Biomarkers for Neurodegeneration with a focus on Alzheimer's and Parkinson's Disease

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5th Sept 2022

Imperial College London

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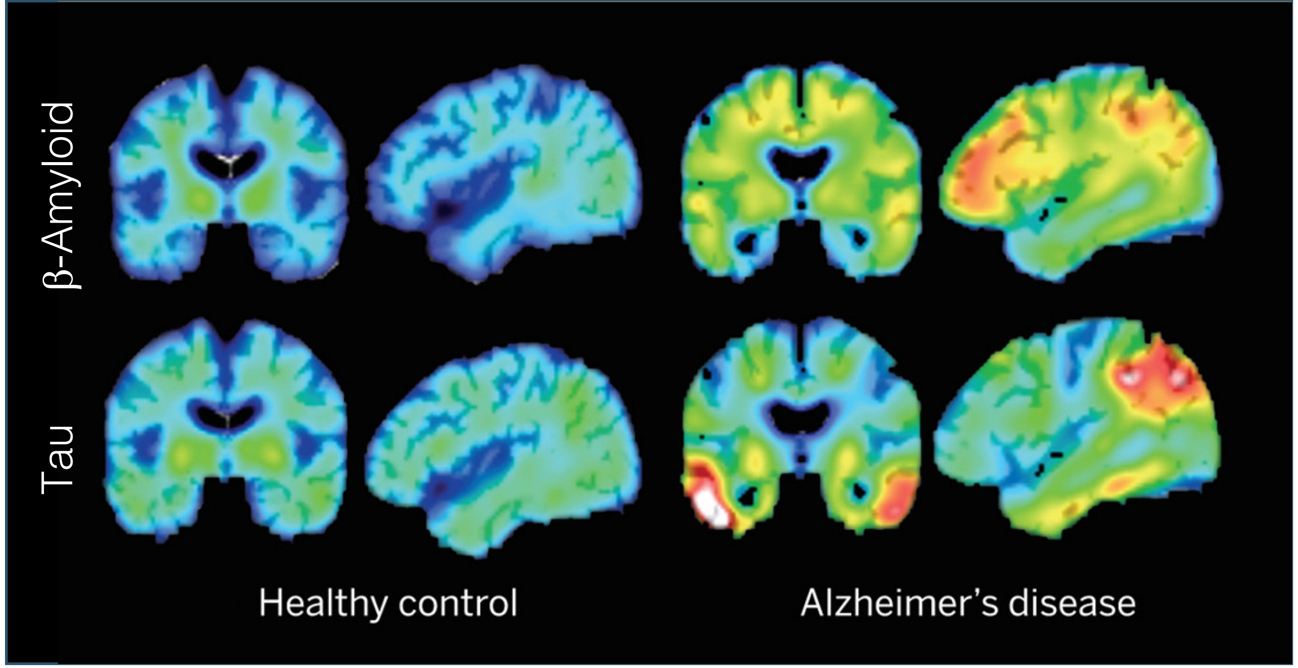
Neurodegeneration - Alzheimer's Disease

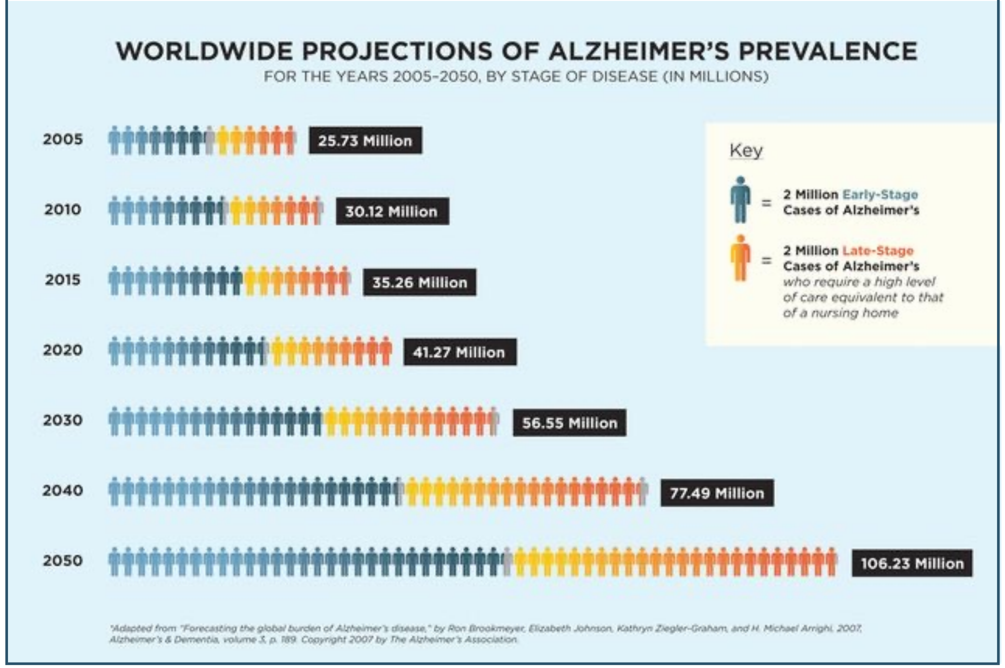
Neurodegenerative Disease

- Cognitive decline > Body function decline > death
- Life Expectancy 3-7 yrs from Diagnosis
- Pathology: β-Amyloid and Tau



A Huge Problem for Society

- Human Suffering
- Strain on Healthcare System & Government Budget
- Increasing Prevalence

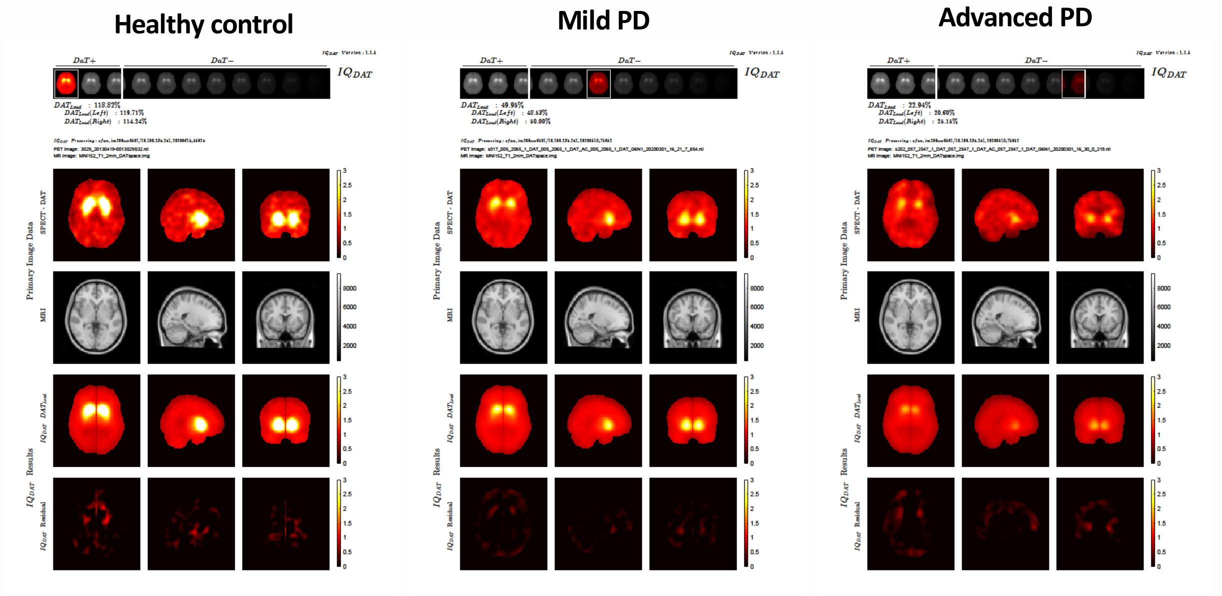


Primary Biomarkers: PET (Ab ▲, Tau ▲) & MRI (T1▼)

Neurodegeneration - Parkinson’s Disease

Neurodegenerative Disease

- 2nd most common ND after AD
- Motor Symptoms > Swallowing/speech/gait > cognitive decline
- Pathology: α-synuclein



A Huge Problem for Society

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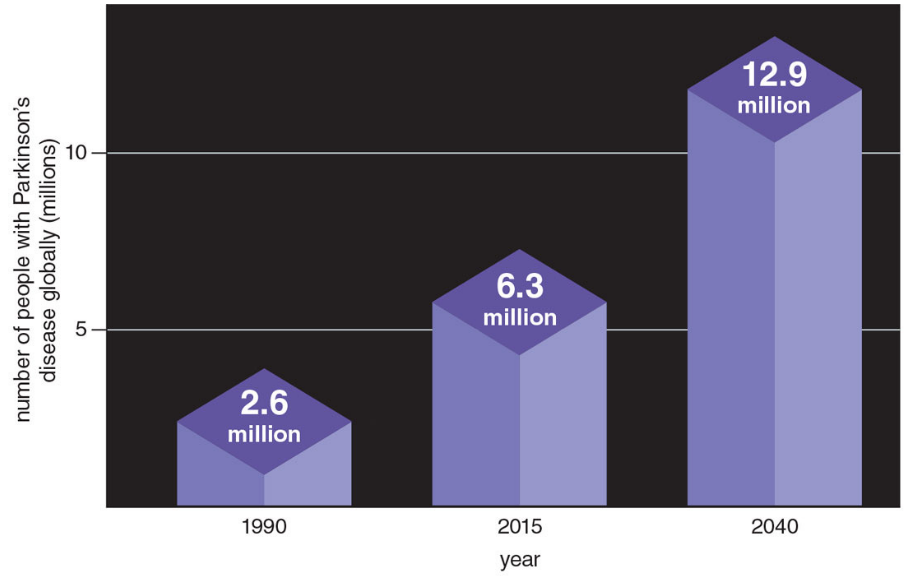
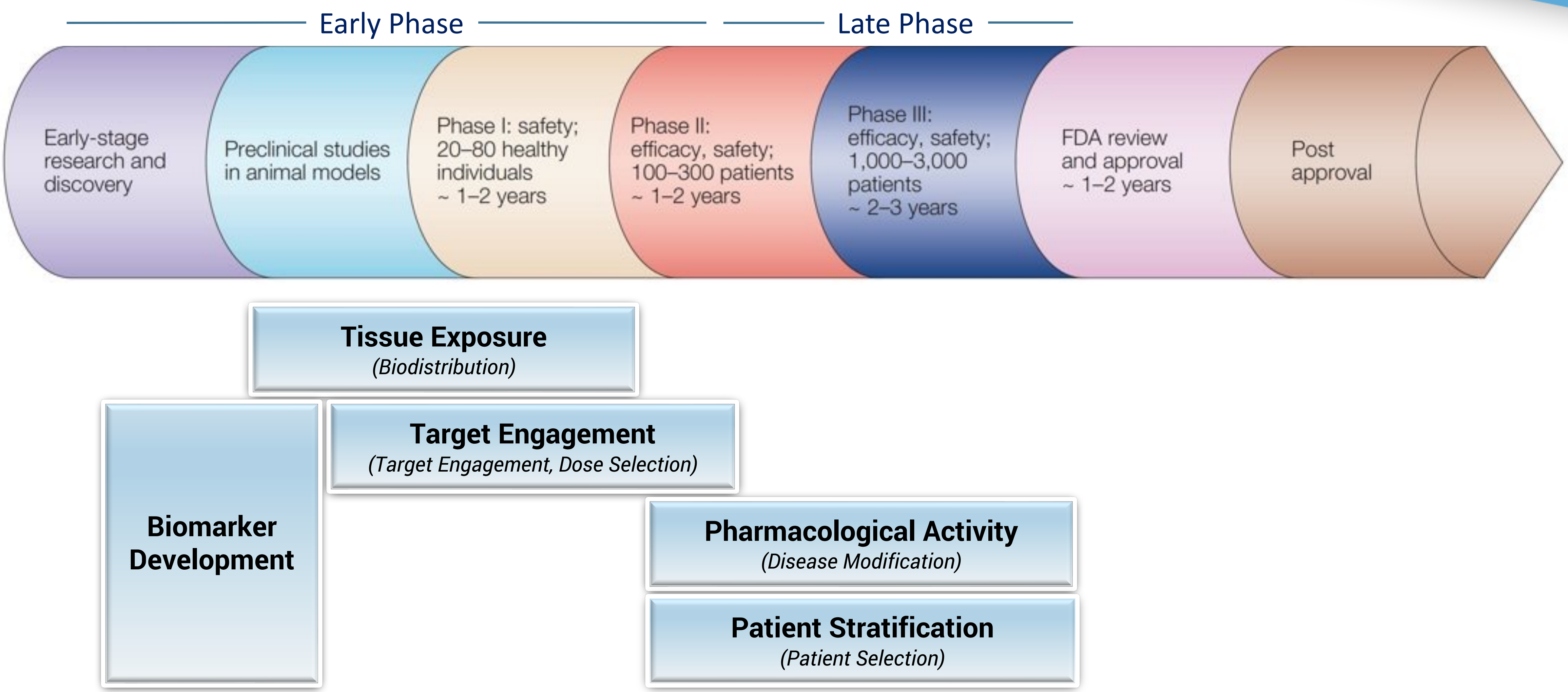


Primary Biomarkers: SPECT (DAT ▼) & PET (DAT ▼ & VMAT2 ▼)

Imaging Enables Drug Development Decision Making



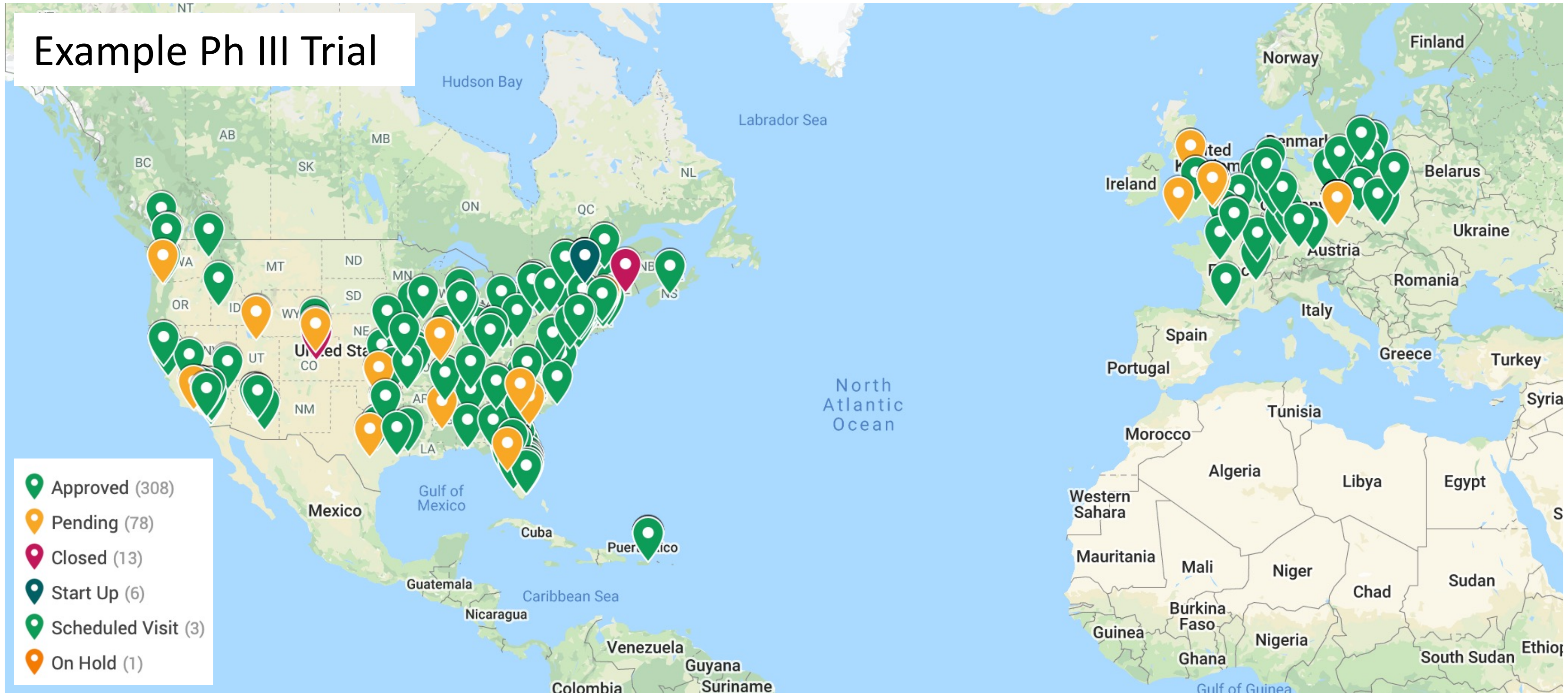
The ***Value*** of Imaging is dependent on ***Timing***

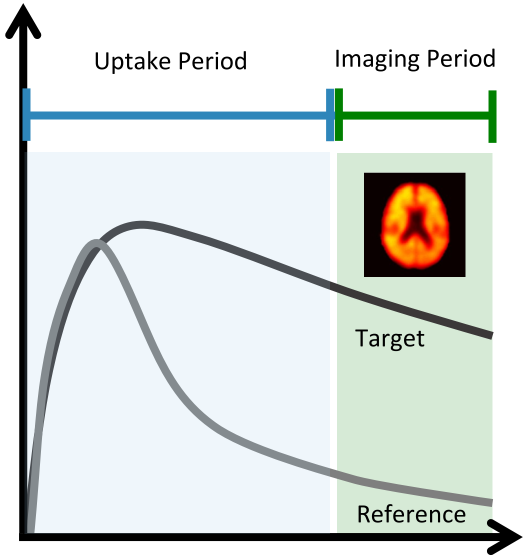
Explaining failures later in the process is of lower value; Decision making data for Go/No Go decisions is of high value; Early phase studies do not add much cost.

