

Neuroimaging for Predicting and Measuring Progression in Preclinical Autosomal Dominant Alzheimer's Disease

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Stock/Equity (any amount): None

Consulting/Advisory Board: Eli Lilly (2011)

Speakers Bureau / Honoraria: None

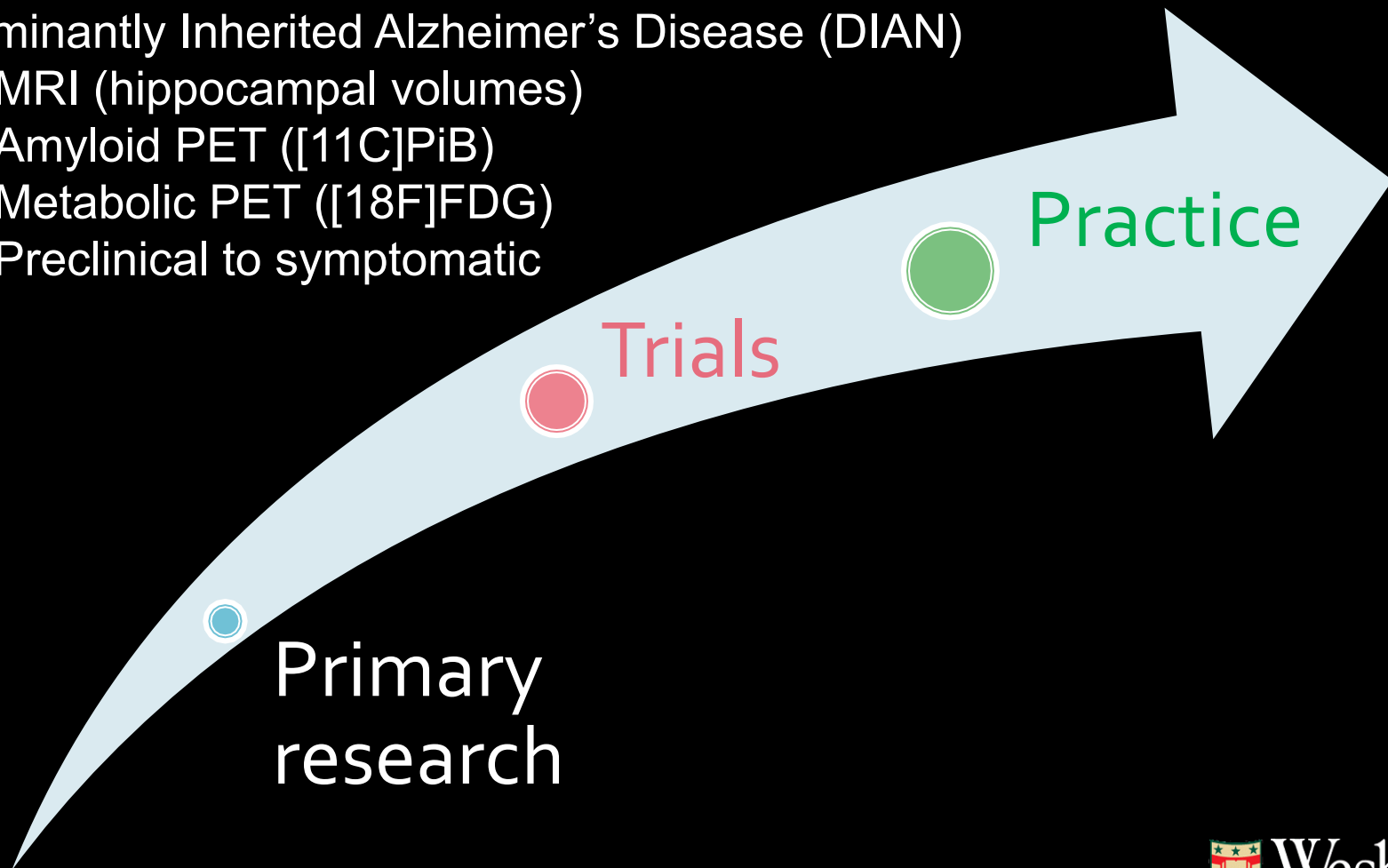
Other: None

Non-FDA approved/ Off-label applications may be discussed.

Imaging Biomarkers

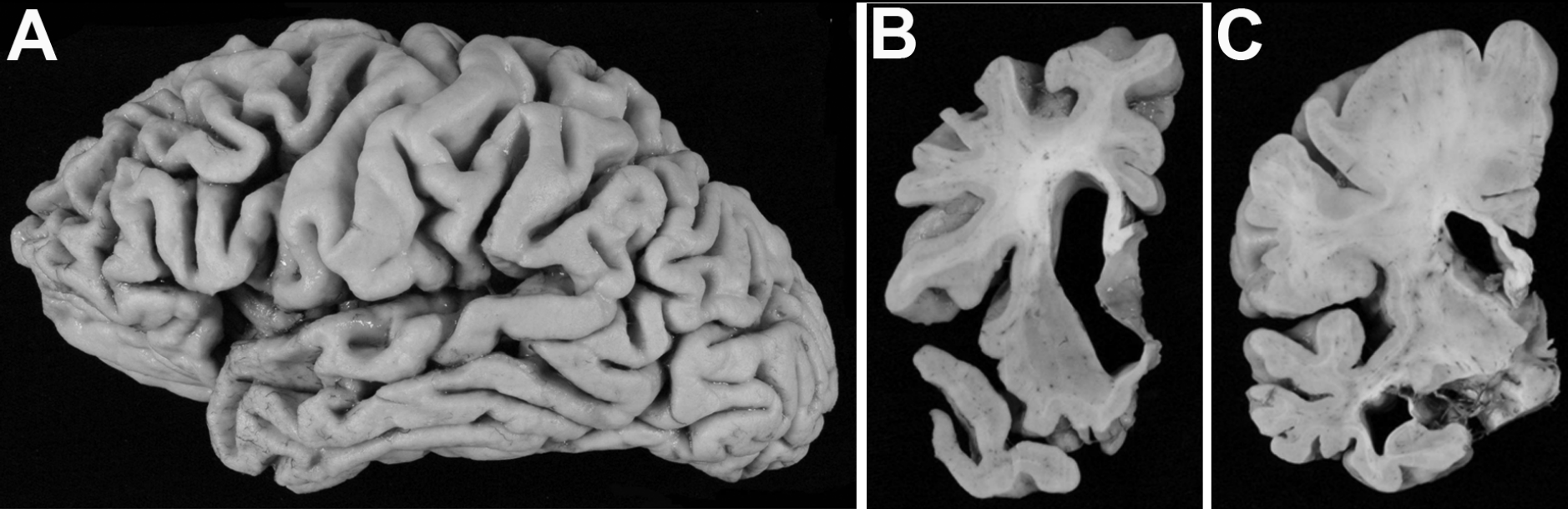
Dominantly Inherited Alzheimer's Disease (DIAN)

