

PET and CSF biomarkers of Alzheimer's Disease and relationships with cognitive decline in the pre-dementia phase

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Disclosures

- Consultant to Roche Diagnostics
- Cerveau Technologies research funding

Alzheimer's Disease in 2020

- AD is defined by its dual proteinopathy: amyloid- β and tau
- AD has a prolonged presymptomatic stage that may or may not progress to symptoms
 - This stage is being intensely studied by the field
- We have PET and CSF biomarkers appropriate for AD
- Other diseases may masquerade or co-occur with AD symptom expression
 - We have MRI markers of cerebrovascular disease but no biomarkers for other neurodegenerative diseases
- AD affects ~5.8m in the U.S.
 - rough estimate-not informed by biomarkers

NIA-AA Research Framework

Biomarker Profiles

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N>	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Syndromal Staging of Cognitive Continuum

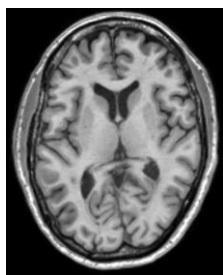
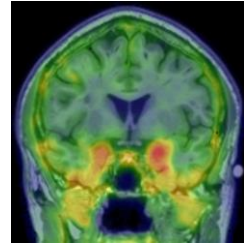
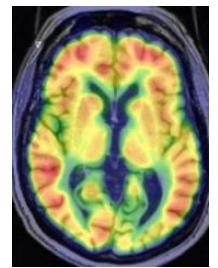
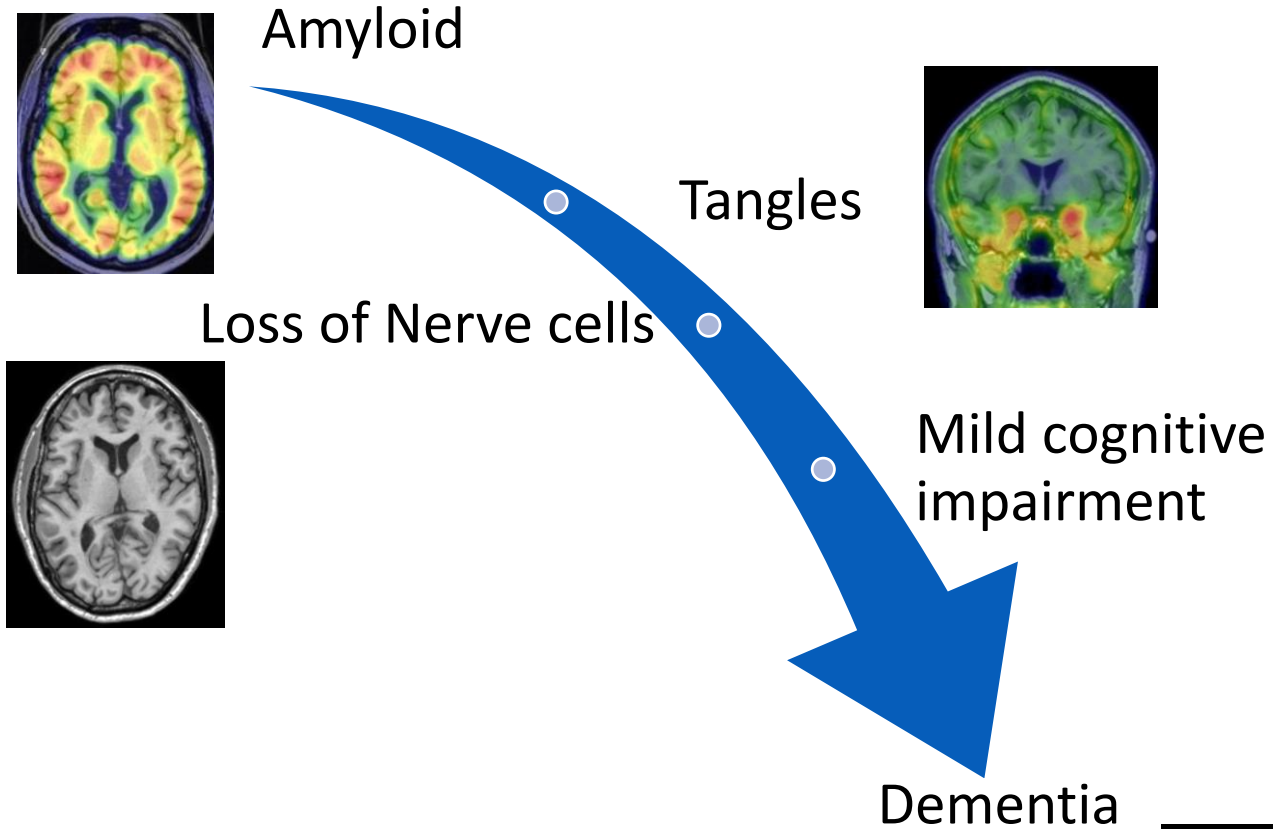
Cognitively unimpaired

Mild cognitive impairment

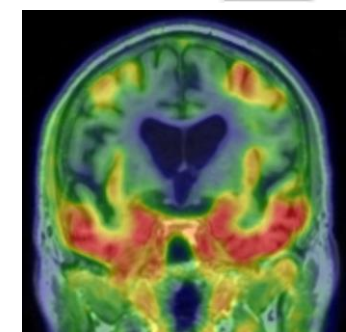
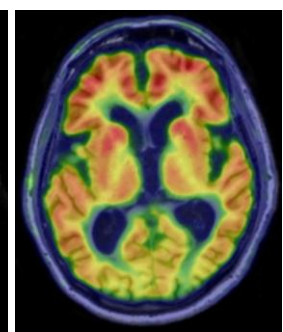
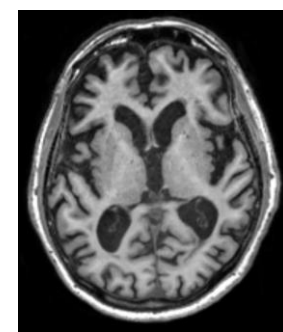
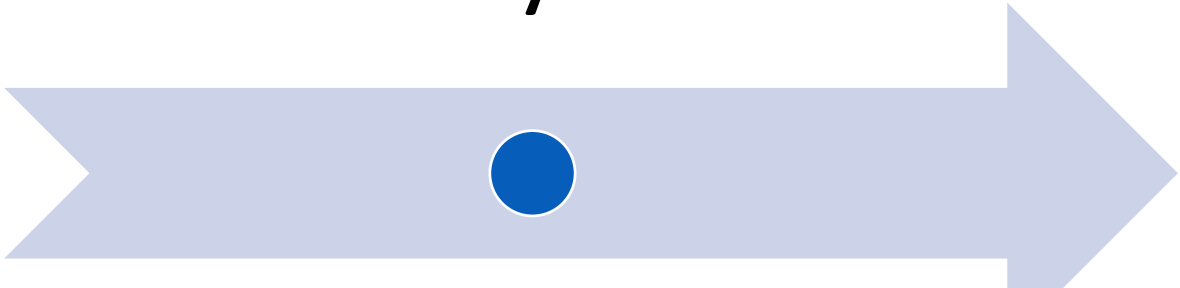
Dementia

“The AT(N) framework”

HOW & WHEN does AD dementia develop?



about 20 years later



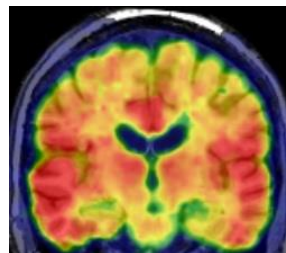
MONTREAL COGNITIVE ASSESSMENT (MOCA)		NAME:	EDUCATION:	SEX:	AGE:
ORIENTATION Name of the state (1) _____ Name of the county (1) _____ Name of the city (1) _____ Name of the street (1) _____ Name of the day of the week (1) _____ Name of the month (1) _____ Name of the year (1) _____					
EXECUTIVE FUNCTION Copy the cube (1) _____ Trace the cube (1) _____ Copy the cube (1) _____ Trace the cube (1) _____ Copy the cube (1) _____ Trace the cube (1) _____					
LANGUAGE Name of the animal (1) _____ Name of the animal (1) _____ Name of the animal (1) _____ Name of the animal (1) _____ Name of the animal (1) _____ Name of the animal (1) _____					
ATTENTION Copy the number (1) _____ Copy the number (1) _____ Copy the number (1) _____ Copy the number (1) _____ Copy the number (1) _____ Copy the number (1) _____					
ABSTRACT REASONING Copy the symbol (1) _____ Copy the symbol (1) _____ Copy the symbol (1) _____ Copy the symbol (1) _____ Copy the symbol (1) _____ Copy the symbol (1) _____					
COGNITIVE SUMMARY Total score (1) _____ Name of the patient (1) _____ Date of the test (1) _____ Name of the doctor (1) _____ Name of the hospital (1) _____ Name of the city (1) _____ Name of the state (1) _____ Name of the country (1) _____					

AD Biomarkers

A amyloid

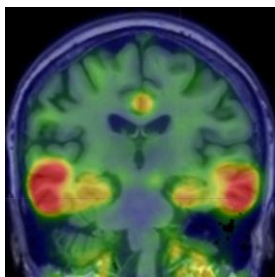
- [F18]florbetapir PET (FDA approved)
- [F18]florbetaben PET (FDA approved)
- [F18]flutemetamol PET (FDA approved)
- [F18]NAV4694 PET
- **[C11]Pittsburgh compound B PIB PET**
- **CSF $A\beta_{42}$; $A\beta_{42/40}$ ratio**

Amyloid scan
[C-11]PiB



T tau PET

- [F18]flortaucipir (FDA approved)
- [F18]PI2620
- **[F18]MK-6240**
- [F18]RO948
- **Ptau₁₈₁**



Tau scan
[F-18]MK-6240

Candidate (N)

- MRI (structure, diffusion, metab)
- FDG PET
- UCB-J SV2A PET
- CSF NFL (axons)
- CSF Neurogranin (post-synaptic)

