Waisman Center Day with the Experts:
Down Syndrome

Saturday, March 9, 2019

"Down Syndrome and Alzheimer's Disease: Defining a Pathway Toward Prevention"

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Waisman Center
UNIVERSITY OF WISCONSIN-MADISON

Outline

- Rationale for Studying AD in Down Syndrome
- Background of Alzheimer's Disease
- Imaging the Brain with PET and MRI
- Findings of the Role of Amyloid and Tau in Alzheimer's Disease
- Neurodegeneration in Aging Down Syndrome
- Defining a Pathway for the Prevention of Alzheimer's Disease

Alzheimer's Disease and Down Syndrome

- General population:
  - Rare before age 50
  - 3% between 65-74yrs
  - 17% between 75-84yrs
  - 32% over 85yrs
- Down syndrome:
  - 9% of adults in 40
  - 33% of adults in 50s
  - 50% of adults in 60s+ yrs

Characteristics of Alzheimer's Disease

- Dementia – progressive deterioration of cognitive function that ultimately prevents a person from independently performing their daily activities

- Alzheimer's Disease – accounts for 70% of cases of dementia
  - Symptoms include difficulty in:

    Language, memory, perception, emotional behavior, cognitive skills (e.g. judgment)

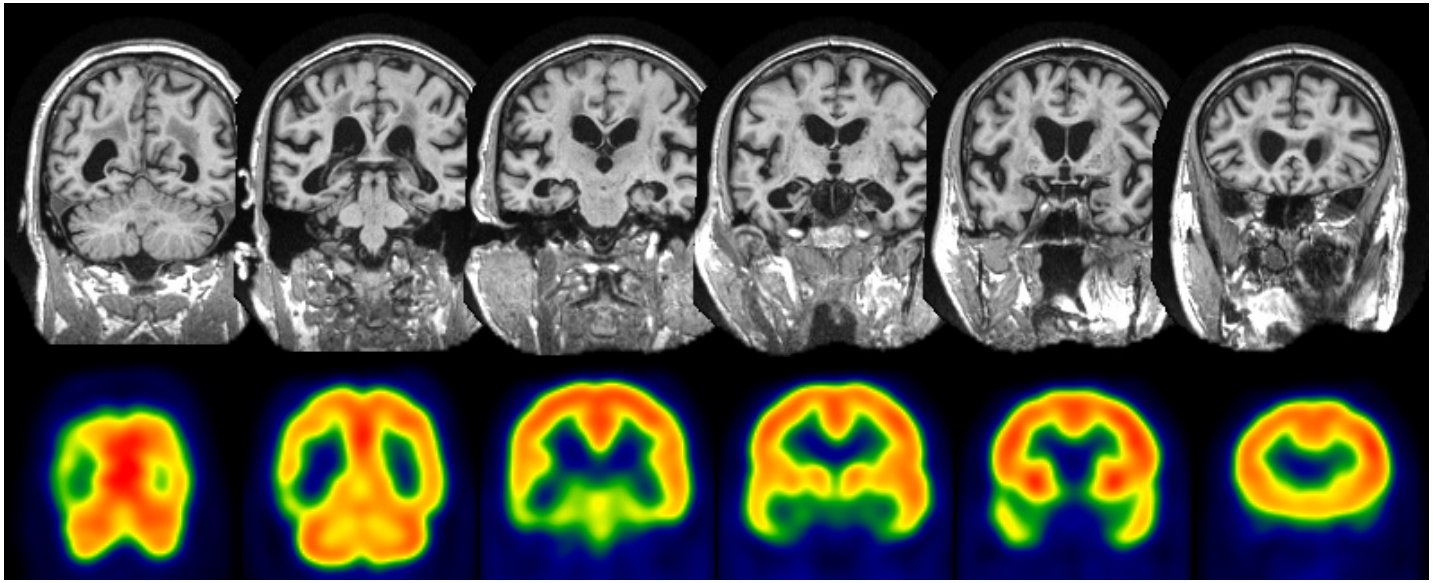
Why is AD a public policy issue?

- AD is the most common form of dementia (60-80%)
  - 5.5M people in the US, estimated to double every 20yrs (16M by 2050)
  - **Age** is the largest risk factor
    - 3% between 65-74yrs
    - 17% between 75-84yrs
    - 32% over 85yrs
  - **Increasing elderly population**
    - Medical advances and improved social and environmental conditions
    - In 2017 alone, there were
      - Estimated 64,000 new AD cases between 65-74yrs
      - Estimated 173,000 new AD cases between 75-84yrs
      - Estimated 243,000 new AD cases above age 85yrs
  - **Large socioeconomic burden** on healthcare systems and families exacerbated by the **decades long disease**
    - National Alzheimer's Project Act (NAPA; 2011): discover an effective treatment by 2025
    - 2013: $504M; 2014: $562M; 2015: $589M; 2016: $929M; 2017: $1,348M: 2018: $1.9B
      2019: $2.3B

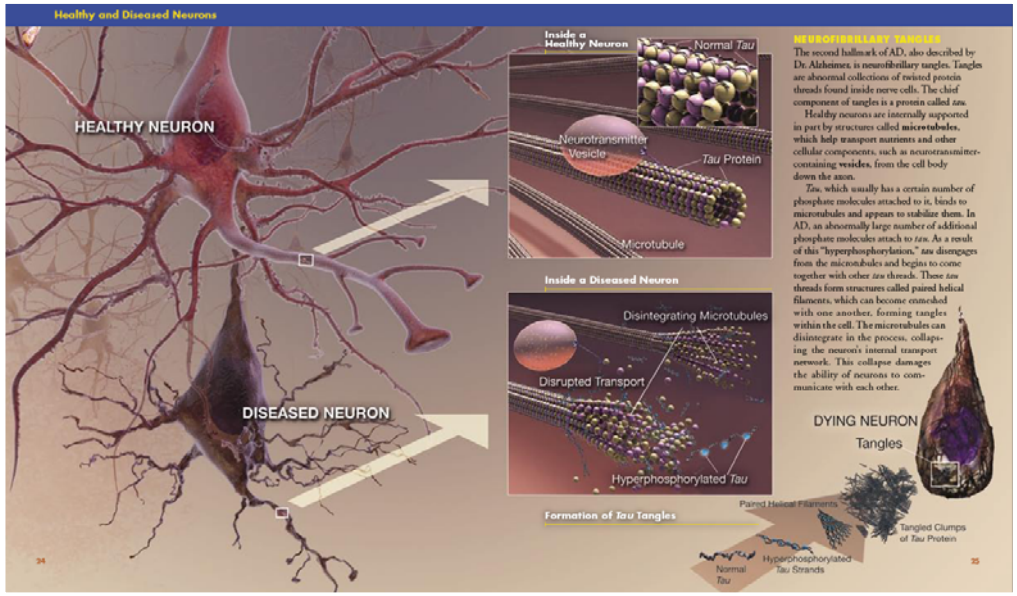
Alzheimer's Association, 2017; National Center for Health Statistics, 2017

Slide provided by Dr. Patrick Lao

Pathology of Alzheimer's Disease



AD Pathology
- tangles and plaques



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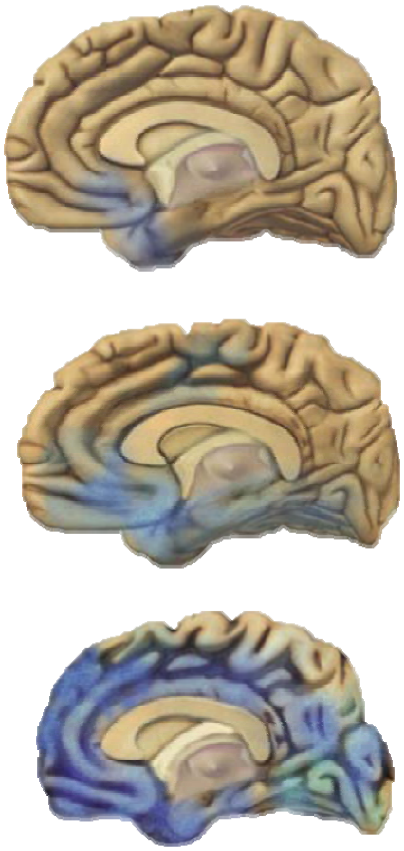
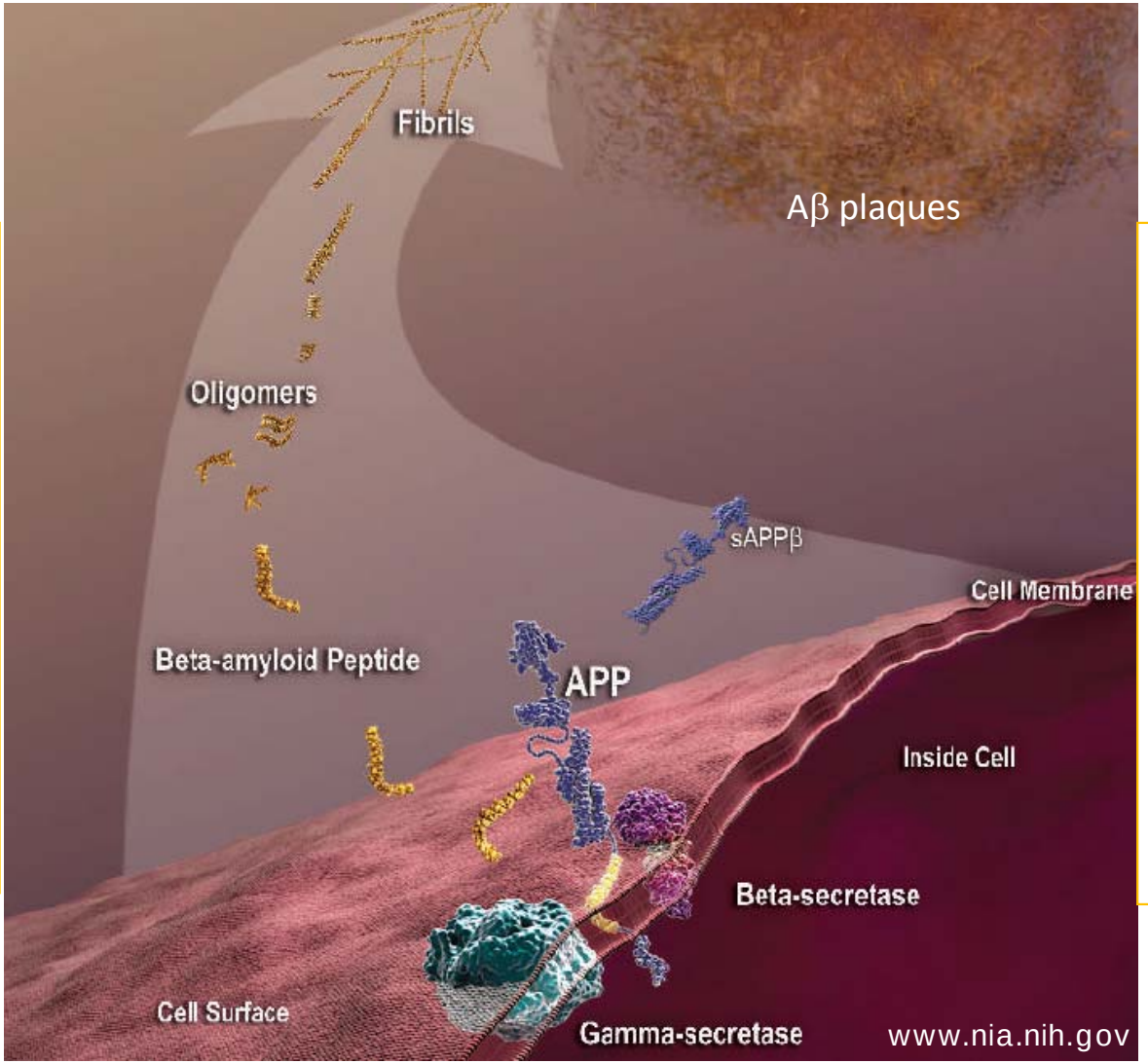
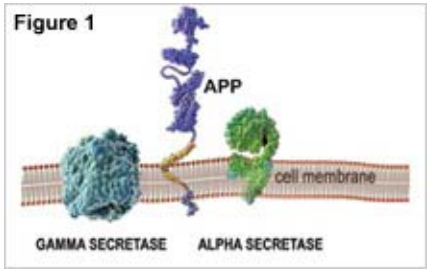
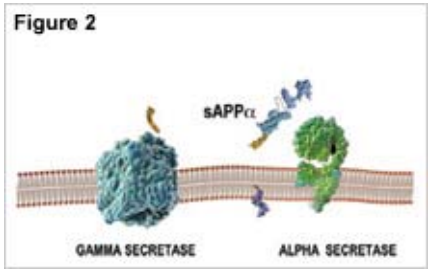


