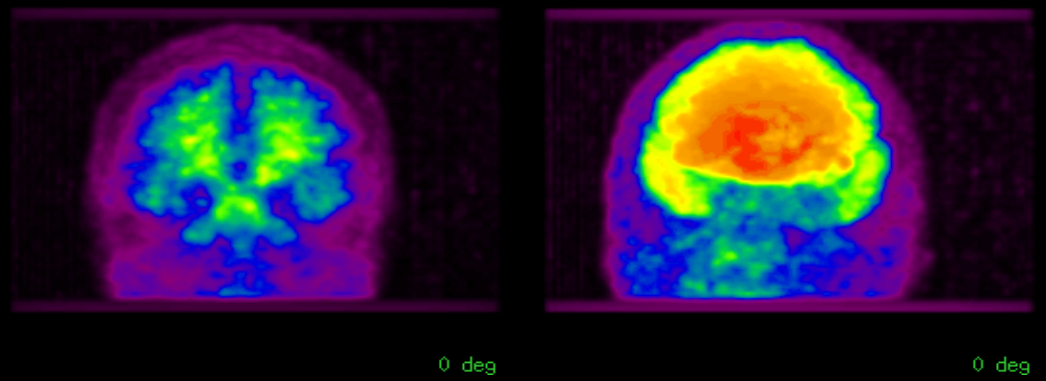
The Cognitive Impact of Soluble Fibrillogenic Aβ Oligomers In Prodromal Dementia



HEALTHY ELDERLY

ALZHEIMER'S DISEASE

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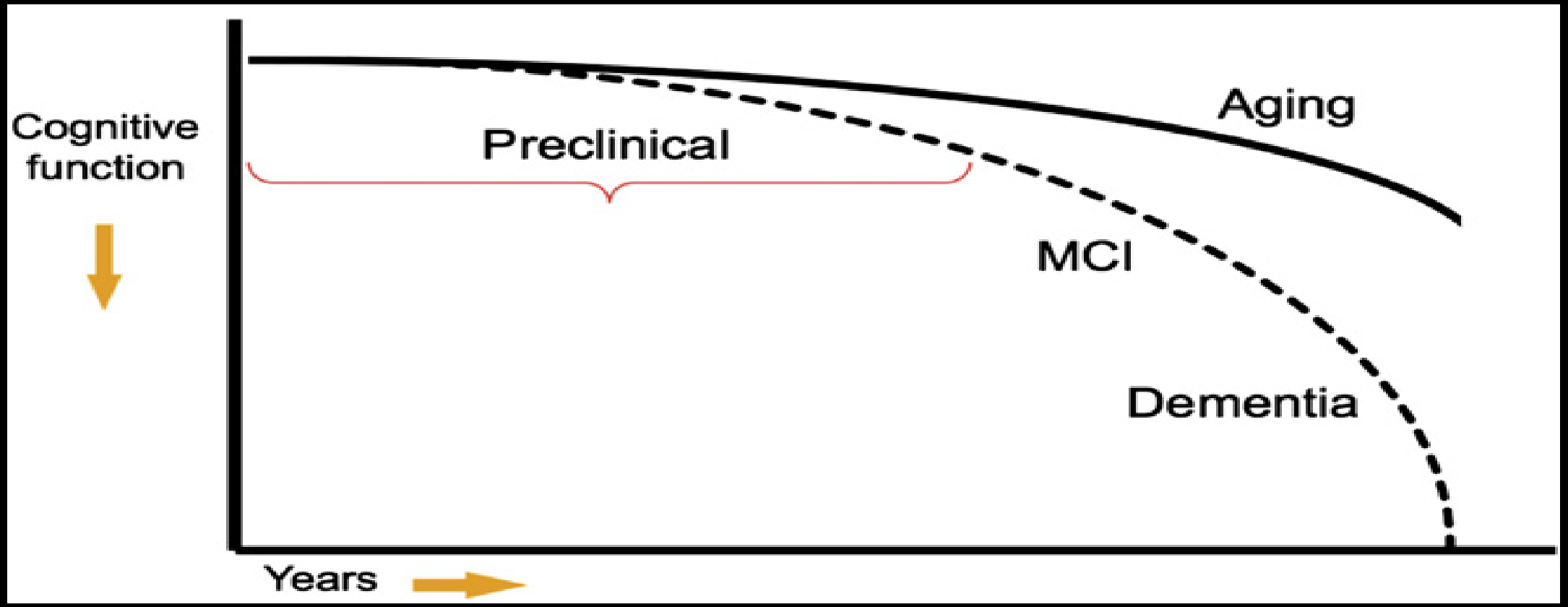
Prof Michael Woodward, AM MBBS MD FRACP
AIBL Research Group

Disclosures

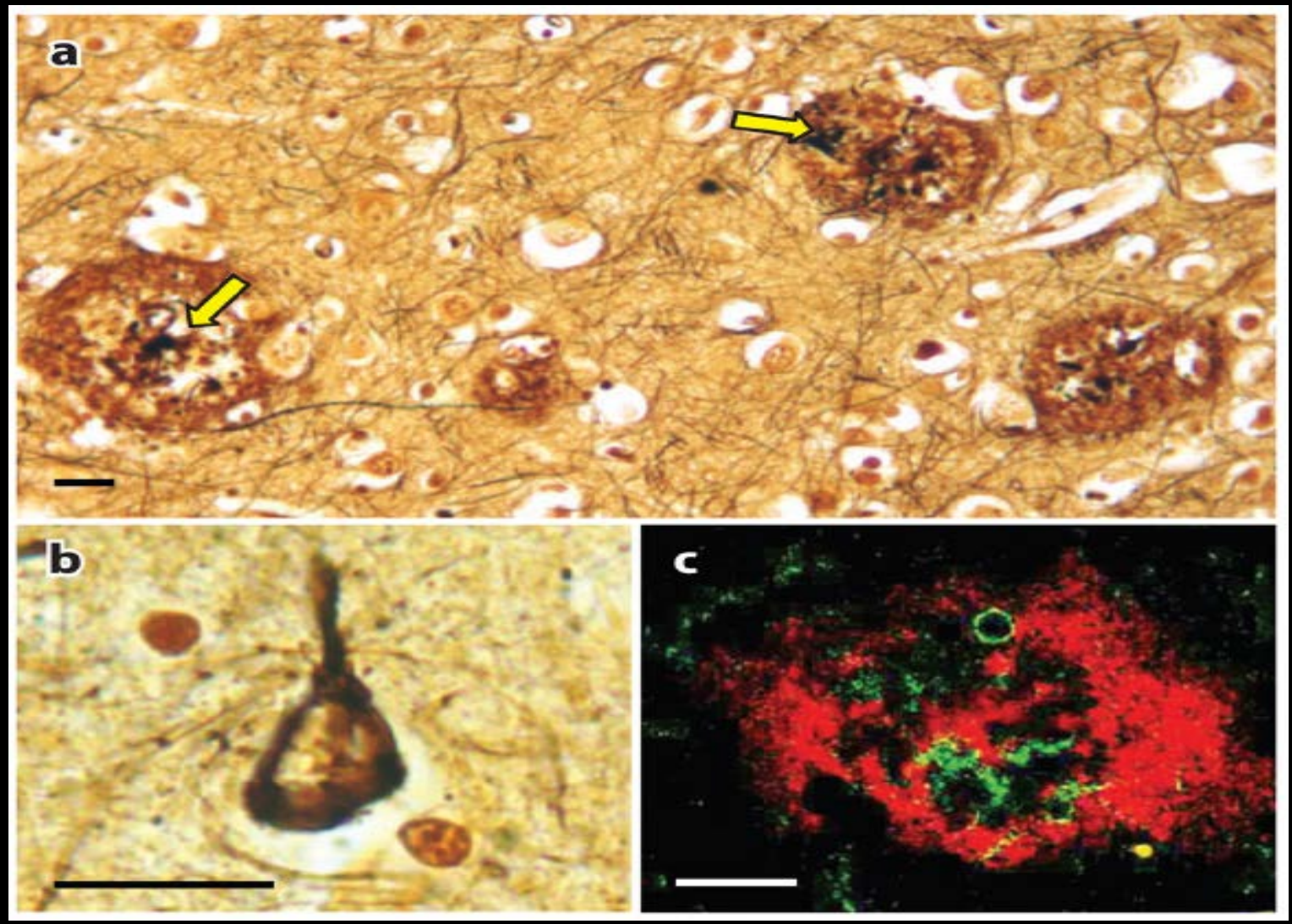
- Michael Woodward has worked on AD drug trials funded by pharmaceutical companies including AbbiVie, Astra Zeneca, AZ therapies, Biogen, Buck, Eisai, Janssen, Lilly, Lundbeck, Merck/MSD, Novartis, Pfizer, Roche, Servier, Takeda, Tau Rx, vTv Therapeutics and Zinfandel. He has also received honoraria for consultancies or presentations at meetings organized by CogRx, Lundbeck, Merk Sharp & Dohme, Novartis, Nestle and Nutricia.

