

GLOBAL RESEARCH & MEDICAL CARE ROUNDTABLE– JUNE 27, 2019

Alzheimer's Disease and Down Syndrome: Research Today and What the Future May Hold

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BACKGROUND

- Extra copy of chromosome 21 (trisomy 21), on which the APP gene resides.
- Glenner and Wong - plaques in AD same as plaques in DS (beta-amyloid).
- By the age of 40, virtually all people with DS show AD-related neuropathological changes including plaques and tangles. By the age of 65, about 80% have dementia¹.
- Dementia is cause of death in 70% of people with DS over age 35.
- There are 6 million people with DS worldwide.
- APP – Disomic in DS– NO AD

1. Head et al, 2012

DOWN SYNDROME – DEMOGRAPHICS

1/695 live births in US
~450,000 with DS in US
~6 million worldwide

Life Expectancy

10 yrs born in 1961
25 yrs born in 1983
49 yrs born in 1997
61 yrs born in 2005
65 yrs born in 2010

CDC MMWR, 2007

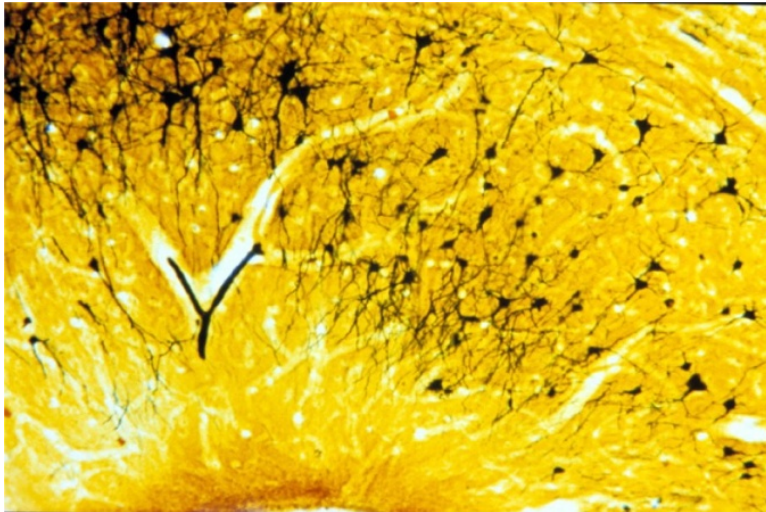
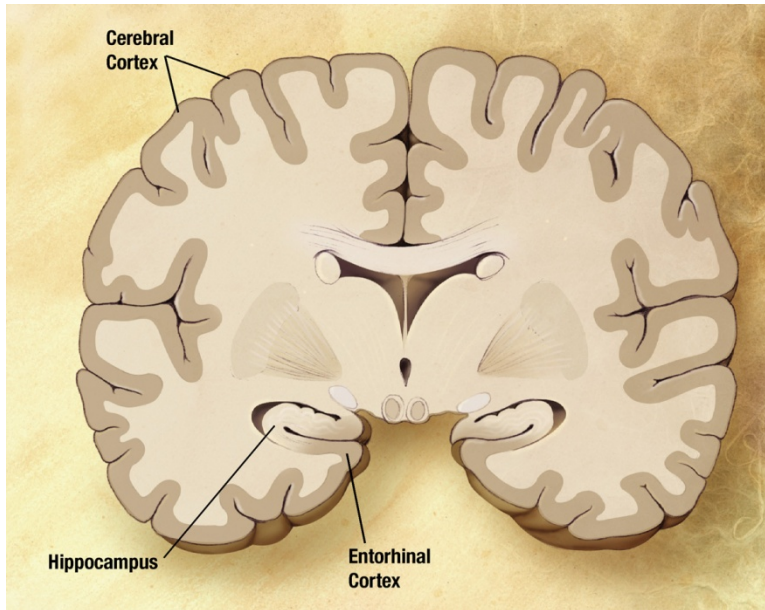
Dementia in Down Syndrome

Age Specific Rates

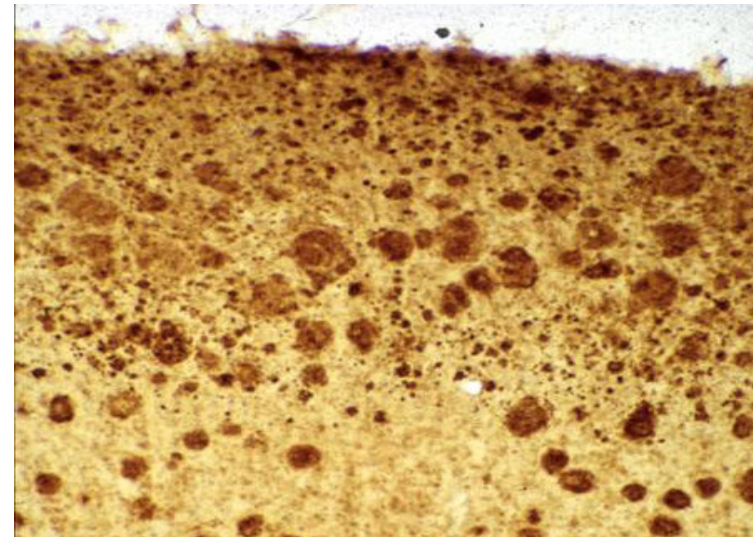
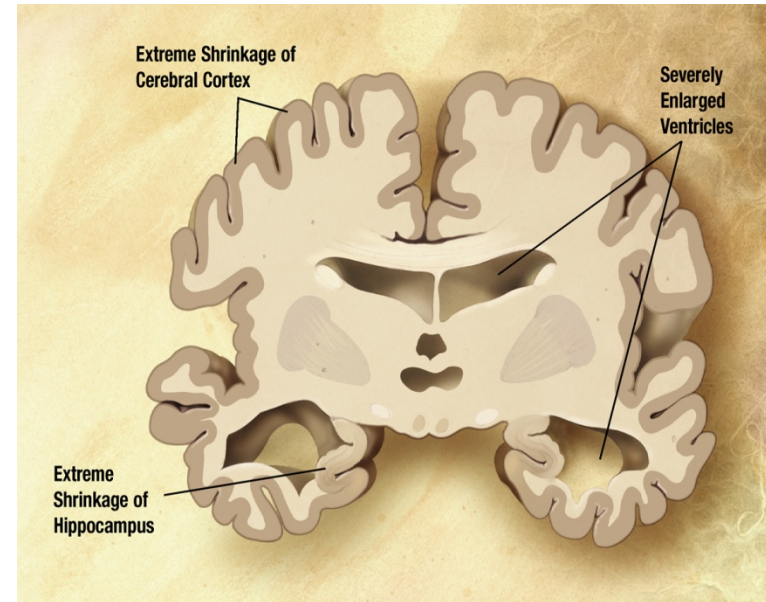
40-49 Years: 9.4%
50-59 Years: 50.1%
60-69 Years: 80.4%

