Mild cognitive impairment (MCI) and dementia in Parkinson Disease (PDD)

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Why is cognition impairment and dementia in PD important?

- The incidence of PD is increasing
- People are living with PD longer
- Over 80% who live with PD for long enough will develop dementia
- PD is presenting *de novo* to Memory Assessment Clinics
Non-motor PD Features

• Pain syndromes
• Parathesias
• Restless leg syndrome
• Fatigue
• Skin symptoms (seborrhoea, facial oiliness)
• Dysautonomia (bladder instability, Δ thermal regulation, orthostatic hypotension)
Other non-motor PD features

- Psychiatric Symptoms
  - depression
  - anxiety
  - sleep disturbance
  - psychosis

- Cognitive Symptoms
Cognition and stage of PD

• Prodromal stage of PD:
• Early-moderate stages of PD:
• Advanced stage PD:

  cognitive change

  MCI-PD

  PDD
Non-motor symptoms correspond to the orderly progression of LB pathology (Braak stages)

- Olfactory bulb → Anosmia
- Dorsal motor nucleus of vagus (DMNX) → Constipation, bladder instability
- Rostral via brain stem → Depression, anxiety
  - Locus coeruleus
  - Dorsal raphe nucleus
- Midbrain substantia nigra → Motor symptoms
Mild Cognitive Impairment in PD (MCI-PD)
Mild cognitive impairment in Parkinson Disease (MCI-PD)

- 25% of people with PD
- MCI-PD may convert to PDD (Janvin 2006; Williams-Grey 2010)
Definition of mild cognitive impairment in PD (MCI-PD): MDS Task Force proposal

(Litvan 2012)

- **Level I:**
  - abbreviated assessment of global cognition
  - limited neuropsychological test batteries
  - classification of “possible PD-MCI”.

- **Level II:**
  - extensive neuropsychological testing
  - tests in five domains
  - impairment on at least 2 tests in one or more domain
  - classification of *PD-MCI subtypes.*
MCI-PD: MDS Task Force proposal: *5 key cognitive domains*

- attention and working memory
- executive dysfunction
- language
- memory
- visuospatial function
Cognitive profile of MCI-PD  
(Aarsland 2011)

- Range of cognitive domains affected
  - 11% *non*-amnestic, single-domain impairment
  - 9% amnestic single-domain
  - 5% amnestic multiple domain
  - 1.3% non-amnestic multiple domain
Clinical correlates of MCI-PD?
(Janvin 2007; Alves 2009)

• Older age
• Longer duration of disease
• More advanced disease
• Increasing neuropsychiatric symptom load
Manchester Study of Neuropsychiatric Symptoms of PD-MCI
(Leroi, Pantula, et al 2012)

• **Aim:**
  - (1) compare the frequency, magnitude of NPS in PD, PD-MCI and PDD
  - (2) explore the relationship of NPS with motor and cognitive profiles

• **Study design:**
  - cross sectional, case control

• **Participants (n=127):**
  - PD-NC (normal cognition): n=54
  - PD-MCI (Litvan 2012): n=48
  - PDD (Emre 2007): n=25
Results: Proportion reporting presence of neuropsychiatric symptoms (on NPI)

- NPI any symptom
  - PD NC
  - PD MCI
  - PDD
- NPI total score ≥4
  - PD NC
  - PD MCI
  - PDD

* denotes statistical significance.
Most commonly reported neuropsychiatric symptoms
(in over 20% of each group, excluding sleep & appetite)

<table>
<thead>
<tr>
<th>In order of frequency</th>
<th>PD NC</th>
<th>PD MCI</th>
<th>PDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Depression</td>
<td>Irritability</td>
<td></td>
</tr>
<tr>
<td>Apathy</td>
<td>Anxiety</td>
<td>Depression</td>
<td>Depression</td>
</tr>
<tr>
<td>Apathy</td>
<td>Irritability</td>
<td>Anxiety</td>
<td>Apathy</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Depression</td>
<td>Irritability</td>
<td>Irritability</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Depression</td>
<td>Anxiety</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Aggress/agitation</td>
<td>Hallucinations</td>
<td>Delusions</td>
<td>Aberrant motor</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Delusions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delusions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Proportion of clinically significant NPI domains (≥ 4)

PD NC vs PD MCI: differed only on apathy
PDD vs PD NC and PD MCI: more frequently on delusions, hallucinations, aggression, depression, irritability, aberrant motor
All three apathy domains significantly worse in PD-MCI vs. PD with normal cognition.
Correlation between apathy, depression and anxiety and cognitive scores in PD NC and PD MCI (rho)

