PARKINSON UPDATE

David G. Standaert, MD, PhD

Chair, UAB Department of Neurology

Director, Alabama Udall Center

March 7, 2024

The University of Alabama at Birmingham

DISCLOSURES

- Dr. Standaert has served as a paid consultant to these companies within the last 12 months:
  - Abbvie Inc.
  - Curium Pharma
  - Appello Pharma
  - F. Hoffman La Roche
  - Coave Therapeutics
  - Blue Rock Therapeutics
  - Sanofi-Aventis Research and Development (DSMB member)
  - Alnylam Pharmaceuticals (DSMB member)
  - Theravance, Inc. (DSMB member)

TODAY'S TOPICS

- Time for a new way of thinking about Parkinson disease?
- Slowing the advance of PD
  - Taking a page from the Alzheimer playbook
  - Cooling off inflammation

Almost quitting time!!!

THE MANY FACES OF PARKINSON DISEASE

James Parkinson 1817

AN

ESSAY

ON THE

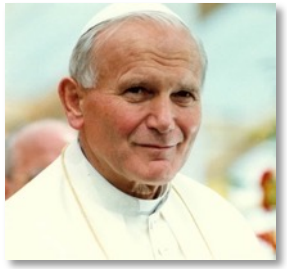
SHAKING PALSY.

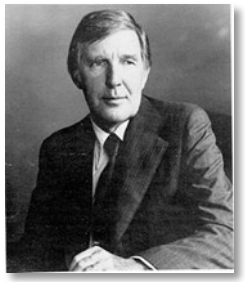
CHAPTER I.

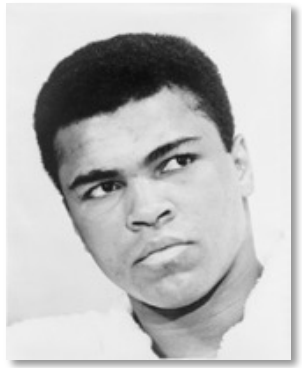
DEFINITION—HISTORY—ILLUSTRATIVE CASES.

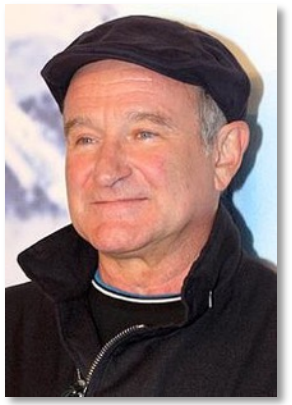
SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.



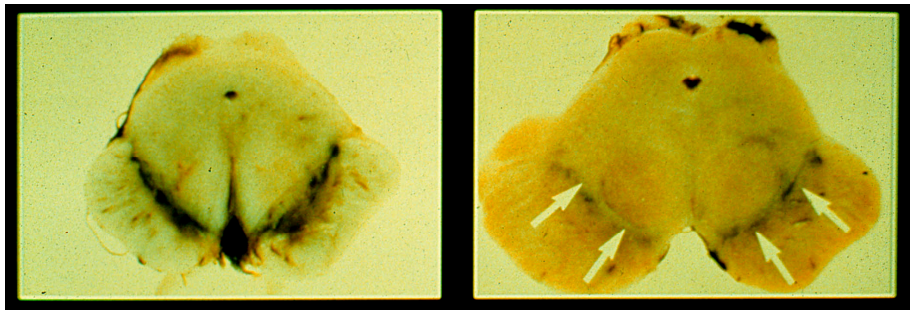


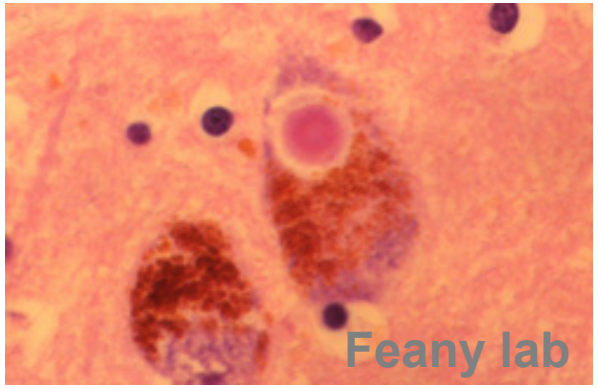


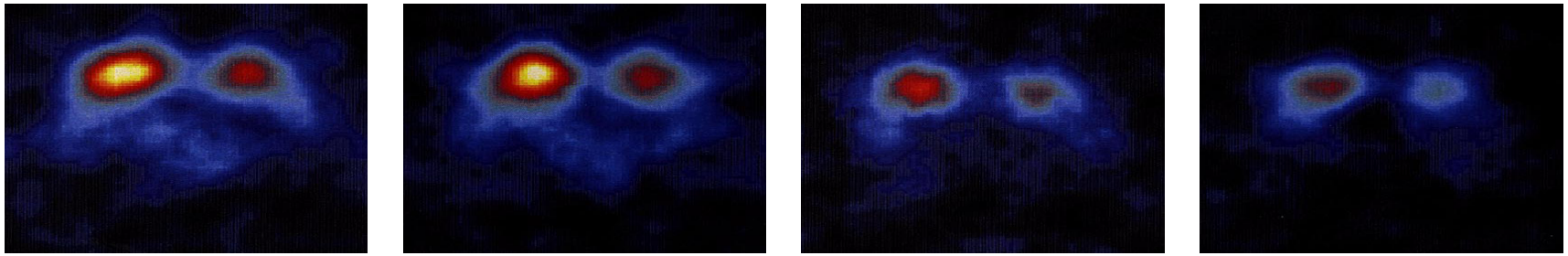


CLASSICAL FEATURES OF PARKINSON DISEASE

- Rest Tremor
- Bradykinesia
- Rigidity
- Postural Imbalance







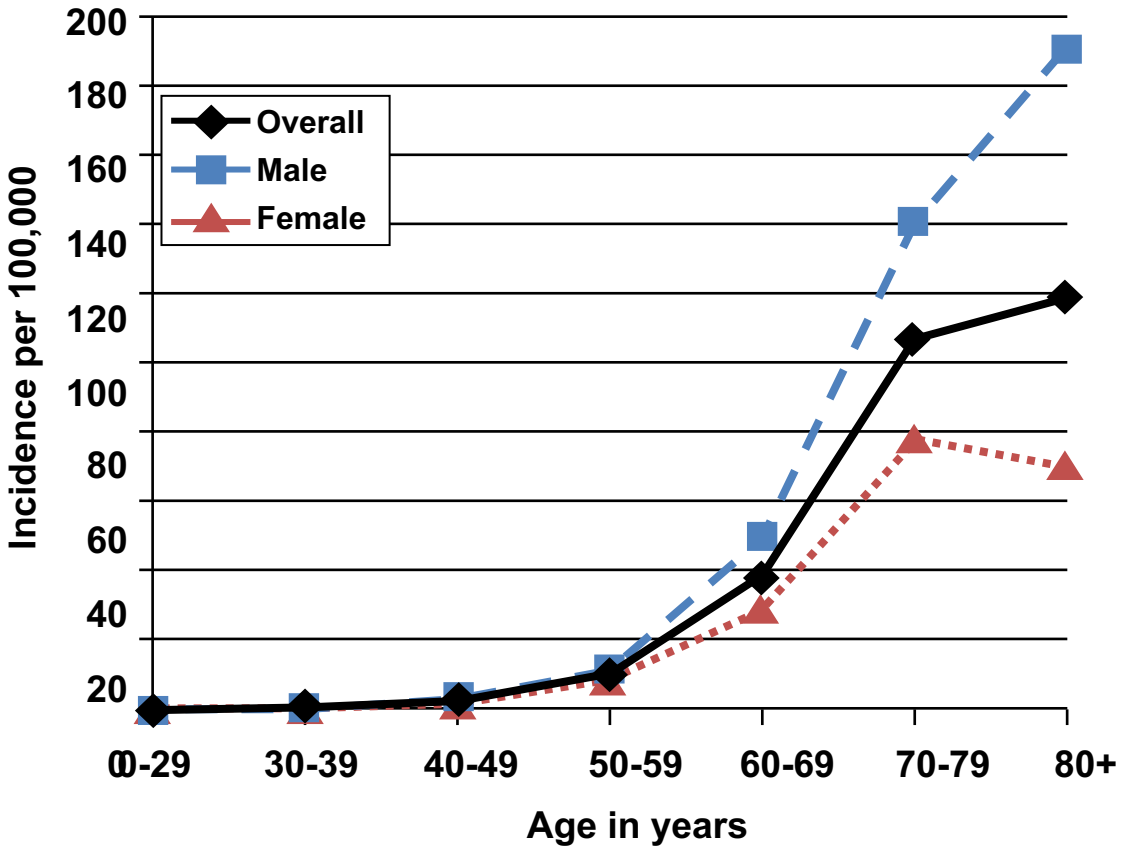
PARKINSON DISEASE: NON-MOTOR FEATURES

- **Early (premotor) Features**
  - Hyposmia
  - REM Behavior Disorder
  - Autonomic disturbances
- **Late Features**
  - Excessive sleepiness
  - Depression and anxiety
  - Dementia

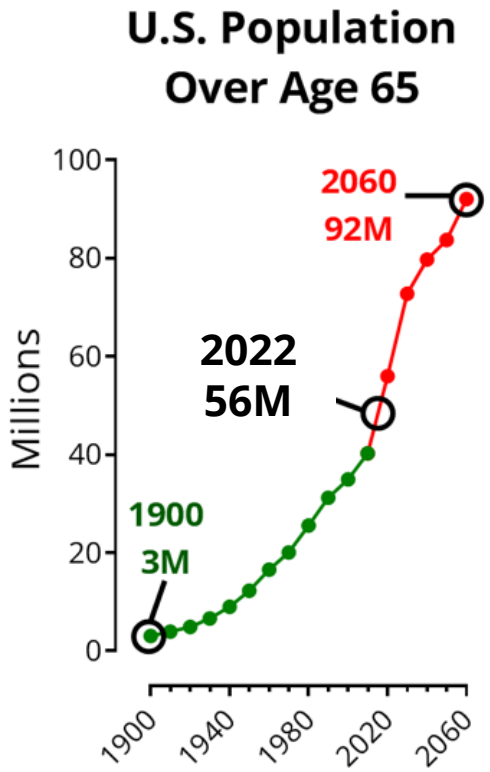
STATES OF PARKINSON DISEASE

At Risk	Prodromal	Early PD	Advanced PD
▪ No symptoms ▪ Genetic risk factors	▪ Hyposmia – loss of the sense of smell ▪ REM Behavior Disorder – “acting out dreams” ▪ Constipation	▪ Tremor ▪ Bradykinesia ▪ Rigidity ▪ Fatigue	▪ Impaired balance ▪ Wearing off ▪ Dyskinesia ▪ Memory problems ▪ Hallucinations