- MRI (hippocampal volumes)
- Amyloid PET ([¹¹C]PiB)
- Metabolic PET ([¹⁸F]FDG)
- Preclinical to symptomatic

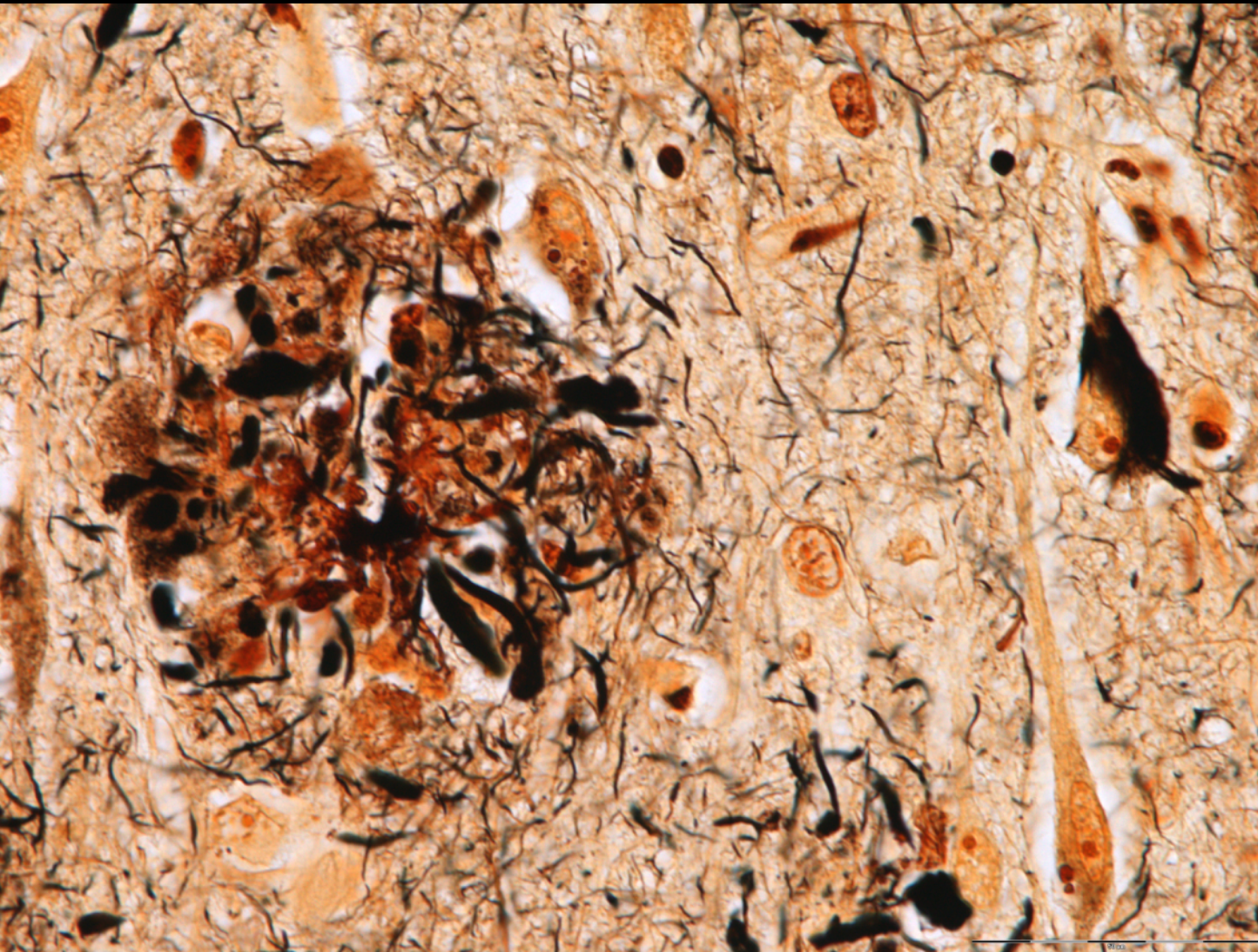


Alzheimer's Disease (AD)

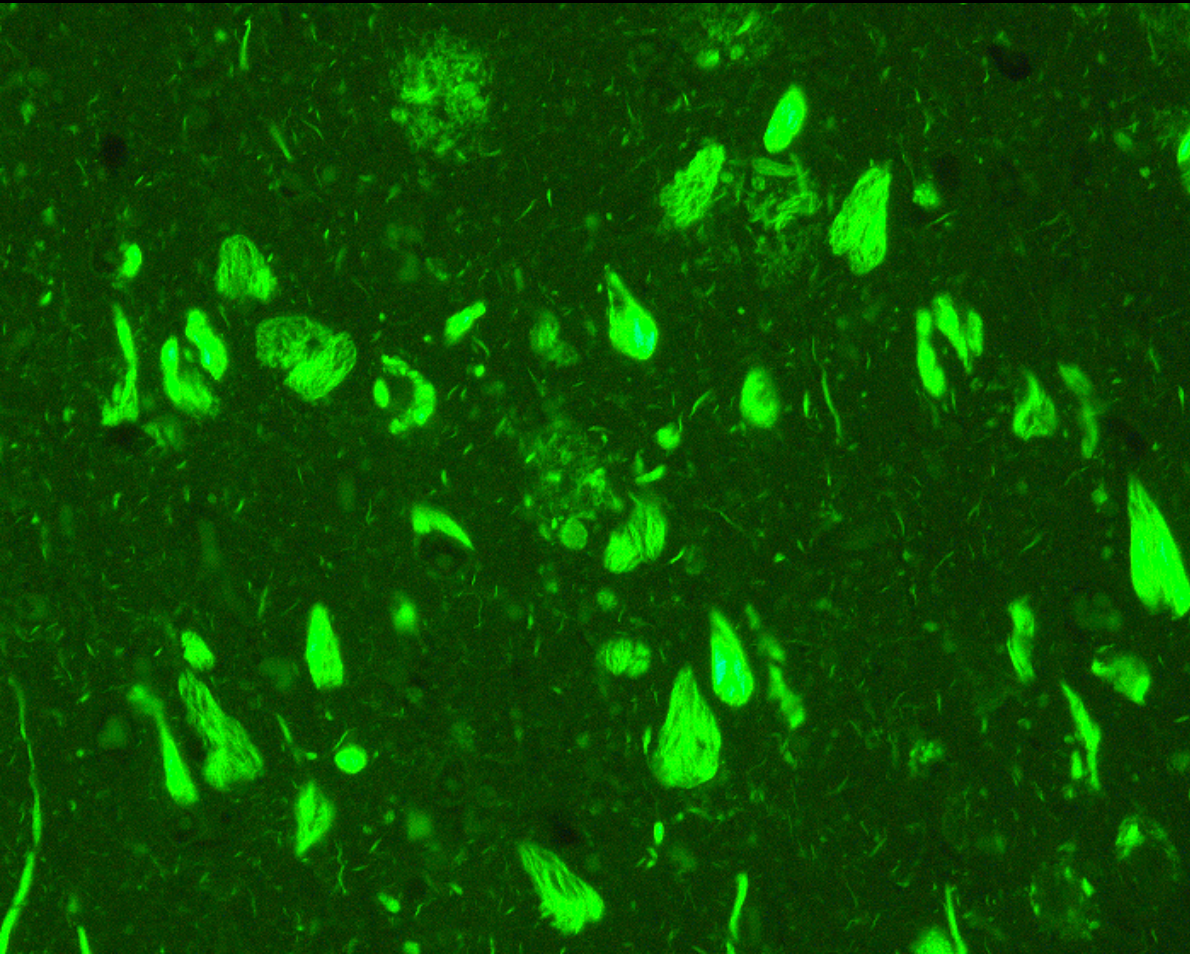
Global Atrophy with Relative Preservation of Sensorimotor Cortex



