Parkinson’s disease
Dementia
Clinical Features and Treatments

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JAN 22nd 2015
Objectives

• To review the clinical features of cognitive impairment in PD

• To review treatment options for cognitive problems.
Neuropsychiatric symptoms in PD

a) Mood:
Anxiety, Depression, irritability, panic attacks, apathy, fatigue

b) Psychotic symptoms;
Euphoria, agitation, hallucinations, delusions, paranoia

c) Cognitive dysfunction:
Dementia; Mild cognitive impairment (MCI)
Neuropsychiatric manifestations in Parkinson's Disease are a major cause of morbidity.

14,354 Medicare beneficiaries with YOPD. Compared to the general population of medically disabled Americans, those with YOPD were more likely to receive medical care for:

- depression (OR: 1.89, 1.83-1.95),
- dementia (OR: 7.73, 7.38-8.09),
- substance abuse/dependence (OR: 3.00, 2.99-3.01)
- psychosis (OR: 3.36, 3.19-3.53),
- personality/impulse control disorders (OR: 4.56, 3.28-6.34)
- psychosocial dysfunction (OR: 3.85, 2.89-5.14).

PD Dementia

- Dementia is common
- Affects 30-80% of advanced PD.


Dementia as Milestone marker of PD progression

- Four ‘milestones’ in progression of PD
  1. Falls …..
  2. Hallucinations
  3. Dementia
  4. Nursing home care

Once milestone is reached the average time to death is the same – about 5y regardless of age-of-disease onset

Kempster PA, et al Brain 2010;133:1755-1762.
What is Dementia in PD?

• Gradual cognitive decline within the context of Parkinson Disease
  – Decline in function
    • what was (premorbid) baseline?
  – Heterogeneous cognitive domains affected
    • Executive function; attention, learning and memory, verbal fluency, visuospatial abilities
    • > 1 domain affected
    • Severe enough to impact Activities of Daily Living
# Diagnostic Criteria for PDD

**TABLE 2. Criteria for PDD**

<table>
<thead>
<tr>
<th>Core Features</th>
<th>Associated Features</th>
<th>Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable PDD</td>
<td>1. PD diagnosis</td>
<td>1. Vascular disease on imaging or other abnormality that may cause cognitive impairment, but not dementia</td>
</tr>
<tr>
<td></td>
<td>2. Slowly progressive dementia syndrome</td>
<td>2. Unknown time interval between motor and cognitive symptoms</td>
</tr>
<tr>
<td></td>
<td>1. Typical cognitive deficits in two of four domains (attention, executive function, visuospatial function, and free recall)</td>
<td>3. Acute confusion resulting from systemic diseases or abnormalities or drug intoxication</td>
</tr>
<tr>
<td></td>
<td>2. At least one behavioral symptom (apathy, depression/anxious mood, hallucinations, delusions, or excessive daytime sleepiness)</td>
<td>4. Features compatible with probable vascular dementia</td>
</tr>
</tbody>
</table>

Emre et al Mov Disord 2007;22:1689-1707
Mild Cognitive Impairment (MCI)

• Definition
  1) A complaint of cognitive dysfunction
  2) Scores of at least 1.5 standard deviations below the age-corrected mean on one or more core psychological tests
  3) No significant *functional* impairment as a result of cognitive deficit

• Affects 15 - 30% of early PD patients

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Litvan et al Mov Disord 2012;27:349-356

- Yarnall et al. Characterizing mild cognitive impairment in incident Parkinson disease; the ICICLE-PD Study: Neurology. 2014 28;82(4):308-16
How to assess cognitive function in PD

1. Cognitive Screening Tests
2. Neuropsychological Assessments
3. Research studies – Diagnostic Criteria/Imaging studies (Dr Monchi)
1. Cognitive Screening Tests