PD IS COMMON. AGE IS THE PRIMARY RISK FACTOR

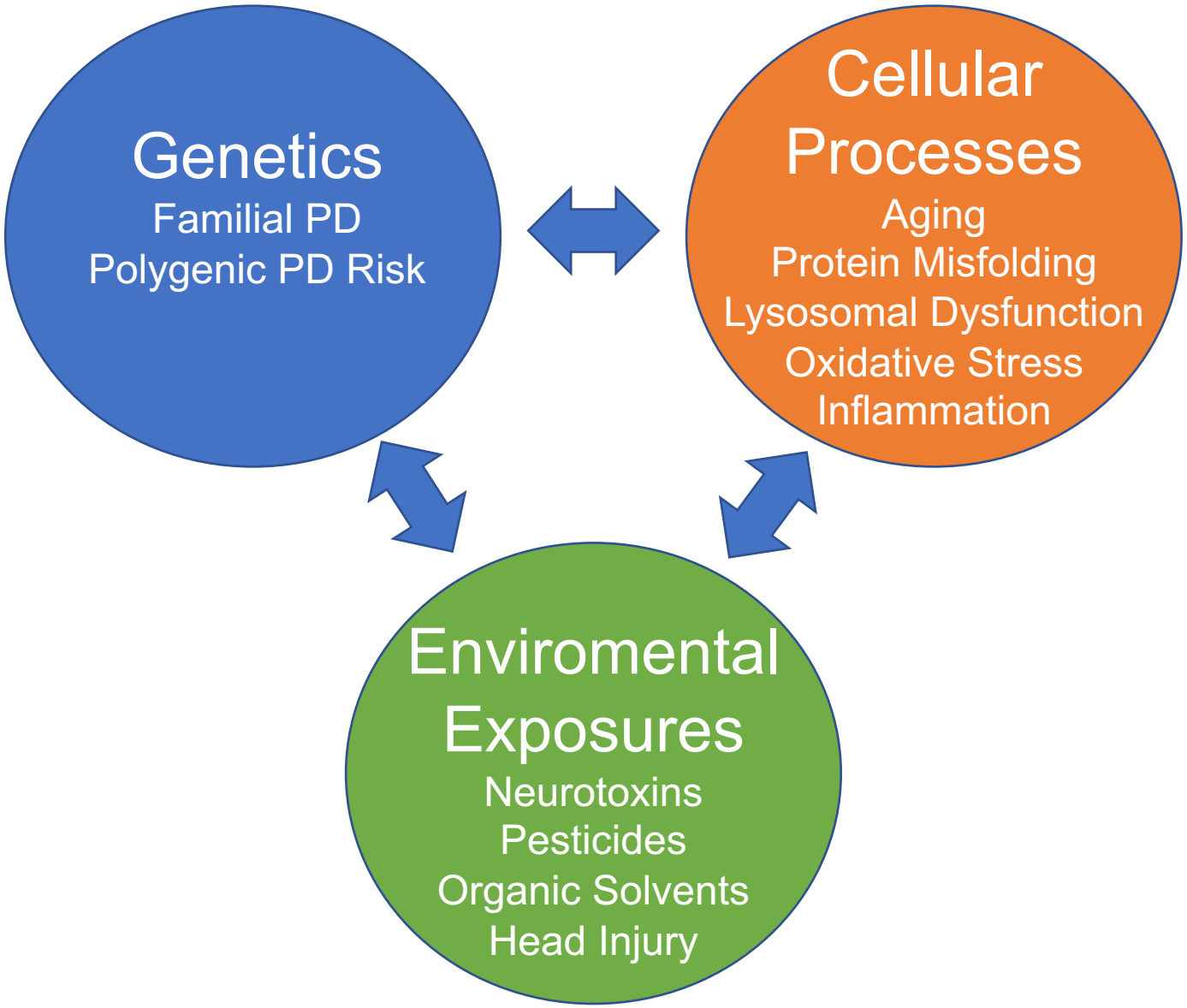


Kaiser Permanente, 1994 -1995 (Van Den Eeden et al, *Am J Epidemiol* 2003; 157:1015-1022)



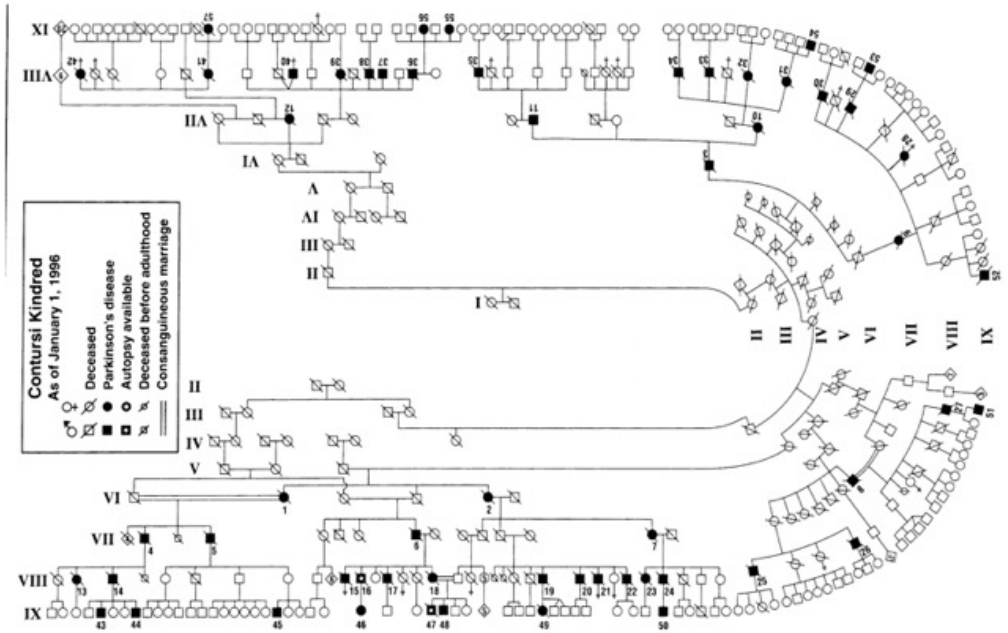
- Parkinson disease today affects about 1M in the US, about 7-10M worldwide.
- The prevalence is increasing rapidly because of aging of the population.

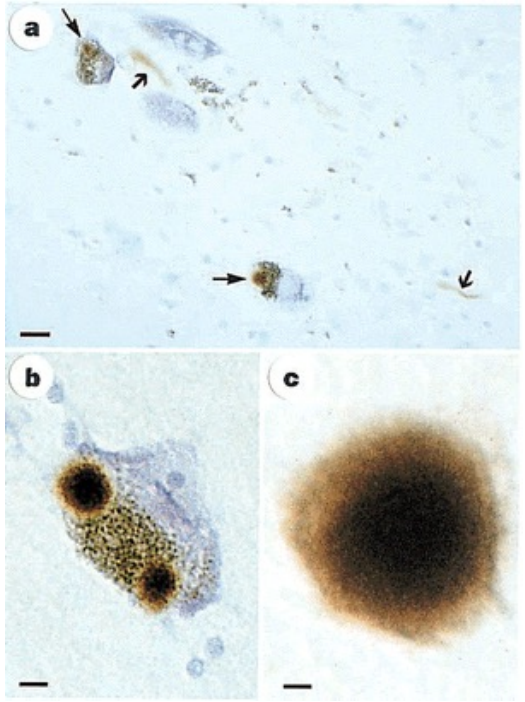
WHAT CAUSES PARKINSON DISEASE?



ALPHA-SYNUCLEIN AND PD

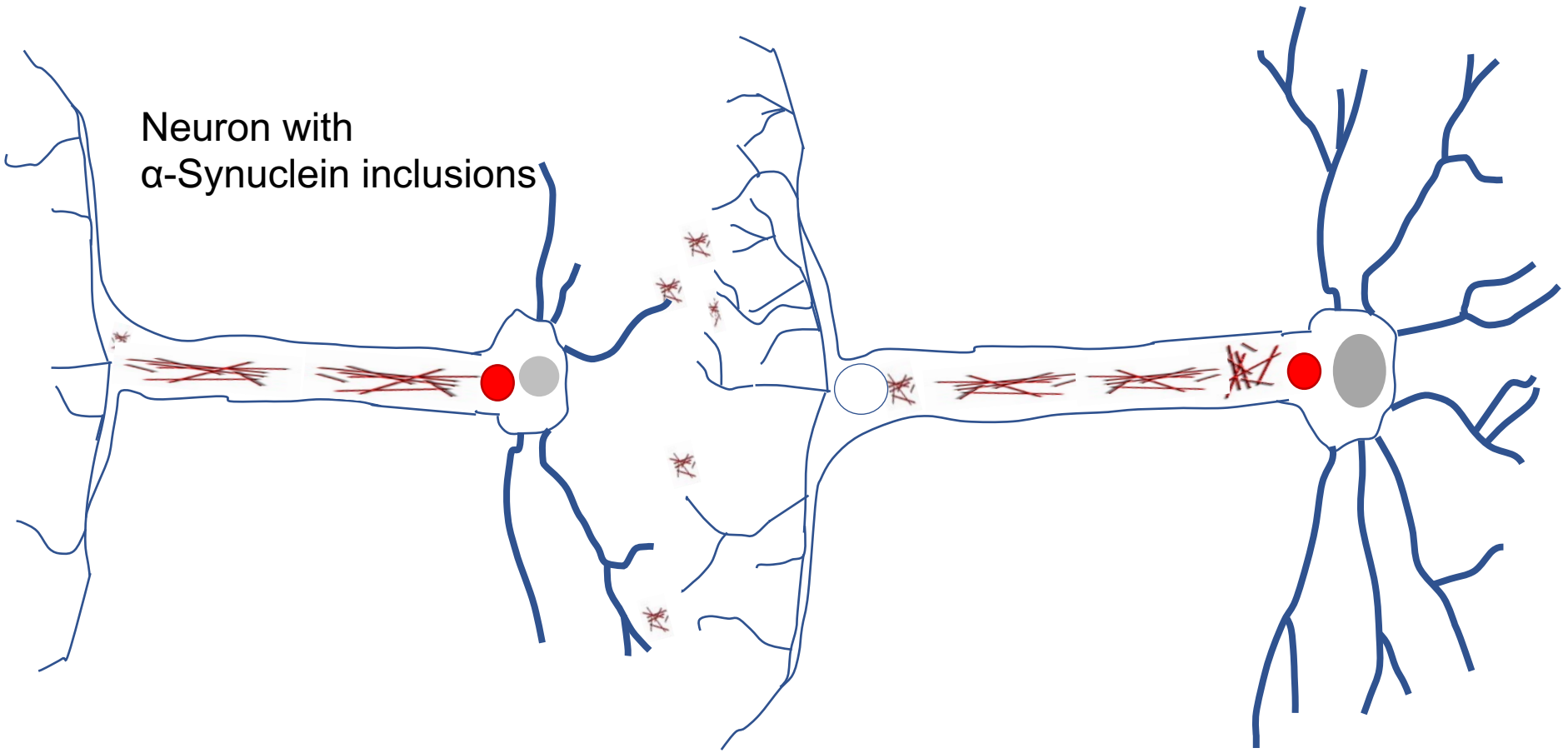
- Linked to PD through the large families
- Mutations and gene duplications cause autosomal dominant PD
- A principal component of Lewy bodies

