Updates in Cognitive and Other Non-Motor Symptoms in PD

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AMDAPP

Association of Movement Disorder Advanced Practice Providers

Arita McCoy – Relevant Financial Relationships

- Speakers' Bureau, consultant, and/or advisory board member for Mitsubishi Tanabe Pharma America.

All relevant financial relationships have been mitigated

Objectives

- Briefly define and review non-motor symptoms in PD
- Focused discussion on cognitive disorders, psychosis and apathy in PD
- Review management and treatment options

What is a Non-Motor Symptom?

- **Non-motor** symptoms of Parkinson's disease (PD) refer to those symptoms which don't affect movement, coordination or mobility (Parkinson's Foundation, 2024).
- Major determinant of **quality of life**, progression of **overall disability**, **hospitalization** and **nursing home placement.**

Thought to arise from **neuron degeneration** in widespread areas of the brain

What is a Non-Motor Symptom?

- Although these symptoms cannot be "seen", they can be **more problematic** for some PD patients than motor signs

- Part of the **"salad bar"** mentality of the disease - no two patients are alike

- Symptoms **may or may not** have an effective treatment

- Select few occur **before** the diagnosis of PD

How do they present?

- Can be categorized in 4 areas:
  - Dysautonomia
  - Sleep Abnormalities
  - **Mood Changes**
  - **Cognitive Issues**
- May arise during different times throughout the trajectory of PD

Cognitive Disorders in PD

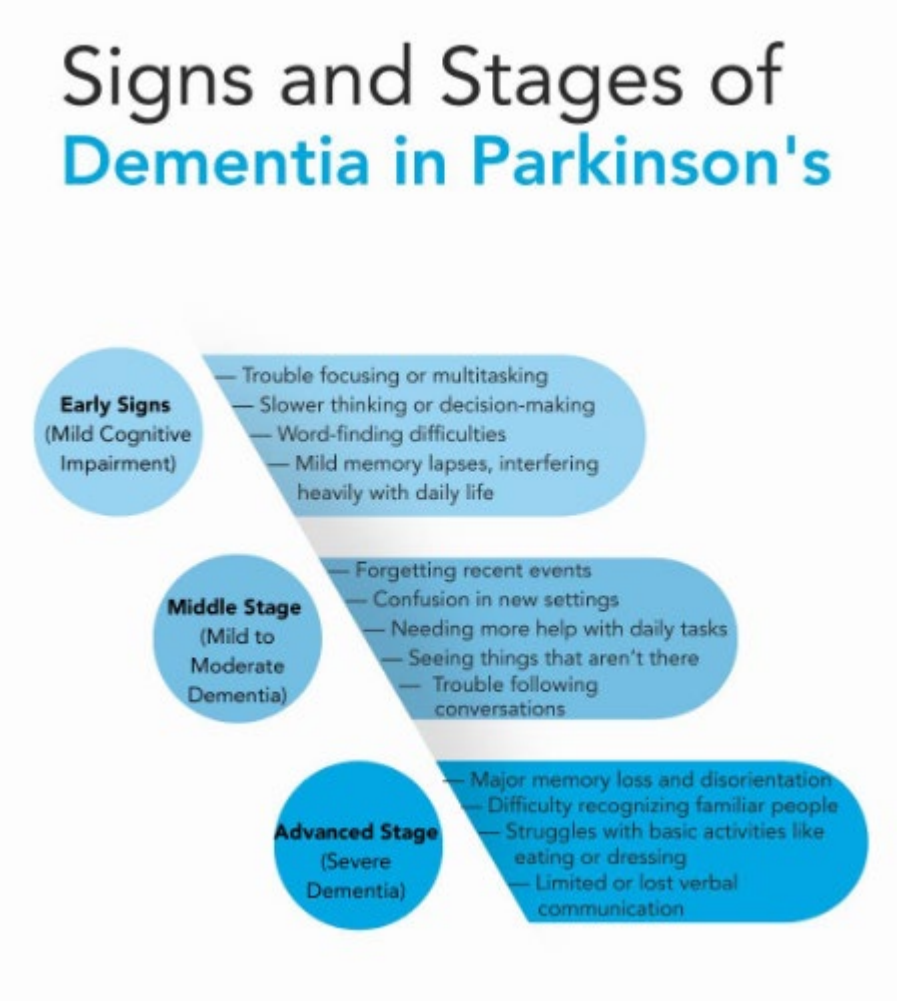
Cognitive Disorders in PD

• Cognitive disorders and dementia can be thought of as occurring on a continuum

• Cognitive disorders and mild cognitive impairment generally affect **narrow aspects** of memory and thinking abilities, conversely dementia affects intellect **more globally** and often impairs one's ability to function independently.