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>Apathy</th>
<th>Depression</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global (MMSE total)</td>
<td>-0.33*</td>
<td>-0.21*</td>
<td>-0.07</td>
</tr>
<tr>
<td>Verbal fluency (FAS)</td>
<td>-0.23*</td>
<td>-0.20</td>
<td>0.18</td>
</tr>
<tr>
<td>Attention (Trails B-A)</td>
<td>0.23*</td>
<td>-0.19</td>
<td>-0.12</td>
</tr>
<tr>
<td>Memory (word list recall)</td>
<td>-0.21*</td>
<td>-0.14</td>
<td>0.00</td>
</tr>
<tr>
<td>Executive function (WCST)</td>
<td>0.27*</td>
<td>-0.016</td>
<td>0.08</td>
</tr>
<tr>
<td>Working memory (n-back)</td>
<td>-0.29*</td>
<td>-0.23*</td>
<td>0.08</td>
</tr>
</tbody>
</table>
Dementia in PD (PDD)
Advanced stage PD

- Motor symptoms more severe
- Falls more common
- “on-off” complications and fluctuations/freezing
- Tremor may be less obvious
- Marked bradykinesia
- Gait assisted
- Less responsive to dopamine replacement therapy
‘The Sydney Multicentre Study’
(Hely 2008)

- Longitudinal observational study
  - N=136 PD participants
  - Followed at 10, 15, and 20 years
  - At 20 years, 100 died
  - *PDD in 83% of 20-year survivors
The Sydney Multicentre Study
(Hely 2008)

- Mean age at PDD diagnosis 71.6 years
- Mean time to onset after dx 10.2 years
- After PDD diagnosis, mean survival 54 months
**Post-mortem PDD: heterogeneous pathology**

<table>
<thead>
<tr>
<th></th>
<th>Hughes 1993 (n=31)</th>
<th>Hely 2008 (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD-changes</td>
<td>9 (29%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Vascular</td>
<td>2 (6%)</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Cortical Lewy bodies</td>
<td>3 (10%)</td>
<td>8 (47%)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (55%)</td>
<td>Pick bodies, FTD 1(6%)</td>
</tr>
</tbody>
</table>
Detecting dementia in PD

• Have a high index of suspicion

• **Risk factors**:  
  • Older age, early psychosis, poor verbal fluency
  
• Concomitant clinical presentation:  
  • EDS, apathy, falls, levo-dopa non-responsiveness, lack of tremor

• Ask carer about functional ability related to cognition  
  • Finances, help choosing clothes, household organisation

Noe *et al* (2003); Galvin (2003); Emre (2003); Aarsland (2003)
Operationalized MDS Criteria for PDD: Simple 5 step algorithm

(Dubois et al, 2007)

- 1. diagnosis of iPD
- 2. PD prior to dementia
- 3. PD with ↓ global cognitive efficiency
- 4. Cognitive ↓ impairs ADL
- 5. Impairment of >1 cognitive domain

- Queen’s Square
  - History/records
  - MMSE < 26
- Carer interview/pill questionnaire
  - Domains: attention, ECF, visuospatial, memory
<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCOPA-Cog</td>
<td>10 items; max score 43 Practical Test-retest reliability .78</td>
<td>20 min</td>
<td>Validated in PD</td>
</tr>
<tr>
<td>MMSE</td>
<td>&gt;94% sensitive; 77% specific; 20 min better for “cortical” total score</td>
<td></td>
<td>AAN (Level B)</td>
</tr>
<tr>
<td></td>
<td>not helpful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-R</td>
<td>no evidence in PD; good frontostriatal testing</td>
<td>30 min</td>
<td>*extract MMSE</td>
</tr>
<tr>
<td>Mattis DRS</td>
<td>Used in RCT of PDD (Leroi et al. 2004)*MMSE</td>
<td>40 min</td>
<td>Cut-off &lt;123/144</td>
</tr>
<tr>
<td>Clock</td>
<td>Good screen but low specificity;</td>
<td>5 min</td>
<td>DLB can’t copy!</td>
</tr>
<tr>
<td>MOCA</td>
<td>Increasingly used in PD</td>
<td>10-15 min</td>
<td>Similar items as ACER; validated in PD</td>
</tr>
</tbody>
</table>
Pill Questionnaire
(Dubois et al. 2008)

- Ability of a patient to **verbally describe** his/her anti-parkinsonian treatment
  - time schedule
  - type of medication
  - dose

- Correlates with impaired ADL
Pattern of Impact (n=127)
PD normal cognition, PD MCI, PDD
(Harbishettar, Pantula, Leroi 2012)
Management of cognitive impairment and dementia in PD
The consequences of dementia...
“Disability Model” (WHO 1998)
The consequences of dementia...

Impairment

Due to underlying pathophysiical changes... extent of cognitive impairment (memory, language...)