Day et al, 2005

Healthy Brain

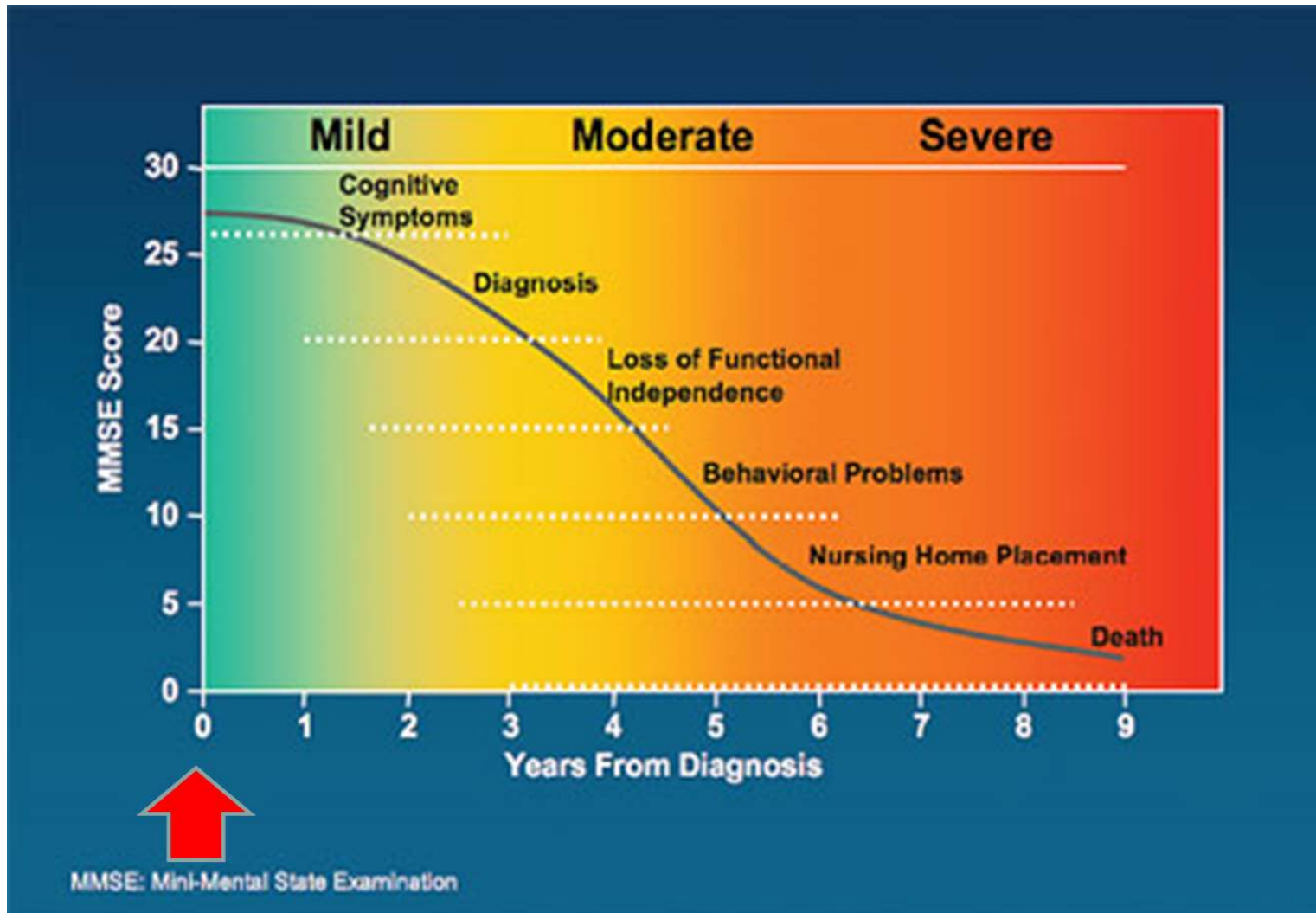


AD Brain

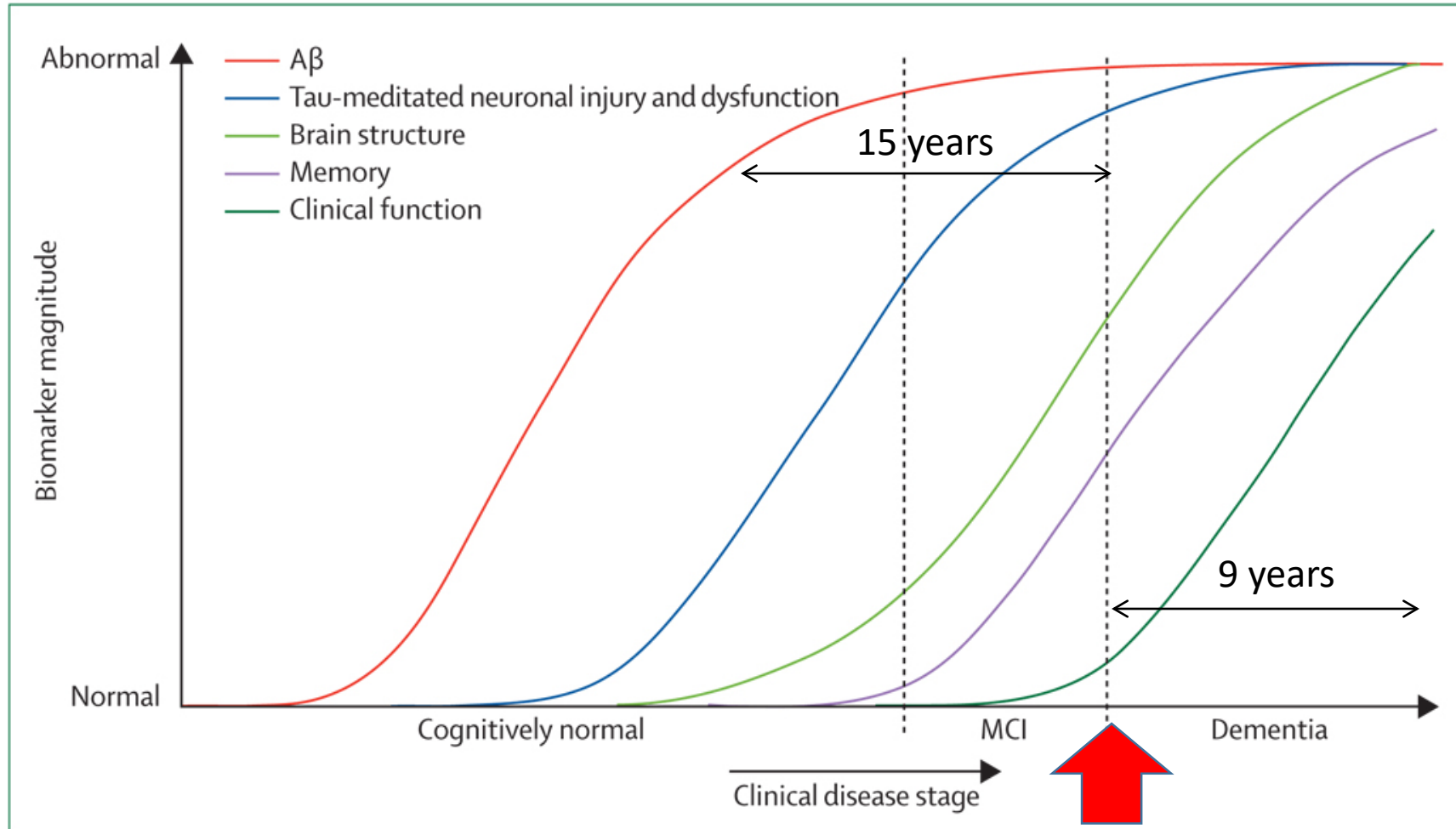


Plaques and Tangles
define Alzheimer's disease

CLINICAL STAGES OF ALZHEIMER'S DISEASE



CLINICAL STAGES OF ALZHEIMER'S DISEASE



Jack et al, Lancet 2009. ADNI Biomarkers in normal aging , MCI and AD

Treatment

Preclinical/
Prodromal



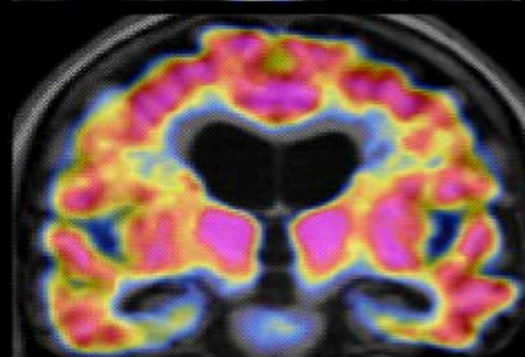
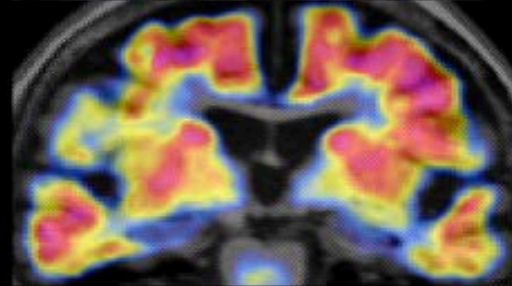
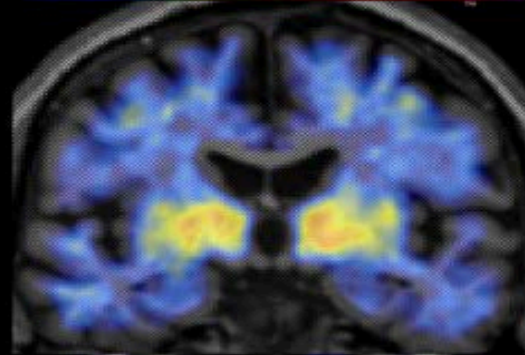
Clinically
Normal
 $A\beta$ -neg

