Cognitive Decline with Parkinson Disease

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March 14, 2019

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of Radiology

Disclosures

No relevant financial interests to disclose.

- Research Support:
  - NIH, **APDA**, Michael J. Fox Foundation, BJH/ICTS
- Stock/Equity: NA
- Consulting: NA
- Speakers Bureau/Honoraria: NA

PD: Clinical Manifestations

Motor Function

- tremor
- rigidity
- bradykinesia
- postural instability

- walking
- facial expression
- voice
- handwriting

Non-Motor Features

- psychiatric disorders
- sleep disorders
- sense of smell
- constipation
- **cognitive dysfunction**

Cognitive Decline with Parkinson Disease

- What is cognition?
- How do we assess cognition?
- What cognitive problems can occur with PD?
- How do we know not age-related or AD?
- What causes it?
- How can we predict it?
- How do we treat or prevent it?

Cognitive Decline with Parkinson Disease

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Cognitive Domains

- **Attention** – focus and sustain attention

- **Learning & Memory** – learn & retain new information; recall previous information

- **Language** – production & comprehension

- **Visual-Spatial Processing** – interpret, recognize, replicate visual & spatial information

- **Executive Functioning-** higher level processing – e.g., decision-making, planning, multi-tasking

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Cognitive Evaluation

- Clinical interview
- Brief screening
- Neuropsychological assessment

Neuropsychological Assessment

- What to expect
  - Brief interview
  - Series of tests – some are like games & puzzles
  - Designed to assess a wide range of abilities
- Goal
  - Determine cognitive strengths & weaknesses
  - Determine possible change in cognition
- Don't stress, just do your best!

Cognitive Changes

- Cognitive Decline
  - can occur with normal aging
- Cognitive Impairment/Mild Cognitive Impairment
  - Deficits greater than expected for age
- Dementia
  - Cognitive deficits that interfere with daily activities

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PD: Cognitive Profile

Attn/EF | Memory | VSP

- Attention
  - sustained and selective attention
- Executive Functioning
  - information processing speed, decision-making, planning
- Memory
  - learning & recollection, but not with retention
  - prospective memory
- Visuospatial (VSP)
  - integrating complex visual information
  - copying simple visual stimuli
- Language
  - intact naming & comprehension
  - reduced verbal fluency
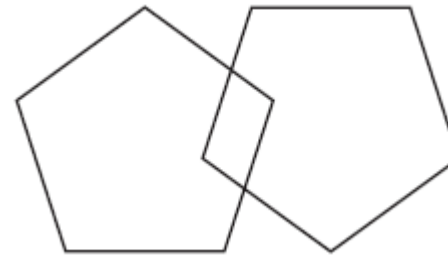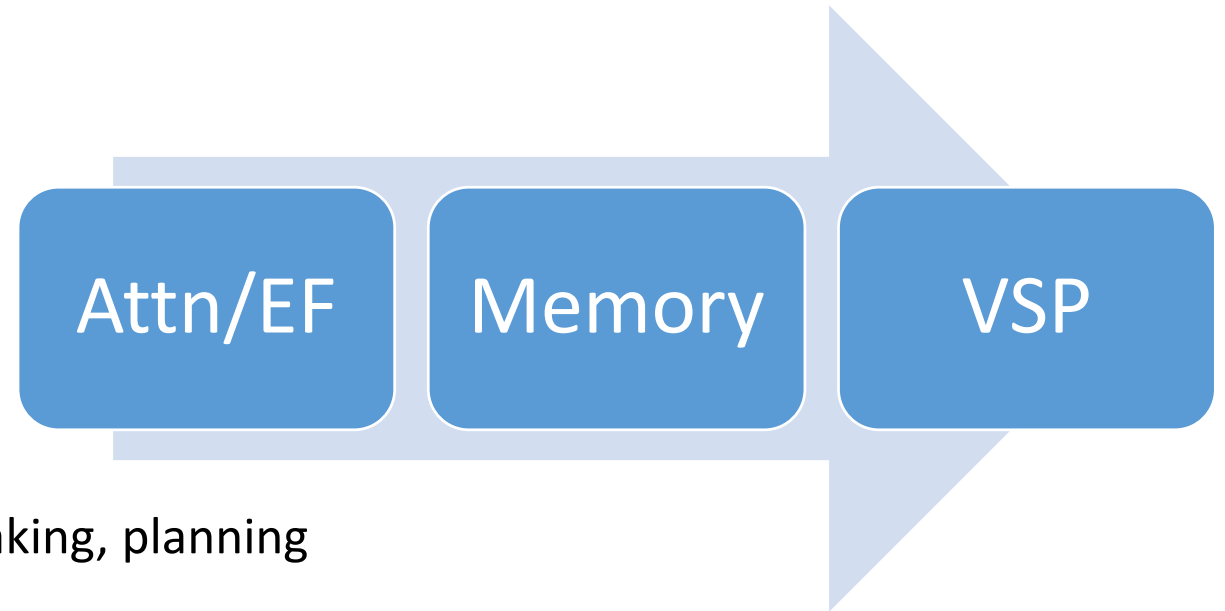
Cognitive Decline & Dementia with PD