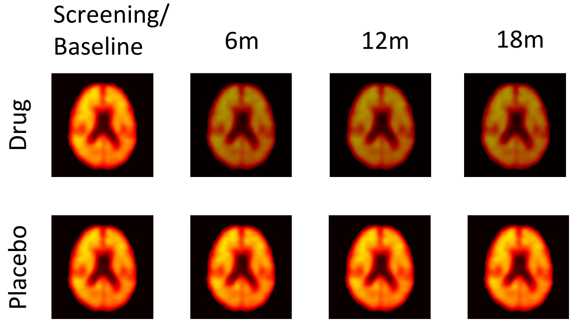
Multicenter Late Phase Imaging Trials

- Neurodegeneration (focus on Alzheimer's and Parkinson's Disease)
- Ph II (~200 Patients) and Ph III (~2,000 Patients)
- Amyloid, Tau, DaT
- Static Imaging

Example Ph III Trial

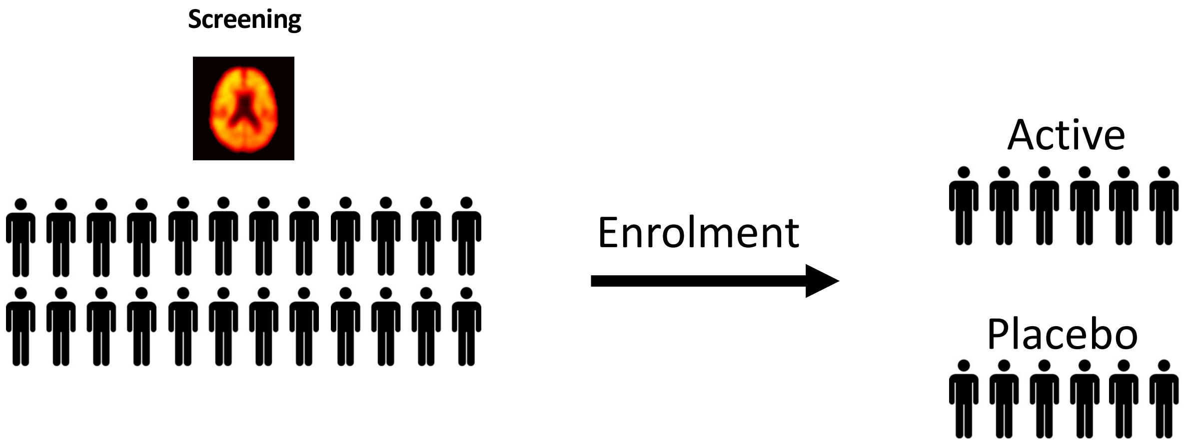






How is Imaging used in Multicenter Trials

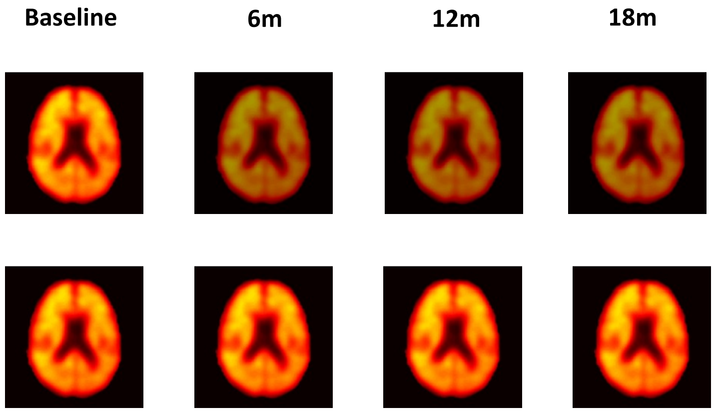
Stratification



Does a subject have the right characteristics to be a trial participant?

Visual Read or Quantitative Analysis

Longitudinal Analysis

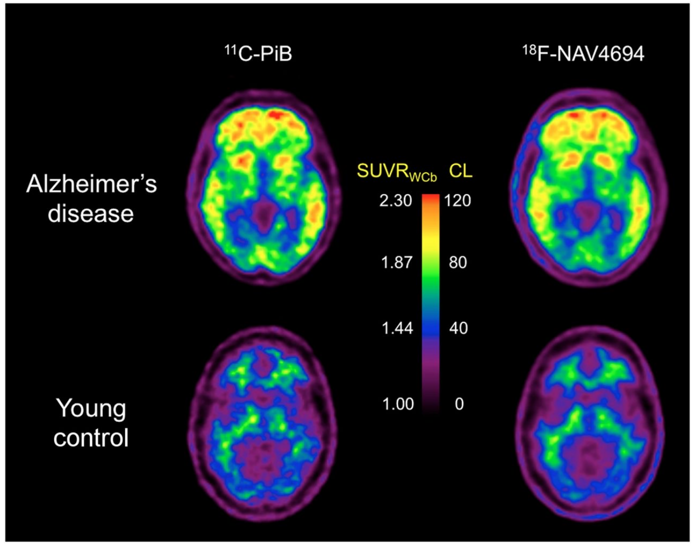


Does the drug change the disease related biomarker?

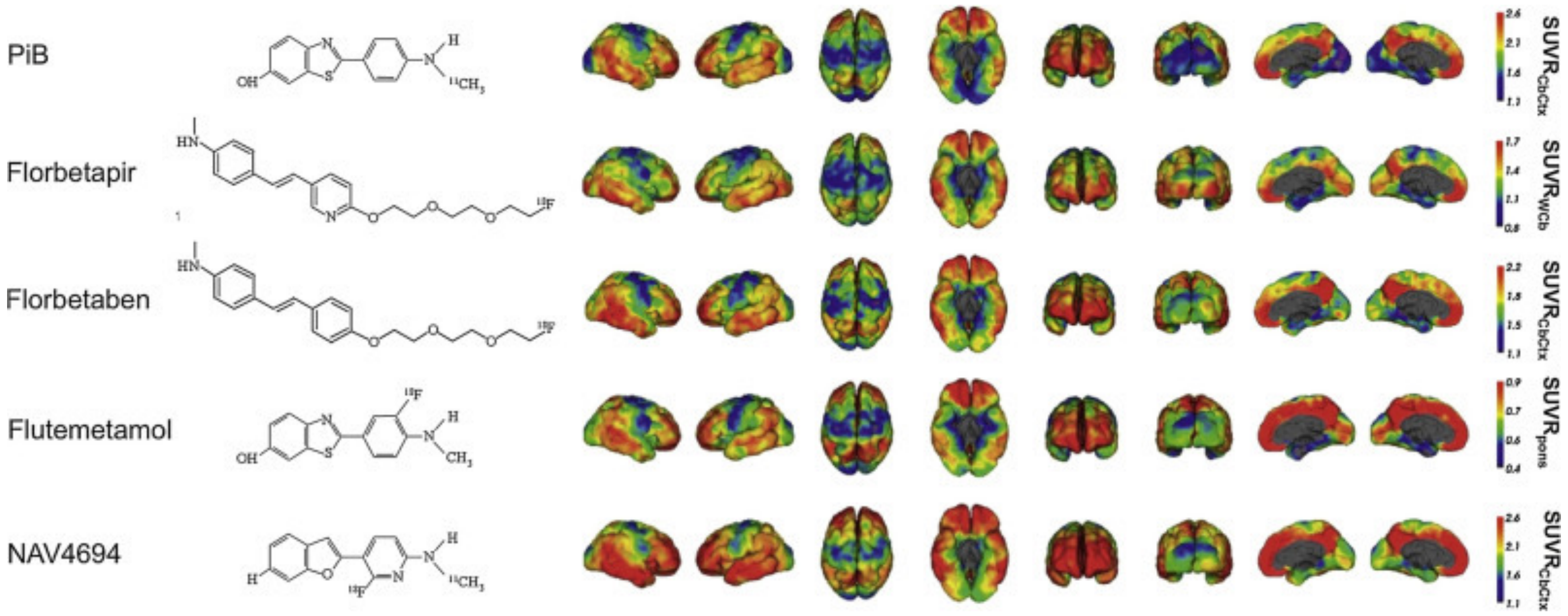
Quantitative Analysis

Established analysis approaches to date have been Visual Reads and SUVr Quantitative Analysis