Disclosures

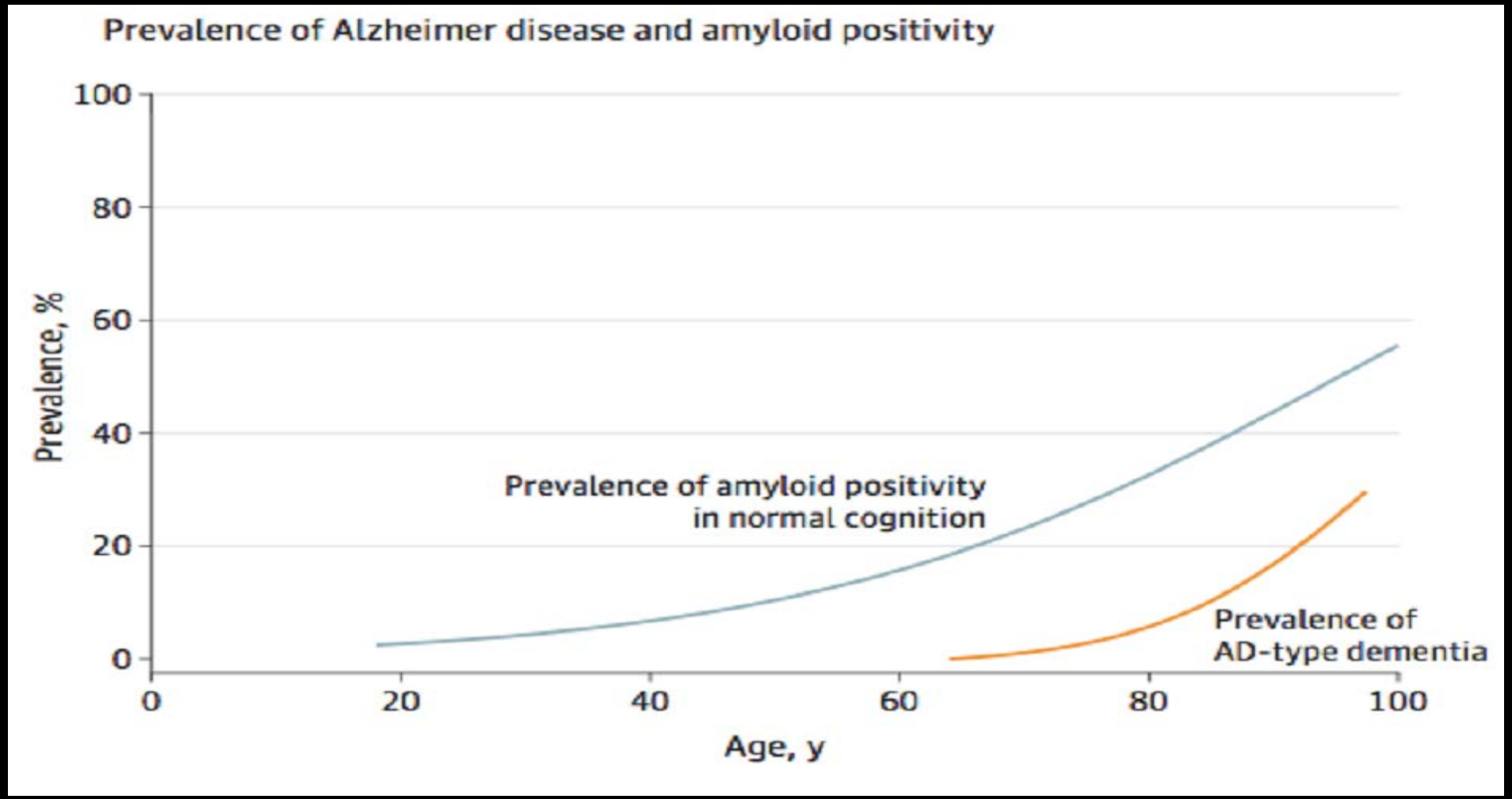
- Kevin Ong wished he had something to disclose.



Sperling et al., Alzheimer's & Dementia, 2011.

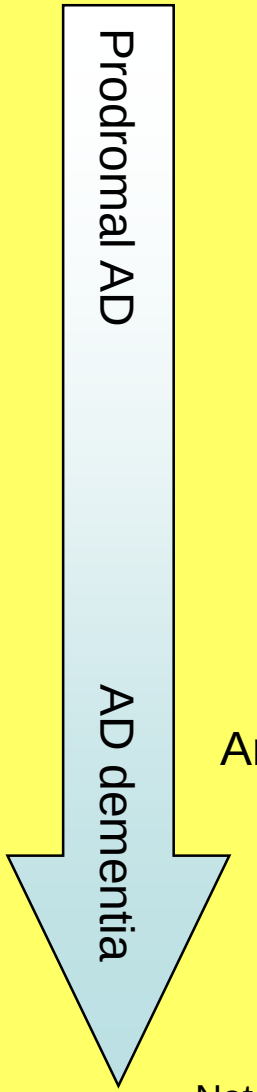


O’Brien & Wong, Annu Rev Neurosci, 2011.



Meta-analysis by Jansen et al., JAMA, 2015.

Tracking The Progression of Alzheimer Changes In Vivo



Mechanism	Biomarker
Upstream events (e.g., Aβ dimers, oligomers)	**? ? ?**
Aβ aggregation; deposition as cerebral diffuse plaques	**Aβ Imaging;** ↓ CSF $A\beta_{42}$ levels
Amyloid plaques exert synaptic/neuronal damage	↓ brain metabolism (FDG); Brain volume loss (MRI)
Substantial synaptic/neuronal damage	Dementia severity marked by increasing volume loss, and ↑ CSF tau&ptau levels

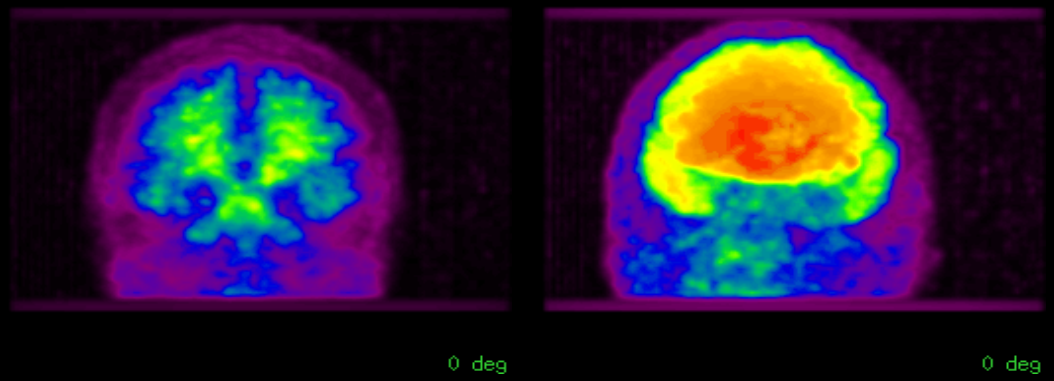
Note: Other processes (e.g., inflammation; oxidative stress; vascular insufficiency) likely contribute

Tracking Aβ Oligomers Upstream

1. $CSF_{A\beta}$ levels are not in equilibrium with cerebral Aβ plaque burden detected by Amyloid PET.
2. We can detect soluble Aβ oligomers in vivo. But are they fibrillogenic?
   - Increased CSF $A\beta_{42}$:$A\beta_{40}$ ratio is associated with FTD, not AD?!
     - Vitali 2004; Pijnenburg 2007; Bernardi 2009; Dermaut 2004.

Tracking Fibrillogenic Aβ

- We can assume the presence of fibrillogenic Aβ oligomers if there is increased tracer uptake on serial amyloid PET



Before

After some time

RESEARCH Open Access

^{18}F-florbetaben Aβ imaging in mild cognitive impairment

Kevin Ong[1], Victor L Villemagne[1,2,3], Alex Bahar-Fuchs[1,4], Fiona Lamb[1,3], Gaël Chételat[1], Parnesh Raniga[5], Rachel S Mulligan[1], Olivier Salvado[5], Barbara Putz[6], Katrin Roth[6], Colin L Masters[3], Cornelia B Reininger[6] and Christopher C Rowe[1,2*]

Ong *et al. Alzheimer's Research & Therapy* 2013, **5**:4
http://alzres.com/content/5/1/4

RESEARCH PAPER

Aβ imaging with 18F-florbetaben in prodromal Alzheimer's disease: a prospective outcome study

Kevin T Ong,[1] Victor L Villemagne,[1,2] Alex Bahar-Fuchs,[1,3] Fiona Lamb,[1] Narelle Langdon,[1] Ana M Catafau,[4] Andrew W Stephens,[4] John Seibyl,[5] Ludger M Dinkelborg,[4] Cornelia B Reininger,[6] Barbara Putz,[6] Beate Rohde,[6] Colin L Masters,[2] Christopher C Rowe[1]

Ong KT, *et al. J Neurol Neurosurg Psychiatry* 2014;**0**:1–6. doi:10.1136/jnnp-2014-308094