- 2-6% increased risk of dementia compared to healthy aging
- At diagnosis, 25-30% of PD w/ cognitive deficits
- Approx. 50% will develop cognitive impairment w/in 5 yrs of diagnosis
- Approx. 30% will develop dementia w/in 3-5yrs of diagnosis
- **Up to 80% will eventually develop dementia**

- **This represents a major concern and challenge for people with PD and their families.**

Cognitive Decline & Dementia with PD
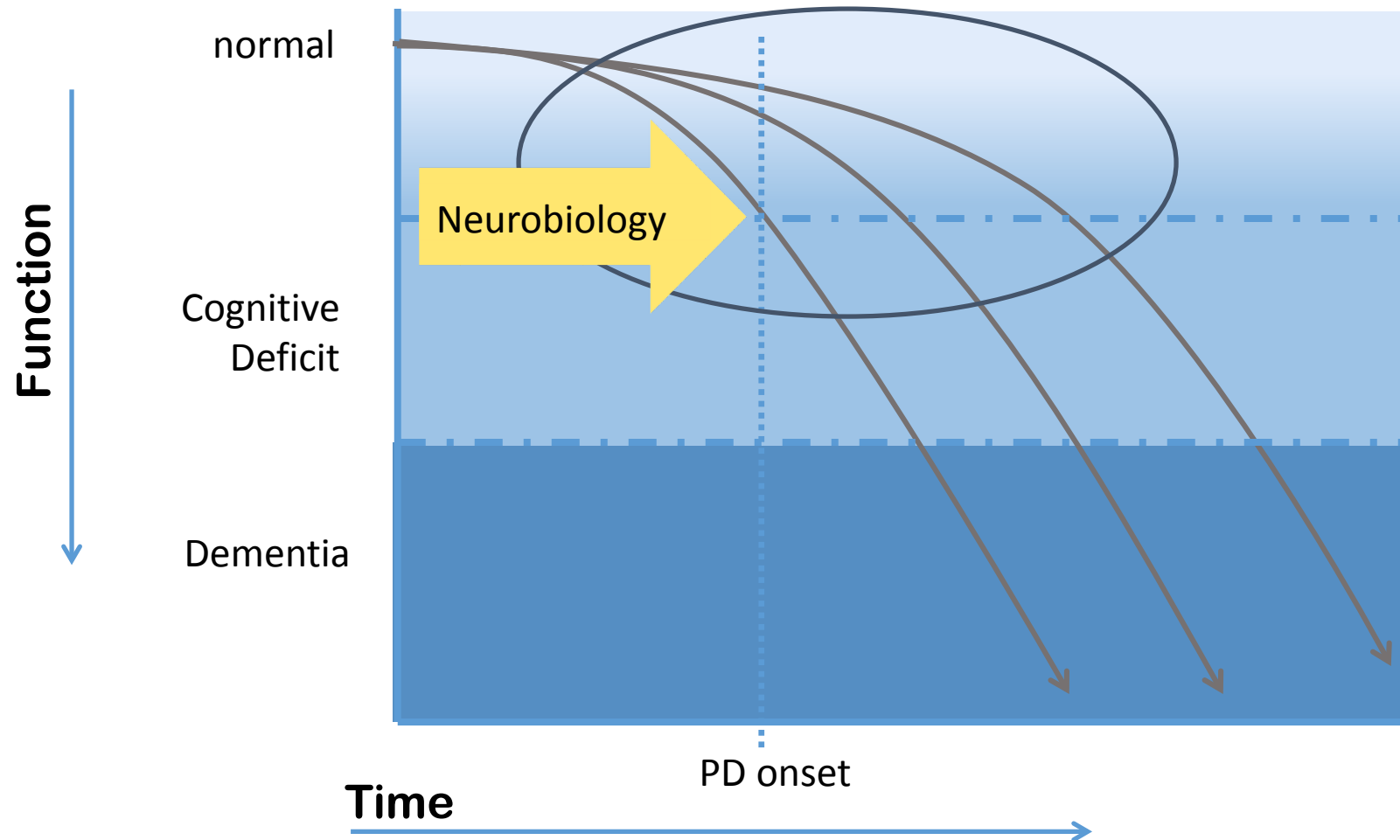
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Baltimore Longitudinal Study of Aging