<table>
<thead>
<tr>
<th>Scale name</th>
<th>Assessed cognitive domains</th>
<th>Approximate administration time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Mental State Examination (MMSE)</td>
<td>Orientation, verbal registration and recall, attention, naming and repetition, verbal comprehension, praxis, visuospatial</td>
<td>10 min</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment (MoCA)</td>
<td>Orientation, attention, memory, naming, fluency, verbal repetition, visuospatial/executive</td>
<td>10 min</td>
</tr>
<tr>
<td>Addenbrooke Cognitive Examination (Revised) - ACE (R)</td>
<td>Attention/orientation, memory, fluency, language, visuospatial</td>
<td>20 min</td>
</tr>
<tr>
<td>Cambridge Cognitive Assessment (Revised) - CAMCOG (R)</td>
<td>Orientation, language, memory, attention, praxis, calculations, abstract reasoning, perception</td>
<td>25 min</td>
</tr>
<tr>
<td>Dementia Rating Scale (2nd edition)/Mattis Dementia Ratings Scale - DRS (2)</td>
<td>Attention, initiation/perseveration, construction, conceptualization, memory</td>
<td>30 min</td>
</tr>
<tr>
<td>Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)</td>
<td>Attention, language, visuospatial/construction, Immediate memory, delayed memory</td>
<td>30 min</td>
</tr>
<tr>
<td>Alzheimer’s Disease Assessment Scale - Cognition (ADAS-Cog)</td>
<td>Memory, language, praxis</td>
<td>30 min</td>
</tr>
</tbody>
</table>

Marras et al Mov Disor 2014;29:584-596
1. Cognitive Screening Tests

• MOCA is possibly better screen than MMSE
  – MoCA possibly better due to ability to detect executive dysfunction; a relative deficiency of the MMSE

• Quick screens?
  – ‘Incorrect hippo response’
  – ‘Pill questionnaire’
  – ‘Head-Turning Sign’
Incorrect response
= Hippo rather than Rhino
The incorrect ‘Hippo’ response can predict an abnormal MoCA

- 117 non-demented PD subjects
- 27 (23%) incorrectly responded “hippo” to the rhinoceros naming item on the MoCA
- “Hippo” responders scored significantly lower on the MoCA and MMSE.
- Poor scores on tasks requiring visuospatial and executive abilities across testing modalities.

Armstrong, Fox, Marras et al ParkRel Dis2013 The meaning of a "hippo" response on the Montreal Cognitive Assessment in Parkinson's disease.
The Pill Questionnaire did not show sensitivity or specificity enough to be used as a single screen.

However – inaccurate reporting is associated with deficits in many cognitive domains and should be an ‘alerting factor’.
# Head-Turning Sign

Head turning sign: pragmatic utility in clinical diagnosis of cognitive impairment

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Diagnostic parameters for head turning test (with 95% CIs)</th>
<th>Cohort minus ‘attended alone’ (n=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole cohort (N=207)</td>
<td></td>
</tr>
<tr>
<td>Overall test accuracy</td>
<td>0.83 (0.77 to 0.88)</td>
<td>0.76 (0.69 to 0.83)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.60 (0.49 to 0.70)</td>
<td>0.63 (0.52 to 0.74)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.98 (0.95 to 1.00)</td>
<td>0.95 (0.89 to 1.00)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.94 (0.88 to 1.00)</td>
<td>0.94 (0.88 to 1.00)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>0.79 (0.72 to 0.85)</td>
<td>0.64 (0.54 to 0.75)</td>
</tr>
<tr>
<td>Diagnostic odds ratio</td>
<td>60.4 (19.5 to 187.3)</td>
<td>29.3 (9.62 to 89.2)</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>24.9 (8.0 to 77.2)</td>
<td>11.5 (3.78 to 35.1)</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.41 (0.13 to 1.28)</td>
<td>0.39 (0.13 to 1.20)</td>
</tr>
<tr>
<td>Clinical utility index +</td>
<td>0.56 (adequate)</td>
<td>0.59 (adequate)</td>
</tr>
<tr>
<td>Clinical utility index −</td>
<td>0.77 (adequate)</td>
<td>0.61 (adequate)</td>
</tr>
</tbody>
</table>
PD-specific Cognitive Screens