Methods

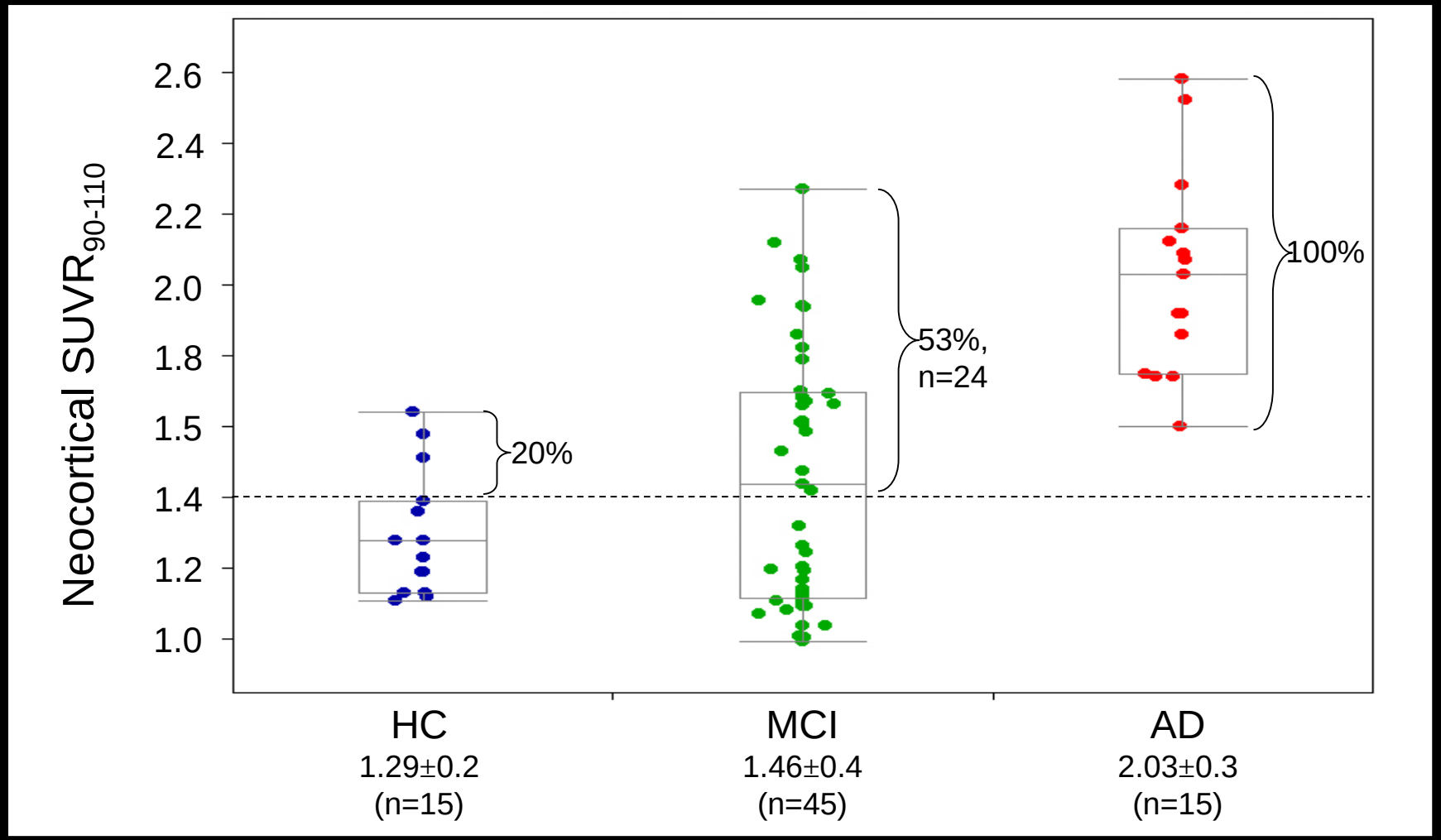
- 45 participants (age 73±6.6) referred from Memory Disorders specialists –
  - At least one cognitive test score < -1.5 SD (Petersen's criteria).
  - Clinical diagnosis of MCI, MMSE 24-30.
- Neuropsychological tests – Logical Memory, CVLT, Rey Figure, etc.
- MRI: 3D T1-MPRAGE, T2, FLARE.
- PET: 90-110 min after 300 MBq of Florbetaben (FBB).
- Image analysis:
  - **Florbetaben (FBB) PET** - SUVR using the cerebellar cortex as reference region.
  - **MRI** – Hippocampal Volume determined by *NeuroQuant®;* WMH determined by manual segmentation with ***MRIcro*** software.
- Statistical analysis:
  - Linear regression.
  - Adjusted for age, gender, and years of education.

Methods

- MRI and Florbetaben **(FBB)** PET repeated at 12 and 24 months from baseline.
  - FBB PET (n=74) 98% sensitivity, 89% specificity for confirming significant plaque load in autopsy studies.
- Clinical assessment annually for 2 years then again at 4 years.