• Thought to be secondary to involvement of limbic/neocortical brain regions with known deficits in acetylcholine and dopamine transmission

• Movement Disorder Society defines dementia as a decline in **>1 cognitive domain** that **impairs daily functionality** and lasts for at least **6 months**.



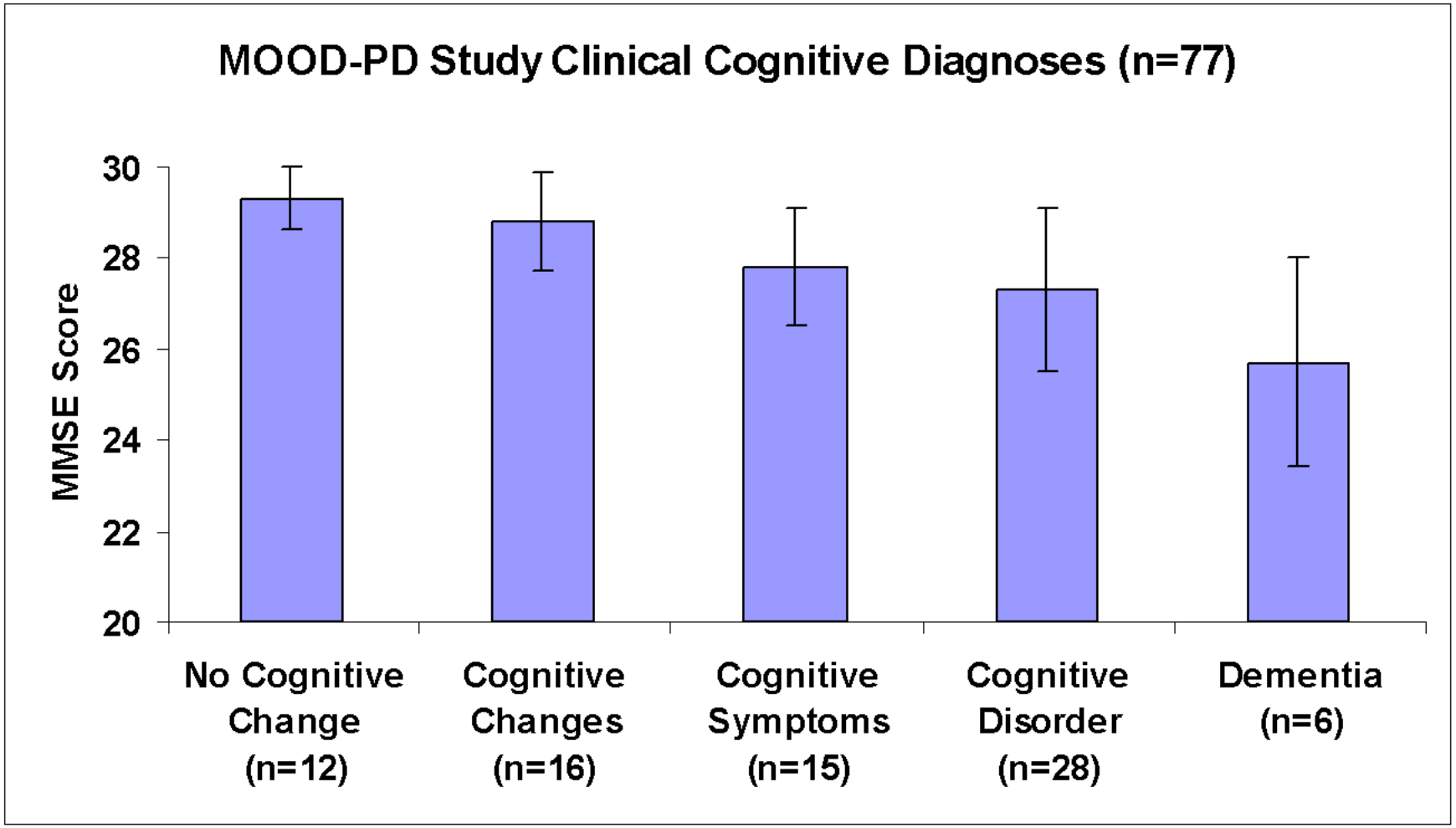
Photopharmics, Celeste Light for PD. University of Rochester, 2025

