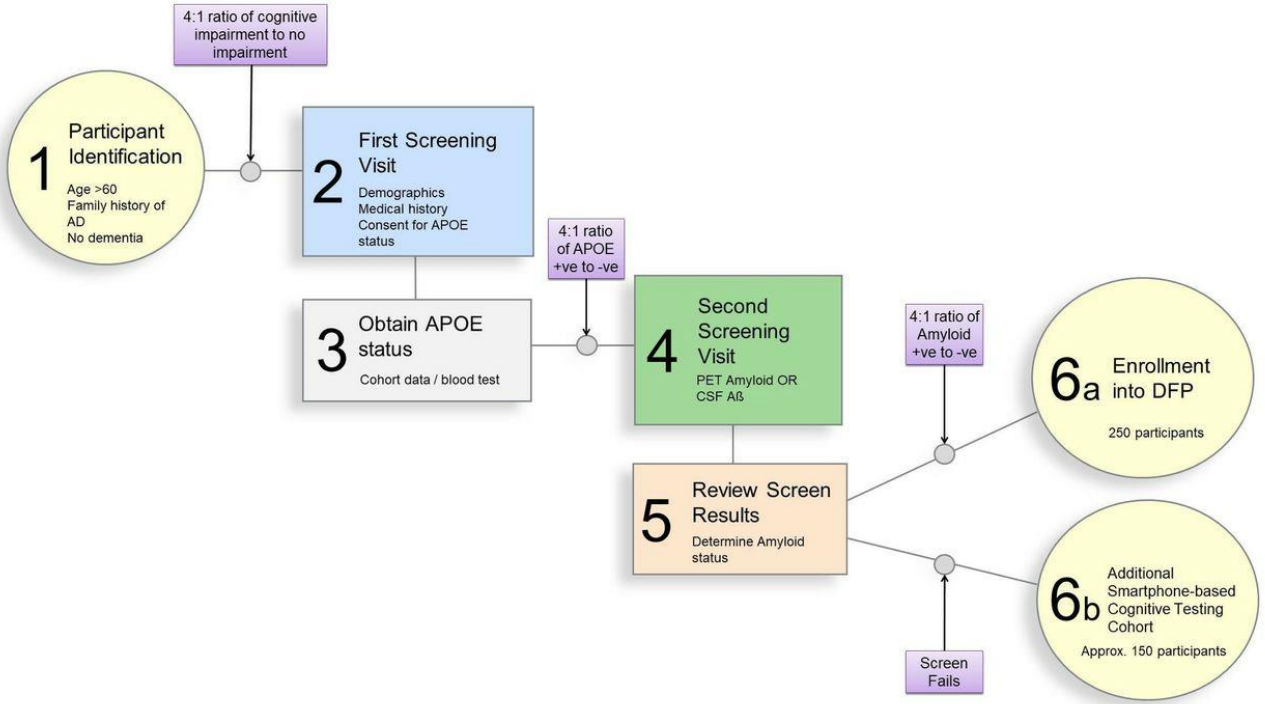
Summary

	Current	Near	Distant
Cognition	Pen and paper Computerised tests	Smartphone cognitive tests	Passive monitoring
Amyloid	CSF	PET amyloid	Blood tests (Abeta42/40 + (P-tau181)
Tau	CSF	PET tau	Blood tests (P-tau181)
Neurodegeneration	CT/MRI	FDG PET	Blood tests (NfL)

Potential use

	Screening	Differential diagnosis	Trial inclusion	Preclinical trial endpoints
Cognition	• Smartphone cognitive tests • Passive monitoring • (Sleep)	• Pen and paper • Computerised tests	• Syndrome	• Smartphone cognitive tests
Amyloid	• Blood tests (Abeta42/40) • Ophthalmology	• CSF • PET amyloid	• PET amyloid • CSF	
Tau	• Blood tests (P-tau181)	• CSF • PET tau • Blood tests (P-tau181)	• (PET tau)	• PET Tau • Blood tests • (synaptic function)
Neurodegeneration	• Blood tests (NfL)	• CT/ MRI, FDG PET • Blood tests (NfL)		• FDG PET

Thank you



Koychev et al. BMJ Open 2019; www.dfpstudy.co.uk

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Summary (1)

Diagnosis and monitoring of progression in Alzheimer's Disease (AD) is crucial to achieving high-quality clinical care. This, in turn, depends on the identification of reliable biomarkers and the development of appropriate methodologies for their measurement and testing.