Amyloid Imaging

^{18}F-Florbetaben



Relationships

Aβ

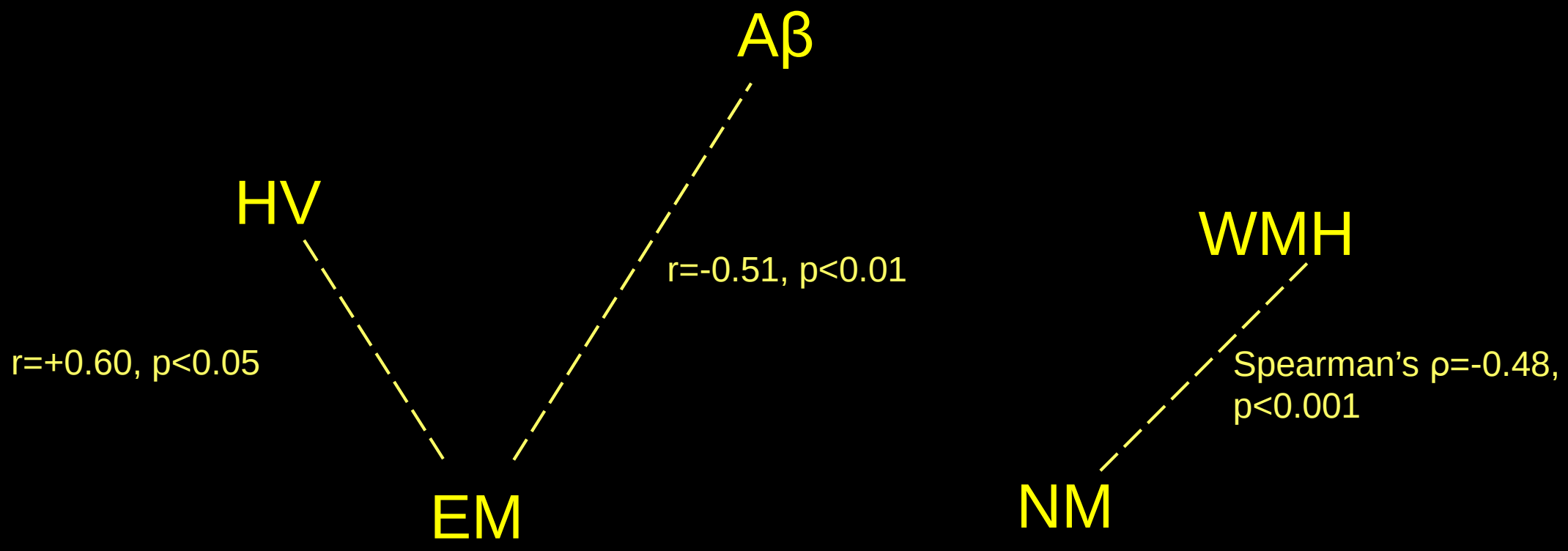
HV

WMH

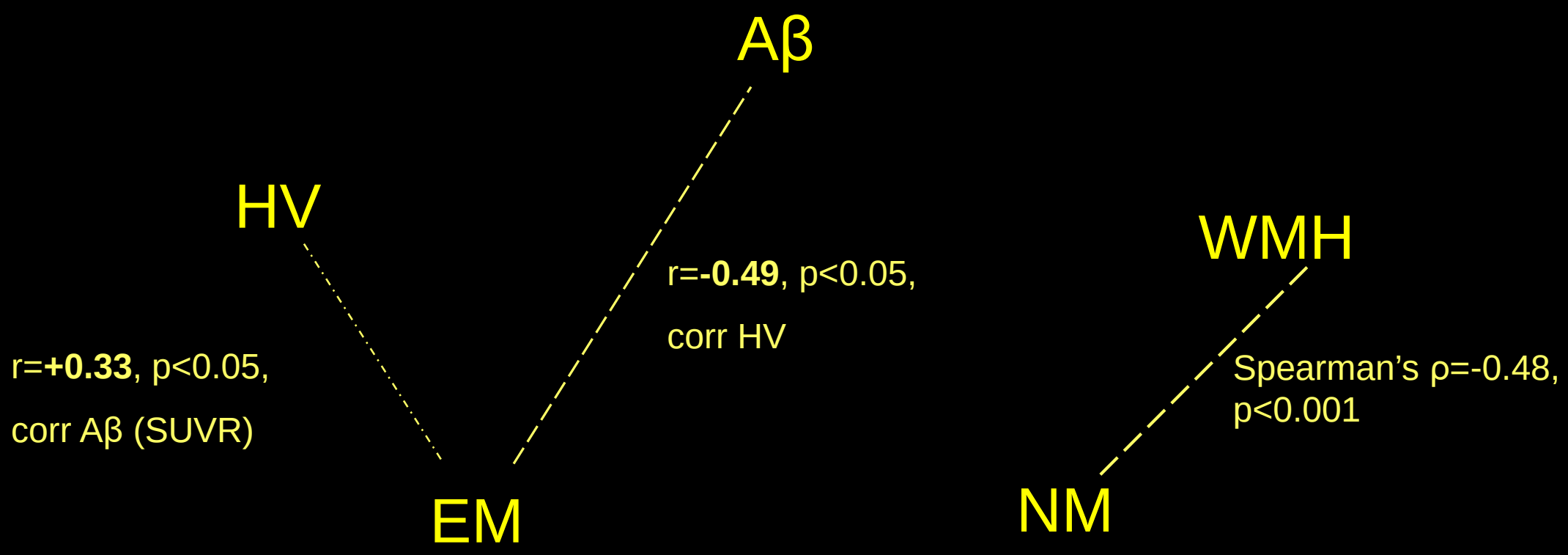
EM

NM

Relationships

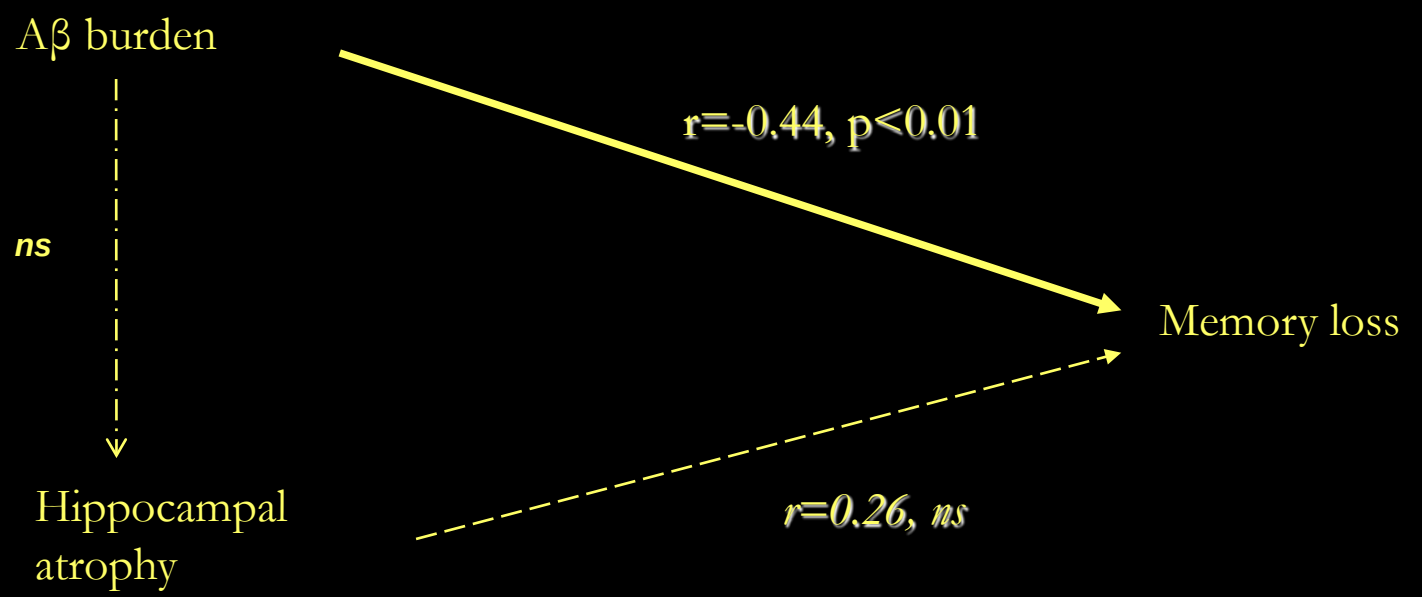


Relationships



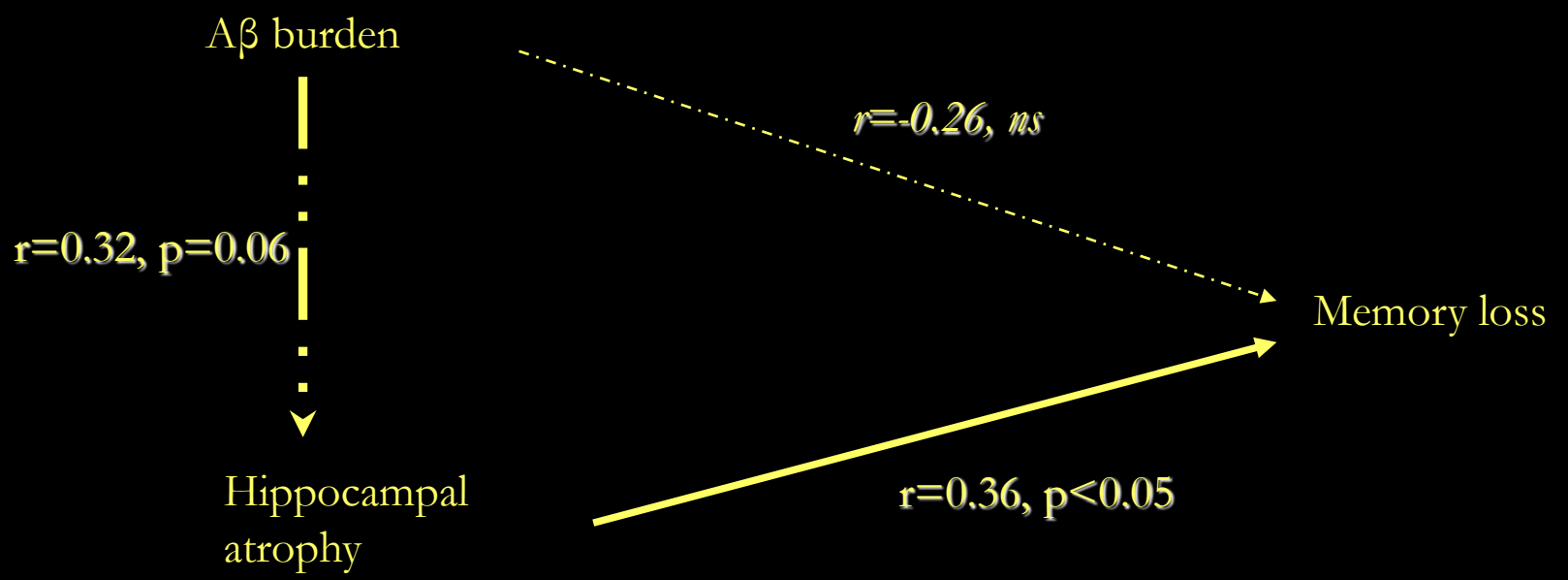
Both **Aβ** and hippocampal atrophy may have a **direct** and **independent** relationship with memory impairment in MCI.

Baseline (excluding 9 drop outs)



n=36

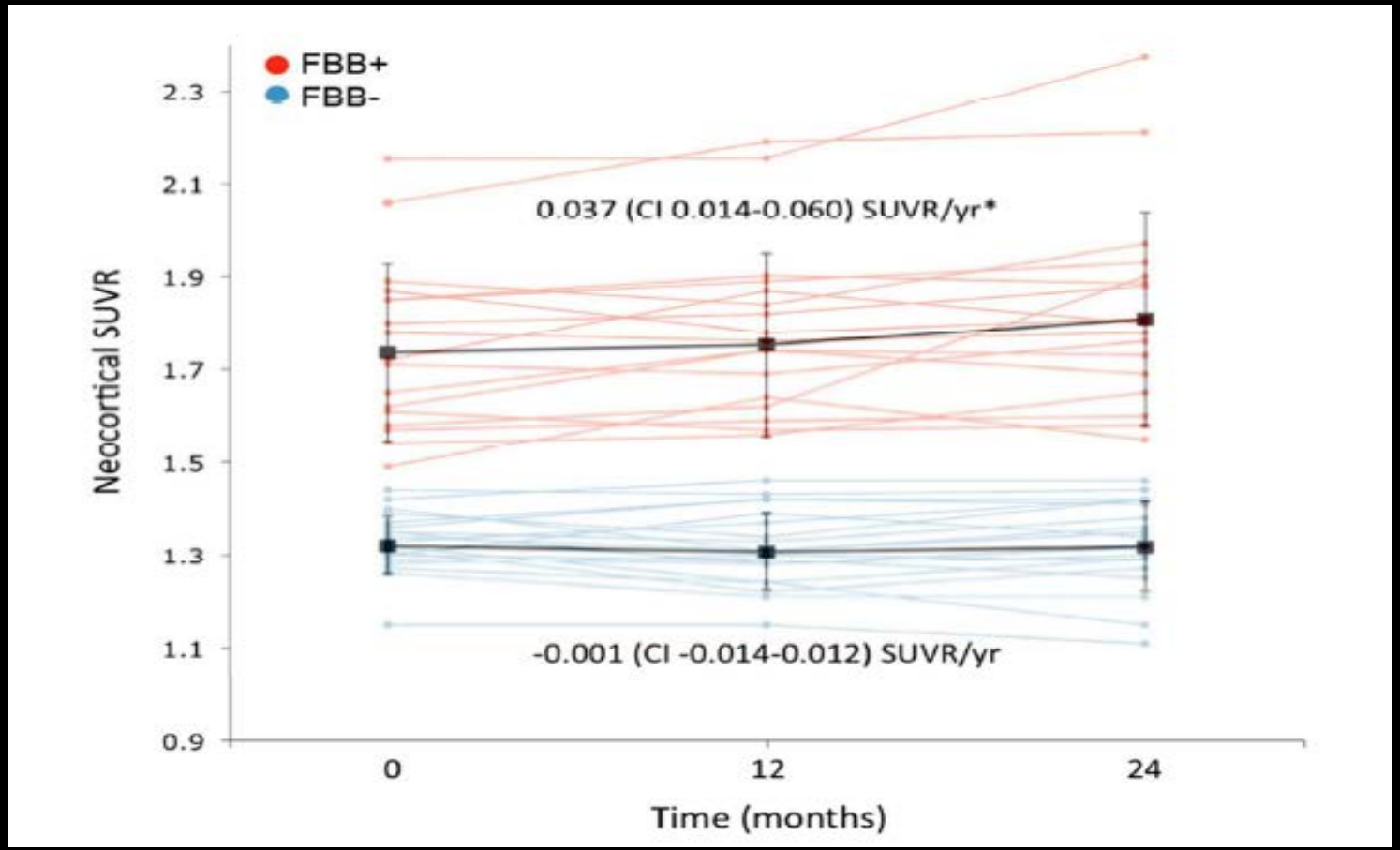
After 2 years



n=36

Hippocampal atrophy overtakes Aβ in driving memory impairment, and increasingly mediates this relationship, as disease progresses.