- Over 3,000 people tracked longitudinally since 1958

- Speed of learning, multi-tasking, and problem solving decline

- Visuospatial abilities and verbal fluency decline

- Naming and short-term memory decline

- General intelligence and procedural memory are preserved

- Vocabulary & comprehension maintained into 80's

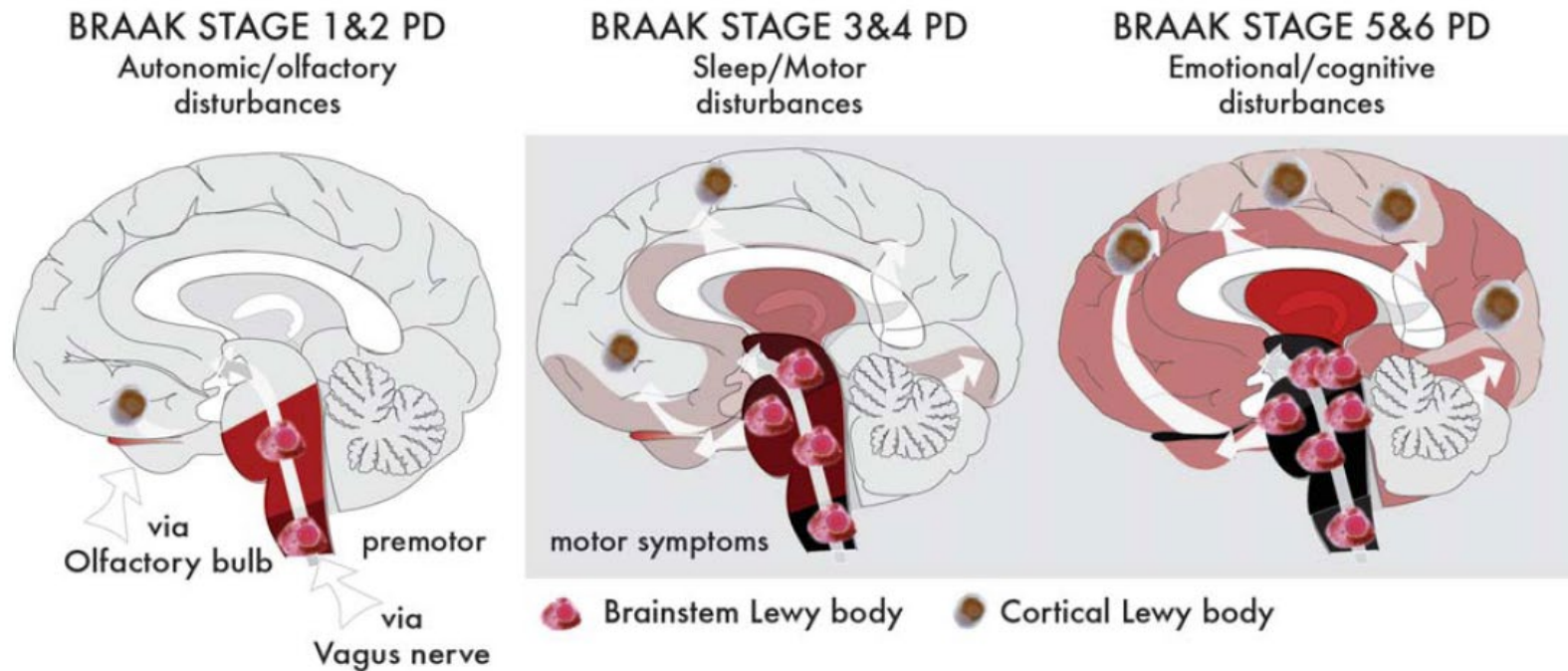# Cognitive Deficits with Alzheimer Disease

- Memory
  - early, prominent memory deficit
  - impaired learning & retention
  - rapid forgetting
- Language
  - difficulty naming objects –forget the names of things
  - reduced verbal fluency
- Attention & Executive Function
- Visuospatial

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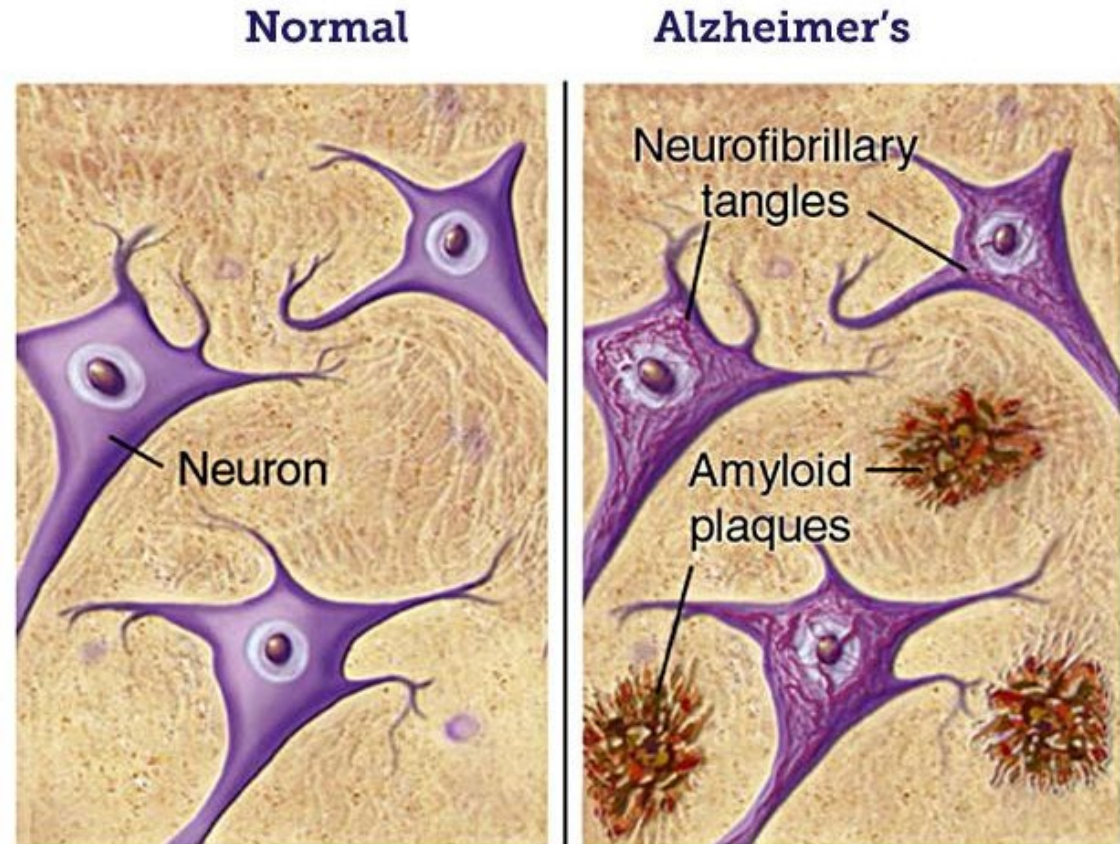- How do we treat or prevent it?