Cognitive Disorders Typical of PD

- Executive dysfunction
  - •Involves disruption of ‘higher order’ mental processes such as planning, focusing, organizing and sequencing
  - •Ability to efficiently shift from one task to another and the ability to multi-task are often impaired
- Language and speech changes
  - Word finding difficulties
  - Bradyphrenia
  - Dysarthria contributes to reduced communication
- Memory, attention and comprehension deficits
  - Short term memory loss
  - Working memory changes
  - Intellectual processing speed reduction
    - ▪May cause conversation withdrawal or carepartners to step in sooner

Cognitive Disorders in PD

Range of Cognitive Dysfunction in PD patients with 'normal' MMSE (≥24)



25 Women, 52 Men
Mean (SD) Age=68.6 (10.2); Duration PD=7.6 (5.8)

Cognitive Disorders in PD

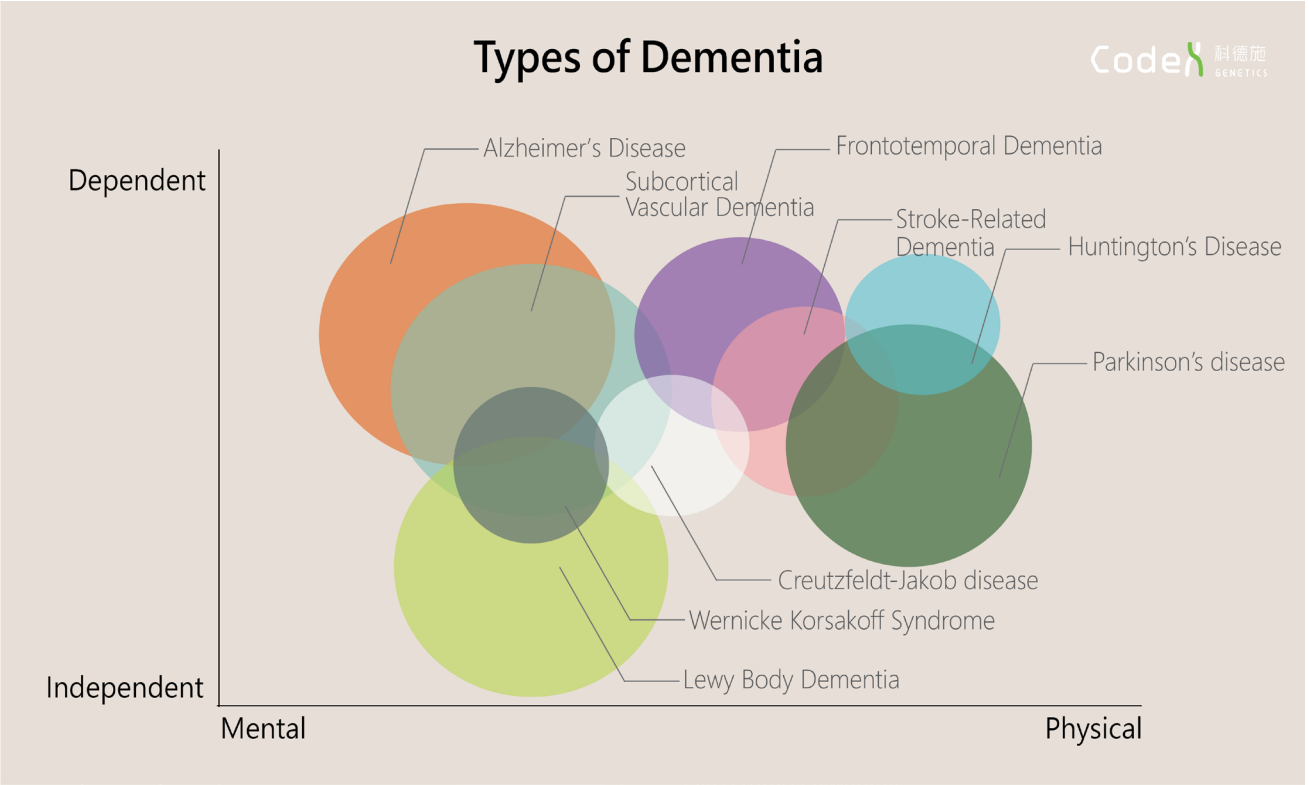
- 24%-36% of PD patients without dementia had some form of cognitive deficit.