Research is being driven by the realisation that the pathological process underlying AD begins up to 25—30 years before clinical symptoms appear. Consequently, **AD should be thought of as a 'life-course' disease** and **prevention should begin much earlier** than it has previously.

Passive, remote monitoring using digital technology (apps, wearables) is likely to be particularly useful for patient stratification, especially in identifying patients in the preclinical stage of dementia. Significantly, these methodologies offer the possibility to analyse memory function repeatedly and over much longer time periods (seven days or more) compared with testing in the clinic (15—20 minutes). Remote monitoring and analysis also overcomes difficulties of access to clinical services for patients living away from specialised centres.

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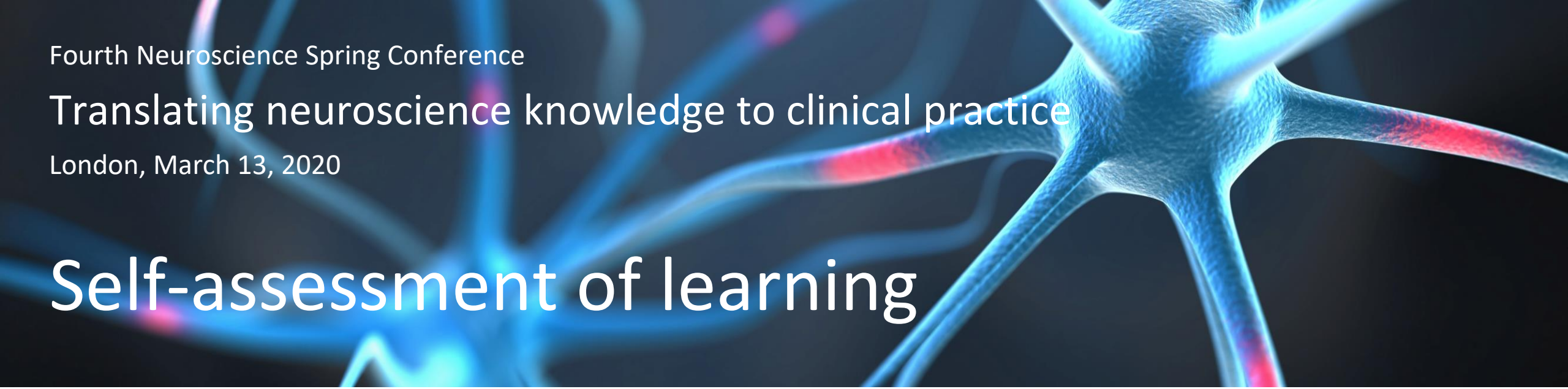
Summary (2)

New **methodologies such as Tau-PET** make it possible to determine a person's disease status in terms of Braak staging, which previously was possible only post mortem. This offers real potential for the staging of AD, much like oncologists' capacity for staging cancer.

Blood tests are likely to become much more common in the near future as disease-modifying therapies become available. **Plasma biomarkers** such as NF-L (neurofilament 'light' [low molecular weight neurofilament protein]), especially used in combination, may be valuable for differential diagnosis. Measuring these is relatively non-invasive (compared with CSF analysis or scans), and of low-cost (compared with PET or MRI). Plasma NF-L has now been strongly correlated with neurodegeneration.



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Self-assessment of learning

For each of the following questions, choose the best answer from the options given. *Answers on the next slide.*

