

# Cognition in Parkinson's Disease

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## Introduction

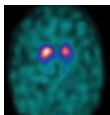
- Cognitive impairment one of the most problematic, non-motor symptom of PD (NMS)
- Point prevalence of dementia in PD is 25-30%
- Cognitive dysfunction associated with poor functioning, low quality of life, caregiver burden, increased health care costs
- PD-dementia associated with increased mortality (RR 4.9) *Louis Arch Neurol (1997)*

## 2 Illustrative Sample Cases

### Case 1

79 yr old retired air force veteran (mechanic) w/17 yrs education presents for mild memory changes

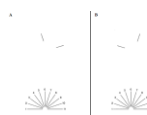
- At age 69 developed left hand tremor, gait change, softening of voice
- Treated with C/L (25/100) 2 tabs QID
- REM sleep disorder
- No hallucinations
- Positive DAT scan



## Case 1

Montreal Cognitive Assessment

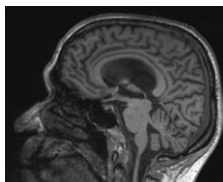
Neuropsychological Testing  
 - Significant impairments (<1.5 SD) in free recall and visuospatial (Judgement of Line Orientation)



Subtest	Score	Max Score
Trail Making Test A	12	30
Trail Making Test B	12	30
Stroop Color Test	10	30
Block Design	10	30
Line Orientation	10	30
Word Recalling	10	30
Word Fluency	10	30
Visuospatial	10	30
Attention	10	30
Executive	10	30
Language	10	30
Global	28	30

## Case 1

MRI



## Clinical Course

Mild progression in symptoms  
 Remains at MCI stage for past three years  
 Continues to drive, shop, cook and clean



## PD-Subjective Decline

Cognitive impairments reported (patient or caregiver) but cognitive tests are within normal ranges

- Subjective cognitive impairment is a known risk factor for the development of AD dementia
  - No established criteria in PD
  - No reliable way to capture
- Preliminary data suggests that subjective complaints may be a predictor of MCI in PD (Erro, Geriatric Psychiatry and Neurology 2014)

## PD-MCI

Stage of cognitive impairment detectable by others or on cognitive testing but not sufficient to interfere with activities of daily living

Construct from Alzheimer's disease, hard to apply to PD



## PD-MCI

Operationalized with Likhan Criteria (Lithuan Mov Disorders 2012)

- Diagnosis of PD
- Gradual decline in cognition (caregiver or patient)
- Objective cognitive deficits on neuropsychological testing or a scale of global cognitive abilities
  - Global Cognitive Scale
    - Montreal Cognitive Assessment
    - PD Cognitive Rating Scale
    - Scales for Outcomes of Parkinson's Disease
    - Mattis Dementia Rating Scale
  - Neuropsychological Battery: impairment on at least 2 tests
    - (can be 2 in one domain or 2 tests in a single domain)
    - \*impairment: 1-2SDs below norm or significant decline from estimated premorbid functioning
- Cognitive deficits are not sufficient to interfere with functional independence
- Rule out other causes of cognitive impairment

## PD-MCI

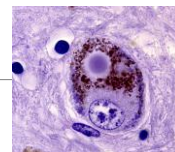
25-30% patients without dementia meet criteria for PD-MCI (Svenningsson 2012)

10-20% have PD-MCI at the time of PD diagnosis (Svenningsson 2012)

Associated with a shorter duration to dementia
 

- Mean time from diagnosis of PD-MCI to PD-D 10 years (Williams, Brain 2009)

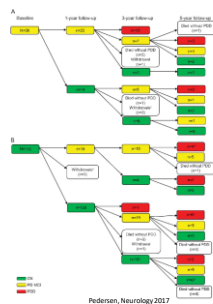
- Two tests in one cognitive domain was a better predictor than across cognitive domains over 4 years (Wood, NPJ Parkinson's Disease 2016)



## PD-MCI

PD-MCI is unstable

- 20% of PD-MCIs in one study reverted back to normal cognition (Pedersen, JAMA Neurology 2013)
- longer duration in PD-MCI was associated with decreased reversion (Pedersen Neurology 2017)



## PD-Dementia

- Diagnosis of PD
- PD prior to cognitive impairment
- Objective cognitive impairment as measured by impairments in global cognitive scale or more than 2 neuropsychological tests in 2 different domains
- Cognitive impairment severe enough to impair functioning