- The relative risk of developing dementia in PD is up to 6 times greater than in the general population.

- Factors associated with increased risk of dementia include older age and more severe motor symptoms.

Cognitive Disorders in PD

- Multifaceted pathophysiology is also possible, which can complicate treatment and require several strategies for treatment.
- As in general dementia, mixed pathology is most common in PD
  - Lewy Body, vascular, Alzheimer's origins should not be excluded



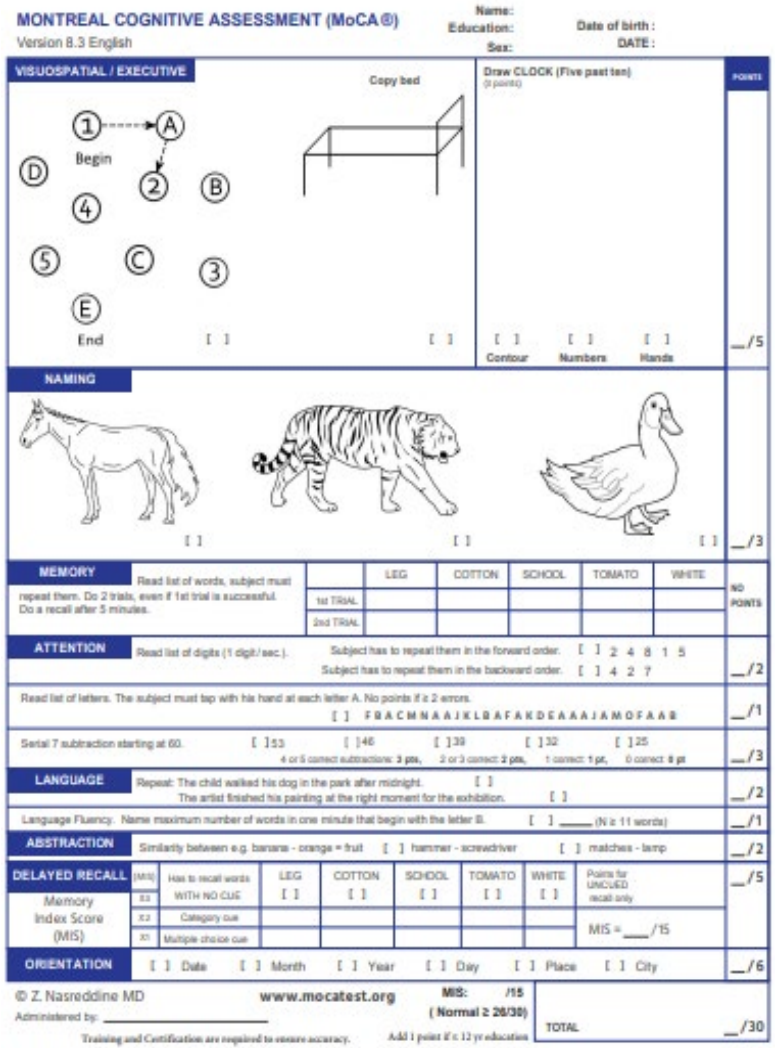
Codex Genetics, 2020. https://www.codexgenetics.com/blog/en/Understanding-Different-Types-of-Dementia

Evaluation of Cognitive Disorders in PD

- MoCA is most utilized general tool in clinic setting to evaluate cognition
  - <26/30: PD-MCI
  - <21/30: PDD
  - Evaluates attention, fluency, memory, naming, orientation, verbal repetition, visuospatial/executive function

- Evaluate acuity/duration of symptoms
  - Presence of orthostatic hypotension
    - Affects executive function, memory and visuospatial function and can be chronic or fluctuate
  - Recent medication adjustments (anticholinergics, gabapentinoids, benzodiazepines, opiates)
  - Evaluate for thyroid/vitamin deficiencies and sleep disorders (RBD, RLS, OSA)
  - Mood history (untreated or uncontrolled anxiety/depression)

- Neuropsychological Evaluation
  - Comprehensive assessment considering performance, intellect, emotional/behavioral health, contributing source observation and medical history
  - Evaluates multiple types of cognitive impairment and tease out likelihood of mixed pathologies
  - Develops appropriate treatment recommendations/strategies