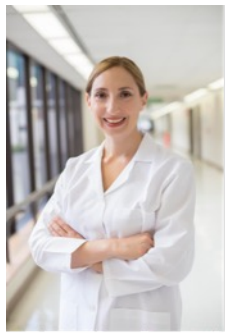




Spillantini et al., Nature, 1997

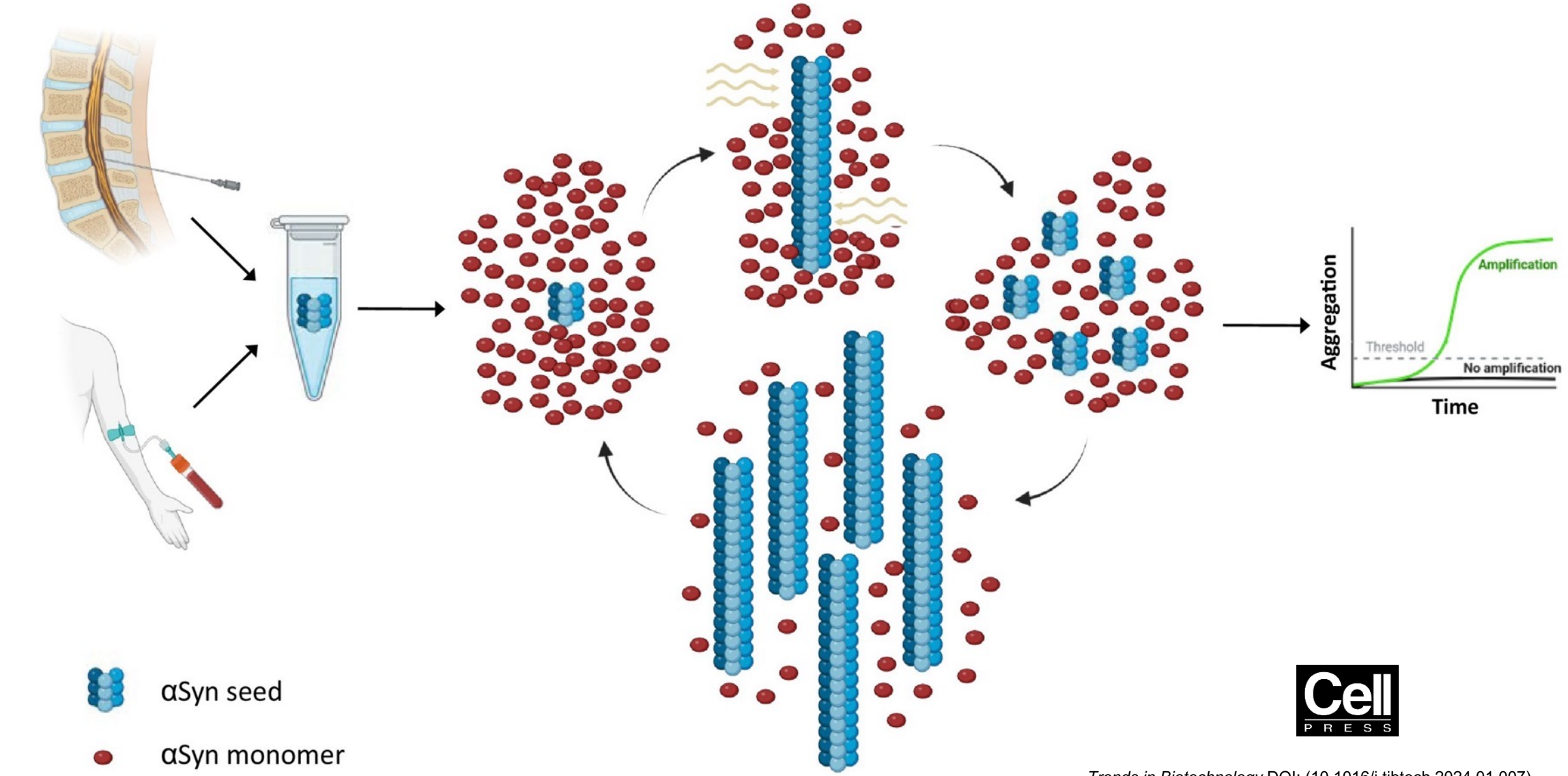
SYNUCLEIN SPREADING





Laura Volpicelli-Daley, PhD

SYNUCLEIN SEEDING ASSAYS



Trends in Biotechnology DOI: (10.1016/j.tibtech.2024.01.007)

Trends in Biotechnology

SEEDING ACTIVITY ASSAY (SAA) IN PPMI

Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study

Andrew Siderowf, Luis Concha-Marambio*, David-Erick Lafontant, Carly M Farris, Yihua Ma, Paula A Urenia, Hieu Nguyen, Roy N Alcalay, Lana M Chahine, Tatiana Foroud, Douglas Galasko, Karl Kieburtz, Kalpana Merchant, Brit Mollenhauer, Kathleen L Poston, John Seibyl, Tanya Simuni, Caroline M Tanner, Daniel Weintraub, Aleksandar Videnovic, Seung Ho Choi, Ryan Kurth, Chelsea Caspell-Garcia, Christopher S Coffey, Mark Frasier, Luis M A Oliveira, Samantha J Hutten, Todd Sherer, Kenneth Marek, Claudio Soto, on behalf of the Parkinson's Progression Markers Initiative†*

Lancet Neurol 2023; 22: 407–17

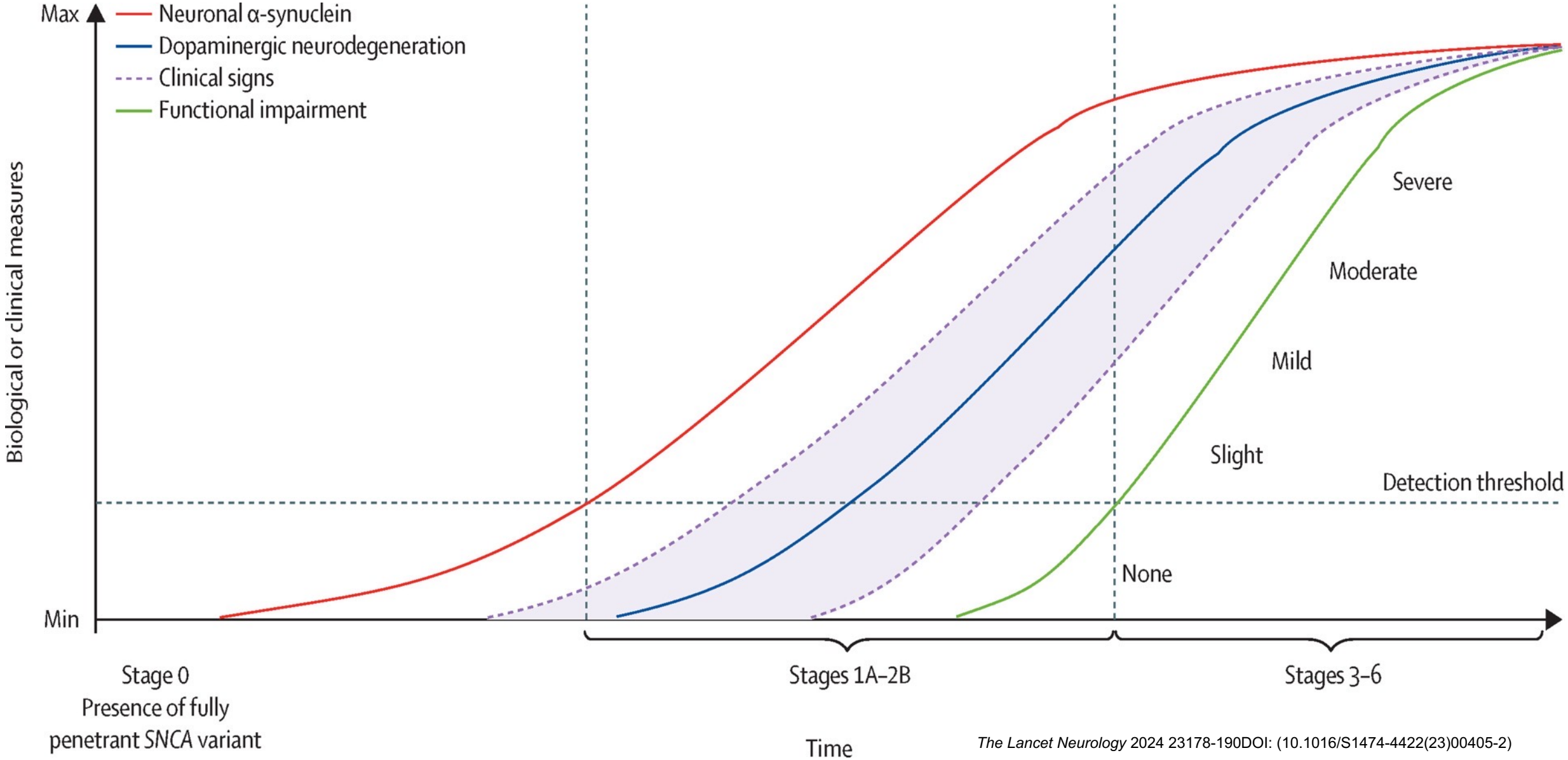
- SAA testing in CSF of more than 1000 participants in the MJFF PPMI study
- SAA test is positive in more than 87% of PD patients, and less than 4% of controls
- Shows that most cases of PD are related to abnormal synuclein

	N	Specificity (95% CI)	Sensitivity (95% CI)
Healthy controls	163	96·3% (93·4–99·2)	NA
SWEDD	54	90·7% (83·0–98·5)	NA
All Parkinson's disease cases	545	NA	87·7% (84·9–90·5)
Hyposmic	390	NA	97·2% (95·5–98·8)
Normosmic	146	NA	63·0% (55·2–70·8)
Sporadic Parkinson's disease	373	NA	93·3% (90·8–95·8)
LRRK2 mutation Parkinson's disease	123	NA	67·5% (59·2–75·8)
GBA mutation Parkinson's disease	49	NA	95·9% (90·4–100·0)
LRRK2 mutation Parkinson's disease			
Male participants	65	NA	78·5% (68·5–88·5)
Female participants	58	NA	55·2% (42·4–68·0)
Hyposmic	69	NA	89·9% (82·7–97·0)
Normosmic	49	NA	34·7% (21·4–48·0)
Normosmic and female participants	24	NA	12·5% (4·3–31·0)

NA=not applicable. SWEDD=participants with scans without evidence of dopaminergic deficit.