Clinically
Normal
 $A\beta$ -pos

AD
Dementia
 $A\beta$ -pos

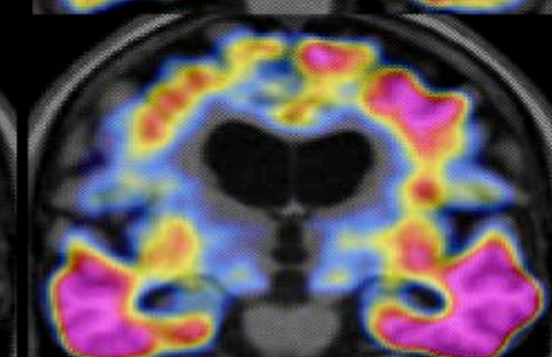
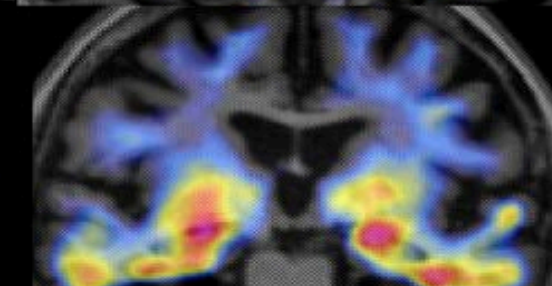
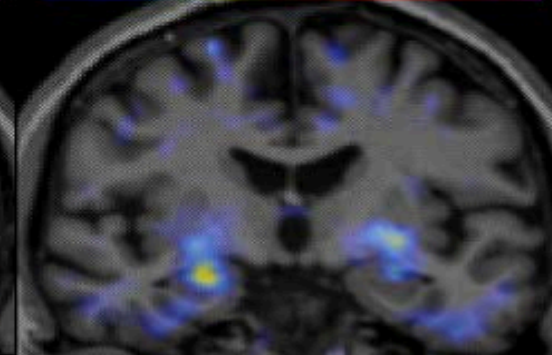
PiB $A\beta$