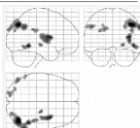
### PDD vs. DLB

Clinical difference: 1 year between onset of motoric symptoms and cognitive decline

- Somewhat arbitrary, length of Parkinsonism does not typically correlate with pathology
- May have more atrophy

DLB compared to PDD

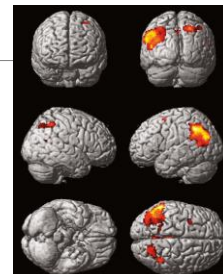
- Faster rate of cognitive decline,
- Less tremor,
- Decreased L-dopa responsiveness
- Earlier onset of hallucinations and delusions



Beyer Neurology 2007

### Visual hallucinations

- Associated with an increased risk of cognitive decline
- OR 3.1 at 8 years when present at baseline (Aarsland Arch Neurology 2003)
- 10.2 at 5 years in another study (also included illusions) (Anang Neurology 2004)



### Mechanisms of Cognitive Decline

Little is known about definitive mechanisms

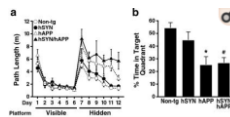
- Protein misfolding
- Neurotransmitter activity
- Synaptic dysfunction
- Neuroinflammation
- Mitochondrion dysfunction
- Microglial activation
- Genetics/Epigenetics
- Adenosine activity
- Cerebral network disruption



### Animal models: Synergistic Effects of Amyloid and Alpha Synuclein

Transgenic mice with alpha synuclein and amyloid pathology

- More severe Lewy body pathology than those bred with just alpha synuclein
- More rapid cognitive decline



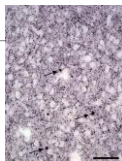
Masilah PNAS 2001

### Synaptic Dysfunction

Initial damage to synapse with retrograde transmission up axon to soma

Alpha synuclein has effects on synaptic homeostasis, neurotransmitter release, and aggregates in synaptic terminal

Several genes associated with PD are associated with synaptic function



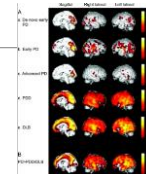
Schulz-Schaeffer 2010

### Neurotransmitters

Mesolimbic and mesocortical dopaminergic activity associated with cognitive functioning

Acetylcholine downregulated in PDD

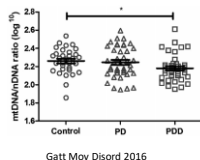
Serotonin system 5HT1B downregulated in one study (Varrone, Synapse 2009)



Schimada Neurology 2009

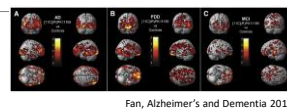
## Mitochondrion Dysfunction

Deficiencies in mitochondrion levels and DNA levels in PDD frontal cortex



## Neuroinflammation

Increased microglial activation in PD-D (Fan 2015)  
 CSF cytokines increased in CSF (Lindqvist Brain and Behavior 2013)



## Genetic Factors

Autosomal dominant PD

- LRRK2-protective cognition
- SNCA-slightly increased risk

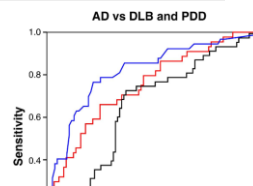
Sporadic

- GBA (glycosylceramidase)-strongest evidence (Alcalay Neurology 2015)
- APOE-overlap with AD
- COMT/MAPT

## Biomarkers: CSF Biomarkers

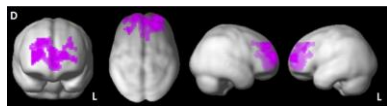
Abeta: decreased in PDD  
 • Predicts cognitive decline  
 Tau: inconsistent findings  
 Alpha synuclein: inconsistent findings

Mollenhauser J Neurochem 2016



## MRI

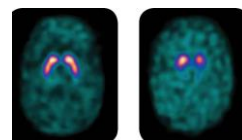
Atrophy: posterior, parietal, frontal, hippocampal  
 Cortical thinning:  
 • PDD: frontal, subcortical  
 • DLB: parietal and occipital