tangles

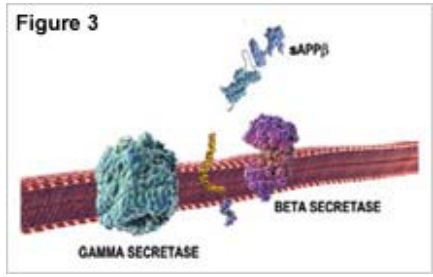
β – Amyloid Plaques

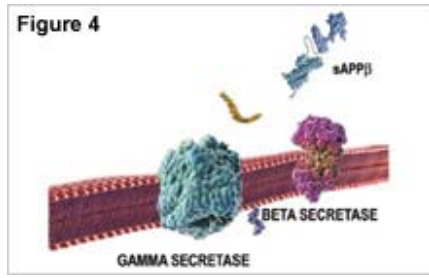






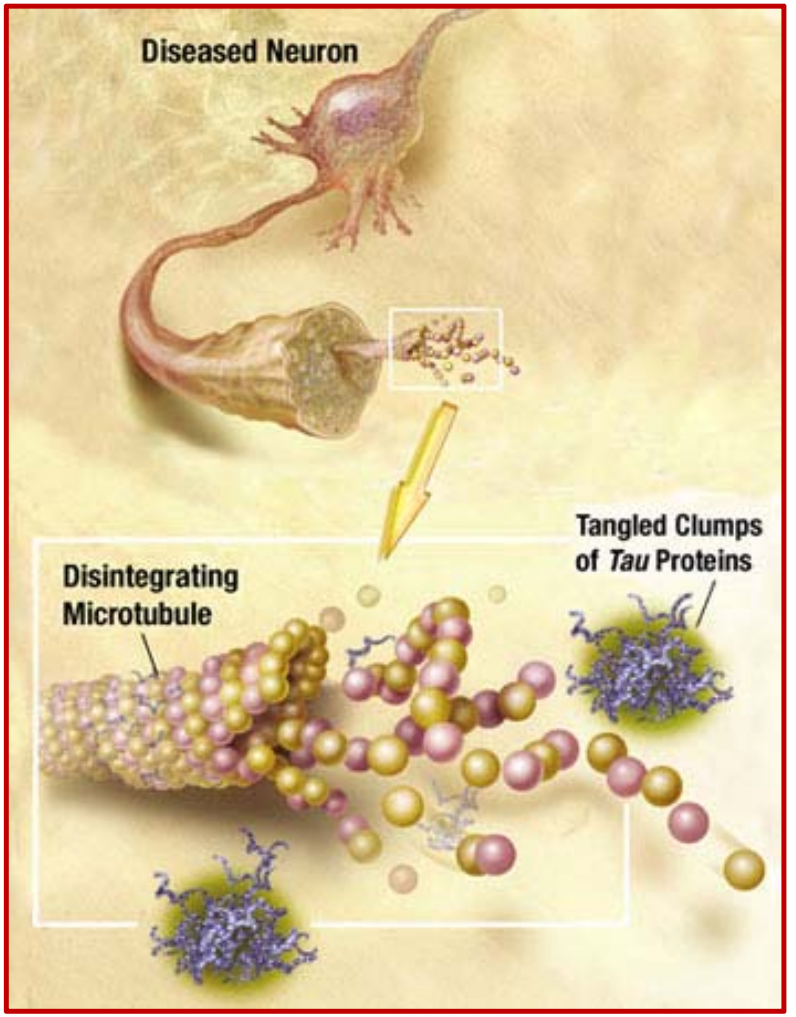
Non-amyloidogenic





Amyloidogenic

Tau Tangles in Alzheimer's Disease



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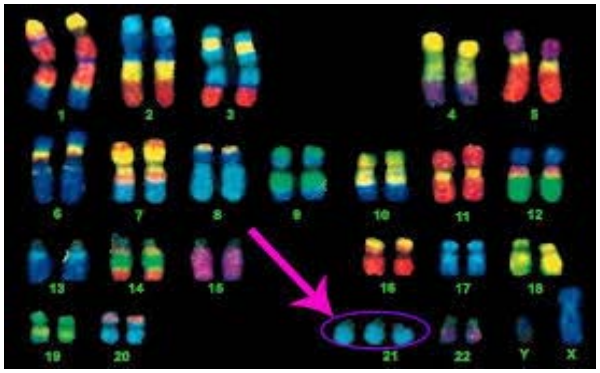
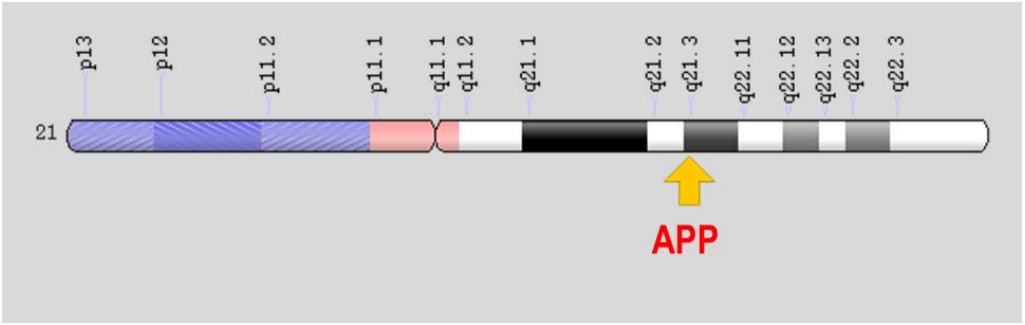
Why the Increased Risk for AD in Down Syndrome?





Reprinted from Shaw, 2013

Trisomy of chromosome 21

- 234 protein encoding genes
- Overproduction (1.5x) of gene products, like amyloid precursor protein (APP)
- Amyloid deposition begins as early as 10-20yrs with DS
- Nearly ubiquitous in adults with DS by 40yrs at autopsy
- Same core protein as plaques in AD

Down Syndrome – Trisomy 21

Life Expectancy

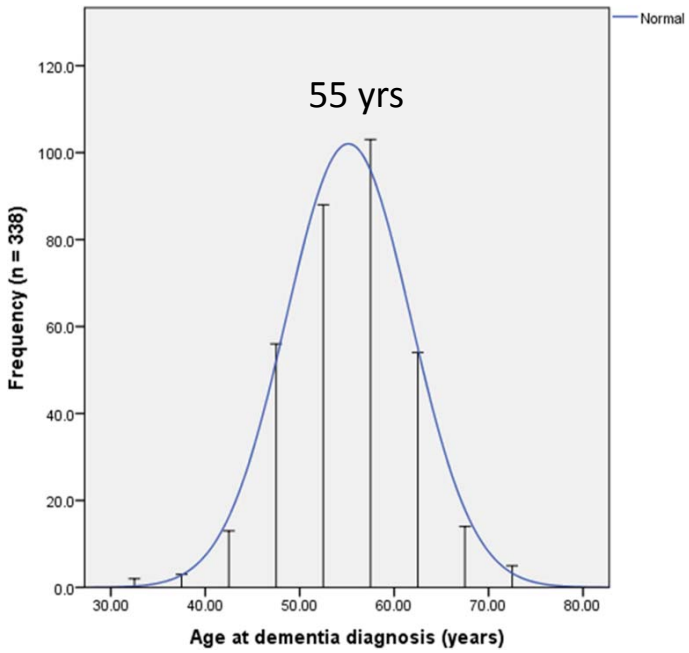
- Average life expectancy:

  9-12 yrs in 1929-1949

  55-60 yrs in 1991-2002

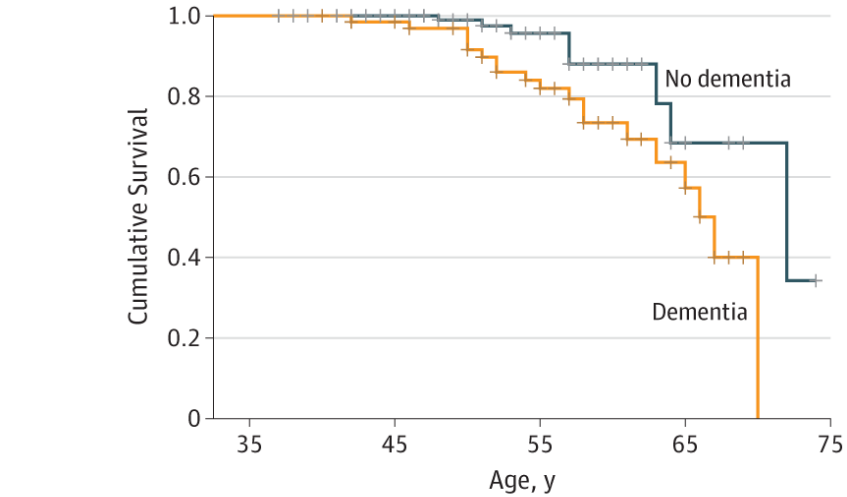
- Improved healthcare, lower infant mortality rate, shift away from institutional care
- Growing elderly DS population is resulting in a higher prevalence of adults with DS having Alzheimer's Disease

Association of Dementia With Mortality in Down Syndrome



Cross-sectional data showing the distribution of age at dementia diagnosis in people with DS.

Alzheimers Dement. 2018; 4:703-713



No. at risk					
Dementia	66	62	29	8	0
No dementia	145	107	107	4	0

JAMA Neurol. 2019;76(2):152-160.

Tracking Biomarkers for Alzheimer's Disease

- Biomarker – "Biological Markers" are medical signs which define a medical state from outside the patient and can be reproduced and measured accurately, unlike the medical symptoms which are mere indications of a patient's condition described and perceived by the patients themselves.

Theoretical relation between dementia status and “IQ”

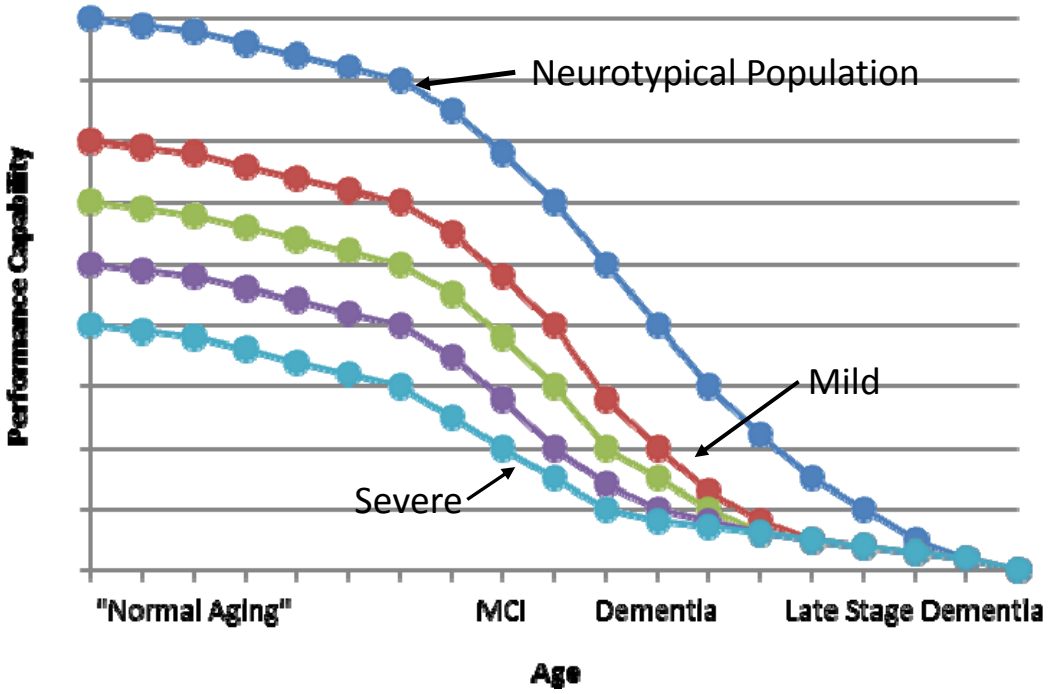
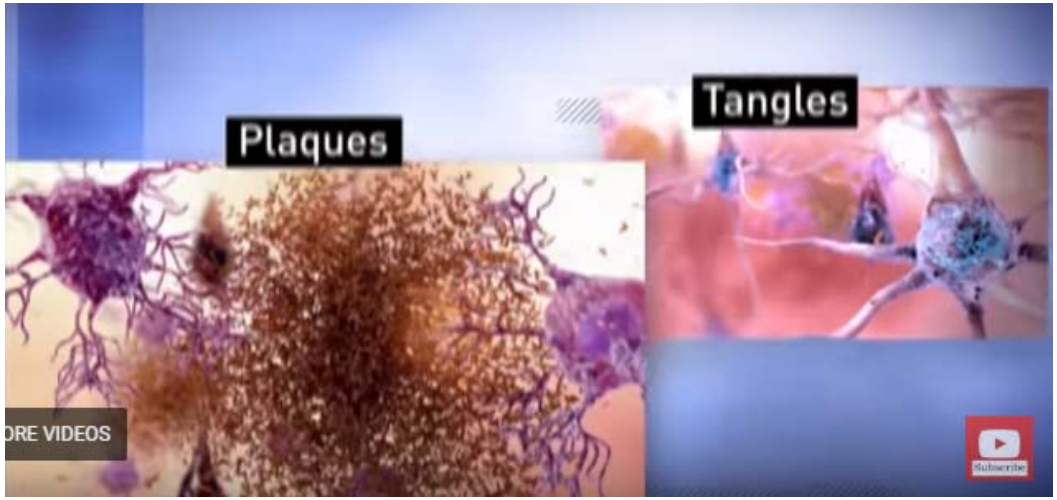


Figure Provided by Dr. Sharon Krinsky-McHale, Columbia University

Biomarkers for Alzheimer's Disease

- amyloid
- tau
- neurodegeneration



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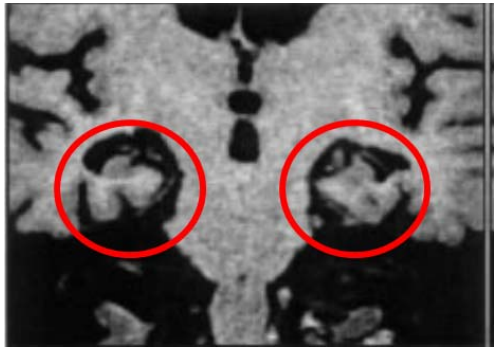
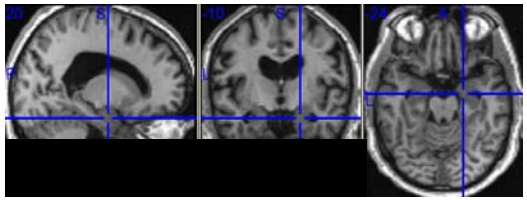
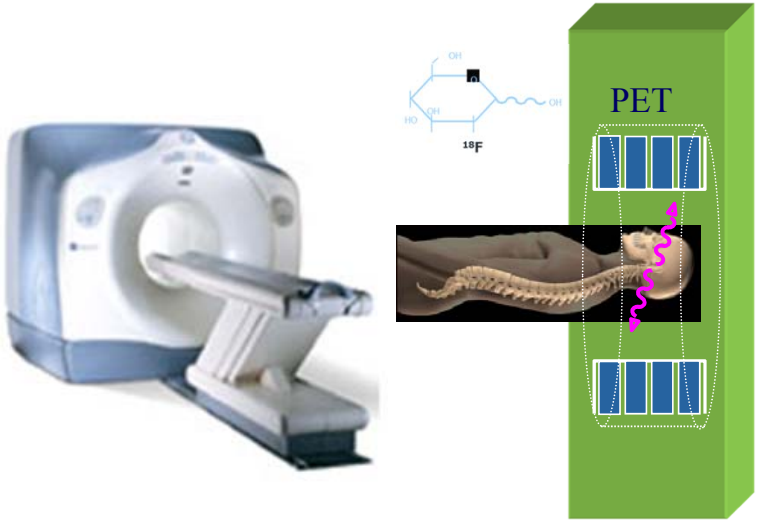
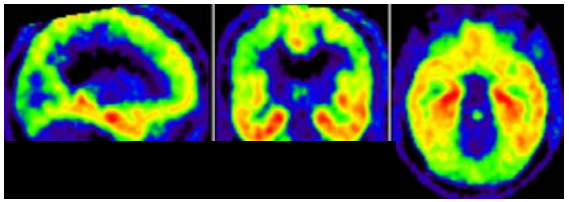


Magnetic Resonance Imaging (MRI)



Positron Emission Tomography (PET)

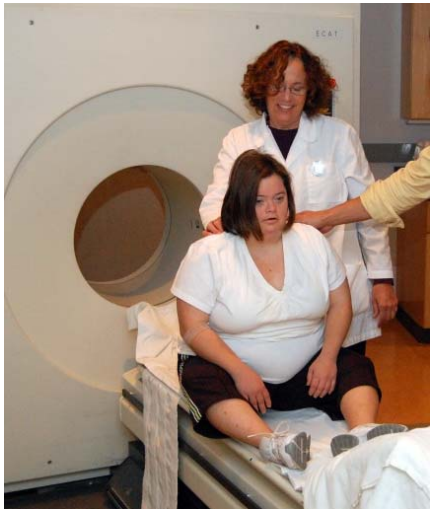




Motivation: Why Study AD Biomarkers in Down Syndrome?