DVR=1.0 2.0

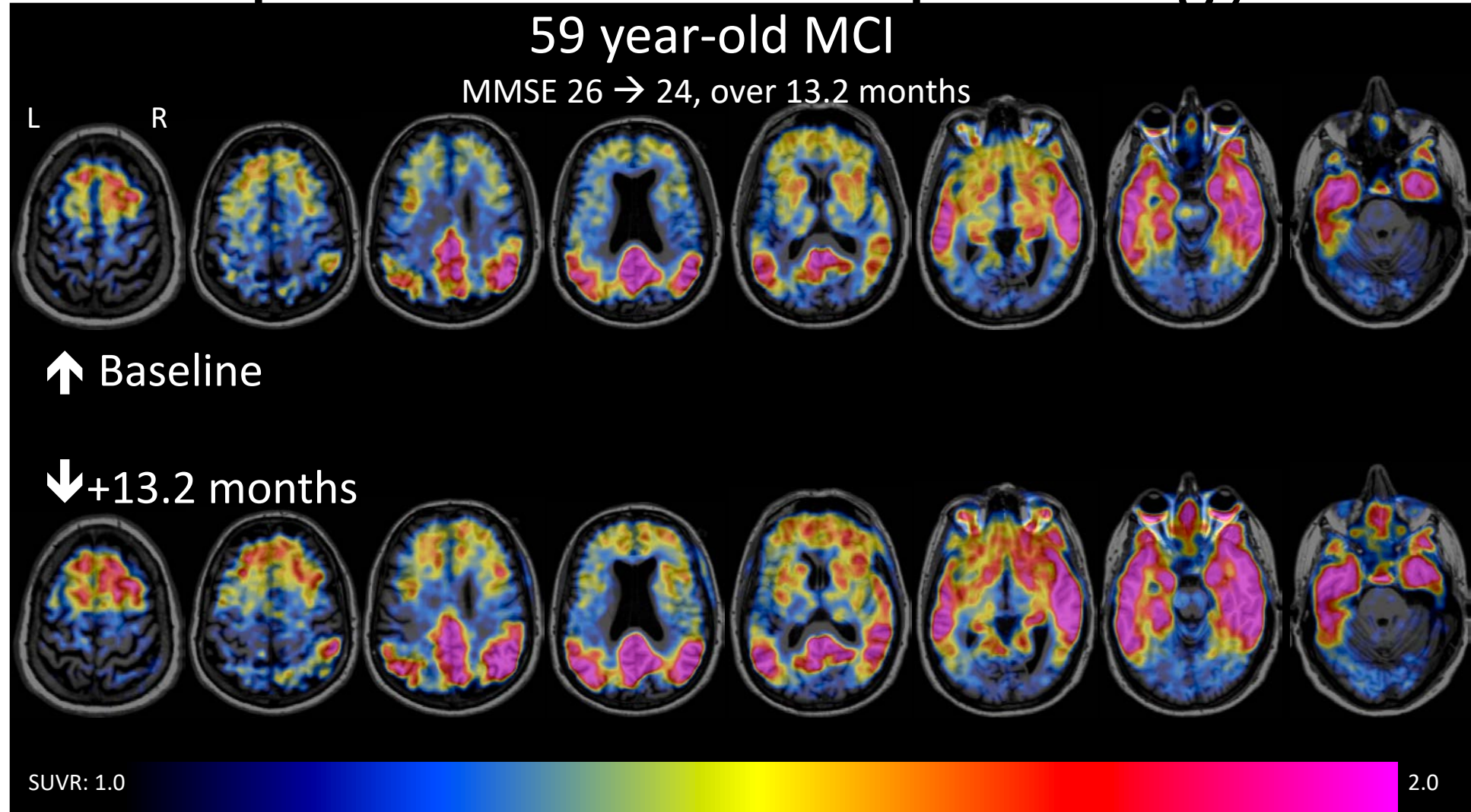


T807 Tau

SUVr=1.0 2.0



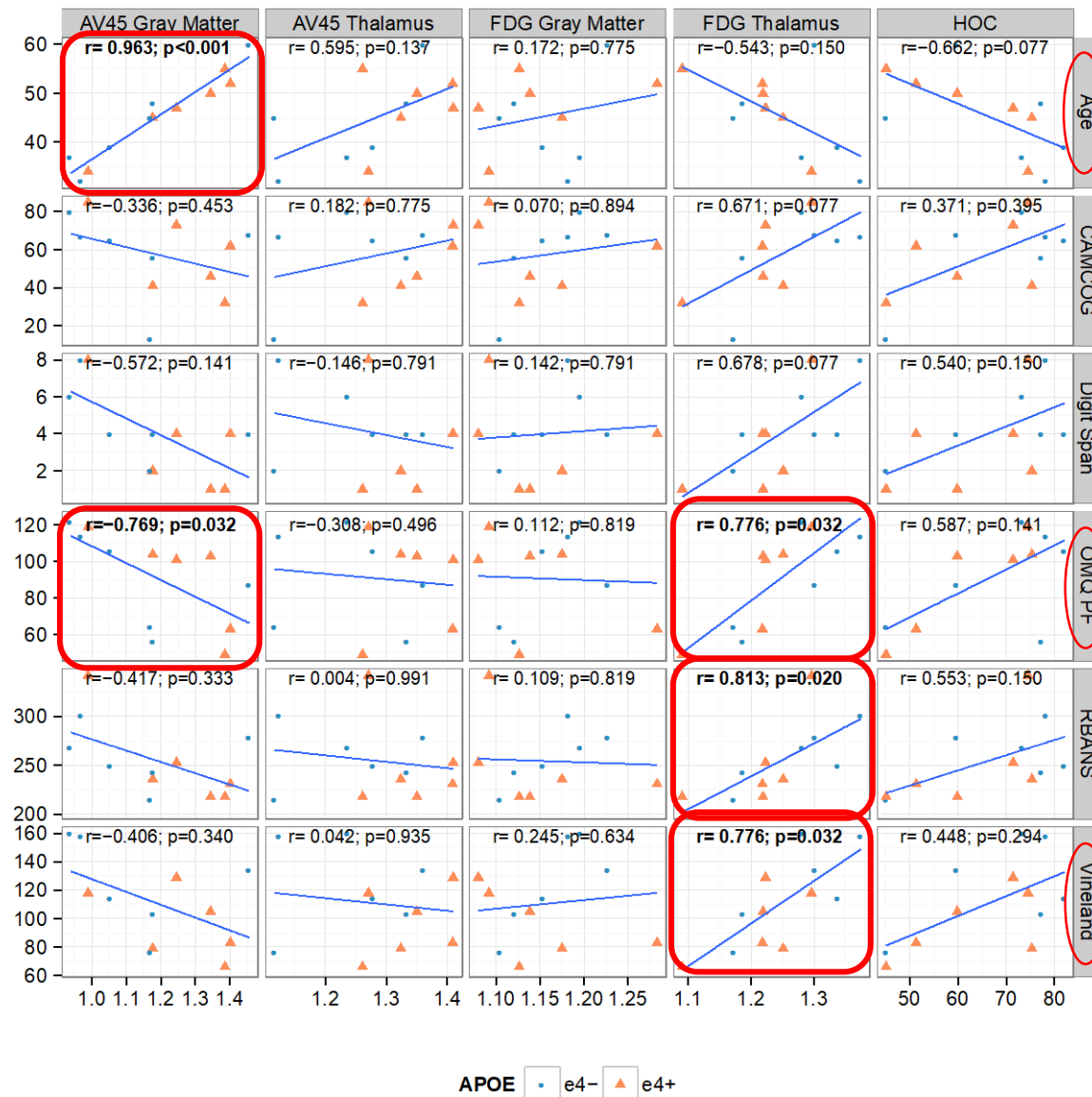
Tau PET enables visualization of the spread of AD neuropathology



MULTIMODAL AD BIOMARKER ANALYSIS IN DOWN SYNDROME

Subject	Age	Mental Age	ApoE 4	Amyloid PET Clinical Read	Grey matter Amyloid PET (SUVR)	FDG PET clinical read	Avg Hippocampus Volume (cm ³)	Retinal Amyloid Index
DP06	37	9	E3-E3	Negative	0.938	Normal	3.19	1.63
DP01	32	7	E3-E3	Negative	0.97	Mildly Hypo	3.22	2
DP07	34	7	E2-E4	Negative	0.988	Normal	3.53	2.47
DP08	39	5	E3-E3	Positive	1.054	Hypo	3.48	1.8
DP02	45	3	E2-E3	Positive	1.171	Hypo	2.91	2.2
DP12	45	6	E3-E4	Positive	1.176	Hypo	3.37	1.83
DP05	48	8	E3-E3	Positive	1.177	Hypo	3.47	1.68
DP11	47	7	E3-E4	Positive	1.245	Hypo	2.99	2.34
DP13	50	8	E3-E4	Positive	1.344	Hypo	3.14	1.58
DP04	55	6	E3-E4	Positive	1.385	Hypo	3.25	1.7
DP03	52	7	E3-E4	Positive	1.401	Hypo	3.01	2.2
DP09	60	7	E3-E3	Positive	1.457	Hypo	2.73	--

CLINICAL AND NEUROIMAGING OUTCOME MEASURES

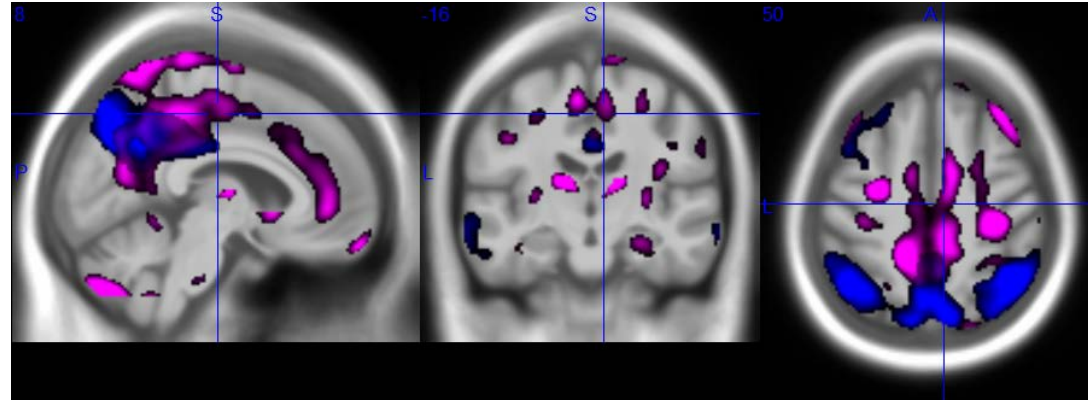


Amyloid burden correlates with age and lower memory performance

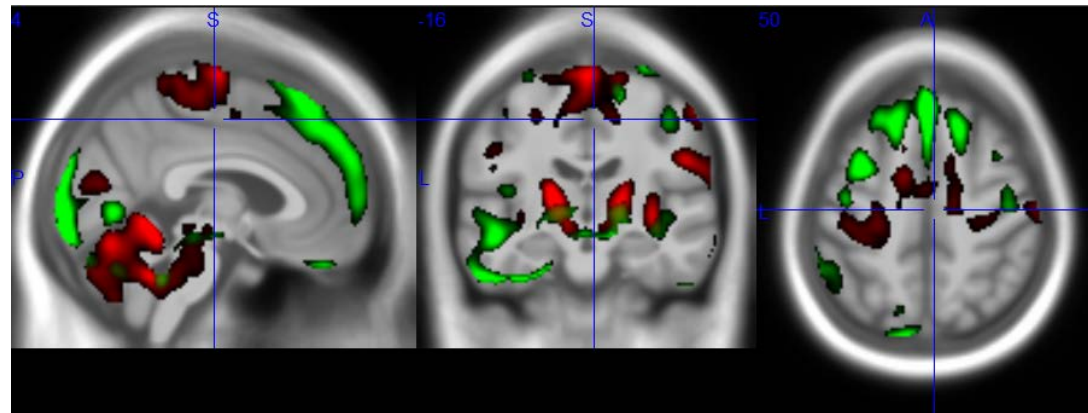
Spearman rank correlations (r) that are significant at the 0.05 level after false discovery rate adjustment.