PD Neuropathology

- Lewy Bodies (aggregated α-syn)

BRAAK STAGE 1&2 PD
Autonomic/olfactory disturbances

BRAAK STAGE 3&4 PD
Sleep/Motor disturbances

BRAAK STAGE 5&6 PD
Emotional/cognitive disturbances

via Olfactory bulb

premotor

via Vagus nerve

motor symptoms

Brainstem Lewy body   Cortical Lewy body

Halliday et al., (2011).

AD Neuropathology

- β-amyloid plaques
- Neurofibrillary tangles

Normal

Alzheimer's

Neuron

Neurofibrillary tangles

Amyloid plaques

BrightFocus® Foundation
Cure in Mind. Cure in Sight.

PD Dementia: Proteinopathy

<u>32 PD with dementia autopsy cases</u>

-ALL had αsyn Lewy bodies

- 38% only had αsyn

- 59% had αsyn + Aβ plaques

- 3% (1) had αsyn, Aβ, tau = PD+AD
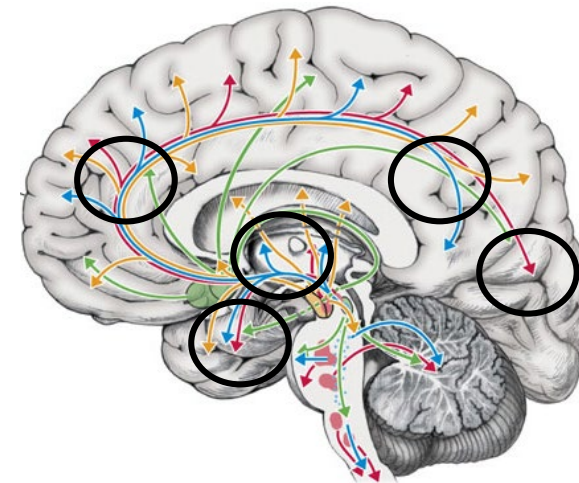
PD dementia is rarely due to AD!

Table 2. Comparison of Neuropathologic Lesions Among 3 Subgroups of Dementia Associated With Patients With Parkinson Disease

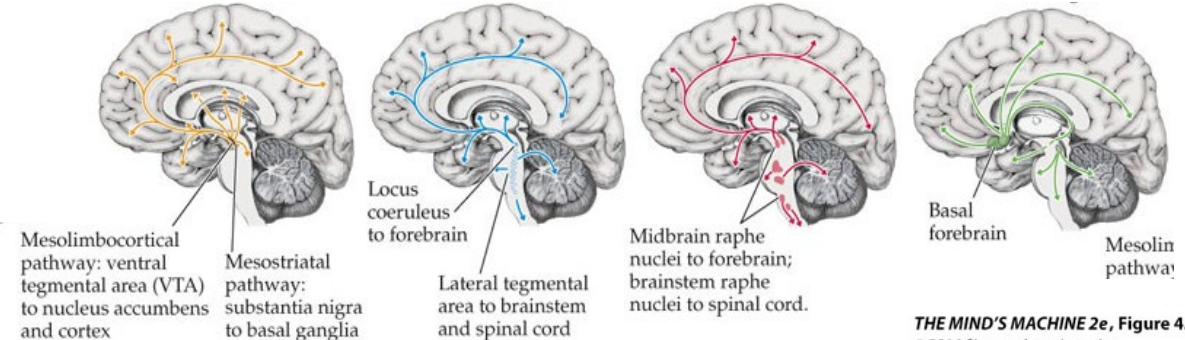| Characteristic	Synuclein Only (n = 12)	Synuclein Plus Aβ (n = 19)	Synuclein Plus Aβ Plus Tau (n = 1)
Braak Lewy body stage for synucleinopathy, mode (range)	6 (5-6)	6 (5-6)	6
Braak amyloid stage for Aβ deposition, mode (range)	0 (0-1)	3 (2-3)	3
Braak NFT stage for tauopathy, mode (range)	1 (1-4)	3 (1-4)	6

Kotzbauer, Cairns, Campbell, et al., (2012). *JAMA Neurology*.