- Provide molecular information during the pre-dementia stage of amyloid-β accumulation
- Inform the timing of future studies (assuming generalizability to other populations)
- Motivate intervention trials, for which the DS population is particularly suited

Natural History of Alzheimer's Disease in Adults with Down Syndrome



- The goal of this project is to track amyloid deposition in adults with DS and to follow these individuals to understand the course of amyloid deposition and its effect on functioning over time.

Objectives

- Identify the patterns of amyloid burden in non-demented individuals with DS
- Examine the relation between amyloid burden and cognitive function
- Identify the longitudinal changes in magnitude and regional distribution of changes in amyloid burden and gray matter volumes
- Examine the relation of changes in neuropsychological measures with the presence of β-amyloid.

Methods: Participants

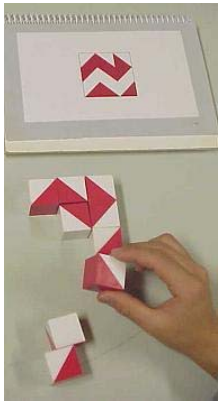
- Enrolled 79 non-demented participants with confirmed trisomy 21
  - Adults with DS ≥ 30 years of age
  - Excluded for any medical or psychiatric condition that would impair cognitive function or contraindicate a PET or MRI scan
  - Screened, but not excluded for any AD or memory enhancing medication

- Dependent Measures
  - Adaptive/Behavioral/AD measures
  - Neuropsychological measures
  - MRI (T1, T2, T2*)
  - PET (PiB, FDG)
  - Genetics (ApoE)

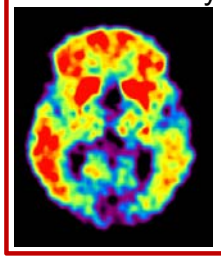
Experimental Details

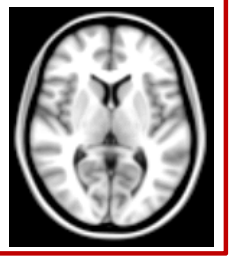
Current Study Procedures and Measures				
Measure	Informant/ Participant	Time (minutes)	Screen/ Baseline	Follow-Up Visit
Day 1 (Informant and Neuropsychological Measures)				
Informed Consent	Caretaker & Subject	45-60	X	
DSDS Interview	Caregiver	30	X	X
SIB/IQ/Neuropsych	Subject	120-150	X	X
Psychiatric Assessment	Subject	15	X	X
Vineland/Reiss Screen	Caregiver	60	X	X
Medical/Psychiatric Hx	Caregiver	15	X	X
Day 2 (Neuroimaging Measures)				
MRI	Subject	30	X	X
PiB PET Scan	Subject	90	X	X

Day 1



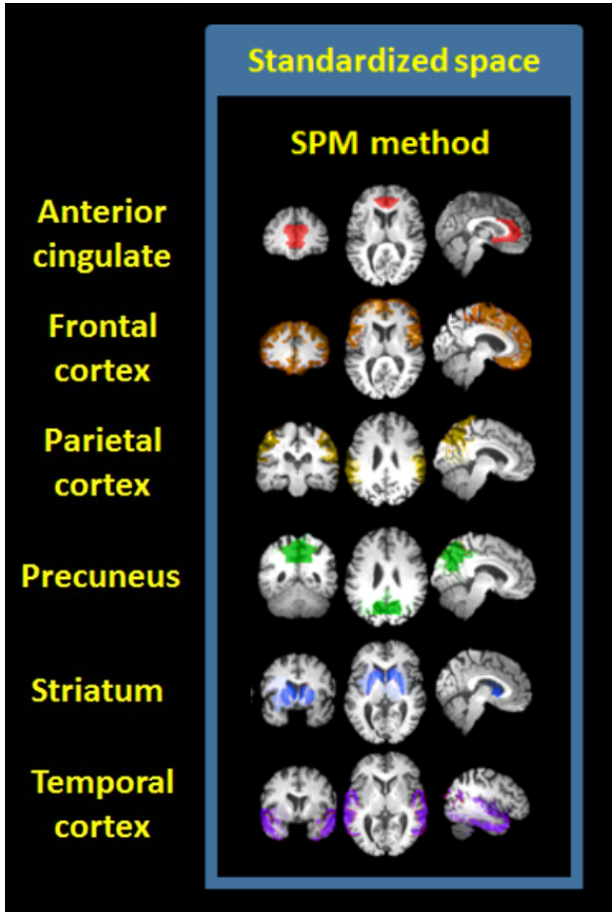
Day 2



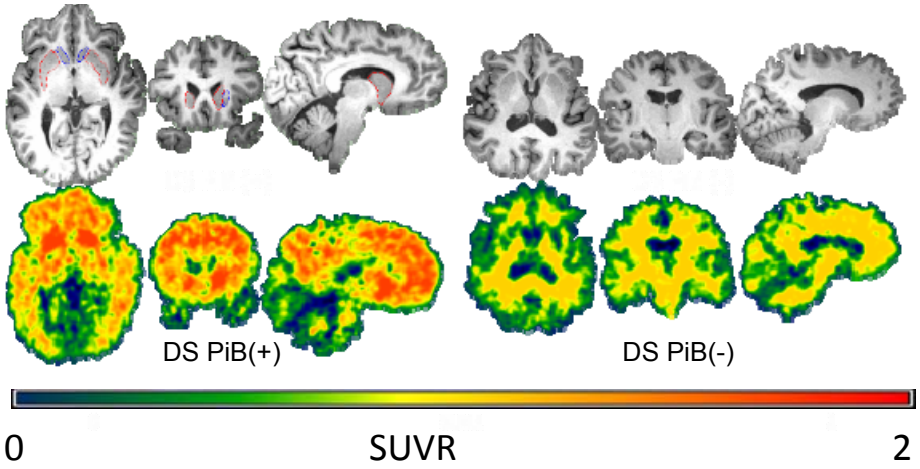


Slide Provided by Dr. Sigan Hartley

PiB Status

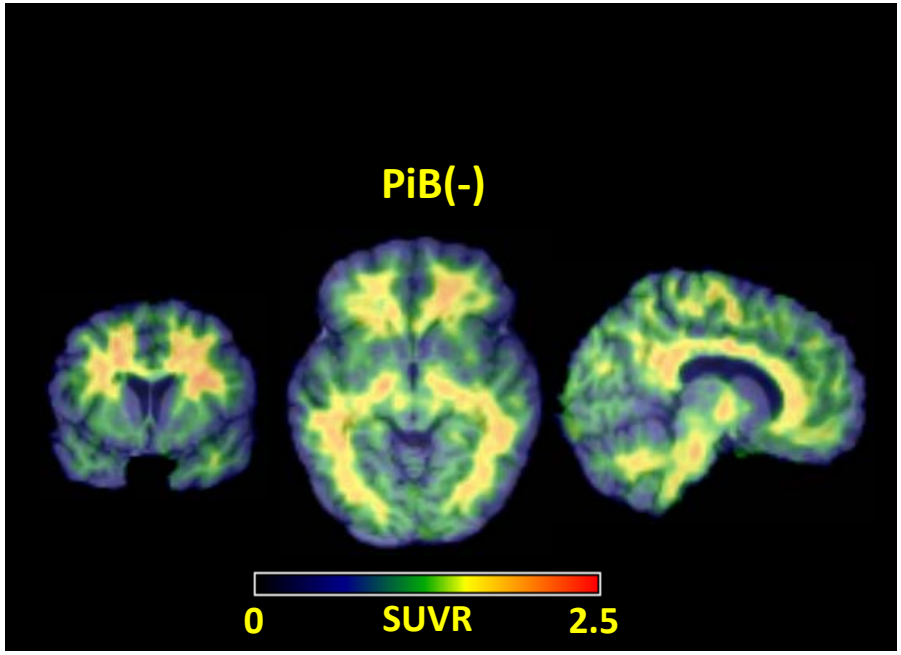


- Tissue ratios calculated for cortical regions-of-interest (ROI) and normalized to cerebellum (SUVR) using 50-70 min PiB uptake.
- PiB(+) = above the cutoff in cortical areas defined using sparse k-means clustering



Slide provided by Dr. Patrick Lao

RESULTS: AMYLOID BURDEN BY PIB POSITIVITY

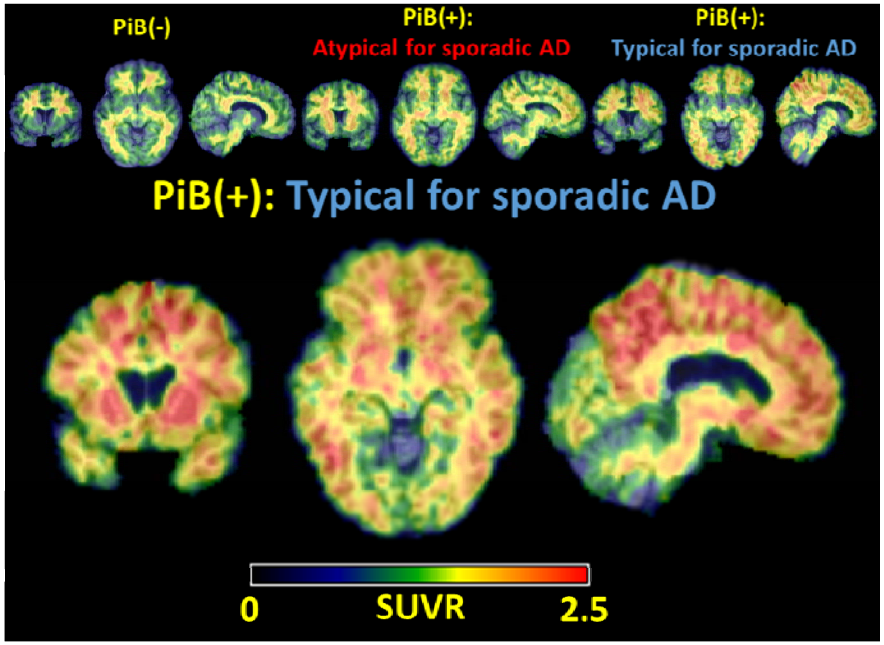


Cross-sectional patterns of amyloid burden

- **PiB(-), n=59: predominantly white matter uptake**

Slide provided by Dr. Patrick Lao

RESULTS: AMYLOID BURDEN BY PIB POSITIVITY



Slide provided by Dr. Patrick Lao

Cross-sectional patterns of amyloid burden

- PiB(-), n=59: predominantly white matter uptake
- PiB(+), n=4: elevated striatum uptake without elevated neocortical uptake
- PiB(+), n=2: elevated neocortical uptake without elevated striatum uptake
- **PiB(+), n=14: elevated neocortical and elevated striatum uptake**

Lao et al., Alz & Dementia 2016.

Significant Neuropsychological Measures (Cycle 1)

	PiB+ (N=17)	PiB- (N=35)	P
Free Recall	14.2 (5.5)	16.9 (6.4)	0.05
Cued Recall Intrusion	4.1 (5.3)	1.9 (2.9)	0.03
Visual Attention Time	94.2 (47.5)	77.0 (35.4)	0.05
Peg Board (both)	4.7 (1.9)	5.7 (1.9)	0.05
Expressive One-Word	66.1 (22.5)	77.4 (25.8)	0.02
Picture Recognition	4.4 (3.5)	6.5 (3.2)	0.01

Table provided by Ben Handen, Ph.D.