**TABLE 6. Parkinson’s disease specific cognitive screening measures**

<table>
<thead>
<tr>
<th>Scale name</th>
<th>Assessed cognitive domains</th>
<th>Approximate administration time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s Disease Dementia - Short Screen (PDD-SC)</td>
<td>Immediate and delayed verbal recall, alternating verbal fluency, visuospatial</td>
<td>7 min</td>
</tr>
<tr>
<td>Parkinson Neuropsychometric Dementia Assessment (PANDA)</td>
<td>Attention/working memory, immediate and delayed recall, alternating verbal fluency, visuospatial</td>
<td>10 min</td>
</tr>
<tr>
<td>Mini-Mental Parkinson (MMP)</td>
<td>Orientation, attention, fluency, visual registration, visual memory, set-shifting, conceptualization</td>
<td>15 min</td>
</tr>
<tr>
<td>Parkinson’s Disease Cognitive Rating Scale (PD - CRS)</td>
<td>Attention, working memory, fluency (alternating and action), naming, visuospatial, immediate and delayed memory</td>
<td>15 - 25 min</td>
</tr>
<tr>
<td>Scales for Outcomes of Parkinson’s Disease - Cognition (SCOPA - Cog)</td>
<td>Attention, memory, executive function, delayed recall, visuospatial</td>
<td>15 min</td>
</tr>
</tbody>
</table>

\(^a\) in demented patients

- Longer to administer
- Not fully evaluated for reliability in PD, as yet

Marras et al Mov Disord 2014;29:584-596
2. Neuropsychological Assessments

1. Estimate of premorbid function/Intelligence
2. Language
3. Attention
4. Processing speed
5. Executive function
6. Learning and Memory
7. Visuo-spatial

• Gold Standard
  – Neuropsychology/Trained administrator
  – Long Time = 2h
  – Affected by:
    • Time of day
    • Medications
    • Co-morbidities - depression etc.
Symptoms that are often associated or preludes to cognitive decline in PD

- Depression and Anxiety
- Apathy
- Psychosis- visual hallucinations
Psychosis

• Features
  – Vivid dreams/nightmares
  – Illusions
  – Hallucinations
  – Paranoid delusions
Hallucinations in PD

• Visual most common
• Can affect up to 50% of PD patients
• Typically are well-formed hallucinations of people, animals, insects; Veridical
• Usually occur on going to sleep and on awakening
• Frequently stable, and chronic
• Rarely auditory; tactile
<table>
<thead>
<tr>
<th>Parkinson's disease Dementia (PDD)</th>
<th>Dementia with Lewy Bodies (DLB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Later onset* dementia</td>
<td>* Early onset* dementia, before or within one year of motor symptoms</td>
</tr>
<tr>
<td>* Occurs after many years of typical levodopa-responsive PD</td>
<td>* Fluctuations* with pronounced variations in attention and alertness</td>
</tr>
<tr>
<td>* Pathological- alpha synuclein deposition</td>
<td>* Visual hallucinations ++</td>
</tr>
<tr>
<td></td>
<td>* Older age</td>
</tr>
<tr>
<td></td>
<td>* Autonomic symptoms ++</td>
</tr>
<tr>
<td></td>
<td>* REM sleep behavior disorder</td>
</tr>
<tr>
<td></td>
<td>* Very sensitive to drugs esp any neuroleptics</td>
</tr>
<tr>
<td></td>
<td>* Cortical Lewy Body Disease (CLBD) = pathological term for extensive alpha synuclein deposition in cortex</td>
</tr>
<tr>
<td></td>
<td>DLB</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td><strong>Extrapyramidal symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>- PIGD subtype</td>
<td>Often more symmetric</td>
</tr>
<tr>
<td>- TD subtype</td>
<td>69%</td>
</tr>
<tr>
<td>- Hypomimia</td>
<td>48.5%</td>
</tr>
<tr>
<td>- Hypophonia</td>
<td>30.8%</td>
</tr>
<tr>
<td>- Rigidity</td>
<td>44.6%</td>
</tr>
<tr>
<td>- Impaired posture/gait</td>
<td>43.1%</td>
</tr>
<tr>
<td>- Bradykinesia</td>
<td>55.4%</td>
</tr>
<tr>
<td>- Impaired chair rise</td>
<td>28.9%</td>
</tr>
<tr>
<td>- Postural instability</td>
<td>26.2%</td>
</tr>
<tr>
<td>- Resting tremor</td>
<td>13.9%</td>
</tr>
<tr>
<td>- Action/postural tremor</td>
<td>12.3%</td>
</tr>
<tr>
<td><strong>Cognitive impairment</strong></td>
<td>Early disturbances in attention &amp; visuoperceptive functions</td>
</tr>
<tr>
<td><strong>Fluctuations in cognition</strong></td>
<td>Prominent, early second to hourly variations</td>
</tr>
<tr>
<td><strong>Neuropsychiatric symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>- Visual hallucinations</td>
<td>Typical, early &amp; persistent</td>
</tr>
<tr>
<td>- Delusions</td>
<td>Typical</td>
</tr>
<tr>
<td>- Depression</td>
<td>Usually present</td>
</tr>
</tbody>
</table>
Treating Cognitive problems in PD
The *Movement Disorder Society* Evidence-Based Medicine Review Update: Treatments for the Non-Motor Symptoms of Parkinson’s Disease