PD Dementia: Neurochemistry

	Controls	PD with Dementia	*P*
Demographics			
Participants, No.	6	15	NA
Age at death, y	84 (70-100)	79 (71-93)	*P* = 0.51[b]
Male/Female, No.	2/4	12/3	*P* = 0.04 [c]
Clinical Characteristics of PD participants with dementia			
Age at PD diagnosis, y	NA	63 (54-82)	NA
Duration of PD, y	NA	14 (8-27)	NA
UPDRS-III score (OFF)	NA	44 (35-73.5)	NA
LEDD, mg	NA	800 (0-1350)	NA

- NT/T: DA & DAT; 5-HT & SERT; NE; VAChT
- brain regions: caudate, ACG, hippocampus, amygdala, precuneus, VAC, MFG, IPL

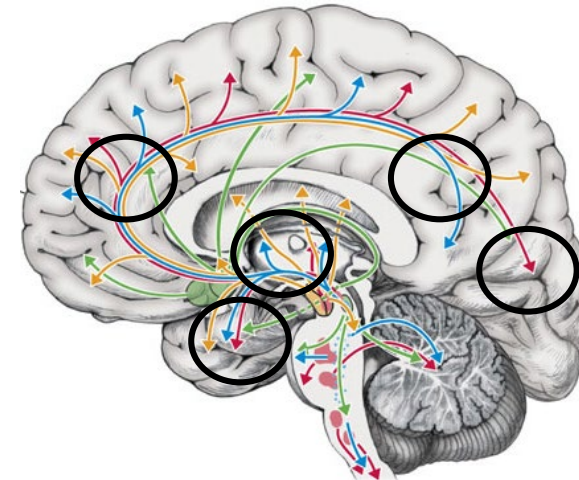Dopaminergic   Noradrenergic   Serotonergic   Cholinergic

Mesolimbocortical pathway: ventral tegmental area (VTA) to nucleus accumbens and cortex

Mesostriatal pathway: substantia nigra to basal ganglia

Locus coeruleus to forebrain

Lateral tegmental area to brainstem and spinal cord

Midbrain raphe nuclei to forebrain; brainstem raphe nuclei to spinal cord.

Basal forebrain

Mesolin pathwa

THE MIND'S MACHINE 2e, Figure 4.4
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Buddhala et al., 2015. *Ann Clin Transl Neurol.*

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Buddhala et al., 2015. *Ann Clin Transl Neurol.*

Other Possible Contributing Factors

- Sleep

- Hearing loss

- Psychiatric disorders – depression, anxiety, apathy

- Medication side effects

- Abnormal hormone & vitamin levels

- Infection (e.g., UTI)

- Other health conditions – diabetes, hypertension

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# Protein & Imaging Biomakers in PD ("PIB" Study at WashU)

- Large sample of PD & healthy controls (N = 293)
- Followed longitudinally until death (N = 76) & brain donation
- In-person visits every 3 years:
  - Comprehensive clinical exam – motor, cognitive, psychiatric
  - MRI – structural & rs-BOLD
  - PET – PIB & VAT
  - Optional: LP & Blood Draw

Protein Aggregation and Neurotransmitter Deficits ("PAND" Study at WashU)

- Large sample of PD & healthy controls (N = 110)
- Followed longitudinally until death (N = 2) & brain donation
- In-person visits every 2 years:
  - Comprehensive clinical exam – motor, cognitive, psychiatric
  - MRI – structural & rs-BOLD
  - NO PET
  - Optional: LP & Blood Draw

Predicting Dementia

- CSF proteins
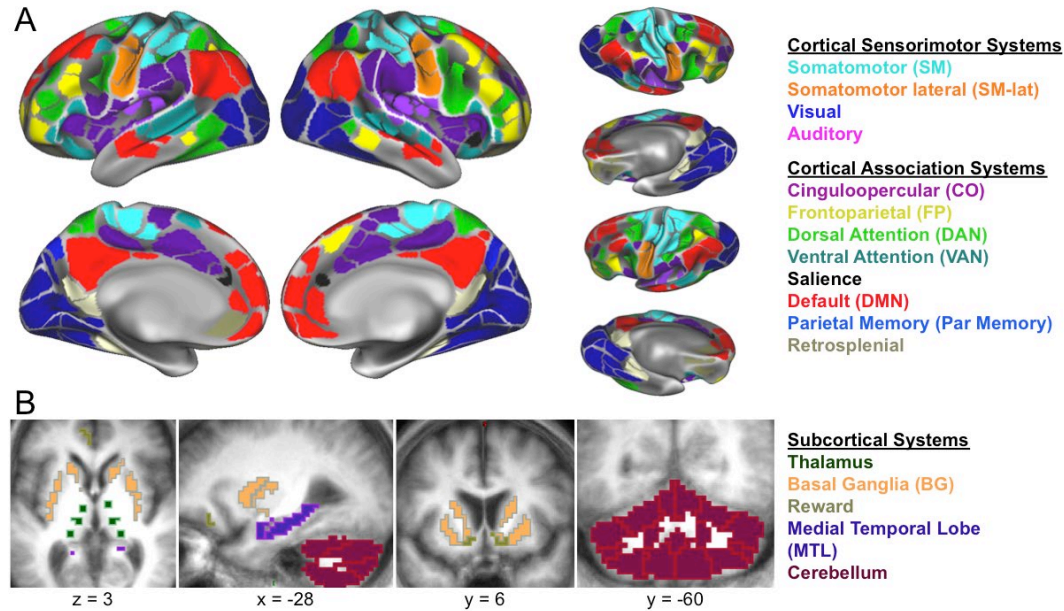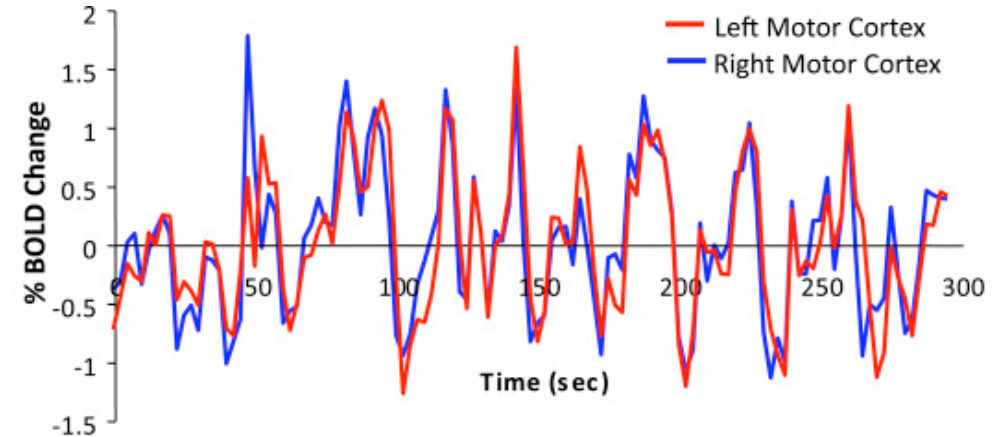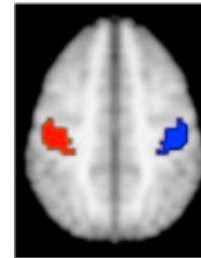- Functional Connectivity MRI (fcMRI)