Hartley SL, et al. Brain (2012)

Objectives

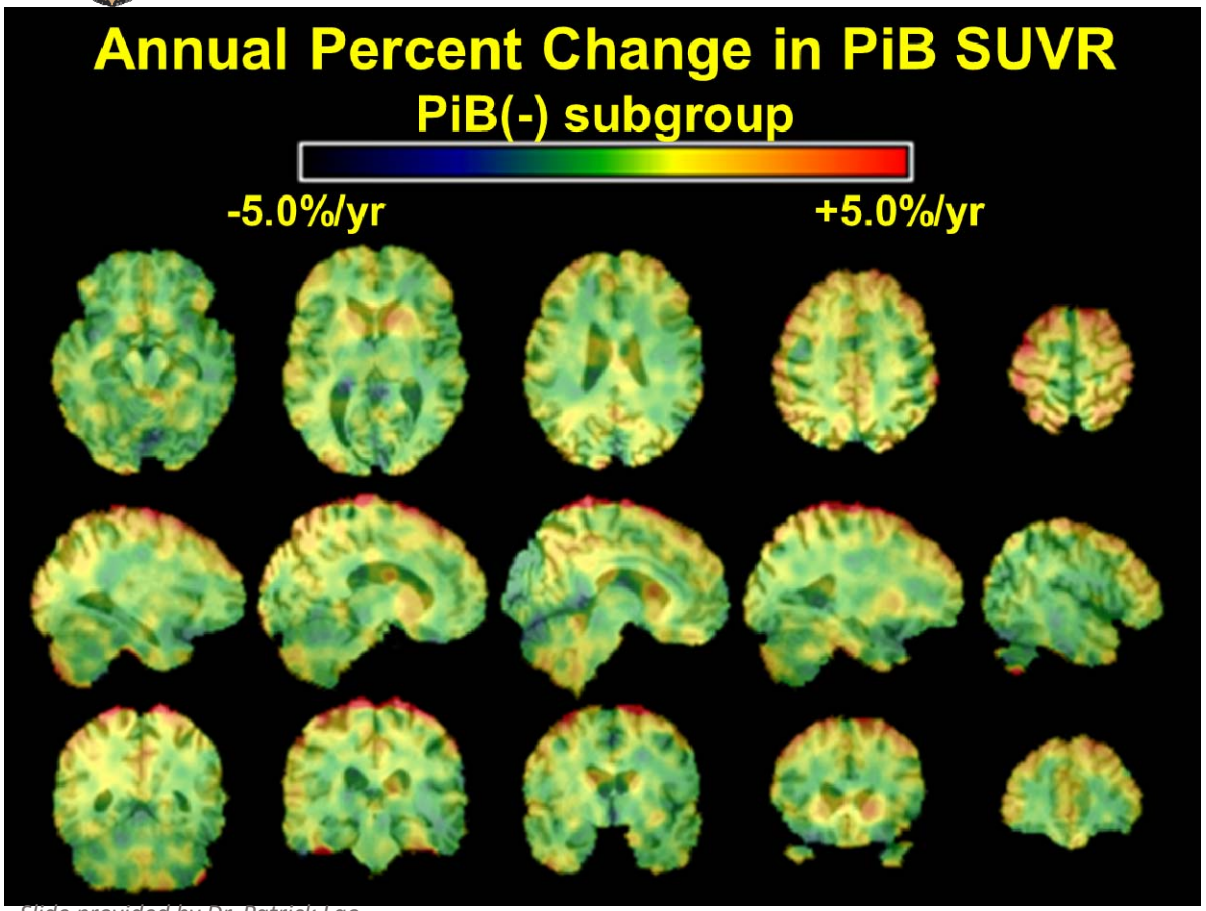
- Identify the regional distribution of amyloid burden in non-demented individuals with DS
- Examine the relation between amyloid burden and cognitive function
- Identify the longitudinal changes in magnitude and regional distribution of changes in amyloid burden and gray matter volumes
- Examine the relation of changes in neuropsychological measures with the presence of β-amyloid.

Longitudinal : Experimental Details

- Enrolled 79 non-demented participants with confirmed trisomy 21
- 52 participants with 2 cycles of data (3.0 ± 0.6 yrs after cycle 1)
  - Age at cycle 1
    - Range: 30-50 yrs
    - Mean ± SD: 37.5 ± 6.7 yrs
  - 46.2% Male / 53.8% Female
  - N=5 APOE4 carriers

Lao et al. NRM 2016

RESULTS: LONGITUDINAL AMYLOID ACCUMULATION

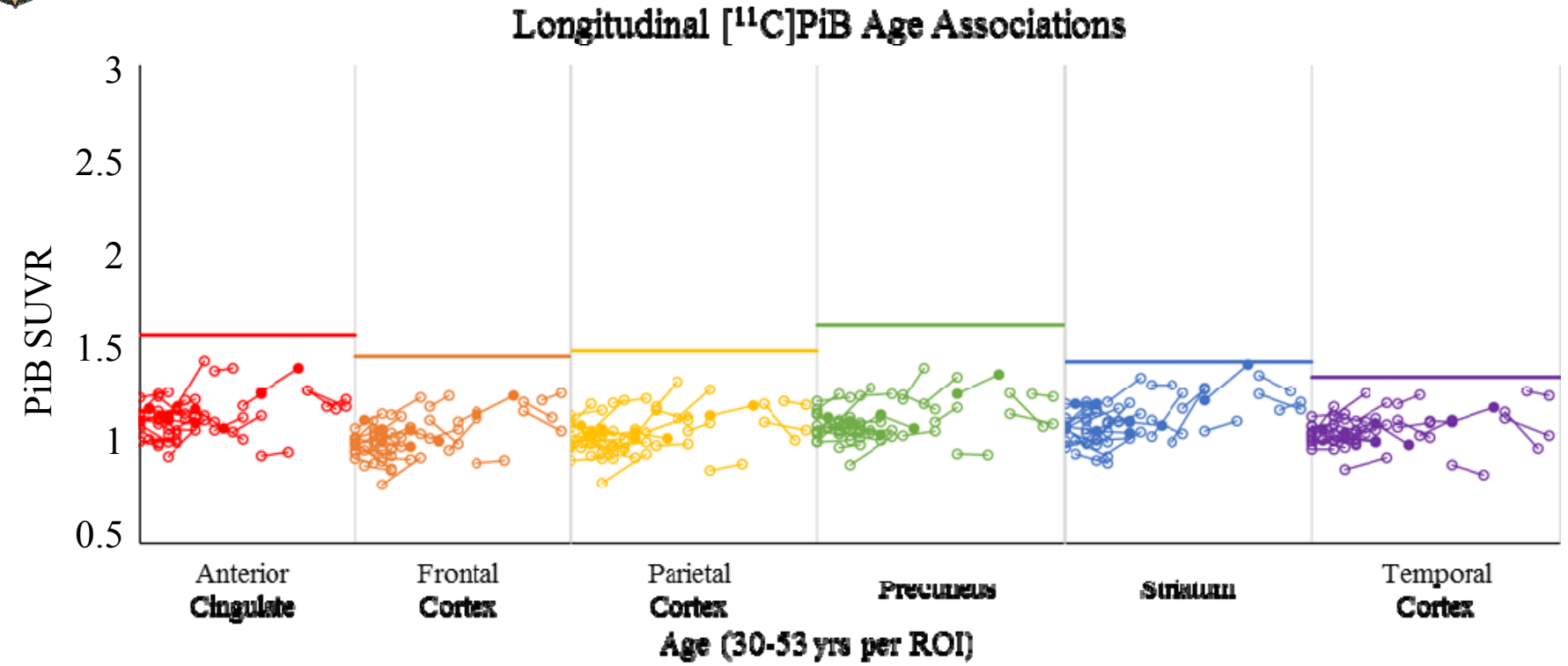


Slide provided by Dr. Patrick Lao

Amyloid Accumulation in the PiB(-) subgroup

- PiB(-) at cycle 1
- PiB(-) at cycle 2
- Annual percent change = ([(Cycle 2 – Cycle 1)/Cycle 1] *100)/ (time between cycles)
- Most areas have no change
- Slight positive change in:
  - **Frontal cortex**
  - **Parietal cortex**
  - **Striatum**

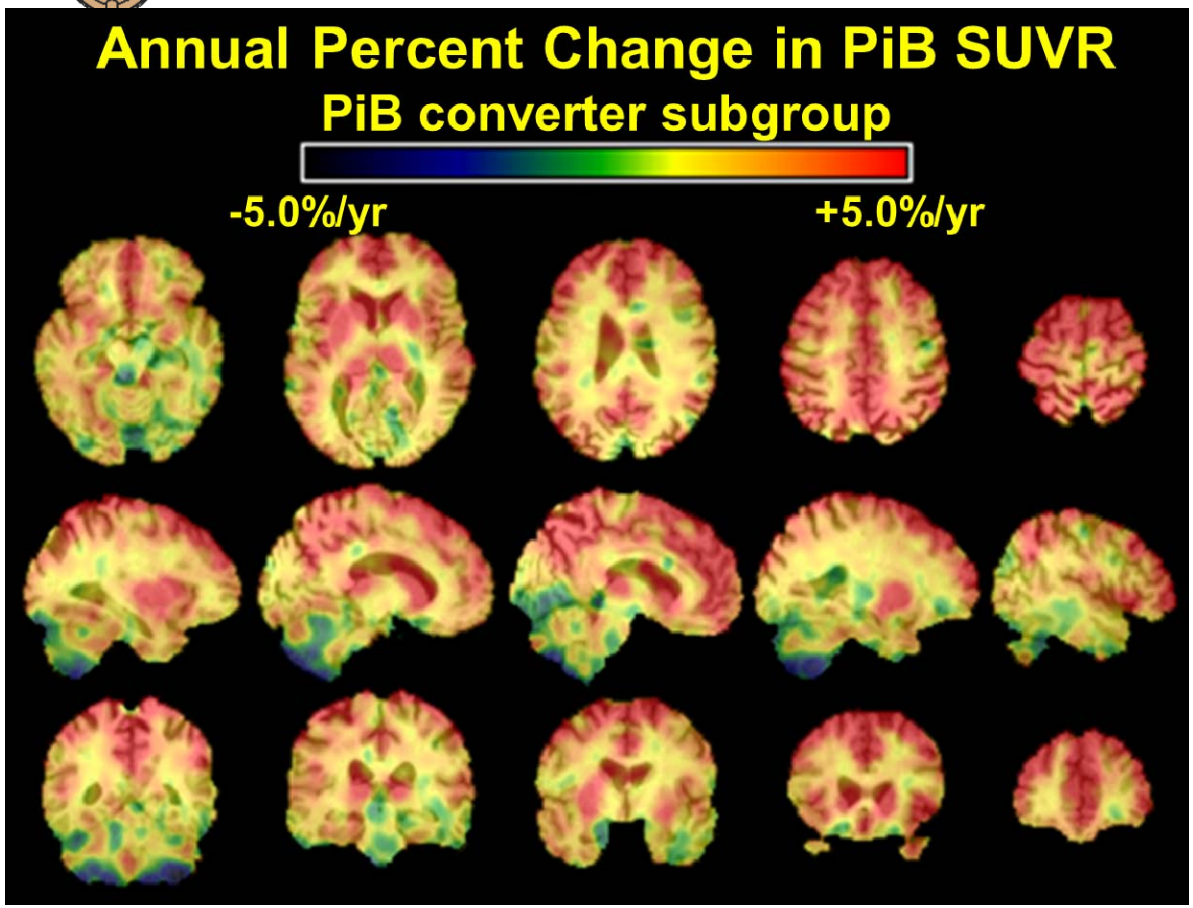
RESULTS: LONGITUDINAL AMYLOID ACCUMULATION



PiB(-) subgroup

Slide provided by Dr. Patrick Lao

RESULTS: LONGITUDINAL AMYLOID ACCUMULATION

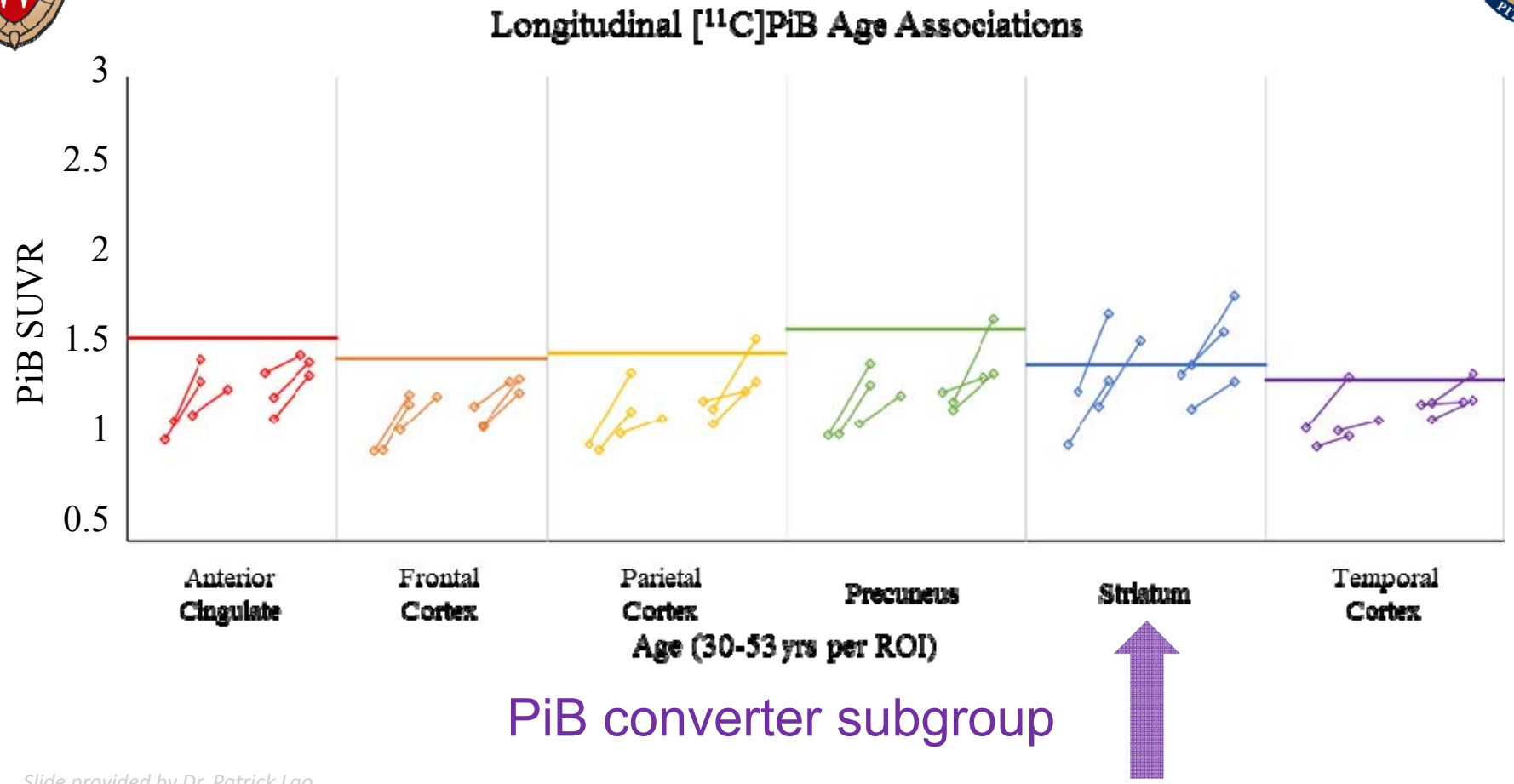


Slide provided by Dr. Patrick Lao

Amyloid Accumulation in the PiB converter subgroup

- PiB(-) at cycle 1
- PiB(+) at cycle 2
- Most areas have a positive change, namely:
  - **Anterior cingulate**
  - **Frontal cortex**
  - **Parietal cortex**
  - **Precuneus**
  - **Striatum**
  - **Temporal cortex**