MONTREAL COGNITIVE ASSESSMENT (MoCA®)

Version 8.3 English

Name:
Education:
Sex:
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — Copy bed — Draw CLOCK (Five past ten) — POINTS

Begin — End — Contour — Numbers — Hands — /5

NAMING — /3

MEMORY — Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes. — FACE VELVET CHURCH DAISY RED — 1st TRIAL — 2nd TRIAL — NO POINTS

ATTENTION — Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order. 2 1 8 5 4. Subject has to repeat them in the backward order. 7 4 2. — /2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors. F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — /1

Serial 7 subtraction starting at 60. 53 — 46 — 39 — 32 — 25. 4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt — /3

LANGUAGE — Repeat: The child walked his dog in the park after midnight. The artist finished his painting at the right moment for the exhibition. — /2

Language Fluency. Name maximum number of words in one minute that begin with the letter B. ____ (N ≥ 11 words) — /1

ABSTRACTION — Similarity between e.g. banana - orange = fruit. train - scooter. watch - ruler. — /2

DELAYED RECALL — Memory Index Score (MIS) — Has to recall words WITH NO CUE. Category cue. Multiple choice cue. LEG. COTTON. SCHOOL. TOMATO. WHITE. Points for UNCUED recall only. MIS = ___/15 — /5

ORIENTATION — Date. Month. Year. Day. Place. City — /6

© Z. Nasreddine MD — www.mocatest.org — MIS: /15 (Normal ≥ 26/30) — Administered by: _____ — Training and Certification are required to ensure accuracy. — Add 1 point if ≤ 12 yr education — TOTAL — /30

Treatment of Cognitive Disorders in PD

- Adaptive strategies
  - Paramount importance to start patterns of keeping notes, calendar use, pill box or packaging for medications
- Regular physical exercise
  - Positively affects processing speed in a dose-dependent matter (Patino and Mahajan, 2025)
  - Stretching, breathing, balance exercises and strength training improve attention and working memory
- Cognitive exercises
  - Adaptive apps, reading/audiobooks, puzzles, etc.
- Speech and music therapy
  - Inclusion of cognitive exercises
- Multimodal Approach
  - Recent evidence supports combining cognitive training with other modalities is best practice
    - Exercise with cognitive training enhances global, memory, visuospatial and executive functioning
    - Transcranial direct current stimulation (tDCS) may improve attention and executive function (Mantovani et al., 2024)

Treatment of Cognitive Disorders in PD

Pharmacologic treatment

- The strongest evidence for treatment of dementia in PD is with cholinesterase inhibitors.
- Rivastigmine is the only medication approved by the US Food and Drug Administration for treatment of dementia in PD
- Oral and patch formulations provide flexibility for those with dysphagia/side effects from oral administration
- Monitor GI side effects (nausea, weight loss)
- Possible antihypotensive effect (Patino & Mahajan, 2025)

TABLE 3. COMMONLY USED MEDICATIONS FOR THE MANAGEMENT OF DEMENTIA IN PARKINSON DISEASE

	Mechanism of action	Dosage, mg/d	Evidence	Common side effects	Approximate cost[a]
Donepezil	Cholinesterase inhibitor	5–10	Did not meet primary end point (ADAS-Cog); improved MMSE and CIBIC+ (only 10 mg)[33]	Nausea, vomiting, diarrhea, insomnia	$13.7 for 5 or 10 mg (30 tablets)
Rivastigmine	Cholinesterase inhibitor	Capsule, 3–12; patch, 4.6–13.3 (5-15 cm2/d)	Moderate improvement in ADAS-Cog compared with placebo[25]	Nausea, vomiting, diarrhea, loss of appetite, dizziness, tremor	$39.4 for 1.5 mg (60 capsules), $358.87 for 4.6 mg (30 patches)
Galantamine	Cholinesterase inhibitor and ligand for nicotinic acetylcholine receptors	8–16	One uncontrolled study did not meet primary end point (MMSE)[34]; 1 controlled study met primary end points (ADAS-Cog and MMSE)[35]	Nausea, diarrhea, sialorrhea, postural hypotension	$60.2 for 8, 16, or 24 mg (30 capsules)
Memantine	NMDA receptor antagonist	5–20	Significant improvement on CGIC and AQT[36]; improvement in attention and episodic recognition memory per CRT[37]	Dizziness, fatigue, fall	$26.8 for 5 mg (30 tablets)

[a]As reported by Drugs.com in 2025. Cost varies by region and could be lower when using coupons.
Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale–cognitive subscale; AQT, A Quick Test of Cognitive Speed; CIBIC+, Clinician's Interview-Based Impression of Change plus caregiver input; CGIC, Clinical Global Impression of Change; CRT, Choice Reaction Time; MMSE, Mini-Mental State Examination; NMDA, N-methyl-D-aspartate.
Data from references 25, 33, 35-37.

