Disturbi cognitivi e comportamentali nella malattia di Parkinson: aspetti teorici ed applicazioni pratiche

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Corso per Neuropsicologi
“LA NEUROPSICOLOGIA DEL LOBO FRONTALE”

Firenze, 16 Aprile 2015
Overview of the presentation

<table>
<thead>
<tr>
<th>Non-motor symptoms of Parkinson’s disease (PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role of cortical-basal ganglia loops in cognition and behaviour</td>
</tr>
<tr>
<td>Cognitive impairment in PD: neuropsychological features</td>
</tr>
<tr>
<td>Diagnostic criteria for Dementia and Mild Cognitive Impairment associated with PD</td>
</tr>
<tr>
<td>Multiple pathogenic mechanisms underlying cognitive impairment in PD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behavioural symptoms/syndromes in PD: clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology of behavioural symptoms/syndromes in PD</td>
</tr>
<tr>
<td>Mechanisms underlying behavioural symptoms/syndromes in PD</td>
</tr>
<tr>
<td>Effects of behavioural symptoms/syndromes on cognition in PD</td>
</tr>
<tr>
<td>Assessment of behavioural symptoms/syndromes in PD</td>
</tr>
</tbody>
</table>
Clinical features of Parkinson’s disease (PD)

CARDINAL MOTOR SYMPTOMS OF PD
✓ akinesia, rigidity, resting tremor, postural instability

NON-MOTOR SYMPTOMS OF PD
✓ Cognitive impairment:
  Deficits of executive & visuo-spatial functions, memory, attention, language
✓ Psychological & behavioural symptoms:
  anxiety, depression, apathy, hallucinations, delusions, impulse control disorder

✓ Olfactory dysfunction
✓ Gastrointestinal symptoms: constipation, drooling of saliva, nausea;
✓ Urinary symptoms: urgency, nocturia, increased frequency;
✓ Skin symptoms: seborrhea, hyperhidrosis
✓ Sleep disorders:
  insomnia, excessive daytime sleepiness,
  REM sleep behaviour disorder: the patient acts out his or her dreams (kicking, screaming, punching, grabbing, and even jumping out of bed)
✓ Others: pain in various body regions, fatigue
Role of cortical-basal ganglia loops in cognition and behaviour
Dorsolateral prefrontal circuit of the basal ganglia

Mainly involved in:
- executive functions:
  - planning
  - problem solving
  - set-shifting and task switching
- working memory/divided attention
- attentional control of actions

Brodmann areas 9, 10, 46
Lateral orbitofrontal circuit of the basal ganglia

Mainly involved in:
- inhibitory control of anti-social behaviours
  - aggressive behaviours
  - improper sexual behaviours
- inhibitory control of emotions
- inhibitory control of impulsive behaviours
“Limbic” circuit of the basal ganglia

Mainly involved in:

- motivational aspects of behaviour
- decision making
  - assessment of the degree of reward resulting from a given option in decision making
- social cognition/theory of mind:
  - attribution of intentions and emotions
“Limbic” circuit of the basal ganglia

- The **medial orbito-frontal cortex** and **anterior cingulate**: receive **dopaminergic projections** from neurons in the **Ventral Tegmental Area (VTA)** of the midbrain.

Such dopaminergic **mesocortical and mesolimbic pathways**: play a critical role in **motivational aspects of behaviour**.
Cognitive impairment in PD: neuropsychological features
Impairment of cognitive functions mainly implemented by the **Dorsolateral prefrontal** circuit of the basal ganglia

**Impairment of executive functions**

**• Impairment of planning:**

- difficulties in **planning** in daily living activities (DLA)
- impairment on **planning** tasks (Tower of London)

(Köstering et al., PLoS One 2012;7(6))

**• Impairment of problem-solving, set-shifting, task switching**

- difficulties in **problem-solving** and **set-shifting** in DLA
- impairment on **problem-solving/set-shifting** tasks (Wisconsin Card Sorting Test)

(Gerrits et al. Neuropsychologia 2015;68:107)

- impairment on tasks assessing **task switching**

(Cools et al., Brain 2001;2503)

**Impairment of executive functions** may **improve** with **dopaminergic drugs** and **Deep Brain Stimulation (DBS)** of the **subthalamic nucleus (STN)**, suggesting a critical role of **dopaminergic depletion** in impairment of executive functions in PD
Interplay between “frontal” cognitive functions” & axial motor symptoms (gait and postural instability) in PD

BACKGROUND:

Freezing of gait is a disabling episodic gait disturbance common in patients with Parkinson's disease. Recent evidences suggest a complex interplay between gait impairment and executive functions. Aim of our study was to evaluate whether specific motor conditions (sitting or walking) influence cognitive performance in patients with or without different types of freezing.

METHODS:

Eight healthy controls, eight patients without freezing, nine patients with levodopa-responsive and nine patients with levodopa-resistant freezing received a clinical and neuropsychological assessment during two randomly performed conditions: at rest and during walking.

RESULTS:

At rest, patients with levodopa-resistant freezing performed worse than patients without freezing on tests of phonological fluency (p = 0.01). No differences among the four groups were detected during walking.

When cognitive performances during walking were compared to the performance at rest, there was a significant decline of verbal episodic memory task (Rey Auditory Verbal Learning Test) in patients without freezing and with levodopa-responsive freezing. Interestingly, walking improved performance on the phonological fluency task in patients with levodopa-resistant freezing (p = 0.04).

CONCLUSIONS:

Compared to patients without freezing, patients with levodopa-resistant freezing perform worse when tested while seated in tasks of phonological verbal fluency. Surprisingly, gait was associated with a paradoxical improvement of phonological verbal fluency in the patients with levodopa-resistant freezing whilst walking determined a worsening of episodic memory in the other patient groups.