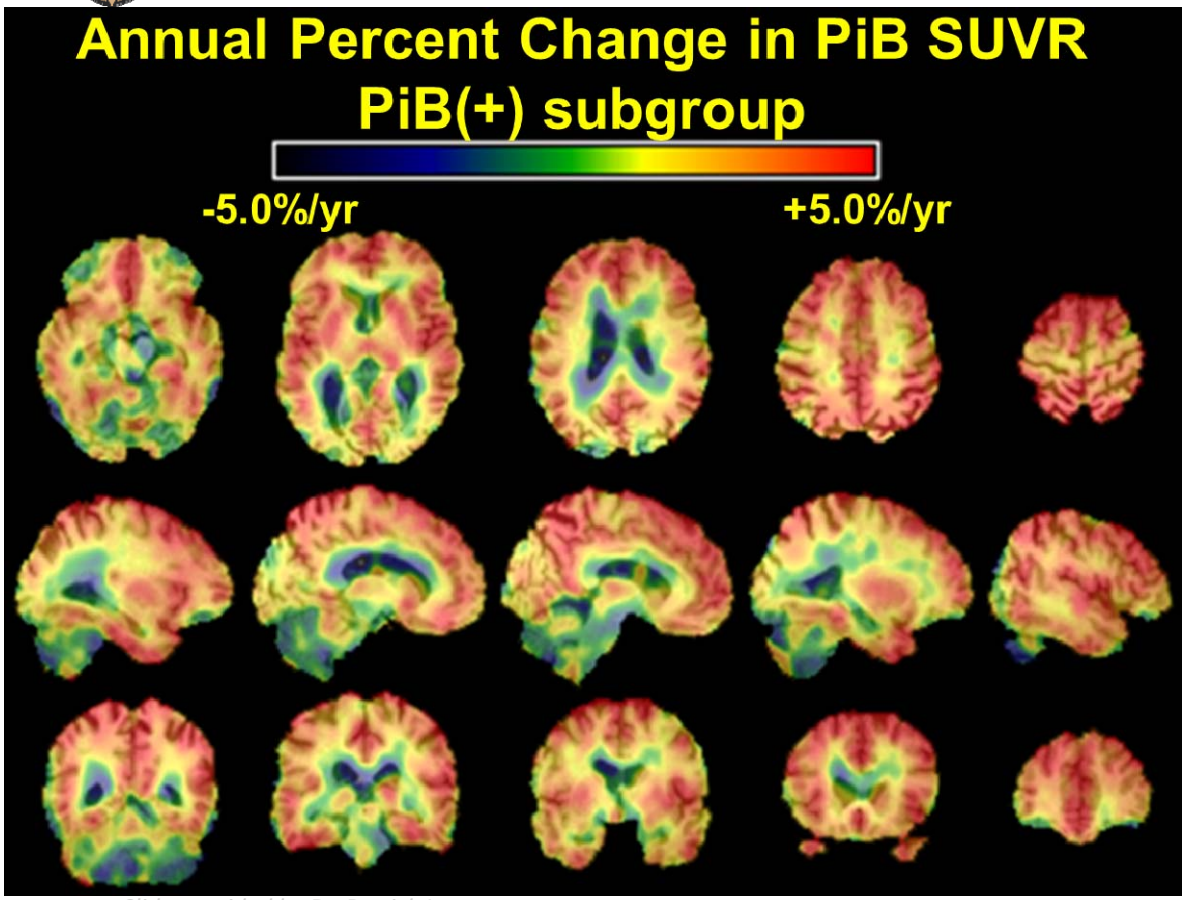
RESULTS: LONGITUDINAL AMYLOID ACCUMULATION



PiB converter subgroup

Slide provided by Dr. Patrick Lao

RESULTS: LONGITUDINAL AMYLOID ACCUMULATION

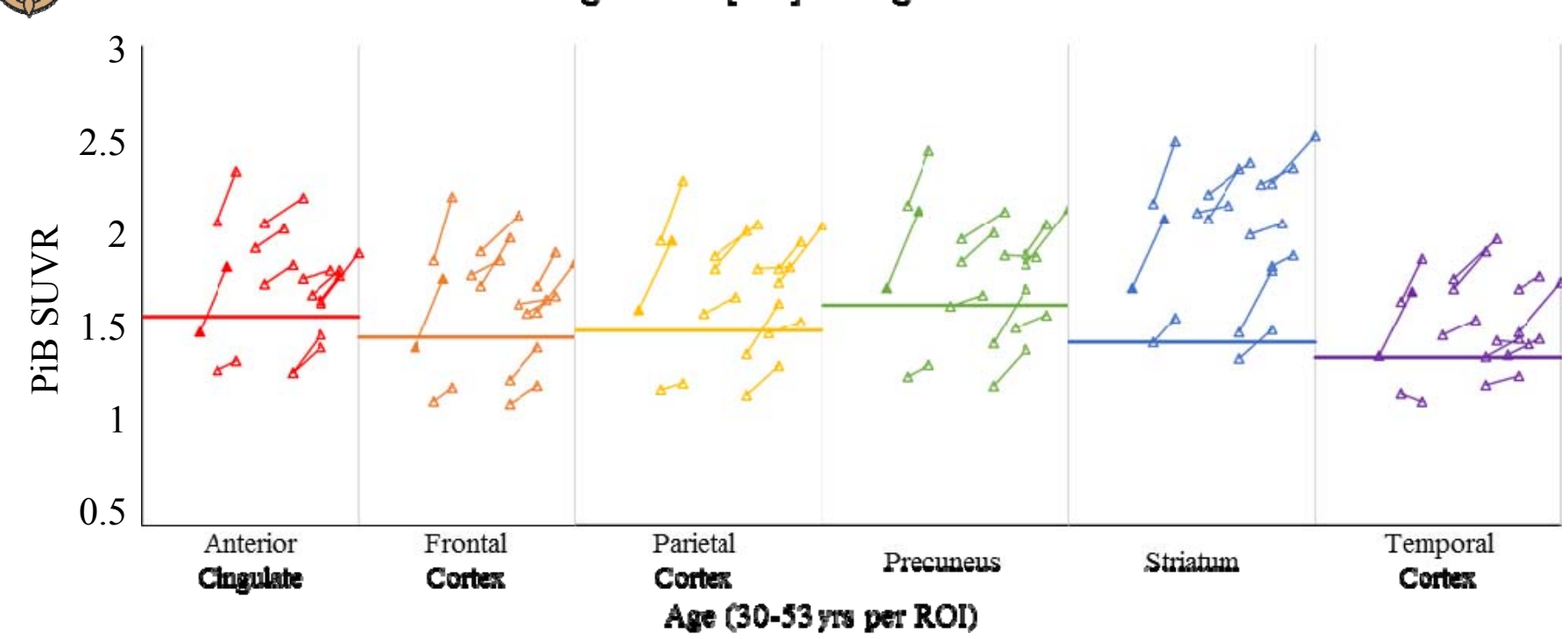


Slide provided by Dr. Patrick Lao

Amyloid Accumulation in the PiB(+)subgroup

- PiB(+) at cycle 1
- PiB(+) at cycle 2
- Most areas have a positive change, namely:
  - **Anterior cingulate**
  - **Frontal cortex**
  - **Parietal cortex**
  - **Precuneus**
  - **Striatum**
  - **Temporal cortex**
- Can see enlarged ventricle spaces in PiB(+) subgroup

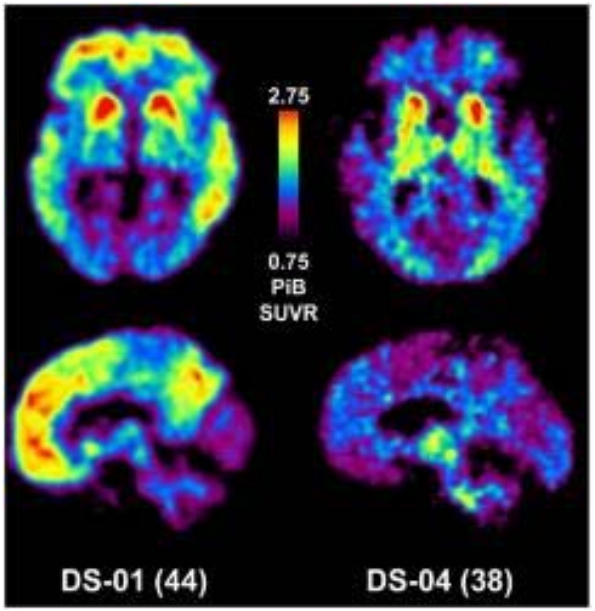
RESULTS: LONGITUDINAL AMYLOID ACCUMULATION



PiB(+) subgroup

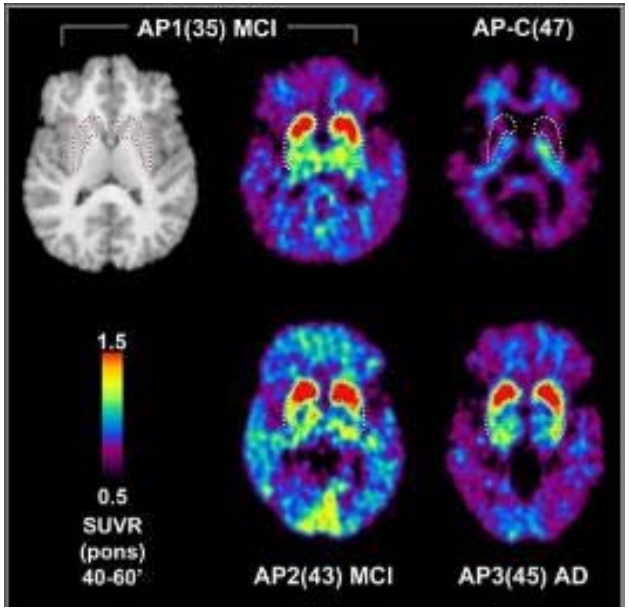
Slide provided by Dr. Patrick Lao

Striatal First Patterns of Amyloid



Handen et al., Alzheimers Dement. 2012

Presenilin (PS1) Mutation Carriers



Klunk et al., J Neurosci. 2007

Results: Significant Correlations between change in Neuropsych & PiB retention

Longitudinal Group Comparisons (one-way ANOVA)

	PiB- to PiB-	PiB- to PiB+	PiB+ to PiB+
Free Recall Total	Improved	Improved	Worse*
Free & Cued Total	No change	Worse	Worse*
Cued Recall Intrusions	Improved	Worse	Worse*
Block Design	Improved	Improved	Worse*
Purdue (single)	No change	Worse	Worse*
Corsi forward	Improved	Improved	Worse*

Table provided by Ben Handen, Ph.D.

Hartley SL, et al. Neurobiology Aging (2017)

Natural History of Amyloid Deposition of Amyloid in Aging Down Syndrome

- Initiated in 2009: University of Pittsburgh, Waisman Center / UWADRC
- Goal: Recruit non-demented adults (n=84, age ≥ 30 yrs) to observe the change in amyloid deposition and its effect on functioning over time

Neurodegeneration in Aging Down Syndrome (NiAD) (U01)

- Initiated in 2015: UPMC, UW, Cambridge U., Barrow/Banner, Washington U., LONI, Mayo, ATRI, NCRAD, NIA / NICHD
- Goal: This longitudinal study will examine progression of AD related neuroimaging, biofluid, genetic and cognitive/functional biomarkers in 180 adults with DS (>25 yrs of age) and 40 "biomarker-controls"