Klaus Seppi, MD, Daniel Weintraub, MD, Miguel Coelho, MD, Santiago Perez-Lloret, MD, PhD, Susan H. Fox, MRCP (UK), PhD, Regina Katzenschlager, MD, Eva-Maria Hametner, MD, Werner Poewe, MD, Olivier Rascol, MD, PhD, Christopher G. Goetz, MD, and Cristina Sampaio, MD, PhD


**UPDATED: 2013:**
Treatments for Non-Motor Symptoms of PD

http://www.movementdisorders.org/publications/ebm_reviews
# Randomized Controlled Trials in PDD

<table>
<thead>
<tr>
<th>Cholinesterase inhibitors (daily dose)</th>
<th>Outcome vs. placebo (n receiving active) (duration)</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (2.5 – 10mg)</td>
<td><strong>POSITIVE</strong> MMSE, <strong>NEGATIVE</strong> CIBIC (n = 14) (10w) <strong>POSITIVE</strong> DRS (n = 16) ; (18w) <strong>NEGATIVE</strong> ADaSCog ; <strong>POSITIVE</strong> MMSE ((n = 22); (10w) <strong>NEGATIVE</strong> ADaSCog /CGI ; <strong>POSITIVE</strong> MMSE ; (n = 550) (24 w)</td>
<td>Aarsland et al 2002 Leroi et al 2004 Ravina et al 2005 Dubois et al 2012</td>
</tr>
<tr>
<td>Rivastigmine (3 – 12mg)</td>
<td><strong>POSITIVE</strong> (ADCS-CGI and ADaSCog (n = 541) (24 w)</td>
<td>Emre et al 2004</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glutamate antagonists</th>
<th>Outcome vs. placebo (n receiving active) (duration)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memantine (10 – 20 mg)</td>
<td><strong>NEGATIVE</strong> DRS, MMSE (n = 25) <strong>POSITIVE</strong> CGI (n = 72 ) <strong>POSITIVE</strong> ADCS-CGIC in DLB not PDD (n = 195)</td>
<td>Lerois et al 2009 Aarsland et al 2009 Emre et al 2010</td>
</tr>
</tbody>
</table>
Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson’s disease dementia, and cognitive impairment in Parkinson’s disease (Review)


Rolinski M, Fox C, Maidment I, McShane R

- 6 Trials using Donepezil, Rivastigmine; n = 1236 subjects

AEs more common in rivastigmine groups
= Nausea and vomiting
Safety and tolerability of cholinesterase inhibitors?

• ECG before starting
  • risk of prolonged QTc interval

• Nausea and vomiting
  • up to 30% of patients
  • Rivastigmine patch may be better tolerated
Safety and tolerability of cholinesterase inhibitors?

- Worsening of Parkinsonism?
  - More patients on rivastigmine vs. placebo reported tremor as an AE but not UPDRS III
    » Rolinski et al Cochrane Review 2012

- Open label safety study of rivastigmine oral vs patch for 76 w in PD dementia
  - Tremor = 24% oral vs 10% patch
  - No significant worsening of motor UPDRS in both
  - Discontinuation rate due to worse motor scores 2% in both
    » Emre et al Clin Neuropharm 2014
Conclusions: PD Dementia Treatments
- Interventions assessed in MDS EBM Reviews -

<table>
<thead>
<tr>
<th>Cholinesterase inhibitors</th>
<th>Practice implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Possibly useful</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Clinically useful</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Possibly useful</td>
</tr>
</tbody>
</table>

| Glutamate antagonists           | Practice implications     |
| Memantine                       | Possibly useful           |
Canadian Guidelines on Parkinson’s Disease

C71 Discontinue potential aggravators;
   • Anticholinergics. EFNS level B
   • Amantadine, tricyclic antidepressants, benzodiazepines, tolterodine and oxybutynin. EFNS Level C

C72 Donepezil should be considered for the treatment of dementia in PD. AAN Level B

C73 Rivastigmine should be considered for the treatment of dementia in PD or Dementia with Lewy Bodies. AAN Level B
## Treatments for PD-MCI?