- ****CSF total tau is too correlated with p-tau₁₈₁ to work for N (r=.99)**

Amyloid [C11]PiB

A+

A-

Unimpaired

n=70

n=253

MCI

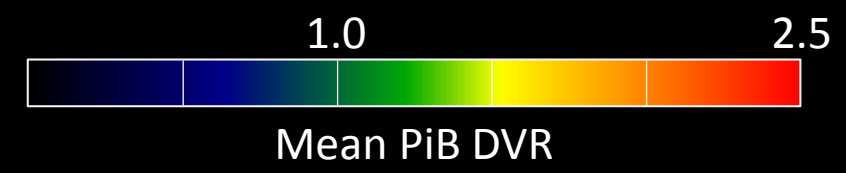
n=22

n=7

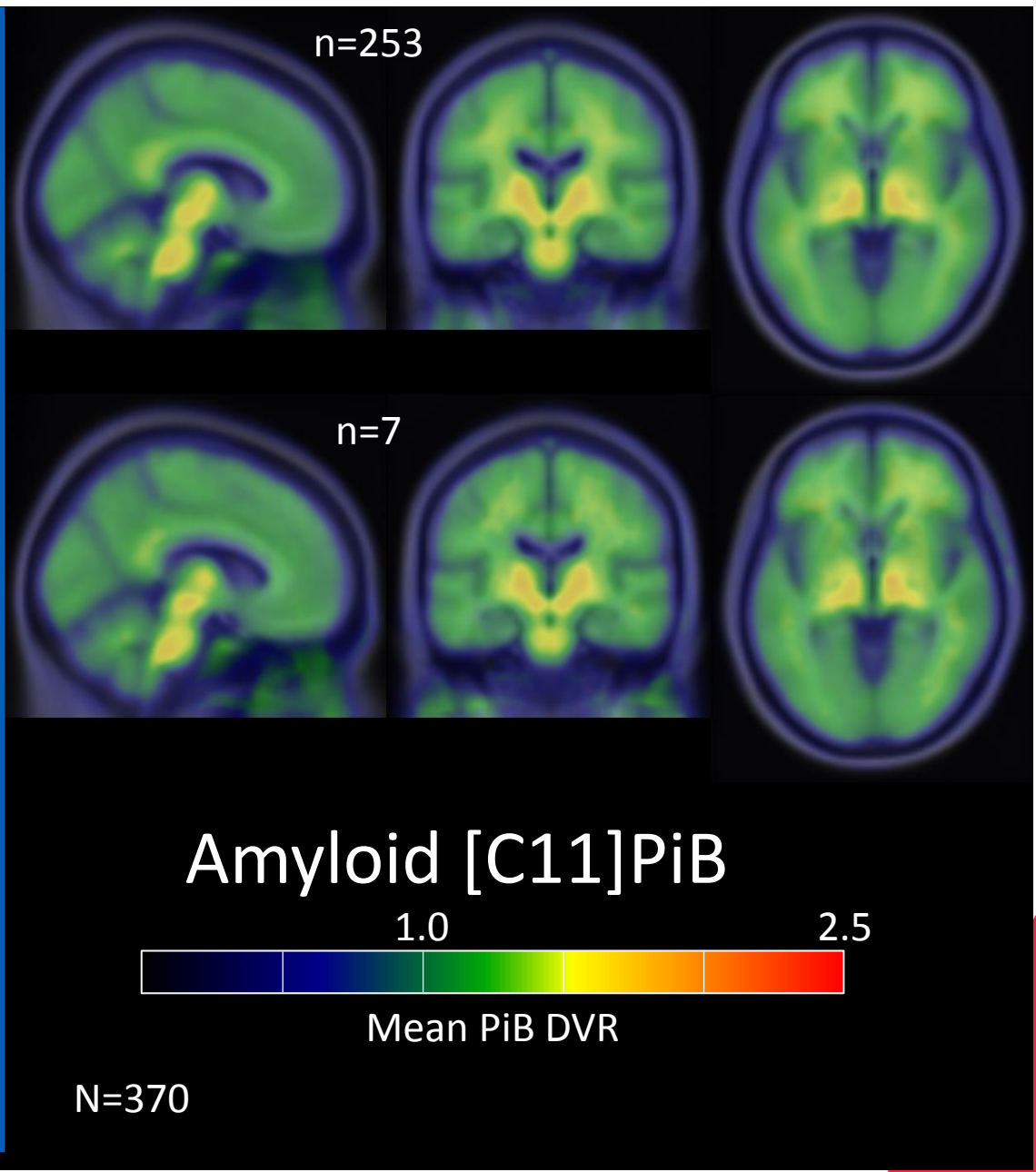
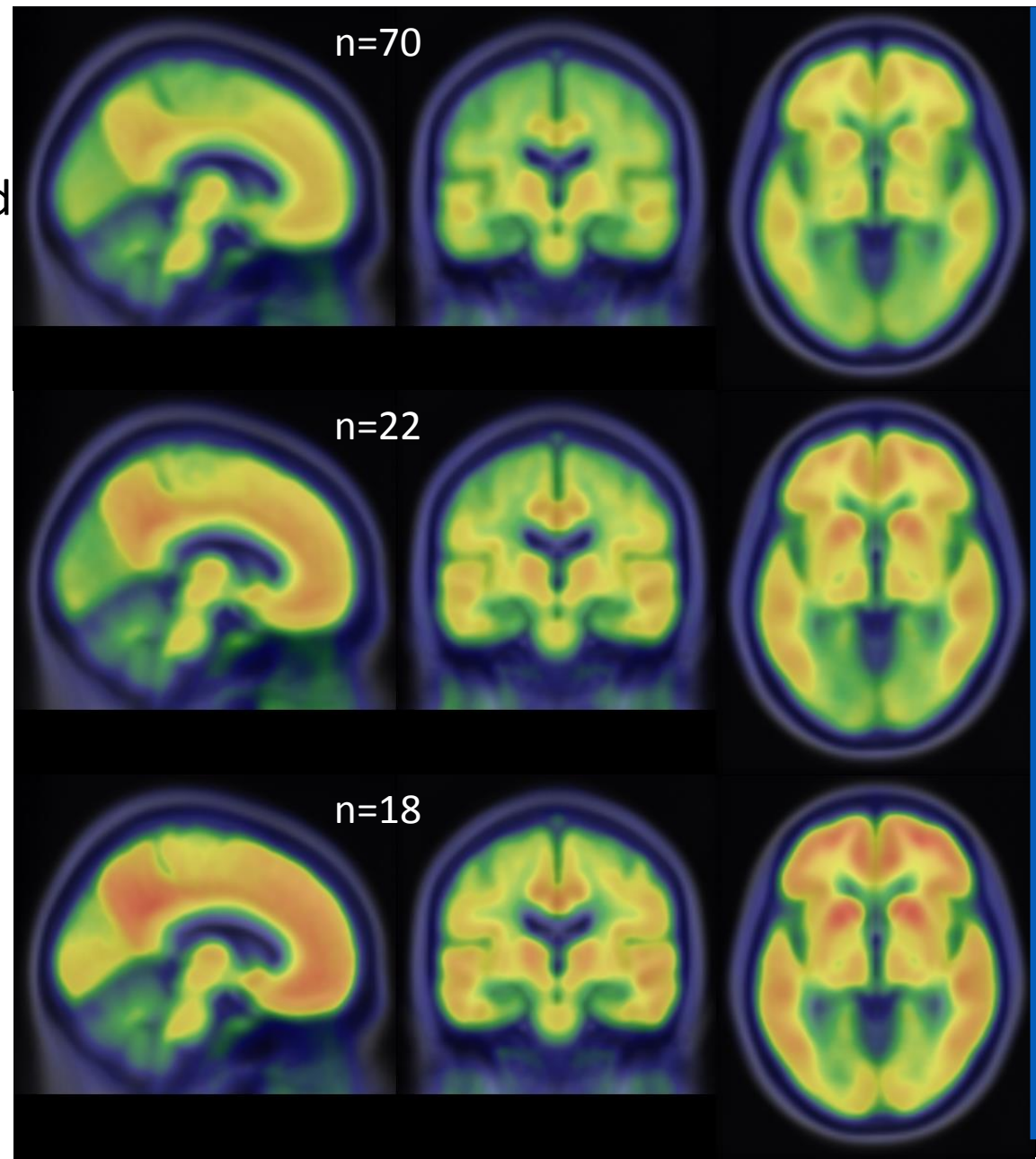
Dementia

n=18

Amyloid [C11]PiB



N=370



[F18]MK-6240 Tau

A+

A-

Unimpaired

n=70

n=253

MCI

n=22

n=7

Dementia

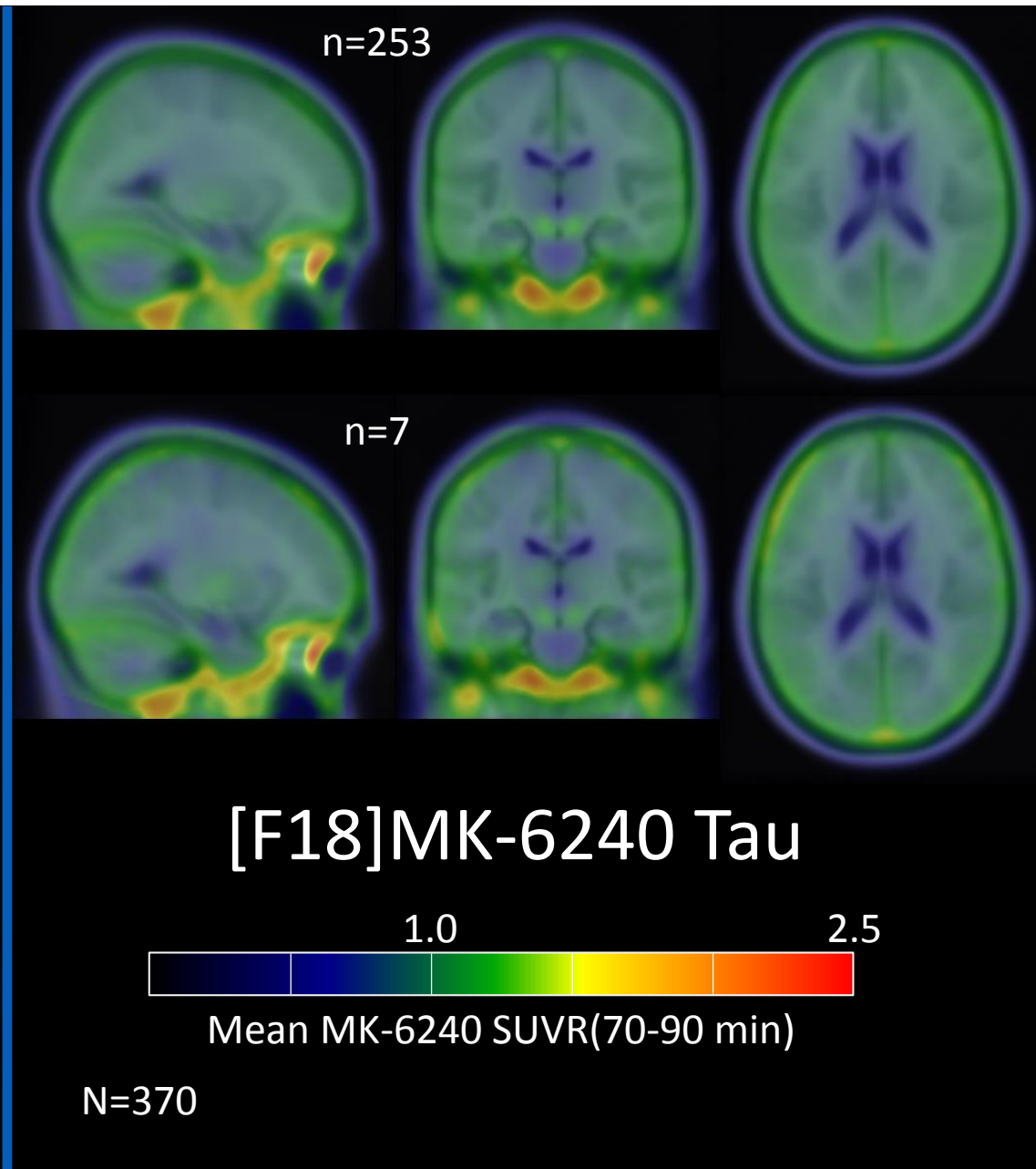
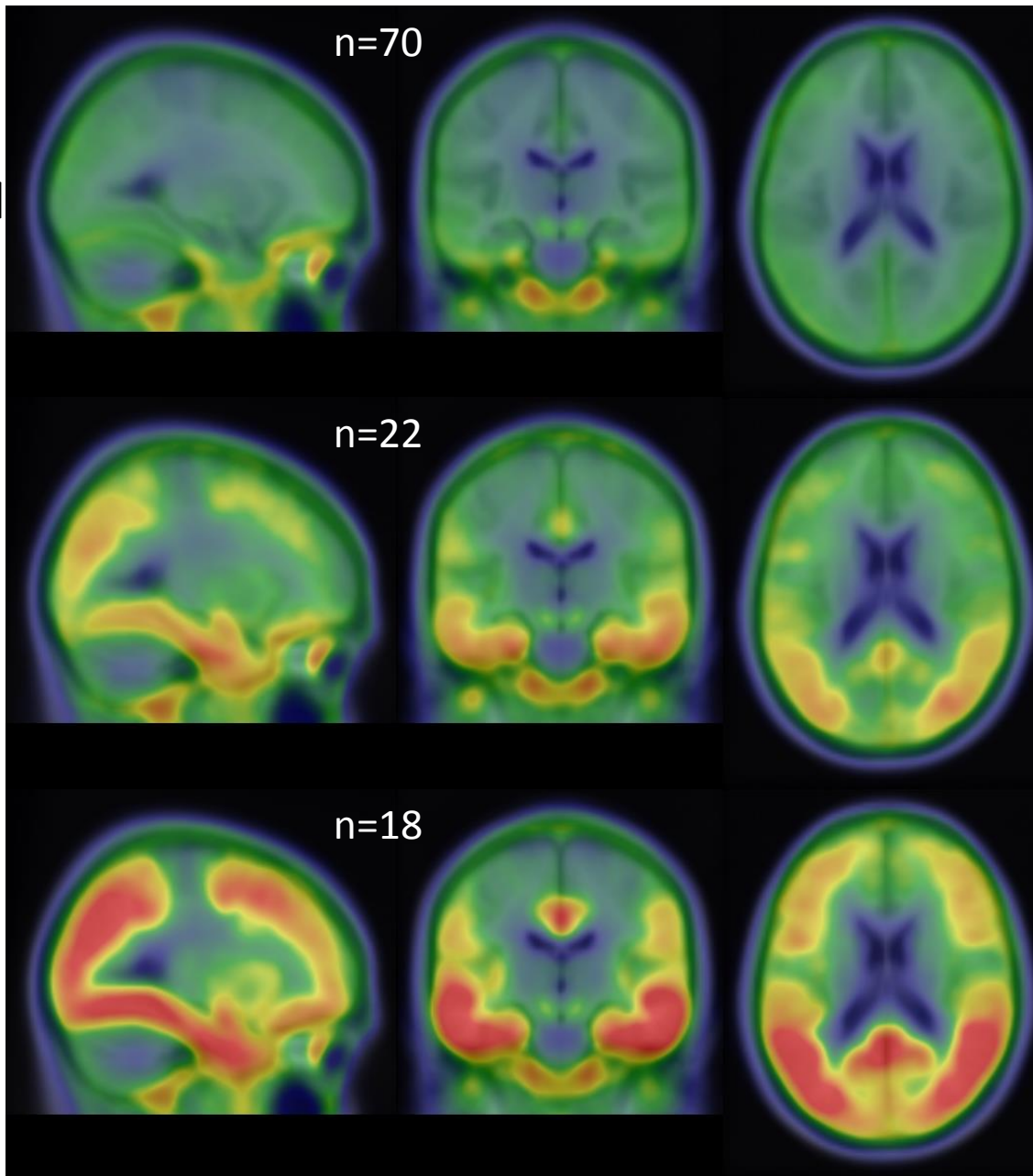
n=18