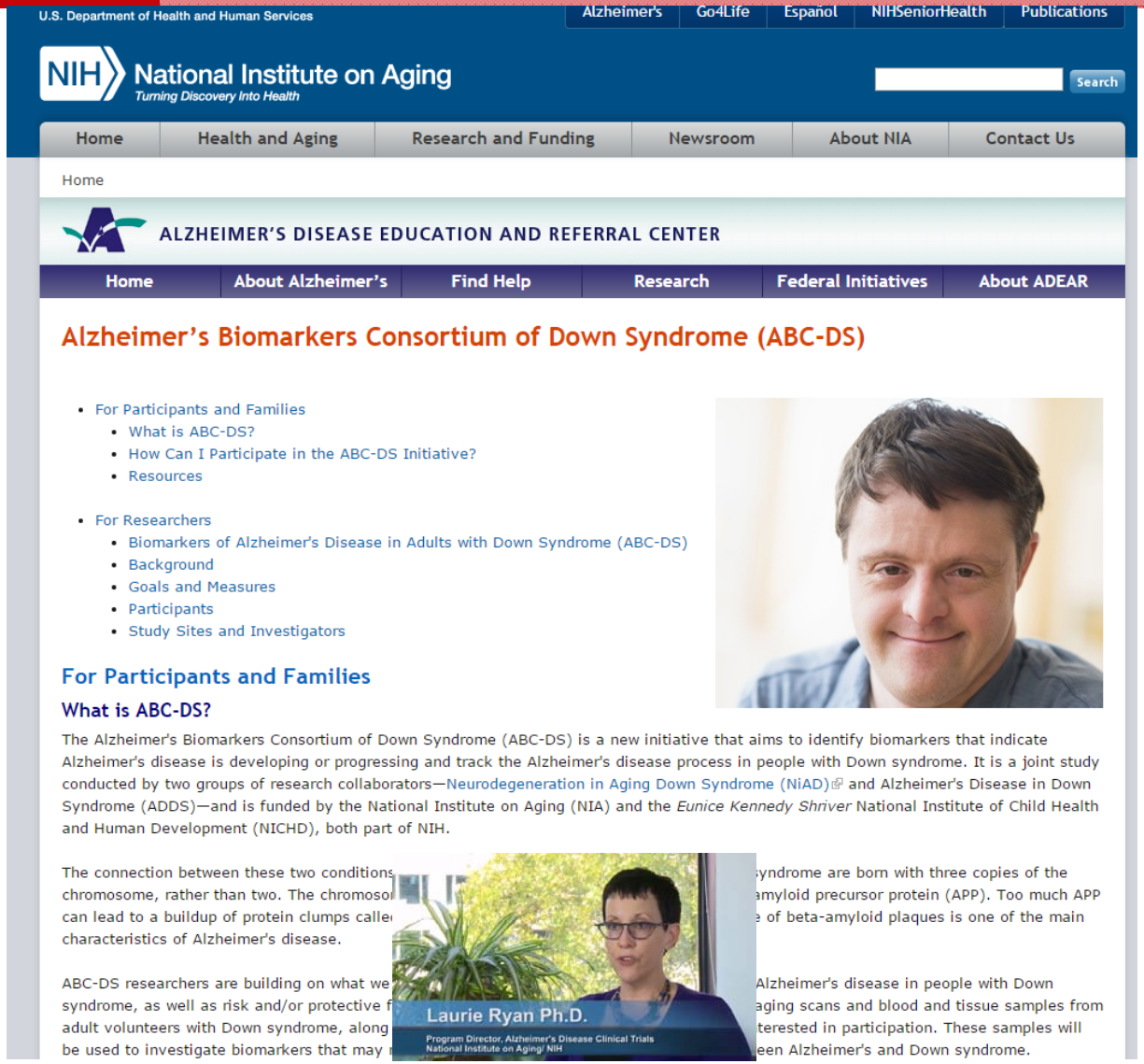
Waisman Center, University of Wisconsin-Madison

University of Cambridge, UK

University of Pittsburgh

ABC-DS

Alzheimer's Biomarkers Consortium — Down Syndrome (ABC-DS)



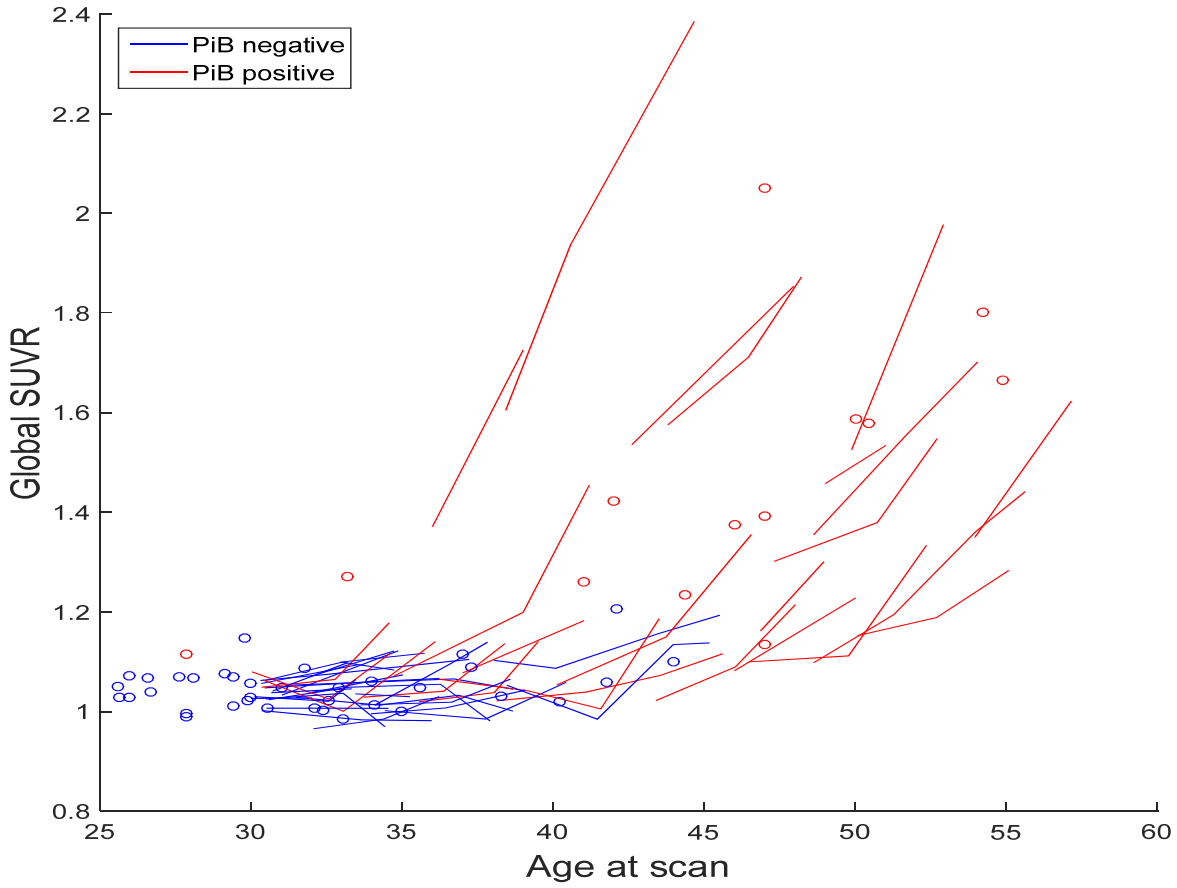
NiAD: Schedule of Biomarker Measures

Measure	Month ->	0	16	32	48
Day 1 (Informant Interview, Neuropsych., MRI)					
**Informed Consent	B*	X			
DSDS Interview & DLD	C*	X	X	X	X
SIB/IQ/Neuropsych Tests	S*	X	X	X	X
Psychiatric Assessment	S	X	X	X	X
Vineland/Reiss Screen	C	X	X	X	X
Medical/Psychiatric Hx	C	X	X	X	X
**MRI	S	X		X	
Day 2 (Fluid Biomarkers, Genetics and PET Scan)					
Trisomy 21-blood	S	X			
**CSF	S	X		X	
**PiB PET	S	X		X	
**FDG PET	S		X		
**ApoE, **Genetics-blood	S	X			
**Blood (Aβ, proteomics)	S	X		X	
Day 3 (PET Scan)					
**[F-18]AV-1451 PET	S	X		X	

*C=Caregiver; S=DS Subject; B=Both

**Biomarker Controls will have these measures

Longitudinal Amyloid Studies

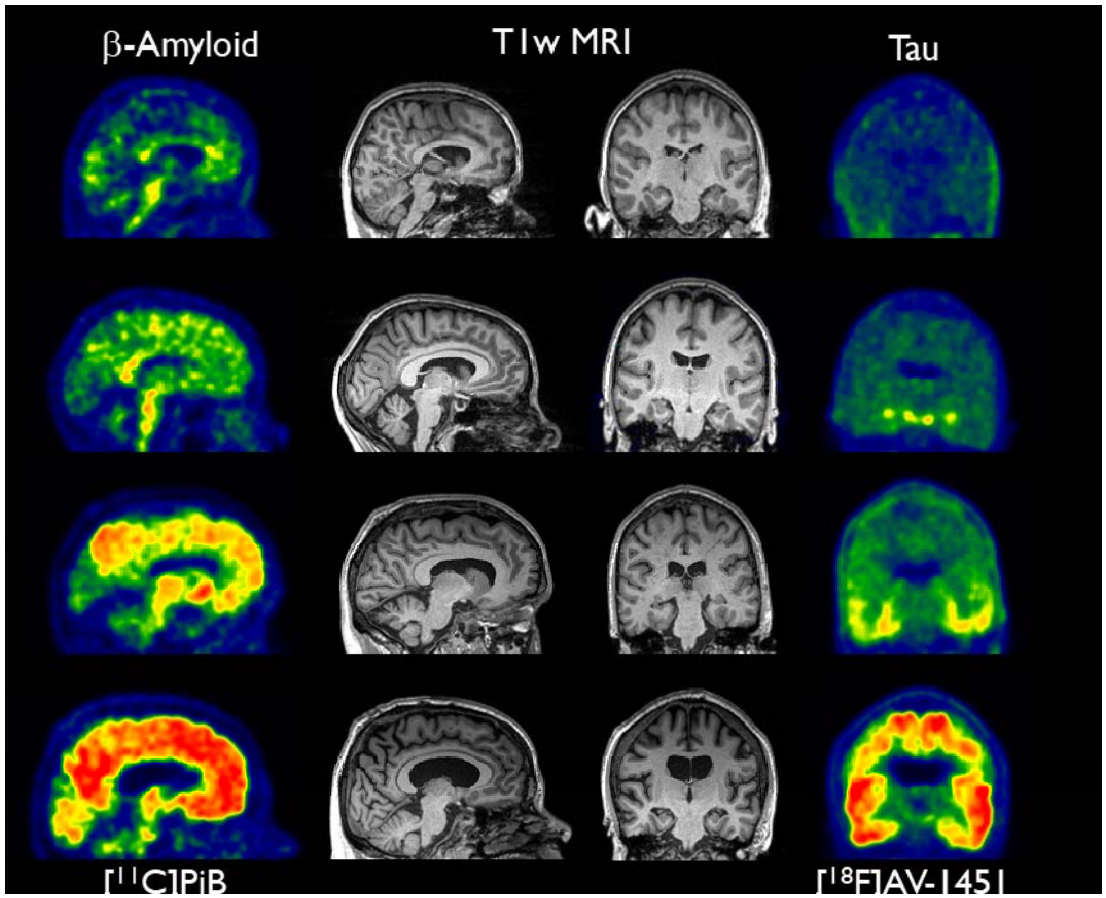


N =166 enrollment to date

Tau Imaging in Down Syndrome

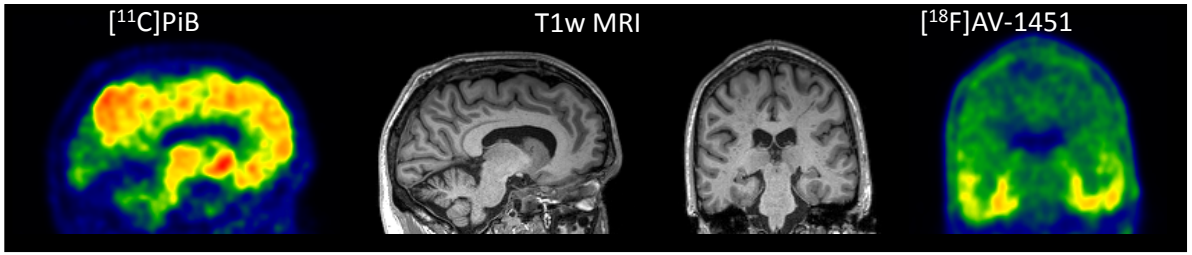
- Acquired at baseline visit, and repeated at 32 months
- Scanned with [F-18]AV-1451
  - SUVR measured from 80 – 100 min
  - N = 166 Down syndrome subjects to date