1. Approximately how many years before symptom onset does β-amyloid deposition in the brain begin?

A) 2 years
B) 20 years
C) 5 years
D) 30 years

2. Neurofilaments are:

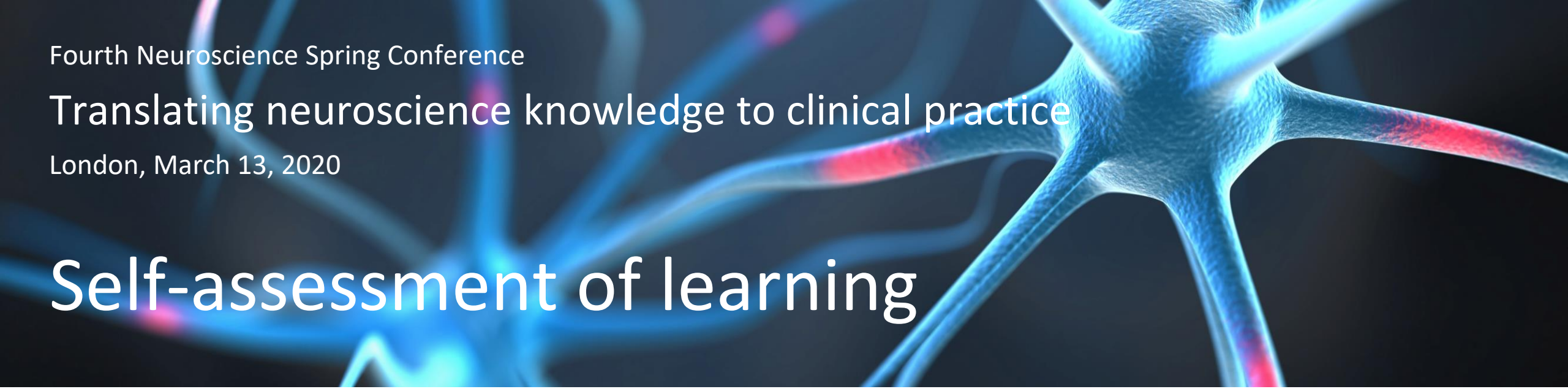
A) Structural proteins found in the presynaptic membrane
B) Structural proteins found in the axon
C) Connected to ion channels in the axon terminal
D) Found in the extracellular space between neurons and glial cells

3. The ATN framework is based on the measurement of which three biomarkers?

A) Amyloid/Tau/Neurofilament
B) Alzheimer's/Tau/Neurodegeneration
C) Alzheimer's/Time/Neurodegeneration
D) Amyloid/Tau/Neurodegeneration

4. Measuring the amyloid Aβ-42/-40 ratio in the CSF is based on the finding that as AD progresses:

A) CSF Aβ-42 decreases while Aβ-40 remains high
B) CSF Aβ-42 remains high while Aβ-40 increases
C) CSF Aβ-42 decreases and Aβ-40 decreases
D) CSF Aβ-42 increases and Aβ-40 increases



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Self-assessment of learning

Answers.

1. Approximately how many years before first symptoms does β-amyloid deposition in the brain begin? A) 2 years B) 20 years C) 5 years **D) 30 years**	2. Neurofilaments are: A) Structural proteins found in the presynaptic membrane **B) Structural proteins found in the axon** C) Connected to ion channels in the axon terminal D) Found in the extracellular space between neurons and glial cells
3. The ATN framework is based on the measurement of which three biomarkers? A) Amyloid/Tau/Neurofilament B) Alzheimer's/Tau/Neurodegeneration C) Alzheimer's/Time/Neurodegeneration **D) Amyloid/Tau/Neurodegeneration**	4. Measuring the amyloid Aβ-42/-40 ratio in the CSF is based on the finding that as AD progresses: **A) CSF Aβ-42 decreases while Aβ-40 remains high** B) CSF Aβ-42 remains high while Aβ-40 increases C) CSF Aβ-42 decreases and Aβ-40 decreases D) CSF Aβ-42 increases and Aβ-40 increases

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Extension activities

Extend your learning by following one of these suggestions:

WATCH Dr Vanessa Raymont on the Deep & Frequent Phenotyping (DFP) study. More details here.

READ Lashley, T. et al. Molecular biomarkers of Alzheimer's disease: progress and prospects. Dis Model Mech. 2018 May 1; 11(5).

WRITE a 750-word article on 'Biomarkers in Alzheimer's Disease' and submit it to '***Psynapse***', the RCPsych's Neuroscience eNewsletter (visit rcpsych.ac.uk/training/neuroscience-in-training/neuroscience-resources for inspiration). Published articles will earn you a £50 discount on registration for the RCPsych 2021 Neuroscience Spring Conference, London, 26 March 2021. *Submit your article* here.