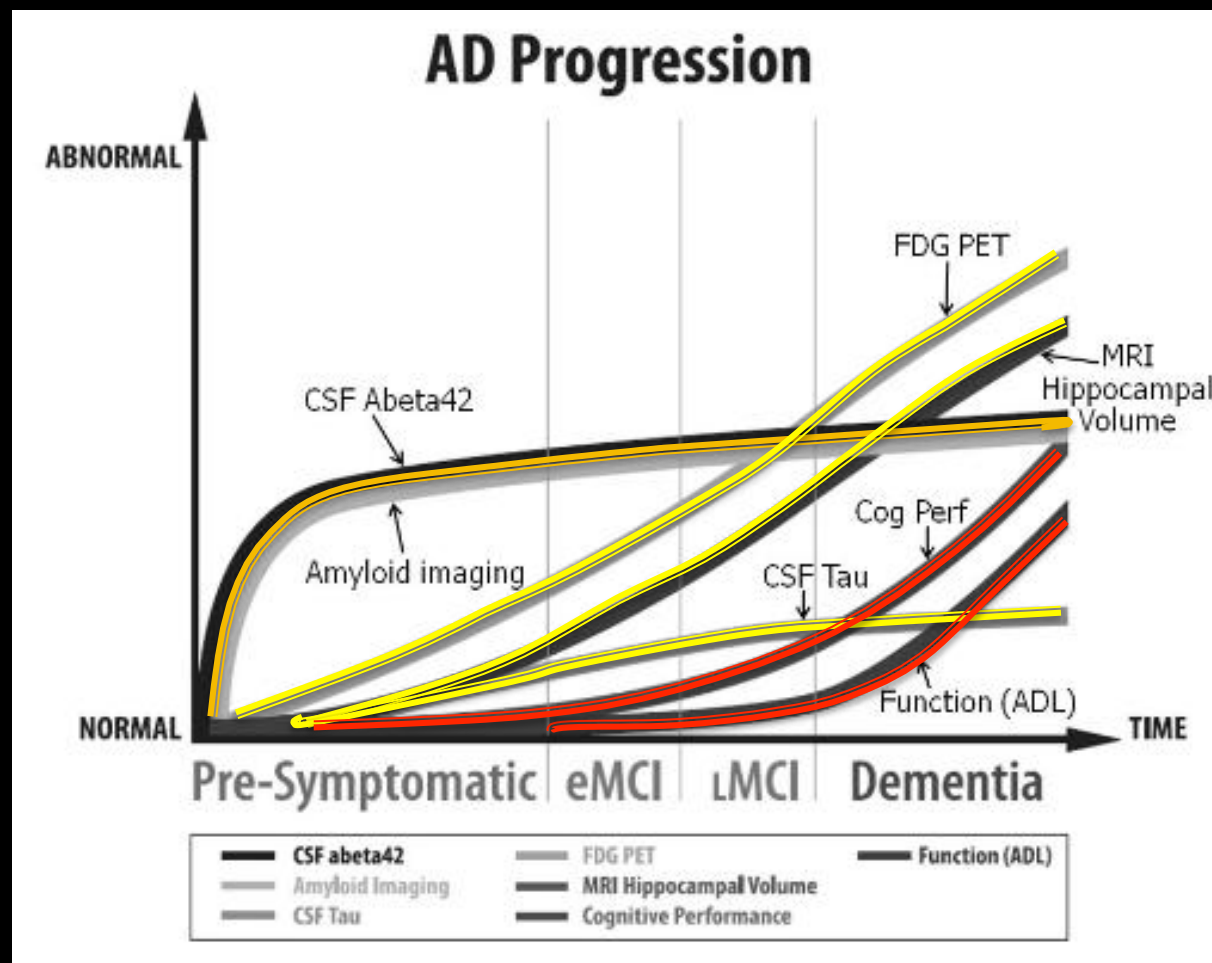
Signature Lesions of AD: Neuritic Plaque (left) and Neurofibrillary Tangle (right)



**AD amyloid is present in neuritic plaques,
neurofibrillary tangles, and dystrophic neurites**



2010 NIH State-of-the-Science Conference, Preventing Alzheimer's Disease and Cognitive Decline



Amyloid deposition
-low CSF Aβ42
-amyloid PET

Neuronal injury
-FDG PET
-Volumetric MRI
-CSF Tau

Cognition

DIAN and DIAN-TU



Dominantly Inherited Alzheimer Network (DIAN) & DIAN Trials Unit (DIAN-TU)

- 10 active sites US, UK, Australia
- Opening sites Mayo-Jacksonville, Munich and Tübingen, Germany, and Barcelona
- Additional international sites planned for DIAN-TU

Autosomal Dominant AD Mutations

- Presenilin-1 (PS-1)
- Presenilin-2 (PS-2)
- Amyloid precursor protein (APP)

Dementia onset prior to age 65 (mean age 45)

Columbia University

Indiana University

University of California, Los Angeles

Brigham and Women's Hospital–Massachusetts

Brown University–Butler Hospital

University of Pittsburgh

University College London

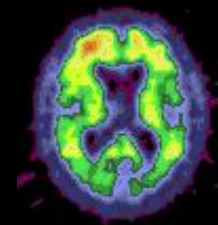
Neuroscience Research Australia

University of Melbourne

Edith Cowan University

Central imaging QC
Mayo Clinic (Jack)
U. Michigan (Koepp)