In a longitudinal study in PD patients treated by DBS of STN at 8-year follow-up post-surgery:

worsening of postural stability
• was significantly greater in the subgroup of patients with postoperative decline of performance (increased number of total errors) on the Modified Wisconsin Card Sorting Test (MWCST) at 8 years
• as compared to the subgroup of patients with unchanged or improved postoperative performance (number of total errors) on the MWCST at 8 years

This finding suggests that in PD patients after DBS of STN:
• a decline of executive functioning may be associated to
• a worsening of postural stability, an axial Parkinsonian motor symptom
Impairment of cognitive functions mainly implemented by the dorsolateral prefrontal cortex-basal ganglia loop

**Impairment of working memory/divided attention**

- difficulties in performing at the same time **more than on mental operations/tasks** in DLA;

- impairment on tasks assessing **working memory**
  
  (Lee et al., Brain 2010:2677-89)

- impairment on tasks of **divided attention** assessing the ability to perform **more than one mental operation at** the same time (**dual tasks/multitasking**)
  
  (Garcia Rodriguez et al., Rev Neurol. 2011 16;53:329)

**Impairment of working memory** may **improve with dopaminergic drugs**, suggesting a critical role of **dopaminergic depletion** in impairment of working memory in PD
Impairment of cognitive functions mainly implemented by the **Lateral orbitofrontal** circuit of the basal ganglia

**Impairment of inhibitory control of behavioural responses**

✓ difficulties in **inhibiting behavioural responses in DLA**, associated with possible **impulsivity**

✓ impairment on **tasks assessing inhibitory control of behavioural responses**:
  - go/no-go tasks
  - interference subtest of the Stroop test

(Bentivoglio et al., Neurol Sci 2013:1207-13)

**Impairment of inhibitory control may worsen with** DBS of STN, suggesting a critical role of STN in inhibitory control of behavioural responses
Possible role of subthalamic nucleus (STN) in inhibitory control of behavioural responses

Neuropsychological evidence:

- **impaired response inhibition** in PD patients treated by deep brain stimulation (DBS) of STN:
  - on Go/NoGo tasks: **more errors in ON stimulation** than in OFF stimulation (**difficulty in inhibiting responses to NoGo signals**)
  - associated with **reduced activation of dorsal anterior cingulate cortex (ACC)** on $^{15}$O PET

Physiological role of STN:

- **“brake”** active in inhibitory control of behaviour, preventing potentially **inappropriate responses**;

(A) in normal subjects, during decision making:

No-go signal $\rightarrow$ ACTIVATION of STN $\rightarrow$ activation (increased inhibitory activity) of GPi $\rightarrow$ reduced activity in the thalamus and cerebral cortex $\rightarrow$ suppression of execution of all responses to the signal

(B) In **PD patients** treated by STN DBS:

STN stimulation $\rightarrow$ functional inhibition of the overactivity of STN) $\rightarrow$ **impaired response inhibition** $\rightarrow$ increased “impulsivity”

Impairment of different components of memory systems

**Impairment of episodic long-term memory (LTM)**

- difficulties in **recollecting recent events** in DLA
- impairment on tasks of **episodic memory** assessing **free recall** of verbal or visual information
- in early disease stages, preserved performance on tasks of **episodic memory** assessing **forced-choice recognition** of verbal or visual information, consistent with an **impaired retrieval of information** that the subject was able to store in episodic LTM

(Costa et al., Plos One 2014 Jan 23;9)

**Impaired retrieval of information from episodic LTM** might be due to a dysfunction of **prefrontal-basal ganglia circuits** involved in the **retrieval** of information from episodic LTM

**Impairment of motor procedural memory, an implicit LTM system involving the striatum**

- difficulties in **acquiring motor skills** through practice in DLA;
- impairment on **tasks assessing learning of motor sequences**, in “non-early” disease stages

(Muslimovic et al., Brain 2007; 2887-2897)

**Impairment of motor procedural memory** might be to a dysfunction of cortico-striatal circuits involved in **motor procedural memory**
Impairment of different components of memory systems

<table>
<thead>
<tr>
<th>• Impairment of PROSPECTIVE MEMORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ difficulties in remembering an intention to carry out an action in the future, at a certain time or when a certain event occurs, in DLA;</td>
</tr>
<tr>
<td>✓ impairment on tasks assessing time-based and event-based prospective memory</td>
</tr>
</tbody>
</table>

(Costa et al, Neuropsychology, 2015 Feb 2)
Impairment of language lexical-semantic processes mainly implemented by posterior frontal cortical-basal ganglia loops

- Impairment on verbal fluency tasks:
  - impairment on tasks assessing **phonological** verbal fluency
  - impairment on tasks assessing **action** verbal fluency
  - less consistent impairment on tasks assessing **semantic** verbal fluency

(Herrera et al., Neuropsychologia 2012;636-40)

(Cooper et al, Brain 1991; 114:2095-2122)
Impairment of language lexical-semantic processes mainly implemented by posterior frontal cortical-basal ganglia loops

- **Impairment on tasks of oral production of VERBS**

  ✓ impairment on tasks in which the examiner says aloud a **verb** (e.g., “to drink”) and the subject is requested to orally produce a semantically related VERB (e.g., “to eat”);

  ✓ good performance on tasks in which the examiner says aloud a **noun** (e.g., “chair”) and the subject is requested to orally produce a semantically related NOUN (e.g., “table”)

  (Peran et al., Mov Disord 2003;18;150-156)

  ✓ impairment on tasks of **oral confrontation naming** of **verbs**, involving the presentation of pictures depicting **actions**

  (Rodriquez Ferreiro et al., Neuropsychologia 2009:3271-4)

- **Less consistent results on tasks of oral production of NOUNS**

  ✓ on tasks of oral **confrontation naming of nouns**, involving the presentation of pictures depicting **objects**:

    o impairment in some studies (Green et al., Neurology 2002; 59:1320-4)
    o normal performance in other studies (Cooper et al, Brain 1991; 114:2095-2122)
DBS in PD: studies comparing cognitive performance in “on” versus “off” STN stimulation conditions