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism of action</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Cholinesterase inhibitor</td>
<td>(MUSTARDD-PD (NCT01014858)- suspended due to low recruitment). DASH-PD in Japan; recruiting early PD subjects and following over 3y</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>+ Allosteric modulator of nicotinic cholinergic receptors</td>
<td>Ongoing study using patch (NCT01519271)</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Mono amine oxidase B inhibitor (MAOB-I)</td>
<td>Negative DBRCT in non-demented PD (Grace et al 2009)</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>MAOB-I/Glutamate release inhibition</td>
<td>Positive on attention and verbal fluency (Hanagasi et al 2011) NCT01723228 and NCT01497652 - ongoing</td>
</tr>
<tr>
<td>Safinamide</td>
<td>Noradrenaline and serotonin re-uptake inhibitor</td>
<td>Ongoing study (NCT01211587)</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Mono amine oxidase B inhibitor (MAOB-I)</td>
<td>Ongoing study vs donepezil for attention in non-demented PD (NCT01340885) Ongoing vs placebo in PD MCI (NCT01738191)</td>
</tr>
<tr>
<td>Cognitive Speed Training</td>
<td></td>
<td>NCT01646333; NCT01393353; NCT02225314 - ongoing Positive outcomes in non-demented PD (Edwards et al 2013)</td>
</tr>
</tbody>
</table>
# Management of PD Psychosis

**Table 2: Evaluation of Acute PD Psychosis**

**Differential Diagnosis**

<table>
<thead>
<tr>
<th>P</th>
<th>Parkinson’s disease medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>SY</td>
<td>Systemic illness</td>
</tr>
<tr>
<td>C</td>
<td>Centrally acting medication</td>
</tr>
<tr>
<td>H</td>
<td>Hepatic, renal, or other metabolic dysfunction</td>
</tr>
<tr>
<td>O</td>
<td>Overdose of medications or intoxication</td>
</tr>
<tr>
<td>S</td>
<td>Sensory deprivation (hearing, visual impairment)</td>
</tr>
<tr>
<td>I</td>
<td>Infection (urinary tract infection, pneumonia)</td>
</tr>
<tr>
<td>S</td>
<td>Structural lesions (stroke, subdural hematoma, intracranial hemorrhage, trauma)</td>
</tr>
</tbody>
</table>

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Vaughan and Goldman, *Movement Disorder Emergencies: Diagnosis and Treatment*, ed. S. Frucht
Specific treatments for psychosis in PD

- **Atypical antipsychotic agents**
  - **Quetiapine**
    - 25 - 150 mg – start with half a tablet (25mg) at night and titrate according to response
  - **Clozapine**
    - 25 – 75 mg - **Very effective** – start with half a tablet (25mg) at night and titrate according to response (average 50 mg)

Pollack et al. J Neurol Neurosurg Psychiatry. 2004 May;75(5):689-95
Parkinson Study Group NEJM;1999 Mar 11;340(10):757-63
Clozapine for PD

- **Safety issues:**
  - Side effects:
    - sedation, increased drooling, occasional Orthostatic hypotension
  - Leukopenia:
    - regular blood counts required (initially weekly – 2 weekly – 2 monthly)
    - 1 - 2% in the pre-CNR period vs. 382 / 99 502 (=0.38%) pts treated with CLZ with 12 leukopenia-related deaths (=0.00012%) *
    - 6 / 187 pts with psychosis in PD included into RCTs (transient)

*Honigfeld et al., J Clin Psychiatry; 1998 (CNR database 1990 - 1994) CNR = Clozaril National Registry
Safety issues with using atypical antipsychotics for psychosis in PD