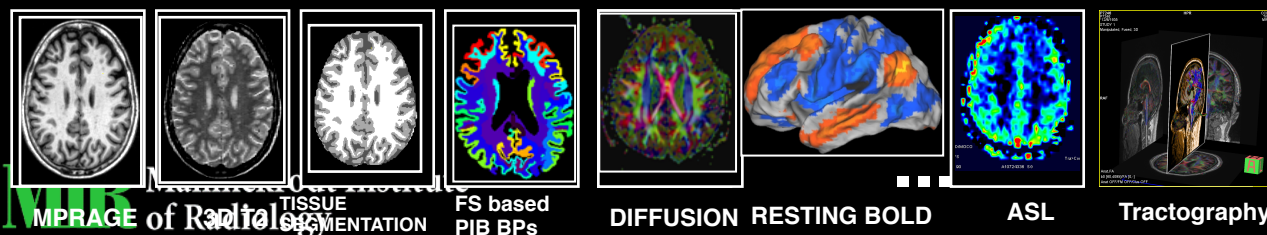
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DIAN Imaging Elements

- PET
 - [11C]PIB for amyloid plaque
 - [18F]AV45 for amyloid plaque
 - [18F]FDG for metabolism
- MRI (ADNI protocol)
 - Volumetric T1
 - FreeSurfer thickness, volumes
 - ARIA eval. (FLAIR, SWI/T2*)
 - Microhemorrhage counts, localization with central reading (Mayo)
 - Resting state fcMRI
 - Diffusion tensor (DTI)
 - Regional FA, ADC, etc & tract based
 - Blood flow (ASL)

Whole brain, regional (FreeSurfer), +/- volume correction



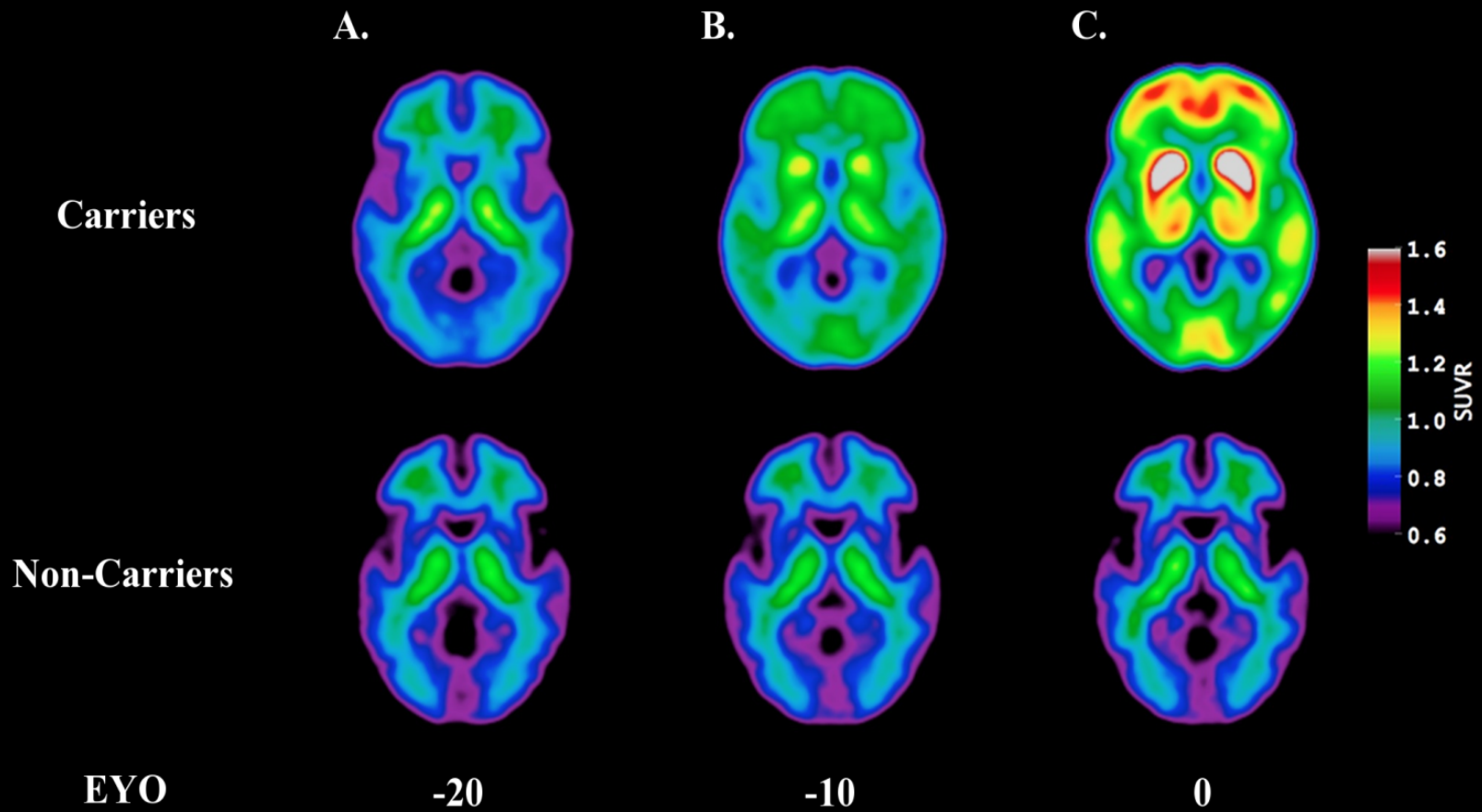
DIAN Imaging Participants

Demographic	Imaging Marker								
	MRI			PIB			FDG		
	M-	M+	<i>p</i>	M-	M+	<i>p</i>	M-	M+	<i>p</i>
<i>n</i> (%)	92 (40.2)	137 (59.8)	-	84 (42)	116 (58)	-	86 (41.5)	121 (58.5)	-
Age (SD) years	39.3 (9.46)	38.8 (10.4)	0.718	39.5 (9.72)	38.6 (10.4)	0.539	39.3 (9.73)	38.5 (10.3)	0.552
EYO (SD) years	-7.49 (11.8)	-7.85 (9.91)	0.807	-7.18 (11.8)	-7.92 (10.3)	0.644	-7.23 (11.9)	-8.47 (9.97)	0.432
Education (SD) years	14.6 (2.61)	14.2 (2.6)	0.215	14.8 (2.65)	14.1 (2.64)	0.0952	14.8 (2.63)	14.3 (2.59)	0.196
Male (%)	38 (41.3)	56 (40.9)	0.949	34 (40.5)	54 (46.6)	0.394	35 (40.7)	52 (43)	0.745
CDR > 0 (%)	5 (5.43)	54 (39.4)	2.60E-11	4 (4.76)	45 (38.8)	3.75E-10	4 (4.65)	45 (37.2)	6.19E-10
Familial Mutation Type (%)	PS1=57 (62), PS2=11 (12), APP=24 (26.1)	PS1=105 (76.6), PS2=11 (8.03), APP=21 (15.3)	-	PS1=51 (60.7), PS2=10 (11.9), APP=23 (27.4)	PS1=88 (75.9), PS2=11 (9.48), APP=17 (14.7)	-	PS1=53 (61.6), PS2=10 (11.6), APP=23 (26.7)	PS1=91 (75.2), PS2=11 (9.09), APP=19 (15.7)	-