Improved postoperative cognitive performance

**Neuropsychological tasks**

- Cognitive flexibility/executive functions:
  - (a) Wisconsin Card Sorting test
  - (b) random number generation

**Effects of STN stimulation on cognitive performance**

- Beneficial effects
  - Beneficial effects (increased accuracy, decreased RTs), more marked on *verbs*

**Putative mechanisms underlying postoperative impairment**

- STN stimulation → increased activity of Dorso-Lateral Prefrontal Cortex
  - STN stimulation → increased activity of *cortico-striatal circuits* involved in processes of selection and retrieval of lexical-semantic information

Jahaanshai et al., *Brain* 2000;123:1142-1154
Daniele et al., *J Neurol Neurosurg Psych* 2003;74:175-182
Silveri et al., *Neuropsychologia* 2012 1980-89
Impairment of visuospatial functions and time perception/estimation

- **Impairment of VISUO-SPATIAL FUNCTIONS**
  - impairment on tasks selectively assessing visuo-spatial functions, such as judgements of line orientation
    - (Green et al., 2002 Neurology:1320-1324)

  Visuo-spatial impairment might be due to a dysfunction of neural circuits involving posterior cortical areas, critical for visuo-spatial processing

- **Impairment of the PERCEPTION AND ESTIMATION OF TIME**
  - difficulties in the perception and estimation of time in DLA
  - impairment on tasks assessing perception and estimation of time
    - (Parker et al., Front Integr Neurosci 2013;7:75)

  Impairment of perception/estimation of time might be due to dysfunction of neural circuits involving the prefrontal dorsolateral cortex of the right hemisphere, critical for time processing
Subject is asked to match two angled lines to a set of 11 lines arranged in a semicircle. Lines 4 and 5 match the orientations of the lines at the top.
Occurrence of impairment of different cognitive domains in 61 non-demented patients with advanced PD, assessed for neurosurgical treatment

<table>
<thead>
<tr>
<th>Impaired cognitive domain</th>
<th>Neuropsychological task(s)</th>
<th>% of patients with impaired performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive functions and verbal fluency</td>
<td>Winsconsin Card Sorting Test: number of criteria total errors, Phonological verbal fluency</td>
<td>67% 42% 31%</td>
</tr>
<tr>
<td>Verbal episodic long-term memory</td>
<td>Learning of a word list: Delayed recall</td>
<td>30%</td>
</tr>
<tr>
<td>Language</td>
<td>Oral naming of objects (Boston Naming Test)</td>
<td>23%</td>
</tr>
<tr>
<td>Visuo-spatial functions</td>
<td>Judgements of line orientation</td>
<td>21%</td>
</tr>
</tbody>
</table>

Green et al., 2002 Neurology:1320-1324
Mild Cognitive Impairment (MCI)

• MCI defined as transitional condition between normal cognition and dementia, in which cognitive deficits have little to no impact on daily living activities.
• PD patients with MCI have a higher risk to develop Dementia, as compared to patients without MCI.

Dementia in PD (PDD)

• Dementia may occur in up to 80% of PD patients over the long term.

Prevalence of MCI in PD patients at the time of diagnosis of PD:

across different studies, prevalence of MCI may vary between 19% and 36%, according to different criteria used for diagnosis of MCI.

Need to have standardized diagnostic criteria for MCI in PD.

Hely et al., Mov Disord. 2008; 23:837–844
Diagnostic criteria of the Movement Disorder Society for PD with Dementia (PDD)

I. Core features of PDD
1. Diagnosis of Parkinson’s disease according to Queen Square Brain Bank criteria
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson’s disease and diagnosed by history, clinical, and mental examination, defined as:
   • Impairment in more than one cognitive domain
   • Representing a decline from premorbid level
   • Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

Emre et al., Mov Disorders 2007, 22;1689-1707
Diagnostic criteria of the Movement Disorder Society for PD with Dementia (PDD)

II. ASSOCIATED CLINICAL FEATURES

1. Cognitive features:
   • **Attention**: Impaired (impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day)
   • **Executive functions**: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
   • **Visuo-spatial functions**: Impaired (impairment in tasks requiring visual-spatial orientation, perception, or construction)
   • **Memory**: Impaired (impairment in free recall of recent events or in tasks requiring learning new info; memory usually improves with cueing, recognition is usually better than free recall)
   • **Language**: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present

2. Behavioral features:
   • **Apathy**: decreased spontaneity; loss of motivation, interest, and effortful behavior
   • Changes in personality and mood including **depressive features** and **anxiety**
   • **Hallucinations**: mostly visual, usually complex, formed visions of people, animals or objects
   • **Delusions**: usually paranoid (e.g., infidelities or phantom boarder (unwelcome guests at home) delusions
   • **Excessive daytime sleepiness

Emre et al., *Mov Disorders* 2007, 22;1689-1707
Diagnosis of the Movement Disorder Society for PD with mild cognitive impairment

**Inclusion Criteria**

1. **Gradual cognitive decline** reported by patient or informant or observed by clinician
2. Cognitive deficits on neuropsychological testing or a global cognitive scale
3. Cognitive impairment does not interfere significantly with functional ability

**Level I criteria** based on abbreviated assessment

Impairment on global cognitive scale validated in PD or impairment on at least 2 tests from a limited neuropsychological battery (2 or more tests per domain or 5 or more domains tested)

**Level 2 criteria** based on comprehensive assessment

Neuropsychological testing includes 2 tests within each of 5 cognitive domains (memory, attention/working memory, language, visuospatial and executive functions)

**Impairment on at least two tests**: either 2 tests within one domain or 1 test in 2 different domains;

**Impairment defined as**: a score 1 or 2 SD below appropriate norms, or significant decline on serial cognitive testing, or significant decline from estimated premorbid levels

## Diagnostic criteria of the Movement Disorder Society for PD with mild cognitive impairment (PD MCI)

### Exclusion Criteria

- Diagnosis of PDD, according to the criteria of the Movement Disorders Society;
- Other plausible explanations for cognitive deterioration (e.g., delirium, depression, medication side effects);
- Other PD-associated factors that may have a significant impact on cognitive testing (motor impairment (e.g., anxiety, sleepiness, psychosis)).