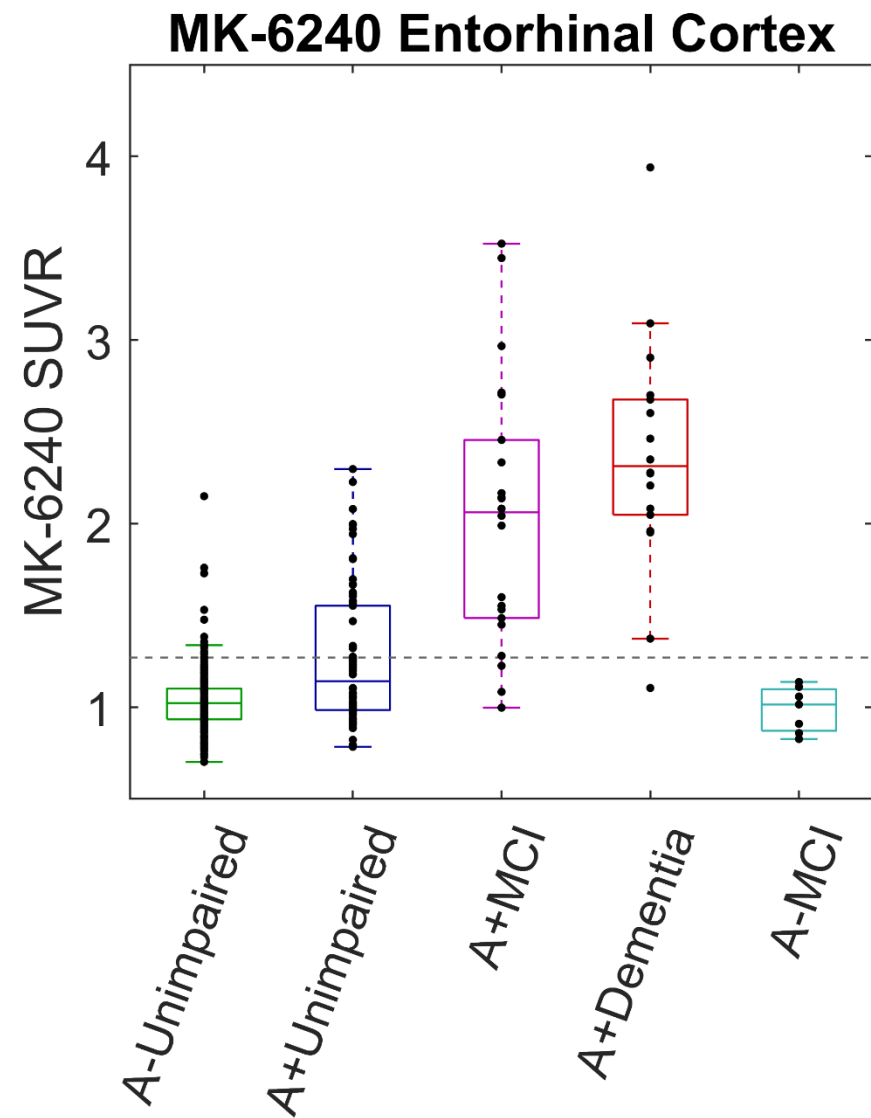
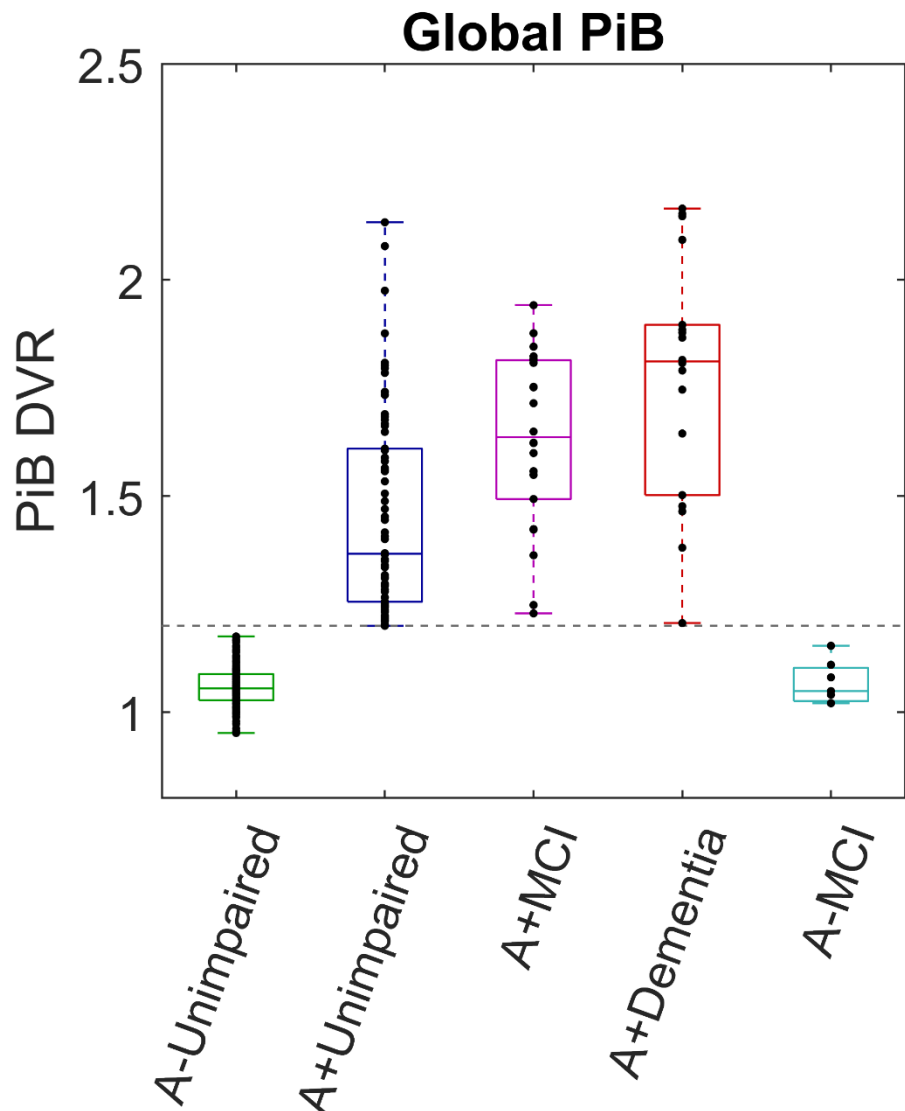
[F18]MK-6240 Tau



Mean MK-6240 SUVR(70-90 min)

N=370





Amyloid PET changes earlier

N=370

Cerebrospinal fluid (CSF) congruence with PET



The NeuroToolKit (NTK) is a panel of exploratory biomarkers on Roche Diagnostics Elecsys[®] platform *Slide from Van Hulle et al CTAD 2019*

- For clinical trials
 - Screening
 - Tracking
- For basic research
 - Data sharing/Collaboration
 - Replication
- For clinic
 - Diagnosis
 - Monitoring

12 assays in CSF in 700 subjects*

Elecsys 601

Amyloid

- A β 42

Tau

- pTau181

(N)eurodegeneration

- tTau

Elecsys 411

- A β 40

Neurodegeneration

- NFL
- alpha-synuclein
- Neurogranin

Glial/Microglial

- sTREM2
- YKL40
- GFAP
- IL-6
- s100B

*The Elecsys[®] CSF assays are not approved for clinical use in the U.S.

Van Hulle et al 2020 *Alz and Dementia*

Rorh et al. *PLoS One* 2016; 11(3): e0149856.

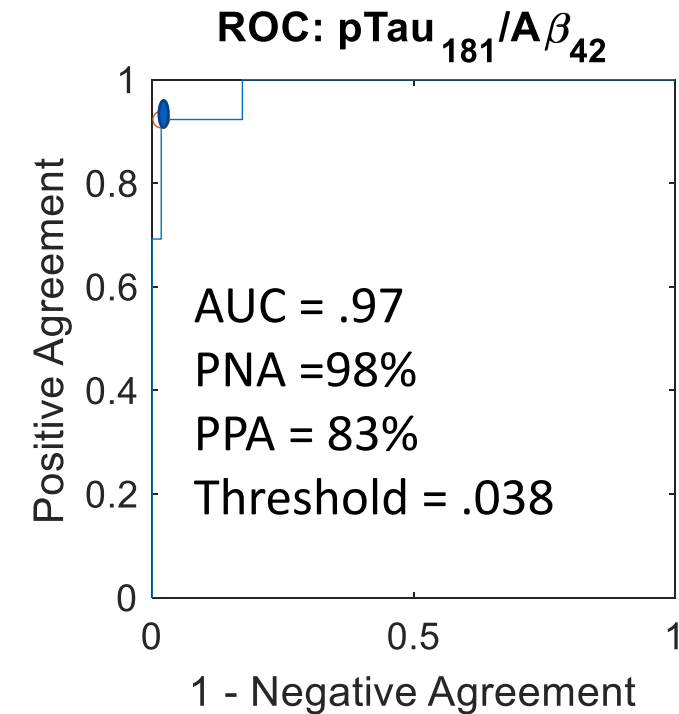
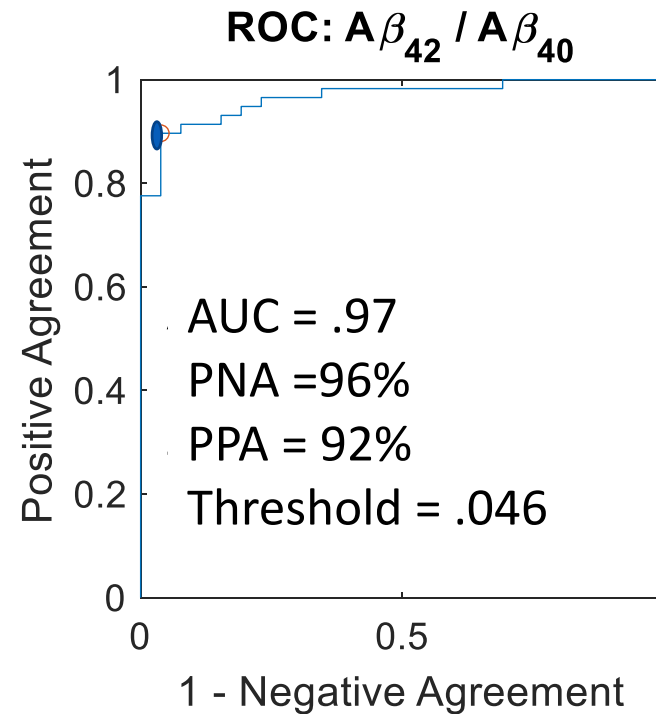
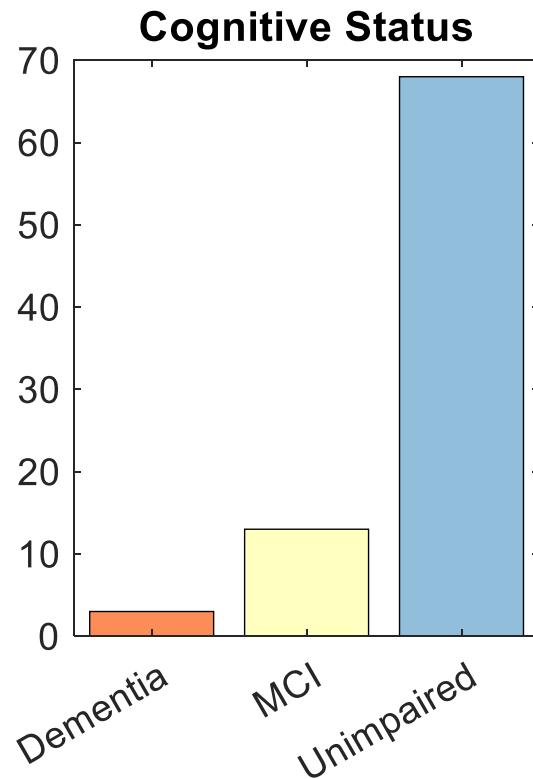
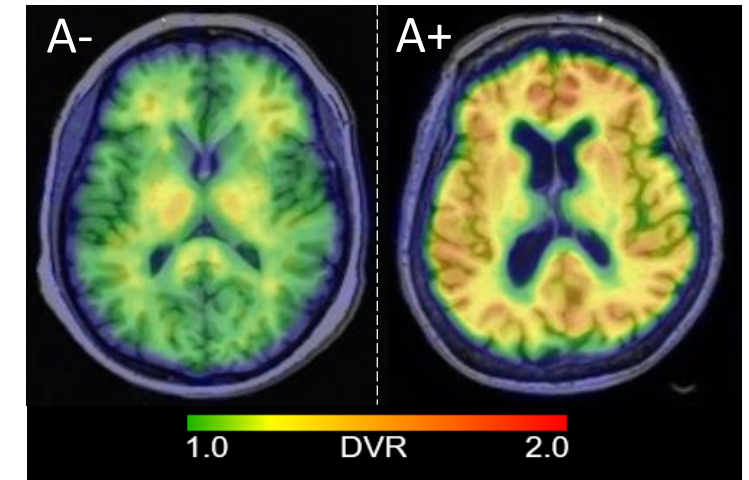
Bittner et al. *Alzheimer's & Dementia* 2016: 12, 517-526