Changes in FBB SUVR over 2 years



- SUVR increased by 2.2% (0.037) per year in those with high Aβ at baseline, $p<0.01$
- We assume the presence of fibrillogenic Aβ oligomers if there is increased tracer uptake on serial amyloid PET.

Early progressive memory loss

- Possibly driven by soluble fibrillogenic Aβ oligomers just upstream to deposited Aβ plaques.

RESEARCH PAPER

Aβ imaging with 18F-florbetaben in prodromal Alzheimer's disease: a prospective outcome study

Kevin T Ong,[1] Victor L Villemagne,[1,2] Alex Bahar-Fuchs,[1,3] Fiona Lamb,[1] Narelle Langdon,[1] Ana M Catafau,[4] Andrew W Stephens,[4] John Seibyl,[5] Ludger M Dinkelborg,[4] Cornelia B Reininger,[6] Barbara Putz,[6] Beate Rohde,[6] Colin L Masters,[2] Christopher C Rowe[1]

Table 2 Mild cognitive impairment: bivariate correlates of progression to Alzheimer's dementia over the first 2 years of follow-up

	Progressed to AD				
At baseline	Yes	No	PPV (%) (95% CI)	NPV (%) (95% CI)	Accuracy (95% CI)
FBB+ (by SUVR)**	18	6	75.0%	90.5%	82.8%
FBB– (by SUVR)	2	19	(60% to 82%)	(74% to 98%)	(61% to 94%)

Ong KT, *et al*. *J Neurol Neurosurg Psychiatry* 2014;**0**:1–6. doi:10.1136/jnnp-2014-308094

- **Accuracy of FBB PET in predicting MCI conversion to AD over 2 years was 82.8%**

POST HOC ANALYSIS:

To compare the risk factors (co-variates) below for MCI progression to AD

1. Age.
2. Years of education
3. Gender.
4. High cerebral amyloid load (FBB+).
5. Hippocampal atrophy.
6. Poor EM.
7. Poor nonmemory-related cognitive function (NM).
8. Clinical dementia rating sum of boxes (CDR SOB).
9. White matter hyperintensity.
10. Number of cardiovascular risk factors.

11. Increase in FBB tracer uptake (≡ presence of fibrillogenic Aβ oligomers)

POST HOC ANALYSIS:

- **Cox regression.**
- Compare (& simultaneously correct) effects of several risk factors on unwanted events occurring.

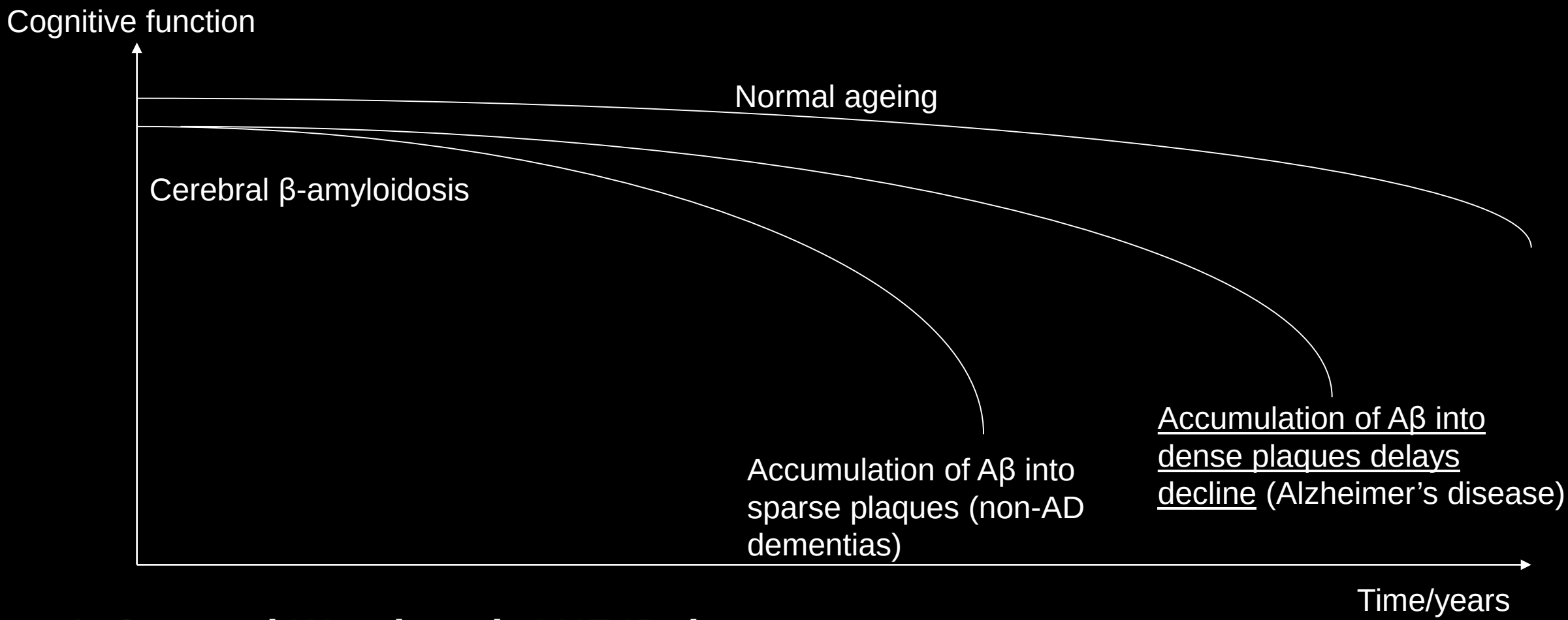
Increased tracer uptake

- Did not predict Alzheimer's disease.
  - Two & four years follow-up: HR *ns*!
- Predicted all cause dementia.
  - Two years follow-up: HR 4.8, p=0.027.
  - Four years follow-up: HR 6.9. p=0.010.

Summary

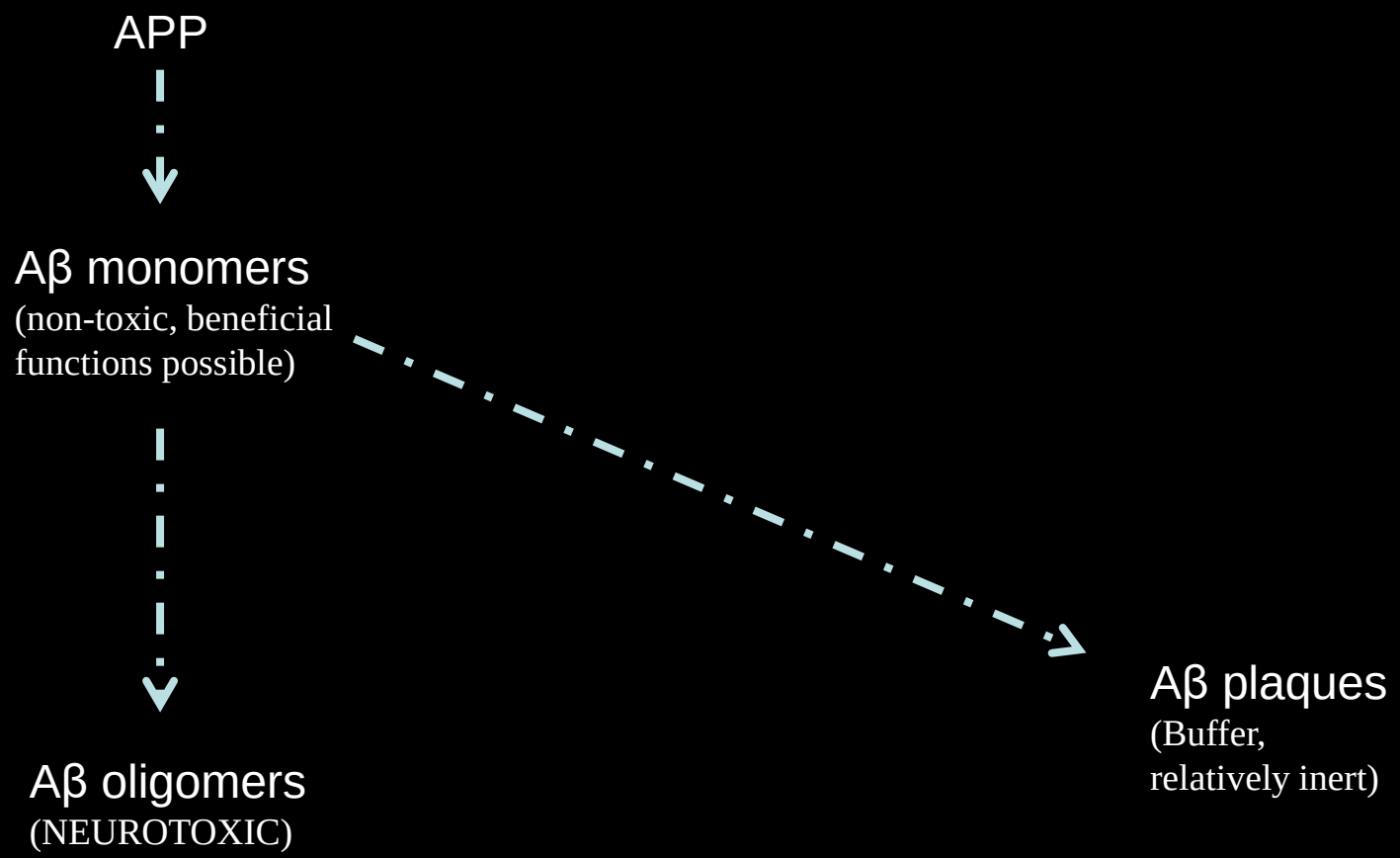
1. Early memory decline and hippocampal atrophy may be caused by soluble fibrillogenic Aβ oligomers upstream to Aβ plaques.
2. Fibrillogenic Aβ oligomers upstream to Aβ plaques are non-specific for AD dementia!
   - Aβ plaque accumulation may be the cause of AD (Amyloid Cascade Hypothesis).
   - **Is Aβ plaque accumulation in AD a means to buffer the effects of Aβ-amyloidosis in non-AD?**
     - **Clinically, non-AD dementia sufferers generally experience a more malignant course compared to those with AD!**