### Subtypes of MCI in PD, by comprehensive neuropsychological assessment

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Single-domain PD MCI</td>
<td>Abnormalities on <strong>two tests within a single cognitive domain</strong></td>
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<tr>
<td>Multiple-domain PD-MCI</td>
<td>Abnormalities on <strong>at least one test in two or more domains</strong></td>
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Multiple pathogenic mechanisms underlying cognitive impairment in PD
Main pathological feature of PD: degeneration of dopaminergic neurons of substantia nigra, pars compacta

**Substantia nigra pars compacta (SNC):**

- intraneuronal accumulation of Lewy bodies (inclusions mainly containing aggregated alfa-synuclein) in SNC and other structures in the brainstem
- loss of nigrostriatal dopaminergic neurons.

**Parkinsonian motor symptoms** may appear when a critical threshold of loss of nigrostriatal dopaminergic neurons is reached,

ranging in humans from a 50–60% loss (Bernheimer et al., 1973; Riederer and Wuketich, 1976) to a 31% loss (Fearnley and Lees, 1991)
Progression of intraneuronal changes (Lewy bodies) in PD: **6-stage model** of Braak and coworkers

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sites of intraneuronal changes</th>
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<tbody>
<tr>
<td>1</td>
<td>medulla oblongata: dorsal motor nucleus of IX and X nerves anterior olfactory nucleus</td>
</tr>
<tr>
<td>2</td>
<td>pons (tegmentum): serotonergic neurons in caudal raphe nuclei noradrenergic neurons in locus coeruleus</td>
</tr>
<tr>
<td>3</td>
<td>midbrain: dopaminergic neurons of the substantia nigra, pars compacta</td>
</tr>
<tr>
<td>4</td>
<td>basal forebrain: magnocellular cholinergic nuclei (medial septum, diagonal band, nucleus basalis of Meynert) temporal mesocortex: entorhinal and parahippocampal cortex</td>
</tr>
<tr>
<td>5</td>
<td>neocortex: prefrontal areas, high-order sensory associative areas</td>
</tr>
<tr>
<td>6</td>
<td>neocortex: premotor areas, first order sensory associative areas</td>
</tr>
</tbody>
</table>

Braak et al. Neurobiol Aging 2003:197-211
Neurodegeneration in serotonergic systems in PD since stage 2 of Braak and co-workers

- Significant role in depression associated to PD
- Potential role in psychotic symptoms of PD (hallucinations and delusions)
- Potential role in cognitive impairment in PD
Neurodegeneration in **noradrenergic systems** in PD since stage 2 of Braak and co-workers

- Potential role in **cognitive impairment** in PD
- Potential role in **depression** associated to PD
Neurodegeneration of dopaminergic neurons of substantia nigra, pars compacta in PD since stage 3 of Braak and co-workers

Substantia nigra pars compacta (SNc):

✓ intraneuronal accumulation of Lewy bodies (inclusions mainly containing aggregated alfa-synuclein) in SNc and other structures in the brainstem

✓ loss of nigrostriatal dopaminergic neurons.
Neurodegeneration in **basal forebrain cholinergic** nuclei in PD since stage 4 of Braak and co-workers.

- Critical role in **cognitive impairment** in PD

**Two major cholinergic projections systems:**

1. **the magnocellular basal forebrain cholinergic system**, which includes:
   - the **medial septal nucleus** (MS), the vertical and horizontal limbs of the **diagonal band** of Broca (DB), the **nucleus basalis di Meynert** (nBM).
   - The horizontal limb of the DB and nBM have diffuse projections to neocortex and projections to basolateral amygdala and olfactory bulb.
   - The MS and vertical limb of the DB project to hippocampus and entorhinal cortices.

2. **The brainstem cholinergic system** includes the **pedunculopontine tegmental nucleus** (PPT) and **laterodorsal pontine tegmentum** (LDT) and projects predominantly to the thalamus, but also to the basal forebrain region.
Neurodegeneration of entorhinal and parahippocampal cortex, since stage 4. and of the neocortex, since stages 5-6 of Braak & co-workers

Critical role of accumulation of Lewy bodies in the cerebral cortex in many PD patients with cognitive impairment

✓ strong correlation between number of cortical Lewy bodies and severity of cognitive impairment in PD patients

(Aarsland et al., Ann Neurol. 2005;58;773-776)
Beta-amyloid plaques and neurofibrillary tangles accumulation in cerebral cortex and cognitive impairment in PD

Critical **role of** accumulation beta-amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex in cognitive impairment: in a subgroup of patients with PD

✓ **Strong correlation** between number of plaques and tangles and severity of cognitive impairment in PD patients

(Compta et al., Brain. 2011;1493-1505)
Premotor symptoms in Parkinson’s disease:

• Olfactory dysfunction
• Constipation
• Rapid Eye Movement (REM) sleep behaviour disorder:

• Psychological symptoms:
  ✓ Depression
  ✓ Anxiety

• Cognitive symptoms:
  ✓ slight difficulties in attention?
  ✓ slight difficulties in planning or problem solving?
Motor and non-motor symptoms across disease progression of PD

- **Only premotor symptoms**
  - olfactory dysfunction
  - autonomic symptoms: constipation
  - sleep disorders: REM sleep behaviour disorder
  - cognitive symptoms
  - behavioural symptoms: depression and anxiety

- **Motor symptoms** + possible **non-motor symptoms** (NMS), including early cognitive and behavioural symptoms