Patino J, Mahajan A. Diagnosis and management of dementia in individuals with Parkinson disease. Practical Neurology (US). 2025;24(7):26-29,36,37.

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Psychiatric Disorders

Psychiatric Disorders in PD

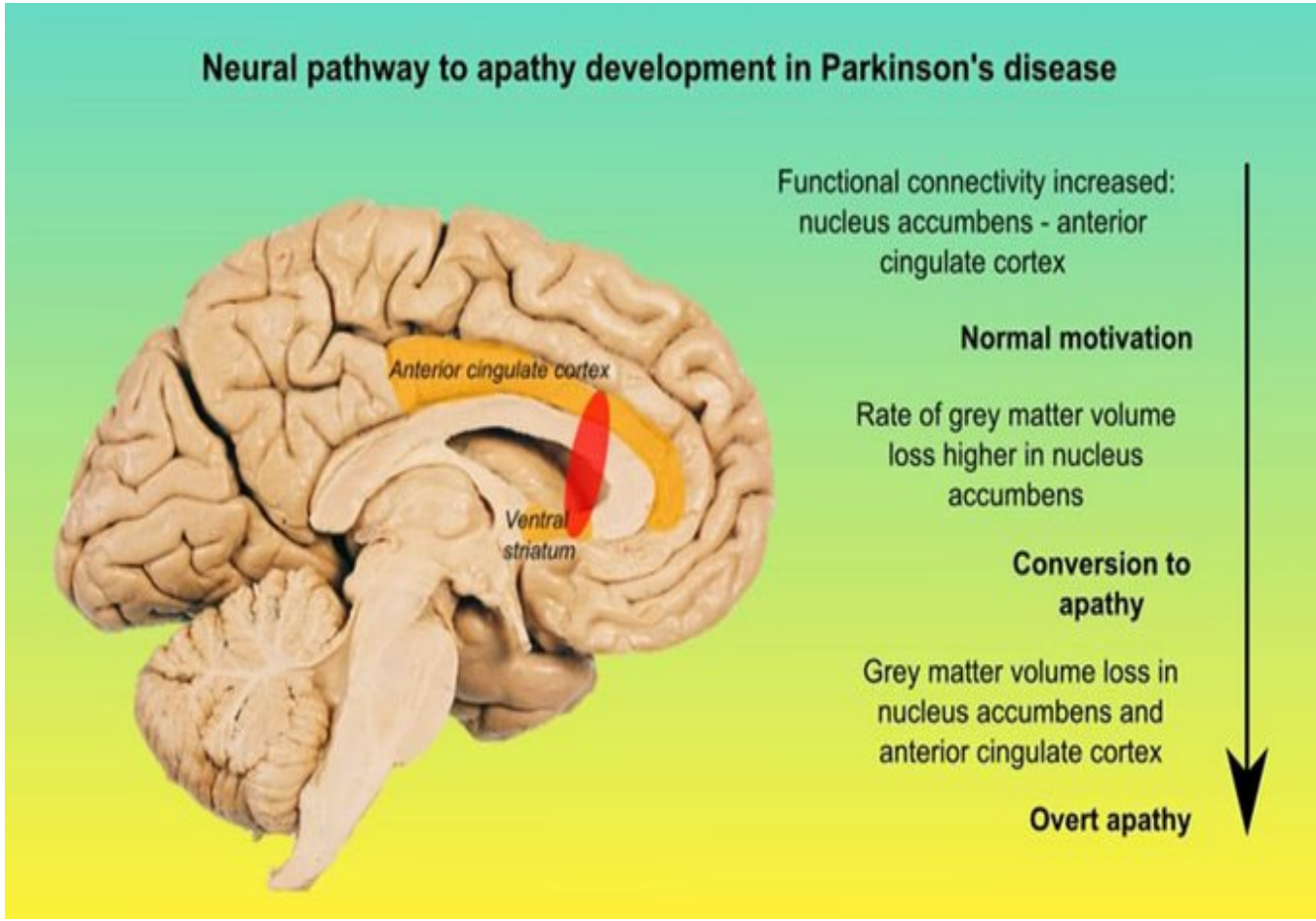
- Anxiety Disorders
- Depressive Disorders
- Impulse Control Disorder
- **Apathy**
- **Psychosis**