The Ong-Woodward Hypothesis[1]



1. Ong and Woodward. ANZJP, *in press.*

Finding the right targets



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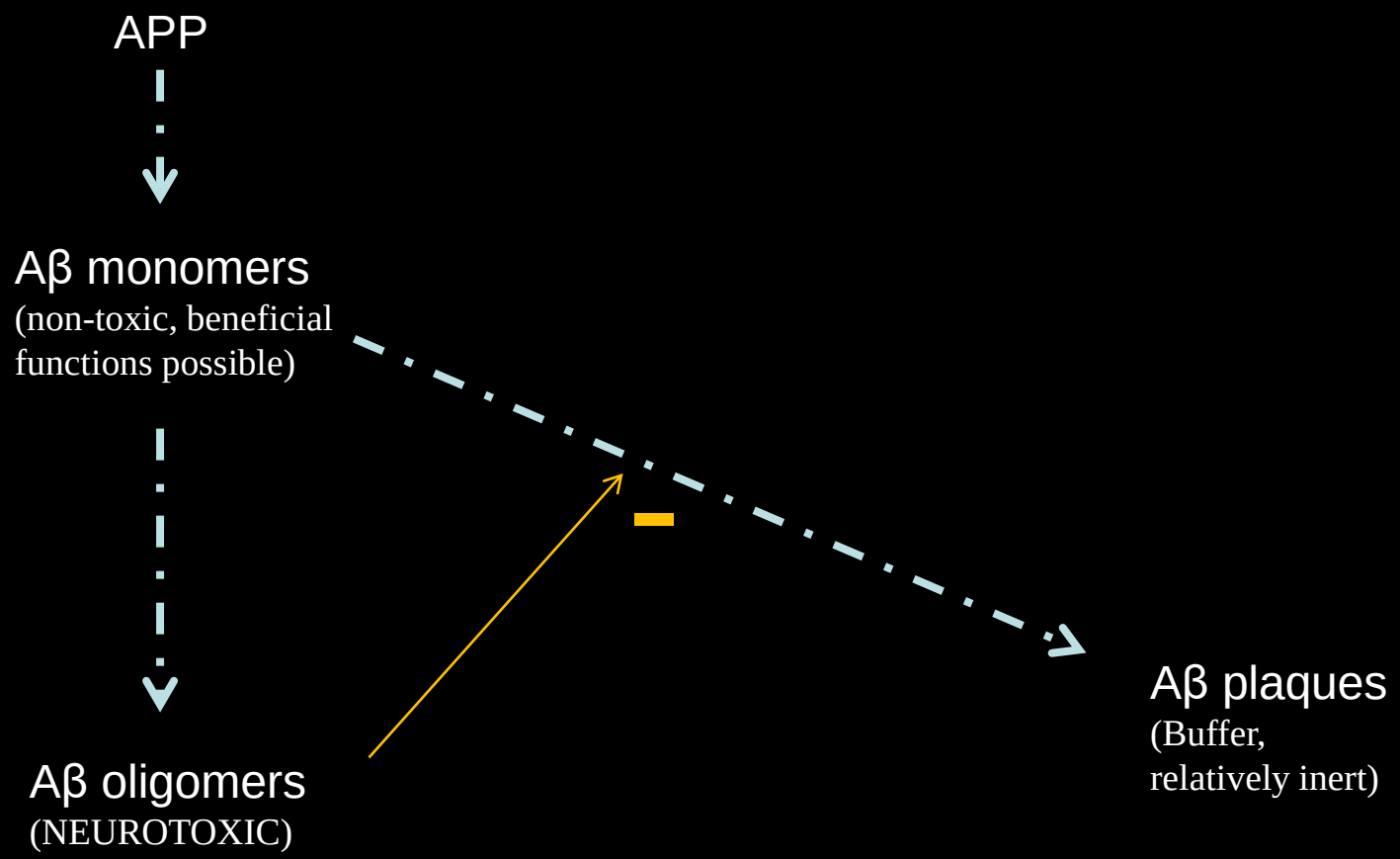

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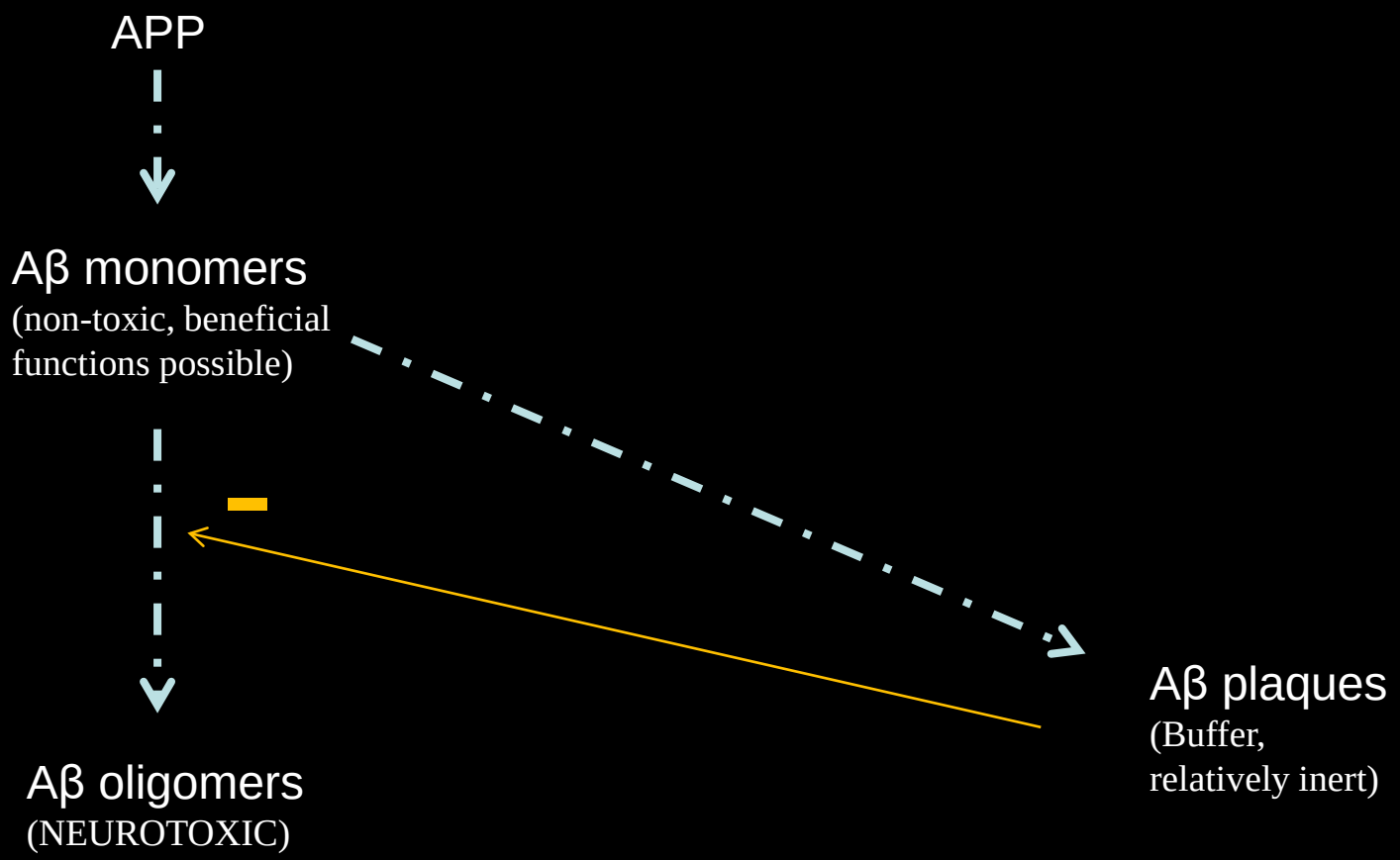