Disability

Handicap
Medication Management of MCI-PD

• No full scale trials yet
• Cholinesterase inhibitors vs placebo in MCI without PD have not favoured active drugs
• But, consider cholinesterase inhibitors if psychosis or fluctuating cognition is present
Medication Management of MCI-PD

- Ensure that dopaminergic therapy has been optimised
- Trial of atomoxetine (NRi for ADHD) in PD cognition *(Johns Hopkins study)*
- Consider Memory Management Groups
- Occupational Therapy input
MUSTARDD study: RCT of donepezil in mild PDD

- Will provide long-term data on efficacy of ACHEI in PDD
- 2 year study
- Donepezil vs placebo
- UK sites

- May give guidance about when to discontinue therapy
Steps before medication management of PDD

• Rule out reversible causes of dementia (TSH, B12, Folate etc)
• Aim for levodopa monotherapy
• Stepwise removal of “deliriogenic”, hallucinogenic medications
  – Graded, gradual withdrawal
  – Anticholinergics > selegilene > amantadine > dopamine agonists > COMT inhibitors

Compliments of Prof David Burn
## Cognitive enhancers in PDD

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose Level</th>
<th>Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (Aricept)</td>
<td>5mg daily → 10mg daily</td>
<td>Leroi et al, 2004 (RCT); Ravina et al 2005 (RCT); EDON Trial</td>
</tr>
<tr>
<td><em>Rivastigmine</em> (Exelon)</td>
<td>1.5 mg daily/BD → 6mg BD; Patch once daily</td>
<td>Emre et al, 2004 (RCT)*</td>
</tr>
<tr>
<td>Galantamine XL (Reminyl)</td>
<td>8mg daily → 24 mg daily</td>
<td>Aarsland et al, 2004</td>
</tr>
<tr>
<td>Memantine (Ebixa)</td>
<td>5mg daily → 10mg BD</td>
<td>Leroi 2010, Aarsland 2011, Emre 2011</td>
</tr>
</tbody>
</table>
Memantine improves goal attainment and reduces caregiver burden in PDD

• **Memantine**: uncompetitive antagonist NMDA

  **Aim**: effect on Patient Reported Outcomes (PROs)...? more sensitive than psychometric measures in complex conditions such as PDD.

• **Study design**: 22-week double-blind RCT: 20 mg of memantine or placebo.

• **Outcome measures**:
  • Goal Attainment Scaling (GAS),
  • Parkinson’s Disease Questionnaire-8 (PDQ-8)
  • Zarit Burden Inventory (ZBI).
Memantine improves goal attainment and reduces caregiver burden in PDD


\[ p=0.007^{**} \quad p=0.04^* \]
The consequences of dementia.

**Restriction in function**
- May vary greatly according to personal, social, environmental factors
- May not be a reflection of the level of impairment
Cognition-based interventions for older adults

- **Cognitive stimulation (CS):**
  - Repeated practising of a cognitive task improves the ability to do that task

- **Cognitive (brain) training (CT):**
  - Learning new methods to enhance information coding or retrieval of previously learnt material

- **Cognitive rehabilitation (CR):**
  - Uses strategies (memory aids, daily routines to support memory etc) to compensate for cognitive impairment
A Novel Psychosocial Therapy to Benefit Patients with Parkinson’s-related Dementia

- **Host Trust:** Manchester Mental Health and Social Care Trust
- **Duration:** 24 months
- **Health Setting:** Participants’ own homes
- **Study design:** pilot feasibility study of adapted *Cognitive Stimulation Therapy* for PDD vs TAU
- **Participants:** n=60; PDD
What does standard Cognitive Stimulation Therapy (CST) involve?

• 45 minute sessions, 2x per week
• Therapist in group form OR individually-based carer delivered
• Sessions prompted by a CST manual
• involves a new themed cognitive activity (word game, categorising objects, debate etc)
• Themes: current affairs, food, childhood etc.
• [www.cstdementia.com/sessions](http://www.cstdementia.com/sessions)
Manchester pilot study
Cognitive Training in PD
(Smith, Leroi, Poliakoff, 2014)

- ‘brain training’
- Computerised cognitive training battery (daily x 2 weeks)
- Simulating real life scenarios
- Targeting several different cognitive domains
- Range of outcomes:
  - Cognitive
  - Functional
  - Behavioural (apathy, mood)
Planning Training with zoo game

- Planning and executing routes through environments
- Map & list of animals to visit
- Must plan & execute the quickest route
- Progressive task: 2 to 7 places (Level 1-7).
- In 15 min, complete as many routes as possible
- The outcome measure was the difficulty level reached at the end of the 15 minute period.

A study of the feasibility and acceptability of a bespoke computerised approach to cognitive training in Parkinson’s disease (Smith SH, McMillan I, Leroi I et al. 2014)
A study of the feasibility and acceptability of a bespoke computerised approach to cognitive training in Parkinson's disease *(in press)*

Smith S, McMillan I, Leroi I et al.
Thank you.