- **general safety issues** to consider in elderly patients:
  - antipsychotics (including atypicals) are associated with a similarly increased risk for
    - all-cause mortality
    - cerebrovascular events
  - in elderly patients with dementia


Avoid other ‘atypical neuroleptics”

- Olanzapine
- Risperdone
- Aripiprezeole

- All worsen PD


Friedmnan et al. Open-label flexible-dose pilot study to evaluate the safety and tolerability of aripiprazole in patients with psychosis associated with Parkinson's disease. Mov Disord 2006 Dec;21(12):2078-81
DLB

• **Treatment options**
  – Cholinesterase inhibitors – help Hallucinations and cognition
  – Quetiapine or Clozapine – Help sleep and Hallucinations

  – Minimise non-essential centrally acting drugs – very poorly tolerated
Clinical pearls for cognitive dysfunction in PD

• Simple in clinic screens – ‘head-turning’ sign; ‘Pill Questionnaire’

• Watch out for younger PD patient with work-related anxiety -‘multi-tasking’ jobs – a common reason for stopping work. Maybe a prelude to cognitive decline

• Depression /anxiety are often a prelude to dementia

• Subjects with MOCA < 25 should stop driving

• PD patients with dementia are extremely sensitive to medications 
  *per se*; Reduce drug ‘load’ to minimum

• Social support networks and education of care givers are important for long term care of PD Dementia
Support

Alzheimer Society's website at www.alzheimer.ca or contact your local Alzheimer Society.

For more information on PD, please visit the Parkinson Society Canada www.parkinson.ca.

Additional Resources:
Alzheimer’s Association: http://www.alz.org/dementia/parkinsons-disease-symptoms.asp
Parkinson’s disease Dementia: Research and non-medication treatments exploration

Oury Monchi, PhD,
Tourmaline Oil Chair in Parkinson's disease,
Movement Disorders Program,
Departments of Clinical Neurosciences and Radiology,
Hotchkiss Brain Institute, Cumming School of Medicine,
University of Calgary.
Parkinson’s Disease

Cut section of the midbrain where a portion of the substantia nigra is visible.

Substantia nigra

Diminished substantia nigra as seen in Parkinson's disease.

- GABA
- Dopamine
- GLU

Diagram showing the cerebral cortex, striatum, GPe, SNigra, STN, GPi/SNpr, and VL with neurotransmitters and neuronal pathways.
Non-motor deficits

Benjamin Ball, France 1855

Visual hallucinations in PD

Intellectual perturbation is not just a coincidence nor irritability linked to the diagnosis, but an integral part of the disease

Largely forgotten until end of 20th century
FRONTAL LOBE DYSFUNCTION IN PARKINSON’S DISEASE

THE CORTICAL FOCUS OF NEOSTRIATAL OUTFLOW

by ANN E. TAYLOR, J. A. SAINT-CYR and A. E. LANG

(From the Departments of Psychology and Medicine, Division of Neurology and Playfair Neuroscience Unit, Toronto Western Hospital, and Departments of Anatomy and Medicine and the Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada)

To investigate the influence of central cholinergic deficit on cognitive function in Parkinson’s disease (PD), we compared the neuropsychological performance of a group of 20 patients who were treated with anticholinergic drugs (mean daily dose, 10.2 mg) with that of a group of 20 patients who received no anticholinergics. The two groups were matched for all the variables of parkinsonism and levodopa therapy. At the dose used, there was no significant difference between the two groups of patients for intellectual, visuospatial, instrumental, and memory function. In contrast, in the group that received anticholinergics severe impairment was observed on tests believed to assess frontal lobe function. These results suggest that the lesion of the ascending cholinergic neurons, which has been demonstrated post mortem in PD, may play a role in the subcorticofrontal behavioral impairment of this disease.

Cognitive deficits

- **Executive deficits:**
  
  ‘higher order processes’ that are used when planning, problem-solving, initiating a new task.

- **Attention difficulties:**
  
  Problems in focusing or dividing attention in complex situations.

In real life, this may translate into difficulties in resisting to distraction.
Cognitive Deficits

- **Visio-spatial problems:**
  
  Problems in estimating distances, discriminating and acting on visual information. This can sometimes increase the risk of falls.