AD Imaging Biomarkers - Amyloid

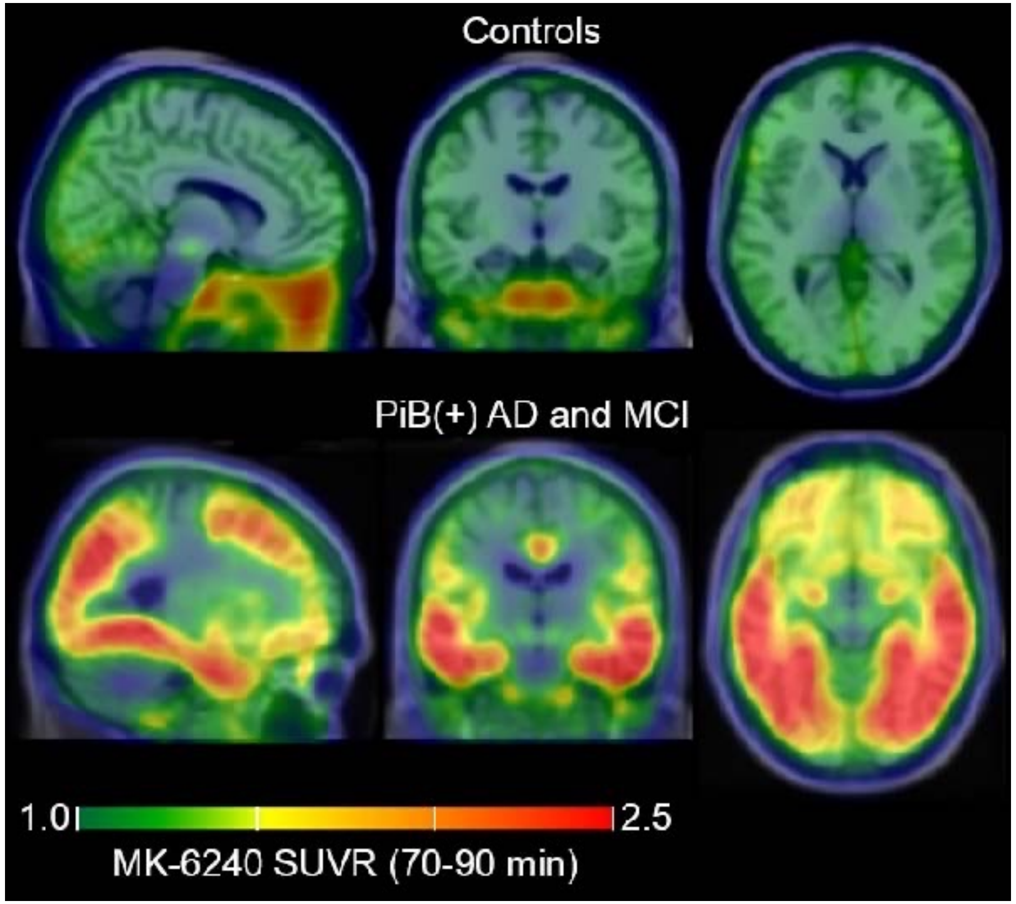


Rowe et al, 2016, JNM

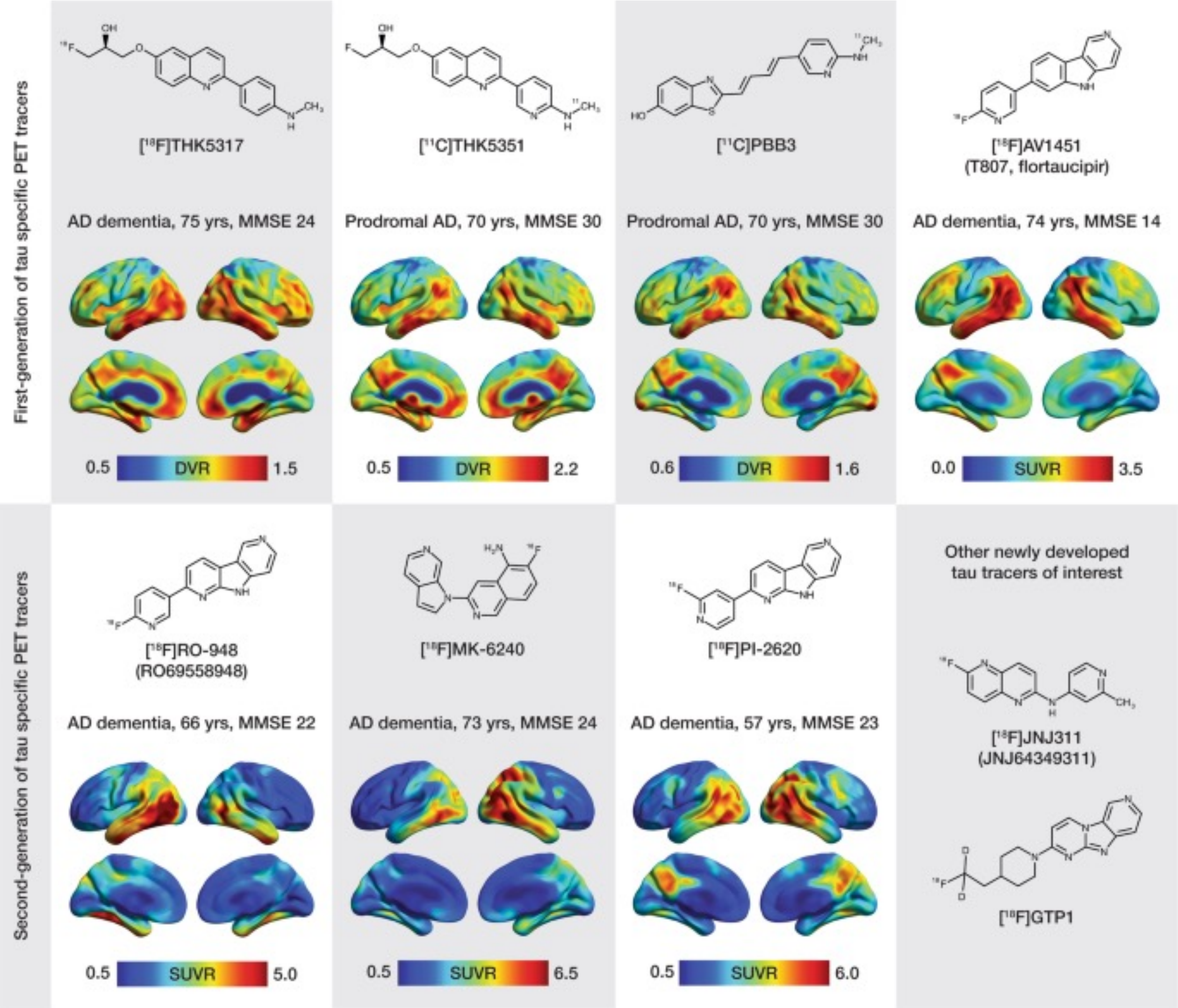


Meyer et al, 2019, Progress in Molecular Biology and Translational Science

AD Imaging Biomarkers - Tau

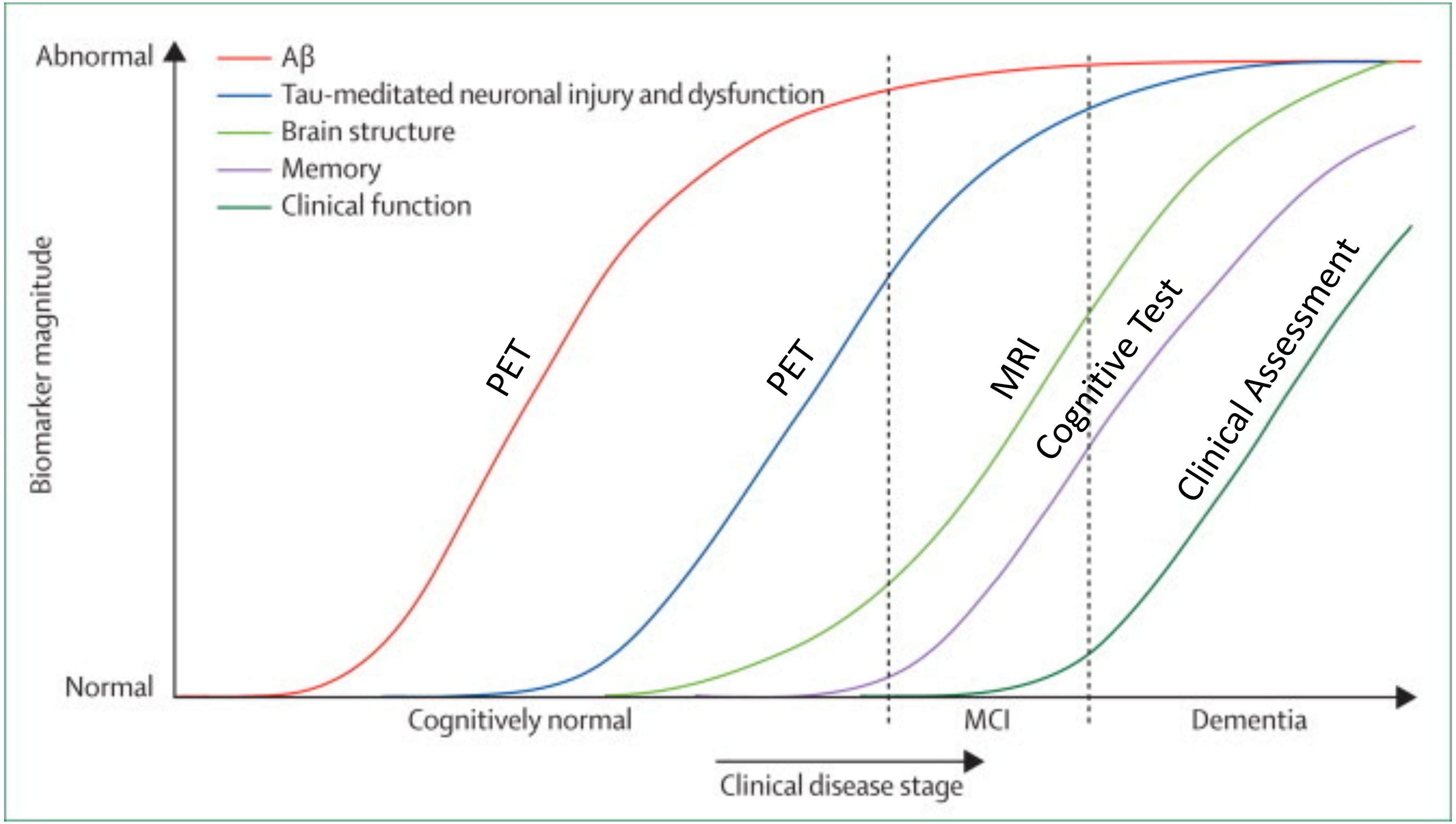


Betthauser et al., 2018



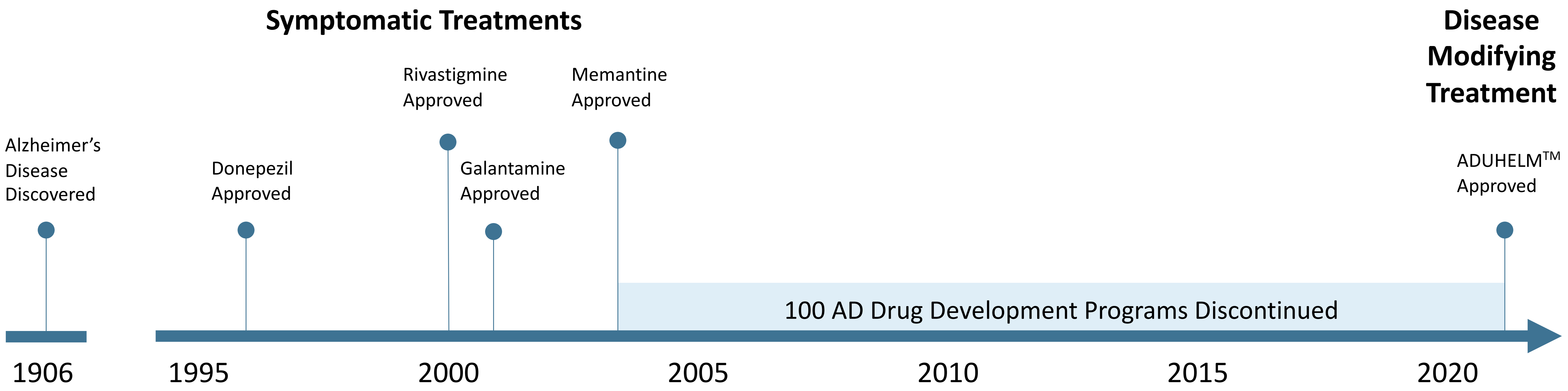
Leuzy et al, 2019 Mol Psych

Biomarker Trajectories in AD



Hypothesized Model of Alzheimer’s (Cliff Jack)

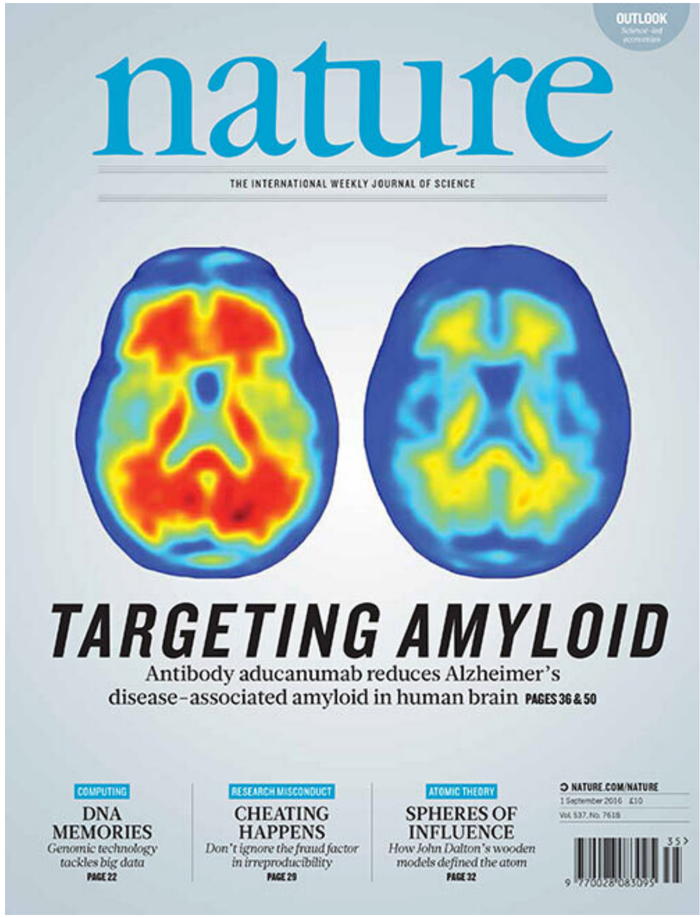
History of Alzheimer's Drug Development



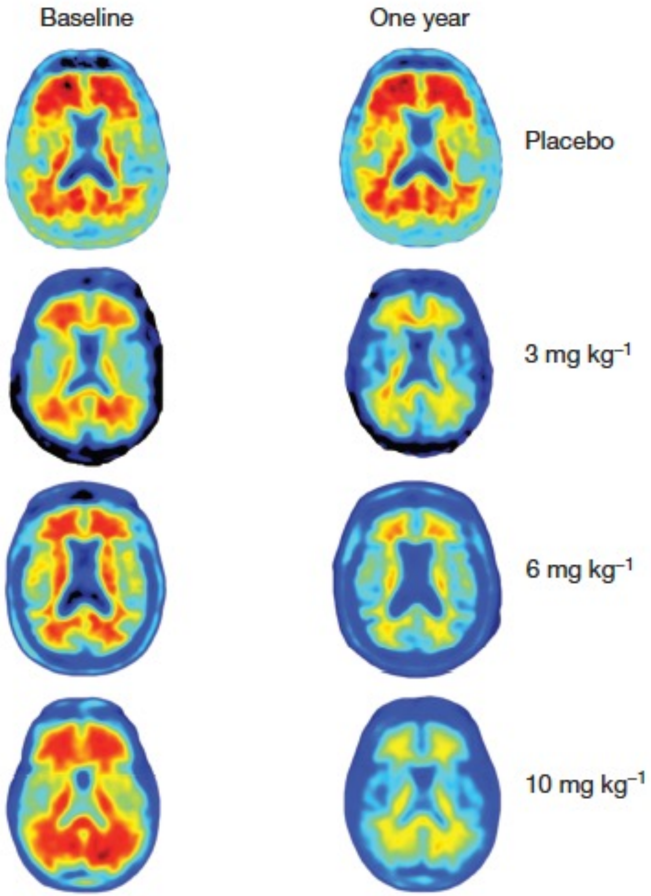
Measuring Amyloid clearance with PET

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

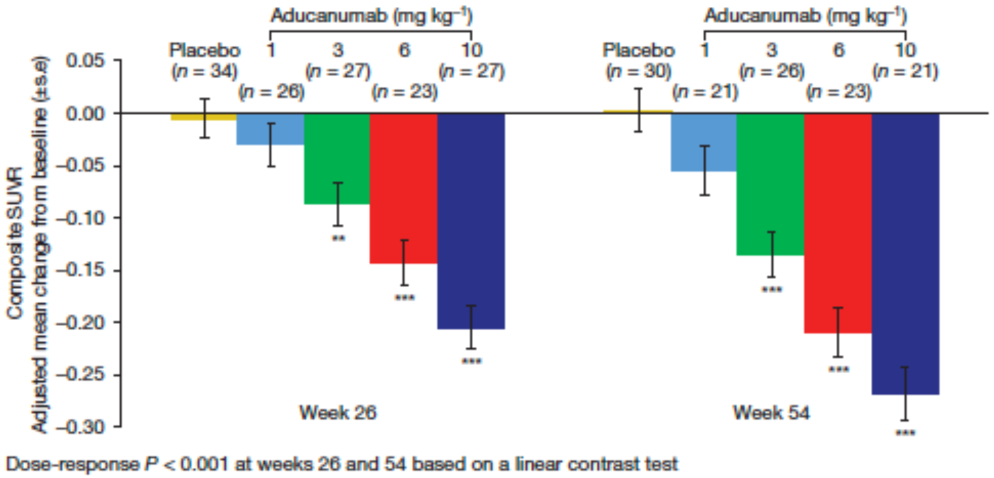
Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§



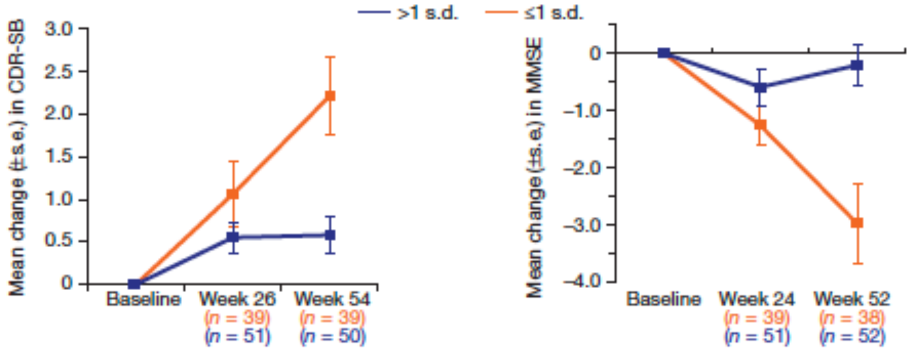
PET Amyloid



PET Amyloid



Clinical Measures



The Disease Modifying AD Therapy Landscape

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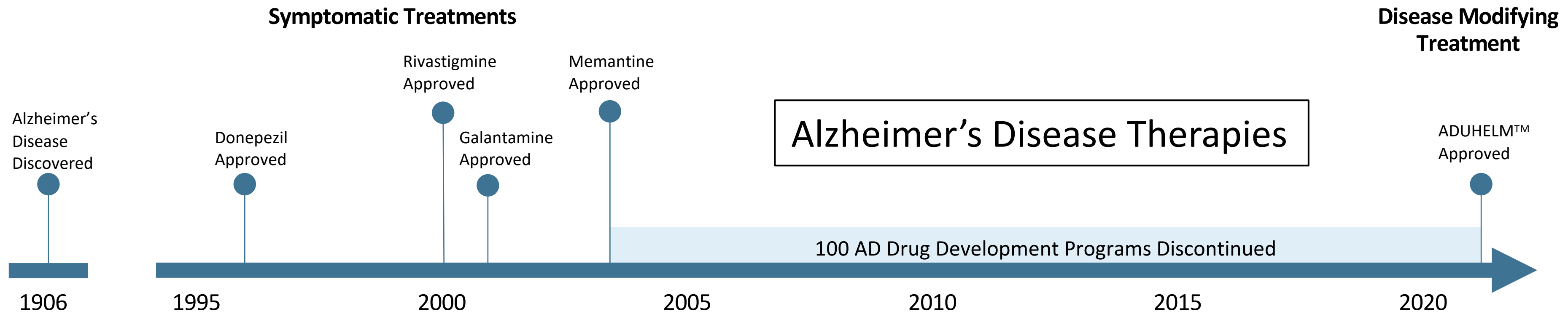


Biogen

Aducanumab

FDA approved
Modest effect
Controversial

Eisai

BAN 2401

In Ph III
Readout: Oct 2022

Roche

Gantenerumab

In Ph III
Readout: Dec 2022

Lilly

Donanemab

In Ph III
Readout: Mid 2023

Advanced Analytics - The IQ Platform

Provides improved analysis of neurodegenerative biomarkers
- Disease driven Analysis Algorithms
- Increase Statistical Power
- Automation

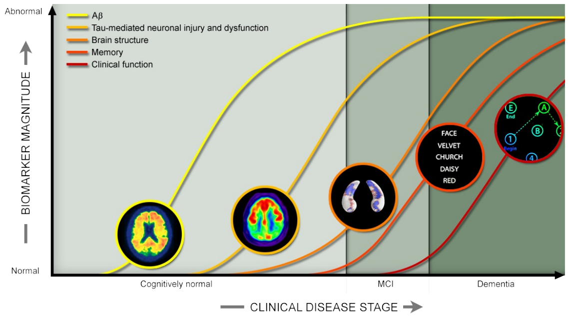
Alzheimer's Disease

AMYLOID IQ

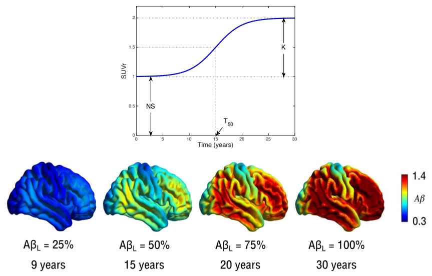
TAU IQ

Parkinson's Disease

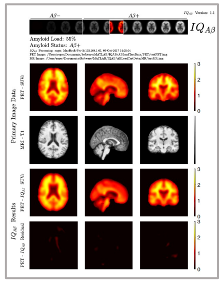
DAT IQ



Big Data



Spatio-Temporal Biomathematical Disease Modelling



IQ for Pharma Trials and Clinical Decision Making

Pharma
- Clinical Trials
  - Patient Stratification
  - Pharmacodynamic Readouts

Advanced Algorithms for Trials & Treatment

Patients
- Patient Treatment
  - Personalized Medicine

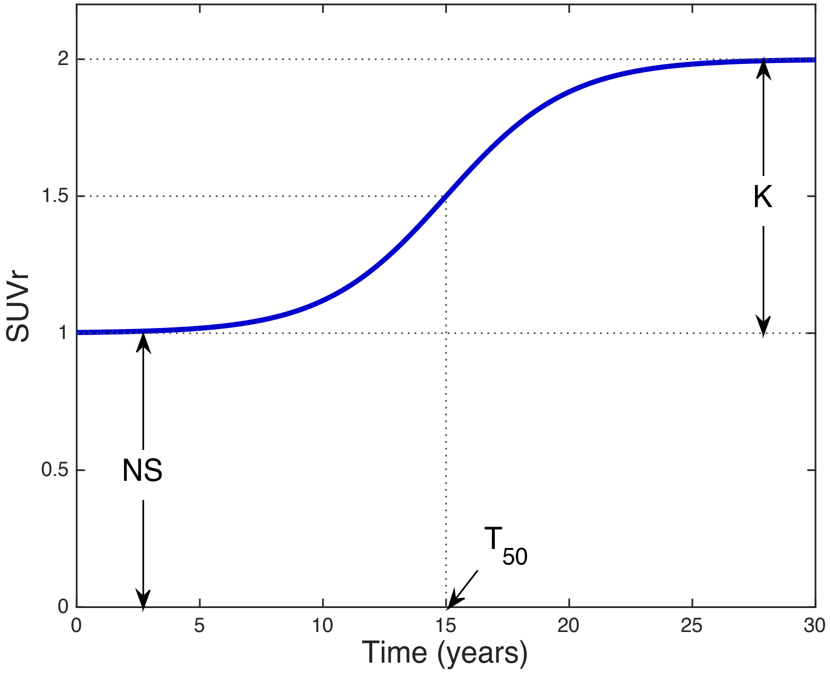
Originated from Spatio-Temporal Analysis of population AD data