Amyloid PET CSF congruence:

from Van Hulle et al DADM accepted Sept 2020

- $A\beta_{42}/A\beta_{40}$ is a marker of amyloid pathology
- $p\text{Tau}_{181}/A\beta_{42}$ is a joint biomarker of AD pathology
- ROC maximized congruence with PET imaging visual rating of [^{11}C -PiB ($n=185$))

Amyloid PET: [^{11}C]PiB



CSF Amyloid and Tau status by clinical status

- applying the cutpoints established by ROC

$A\beta_{42/40}$

- 92% of dementia cases (46/50) were positive
- 61% of MCI cases (31/54)
- 16% of Cognitively unimpaired (98/604)

$Ptau_{181}/A\beta_{42}$

- 92% of dementia cases (46/50) were positive
- 61% of MCI cases (31/54)
- 11% of Cognitively unimpaired (66/606)

Ratio agreement
 $A\beta_{42/40}$ and $ptau/A\beta_{42}$
agreed 94% of the time



Section 2: Applications of amyloid and tau PET to preclinical AD



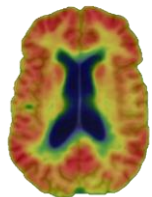
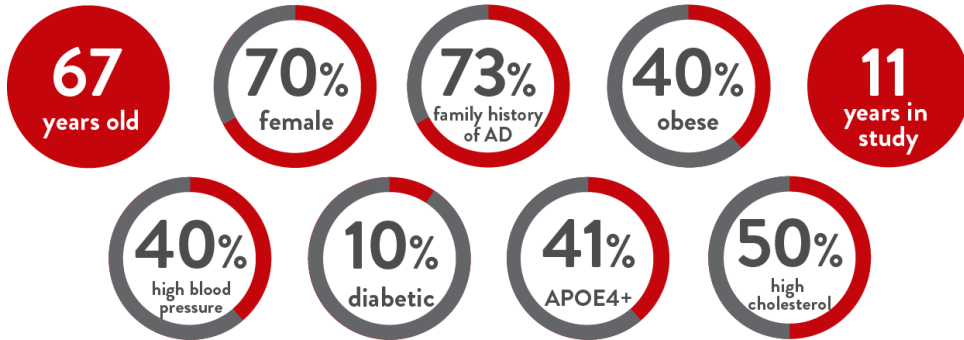
Wisconsin Registry for Alzheimer's Prevention

UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

WRAP: One of the world's largest and longest running studies of individuals at risk for Alzheimer's dementia

Risk from parental family history of dementia presumed due to AD

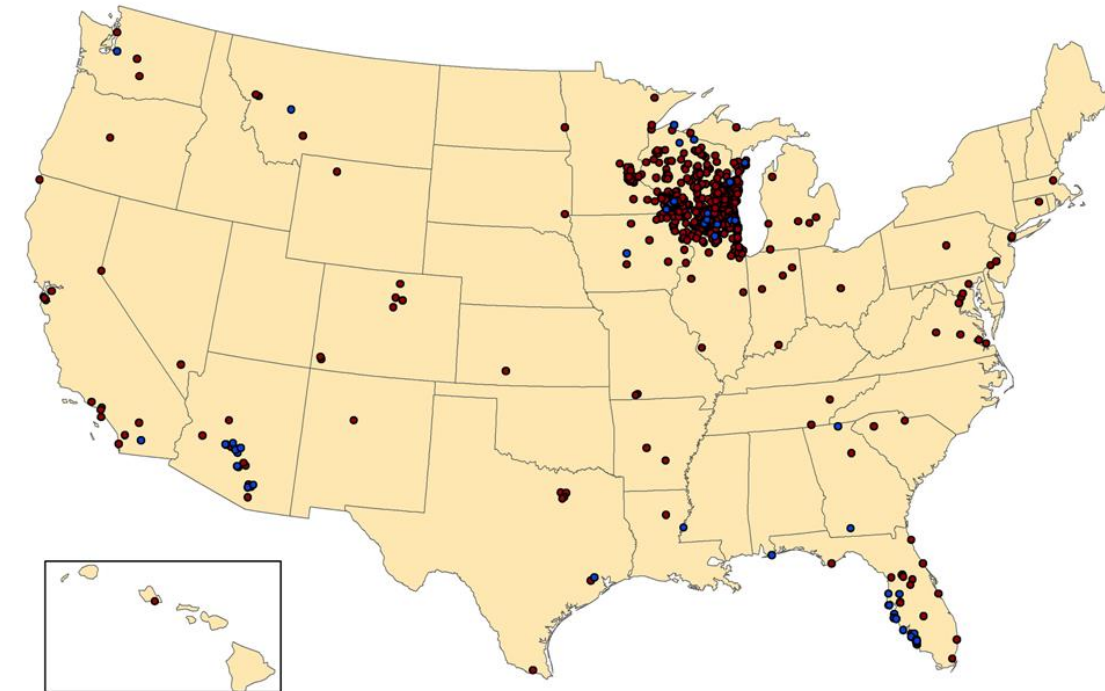
Average WRAP Participant



Current focus on biomarker research

25% have amyloid in their brains

WRAP Participants Come From...



See Johnson et al 2018 *A&D DADM*

DOI: <https://doi.org/10.1016/j.dadm.2017.11.007>



Research Goals



Wisconsin Registry
for Alzheimer's Prevention
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Identify
Alzheimer's
before symptoms

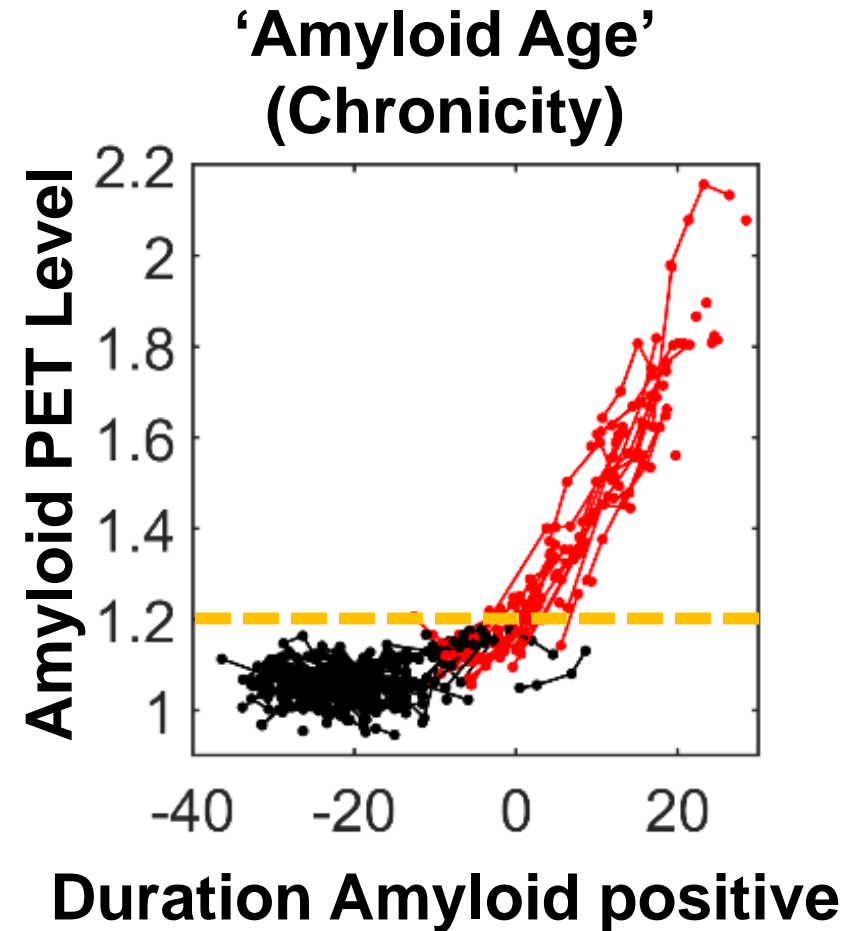
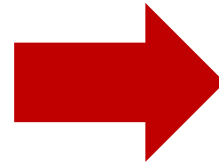
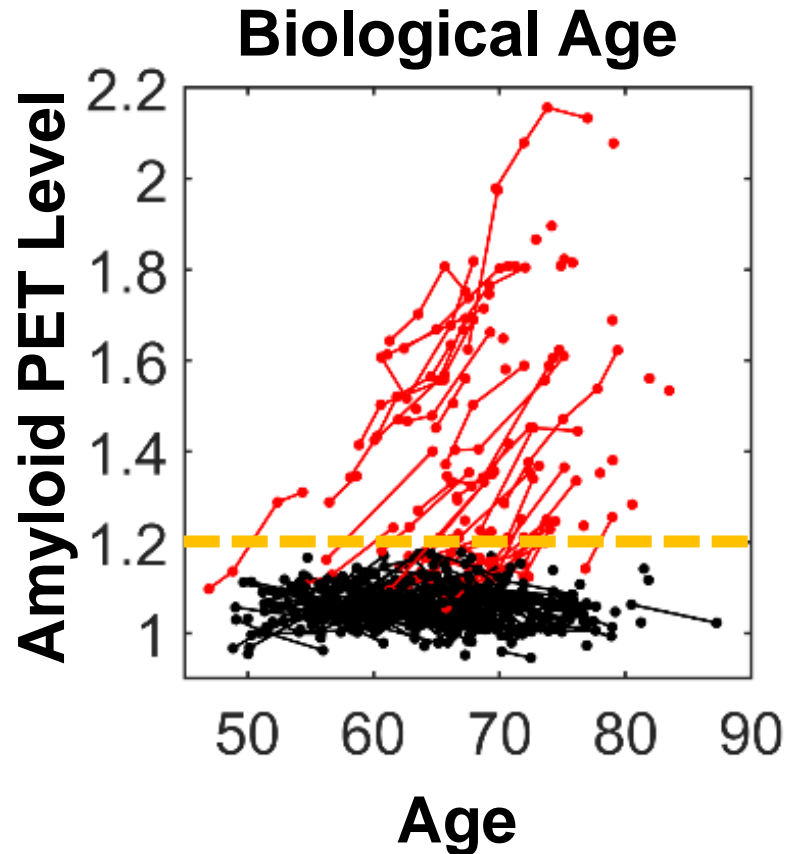
Identify **genetic,**
health, and
lifestyle factors that
prevent Alzheimer's



Wisconsin Alzheimer's
Disease Research Center
UNIVERSITY OF WISCONSIN
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Biomarker Core

When amyloid starts



- Slopes of amyloid accumulation are uniform > age of onset is estimable! chronicity (years with amyloid positivity) is estimable!