EYO

- Parental age of onset (AOO) used to estimate the children's time (years) to of onset of dementia (EYO)
- $EYO = AOO - (\text{current age})$
- *I*e a 40 year old whose parent developed symptoms at age 45 would be 5 years from expected age of onset

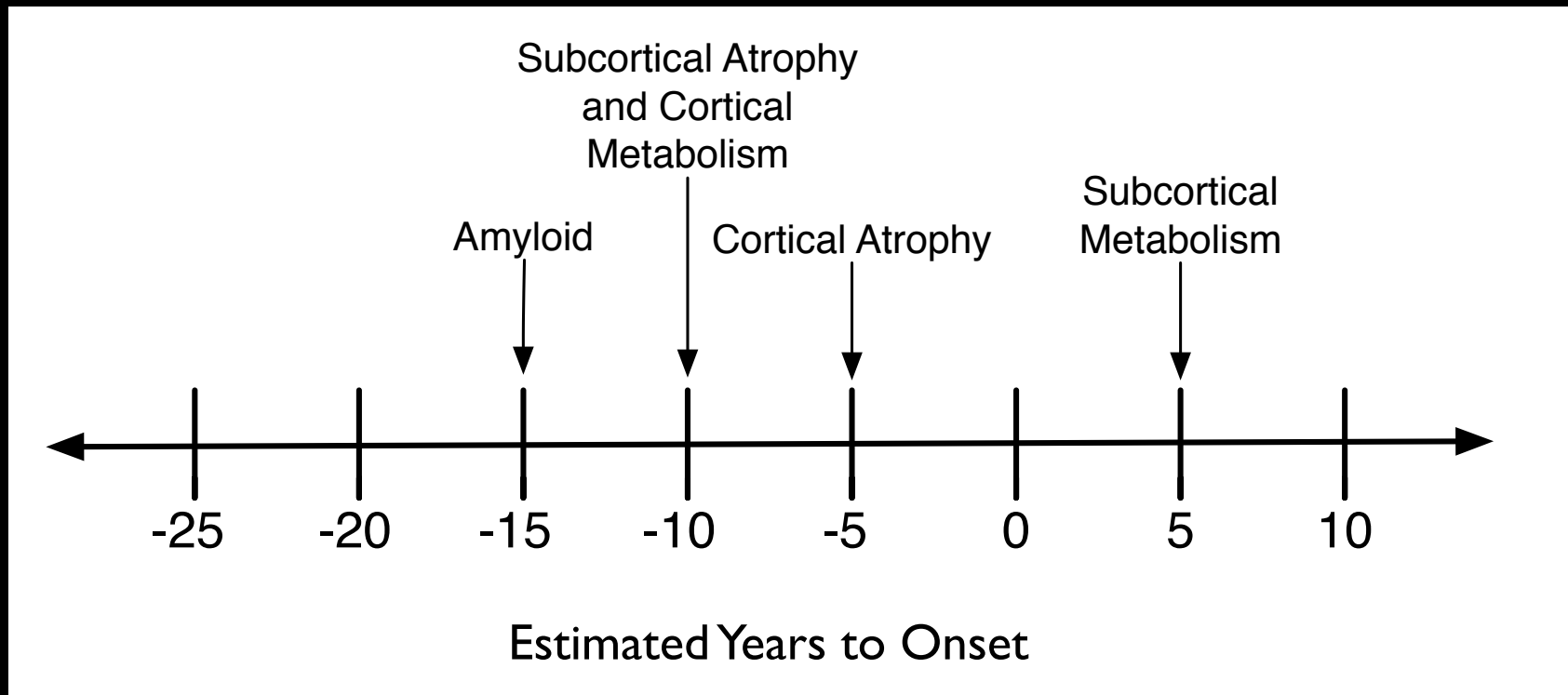
Amyloid deposition begins at least 15 years prior to dementia onset in mutation carriers



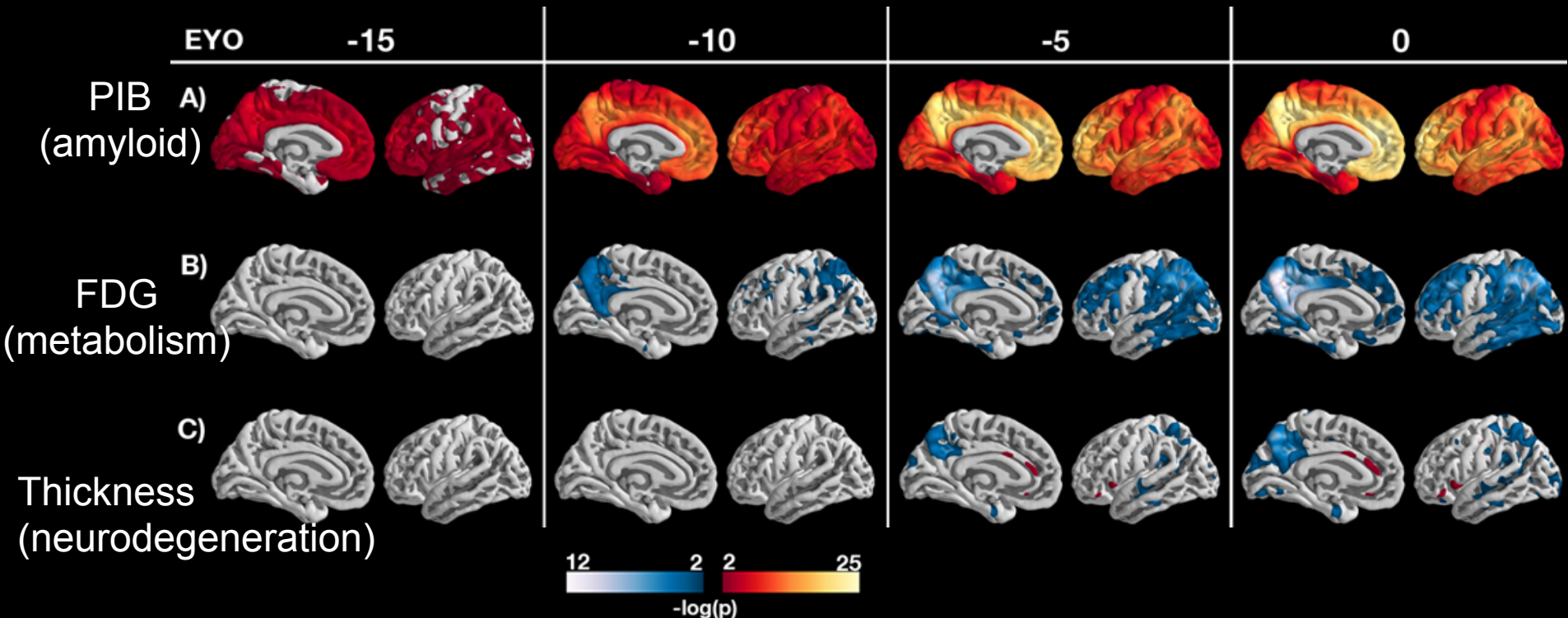
Estimates of amyloid (PIB) accumulation in the DIAN cohort