MODELLING ACCUMULATION OF $A\beta$

$$\frac{dA\beta(t)}{dt} = rA\beta(t)\left(1 - \frac{A\beta(t)}{K}\right) \Rightarrow A\beta(t) = \frac{K}{1 + e^{-r(t-T_{50})}}$$

$$SUVr(t) = NS + A\beta(t)$$

$$SUVr(t) = NS + \frac{K}{1 + e^{-r(t-T_{50})}}$$

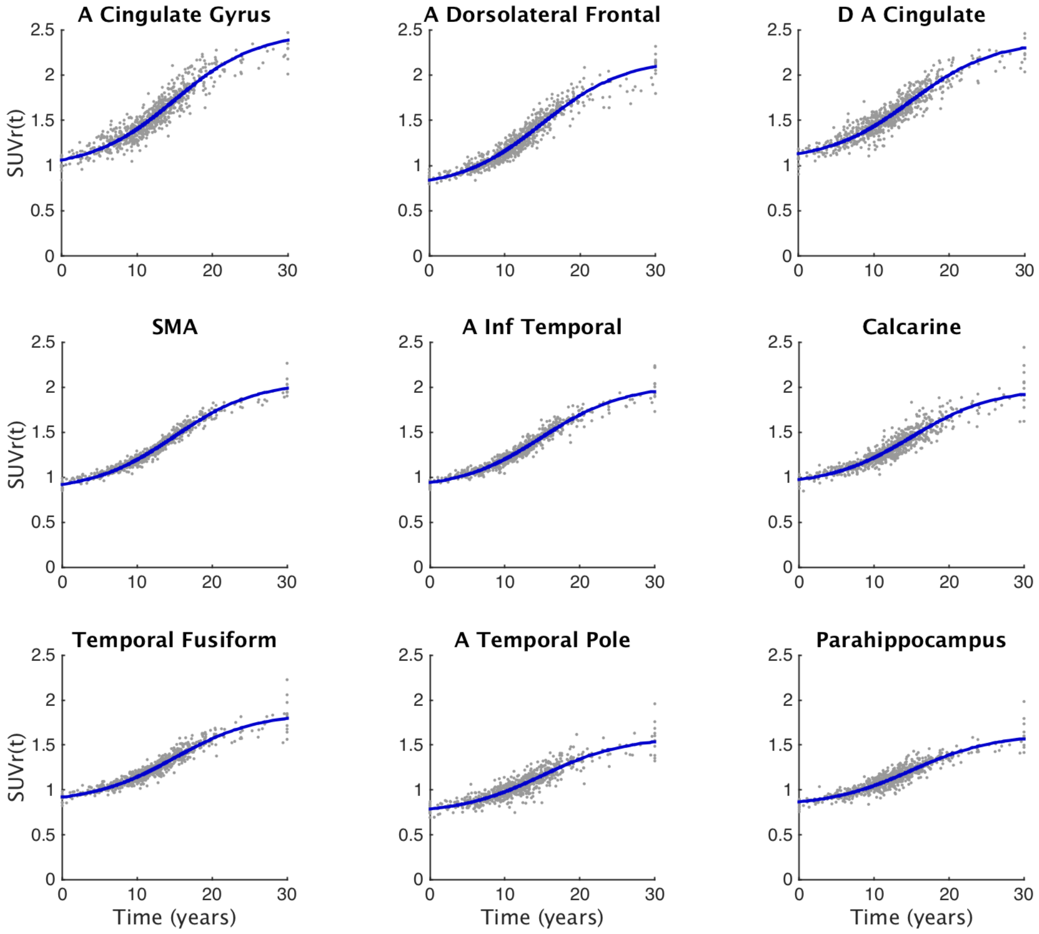


K Carrying Capacity
Varied across regions

NS Non-Specific
Varied across regions

T_{50} Time of Half Maximal Aβ concentration
Constant across regions

r Uninhibited Exponential Aβ Growth Rate
Constant across regions

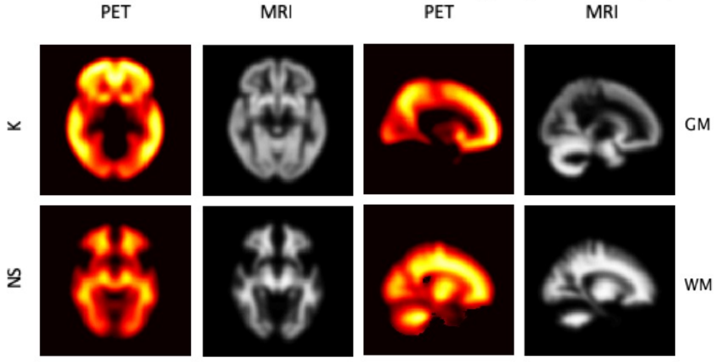


Whittington, Sharp & Gunn, JNM, 2018

The IQ Platform

AMYLOID^IQ

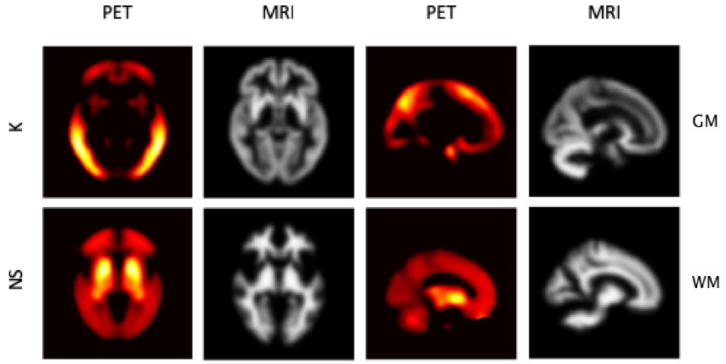
Amyloid^{IQ} - Canonical Images ([^{18}F]Florbetapir)



Whittington and Gunn, 2019, JNM

TAU^IQ

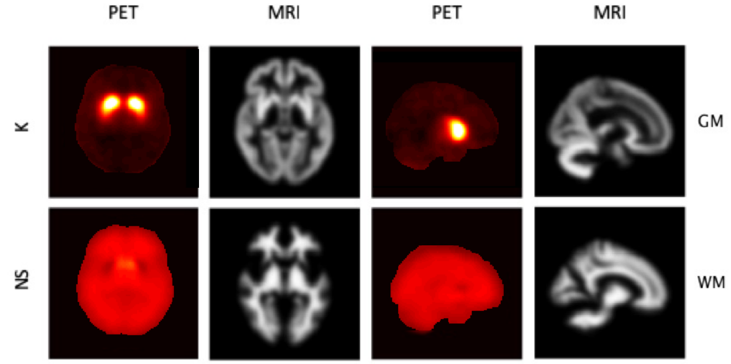
Tau^{IQ} - Canonical Images ([^{18}F]Flortaucipir)

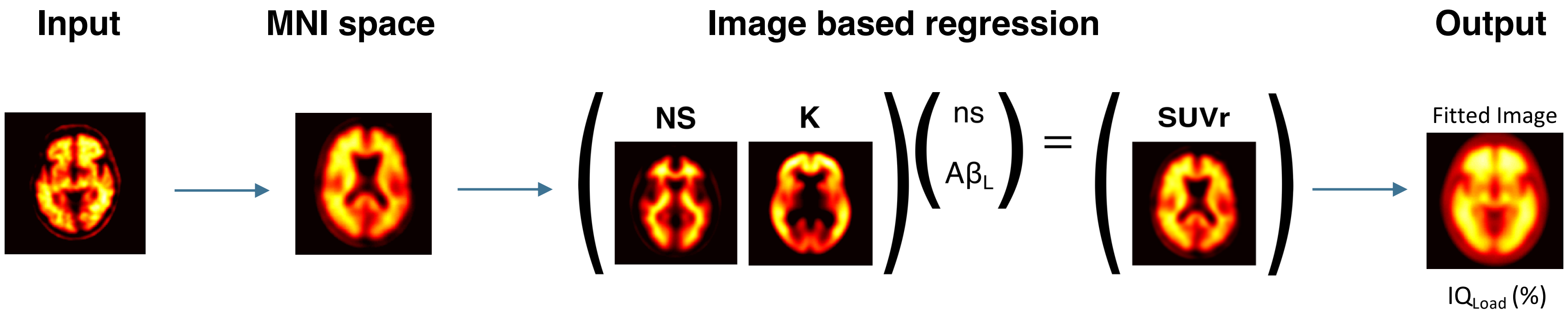


Whittington and Gunn, 2021, JNM

DAT^IQ

DAT^{IQ} – Canonical Images ([^{123}I]Ioflupane)





AMYLOID IQ

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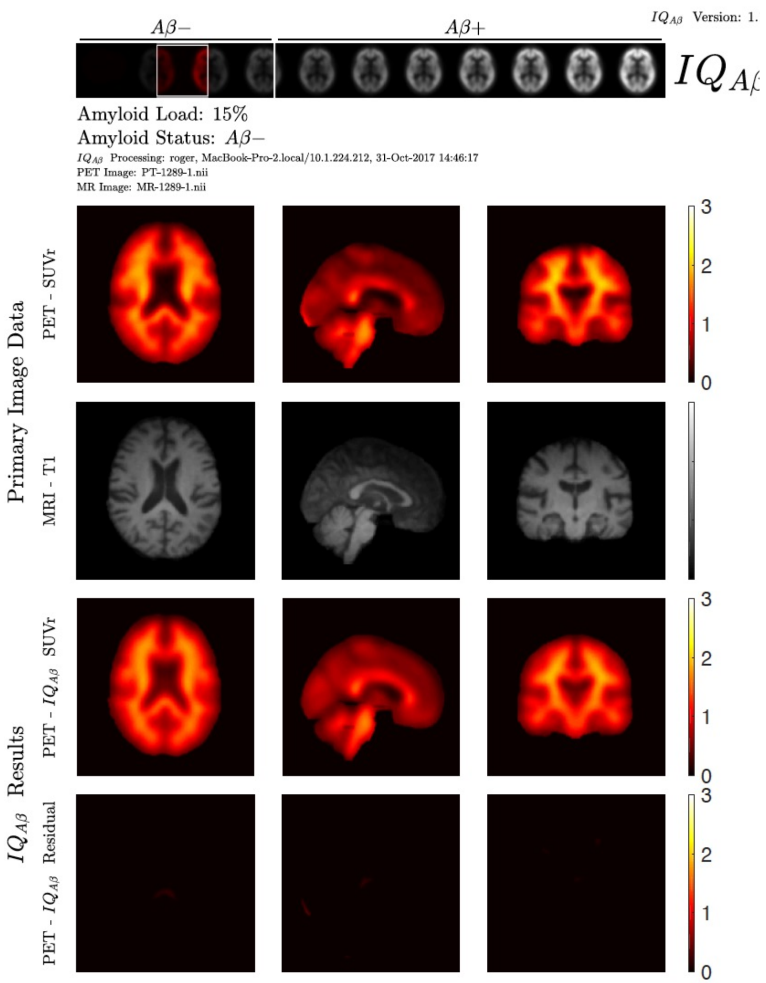
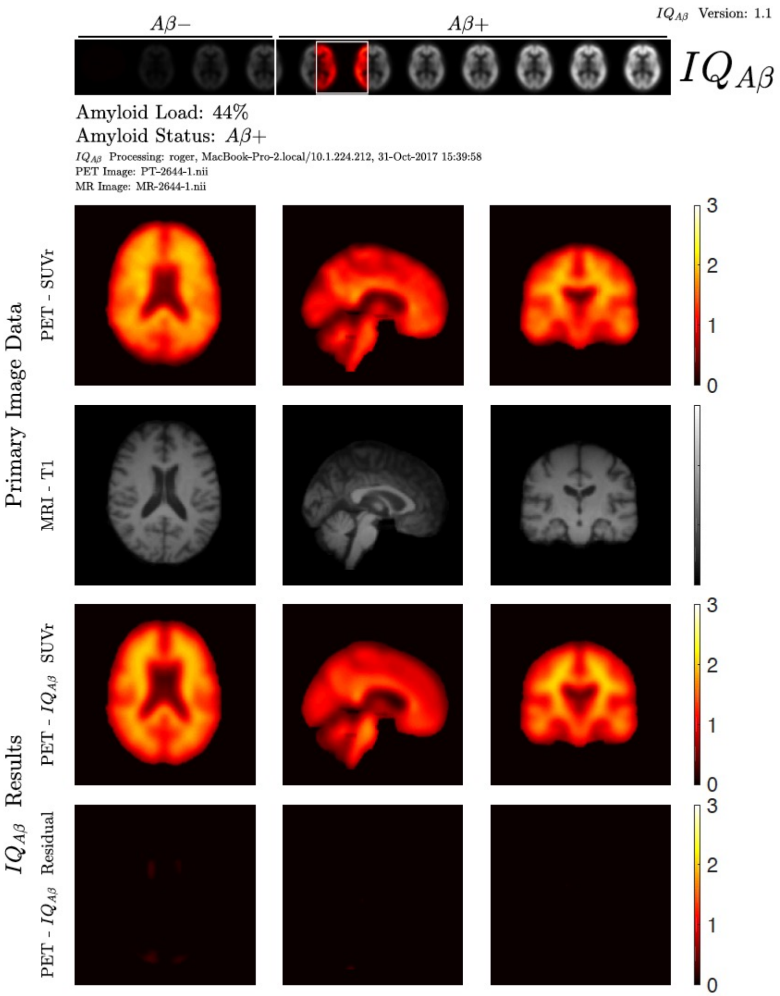
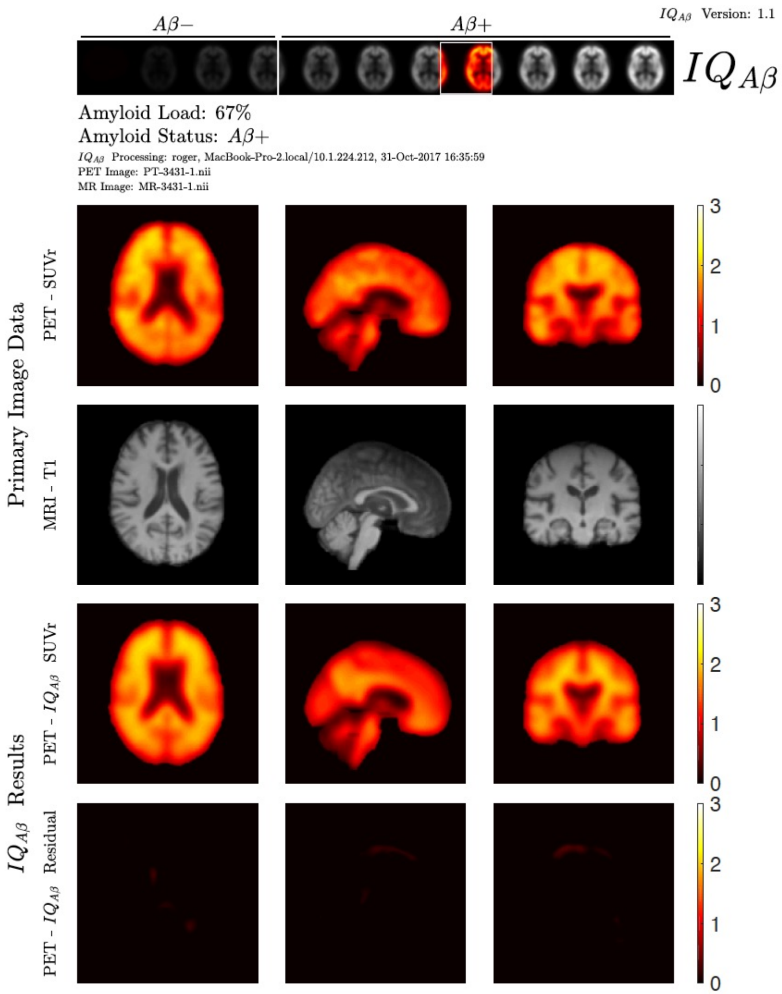
Healthy	MCI	AD
Low Aβ	Moderate Aβ	High Aβ