Predicting Dementia

- **CSF proteins**
- fcMRI
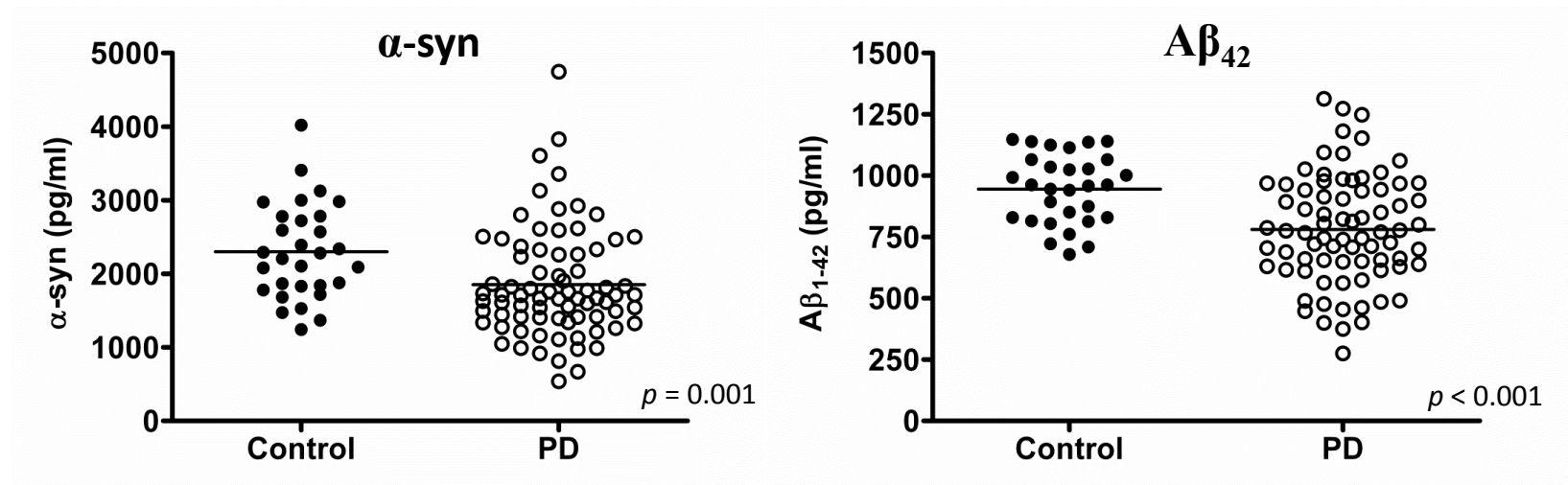
- Both CSF αsyn & Aβ are significantly lower in PD
- Lower CSF asyn & AB = greater burden in the brain
- Occurs prior to dementia onset

Buddhala, Campbell, et al., (2015). Neurobiology of Aging.
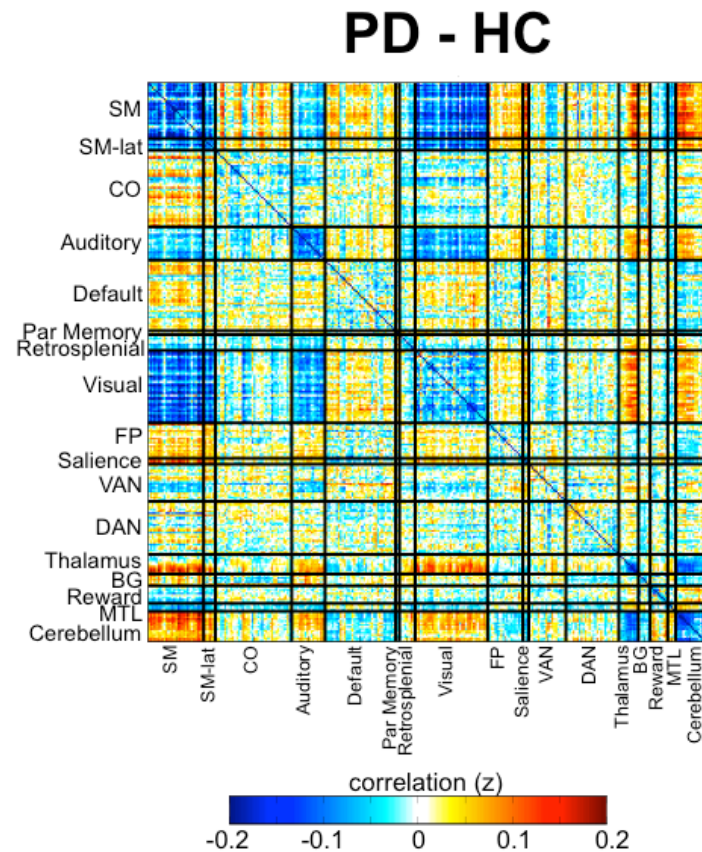
Predicting Dementia