Tau Imaging in Down Syndrome

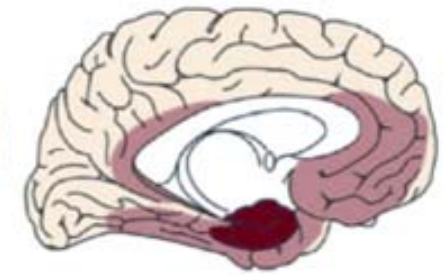


NIAD

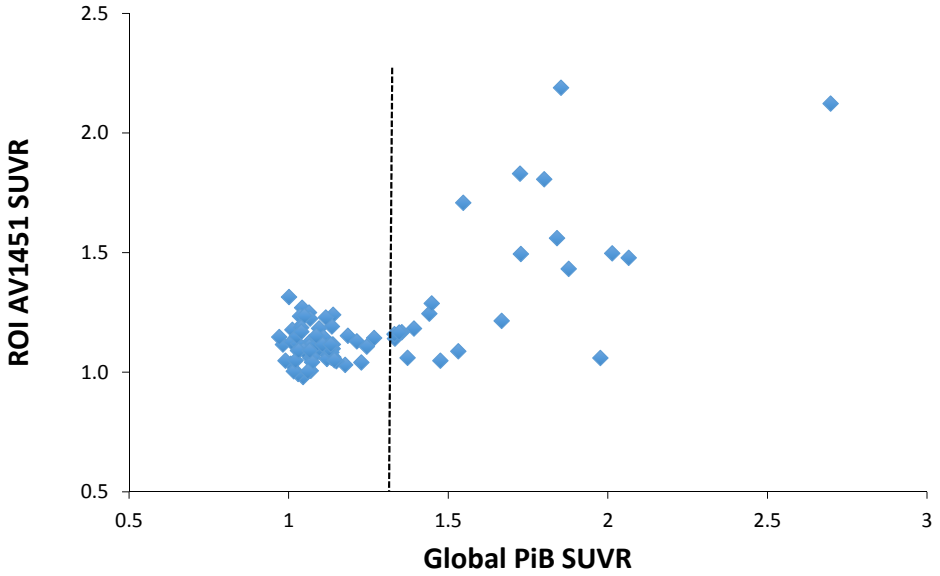
Tau Imaging in Down Syndrome



Stages III-IV



Adapted from Braak, et al. J Neuropathol Exp Neurol. 2011

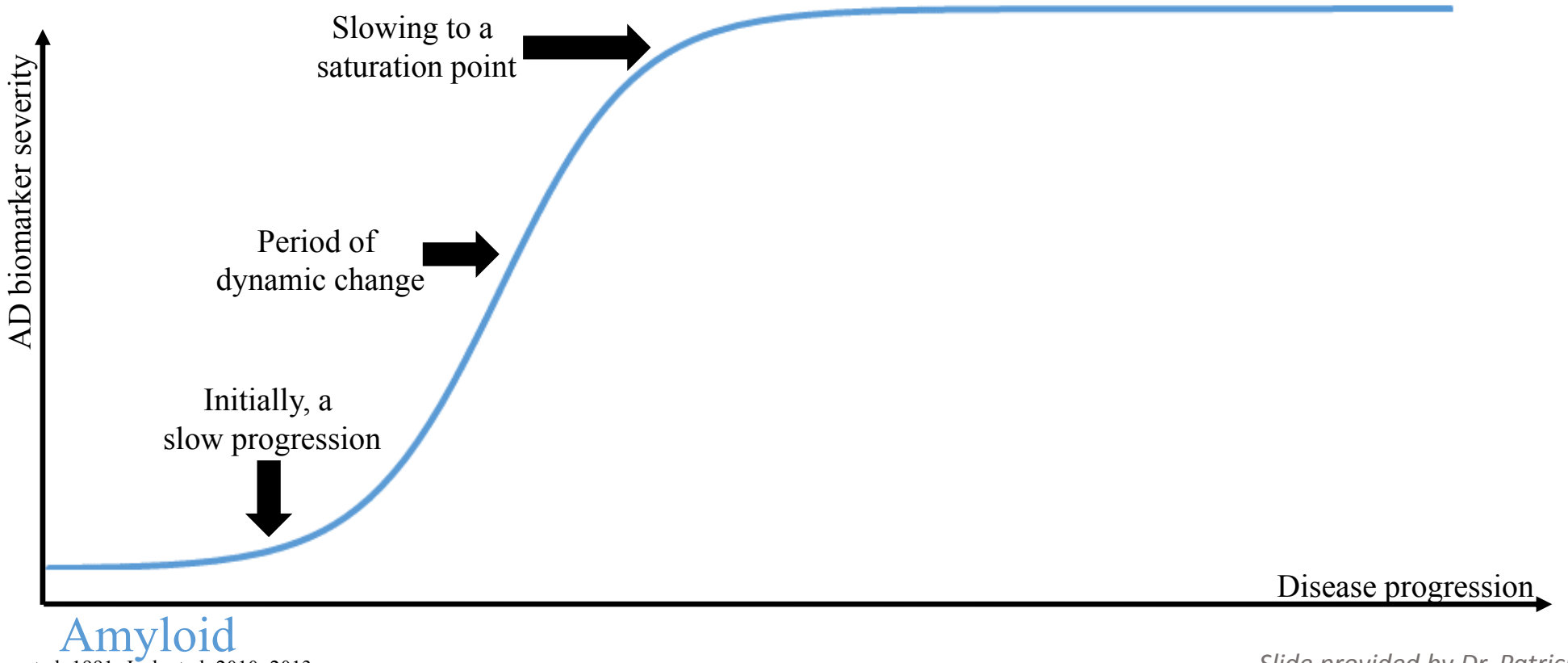


Zammit et al, Human Amyloid Imaging 2019

Amyloid cascade hypothesis

Note: sigmoid curves (slopes, spacing) are **arbitrary** in this illustrative figure

- **Rates change over time**



Selkoe et al, 1991; Jack et al, 2010; 2013

Slide provided by Dr. Patrick Lao

Amyloid cascade hypothesis

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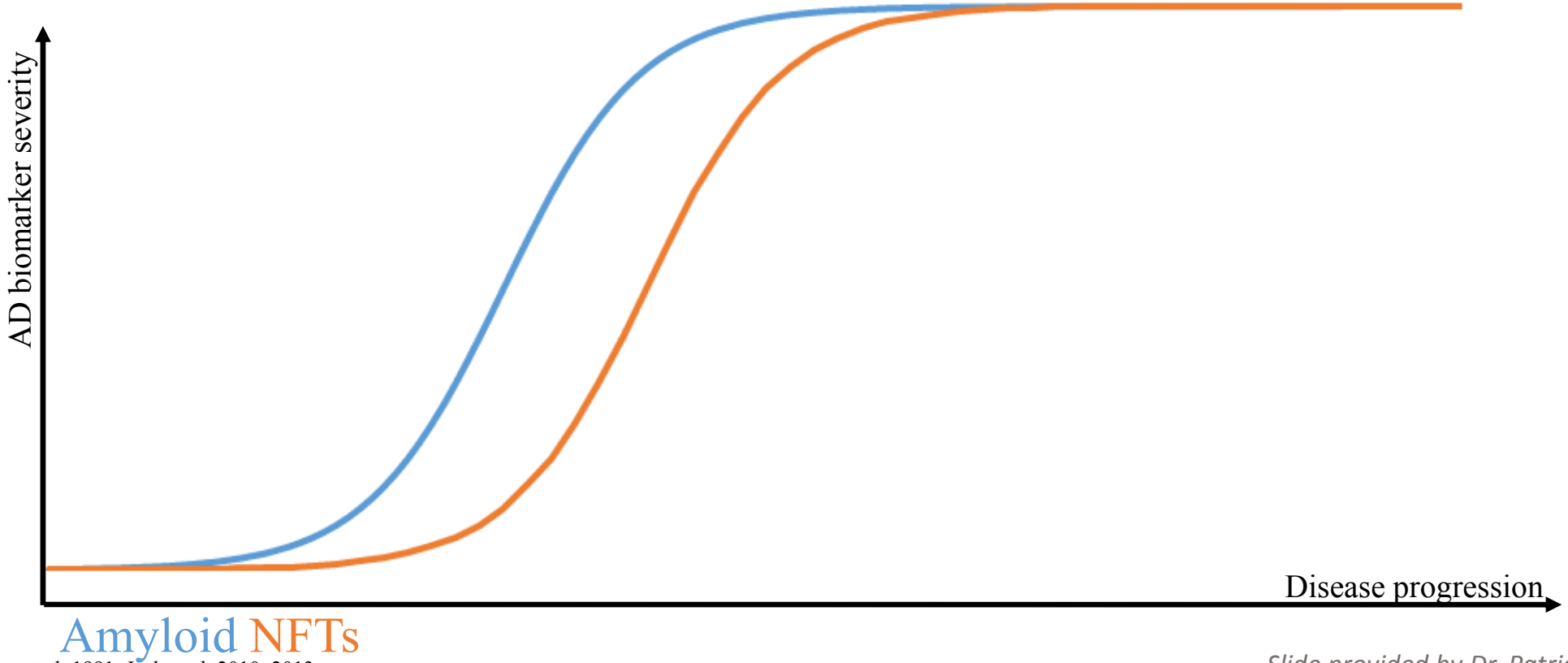
- **Rates change over time**
- **Proposed temporal order**



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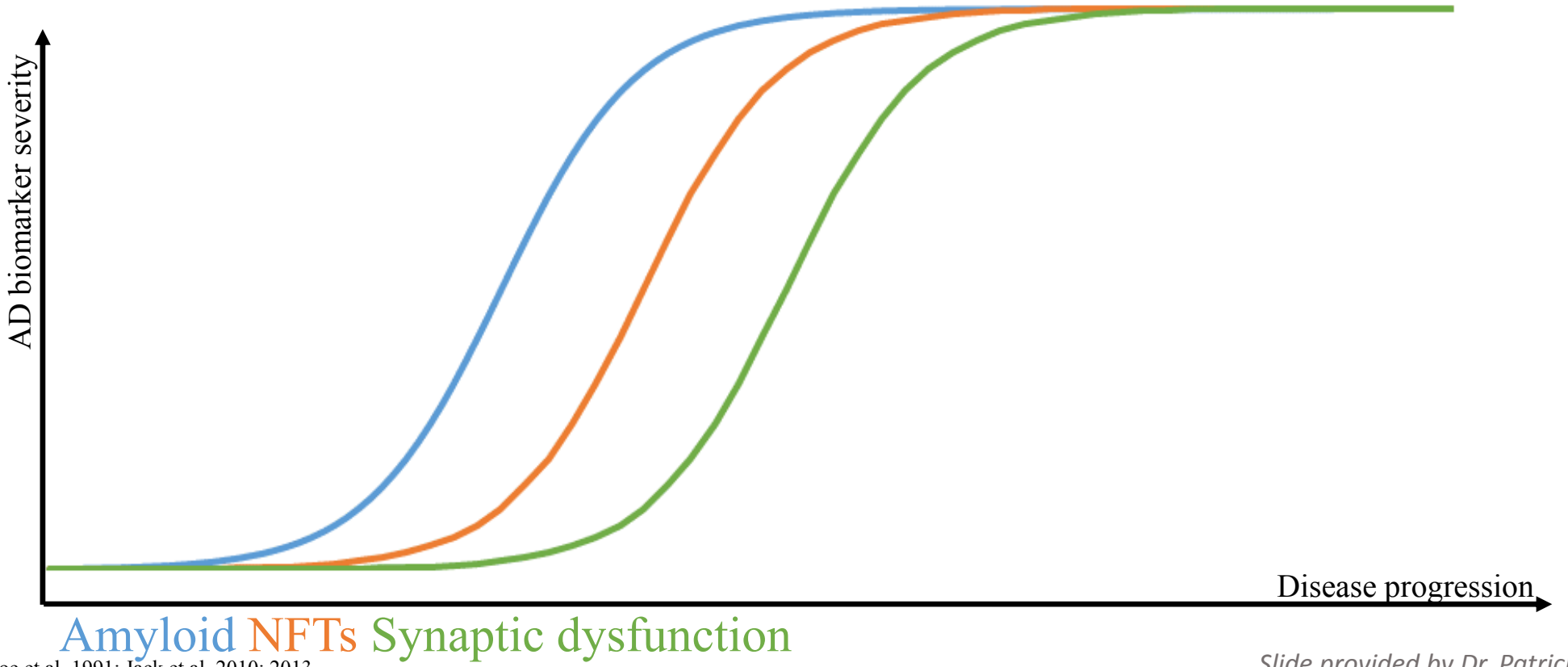

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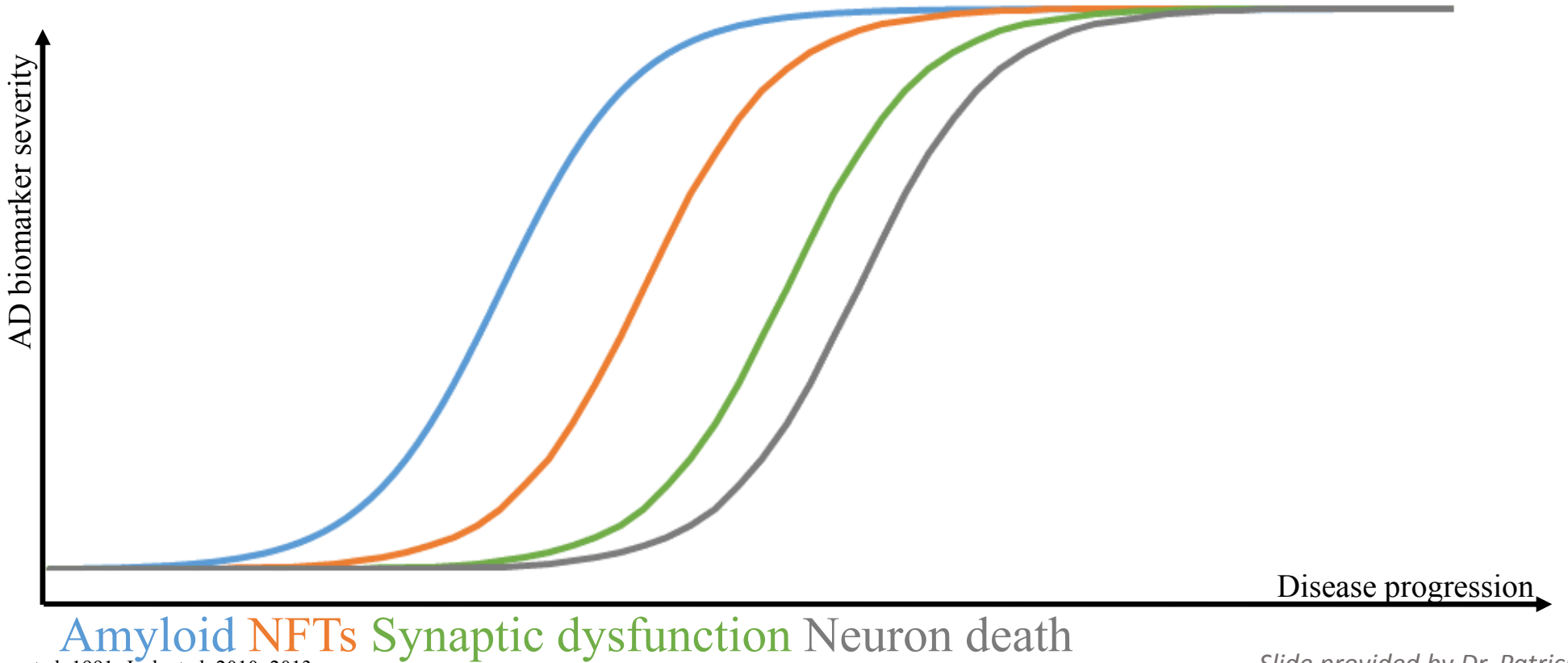