  In real life this may translate in difficulties in orientation in an environment with complex visual stimuli, such as finding a specific isle in a supermarket.

- At the later stages of the disease, illusions or little hallucinations are observed in some patients only.
Cognitive Deficits

- **Language dysfunction:** Word finding and naming deficits.

- **Memory:** Retrieving information that has already been learned.

In PD the problem is mostly with recall, and not with pure semantic or encoding like can occur in Alzheimer’s disease.

Using a notepad can help

- **IMPORTANT:** Not all these symptoms are present in patients, and great differences exist between them.
Depression and Anxiety

- Depression is common in PD patients. A depressed person has trouble experimenting joy, may stop hobbies enjoyed before, and may not want to perform his daily routine. Diagnosis of Parkinson's disease can certainly cause stress and sadness, but depression can occur independently.

- Indeed a large number of patients with PD have experienced depression before they had the diagnosis.

- Anxiety often occurs with depression in PD. They may have excessive worry about everyday things they can not control. Some people have outbreaks of anxiety called "panic attacks". 
Normal Aging: Everyone experiences slight cognitive changes during aging.

Preclinical:
- Silent phase: brain changes without measurable symptoms
- Individual may notice changes, but not detectable on tests
- "A stage where the patient knows, but the doctor doesn't"

MCI:
- Cognitive changes are of concern to individual and/or family
- One or more cognitive domains impaired significantly
- Preserved activities of daily living

Dementia:
- Cognitive impairment severe enough to interfere with everyday abilities

Time (Years)
MCI very heterogeneous in Parkinson’s Disease

Caviness et al. (2007)
Prevalence longitudinal studies

Baseline
- No PD-MCI (n=80)
- PD-MCI (n=43)

Year 3
- No PD-MCI (n=41)
- PD-MCI (n=47)
- PDD (n=9 (5))

Year 5
- No PD-MCI (n=28)
- PD-MCI (n=28)
- PDD (n=17 (3))

Attrition
- n=26
- n=24

Broeders et al., Neurology, 2013
The Pattern of Cortical Atrophy in Patients with Parkinson’s Disease According to Cognitive Status

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Method

- 17 PD patients with MCI
- 15 PD patients without MCI
- 18 Healthy Controls

- MRI 3T
- FreeSurfer
  - Cortical thickness
  - Subcortical segmentation

Time 1: Neuropsychological evaluation + MRI

20 months

Time 2: Neuropsychological evaluation + MRI

MCI = Mild Cognitive Impairment
PD = Parkinson’s disease
Results - thickness

Blue clusters = increased rate of cortical thinning

Hanganu et al., Brain 2014
# Results – subcortical

## Mean percentage of change over time

<table>
<thead>
<tr>
<th></th>
<th>PD-MCI</th>
<th>PD-non-MCI</th>
<th>HCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>-1.51%</td>
<td>-1.80%</td>
<td>-3.71%</td>
</tr>
<tr>
<td>Caudate</td>
<td>-1.92%</td>
<td>-2.05</td>
<td>-0.99%</td>
</tr>
<tr>
<td>Putamen</td>
<td>-1.64%</td>
<td>-1.41</td>
<td>-0.40%</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>-2.07%</td>
<td>-1.96</td>
<td>-3.08%</td>
</tr>
<tr>
<td>Amygdala</td>
<td>-6.05%</td>
<td>+0.58</td>
<td>+0.80%</td>
</tr>
<tr>
<td>N. Accumbens</td>
<td>-5.98%</td>
<td>-0.91</td>
<td>+2.19%</td>
</tr>
</tbody>
</table>

Hanganu et al., Brain 2014

Ventral striatum has an increased degradation.
Neuroimaging studies fMRI
Isolation of a cognitive cortico-striatal loop including the ventrolateral PFC in the planning of a set-shift

Monchi et al., 2001: Journal of Neuroscience, editor’s choice Science and Nature Reviews Neuroscience
fMRI WCST Results in PD-OFF and matched Controls: **Shift-planning**

Decreased activity in PD in the ‘cognitive’ cortico-striatal loop during planning the set-shift

Monchi et al., Journal of Neuroscience 2004
Highlighted in ‘This Week in the Journal’
fMRI WCST MCI vs. NON MCI OFF