- CSF proteins

- **fcMRI**

- fcMRI = correlation of changes in brain activity between brain regions and networks
- Can be measured across many areas, covering the whole brain
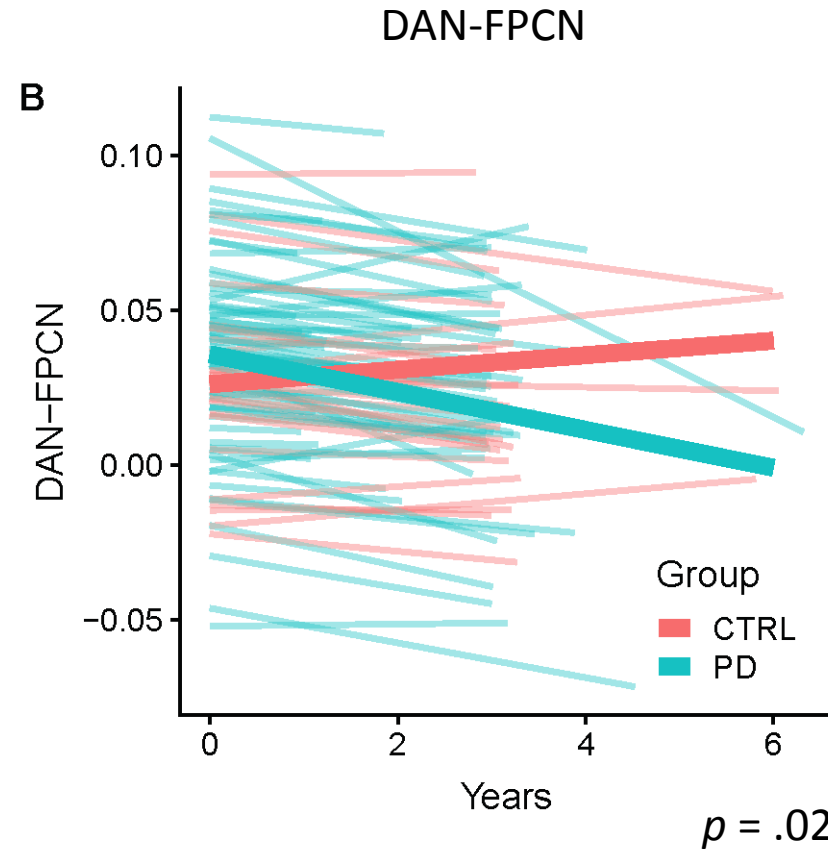
Predicting Dementia