Table 2: **Sensitivity of CSF α-synuclein seed amplification assay for Parkinson's disease, and specificity for healthy controls and SWEDD**

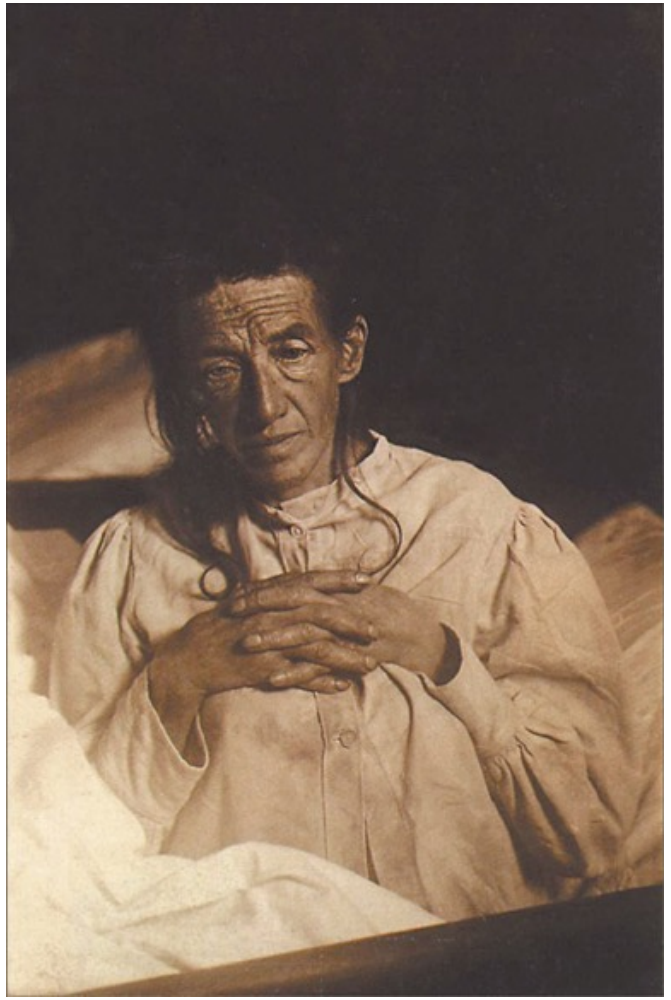
A NEW WAY TO LOOK AT PD



The Lancet Neurology 2024 23178-190DOI: (10.1016/S1474-4422(23)00405-2)

WHAT CAN WE LEARN FROM ALZHEIMER'S?

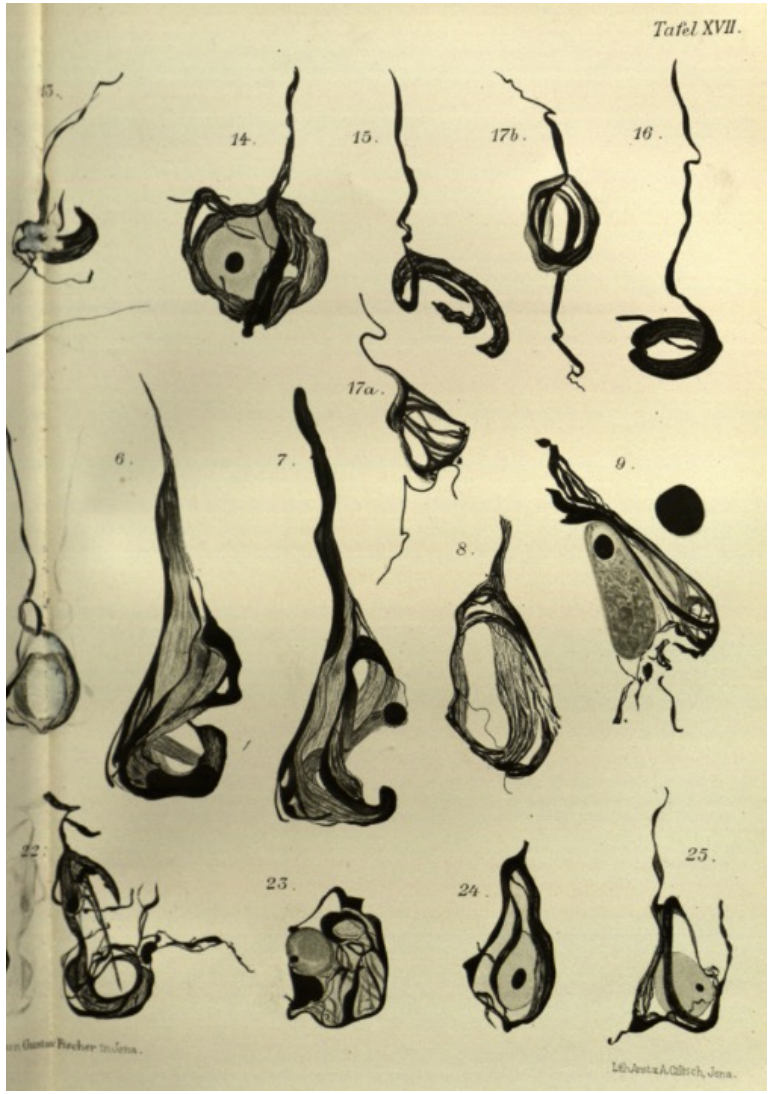
Dr. Aloysius "Alois" Alzheimer
1864-1915



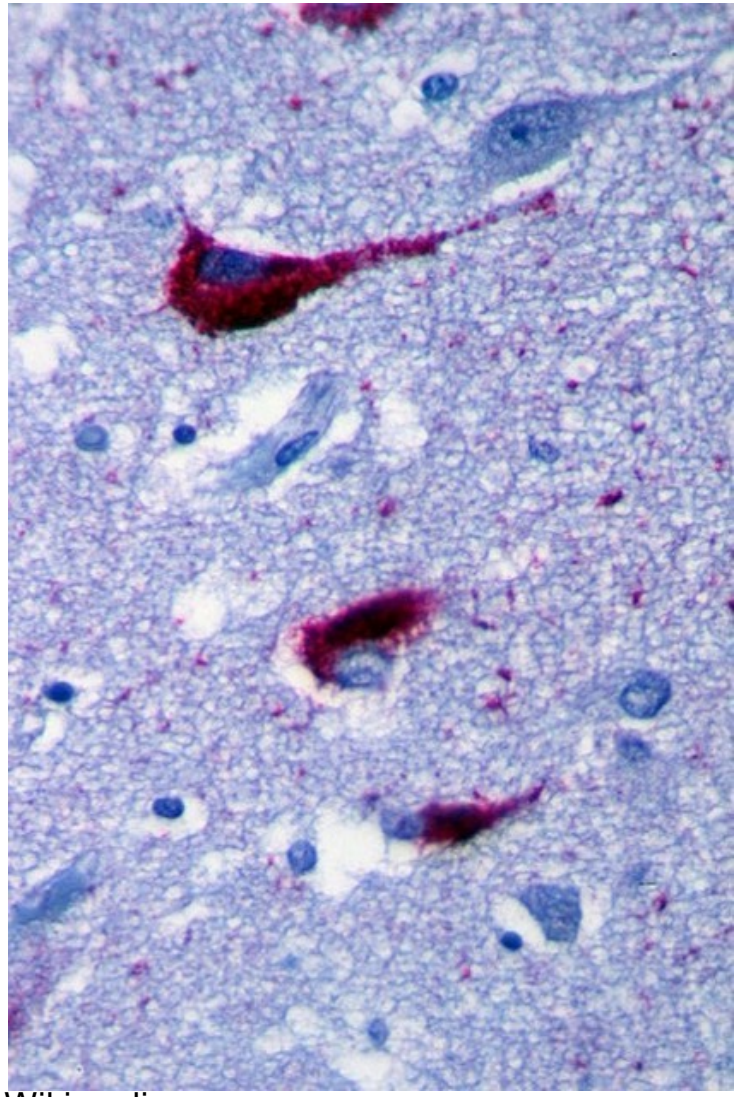
Auguste D.
1850-1906

"How old are you?"
"Fifty-one."
"Where do you live?"
"Oh, you have been to our place."
"Are you married?"
"Oh, I am so confused."
"Where are you right now?"
"Here and everywhere, here and now, you must not think badly of me."