COMPARISON OF CEREBRAL GLUCOSE METABOLISM IN DS VERSUS AD

Violet: Relative hypometabolism DS
Blue: Relative hypometabolism in AD
(166 ADNI subjects)



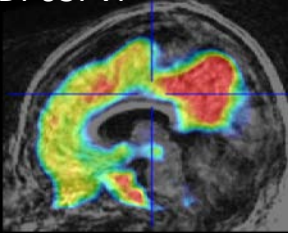
Green: Relative hypermetabolism in DS
Red: Relative hypermetabolism in AD
(166 ADNI subjects)



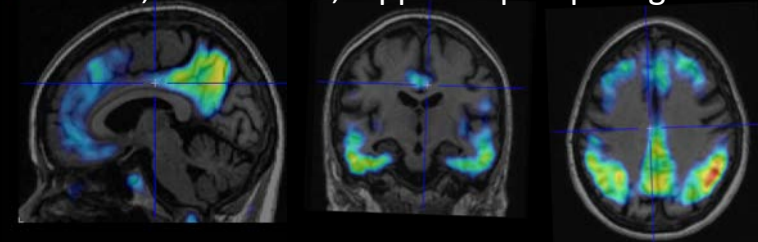
Dissociation of DS and AD effects using imaging

TAU PET IN DSBI PARTICIPANTS

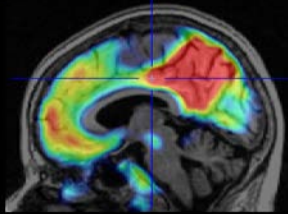
DP03: VI



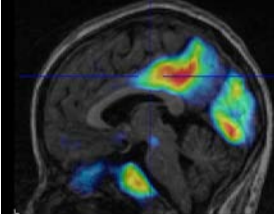
DP09: IV, threshold V, hippocampal sparing