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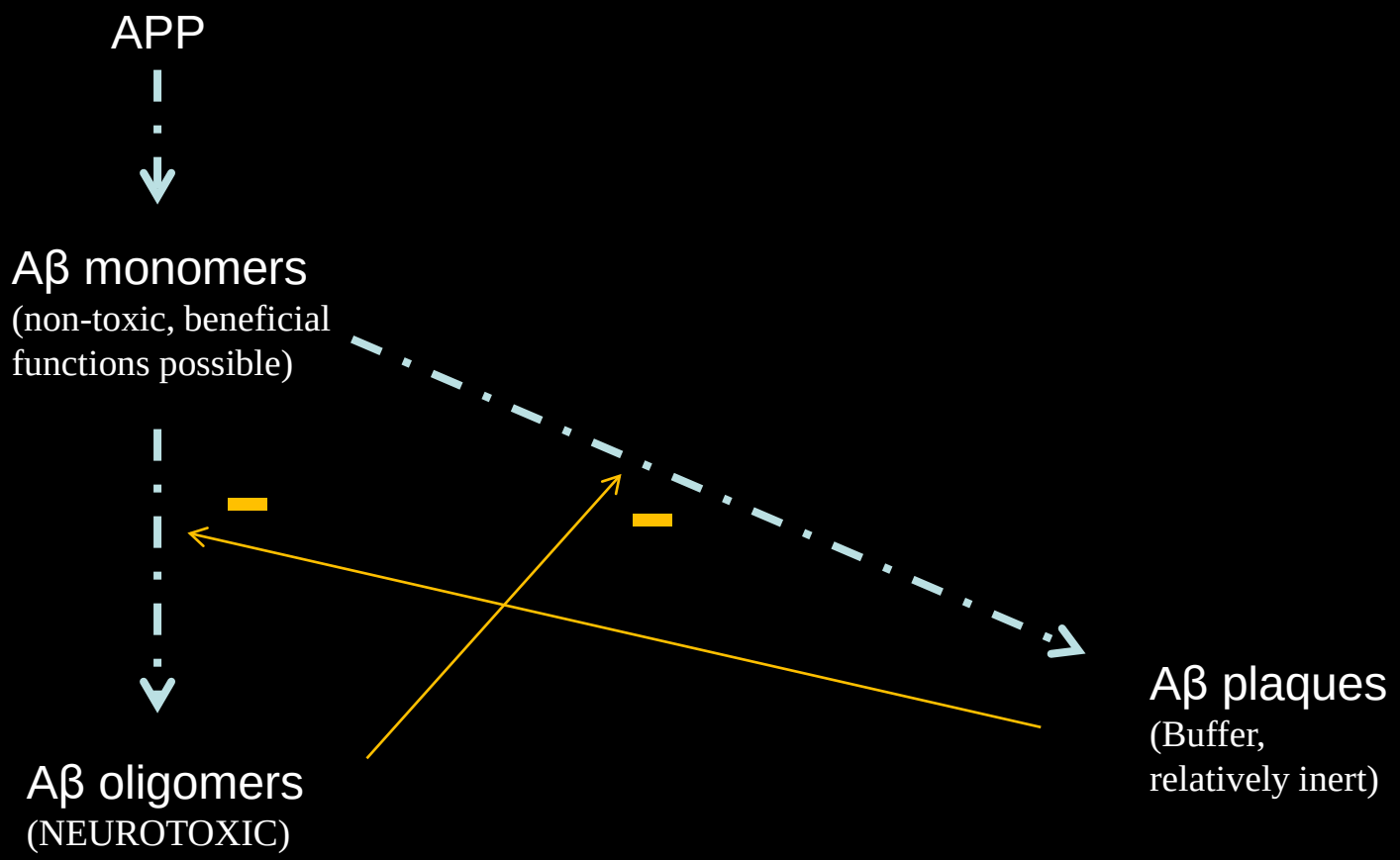

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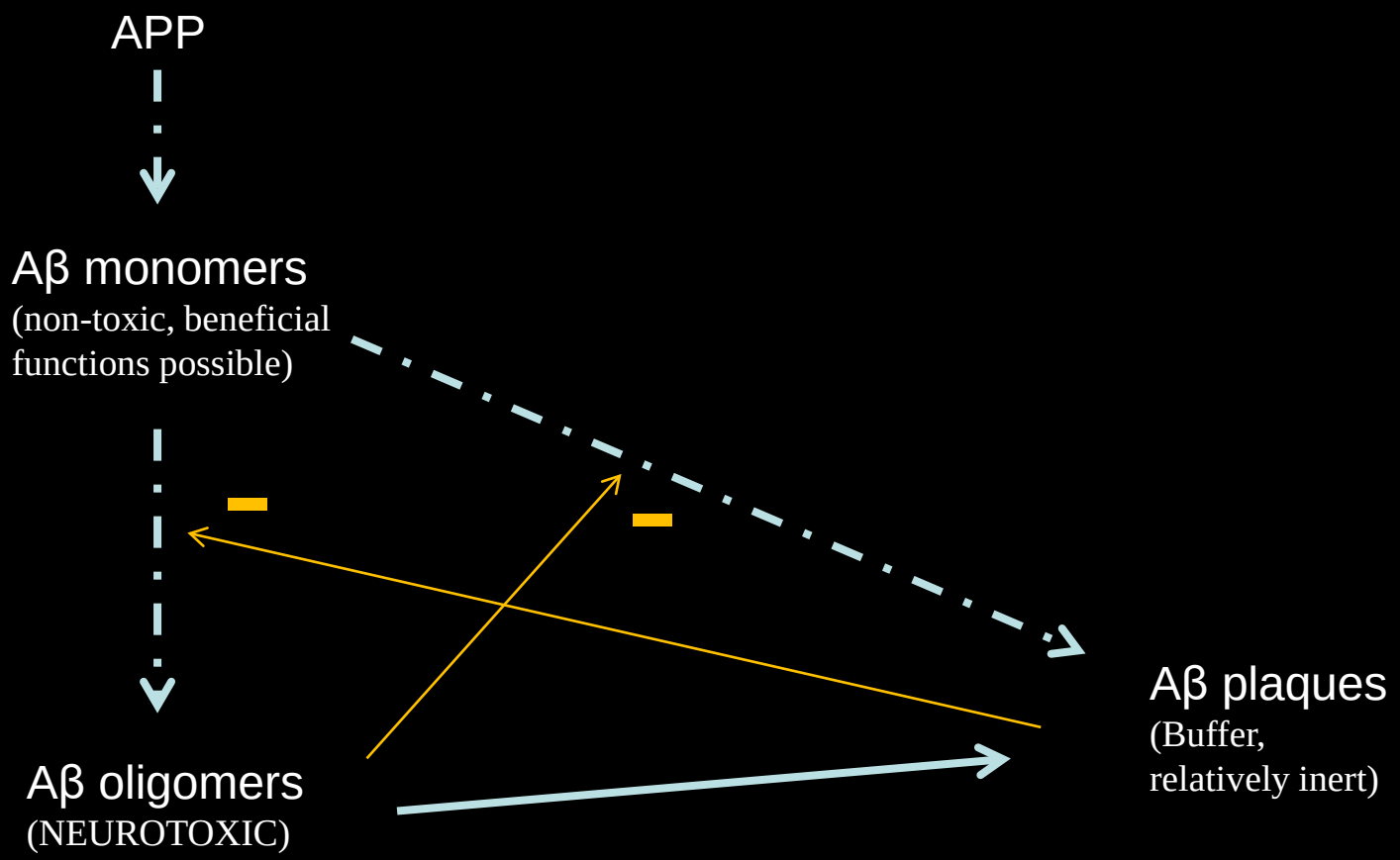

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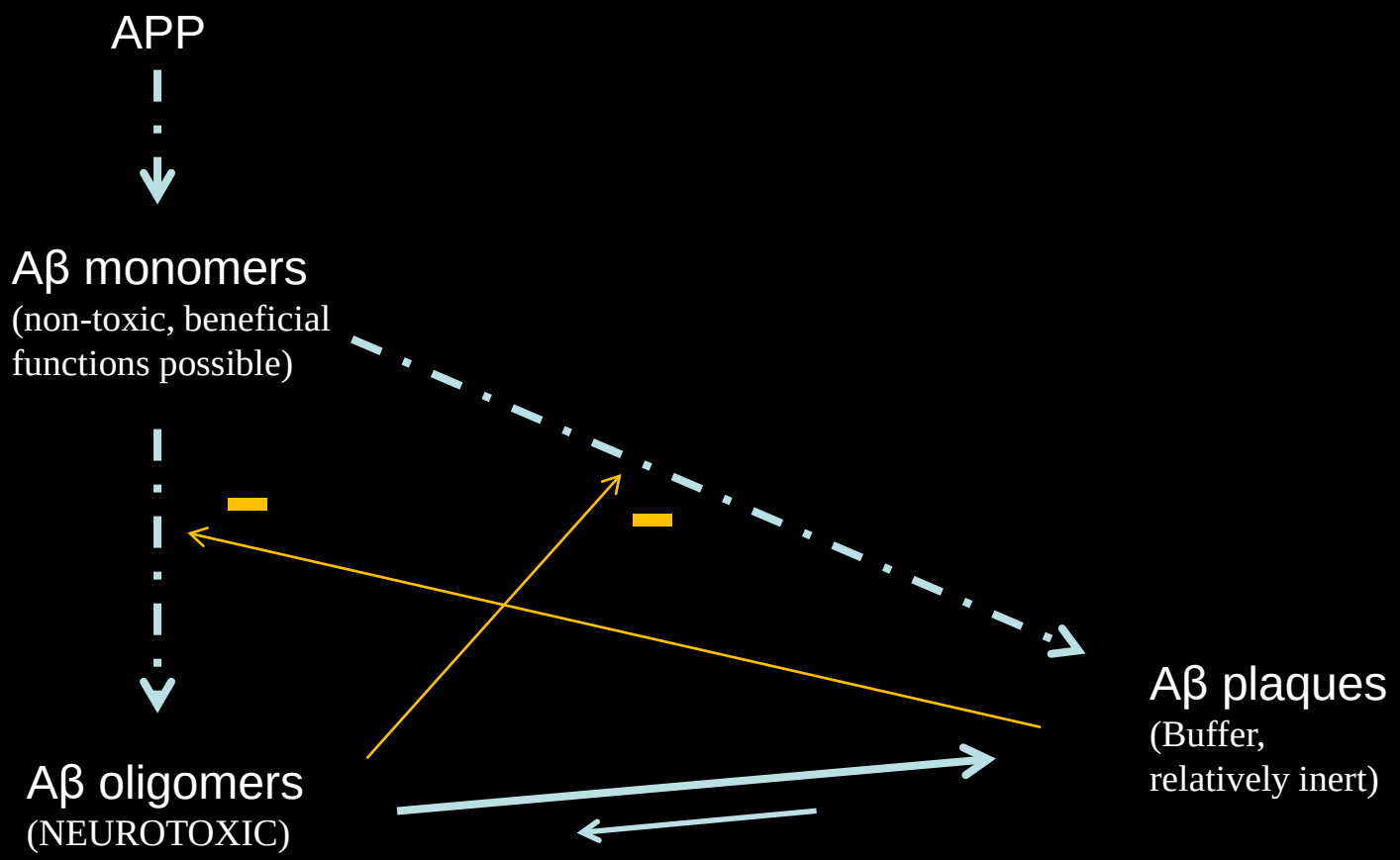