Apathy in Parkinson's Disease

- Occurs in up to 40% of people with PD, yet remains one of the poorest understood non-motor symptoms

- Normal maintenance of motivation depends on subcortical structures that link the prefrontal cortex to the limbic system

- Dysfunction of this network alters circuits that initiate spontaneous mental activity and associate emotions with stimuli



Morris et al., Altered nucleus accumbens functional connectivity precedes apathy in Parkinson's disease, *Brain*, Volume 146, Issue 7, July 2023, Pages 2739–2752, https://doi.org/10.1093/brain/awad113

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Apathy in Parkinson's Disease

- Defined as lack of interest, enthusiasm or self-motivation

- Physiologically separate from both anxiety and depression, although may occur in tandem

- Can be confused with fatigue or lack of response to pharmacologic therapy

Recognizing Apathy in Parkinson's Disease

- Reduced interest/spontaneous interactions and curiosity in people, activities, pets and hobbies once enjoyed
- Lack of motivation, decreased activity initiation
- Flat or reduced affect (separate from facial expression)
- Difficulty participating in cognitively demanding situations
- Minimal or no goal-directed behavior

Apathy in Parkinson's Disease

- Chief issue is that this causes reduced motivation to follow PD care plan
  - Medication timing
  - Exercise/activity
  - Making/attending rehab or other specialist appointments
  - May exacerbate isolation already present in disease state

- Often leads to frustration with family members, care partners and healthcare team - disproportionate to patient's awareness/desires

Apathy Treatment Strategies

- Important to screen for this symptom and other mood disorders at diagnosis and follow up visits
- Take time to explain - understand that the patient may be unaware of the presence/impact of this on overall treatment
- Recommend setting small, realistic goals at patient's agreement and making attempts regularly
- Often people are happy after they did the activity that they accomplished it even if they are indifferent at the time of the ask
- Increased amounts of physical exercise (150 min/week) has been associated with lower levels of apathy and anxiety (Ng et al., 2021)
- Maintain regular sleep schedule and daily routine
- Cognitive behavioral therapy (CBT)

Apathy - Pharmacologic Treatment Approach

- There are no approved treatments specifically for apathy in PD

- Treatment of comorbid mood disorder can regulate neurotransmitter pathways, but SSRIs alone may worsen apathy in non-depressed patients

- Stimulant therapy (methylphenidate) showed preliminary benefit in small studies but more work is needed (Pagonabarraga et al., 2015)

- Dopamine agonists targeting D2/D3 receptors have been most studied pharmacologic agent
  - Piribedil (EU) was shown to reduce apathy scores from 34.6% to 3.2% compared to placebo
  - Pramipexole, ropinirole, and rotigotine have also shown benefit in open-label studies

- Cholinesterase inhibitors (rivastigmine) improved apathy scores in patients without dementia or depression after 6 months at 9.5 mg dose (Devos et al., 2014)

Psychosis in PD

- Encompasses a range of symptoms including illusions, well-formed visual hallucinations, hallucinations of other sensory modalities (tactile, auditory, olfactory) and paranoid delusions