Insert AVI here
(NEJM axial amyloid movie)

Imaging Biomarker Timeline



Imaging of disease timecourse in autosomal dominant AD



EYO Estimated years to onset of symptoms

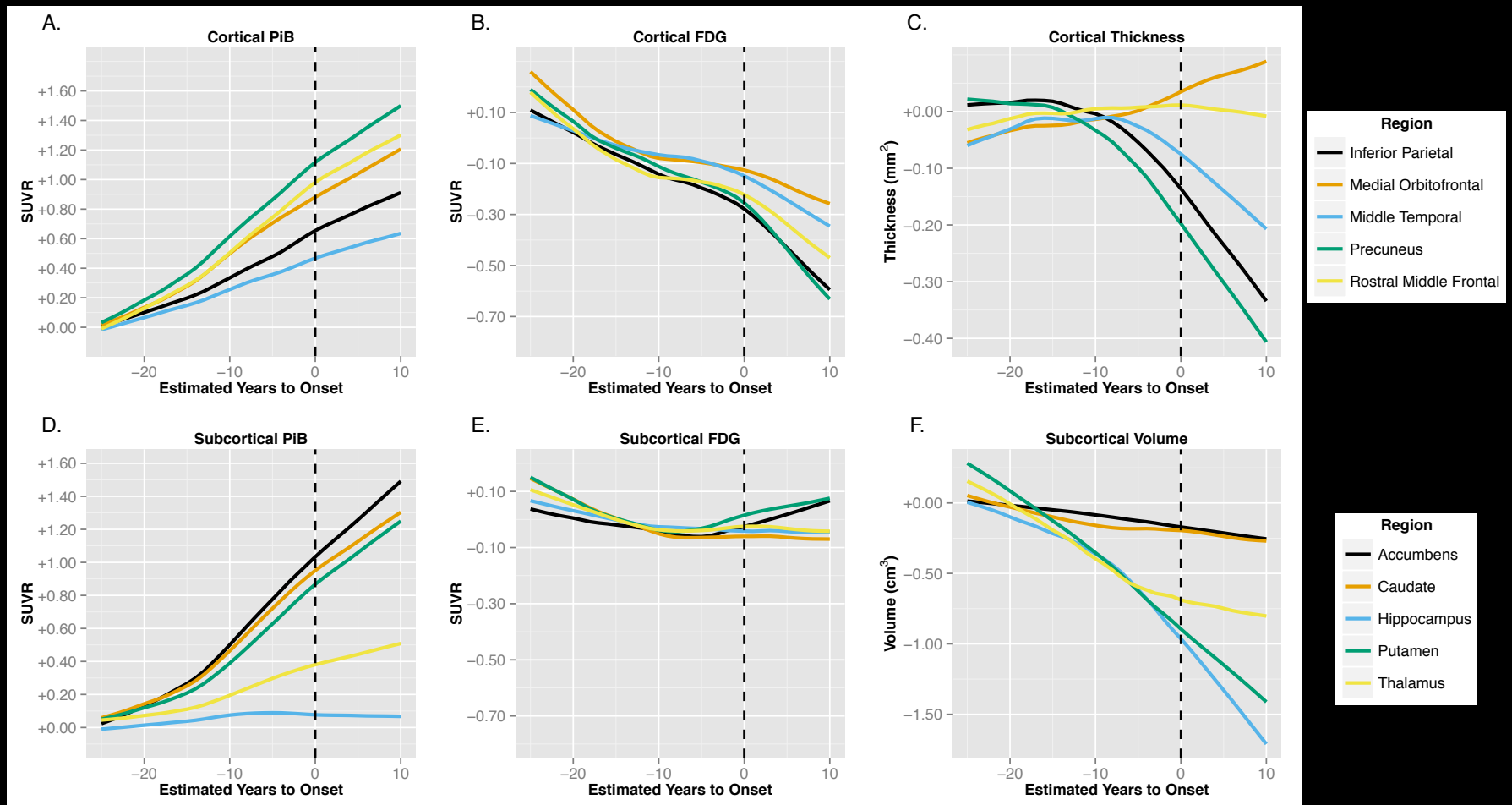
EYO = parental age of onset – current participant age

Insert AVI file here
Surface movies, multiple biomarkers (AAIC)

Subcortical grey matter

Region	Modality	Estimated Years to Onset							
		-25	-20	-15	-10	-5	0	5	10
Caudate	PiB	-0.089 ± 0.075	0.11 ± 0.06	0.3 ± 0.048***	0.5 ± 0.041***	0.7 ± 0.042***	0.89 ± 0.049***	1.1 ± 0.062***	1.3 ± 0.076***
	FDG	0.067 ± 0.044	0.043 ± 0.035	0.018 ± 0.028	-0.0059 ± 0.024	-0.03 ± 0.025	-0.055 ± 0.03	-0.079 ± 0.037	-0.1 ± 0.046
	Volume	-0.073 ± 0.2	-0.11 ± 0.16	-0.14 ± 0.13	-0.17 ± 0.11	-0.21 ± 0.11	-0.24 ± 0.13	-0.27 ± 0.16	-0.31 ± 0.2
Hippocampus	PiB	0.018 ± 0.022	0.029 ± 0.018	0.04 ± 0.014*	0.05 ± 0.012***	0.061 ± 0.012***	0.071 ± 0.014***	0.082 ± 0.018***	0.093 ± 0.022***
	FDG	0.033 ± 0.02	0.019 ± 0.016	0.0048 ± 0.013	-0.0094 ± 0.011	-0.024 ± 0.012	-0.038 ± 0.014*	-0.052 ± 0.017*	-0.066 ± 0.021*
	Volume	0.4 ± 0.23	0.13 ± 0.19	-0.13 ± 0.15	-0.4 ± 0.13*	-0.67 ± 0.13***	-0.94 ± 0.15***	-1.2 ± 0.19***	-1.5 ± 0.24***