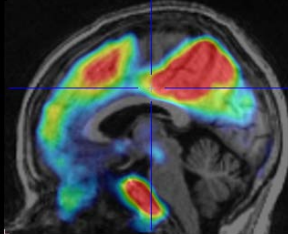
DP13: V, threshold VI



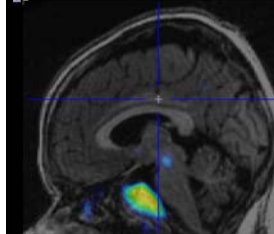
DP12: III, threshold IV



DP05: V, threshold VI



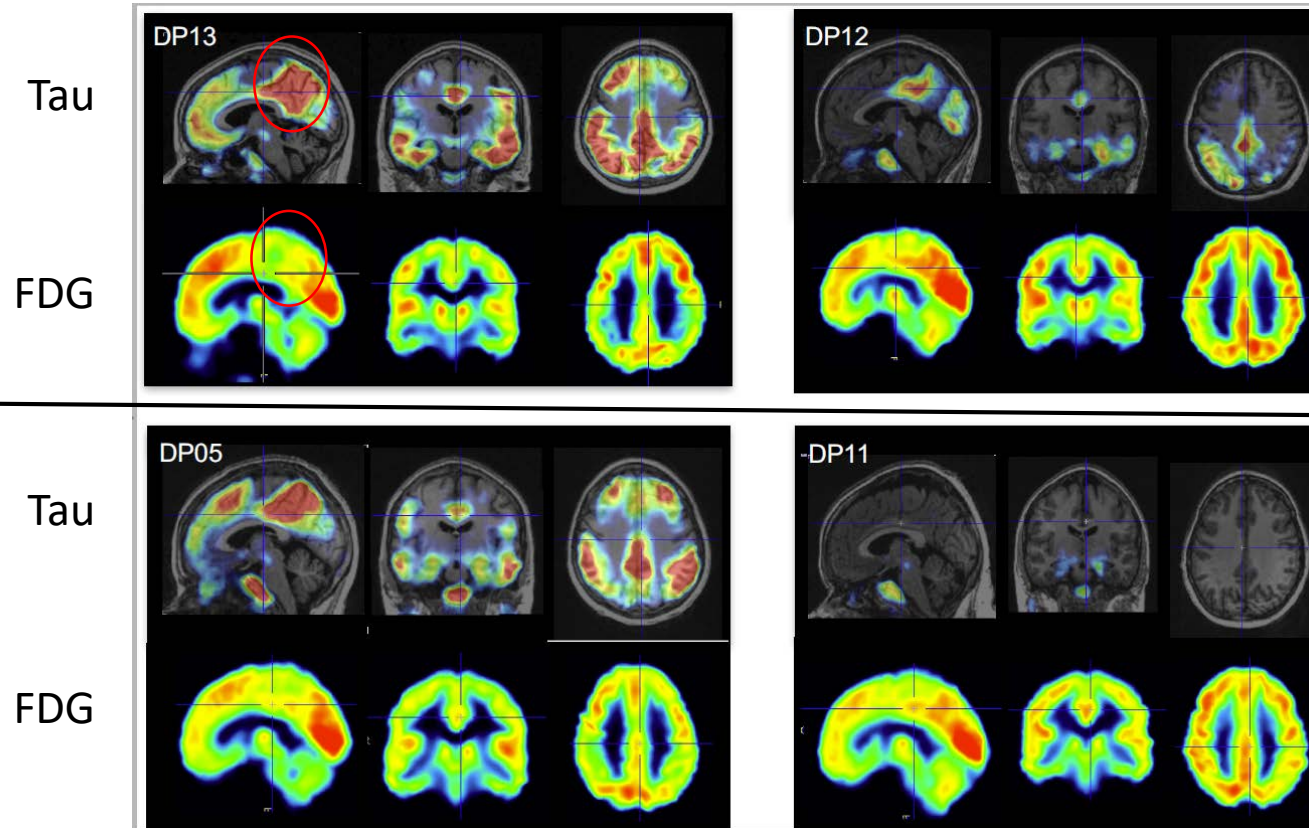
DP11: II



Tau positivity only seen in amyloid-positive subjects but to varying degrees

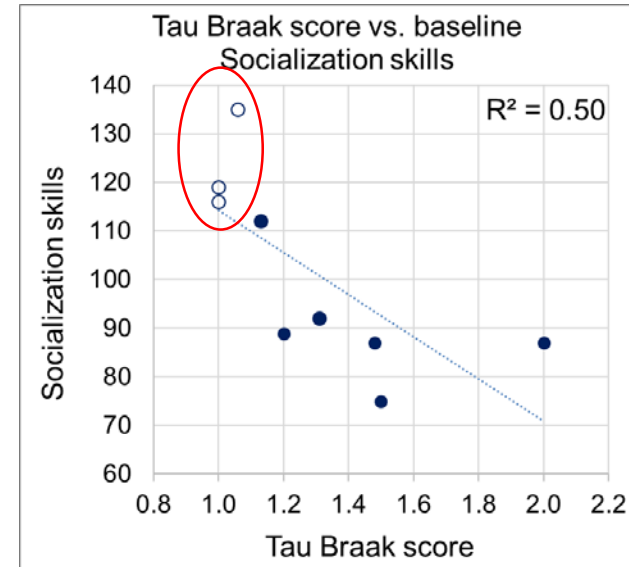
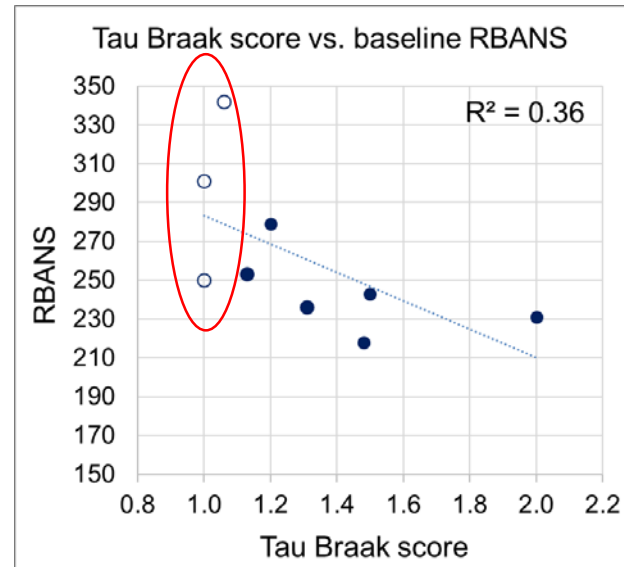
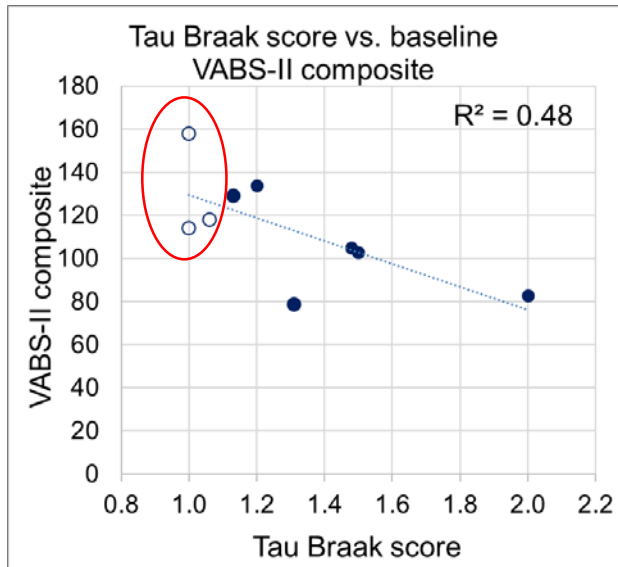
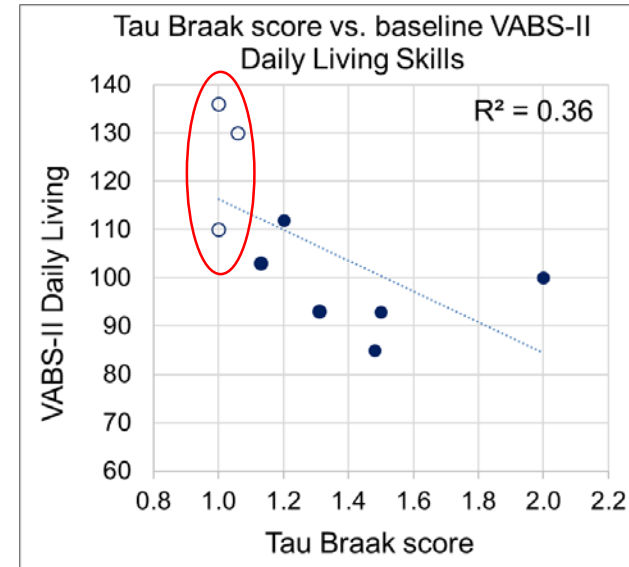
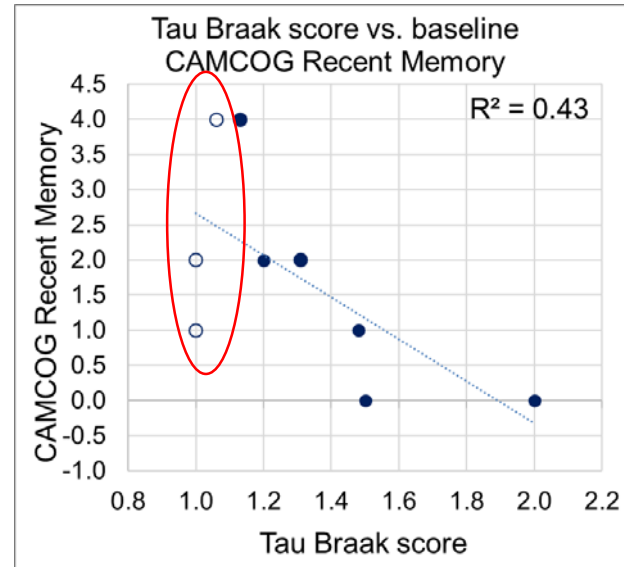
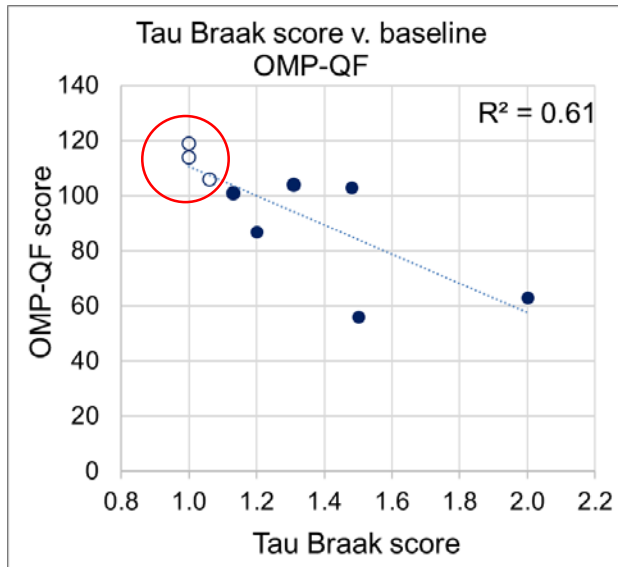
Rafii et al, 2017

INVERSE RELATIONSHIP OF TAU PATHOLOGY AND REGIONAL GLUCOSE METABOLISM



Areas with greater tau burden have less regional glucose metabolism

TAU PATHOLOGY CORRELATES WITH BASELINE COGNITIVE MEASURES



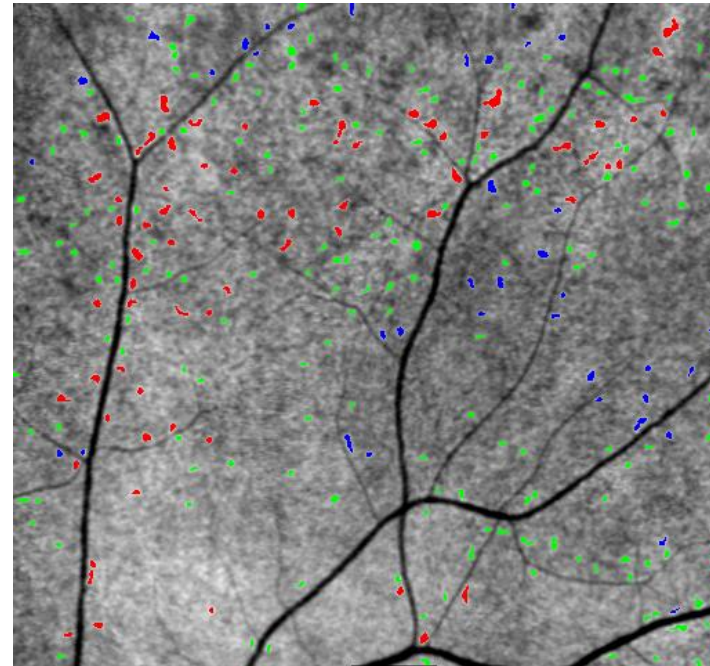
Higher tau correlates with lower cognitive and functional scores