ALZHEIMER DISEASE: TANGLES AND PLAQUES



A. Alzheimer, wustl.org



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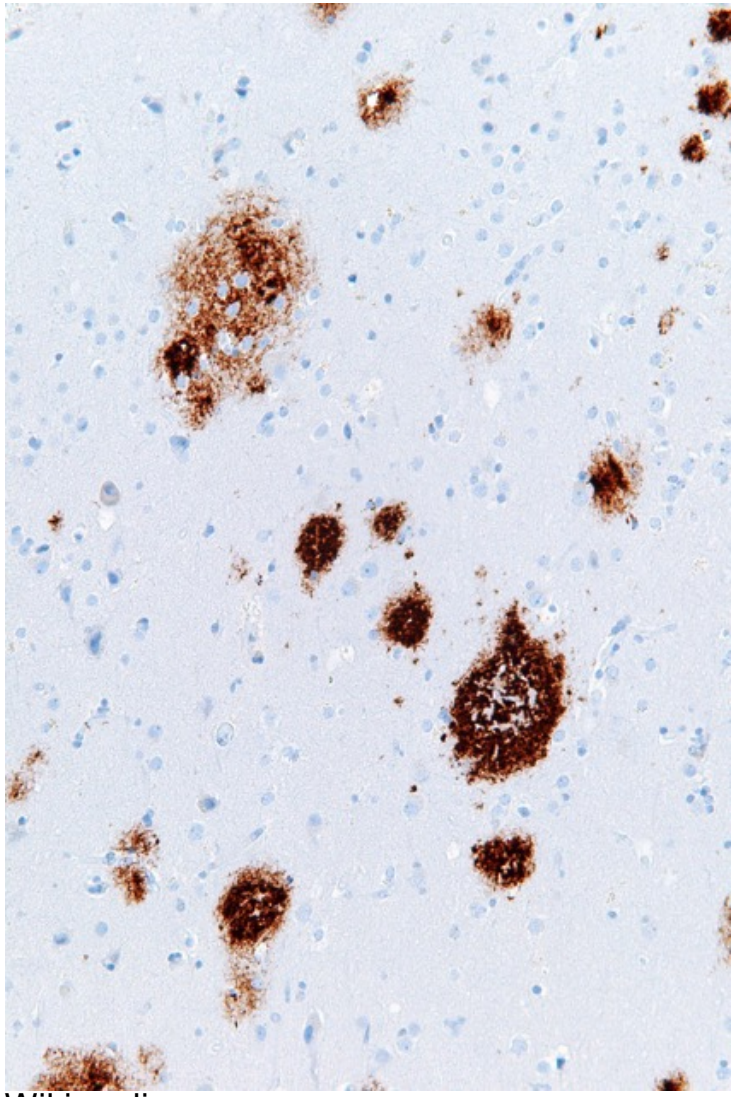

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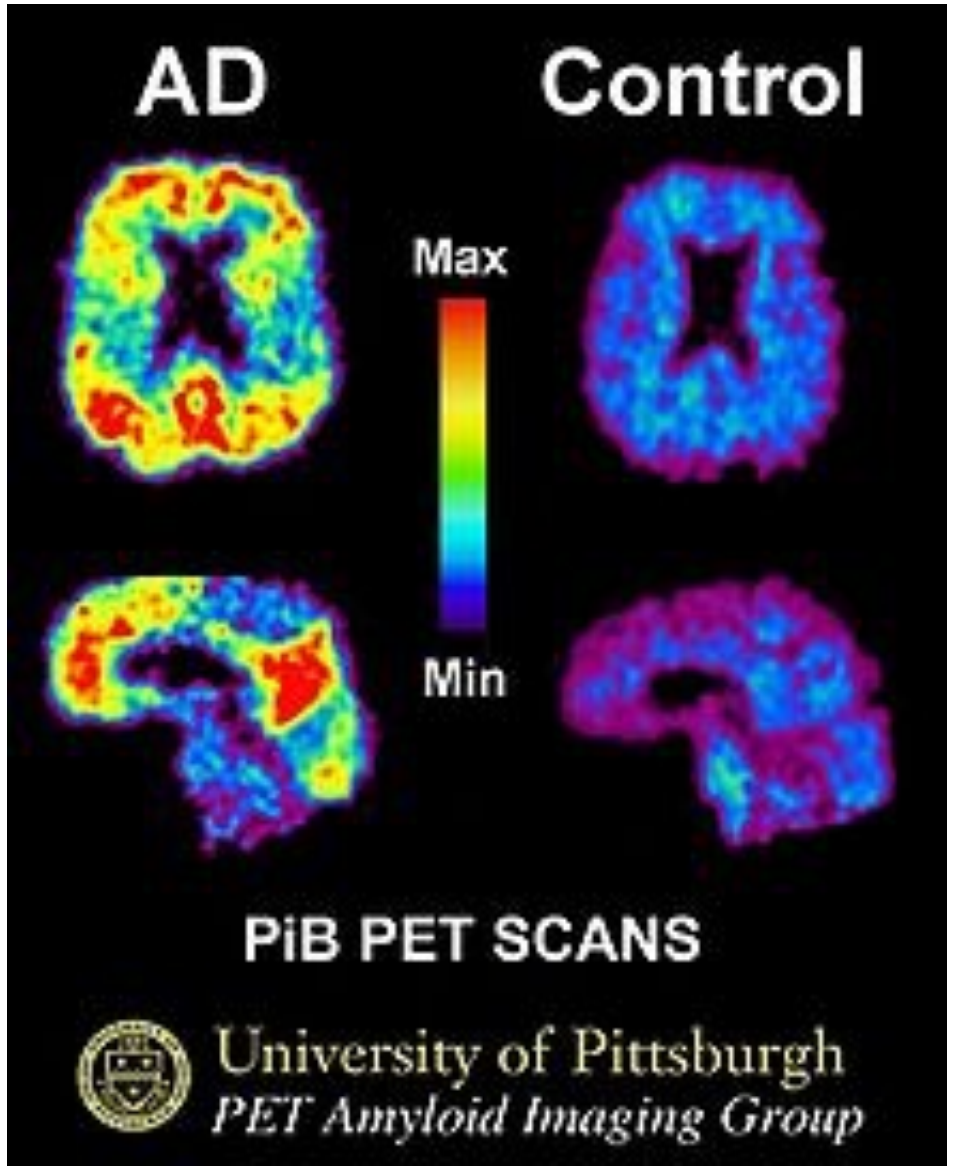
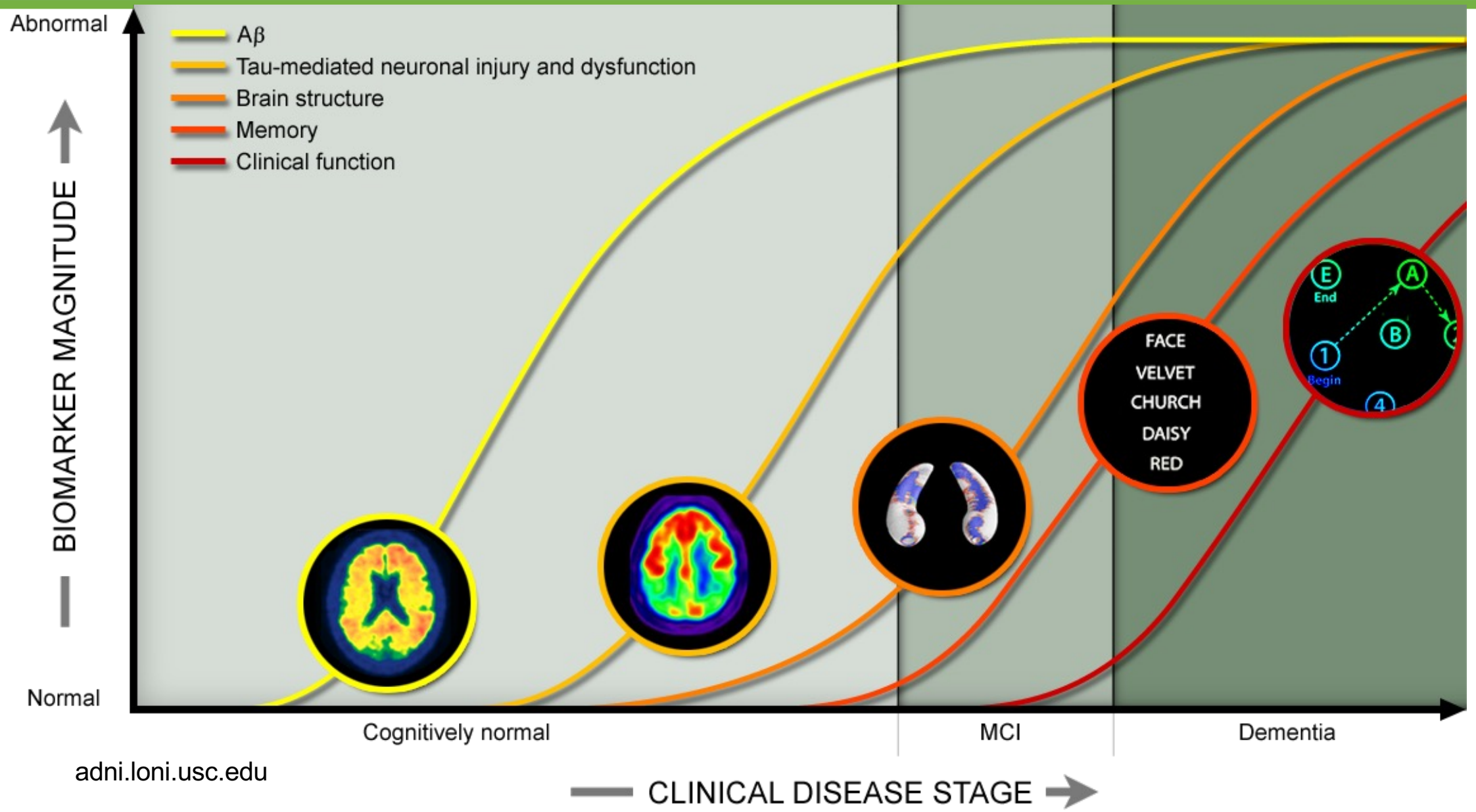
ROLE OF MISFOLDED PROTEINS IN ALZHEIMER DISEASE

- Senile plaques are composed mostly of the protein beta-amyloid, while tangles are made of tau protein
- Both are normal brain proteins, but builds up in excessive amounts and aggregate in AD
- PET imaging methods allows the buildup of beta- amyloid to be detected during life