Imaging Biomarker Trajectories

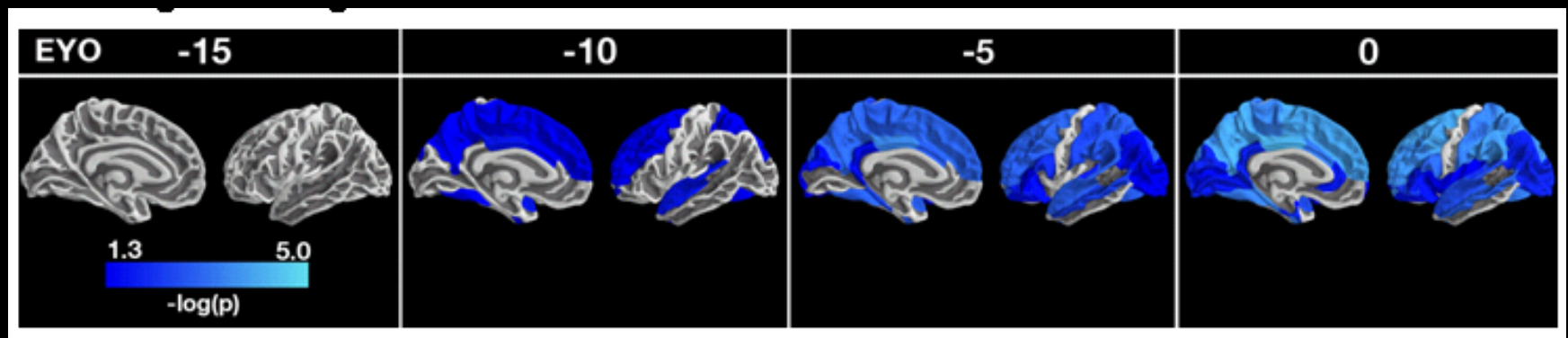


White matter

Demographic	Imaging Marker					
	White Matter Volume			DTI		
	M-	M+	p-value	M-	M+	p-value
n (%)	72 (37.7)	119 (62.3)	-	30 (36.1)	53 (63.9)	-
Age (SD) years	40.8 (8.94)	38.7 (10.6)	0.161	41.5 (8.27)	38.7 (10.5)	0.183
EYO (SD) years	-5.75 (11.5)	-7.98 (10)	0.174	-4.6 (11.4)	-7.42 (10.7)	0.274
Education (SD) years	14.8 (2.54)	14.1 (2.57)	0.0776	14.9 (2.59)	14 (2.93)	0.154
Male (%)	31 (43.1)	52 (43.7)	0.931	18 (60)	30 (56.6)	0.767
CDR > 0 (%)	4 (5.56)	48 (40.3)	4.50E-10	1 (3.33)	22 (41.5)	3.56E-06
Familial Mutation Type (%)	PS1=47 (65.3), PS2=9 (12.5), APP=16 (22.2)	PS1=96 (80.7), PS2=9 (7.56), APP=14 (11.8)	-	PS1=17 (56.7), PS2=8 (26.7), APP=5 (16.7)	PS1=40 (75.5), PS2=8 (15.1), APP=5 (9.43)	-

White matter volume

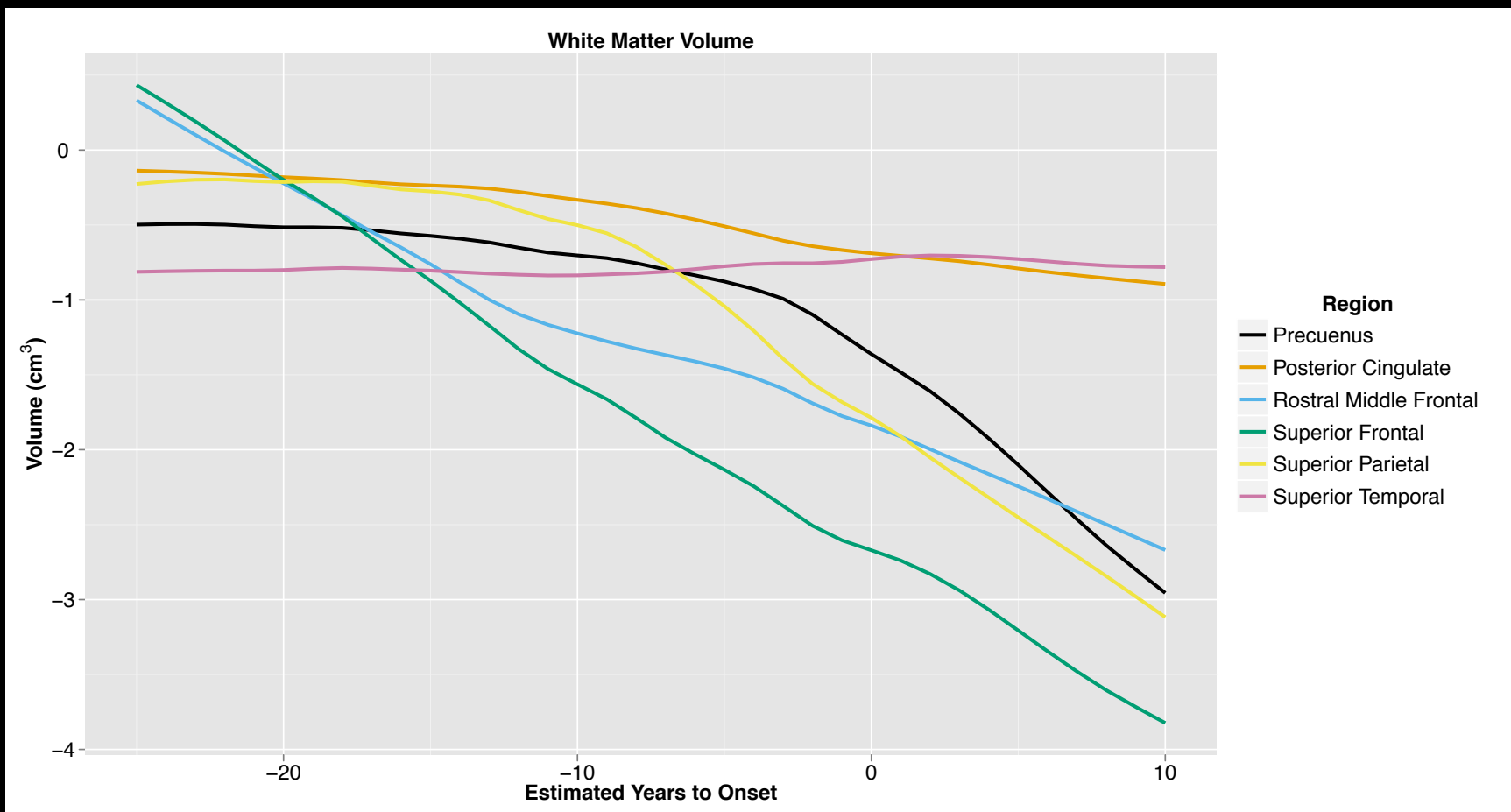
- Significant differences between carriers and non-carriers detectable at 10 years before estimated age of onset