- **Motor symptoms** + **MCI** & behavioural symptoms + other NMS

- **Motor symptoms** + **DEMENTIA** & behavioural symptoms + other NMS
Thanks to……

Istituto di Neurologia, Università Cattolica, Roma

Anna Rita Bentivoglio
Carla Piano
Francesco Bove
Chiara Piccininni

M. Caterina Silveri
Nicoletta Ciccarelli
Eleonora Baldonero

Istituto di Neurochirurgia, Università Cattolica, Roma

Beatrice Cioni

Clinica Neurochirurgica, Università di Ancona

Massimo Scerrati

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Università Cattolica, Milano

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. Luciana Ricciardi
Clinical features in PD, dementia with Lewy bodies, Alzheimer’s disease

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>DLB</th>
<th>AD</th>
</tr>
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<tbody>
<tr>
<td>Dementia</td>
<td>Later onset, usually 1 year after parkinsonism onset. Less prominent than DLB &amp; AD</td>
<td>Earlier compared to PD, less than a year after parkinsonism. Compared to AD, visuospatial and visual memory more severe.</td>
<td>Prominent features</td>
</tr>
<tr>
<td>Fluctuation of cognitive impairment</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Visual Hallucination</td>
<td>Not common</td>
<td>Common, usually non-threatening and insight remain.</td>
<td>Not common</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Prominent features</td>
<td>Relatively mild, rarely asymmetry, tremor not prominent</td>
<td>Rarely present</td>
</tr>
</tbody>
</table>
Hyperdopaminergic and hypodopaminergic behavioural disorders in PD

Hyperdopaminergic behavioural disorders in PD:
- mania
- ICDs: pathological gambling, compulsive shopping and eating, hypersexuality
- dopamine dysregulation syndrome:
  overuse of dopaminergic drugs
- punding: repetitive, non-goal-oriented activities

- Assumption of high doses of dopaminergic drugs/abnormal sensitization of dopaminergic mesocorticolimbic system

Hypodopaminergic behavioural disorders in PD:
- depression
- apathy
- anxiety

- withdrawal of dopaminergic drugs/reduced activity of dopaminergic mesocorticolimbic system

Aarsland et al., Mov Disord 2009; 24: 2175-86; Ardouin et al., Rev Neurol, 2009;165: 845-56.

Mesolimbic dopamine (DA) system in the rat highlighting the inputs to nucleus accumbens (NAc) and ventral tegmental area (VTA) (glutamatergic excitatory projections, blue; dopaminergic projections, red; GABAergic inhibitory projections, orange; orexinergic projections, green). The release of DA from VTA neurons increases in response to all drugs of abuse. VTA neurons also fire in response to novelty and their firing patterns may encode a prediction signalling the reward value of a stimulus relative to its expected value: PFC, prefrontal cortex; VP, ventral pallidum; AMG, amygdala; BNST, bed nucleus of the stria terminalis; LDTg, laterodorsal tegmental nucleus; LH, lateral hypothalamus;
**COGNITION**

- **Comparisons** between preoperative and postoperative cognitive assessments in 16 (out of 20 consecutive) PD patients treated by bilateral DBS of STN with **8-year follow-up**:
  - significant postoperative decline on a phonological verbal fluency task (F,A,S);
  - mild postoperative decline on Raven’s Matrices’47, Rey’s Auditory Verbal Learning Test (immediate & delayed recall), Modified Wisconsin Card Sorting Test (number of correct criteria).
- Only 1 patient out of 20 (5%) developed Dementia 5 years after surgery, with progression at 8 years.

**BEHAVIOUR**

- **Transient behavioural disorders**: mania (15%), apathy (10%)
- **Persistent behavioural disorders**: depression (25%), apathy (20%).
- In the overall group of 16 patients, no significant postoperative change on the Zung’s Depression and Anxiety scales, as compared to preoperative baseline.

---

**Table 3 Results obtained on cognitive and behavioural variables in patients at baseline and at 5- and 8-year follow-up**

