Cognitive Decline with Parkinson Disease

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Associate Professor
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• Speakers Bureau/Honoraria: NA
### PD: Clinical Manifestations

<table>
<thead>
<tr>
<th>Motor Function</th>
<th>Non-Motor Features</th>
</tr>
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<tbody>
<tr>
<td>• tremor</td>
<td>• psychiatric disorders</td>
</tr>
<tr>
<td>• rigidity</td>
<td>• sleep disorders</td>
</tr>
<tr>
<td>• bradykinesia</td>
<td>• sense of smell</td>
</tr>
<tr>
<td>• postural instability</td>
<td>• constipation</td>
</tr>
<tr>
<td></td>
<td>• cognitive dysfunction</td>
</tr>
</tbody>
</table>

|                                 | • walking                               |
|                                 | • facial expression                     |
|                                 | • voice                                 |
|                                 | • handwriting                           |
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
Cognitive Decline with Parkinson Disease

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PD: Cognitive Profile

• 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

Function

Cognitive Deficit

Dementia

Time

PD onset

normal

Neurobiology
Cognitive Decline with Parkinson Disease

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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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PD Neuropathology

- Lewy Bodies (aggregated α-syn)

AD Neuropathology

- β-amyloid plaques
- Neurofibrillary tangles

[Diagram showing normal and Alzheimer's neurons with labeled features: Neuron, Neurofibrillary tangles, Amyloid plaques]
PD Dementia: Proteinopathy

32 PD with dementia autopsy cases
- 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!

# PD Dementia: Neurochemistry

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Controls</th>
<th>PD with Dementia</th>
<th>( P )</th>
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<tbody>
<tr>
<td>Participants, No.</td>
<td>6</td>
<td>15</td>
<td>NA</td>
</tr>
<tr>
<td>Age at death, y</td>
<td>84 (70-100)</td>
<td>79 (71-93)</td>
<td>( P = 0.51^b )</td>
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<tr>
<td>Male/Female, No.</td>
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## Clinical Characteristics of PD participants with dementia

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<td>Duration of PD, y</td>
<td>NA</td>
<td>14 (8-27)</td>
<td>NA</td>
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<tr>
<td>UPDRS-III score (OFF)</td>
<td>NA</td>
<td>44 (35-73.5)</td>
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<td>LEDD, mg</td>
<td>NA</td>
<td>800 (0-1350)</td>
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- **NT/T**: DA & DAT; 5-HT & SERT; NE; VACHT
- **brain regions**: caudate, ACG, hippocampus, amygdala, precuneus, VAC, MFG, IPL


![Brain Diagram](image)
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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 Biomarkers 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

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**

  - 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

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

Campbell et al., under review.
Cognitive Decline & Dementia with PD

- Normal
- Cognitive Deficit
- Dementia

Time: PD onset

Function: CSF & fcMRI
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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
• 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

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

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- Joshua Jackson, PhD

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- Lab Techs: Susan Loftin
- Undergraduate Army