SEQUENCE OF BIOMARKER CHANGES IN AD

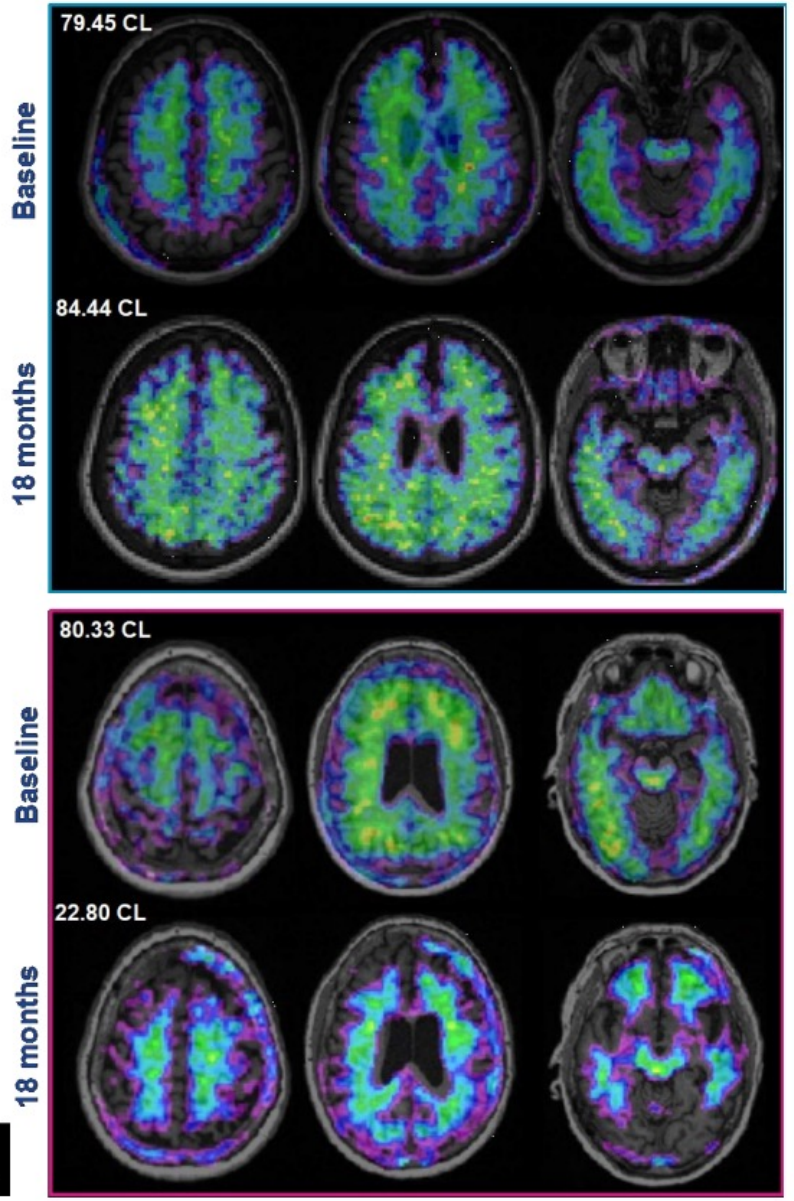


adni.loni.usc.edu

ANTI-AMYLOID THERAPY

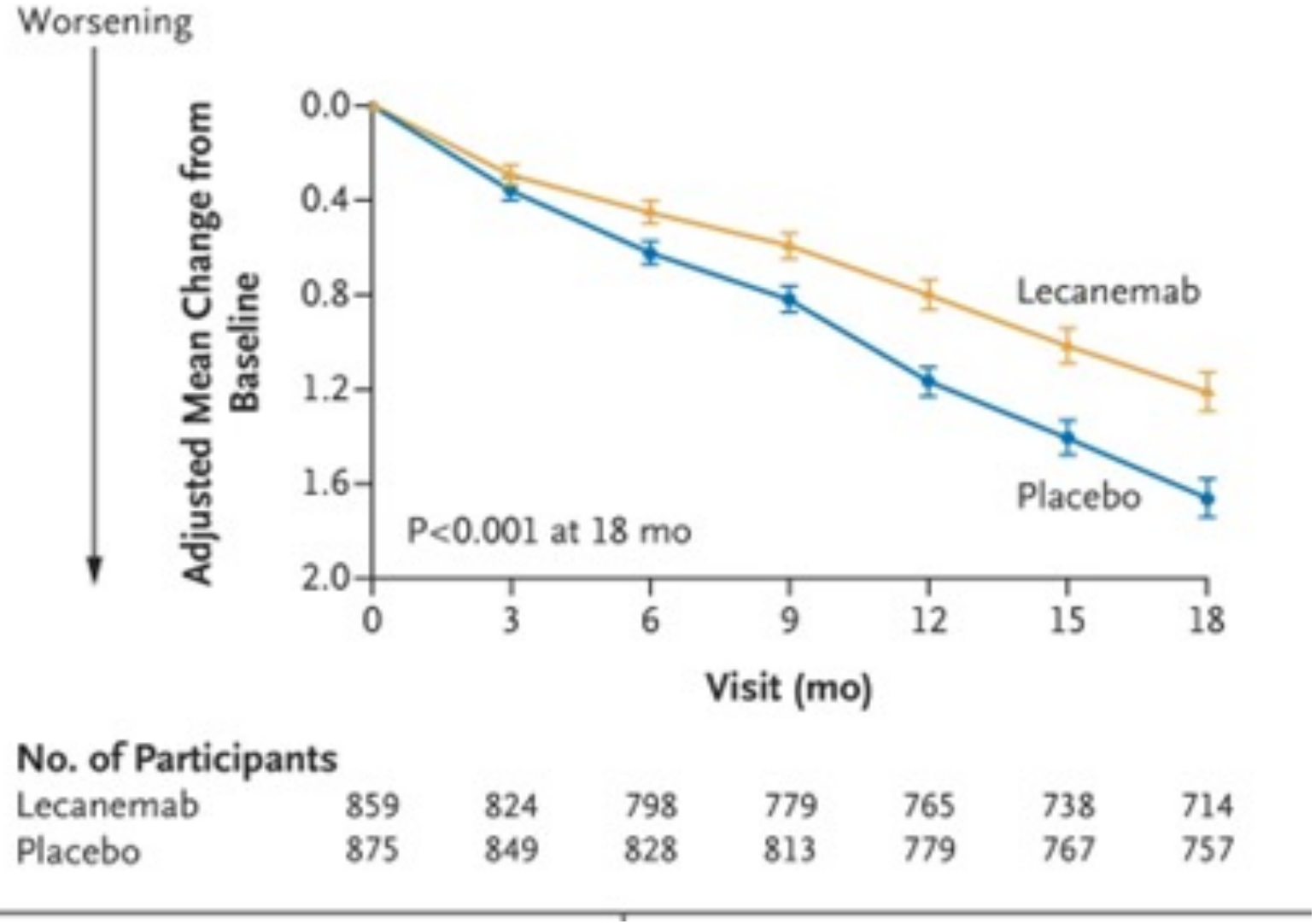
Placebo

Lecanemab



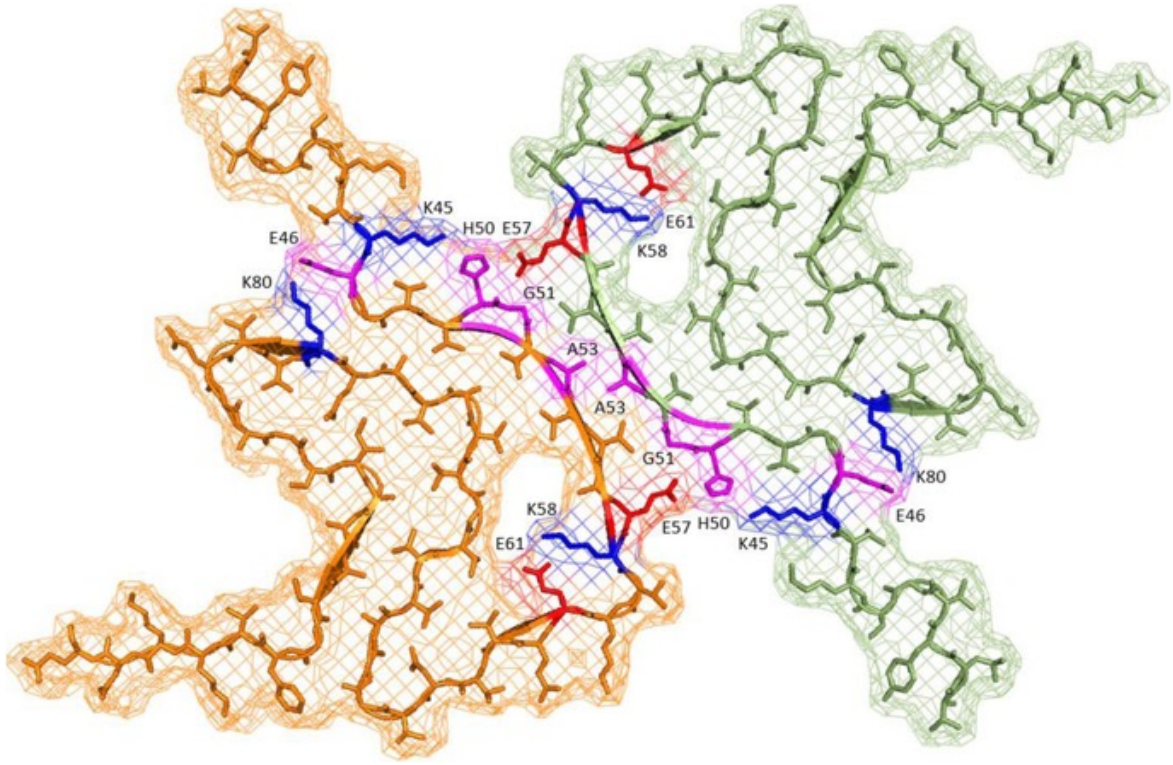
ANTI-AMYLOID OUTCOMES

- Studied in amyloid-positive MCI and mild dementia
- Efficacy
  - ~25-35% slowing of clinical decline
- Adverse events
  - 26% infusion reactions
  - 12% rate of ARIA-E
  - 17% rate of ARIA-H



CAN WE TARGET ALPHA-SYNUCLEIN FOR PD?