AMYLOID^IQ *outperforms Conventional Analytics*

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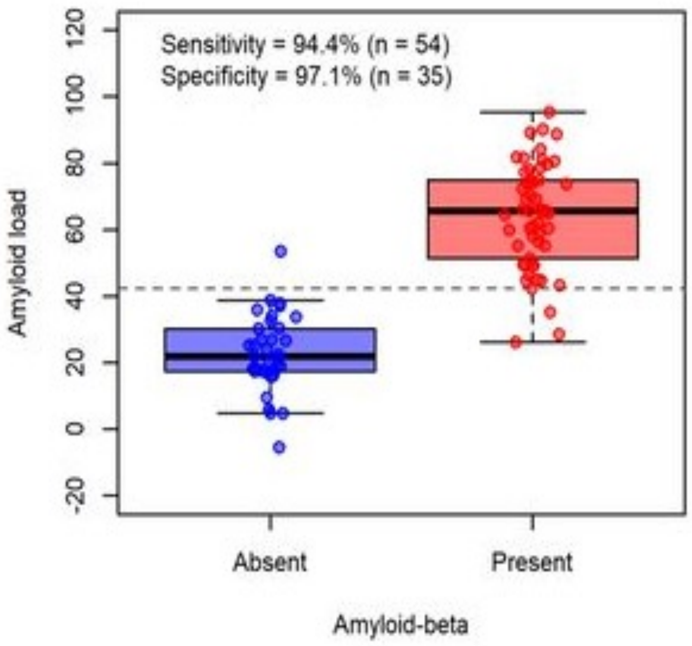
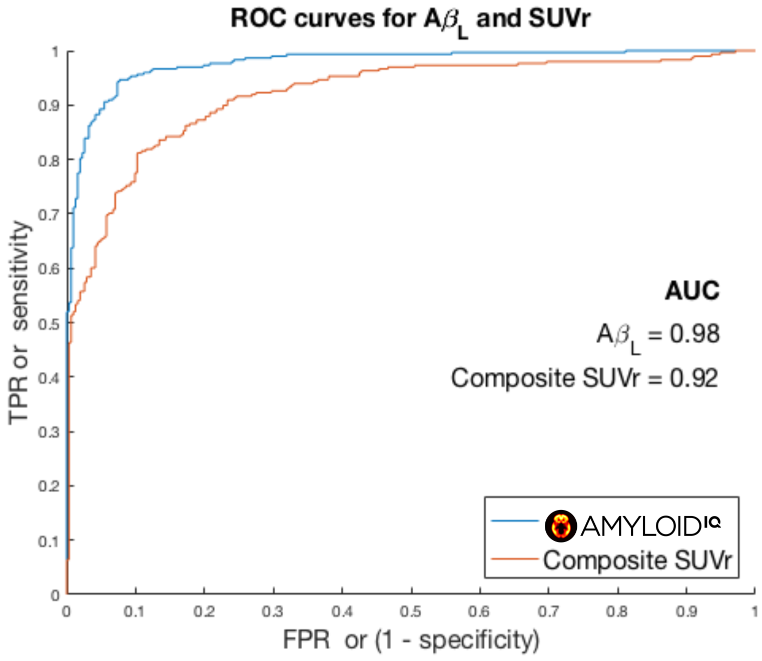
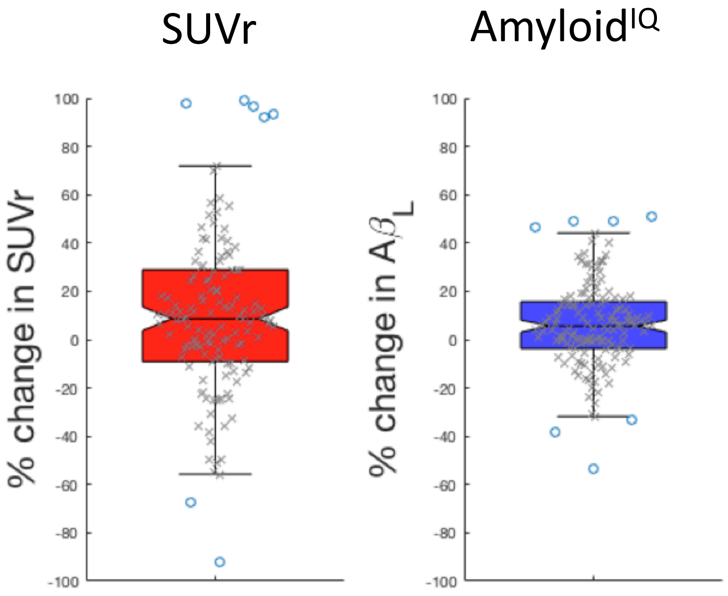
Comparison with Post-Mortem Data



Comparison with Visual Reads



Longitudinal Analysis



Amyloid^IQ	$A\beta_L$ Positive	$A\beta_L$ Negative
Post-Mortem Positive	**51**	**3**
Post-Mortem Negative	**1**	**34**

Amyloid^IQ	$A\beta_L$ Positive	$A\beta_L$ Negative
Visual Read Positive	**318**	**19**
Visual Read Negative	**25**	**310**

SUVr

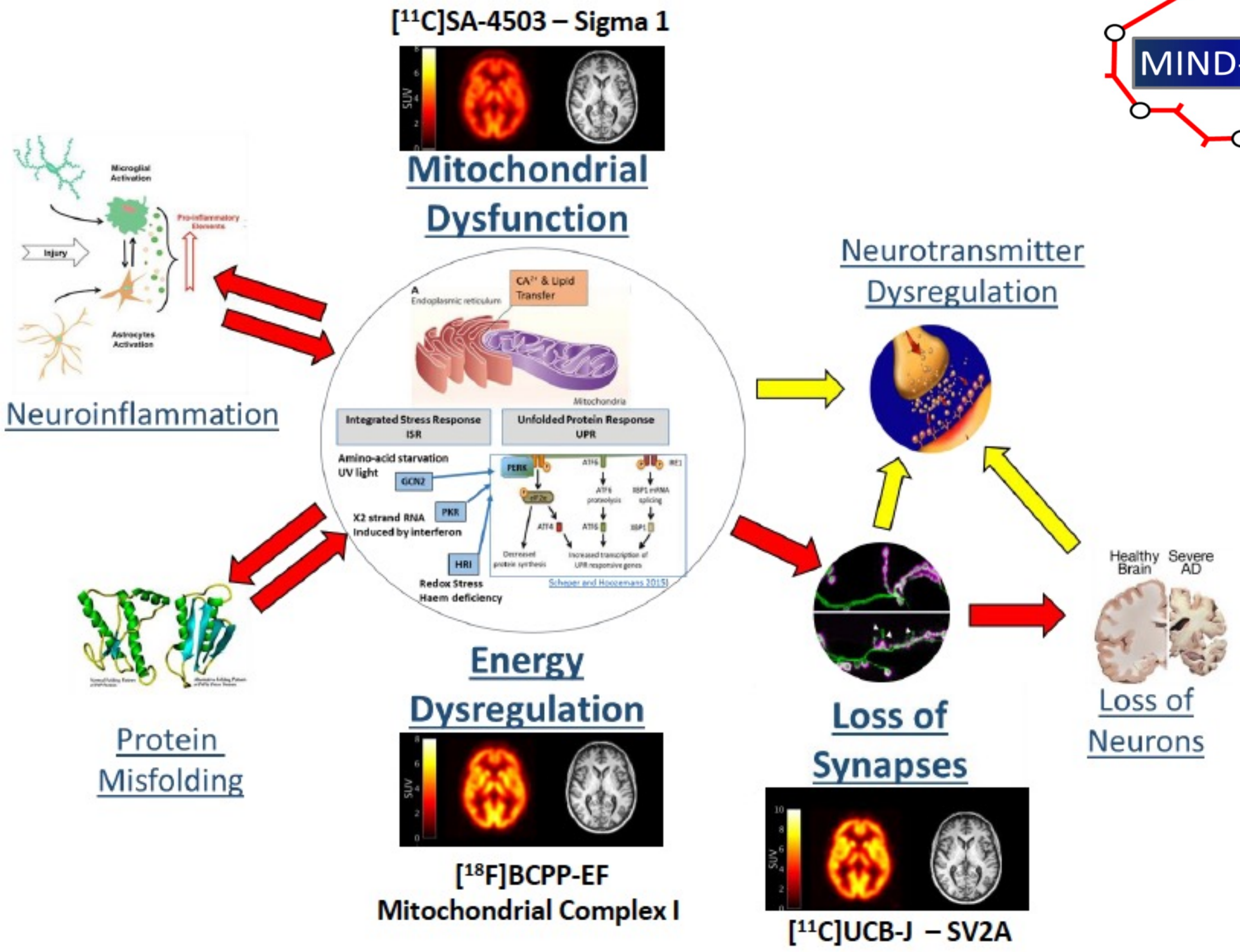
ΔSUVr = 0.026
s.d. = 0.11
Effect Size = 0.35

Amyloid^IQ

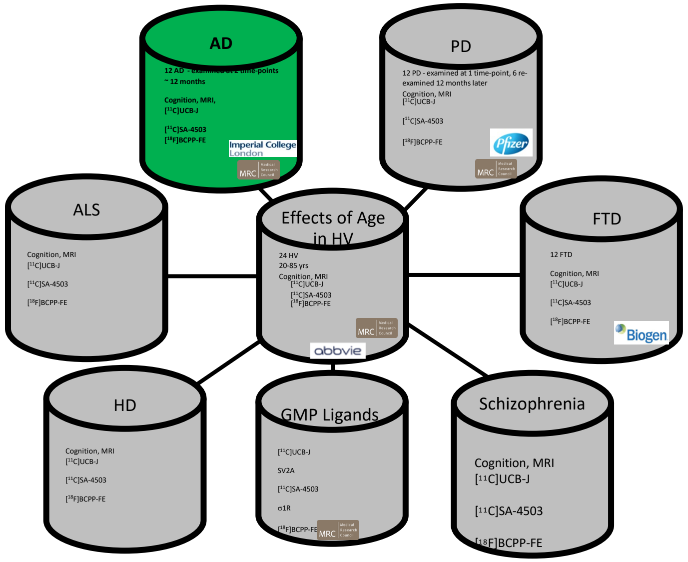
$\Delta A\beta_L$= 0.02
s.d. = 0.058
Effect Size = 0.49

BETTER THAN **OTHER APPROACHES** WHEN COMPARED TO **"GOLD STANDARD"**

Novel Biomarkers for AD - MIND MAPS



Molecular Imaging of Neuro Degeneration – Mitochondria, Associated Proteins & Synapses



Cell stress & Mitochondrial changes in AD

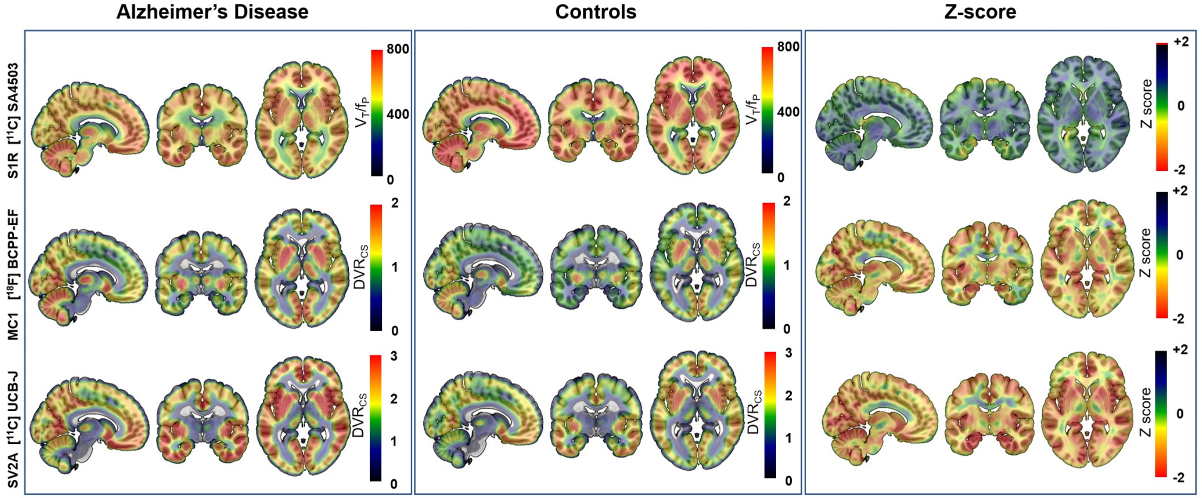
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

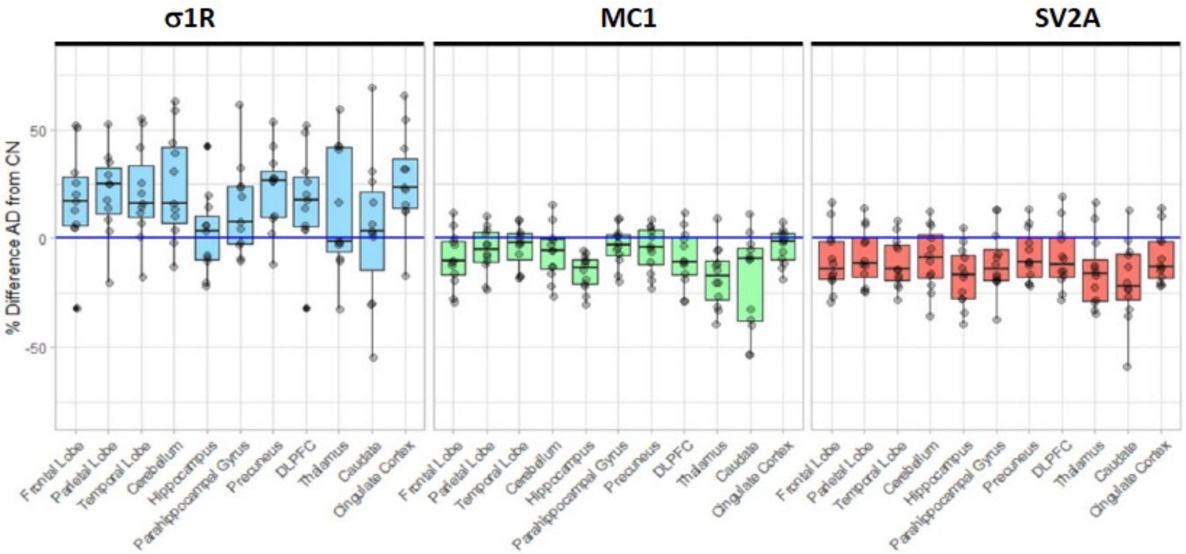
ALZHEIMER'S DISEASE

Widespread cell stress and mitochondrial dysfunction occur in patients with early Alzheimer's disease

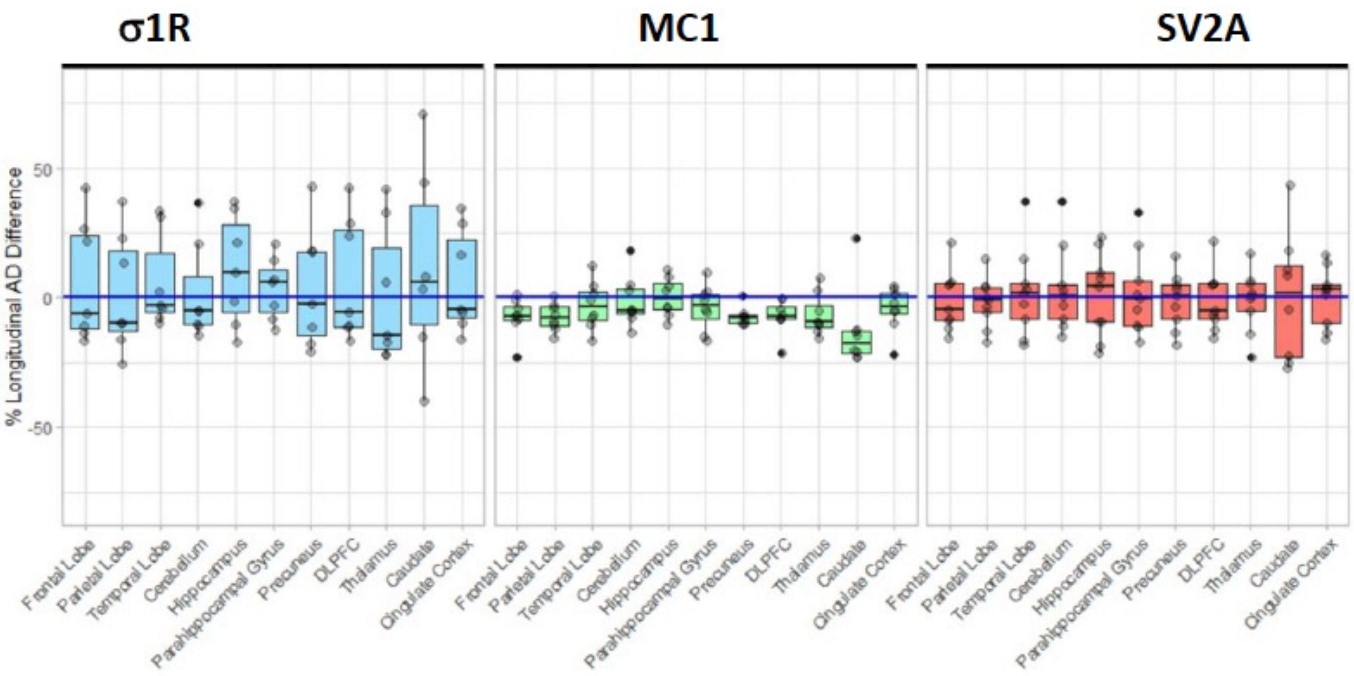
Ashwin V. Venkataraman[1,2], Ayla Mansur[3], Gaia Rizzo[1,3], Courtney Bishop[3], Yvonne Lewis[3], Ece Kocagoncu[4], Anne Lingford-Hughes[1], Mickael Huiban[3], Jan Passchier[3], James B. Rowe[4], Hideo Tsukada[5], David J. Brooks[6,7], Laurent Martarello[8], Robert A. Comley[9], Laigao Chen[10], Adam J. Schwarz[11], Richard Hargreaves[12], Roger N. Gunn[1,3], Eugenii A. Rabiner[3,13]†, Paul M. Matthews[1,2]*†