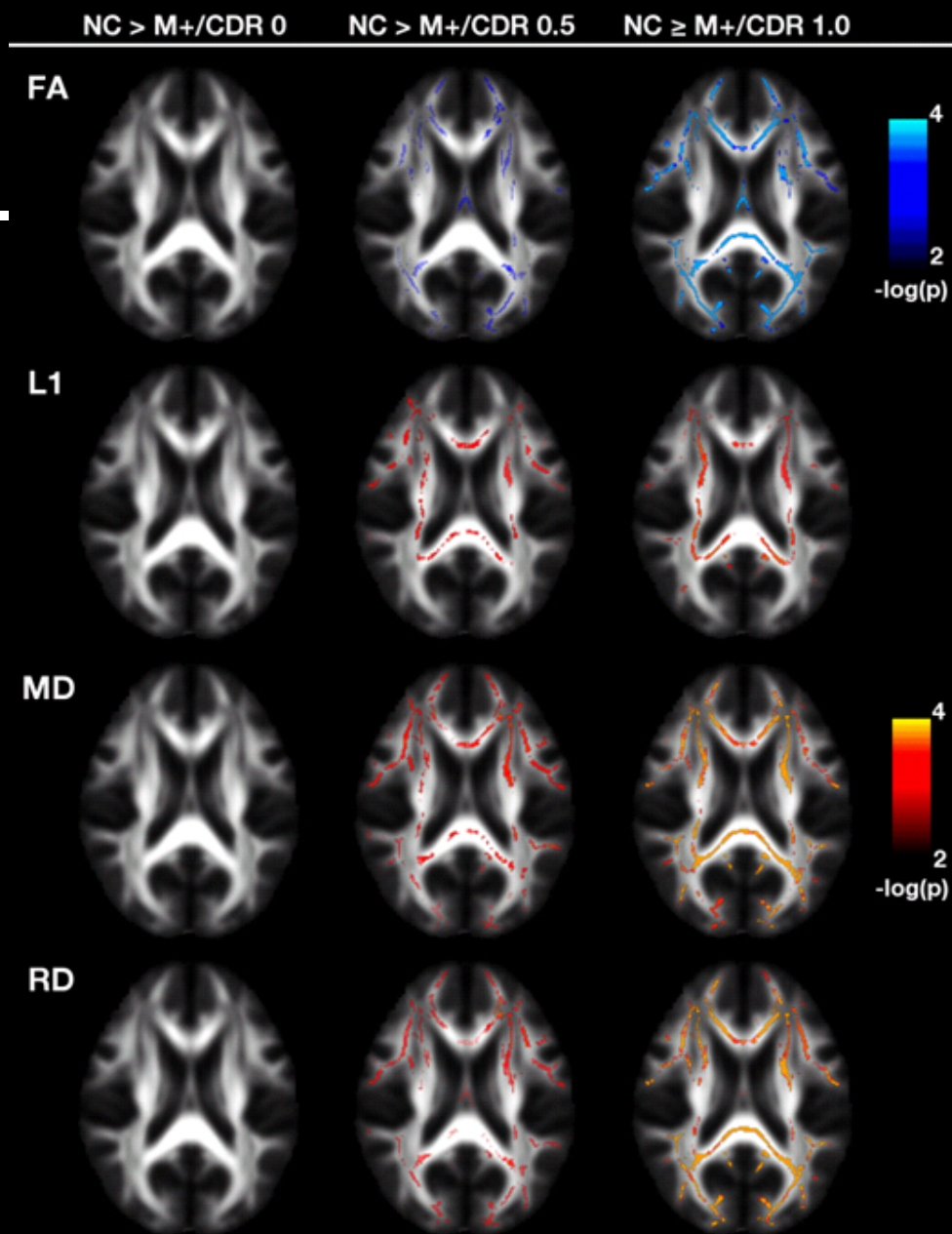
Deep white matter volumes

Region	Estimated Years to Onset					
	-15	-10	-5	0	5	10
Unsegmented	-171 ± 1039	-1139 ± 864	-2107 ± 844*	-3076 ± 987**	-4044 ± 1238**	-5012 ± 1545**
CC: Posterior	2 ± 28	-8.3 ± 23	-19 ± 23	-29 ± 27	-39 ± 33	-49 ± 42
CC: Mid Posterior	9.3 ± 18	-9.2 ± 15	-28 ± 15	-46 ± 17*	-65 ± 21**	-83 ± 27**
CC: Central	6.5 ± 18	-10 ± 15	-27 ± 15	-43 ± 17*	-60 ± 22*	-77 ± 27*
CC: <u>Mid Anterior</u>	6.2 ± 20	-5 ± 17	-16 ± 16	-27 ± 19	-39 ± 24	-50 ± 30
CC: Anterior	-20 ± 28	-34 ± 24	-48 ± 23	-63 ± 27*	-77 ± 34*	-91 ± 42*

LOESS estimated WM atrophy



DTI



Conclusions

- Amyloid accumulation detectable by PiB PET ~15 years before expected symptom onset
 - Followed by changes in subcortical volumes and cortical metabolism (FDG) at EYO=-10
 - Cortical thickness declines become significant at EYO=-5
 - White matter changes detected at EYO = -5
 - Small declines in subcortical FDG become significant around 5 years after disease onset
- The precuneus appears to be one of the most affected regions for all imaging biomarkers

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Columbia University

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Brown University–Butler Hospital

University of Pittsburgh

University College London

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University of Melbourne

Edith Cowan University

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