<table>
<thead>
<tr>
<th>Test (range)</th>
<th>Baseline</th>
<th>5 years</th>
<th>Variation versus baseline (%)</th>
<th>8 years</th>
<th>Variation versus baseline (%)</th>
<th>Variation versus 5 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE (0–30)</td>
<td>26.7 ± 2.7</td>
<td>27.1 ± 2.4</td>
<td>+0.5*</td>
<td>25.7 ± 4.3</td>
<td>-4.2</td>
<td>-5.4</td>
</tr>
<tr>
<td>RPM ’47 (0–36)</td>
<td>28.4 ± 5.2</td>
<td>26.2 ± 5.7</td>
<td>-11.6*</td>
<td>25.7 ± 6.4</td>
<td>-15.0*</td>
<td>-4.4</td>
</tr>
<tr>
<td>RAVLT: immediate recall (0–75)</td>
<td>39.5 ± 12.6</td>
<td>37.0 ± 14.2</td>
<td>-7.1</td>
<td>30.6 ± 10.9</td>
<td>-18.5*</td>
<td>-19.0*</td>
</tr>
<tr>
<td>RAVLT: delayed recall (0–15)</td>
<td>8.6 ± 3.9</td>
<td>7.7 ± 3.8</td>
<td>-18.3*</td>
<td>5.9 ± 3.3</td>
<td>-26.2*</td>
<td>-12.8</td>
</tr>
<tr>
<td>Digit span forward</td>
<td>5.6 ± 1.0</td>
<td>5.3 ± 1.1</td>
<td>-5.7</td>
<td>5.1 ± 1.1</td>
<td>-6.9</td>
<td>-0.02</td>
</tr>
<tr>
<td>Digit span backward</td>
<td>3.75 ± 0.9</td>
<td>3.8 ± 1.8</td>
<td>-2.5</td>
<td>3.6 ± 1.2</td>
<td>-3.6</td>
<td>-0.7</td>
</tr>
<tr>
<td>Corsi’s span forward</td>
<td>4.7 ± 1.1</td>
<td>4.6 ± 1.0</td>
<td>-4.8</td>
<td>4.3 ± 0.9</td>
<td>-2.4</td>
<td>-0.7</td>
</tr>
<tr>
<td>Corsi’s span backward</td>
<td>4.1 ± 1.2</td>
<td>3.5 ± 1.1</td>
<td>-10.3</td>
<td>3.7 ± 1.0</td>
<td>-8.6</td>
<td>+14</td>
</tr>
<tr>
<td>Letter verbal fluency</td>
<td>32.4 ± 13.1</td>
<td>23.5 ± 8.6</td>
<td>-30.7*</td>
<td>21.3 ± 8.8</td>
<td>-29.8*</td>
<td>+3.8</td>
</tr>
<tr>
<td>MWCST: correct criteria (0–6)</td>
<td>4.7 ± 1.7</td>
<td>4.0 ± 1.8</td>
<td>-4.6</td>
<td>3.4 ± 2.1</td>
<td>-24.5*</td>
<td>-20.5</td>
</tr>
<tr>
<td>MWCST: total errors (0–48)</td>
<td>11.1 ± 11.2</td>
<td>14.2 ± 9.9</td>
<td>-79.8</td>
<td>17.4 ± 12.7</td>
<td>+194.8</td>
<td>+96.5</td>
</tr>
<tr>
<td>MWCST: perseverative errors (0–48)</td>
<td>5.7 ± 4.3</td>
<td>4.4 ± 4.9</td>
<td>-30.5</td>
<td>6.6 ± 6.0</td>
<td>+61.0</td>
<td>+123.3</td>
</tr>
<tr>
<td>Zung's depression scale (20–80)</td>
<td>46.7 ± 8.5</td>
<td>43.3 ± 11.0</td>
<td>3.9 ± 12.2</td>
<td>39.7 ± 12.2</td>
<td>3.4 ± 11.0</td>
<td>-20.5</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*P < 0.05; **P < 0.01.

MMSE = Mini Mental State Examination.
epIDEMIOLOGIA DISTURBI COGNITIVI

- Fattori rischio:
- Citare GBA e paper nostro editoriale su disturbi di memoria visiva
<table>
<thead>
<tr>
<th>“Patogenesi disturbi cognitivi”)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMPAIREDMENT OF EXECUTIVE FUNCTIONS AND WORKING MEMORY:</strong></td>
</tr>
<tr>
<td>• difficulties in planning, problem-solving, set-shifting and task-switching</td>
</tr>
<tr>
<td>• difficulties in performing simultaneously two or more mental operations</td>
</tr>
<tr>
<td>Dysfunction of <strong>dorsolateral prefrontal</strong>-basal ganglia loops due to dopaminergic depletion; Possible improvement with dopaminergic drugs…and DBS..</td>
</tr>
<tr>
<td><strong>IMPAIREDMENT OF EPISODIC LONG-TERM MEMORY (LTM)</strong></td>
</tr>
<tr>
<td>• difficulties in recollecting recent events an on tasks assessing free recall of verbal or visual information</td>
</tr>
<tr>
<td>Dysfunction of prefrontal circuits involved in retrieval of information from LTM</td>
</tr>
<tr>
<td><strong>IMPAIREDMENT OF VISUO-SPATIAL ABILITIES</strong></td>
</tr>
<tr>
<td>• difficulties on visuo-spatial tasks such as judgements of line orientation.</td>
</tr>
<tr>
<td>Dysfunction of posterior cortical areas</td>
</tr>
<tr>
<td><strong>IMPAIREDMENT OF SPECIFIC LANGUAGE ABILITIES</strong></td>
</tr>
<tr>
<td>• difficulties in word-finding and on specific language tasks, such as verbal fluency and naming of verbs</td>
</tr>
<tr>
<td>Dysfunction of posterior frontal cortical areas–basal ganglia loops</td>
</tr>
</tbody>
</table>
Calabresi
• CITARE FUINZIONI COGNITIVI CHE MIGLIORANO E PEGGIORANO CON L-DOPA (VEDI PEWSCCOSTANZO)
PDD diagnostic criteria (Emtre 2007, poi Dubois 2007)

dementia, can occur in up to 80% of PD patients over the long term. Ref 2–4 di Litvan 2012

• Epidemiologia: vedi emre 2007
Dementia in PD (PDD). epidemiology

• Vedi pagonabarraga 2012
PDD: pathogenesis

Da paèer under review

- Mild cognitive impairment in PD (PDMCI) is present in a significant proportion of patients even in early disease [1], and may represent a risk factor for the future development of PDD. The underlying pathophysiology of cognitive decline in PD is complex and may vary between individuals, but is likely to involve Lewy body (LB) deposition and amyloid-β plus tau accumulation [2]. Furthermore, there is evidence from imaging,
- neuropathological and neurophysiological studies that cholinergic dysfunction may contribute [3, 4]

- Vedi qualcosa Svenningson 2012p. 698
Effects of dopaminergic treatment on cognition in patients with Parkinson’s disease
Effects of dopaminergic drugs on **cognitive functions** in PD: effects of chronic treatment with **pergolide** and **levodopa** in de novo PD

**Aim of the study:**

to assess in **20 de novo PD patients**
the effects on cognitive performance of chronic treatment with **l-dopa** (acting on D1 and D2 receptors) and **pergolide** (preferential D2, but also D1 agonist)

**Study design**

10 pts:

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Pergolide months 0-6</th>
<th>Pergolide+ levodopa months 7-24</th>
</tr>
</thead>
</table>

10 pts:

<table>
<thead>
<tr>
<th>Baseline</th>
<th><strong>Levodopa monotherapy</strong> months 0-24</th>
</tr>
</thead>
</table>