- **Reducing synuclein production**
  - Antisense strategies
  - Transcriptional Inhibitors
- **Enhancing synuclein removal**
  - Enhances of autophagy and lysosomal
  - Antibody mediated clearance
- **Targeting abnormal forms**
  - Anti-aggregation strategies
  - Antibodies specific for misfolded forms



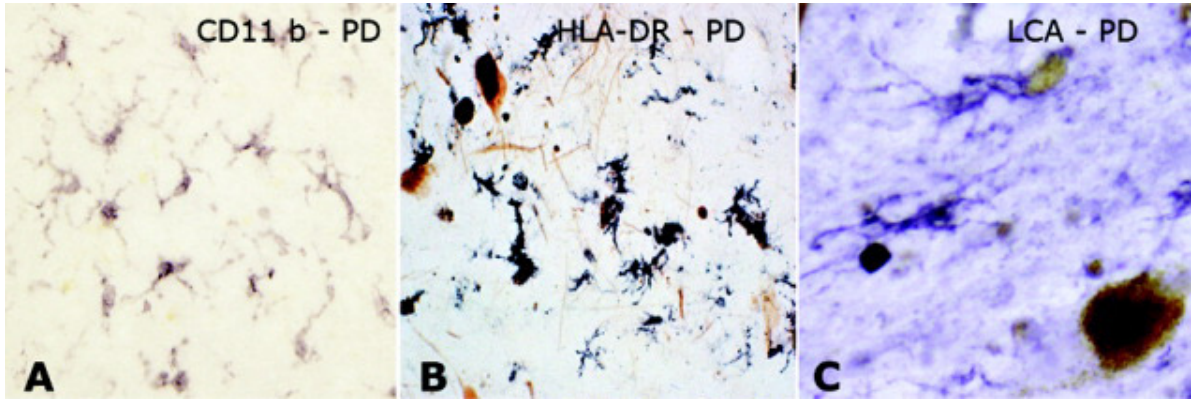
Meade et al., *Mol Neurodegeneration* **14,** 29 (2019)

IMMUNOMODULATORY THERAPY FOR PD

- Can immune modulation modify the course of PD?
- What are the targets for immune modulating therapy?
- When in the course of the disease is immune modulation effective?

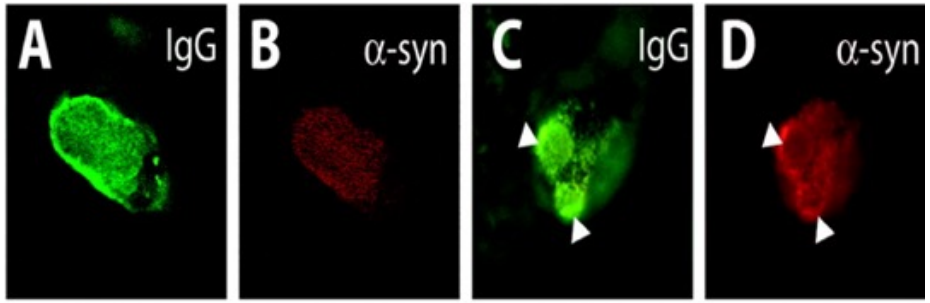
IMMUNE SYSTEM INVOLVEMENT IN PD

Microglia Activation in Human PD



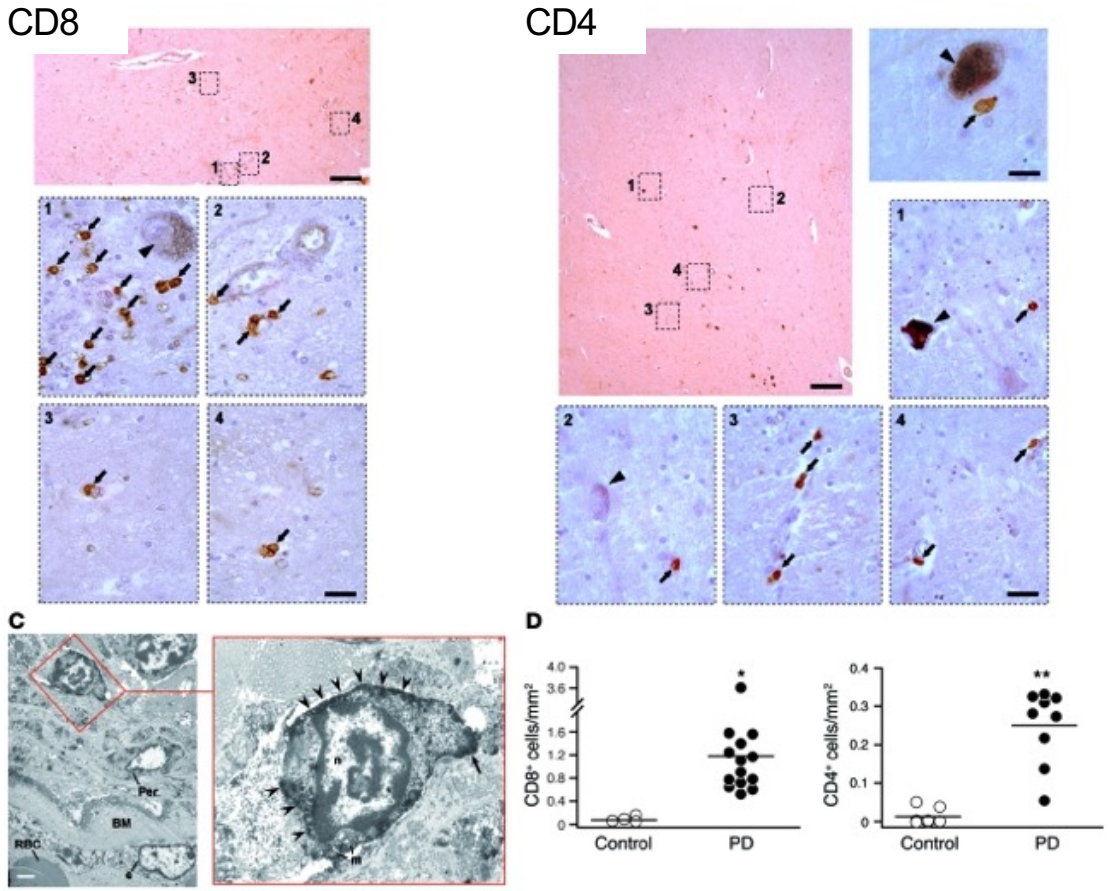
McGeer and McGeer, 2008

IgG Deposition on Nigral Neurons



Orr et al., 2007

CD4 and CD8 T Cells in Human PD brain



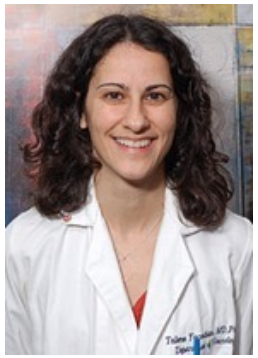
Brochard et al., 2009

Alabama Udall Center

David Standaert
Program Director
Project 1
Admin Core

Tika Benveniste
Project 2

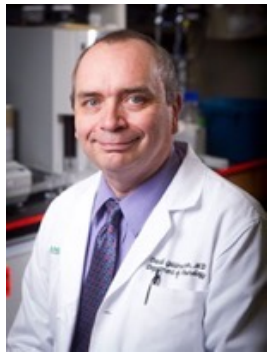
Andy West
Project 3
Duke UNIVERSITY



Talene Yacoubian
Clinical Core

Laura Volpicelli-Daley
Animal Model Core

Katherine Belue
Administrator



David Geldmacher
Project 4

Our central hypothesis is that immune cells are activated early in PD, and that inhibiting their pro-inflammatory activities will protect from neurodegeneration

Studying inflammation in early PD patients using PET imaging, blood and CSF studies

ALABAMA UDALL CENTER COHORT

RESEARCH ARTICLE

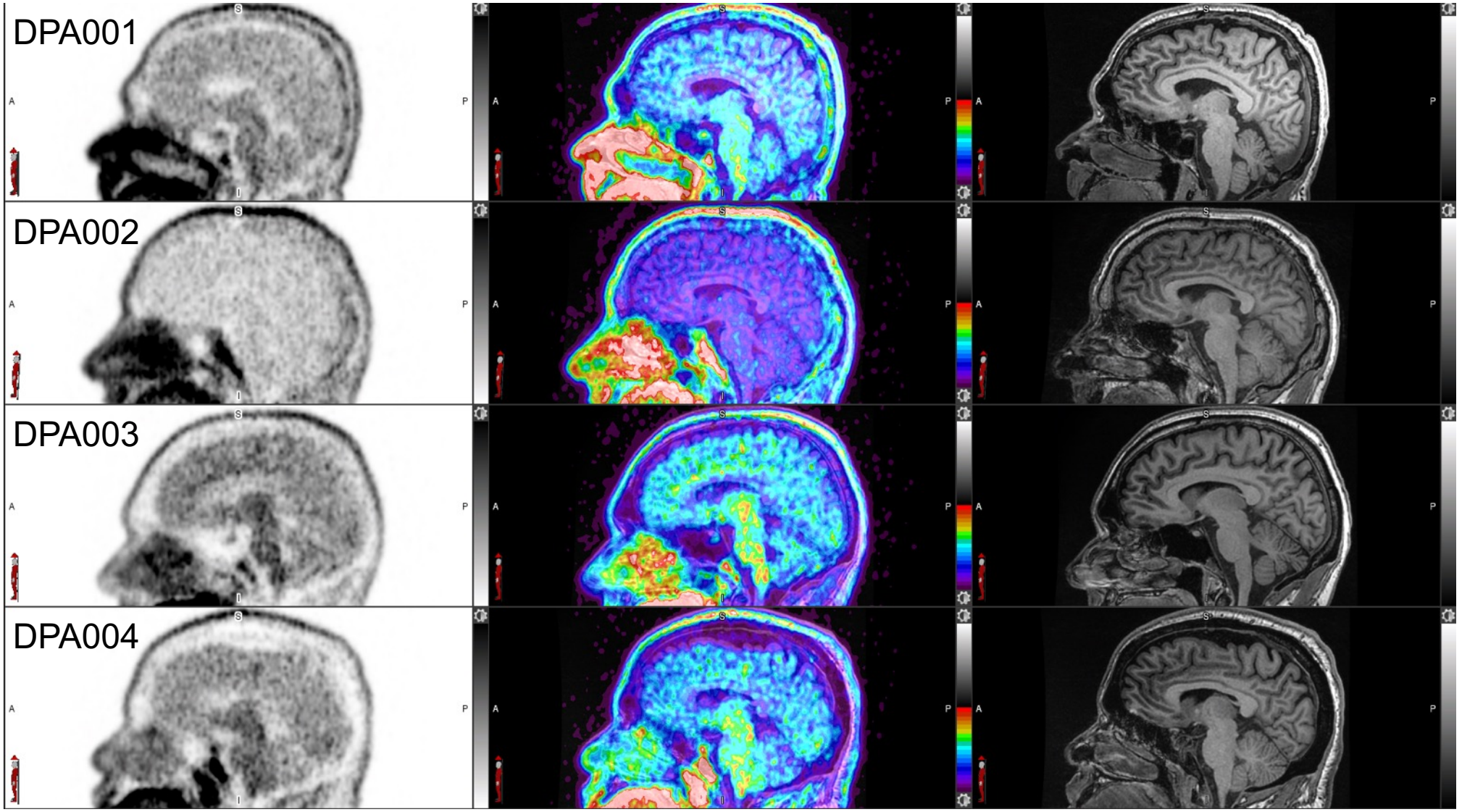
Brain and Systemic Inflammation in De Novo Parkinson's Disease