Case example

Demographics

Female, APOE-e3e3

Baseline Age 54, last WRAP
assessment Age 64

- 5 visits and 10 years of follow-up
- Paternal and maternal history of dementia

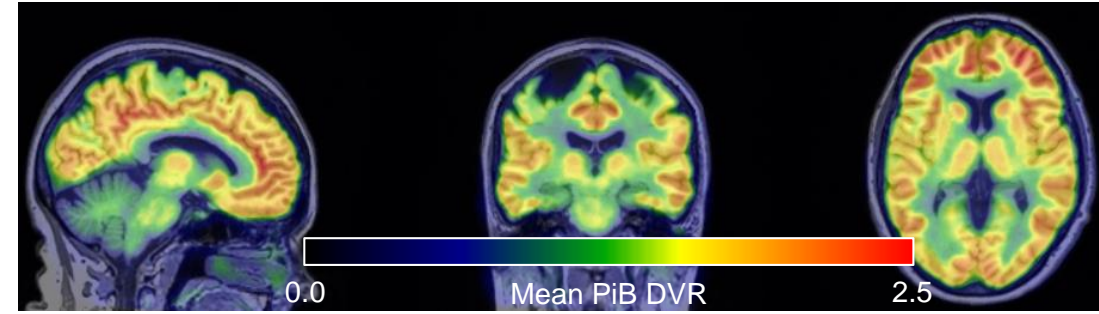
Baseline IQ - 120

MK-6240 and PiB PET at Age 64

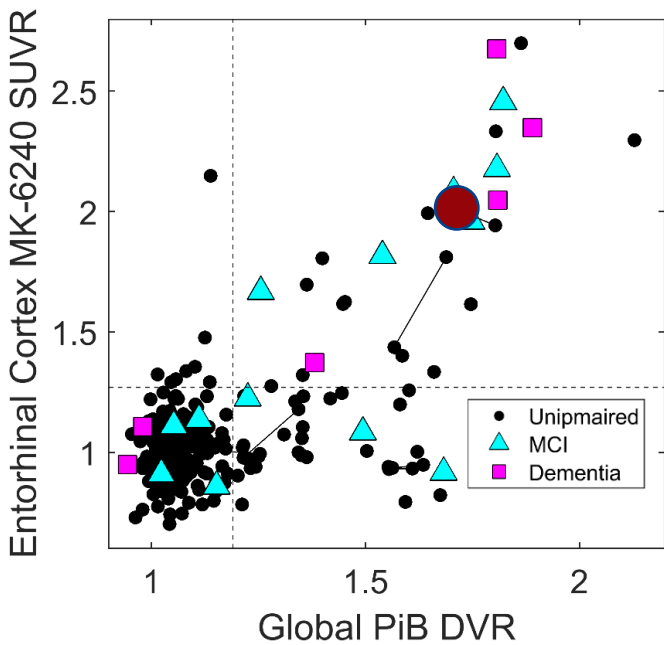
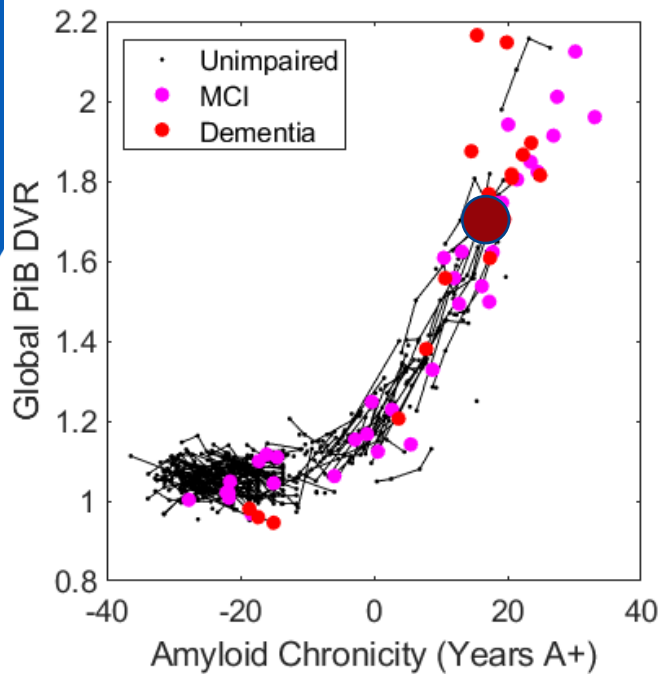
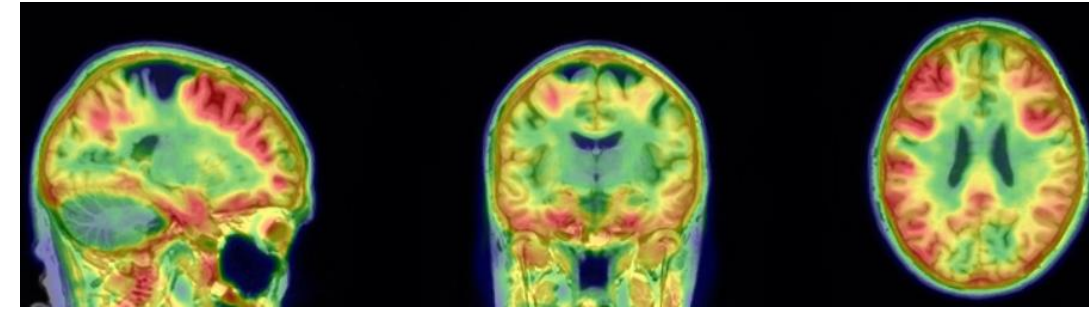
- Entorhinal SUVR = 2.08
- Global DVR = 1.73
- Est Duration A+ = ~18 years
- **Est Age A+ = 47**

Cognitively normal and stable for 10 years!! When will decline be evident?