**Neuropsychological assessments:**

- Off-medication baseline
- On-medication: 3, 6, 12, 18, 24 months after baseline

**Results:**

- **No significant effect** of anti-PD drugs on:
  - visual and verbal short-term memory tasks;
  - Stroop test
- Both **l-dopa** and **pergolide** significantly improved cognitive performance (compared to baseline) up to 12-18 months on
  - verbal and visual **long-term memory tasks**;
  - **copy of a drawing** task;
  - **phonological & semantic verbal fluency**

<table>
<thead>
<tr>
<th></th>
<th>Phonological F.</th>
<th>Semantic F.</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>l-dopa</td>
<td>19.7 (9.0)</td>
<td>42.8 (7.9)</td>
</tr>
<tr>
<td>pergolide</td>
<td>19.4 (13.0)</td>
<td>46.7 (14.3)</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>l-dopa</td>
<td>26.3 (9.7)</td>
<td>48.4 (8.3)</td>
</tr>
<tr>
<td>pergolide</td>
<td>24.1 (17.0)</td>
<td>50.7 (15.1)</td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>l-dopa</td>
<td>24.1 (7.9)</td>
<td>48.4 (7.8)</td>
</tr>
<tr>
<td>pergolide</td>
<td>23.0 (13.1)</td>
<td>50.0 (13.1)</td>
</tr>
</tbody>
</table>

Kulisevsky et al., Mov. Disord.2000; 15;613-626
Effects of dopaminergic drugs on **cognitive functions** in PD: effects of treatment with **levodopa** and **pramipexole** in mild PD

**Aim of the study:**
to assess in **20 mild PD patients** the effects on cognitive performance of treatment with **l-dopa** and **pramipexole**

**Study design:**
10 pts

<table>
<thead>
<tr>
<th></th>
<th>Phonolog.</th>
<th>Semantic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>28.9 (10.4)</td>
<td>13.7 (2.7)</td>
</tr>
<tr>
<td>levodopa months 1-2</td>
<td>29.8 (6.8)</td>
<td>16.1 (2.4)</td>
</tr>
<tr>
<td>pramipexole months 3-4</td>
<td>26.9 (7.6)</td>
<td>13.0 (4.3)</td>
</tr>
</tbody>
</table>

**Neuropsychological assessments:**
- **off medication** baseline, after a **wash-out**
- **on medication**, 2 and 4 months after baseline

**Results:**
- As compared to baseline:
  - after **pramipexole**, significant **worsening** on tasks of **short-term memory** and **attention**;
  - after **levodopa**, slight non-significant improvement on **verbal fluency** tasks and on the Stroop test.

**Conclusions:**
**Pramipexole**, DA agonist with selective affinity only for the D2-like (D2, D3, D4) family of DA receptors, unlike levodopa, may slightly impair cognitive functioning in PD

Brusa et al., *J. Neural Transm.* 2003; 110:373-380
Effects of dopaminergic drugs on cognitive functions in PD: effects of treatment with levodopa, rotigotine and cabergoline in mild PD

**Aim of the study:**

to assess in 40 mild PD patients the effects of treatment with l-dopa, rotigotine and cabergoline

**Study design:**

20 pts

<table>
<thead>
<tr>
<th>Baseline</th>
<th>levodopa (n =20) months 1-3</th>
<th>rotigotine (n=10) or pergolide (n =10) months 4-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 pts</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline</th>
<th>rotigotine (n=10) or pergolide (n =10) months 1-3</th>
<th>Levodopa (n =20) months 4-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 pts</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Neuropsychological assessments:**

*off medication* baseline: (after a wash-out)

*on medication*: 3 and 6 months after baseline

**Results:**

- on all tasks, no significant difference between *off-medication* baseline and *on-medications* conditions with levodopa, rotigotine, cabergoline

- on a phonological verbal fluency task: slight non-significant improvement after levodopa and rotigotine.

<table>
<thead>
<tr>
<th></th>
<th>Phonolog.</th>
<th>Semantic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>30.0 (11.4)</td>
<td>16.8 (5.7)</td>
</tr>
<tr>
<td>levodopa</td>
<td>36.7 (12.4)</td>
<td>17.4 (6.0)</td>
</tr>
<tr>
<td>rotigotine</td>
<td>35.0 (7.8)</td>
<td>18.8 (5.3)</td>
</tr>
</tbody>
</table>

**Conclusions:**

Drugs that act on both D1-like (D1, D5) and D2-like (D2, D3, D4) families of DA receptors do not impair cognitive functioning

Brusa et al., *Funct Neurol* 2013; 28;13-17
Effects of dopaminergic drugs on cognitive functions in PD: effects of short-term withdrawal of levodopa in moderate-to-severe PD

Aim of the study:

• to assess cognitive performance in 16 moderate-to-severe PD in 2 conditions, 6-7 weeks apart:
  ✓ on-medication optimal treatment with levodopa
  ✓ off-medication after 10-15 hours of levodopa withdrawal

Results:

• only on a language task of oral confrontation naming of nouns (Boston Naming task):
  slightly but significantly worse performance in on-medication, as compared to off-medication condition;
• on the remaining neuropsychological variables, no significant difference between the 2 conditions.

Conclusions:

in moderate-severe PD, both the administration and the withdrawal of levodopa may have no significant impact on cognitive functioning.

Morris et al., J. Neural Transm. 2004; 111; 1333-1341
Variable effects of dopaminergic drugs on cognitive functions in PD!!

- **Dopaminergic drugs** may have different effects (beneficial, detrimental, no change) on cognitive performance in PD patient, depending on several factors:
  - their action on specific **subtypes of dopamine receptors**
  - and the **kind of task/cognitive function** under investigation:
    - e.g.: the activation of **D2 receptors** may result in improved performance on tasks of set-switching (cognitive flexibility)
  - **individual variability:**
    - across **different individuals**, different effects on performance on the **same cognitive task** in the same study.