Borroni, Parkinsonism and related dementia 2006

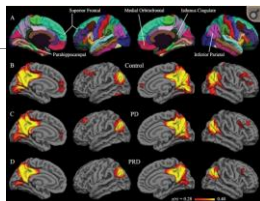
## DAT

Not generally helpful to differentiate PD from PDD  
 • Some studies: reduced caudate dopamine transporter uptake correlates with executive functioning (Marques, Adv Res Therapy 2007)



## Others

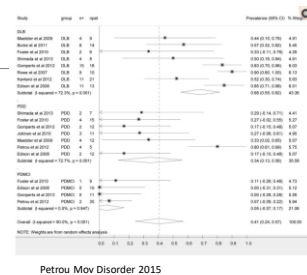
- DTI
  - Frontal, parietal, hippocampus
- Resting State
  - Corticostriatal
- FDG PET
  - Parietal, temporal, and cingulate



Seibert Radiology 2012

## Amyloid PET

- Positive in 15-20% of PDD
- Associated with worse cognitive decline



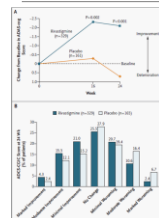
## Management: Cholinesterase Inhibitors

Most, but not all, studies of AChEIs have noted a mild to moderate benefit in PD

Side effects: tremor and nausea

May benefit have a benefit on hallucinations

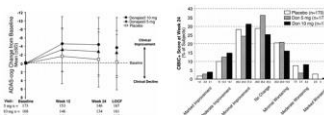
## Rivastigmine



- Mild to moderate PDD
- 2.1 pts improvement on ADCS-cog vs. 0.7 pt decline
- Clinically meaningful in 20% of treatment/14.5% placebo
  - 15% benefitted from therapy

EXPRESS Study  
Emre, NEJM 2004

## Donepezil



EDON Study  
Dubois, Mov Dis 2012

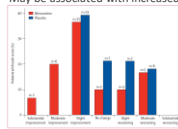
- Smaller benefit on ADCS
- Due to statistical anomaly did not meet primary endpoints
- Did benefit
  - Executive function
  - Attention

## Management: Memantine

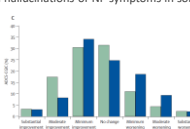
Benefit in 1 of 2 studies

DLB benefitted more

May be associated with increased risk of hallucinations or NP symptoms in some patients



Aarsland Lancet Neurology 2009



Emre Lancet Neurology 2010

## PD-MCI

### Rivastigmine

- No benefit on primary endpoint: CGIC
- Secondary endpoint: everyday cognitive activities

TABLE 4. Cognitive and disease-related functioning

Model	Regression Coefficient	df	F Value	P Value
Everyday Cognition Battery				
Drug	-2.41	1, 22	0.05	0.83
Parkinson's Disease Questionnaire-8				
Drug	4.55	1, 14	3.39	0.08
Mini Daily Activities Questionnaire				
Drug	-0.55	1, 5	0.09	0.78

• Mankibyan Mov Disorders 2015

TABLE 2. Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change

Parameter	Regression Coefficient	df	F Value	P Value
Intercept	3.56	—	—	—
Sequence	-0.20	1, 24	0.82	0.44
Phase	0.06	1, 24	0.05	0.82
Drug	0.44	1, 24	3.01	0.088

## Others

### Rasagiline

- No benefit in a large placebo controlled trial (Weintraub Mov Dis 2016)

### Atomoxetine

- Improvement in MMSE (Weintraub Neurology 2010)
- Decision making and attention (Kehagia Brain 2014)

### L-dopa

- Improvement in some studies (Cools, Cereb Cortex 2001)
- Others show negative effects (Cools Neurosci Biobehav 2006)

## Non-cognitive

### Cognitive training

- Meta-analysis 272 patients with MMSE 27-29 showed small but statistical improvements in working memory, processing speed, executive functioning (Martinez-Martin, Neurology 2015)

### Physical exercise

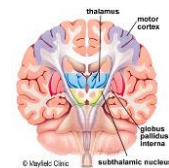
- Preliminary data
  - Study 51 PD without dementia-stretching or strengthening: both groups improvements in working memory and attention (David, Mov Disord 2015)
  - Mechanism: Promoting perfusion or growth hormone release

## DBS

### No clear benefit

### Possible some worsening

- Bilateral subthalamic DBS can result in small decline in executive functioning and verbal fluency (Parson 2006)



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