Science Translational Medicine



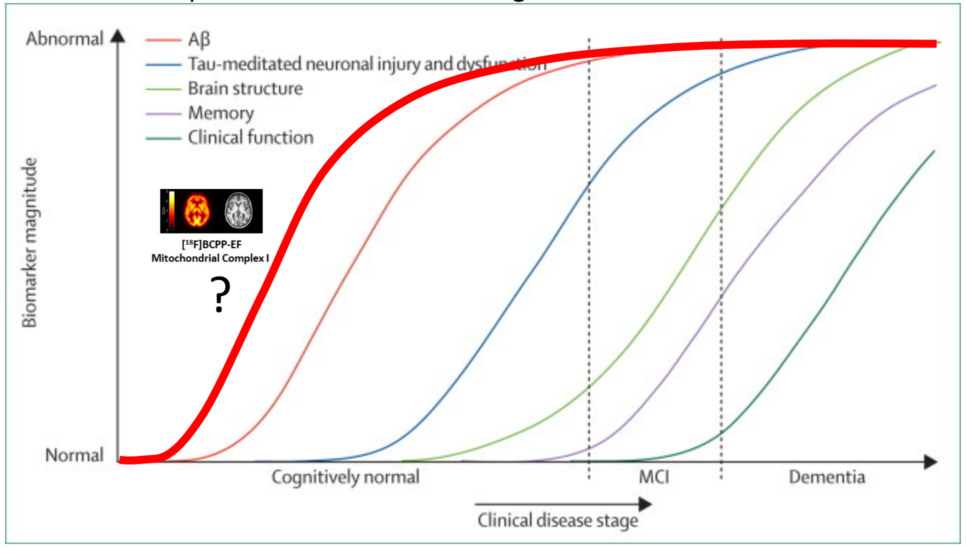


Longitudinal Changes in AD patients



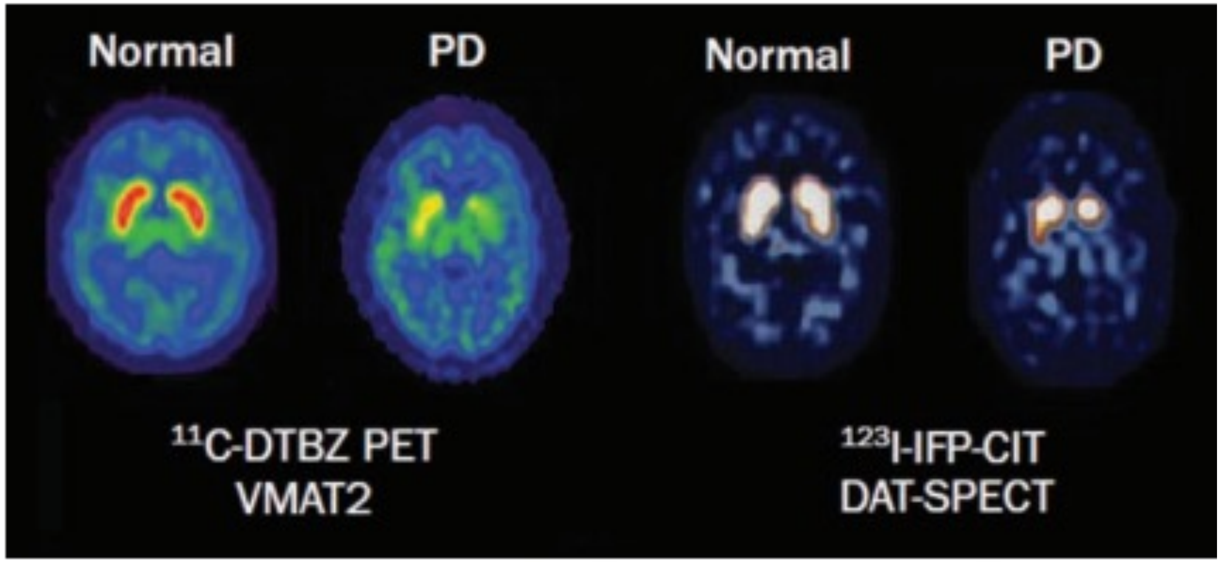
Longitudinal changes over 12-18 mths

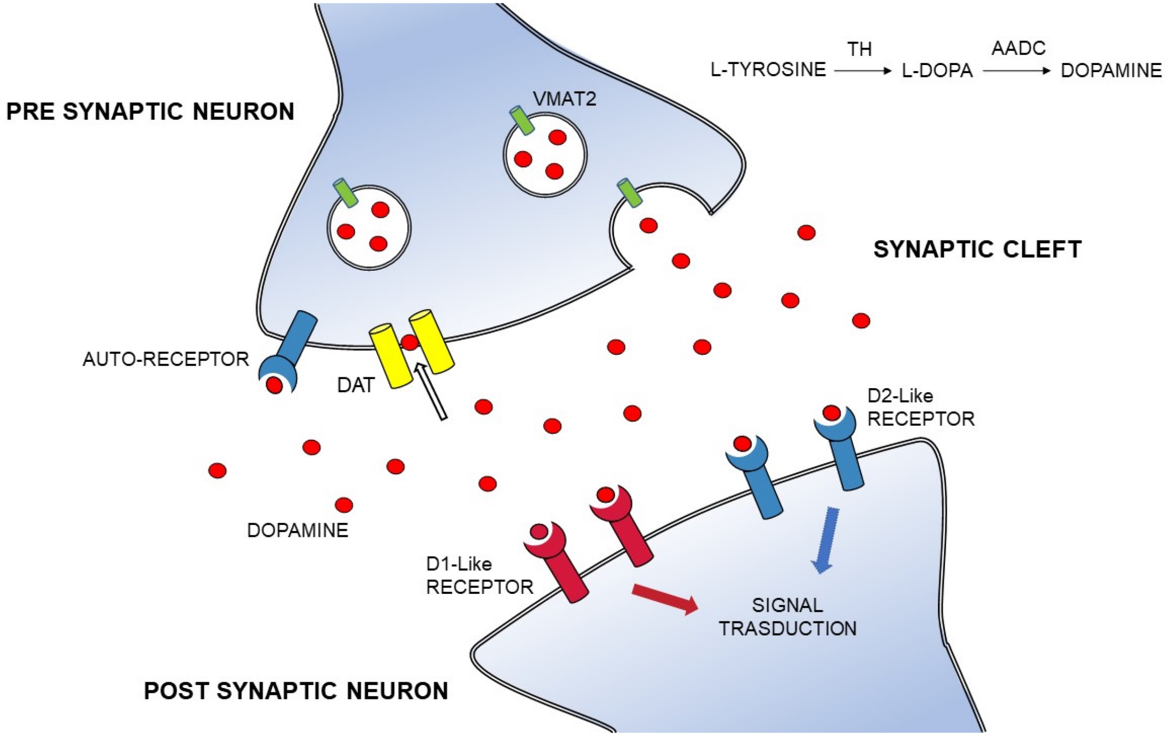
Can we develop biomarkers for earlier stages of the disease?



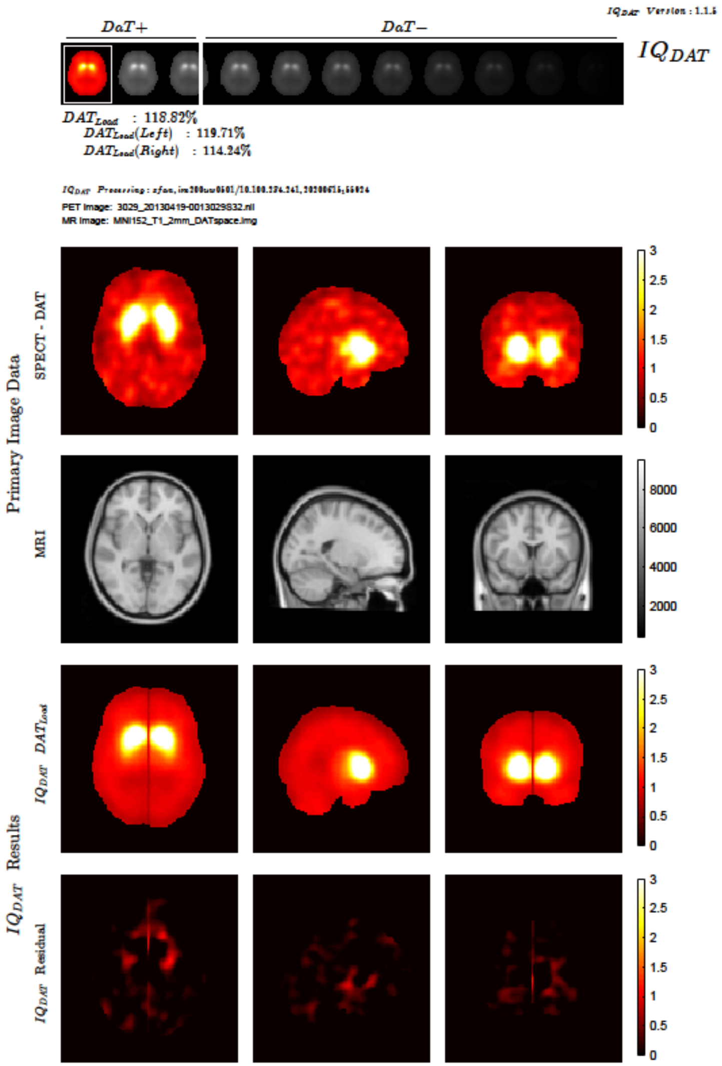
Hypothesized Model of Alzheimer's (Cliff Jack)

PD Imaging Biomarkers

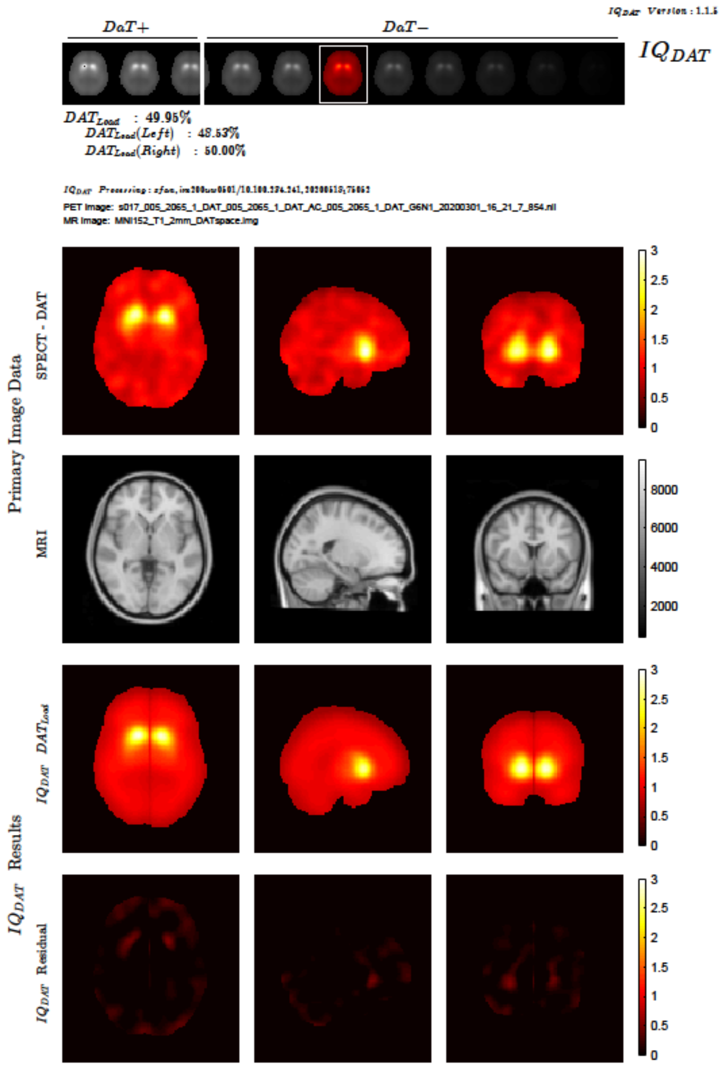




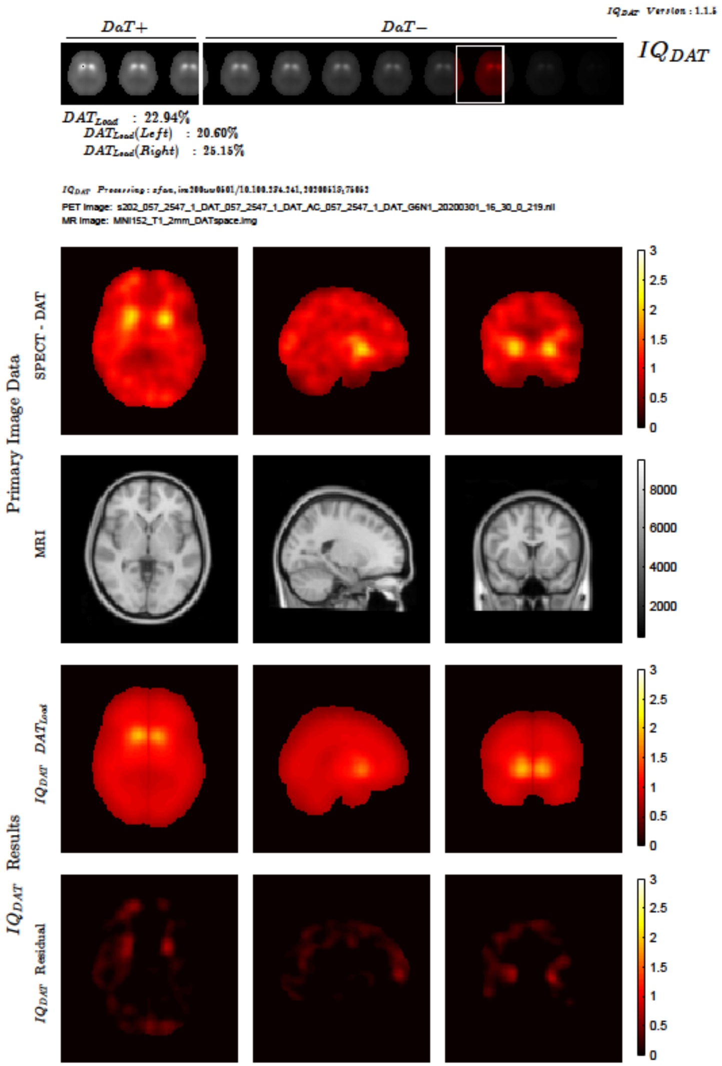
Healthy control



Mild PD



Advanced PD

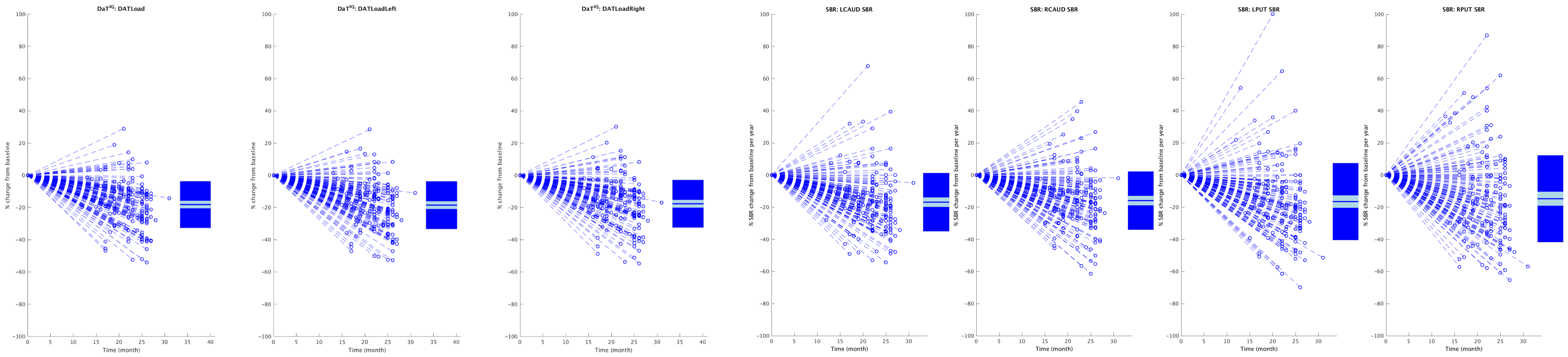


DAT[IQ] SURE-PD Dataset and Analysis

SURE-PD3 was designed to assess whether urate-elevating inosine treatment slows PD clinical decline. The trial was terminated after an interim analysis showed futility. DaT imaging was performed 1 month before baseline and 22 months after randomization to placebo or active-drug in 154 participants.