- CSF proteins
- **fcMRI**

PD - HC

correlation (z)
-0.2   -0.1   0   0.1   0.2

- Weaker fcMRI in PD compared to healthy controls (HC)
- Select regions and networks, not a global effect
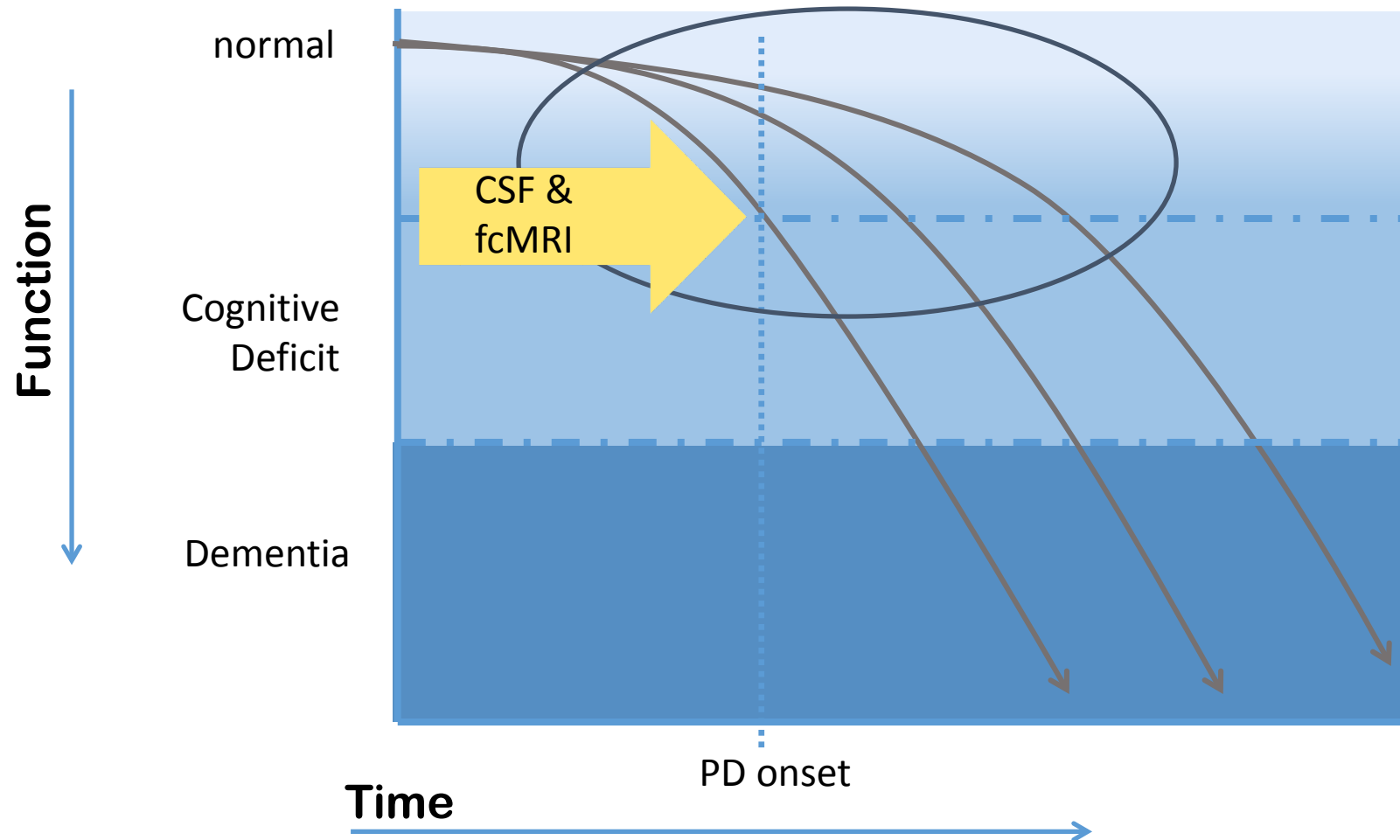- Reduced fcMRI relates to worse motor & cognitive function

Gratton, …, and Campbell, 2018. *Cerebral Cortex*.

Predicting Dementia

- CSF proteins

- **fcMRI**

DAN-FPCN

p = .02

Brain functional connectivity declines over time with PD, prior to dementia onset.

Campbell et al., *under review*.

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Treatment

- We don't have a cure for PD or dementia **yet…**
  - **But there is progress and hope!**
- Only one FDA approved medication for PD dementia - Exelon
- Behavioral interventions & prevention

Behavioral Interventions & Prevention

- Exercise & physical activity

- Engage in mental & social activities

- Good diet – DASH, Mediterranean, MIND

- Get a good night's sleep!

- Cognitive strategies

Cognitive Strategies

- Minimize distraction
- Use reminders – calendar, pill box, alerts on phone
- Simplify activities into smaller steps
- Maintain a regular routine
- Provide choices or yes/no options

Research Information

Cognitive &
Occupational
Performance Lab

- Projects and programs to help people with PD deal with cognitive challenges in their daily lives
  - Work, home, family, community
  - Across the spectrum of cognitive decline

Principal Investigator: Erin Foster, PhD, OTD
Research coordinator: Tasha Doty, MA
(314) 362-7160; tdoty@wustl.edu

PIB & PAND longitudinal studies of PD & healthy aging

- Recruiting PD and healthy older adults
- Cognitive and motor testing
- MRI, PET, lumbar punctures (optional)
- Longitudinal – study visits every 2-3 years

Principal Investigators: Meghan Campbell, PhD; Joel Paul Kotzbauer, PhD/MD; Joel Perlmutter, MD
Research coordinators: Selma Avdagic (314-362-3483) and Kelly McVey (314-362-0420)
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Acknowledgments

Collaborators

□ **Joel S. Perlmutter, MD**

□ **Paul T. Kotzbauer, MD/PhD**

□ Erin R. Foster, PhD, OTD

□ Gammon Earhart, PhD

□ Jay Maiti, PhD/MD

□ Chandana Buddhala, PhD

□ John O'Donnell, PhD

□ Peter S. Myers, PhD

□ Christina Lessov-Schlaggar, PhD

□ Nigel Cairns, PhD

□ Rick Perrin, MD/PhD

□ Steve Petersen, PhD

□ Caterina Gratton, PhD

□ Avi Snyder, MD/PhD

□ Bill Shannon, PhD

□ Joshua Jackson, PhD

Research Team

- Nurse Coordinators: Johanna Hartlein, NP; Barb Merz; Katharine Cummings; Kelly McVey

- Research Coordinators: Phil Lintzenich, Thomas Belcher, Jenny Zen-Duan; Anja Pogarcic, Jennifer Petros, My Vu, Selma Avdagic

- Imaging Analysts: Jon Koller, Hugh Flores, Tunde Adeyamo

- LP Physicians: Scott Norris, MD, Mwiza Ushe, MD; Jay Maiti MD/PhD; John Younce, MD

- Lab Techs: Susan Loftin

- Undergraduate Army