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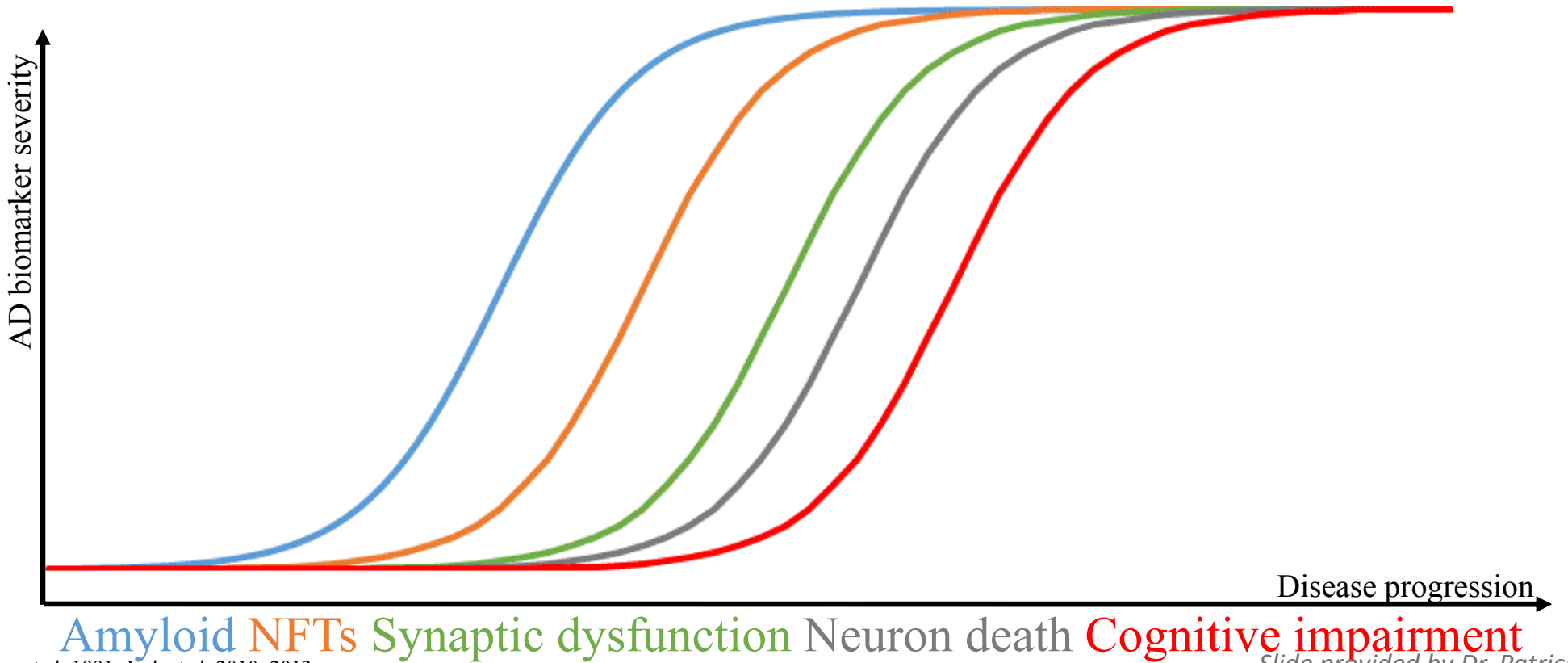

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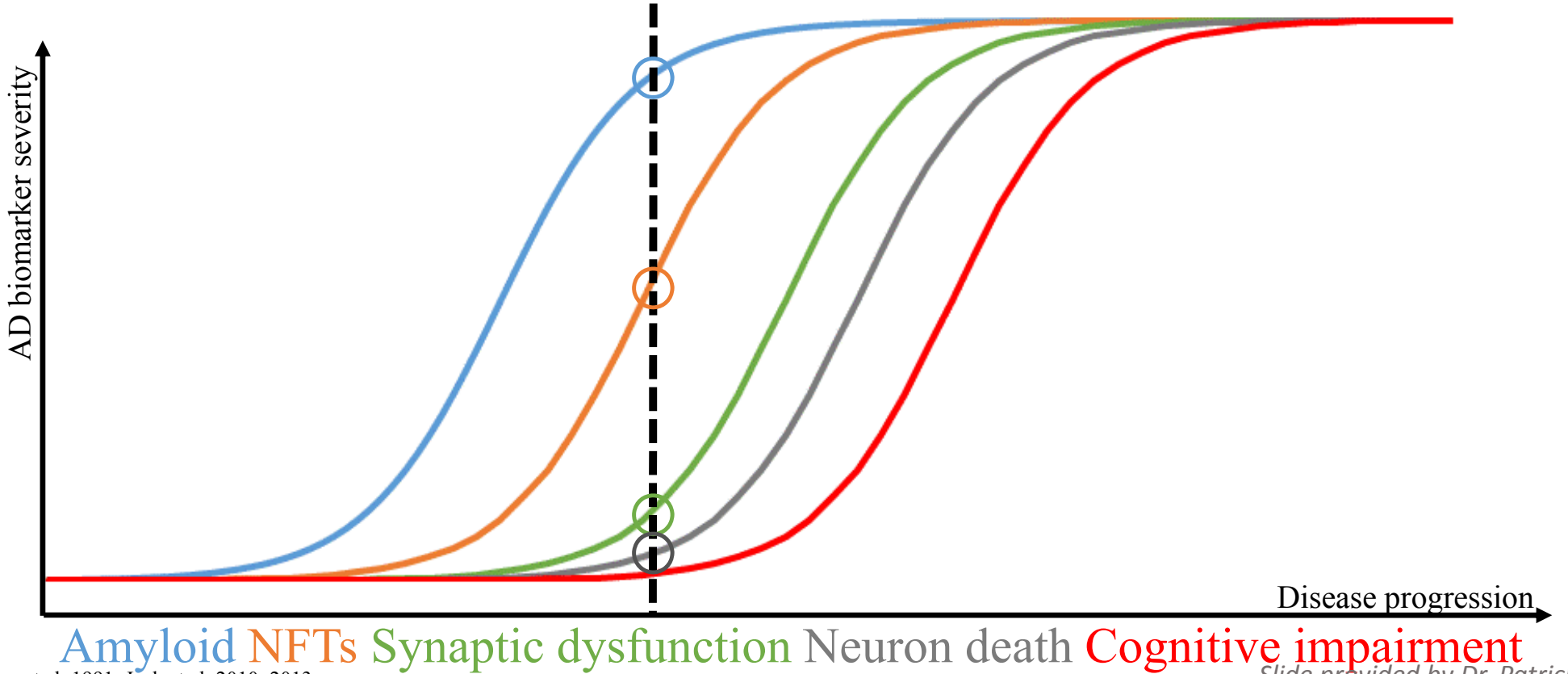

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Slide provided by Dr. Patrick Lao

Amyloid cascade hypothesis

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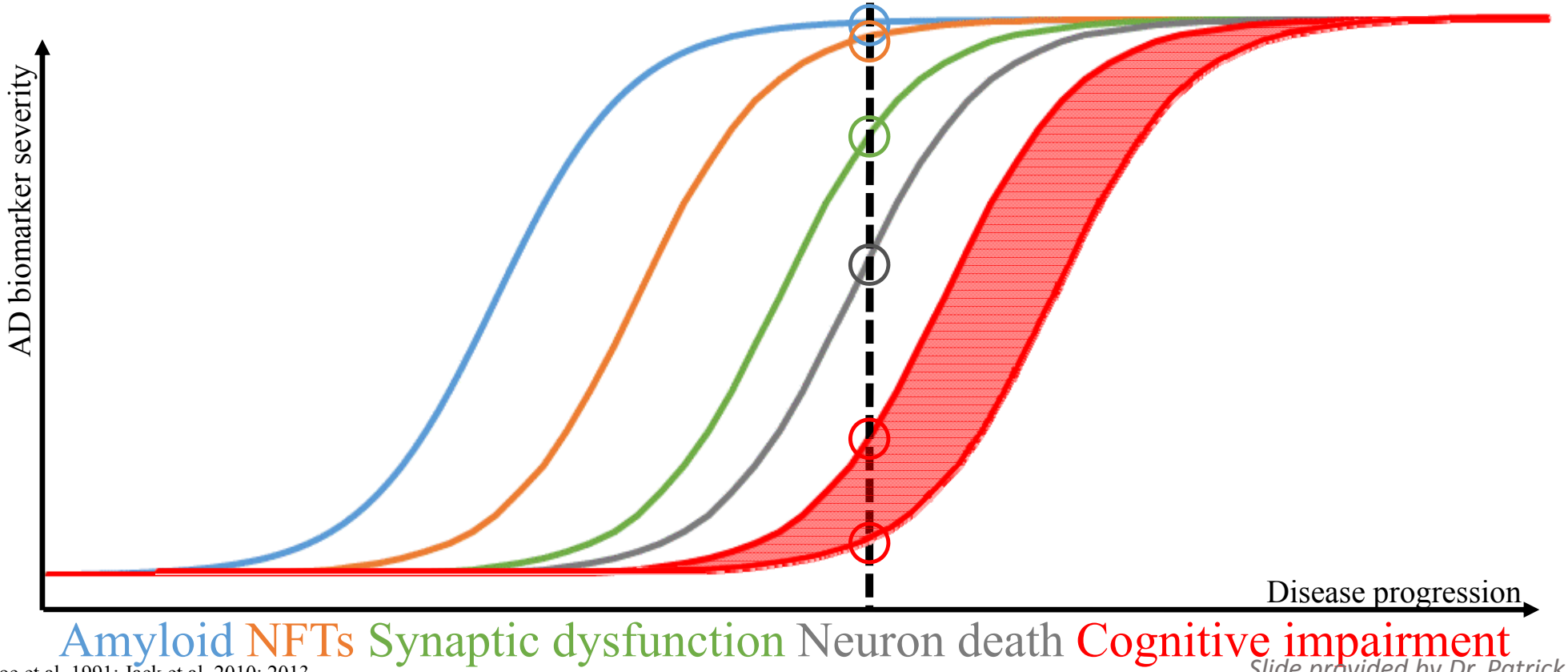
- Profile of biomarker abnormality can lead to **range of cognitive function** (cognitive reserve; neuroprotective effect)



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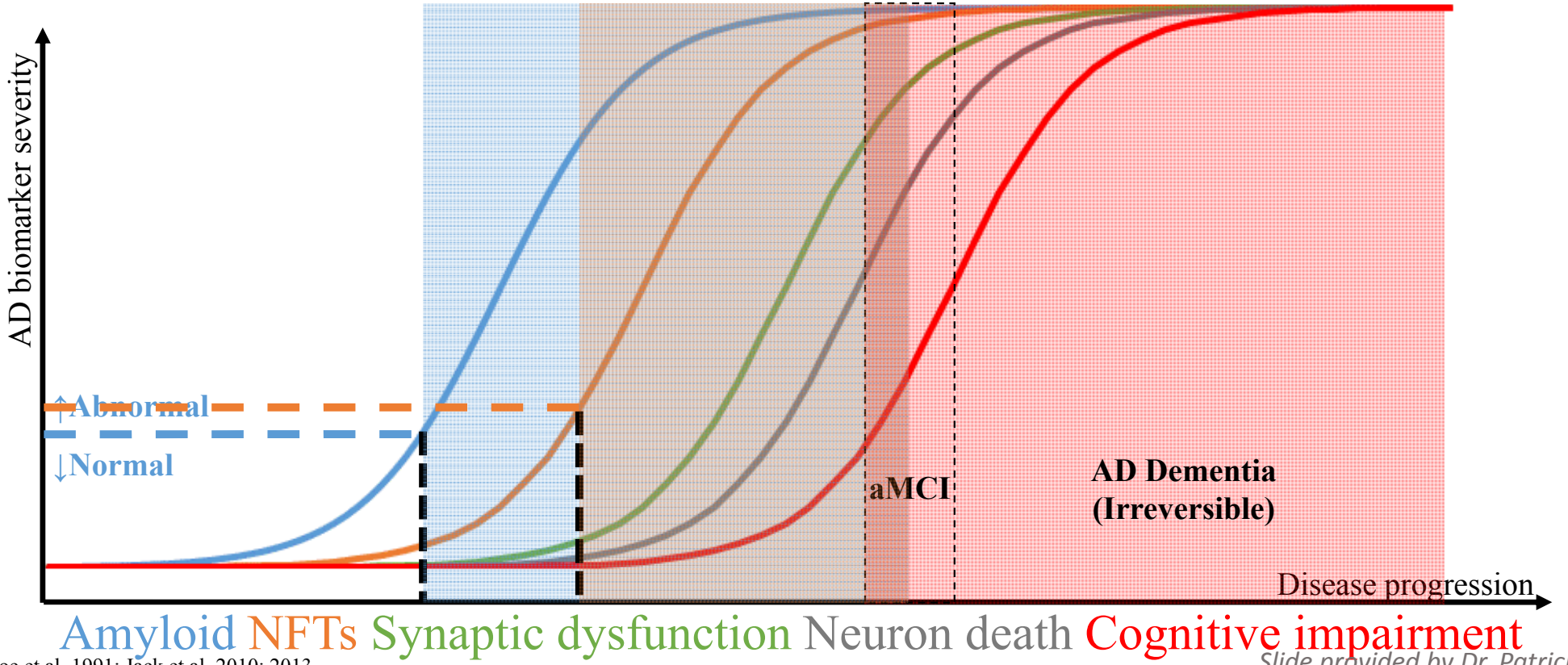

Selkoe et al, 1991; Jack et al, 2010; 2013

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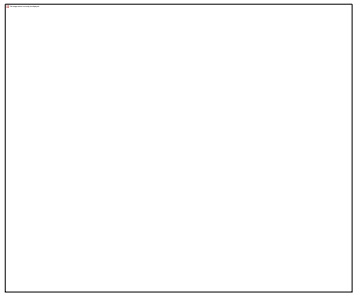
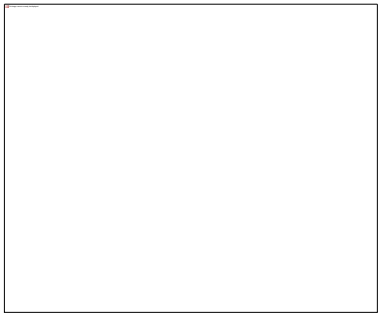
Future Directions

- Alzheimer's Clinical Trial Consortium (ACTC) launched in 2017
  - Initiating ACTC – Down Syndrome (DS)

- INCLUDE – INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE

- Project modeled after Dominantly Inherited Alzheimer Network (DIAN)





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