DAT-IQ

SBR



Method	Parameter Name	% Change (per year)	SD	Effect size	Sample size (each arm) 50% change in signal with power of 80%
DAT[IQ]	**DAT_{Load}**	-9.84	7.97	**-1.23**	**43**
SBR method	caudate	-9.10	9.04	**-1.01**	**60**

VMAT2 – Longitudinal Analysis (N=30)

Optimising Target and Reference Regions for SUVR Analysis

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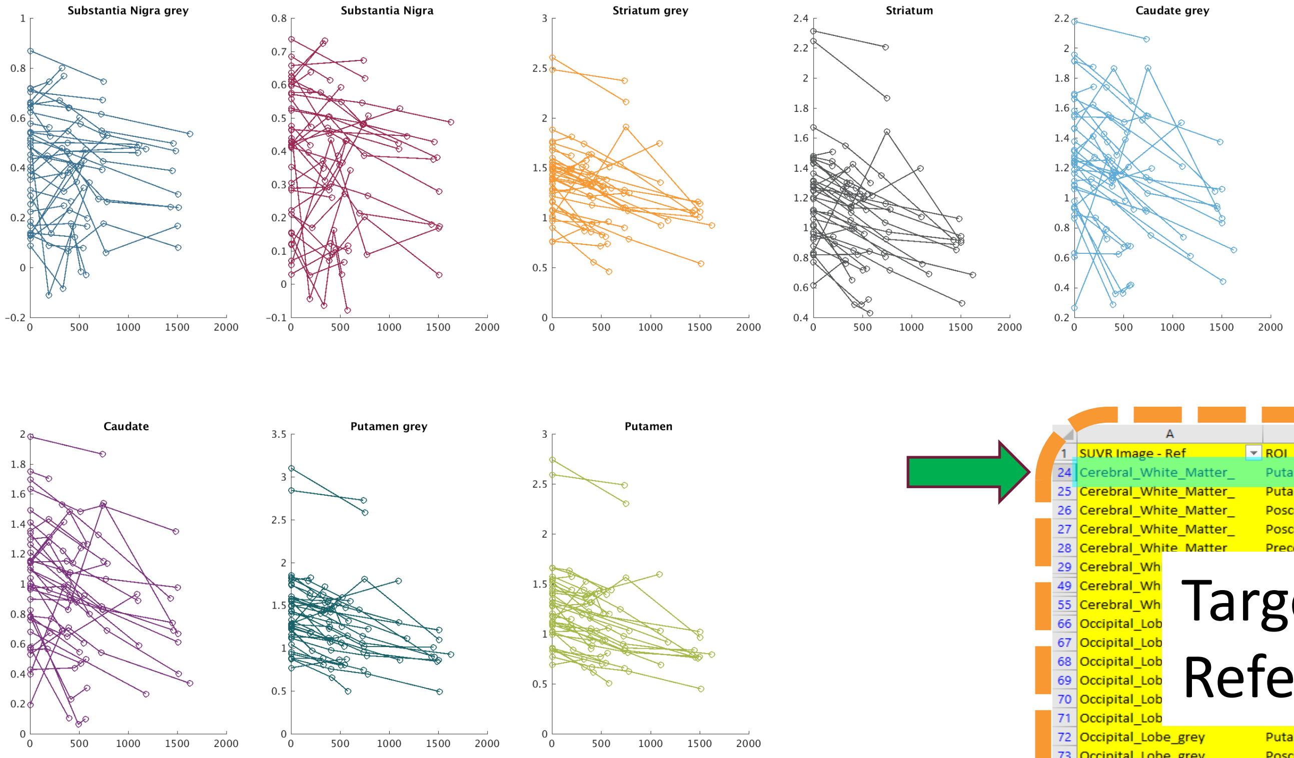


	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	SUVR Image - Ref	ROI	Parameter	Stats_g	Stats_g	Stats_g	Stats_g	Stats_g	Stats_g	Stats_g	Stats_g	Stats_p	Stats_p	Stats_perSca	Stats_perScan
24	Cerebral_White_Matter_	Putamen_	2yr mean/sd	NaN	-1.0221	-1.1225	-1.6921	NaN	-0.96407	-1.0795	-2.2066	-1.0478	-0.9835	-1.1087	-1.0642
25	Cerebral_White_Matter_	Putamen_grey	2yr mean/sd	NaN	-1.0122	-0.91518	-1.7205	NaN	-0.95724	-0.83347	-2.1892	-1.0238	-0.96369	-1.0351	-0.97808
26	Cerebral_White_Matter_	Poscommissural_Putamen_	2yr mean/sd	NaN	-0.90049	-1.1325	-1.4559	NaN	-0.8473	-1.165	-1.864	-0.95183	-0.8718	-0.98097	-0.96523
27	Cerebral_White_Matter_	Poscommissural_Putamen	2yr mean/sd	NaN	-0.85073	-1.2526	-1.4671	NaN	-0.6833	-1.3242	-1.8713	-0.92887	-0.7108	-0.98049	-0.84892
28	Cerebral_White_Matter	Precommissural_Putamen	2yr mean/sd	NaN	-0.84771	-0.73577	-1.7041	NaN	-0.78215	-0.66519	-2.0652	-0.91126	-0.842	-0.87823	-0.80909
29	Cerebral_Wh													82738	-0.73452
49	Cerebral_Wh													86702	-0.73149
55	Cerebral_Wh													86773	-0.72006
66	Occipital_Lob													.6708	-0.67196
67	Occipital_Lob													63345	-0.65652
68	Occipital_Lob													0.625	-0.62901
69	Occipital_Lob													62841	-0.6256
70	Occipital_Lob													59465	-0.62286
71	Occipital_Lob													.6404	-0.58419
72	Occipital_Lobe_grey	Putamen_grey	2yr mean/sd	NaN	-0.59644	-0.47509	-1.5688	NaN	-0.57911	-0.41857	-2.011	-0.63545	-0.6240	-0.608	-0.57523
73	Occipital_Lobe_grey	Poscommissural_Putamen	2yr mean/sd	NaN	-0.5025	-0.68896	-1.3656	NaN	-0.4872	-0.71774	-1.5907	-0.58872	-0.57116	-0.58003	-0.5738
74	Cerebellum_	Temporal_Lobe_	2yr mean/sd	NaN	0.53721	0.50082	0.80176	NaN	-0.49739	-0.521	-0.8228	0.49928	-0.4666	0.50783	-0.50224
75	Occipital_Lobe_	Striatum_	2yr mean/sd	NaN	-0.43254	-0.45735	-1.701	NaN	-0.43741	-0.47887	-1.9623	-0.49289	-0.4940	-0.4925	-0.49231
76	Cerebellum_	Temporal_Lobe_grey	2yr mean/sd	NaN	0.49567	0.50513	0.86156	NaN	-0.45864	-0.52752	-0.86304	0.47645	-0.4465	0.4899	-0.48788
77	Occipital_Lobe_	Precommissural_Putamen_	2yr mean/sd	NaN	-0.54246	-0.40583	-1.5804	NaN	-0.48334	-0.31551	-2.0297	-0.60163	-0.538	-0.55651	-0.47806
78	Occipital_Lobe_grey	Precommissural_Putamen	2yr mean/sd	NaN	-0.52211	-0.38071	-1.5778	NaN	-0.48165	-0.31607	-2.0281	-0.58228	-0.541	-0.53385	-0.47787
79	Occipital_Lobe_	Striatum_grey	2yr mean/sd	NaN	-0.43904	-0.38888	-1.6667	NaN	-0.44188	-0.37446	-1.913	-0.48108	-0.478	-0.47594	-0.46602
80	Occipital_Lobe_grey	Striatum_	2yr mean/sd	NaN	-0.40612	-0.422	-1.6766	NaN	-0.40203	-0.443	-1.9601	-0.46979	-0.459	-0.46194	-0.454
117	Cerebellum_grey	Temporal_Lobe_	2yr mean/sd	NaN	0.53601	0.49267	0.81943	NaN	-0.42684	-0.49833	-0.84822	0.49885	-0.389	0.50203	-0.45015
118	Occipital_Lobe_grey	Striatum_grey	2yr mean/sd	NaN	-0.41634	-0.3608	-1.6463	NaN	-0.42075	-0.36572	-1.9156	-0.46192	-0.463	-0.45033	-0.44793
120	Cerebellum_grey	Putamen_grey	2yr mean/sd	NaN	-0.42472	-0.23705	-1.5636	NaN	-0.4843	-0.28428	-2.1108	-0.43981	-0.50088	-0.40628	-0.44726
121	Cerebellum_	Putamen_	2yr mean/sd	NaN	-0.40554	-0.28383	-1.5484	NaN	-0.43174	-0.30867	-2.1781	-0.44635	-0.46	-0.41396	-0.43353
126	Cerebellum_grey	Precommissural_Putamen	2yr mean/sd	NaN	-0.4137	-0.18269	-1.5892	NaN	-0.48459	-0.25406	-2.2363	-0.43487	-0.503	-0.38267	-0.43305
131	Cerebellum_grey	Precommissural_Putamen	2yr mean/sd	NaN	-0.38249	-0.18507	-1.5725	NaN	-0.47088	-0.23819	-2.1786	-0.41414	-0.49487	-0.36521	-0.42283
151	Cerebellum_grey	Poscommissural_Putamen_	2yr mean/sd	NaN	-0.40015	-0.3414	-1.2958	NaN	-0.39149	-0.36178	-1.6054	-0.42534	-0.403	-0.41211	-0.41763
153	Cerebellum_grey	Temporal_Lobe_grey	2yr mean/sd	NaN	0.51009	0.50795	0.89392	NaN	-0.36053	-0.50973	-0.91448	0.48581	-0.334	0.49666	-0.41633
159	Cerebellum_	Poscommissural_Putamen	2yr mean/sd	NaN	-0.43447	-0.36603	-1.2937	NaN	-0.37	-0.3609	-1.7428	-0.46304	-0.384	-0.44447	-0.40396
160	Cerebellum_grey	Poscommissural_Putamen	2yr mean/sd	NaN	-0.3238	-0.34709	-1.3492	NaN	-0.36477	-0.43218	-0.82537	-0.38067	-0.372	-0.36246	-0.39653
161	Cerebellum_grey	Putamen_	2yr mean/sd	NaN	-0.36839	-0.26379	-1.5658	NaN	-0.3784	-0.31774	-1.885	-0.40922	-0.404	-0.38117	-0.37712
162	Occipital_Lobe_	Precommissural_Putam	2yr mean/sd	NaN	-0.5696	-0.39596	-1.5984	NaN	-0.38986	-0.20559	-2.0569	-0.61848	-0.427	-0.57029	-0.37334
163	Occipital_Lobe_grey	Precommissural_Puta	2yr mean/sd	NaN	-0.55115	-0.37246	-1.5976	NaN	-0.37741	-0.19356	-2.0582	-0.60079	-0.418	-0.54948	-0.3617

Target ROI: **Putamen**

Reference region: **Cerebral white matter**

Improved power over current standard of occipital cortex reference region

VMAT2 – Longitudinal Analysis (N=30)

Comparison with DAT

	VMAT2			*DAT*	
power	YEAR 1	YEAR 2	power	YEAR 1	YEAR 2
80%	63	30	80%	117	56
90%	85	40	90%	157	75

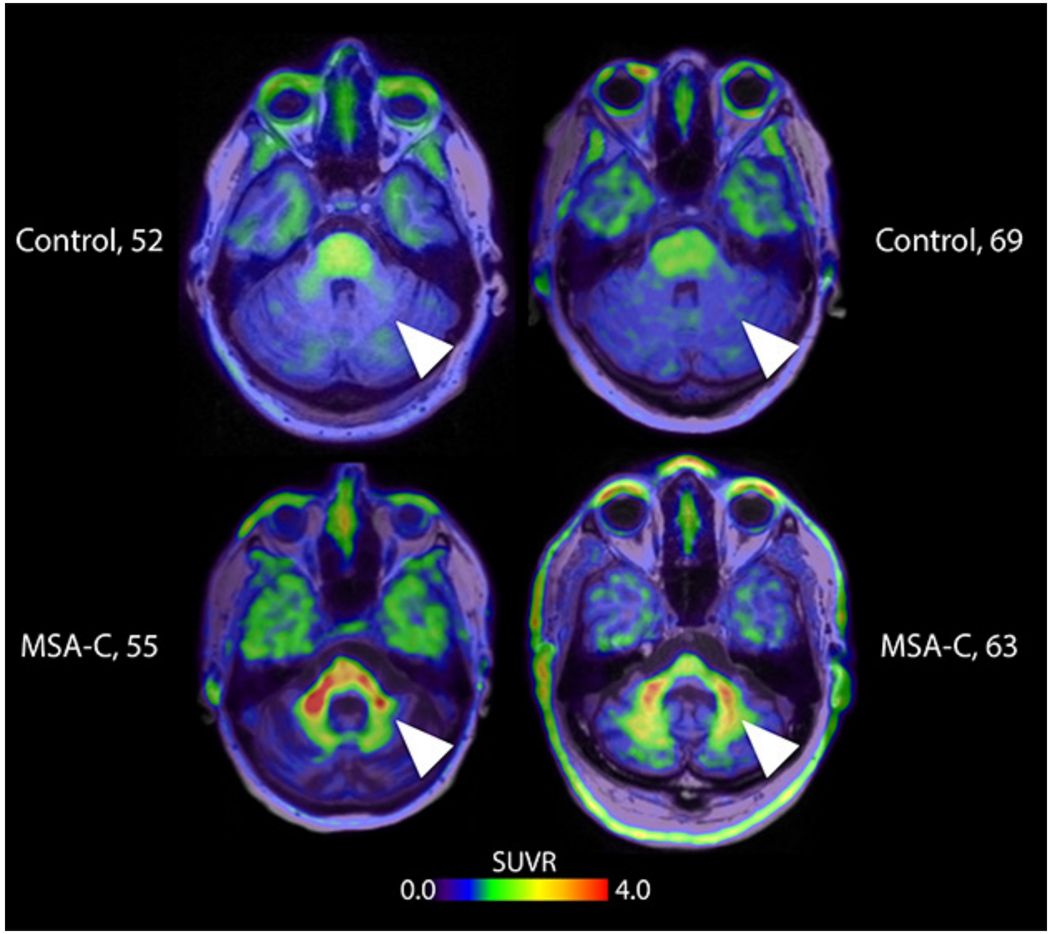
Data are Subjects/arm

Assumptions:

- Placebo controlled, double blind trial
- Two arms
- Power 80 or 90% power to detect 50% slowing of the rate of signal loss
- $p<0.05$, two-tailed