PiB Amyloid PET DVR



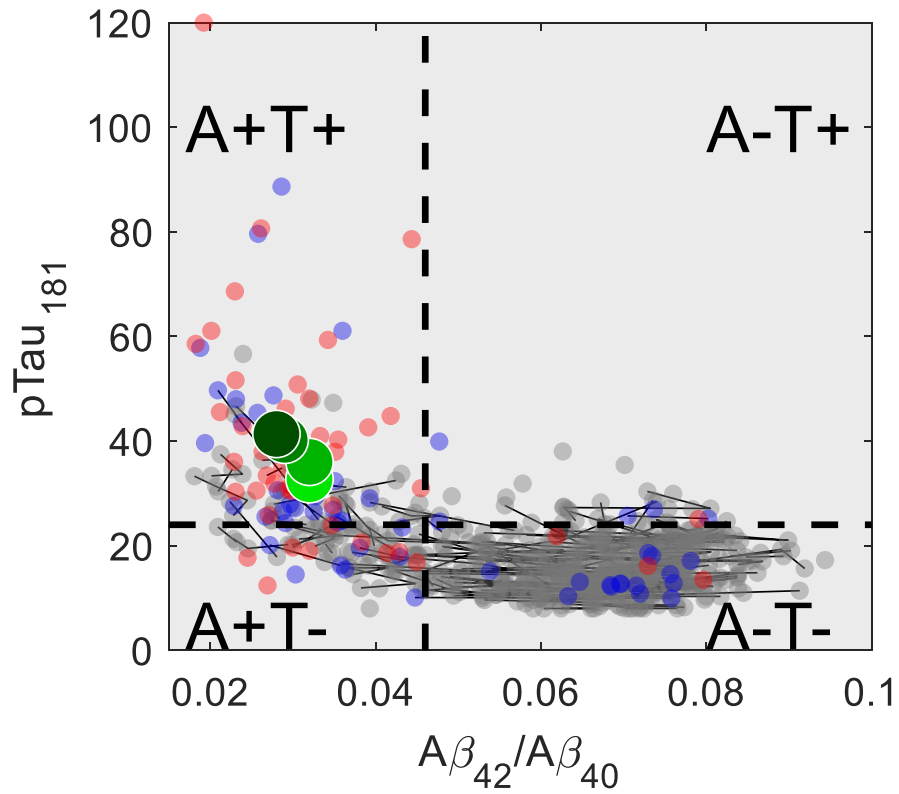
MK-6240 Tau PET SUVR



Consensus diagnosis of advanced MCI at age 74

Slide courtesy of Tobey Betthausen, PhD

NTK CSF Results

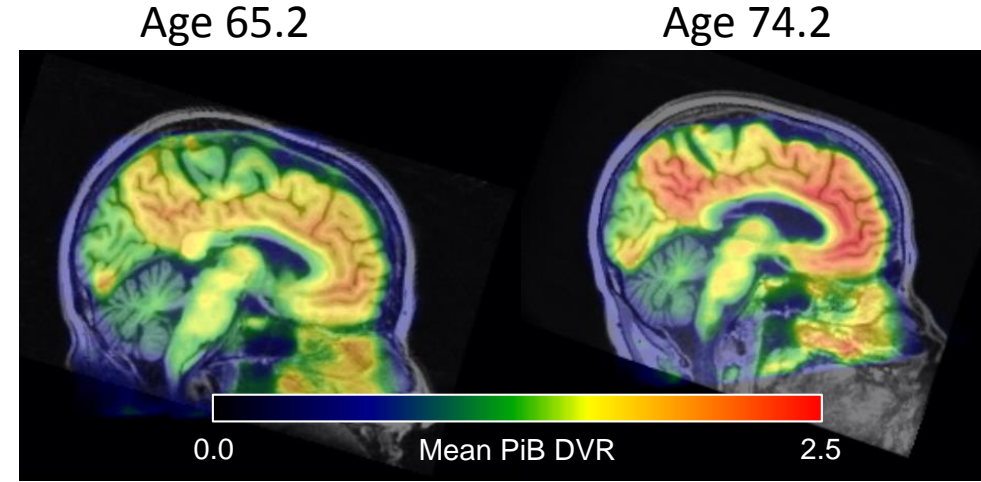


- Unimpaired
- MCI
- Dementia

Age	PET	CSF
65.2	A+	A+T+
67.28	A+	A+T+
69.07	A+	A+T+
70.28	-	A+T+
72.04	A+T+	-
74.15	A+T+	-

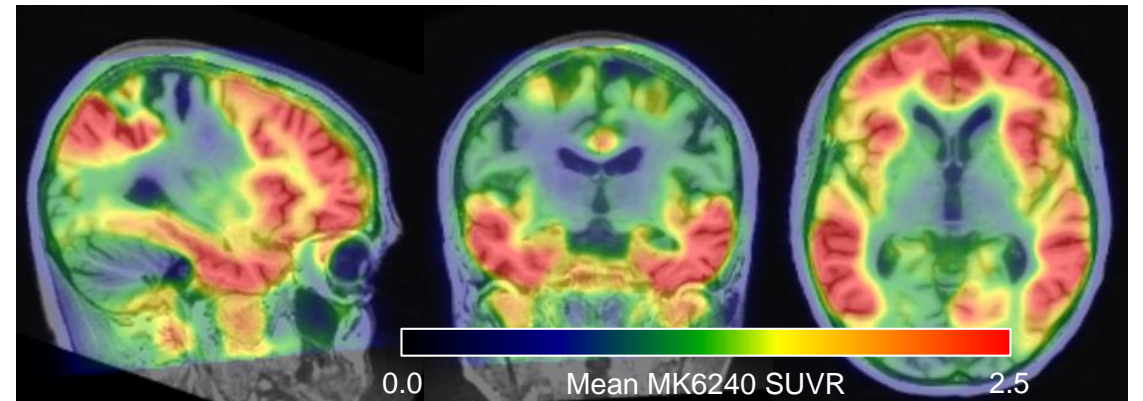
Est PiB(+) Age = 50.6 years

PIB

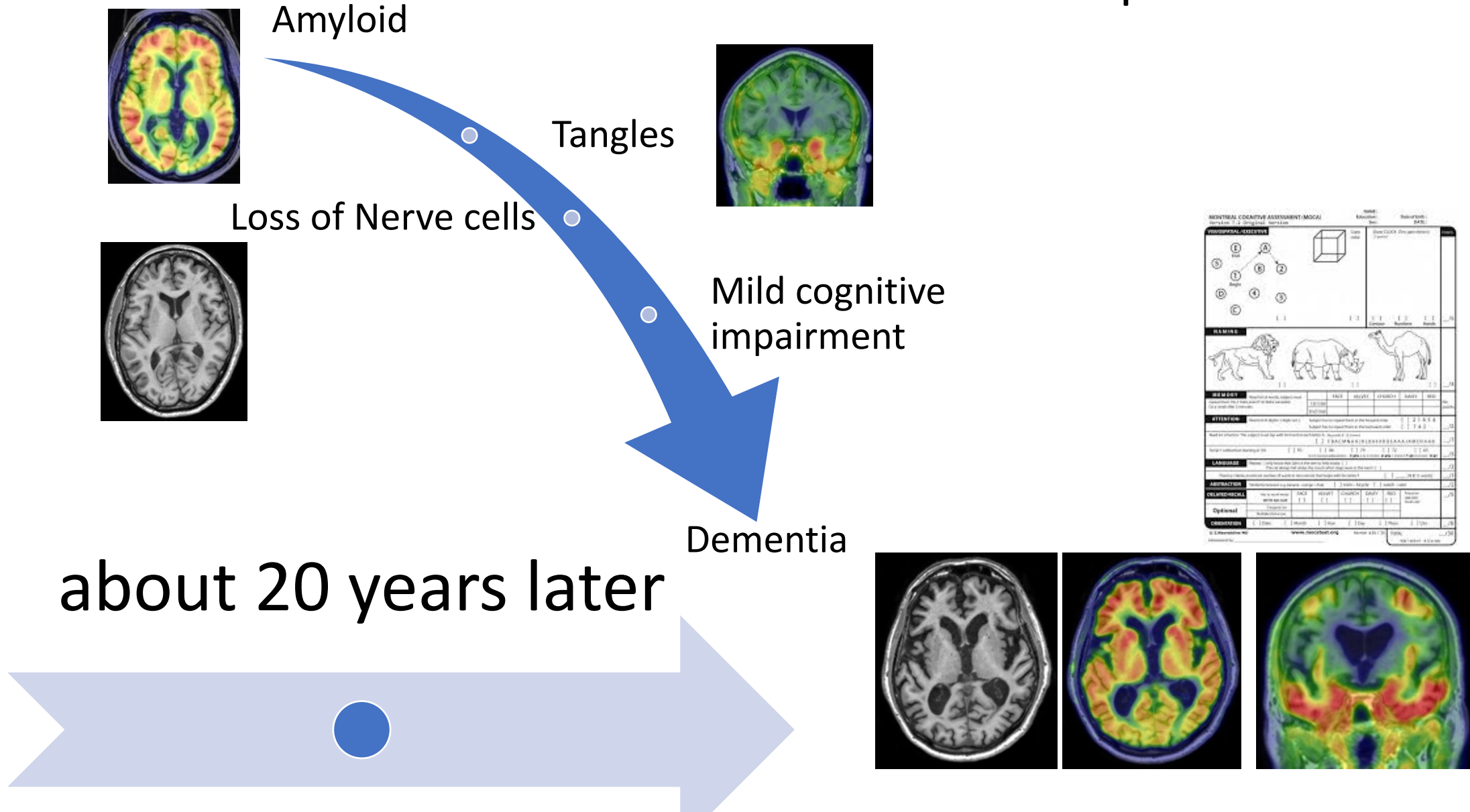


MK-6240

Age 74.2



HOW & WHEN does dementia develop?



**Three studies:
How does A⁺ and A+ chronicity relate
to cognitive decline and health
factors in WRAP?**

Betthausen et al., 2020, *Brain*

Birdsill (in preparation)

Cody (in preparation)



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Betthausen et al 2020

- All healthy and cognitively normal adults from WRAP
- Do A/T groups differ in their cognitive trajectories?
- Cognitive outcome was a composite of memory and executive function tests



Results: Demographics at PET

	A-T- (n=124)	A-T+ (n=5)	A+T- (n=23)	A+T+ (n=15)	Group P-Val	Total (N=167)
Demographics						
Age at Most Recent Cognitive Assessment (yrs)	<u>65.7 ± 6.4</u>	72.0 ± 6.0	69.3 ± 4.9*	69.9 ± 4.5	0.001 §	66.7 ± 6.3
% Female	67.7	100	60.9	80.0	0.27‡	68.9
% Non-Caucasian	8.1	0.0	4.3	0.0	0.57‡	6.8
% Family History of Dementia	70.2	100.0	69.6	93.3	0.13‡	73.1
WRAT-III Reading Score	109 [103,115]	104 [99, 115]	111 [106, 115]	109 [105, 113]	0.73†	110 [103, 114]
% Carriers	33.3**	20.0*	<u>65.2</u>	<u>86.7</u>	<0.001‡	42.5
<i>APOE-ε4</i> % Non-Carriers	66.7**	80.0*	<u>36.4</u>	<u>13.3</u>		58.2
% Heterozygous	31.7**	20.0*	<u>54.5</u>	<u>66.7</u>	<0.001‡	37.6
% Homozygous	1.6**	0.0*	9.1	20.0		4.2

† Kruskal-Wallis ‡ χ^2

- Age Difference (A-T- and A+T-)
- No difference in WRAT-III, sex, race, or family history
- Significant difference in *APOE-ε4* status

Results: Group Mean Images

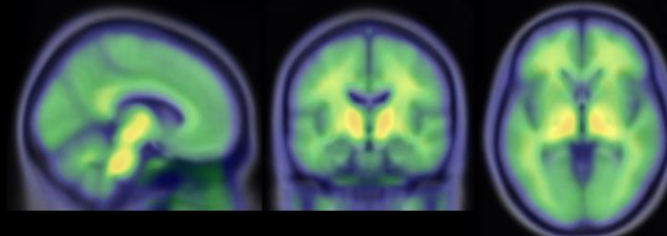
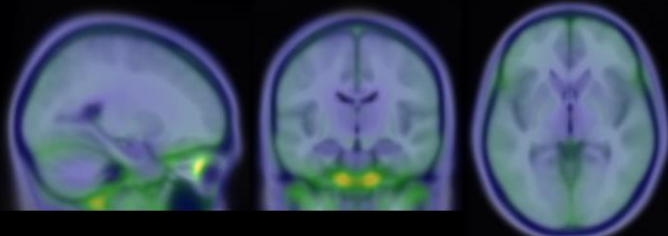
Betthausen et al 2020, *Brain*



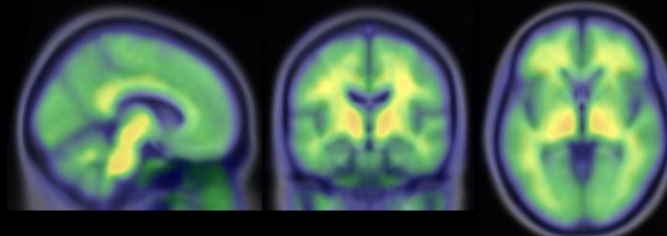
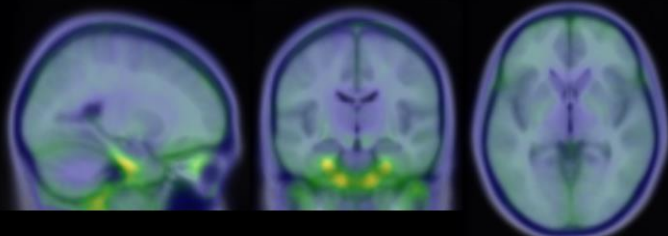
MK-6240

PiB

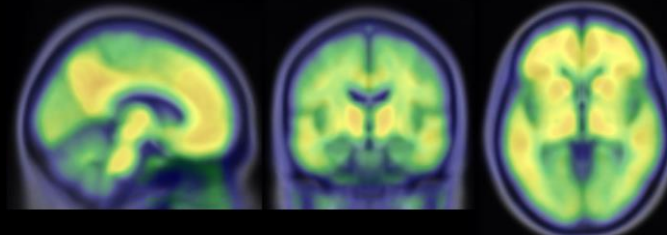
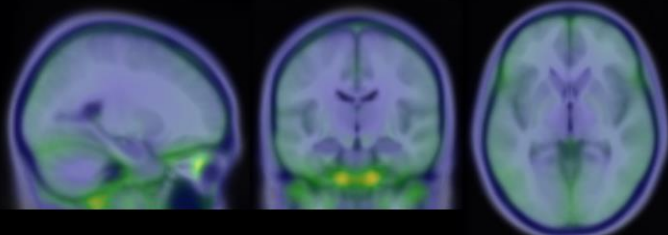
A-/T-
n=124



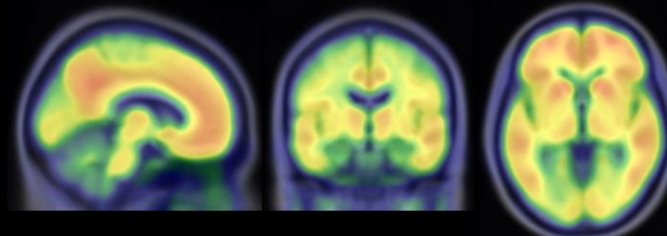
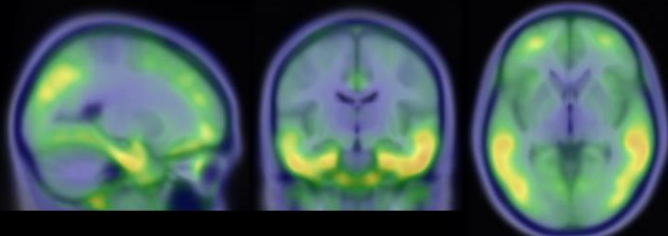
A-/T+
n=5