RETINAL AMYLOID IMAGING

**Scanning Laser Ophthalmoscope
(Operator View)**

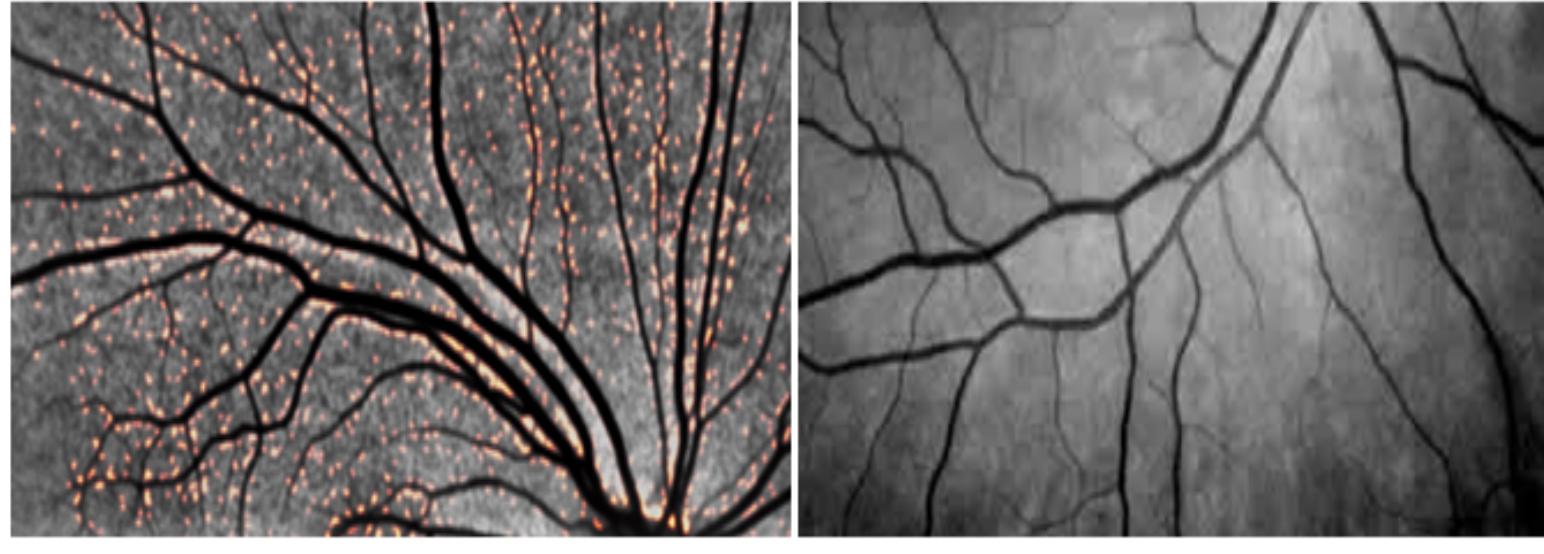


Retinal Amyloid Index



Courtesy of Neurovision

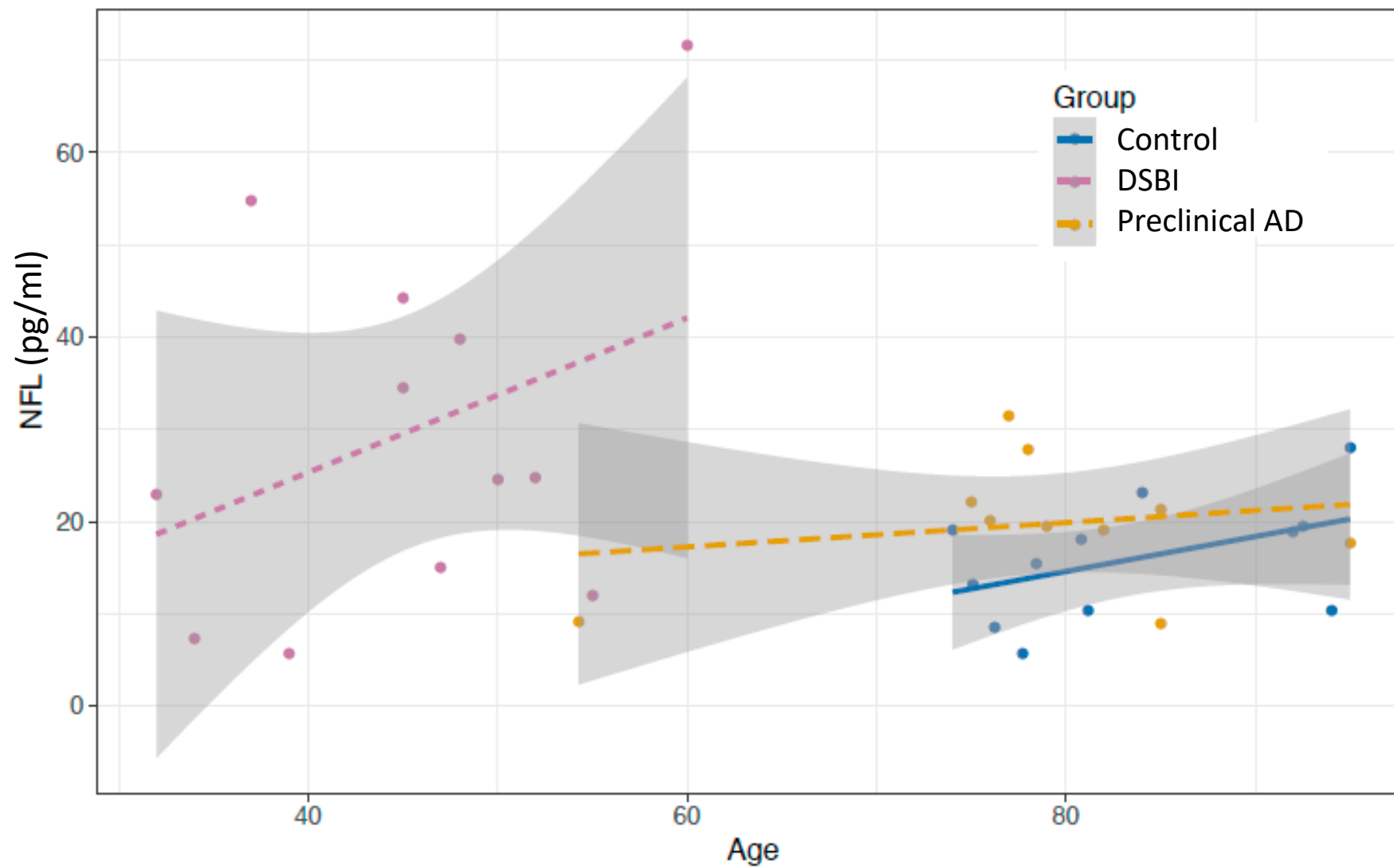
RETINAL AMYLOID IMAGING



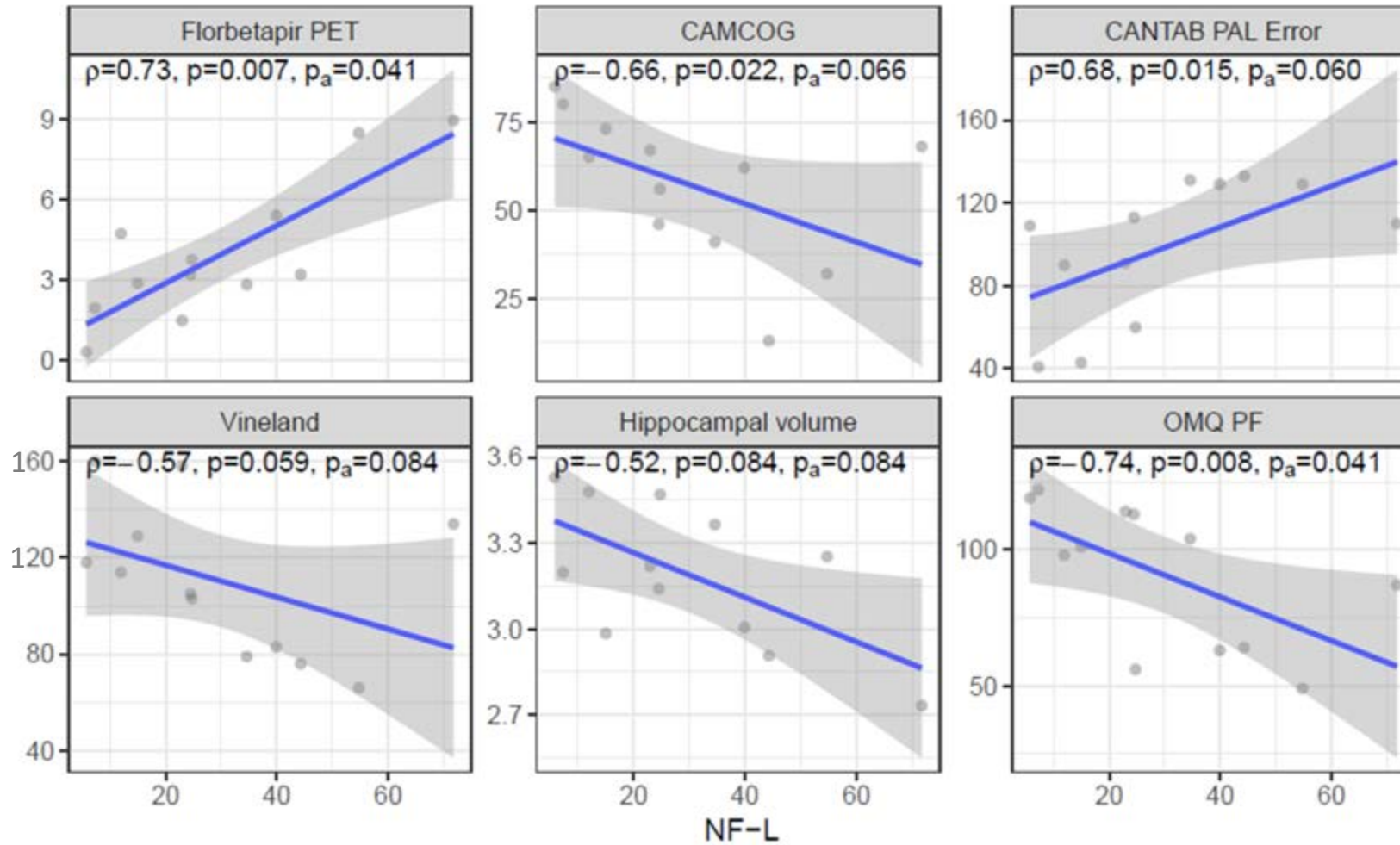
Down Syndrome

Non-Down Syndrome

Blood Biomarkers: Plasma NF-L and Age



Plasma NF-L levels Correlate with various AD Biomarkers in DS

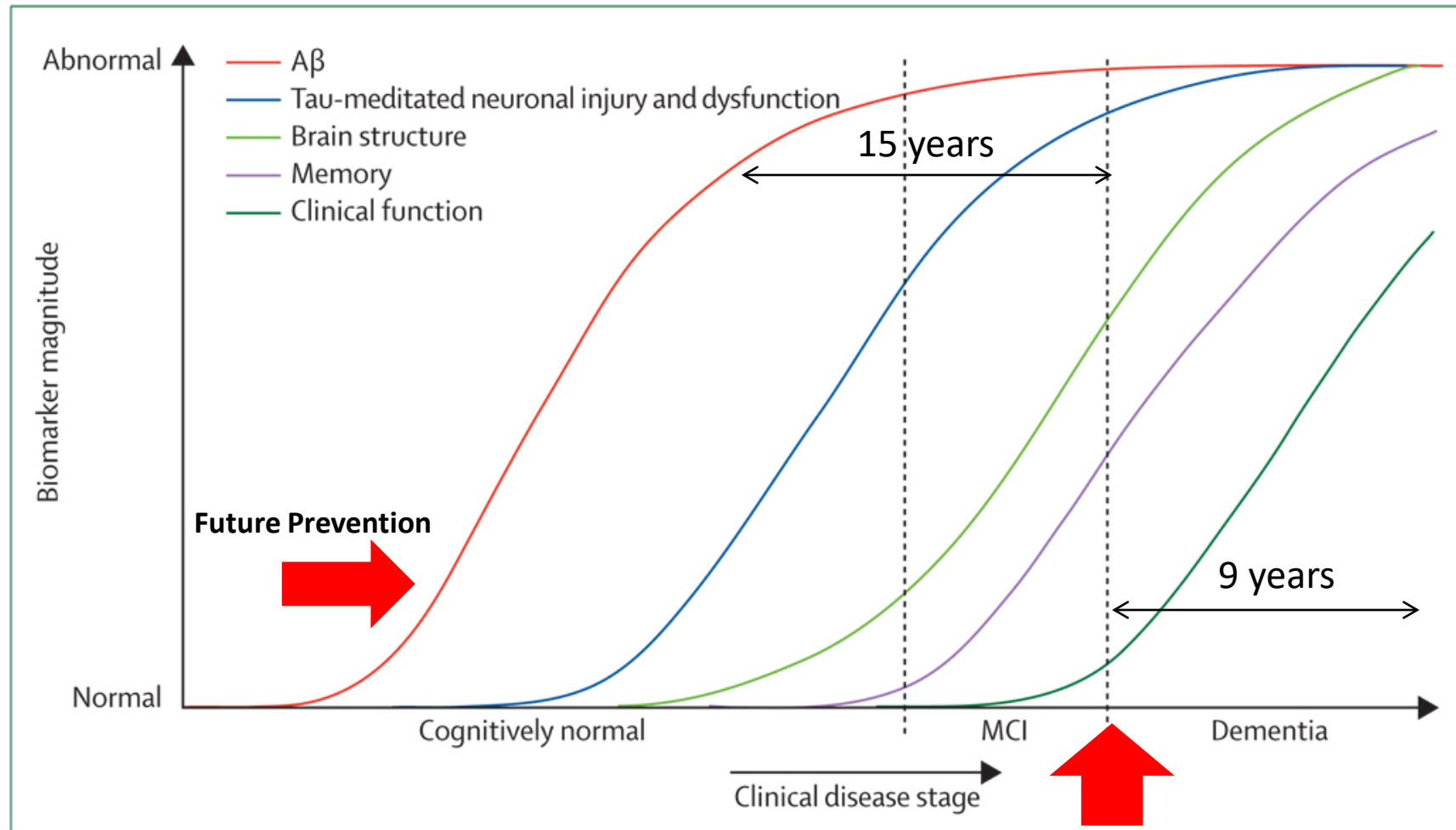


Correlations of Plasma NF-L with a. brain amyloid; b. CAMCOG total score; c. CANTAB PAL Errors; d. Vineland Score; e. Hippocampal volume; f. OMQ-PF score.

Blood Biomarkers

- Plasma NF-L:
 - Correlates with age and clinical dementia status
 - Correlates with amyloid-burden, glucose hypometabolism, cognitive and functional decline
 - Levels greater than 50 pg/ml may indicate presence of neurodegeneration
 - Increases 25% per year once above threshold level 50 pg/ml
- Further studies are needed on larger sample size to confirm and extend these findings.

BIOMARKERS OF ALZHEIMER'S DISEASE IN DS



Jack et al, Lancet 2009. ADNI Biomarkers in normal aging , MCI and AD

Current Treatment

CLINICAL TRIALS FOR AD IN DS

Compound	Mechanism of Action	Phase	Status
Scyllo-inositol	Amyloid binding	2a	Published (Rafii et al, 2017)
Vitamin E	Anti-oxidant	2	Published (Sano et al, 2016)
ACI-24	Active vaccine against beta-amyloid	1b	Ongoing (PI: Rafii)

CONCLUSIONS

- Amyloid positive is nearly universal by age 40
- Tau PET positivity is seen only in the presence amyloid PET positivity, just as in sporadic AD
- Tau PET signal seems to correlate with age and amyloid burden and with greater cognitive decline in DS, just as in sporadic AD
- Many biomarkers of AD, including plasma NfL, behave similarly in adults with DS as in other preclinical AD populations.
- The data indicate that a large, multicenter longitudinal study is feasible to better understand the trajectories of AD biomarkers in this enriched population → NIH ABC-DS
- Such data will inform clinical trials for AD in DS