Talene A. Yacoubian, MD, PhD,[1*] Yu-Hua Dean Fang, PhD,[2] Adam Gerstenecker, PhD,[1] Amy Amara, MD, PhD,[1]
Natividad Stover, MD,[1] Lauren Ruffrage, MS,[1] Christopher Collette, BS,[1] Richard Kennedy, MD, PhD,[3]
Yue Zhang, PhD,[3] Huixian Hong, MD, PhD,[4] Hongwei Qin, PhD,[4] Jonathan McConathy, MD, PhD,[2]
Etty N. Benveniste, PhD,[4] and David G. Standaert, MD, PhD[1]

- 58 subjects with early stage, untreated PD and 62 controls
  - Diagnosis of PD by UK Brain Bank criteria - must have bradykinesia and at least one of the following: resting tremor, rigidity, or postural instability.
  - Male or female age 40 years or older at time of PD diagnosis.
  - Hoehn and Yahr stage I-III.
  - Less than 2 years from diagnosis
- Balanced with respect to sex (males 56% in PD, 45% in controls)
- Baseline and annual assessment
- Reviewed annually by a diagnostic consensus committee

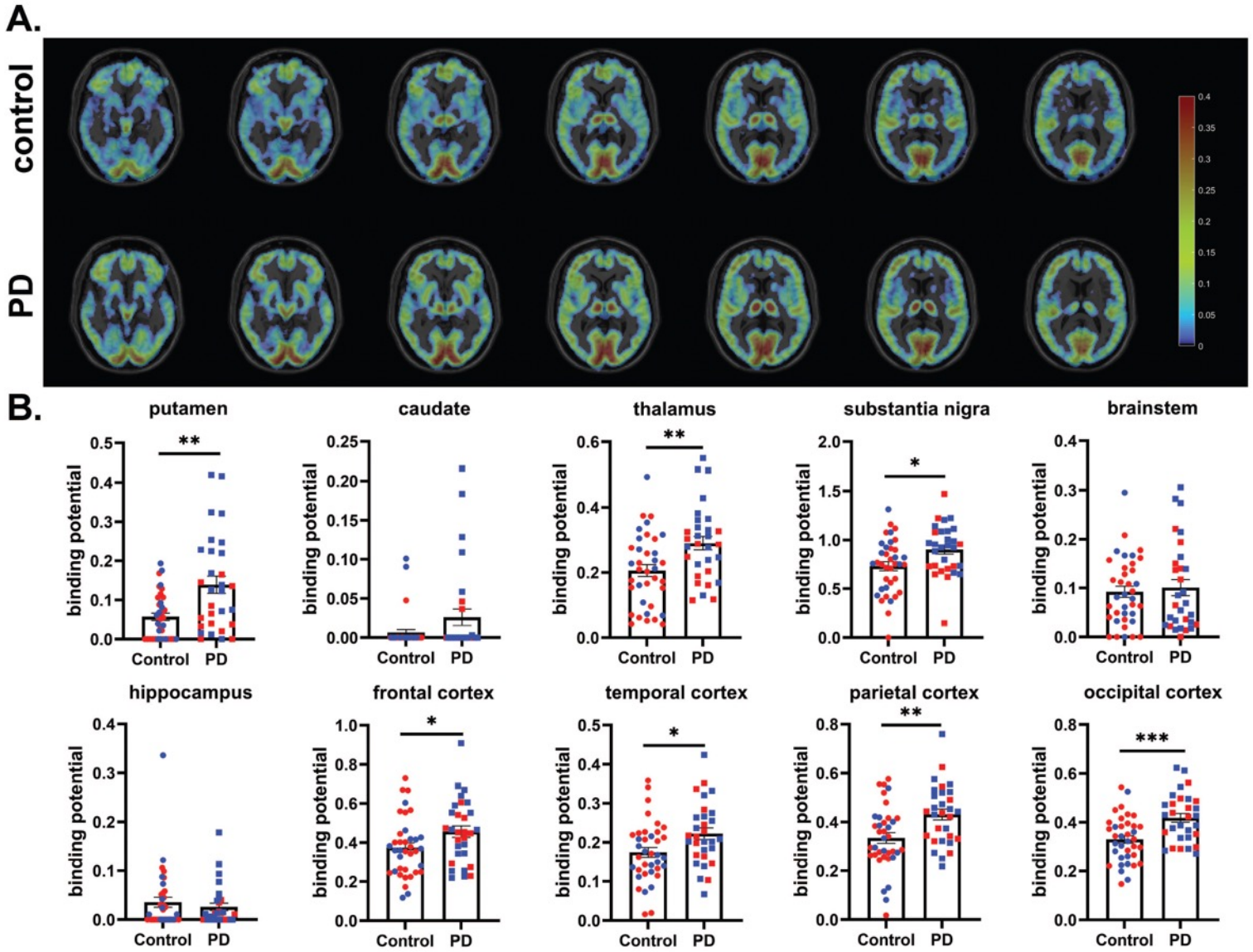
Movement Disorders 2023, DOI: 10.1002/mds.29363

PILOT STUDY: ^{18}F-DPA-714 PET/MRI IN 4 SUBJECTS WITH PD



BRAIN INFLAMMATION BY TSPO IMAGING IN EARLY PD

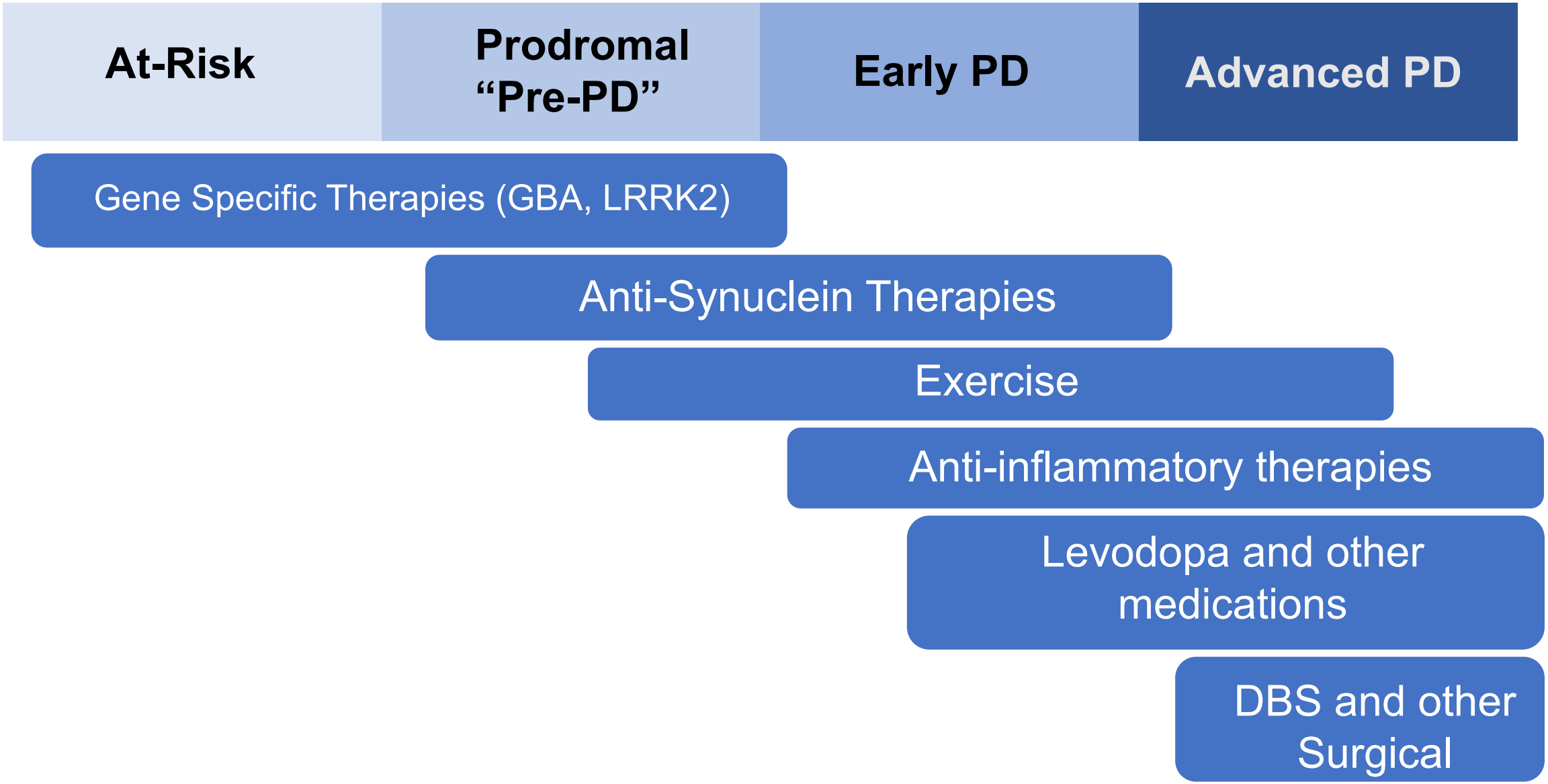
- Increased TSPO binding in putamen, thalamus, SN, and cortical regions
- TSPO binding potential correlates with composite and domain cognitive scores in the thalamus
- TSPO binding potential correlates with CSF MDC/CCL21 levels
- TSPO binding potential correlates with plasma eotaxin 3/CCL16 levels



TARGETING INFLAMMATION IN PD

- NLRP3 Inflammasome inhibitors
- GLP1 Receptor agonists (exenatide, semaglutide)
- Anti-TNF therapies
- T cell therapies

WHAT WILL THE PD THERAPY OF THE FUTURE LOOK LIKE?



UAB DIVISION OF MOVEMENT DISORDERS

- Physicians
  - Paul Atchinson
  - Juliana Coleman
  - Marissa Dean
  - Anthony Nicholas
  - David Standaert
  - Natividad Stover
  - Victor Sung
  - Harrison Walker
  - Ray Watts
  - Talene Yacoubian
- Fellow
  - Rebeca Sipma
- Advanced Practice Providers
  - Stephanie Guthie
  - Laura Lieb
  - Melissa Wade
  - Bradleigh Pfitzer

205-934-0683