- **Large individual variability** across PD patients in performance on a given cognitive task may in turn depend on various factors:
  - **individual differences** in the **basal levels of dopaminergic function** in **cortico-striatal loops** involved in the task:
    - both **insufficient and excessive** (after DA drugs) levels of **dopaminergic function** may impair cognitive performance;
    - **baseline levels of dopaminergic function** in different **circuits** depend on
      - disease stage in PD patients
      - genetic factors (e.g. polymorphisms in dopamine transporter gene) in both PD patients and healthy controls;
  - **individual differences in anatomical connectivity** between critical structures (prefrontal cortex, thalamus, striatum) in **cortico-striatal loops**, that can be measured by **Diffusor Tensor imaging (DTI)**
treatment

- Srtudio pivamserin, in cui in inytropduzione si fa riepiologos su studi antipsicotici in AD
- Per Dememnza, vedi Emre 2014

- Broadstock M1, Ballard C, Corbett A.
- Author information
- Abstract
Parkinson's disease (PD) affects 10 million people worldwide. Half will develop psychosis, the majority experiencing hallucinations rather than delusions. Emergence of psychosis increases the likelihood of institutionalization and mortality. Where pharmacological treatment is warranted, options are limited. Most currently licensed atypical antipsychotics are ineffective or worsen motor symptoms in people with PD. This review of provides an overview of the current landscape of treatments and the opportunities in emerging research. Clozapine is the only licensed antipsychotic with proven efficacy, although the associated side effects limit its use. With recent advances in understanding the role of serotonin, rational drug design approaches have delivered a novel pharmacological treatment with recently proven efficacy in clinical trials of people with PD and psychosis. Pimavanserin represents an important addition to treatment.

- KEYWORDS:
- Parkinson’s disease; hallucinations; psychosis; treatment; trials
Impulse control disorders (ICDs) in PD

Clinical features:
- Pathological gambling
- Hypersexuality
- Compulsive eating
- Compulsive buying/shopping

Overall prevalence:
- up to 13.6% in unselected PD populations

Risk factors for ICDs in PD:
- male gender
- young age of PD onset
- treatment with dopamine agonists
- pre-existing psychiatric disorders

Main pathogenic mechanism:
overstimulation of mesolimbic dopaminergic system induced by dopamine replacement therapy
Progression of PD-related intraneuronal pathology
Cognitive impairment in PD-1

Impairment of executive functions, working memory/divided attention

- Impairment of **PLANNING:**
  - difficulties in **planning** in daily living activities (DLA)
  - impairment on **planning** tasks (Tower of London)

  (Köstering et al., PLoS One 2012;7(6))

- Impairment of **PROBLEM-SOLVING, SET-SHIFTING, TASK SWITCHING**
  - difficulties in **problem-solving** and **set-shifting** in DLA
  - impairment on **problem-solving/set-shifting** tasks (Wisconsin Card Sorting Test)

  (Gerrits et al. Neuropsychologia 2015;68:107)

- Impairment of **working memory/divided attention**
  - difficulties in performing at the same time **more than on mental operations/tasks** in DLA;
  - impairment on tasks assessing **working memory**

  (Lee et al., Brain 2010;2677-89).

  - impairment on tasks assessing the ability to perform **more than one mental operation** at the same time (**dual tasks/multitasking**)

  (Garcia Rodriguez et al., Rev Neurol. 2011 Sep 16;53(6):329-3)
# Cognitive impairment in PD-2

## Impairment of inhibitory control of behavioural responses

- difficulties in withholding behavioural responses/impulsivity in DLA
- impairment on tasks assessing inhibitory control of behavioural responses:
  - Go/no-go tasks, interference subtest of the Stroop test

(Bentivoglio et al., Neurol Sci 2013:1207-13)

## Impairment of episodic long-term memory (LTM)

- difficulties in recollecting recent events in DLA
- impairment on tasks of episodic memory assessing free recall of verbal or visual information
- in early disease stages, preserved performance on tasks of episodic memory assessing forced-choice recognition of verbal or visual information, consistent with an impaired retrieval of information that the subject was able to store in LTM

(Costa et al., Plos One2014 Jan 23;9)

## Impairment of motor procedural memory, a component of implicit LTM involving striatum

- difficulties in acquiring motor skills through practice in DLA;
- impairment on tasks assessing learning of motor sequences, in “non-early” disease stages

(Muslimovic et al., Brain 2007; 2887-2897)
## Cognitive impairment in PD-3

### Impairment of PROSPECTIVE MEMORY
- **difficulties in remembering an intention to carry out an action in the future, at a certain time** or when a certain event occurs, in DLA;
- Impairment on tasks assessing time-based and event-based prospective memory (Costa et al, Neuropsychology, 2015 Feb 2)

### Impairment of the PERCEPTION AND ESTIMATION OF TIME
- **difficulties in the perception and estimation of time** in DLA
- Impairment on tasks assessing perception and estimation of time
  (Parker et al., Front Integr Neurosci 2013;7:75)

### Impairment of VISUO-SPATIAL FUNCTIONS
- Impairment on tasks selectively assessing visuo-spatial functions, such as judgements of line orientation
  (Green et al., 2002 Neurology:1320-1324)
“Limbic” circuit of the basal ganglia

The **medial orbito-frontal cortex** and **anterior cingulate**:  
- receive **dopaminergic projections** from neurons in the **Ventral Tegmental Area (VTA)** of the midbrain

Such dopaminergic **mesocortical and mesolimbic projections** play a critical role in **motivational aspects of behaviour**.

Dopaminergic pathways:  
a = nigrostriatal, b = mesocortical, c = mesolimbic; d = tubero-infundibolar
Figure 1 - Frontal-striatal connections.

DL: dorsolateral; DM: dorsomedial; VL: ventrolateral; VA: ventroanterior; VM: ventromedial.