A+/T-
n=23



A+/T+
n=15



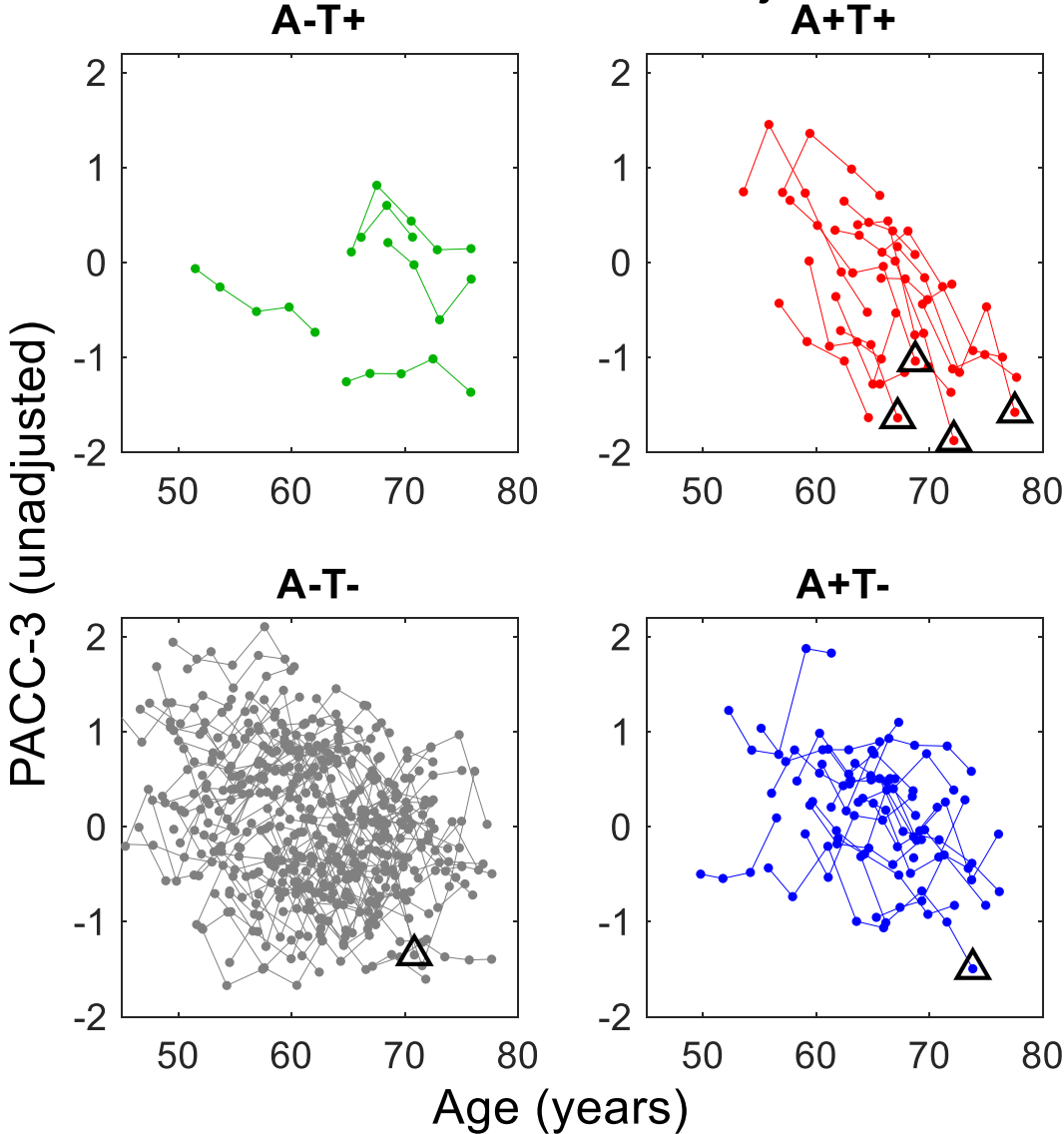
- A-T+ only positive in entorhinal cortex
- A+T+ elevated SUVR in Braak regions I-V
- A+T+ higher PiB DVR than A+T-
- minimal off target brain signal

Results: Retrospective PACCC-3 and A/T Groups



Betthausen et al 2020, *Brain*

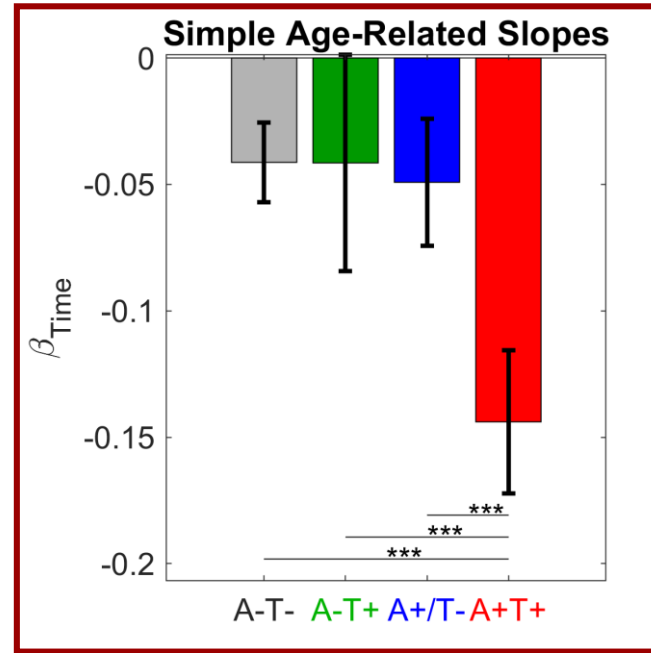
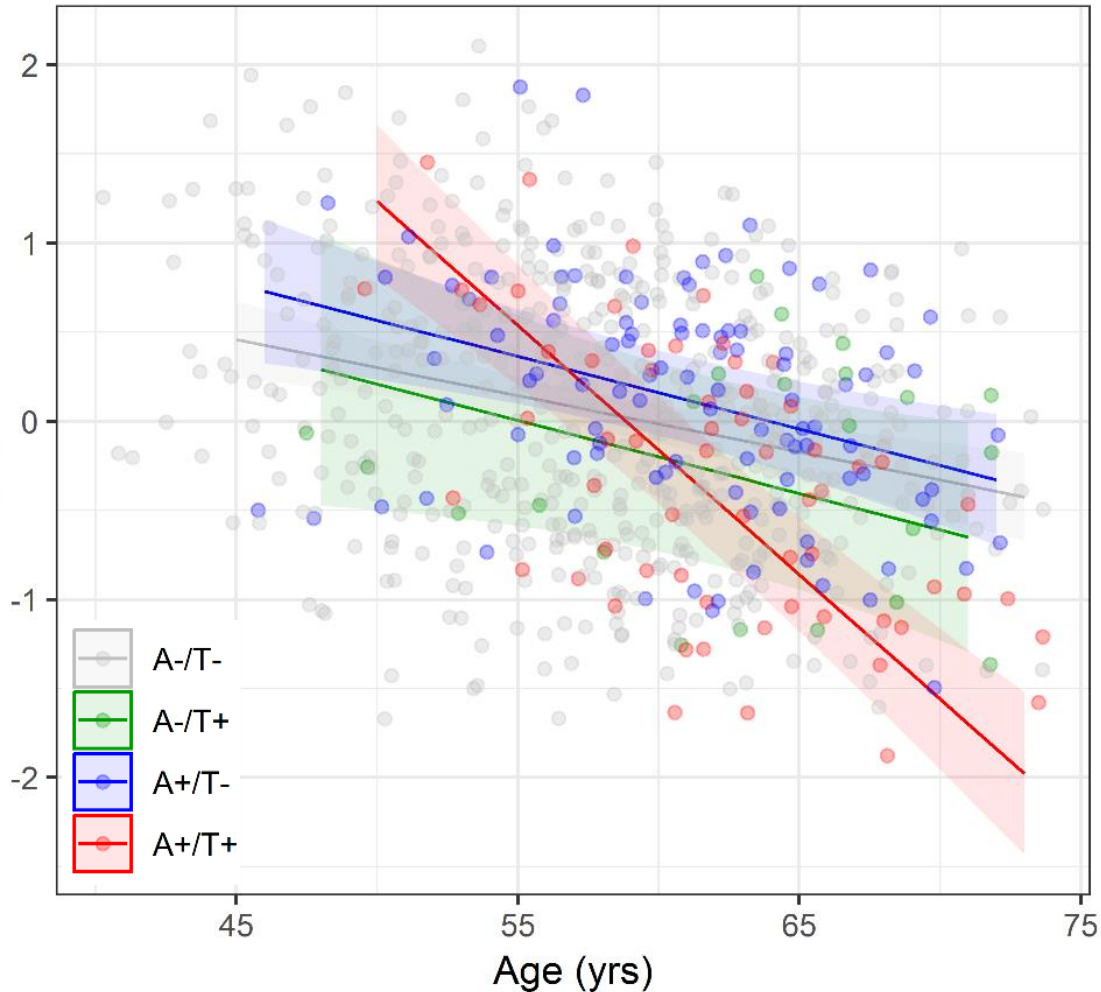
Observed PACCC-3 Trajectories



Results: Retrospective Cognitive Decline by Biomarker Group



Modeled Cognitive Trajectories by Biomarker Group



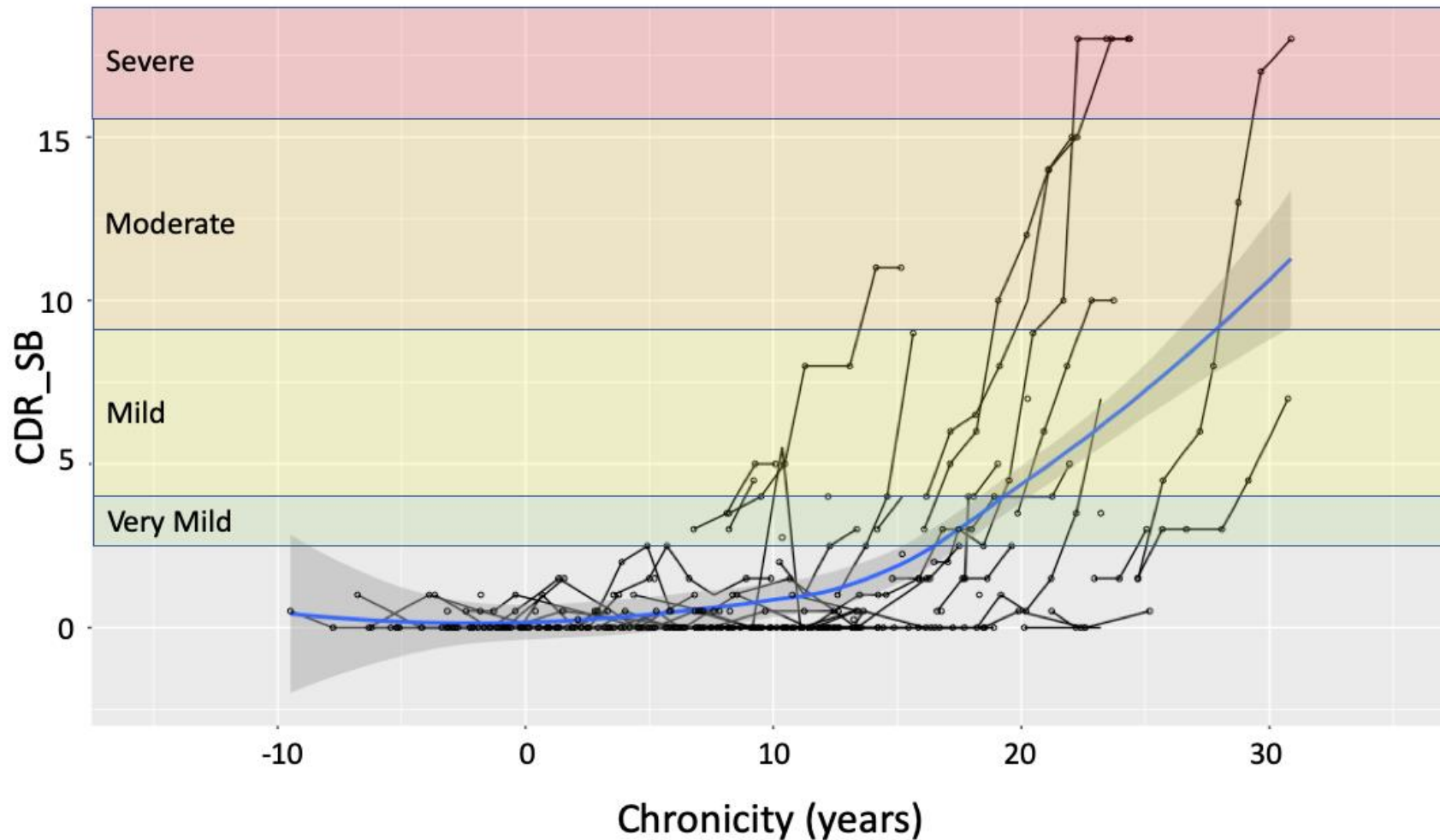
- Significant Group \times Time Effect
- +/- ~3x faster decline than -/-



Other results

- Neurodegeneration
 - Marginally more MRI hippocampal volume loss in A+T+ group
- Health and vascular features
 - No meaningful differences at WRAP baseline or at time of later PET
 - BMI, WHR, cholesterol, blood pressure, blood glucose, Vit B12

Study 2: Amyloid duration is related to clinical dementia rating sum of boxes (CDR-SB)



Study 3: What increases or decreases risk for AD and its cognitive syndrome of dementia?