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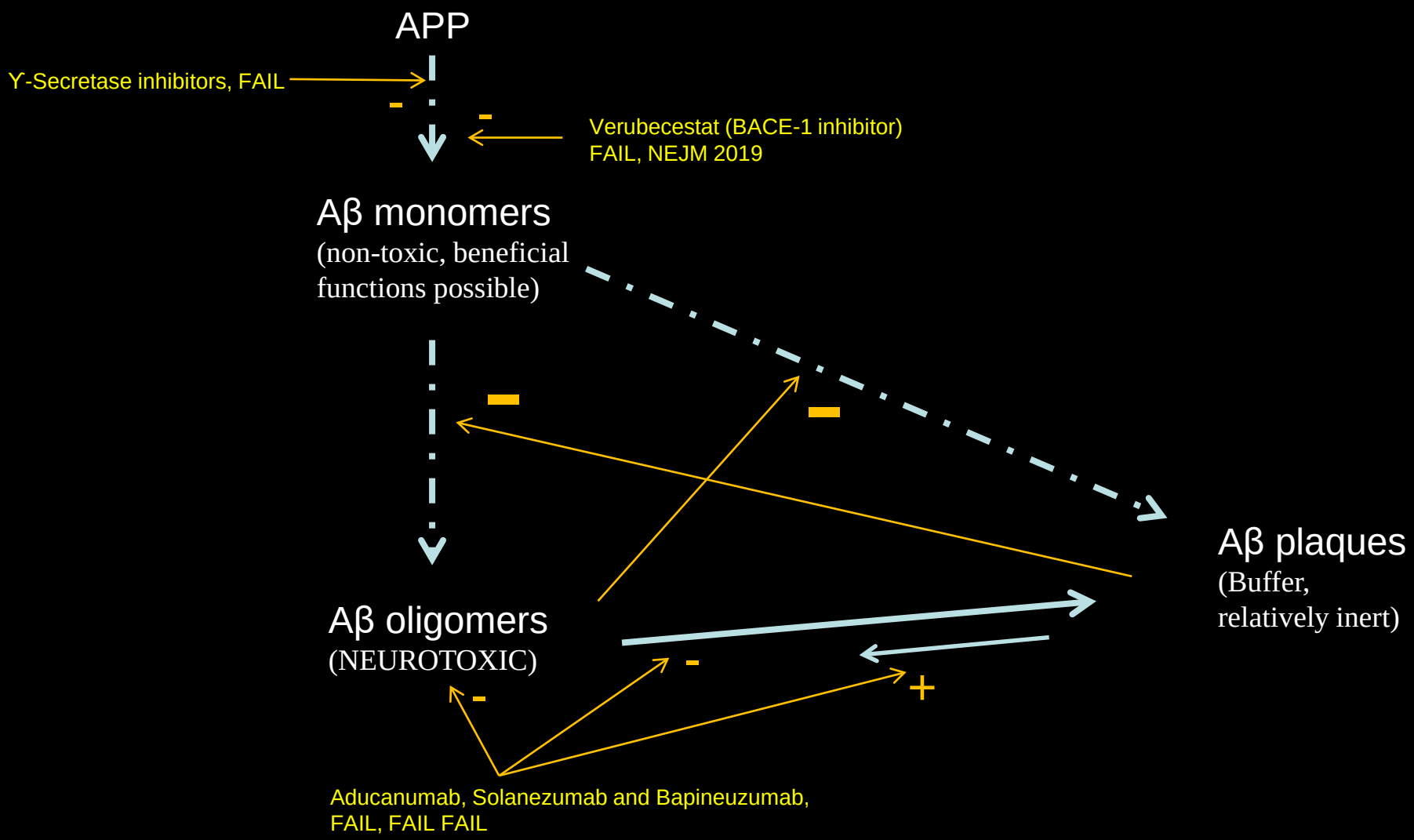


The Woodward-Ong Hypothesis

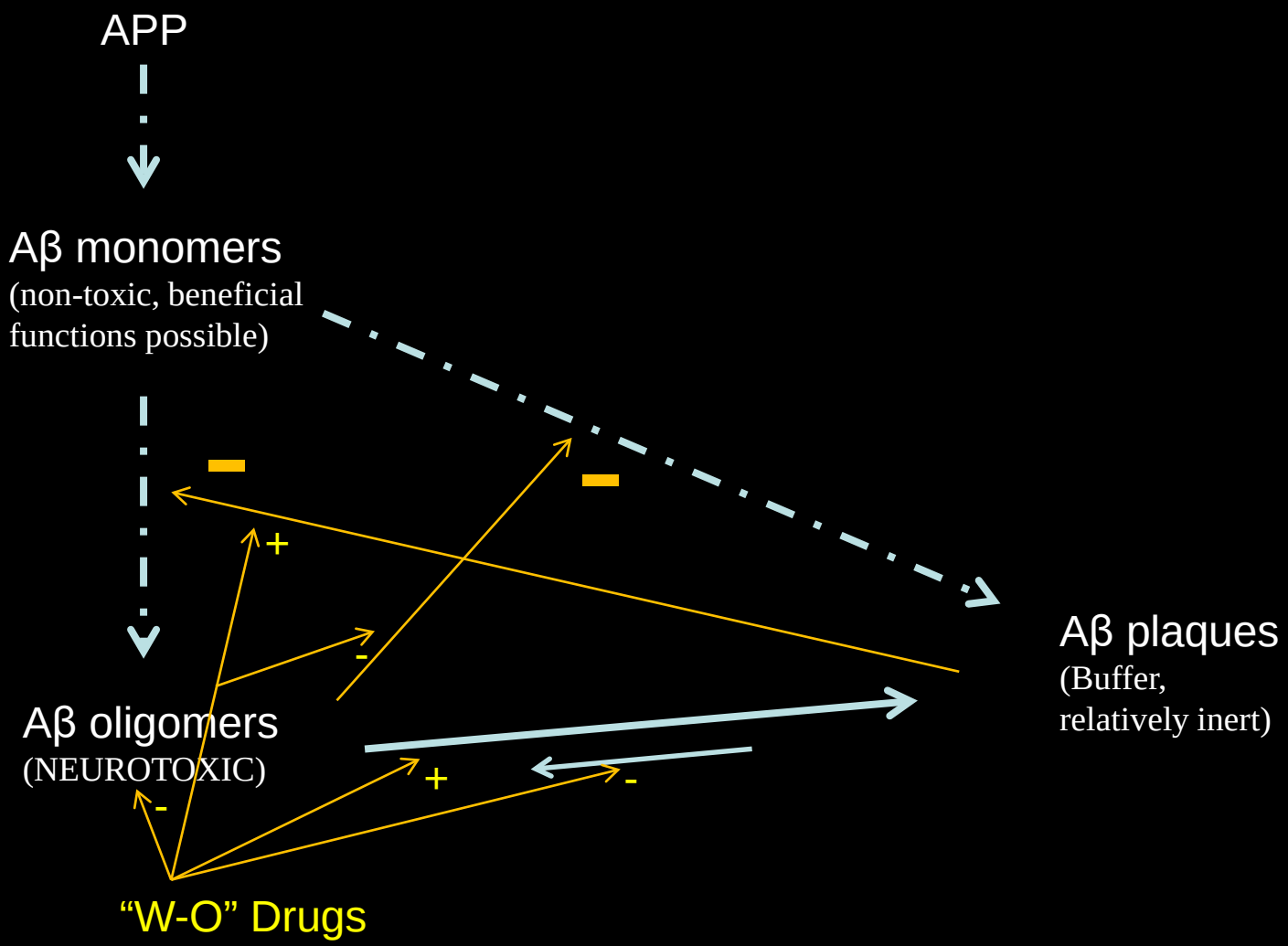
AD drugs are more likely to work if they:

1. Specifically reduce soluble Aβ oligomers levels cerebrally,

AND

2. Enhance Aβ plaque formation and stability.

Finding the right targets



Limitations

- Single centre.
- Limited data.
- Serial scanning increases noise.

Acknowledgements

Austin Health (Melbourne):

- **Christopher Rowe**
- **Victor Villemagne**
- Kerryn Pike
- Alex Bahar-Fuchs
- Fiona Lamb
- Narelle Langdon
- Colin Masters
- Gael Chetelat

Bayer/Piramal employees:

- Ana Catafau
- Andrew Stephens
- Ludger Dinkelborg
- Cornelia Reininger
- Barbara Putz
- Beate Rohde

Participants and their families

Supported in part by Bayer-Schering Pharma, Austin Health Medical Research Foundation, NHRMC grant 509166