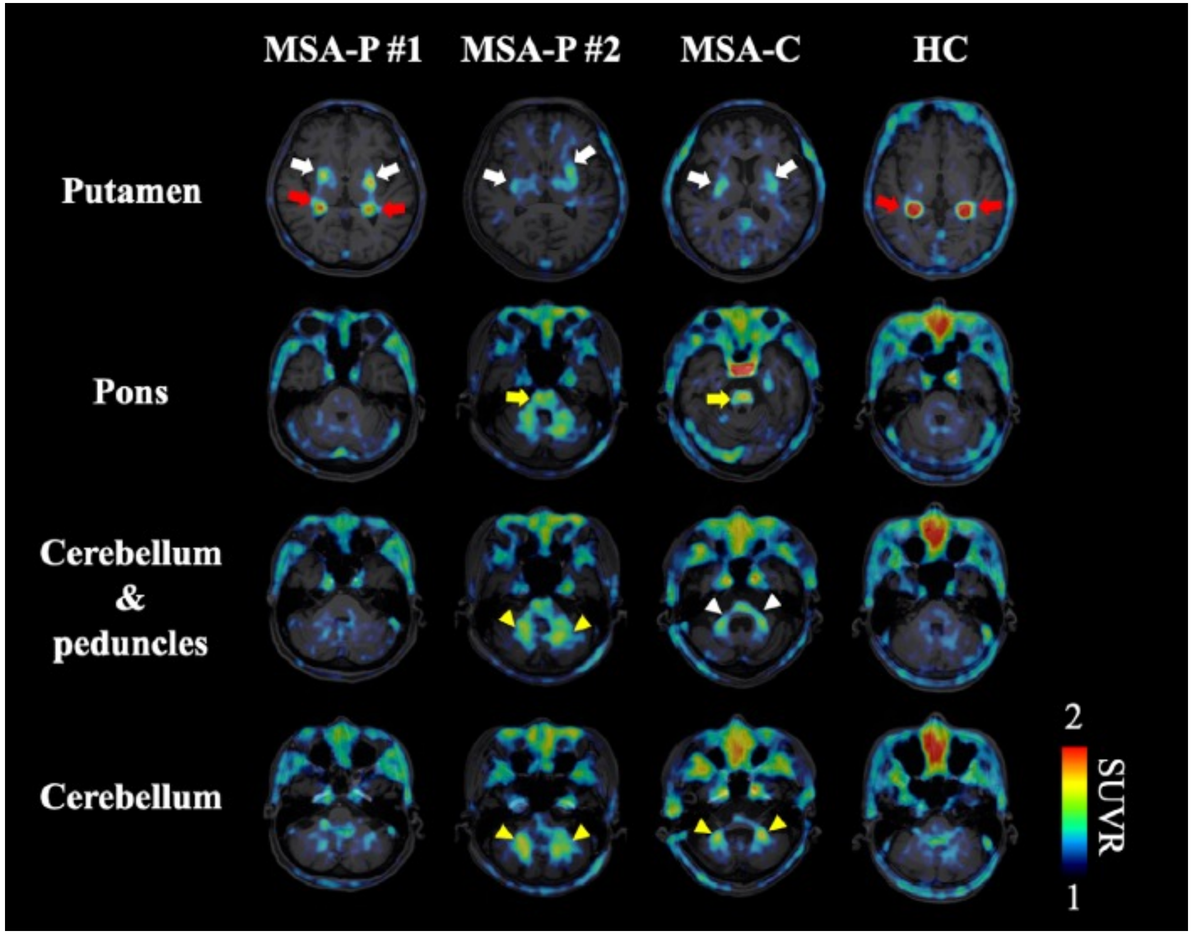
Alpha-Synuclein Imaging in MSA

18F-ACI-12589



AC Immune, 2022

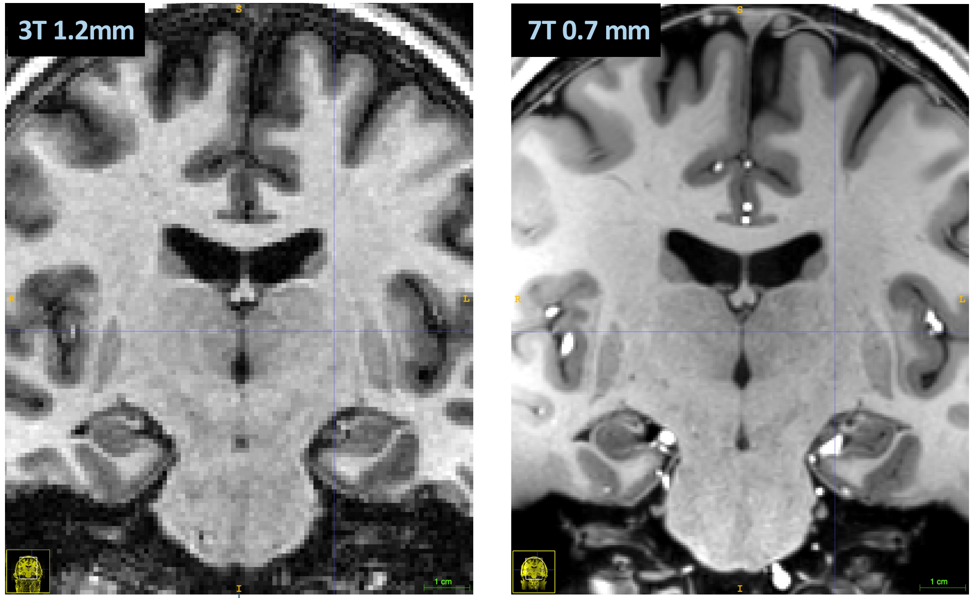
18F-SPAL-T-06



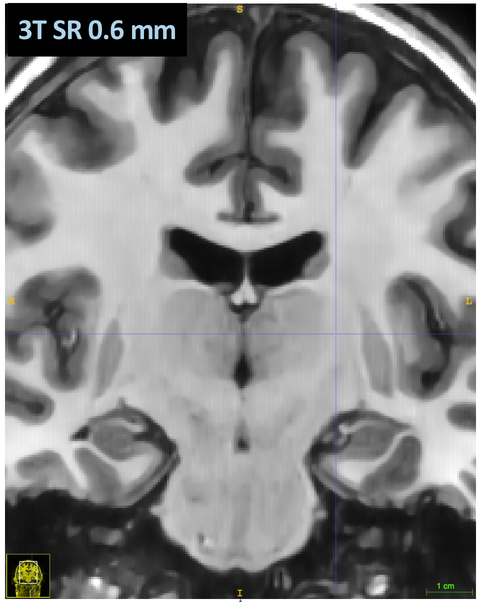
Matsuoka et al., 2022, Movement Disorders

MRI Biomarkers for Neurodegeneration
Maximizing Signals using Super Resolution Processing

Actual Acquisition of same subject on 3T and 7T scanner

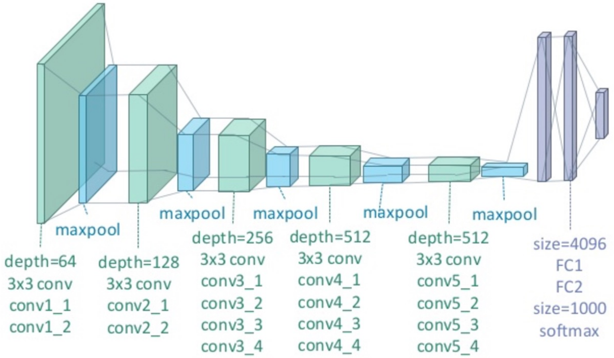


SR processed 3T data



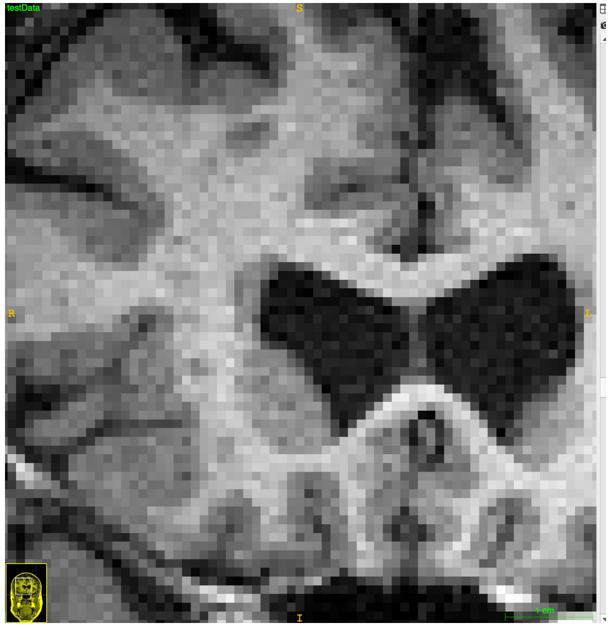
Deep Learning Network

VGG 19

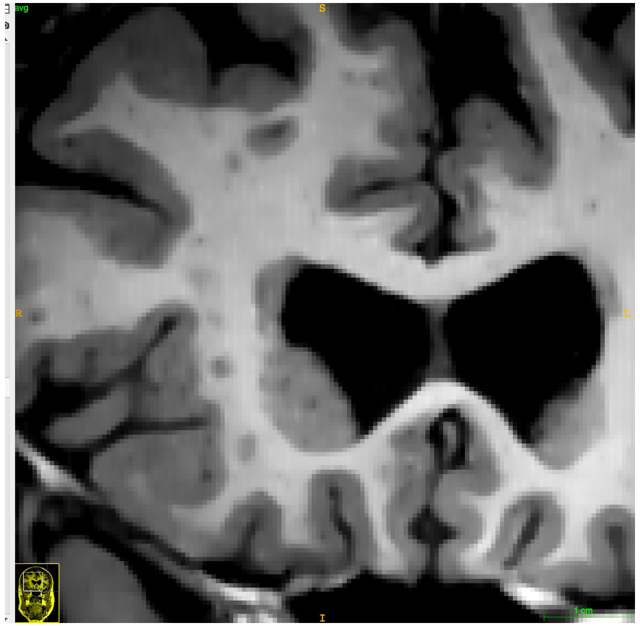


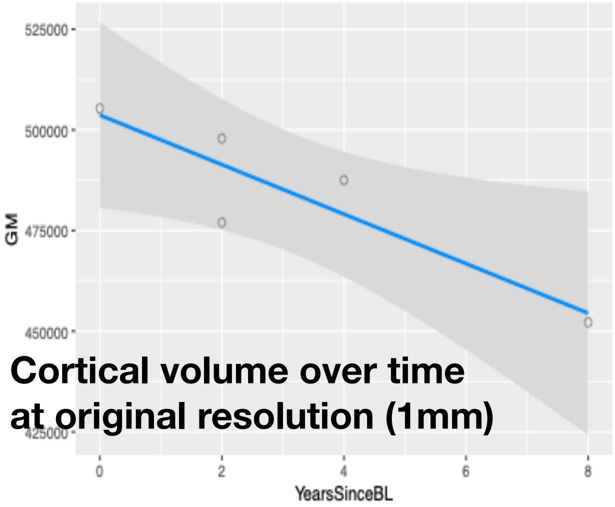
T1 Super Resolution MRI in AD

Original resolution MRI

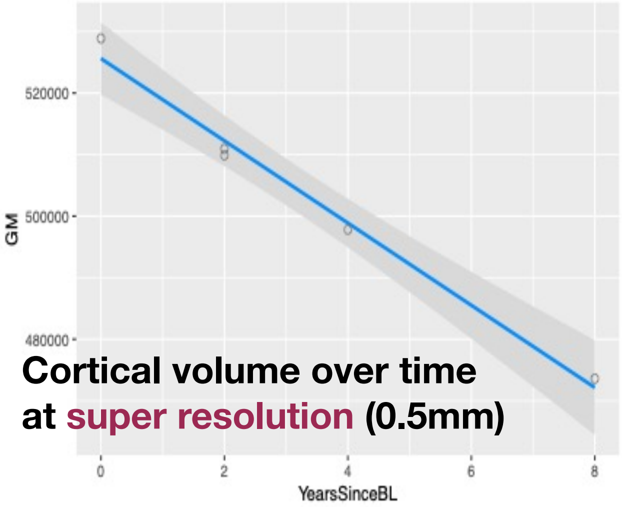


Super resolution MRI





Cortical volume over time at original resolution (1mm)

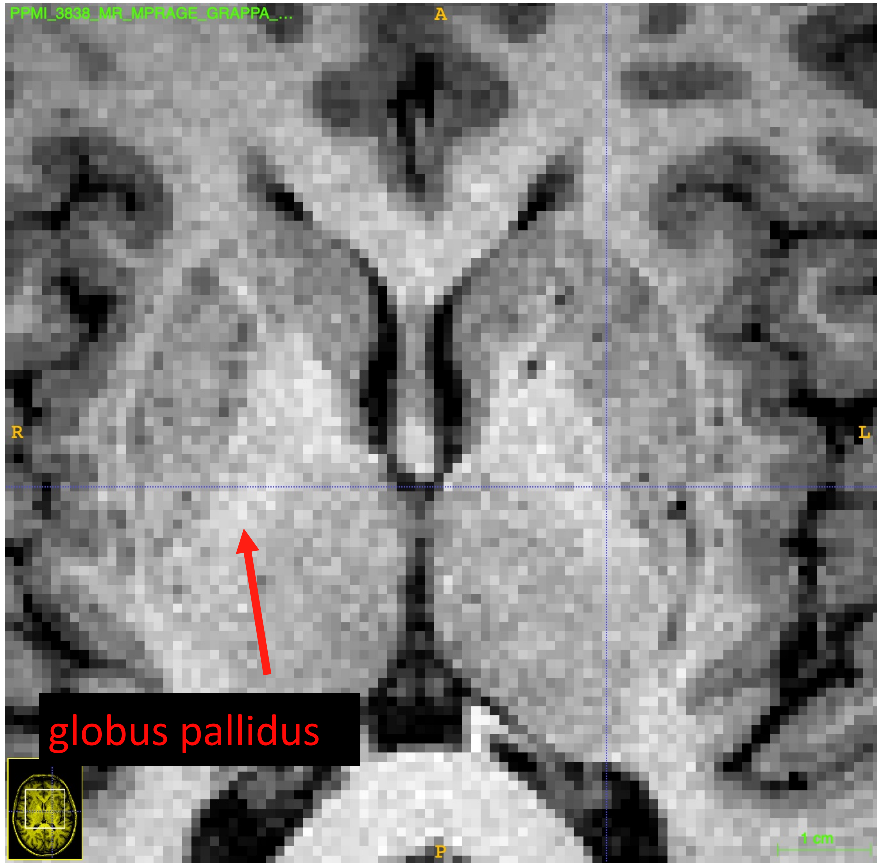


Cortical volume over time at super resolution (0.5mm)

T1 Super Resolution in PD

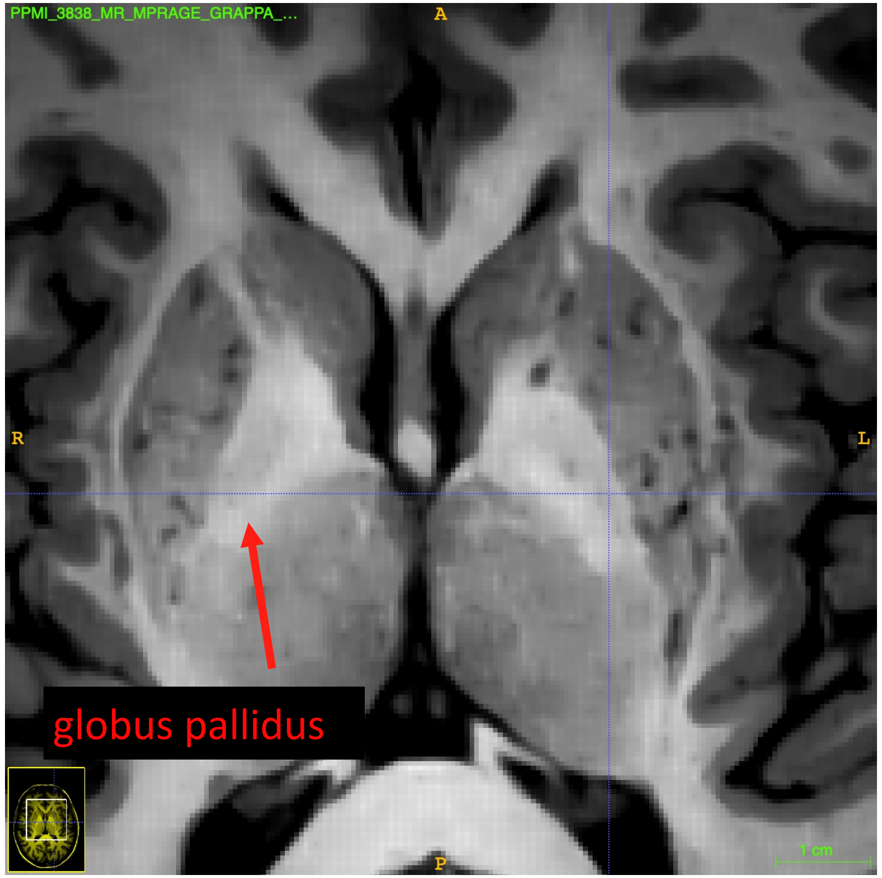
Impact of 3D super-resolution on quantification of Basal Ganglia

Individual T1-weighted MRI from PPMI



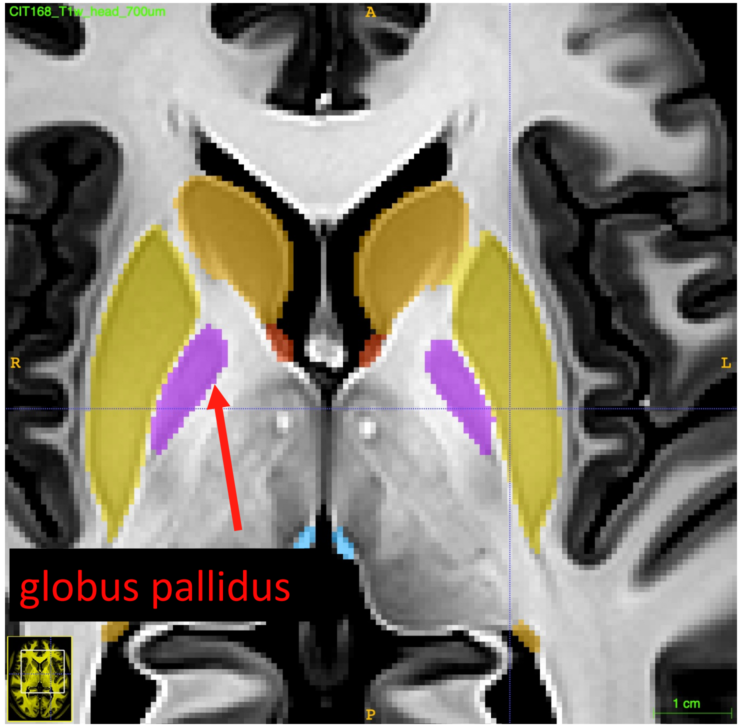
Subject 3838

Super-Resolution T1-w MRI from PPMI



Subject 3838: SR quality approaches that of a true high-res (**0.5 mm**) study and that of the population-aggregated template at right.

These tissue boundaries are difficult to delineate accurately in individual studies.



A high-resolution probabilistic *in vivo* atlas of human Subcortical nuclei

Summary

- Imaging Biomarkers are important for
  - **Stratification** of subjects into clinical trials
  - Longitudinal markers of **Disease Progression**

- Maximizing the Value of Biomarkers
  - The right **biological targets**
    - Sensitivity to disease progression
  - The right **tracer characteristics**
    - Uptake/Specificity/Selectivity
  - The right **analytics**
    - Maximize Power for signal detection

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