Negative Feedback

PD NON MCI

PD MCI

Z = +4

T-stat

5

2.5

Effect more pronounced in patients with MCI
Correlation with retrieval list of RAVLT

Shift Execution

Patients with better scores (memory) use more the MTL even though it is not required for the task

Nagano-Saito et al., 2014, Neurobiology of Aging
Could the lack of MTL compensation be a marker of dementia in PD?
Longitudinal study fMRI WCST All PD T1 correlated with MOCA evolution, Planning set-shift

X=-34

X=+36

T-stat

4

2.75

T-stat

4.5

3.5

Z=+8
Genotypes and cognitive deficits


APOE, MAPT, and SNCA genes and cognitive performance in Parkinson disease.

Author information


Catechol-O-methyltransferase val158met and cognitive function in Parkinson's disease.
Hoogland J, de Bie RM, Williams-Gray CH, Muslimović D, Schmand B, Post B.


Dopamine transporter SLC6A3 genotype affects cortico-striatal activity of set-shifts in Parkinson's disease.


Cognitive impairment in carriers of glucocerebrosidase gene mutation in Parkinson disease patients.
Malec-Litwinowicz M, Rudzińska M, Szubiga M, Michalski M, Tomaszewski T, Szczudlik A.
• Cognitive decline is very heterogeneous in PD

• PD dementia may occur from mixed pathologies, including some associated with AD.

• Studies currently taking place to find out longitudinally the differences between PD-MCI and nonPD-MCI

• Other factors such as age, neuropsychiatric symptoms and genetics also play a role in the occurrence of dementia in PD
Cognitive training in Parkinson's disease reduces cognitive decline in the long term.

Petrelli A¹, Kaesberg S, Barbe MT, Timmermann L, Rosen JB, Fink GR, Kessler J, Kalbe E.

Task force WANTED: Many reasons to promote research on cognitive rehabilitation to prevent, delay, and treat cognitive dysfunctions in patients with Parkinson’s disease.

Kalbe E¹, Kessler J².
Exercise programs in PD


**Aerobic exercise to improve executive function in Parkinson disease: a case series.**
Tabak R¹, Aquije G, Fisher BE.


**The Efficacy of Exercise Programs for Parkinson's Disease: Tai Chi versus Combined Exercise.**
Cheon SM¹, Chae BK, Sung HR, Lee GC, Kim JW.
DANCING PARKINSON'S

A PARTNERSHIP BETWEEN DECIDEDLY JAZZ DANCEWORKS & UNIVERSITY OF CALGARY DIVISION OF DANCE
WITH SUPPORT FROM THE ROZSA FOUNDATION & THE SOCIAL SCIENCES AND HUMANITIES RESEARCH COUNCIL
New possible treatments Transcranial Magnetic Stimulation (TMS)
Fronto-striatal connectivity during ‘rest’

TBS of PFC and ‘resting-state fMRI’
iTBS and rsfMRI correlation analysis
L caudate nucleus seed

Pre-iTBS

Sham TBC

Post-iTBS

Loop affected in PD-MCI
Therapeutical TMS trial in PD-MCI

Pre-assessment

Visit 1
Neuropsy
fMRI
(N=60 PD-MCI)

1-3 days

Group

Visit 2
Real iTBS (N=30)

Clinical tests
TMS 1
TMS 2

1-2 days

TMS protocol

Visit 3
TMS 3
TMS 4

1-2 days

Visit 4
TMS 5
TMS 6

1 day

Follow-up assessment

Visit 5
Clinical tests
Neuropsy
fMRI

9 days

Visit 6
Neuropsy
Clinical tests

20 days

Visit 7
Clinical tests

(N=30)
Preliminary results 10 patients active
iTBS neuropsychological tests
Preliminary results 10 patients active
iTBS neuropsychological tests

\[ p < 0.05 \]
Data on non-medication treatment is not yet conclusive

Not enough studies

Lack of guidelines

Which is more beneficial?

Confounding factor, ‘being taken care of’, placebo effect, social effect.....

In need of proper large-scale clinical trials like for medication

Nevertheless, get involved always some benefits and keep active mentally and physically as much as possible

Regularity more important than intensity