Do

- Hypertension
- Sleep
- Physical Activity
- Stress / Mood
- Neighborhood
- Diet
- Inflammation
- Cognitive Activity
- Social Support
- Genetics

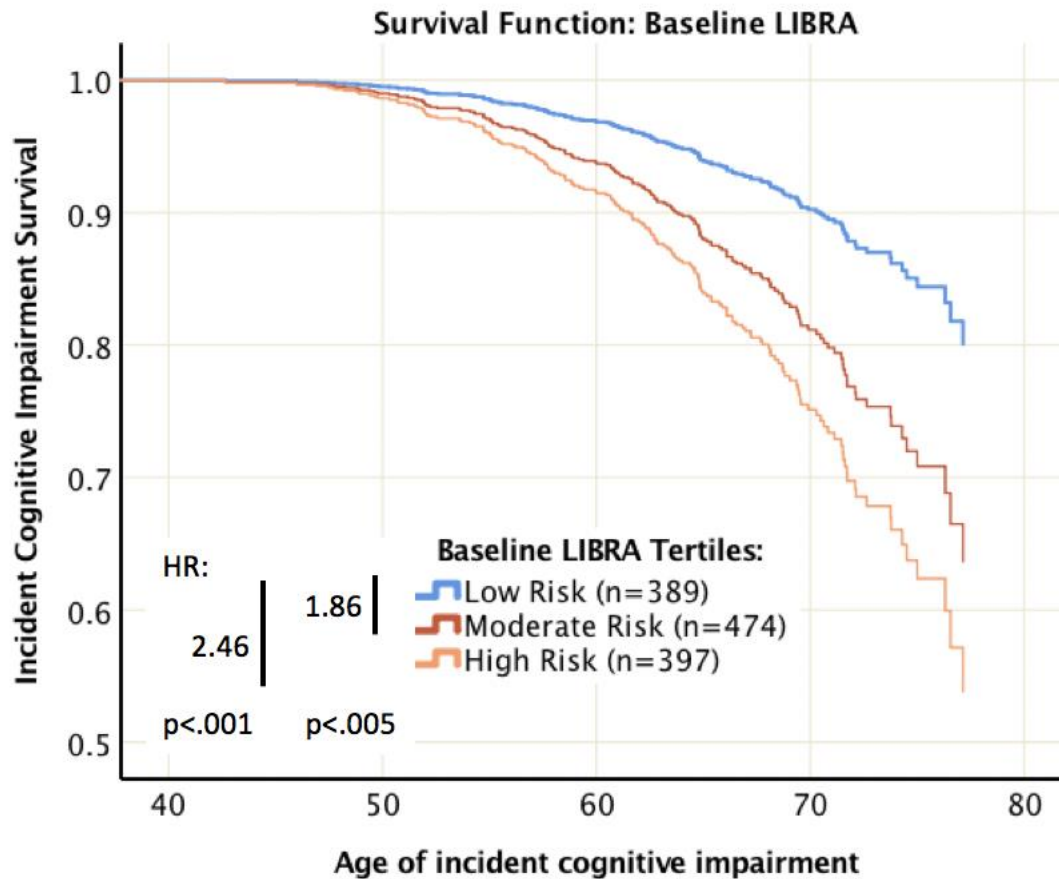
prevent or slow
amyloid burden
or cognitive
symptoms ??

The Lifestyle for Brain Health (LIBRA) index

Deckers et al 2020

Table: Factor scores and definitions used to calculate the LIBRA index

	Definition	Score
<i>Modifiable factors</i>		
Low/moderate alcohol use	Self report, drink < 2 units/day (including non-drinkers)	-1.0
Cardiovascular disease	Self report, history of heart attack, recurrent chest pain with exercise, or coronary bypass	+1.0
Physical inactivity	Self report, < 30 minutes of moderate exercise 5 days/week or < 7.5 MET hours/week ^a	+1.1
Renal dysfunction	Kidney disease diagnosis or estimated glomerular filtration rate < 60 ml/min/1.73m ^{2b}	+1.1
Diabetes	Diabetes diagnosis or fasting glucose ≥ 126 mg/dL	+1.3
High cholesterol	Hypercholesterolemia diagnosis or total serum cholesterol ≥ 240 mg/dL	+1.4
Smoking	Self report of smoking in the past month	+1.5
Obesity	Body mass index ≥ 30	+1.6
Hypertension	Hypertension diagnosis or SBP ≥ 130mmHg / DBP ≥ 80mmHg	+1.6
Depression	Sum score ≥ 16 on the Center for Epidemiologic Studies-Depression Scale	+2.1
High cognitive activity	Games score ≥ 4, on the Cognitive Activity Scale	-3.2
<i>Non-modifiable factors</i>		
Age		
Sex		



LIBRA results

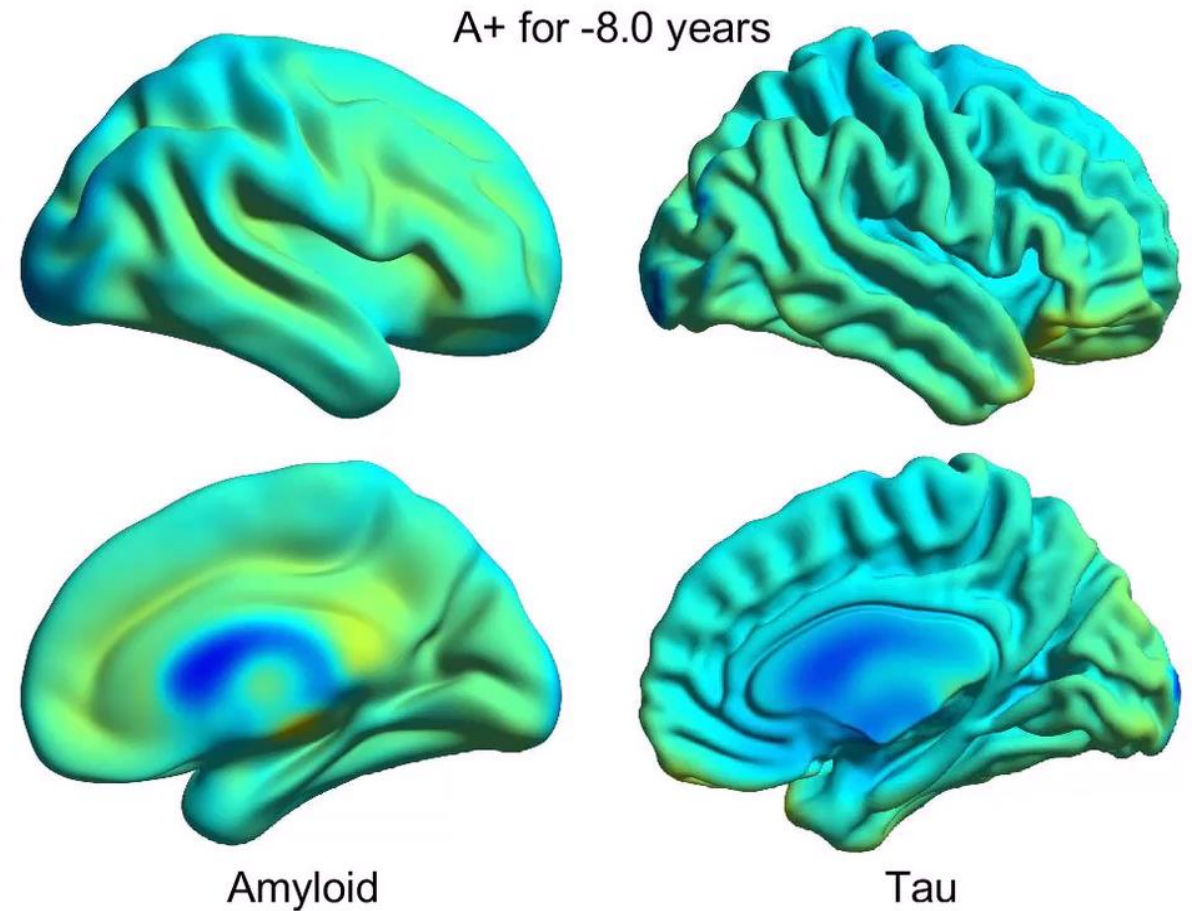
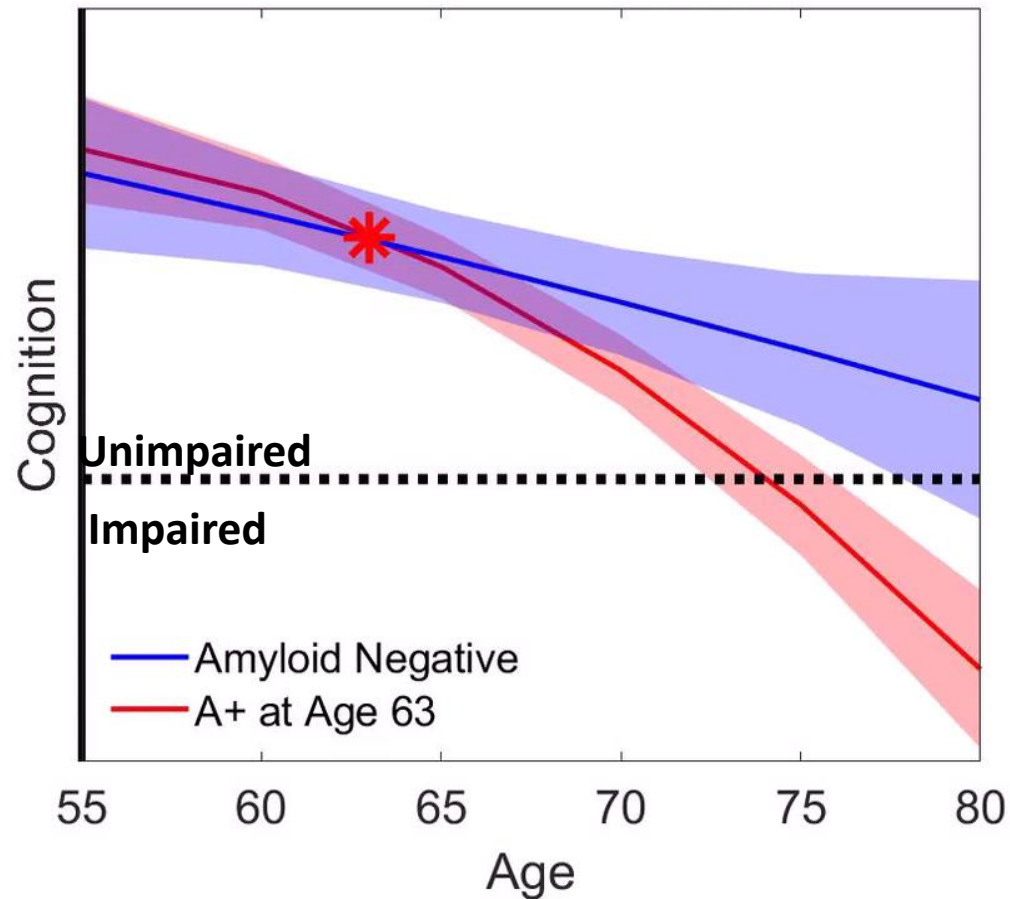
Cody et al, in preparation

- Poorer lifestyle is related to cognitive decline over time
- *Not* related to amyloid PET rate of progression
- *Not* related to onset age or duration of amyloid PET
- It is possible that modifiable factors may confer brain resilience to dementia in the presence of amyloid;
 - but they don't affect amyloid itself

Outcome measure	Risk index	HR (95% CI)	p-value ^b
Incident cognitive impairment ^a (n=1244)	Baseline LIBRA	1.18 (1.10, 1.27)	<0.001
	Baseline LIBRA Risk Tertiles: Low (reference)	--	--
	Moderate	1.86 (1.20, 2.86)	0.005
	High	2.46 (1.60, 3.78)	<0.001

Note: HR, hazard ratio.
^aIncident cognitive impairment was defined as 1.5 SD below mean performance on a covariate-adjusted PACC-3
^bTertiles, p-value for significant difference from low risk (reference) category

Piecing the Puzzle Together



Summary

- AD begins in midlife
- AD is detectable with biomarkers
- Amyloid in the brain accrues slowly, is not benign
- The longer you have had it (chronicity), the more likely you are to exhibit cognitive decline
- The AT(N) framework (at least the A and T parts) works!
 - But binarizing overlooks important temporal info
- Lifestyle and health factors influence cognition, but not amyloid proteinopathy (what about tau?)

Thank you

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