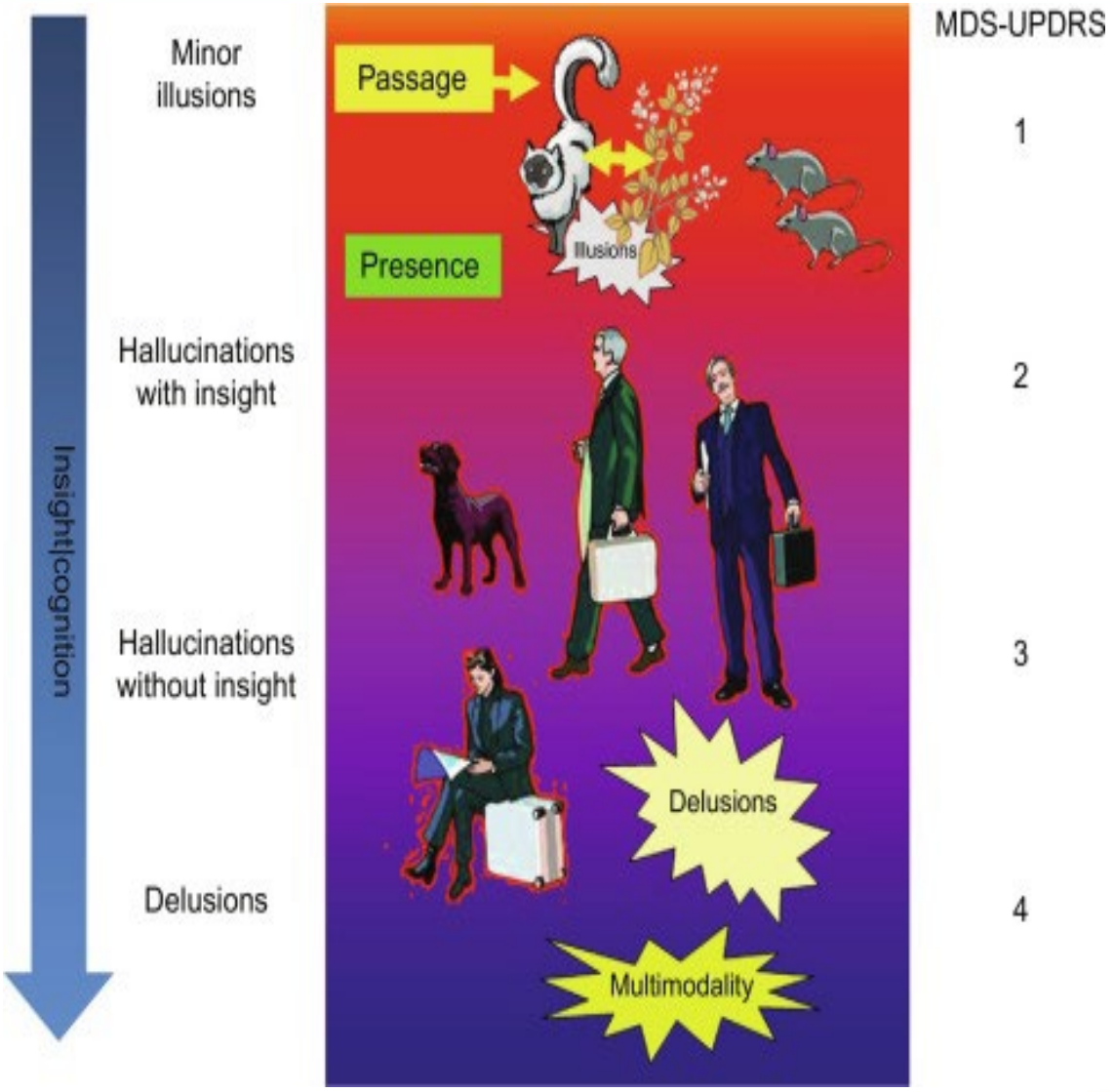
- Affects 18-50% of PD population

- Higher predisposition in tandem with cognitive impairment, but can occur independently

- Once thought to be chiefly medication-induced, also occurs in 10% of untreated PD patients

- Frequent cause of hospitalization

- Persistent psychotic symptoms are associated with greater functional impairment, caregiver burden, and nursing home placement.



Dominic H. ffytche, Dag Aarsland, Chapter Nineteen -Psychosis in Parkinson's Disease. International Review of Neurobiology.

Psychosis in PD

- Risk factors for PD psychosis include:
  - Exposure to PD medications
  - Older age
  - Greater cognitive impairment
  - Increasing severity and duration of PD
  - Comorbid depression or anxiety
  - Visual impairment
  - Polypharmacy

- Psychotic syndromes can be roughly categorized into two phenomenological groups; those with insight and those without.
- Benign hallucinosis
  - Individuals retain insight - the most common symptom is visual hallucinations or illusions.
- Individuals without insight often have complex psychotic symptoms, including delusions.

Psychosis Treatment

Initial management – at onset or worsening

- Workup for reversible causes
  - Acute infection (urinary tract, skin, upper respiratory most common)
  - Constipation
  - Metabolic disturbances
- Vision history
- Identify triggers/timing
  - Lighting, clothing, placement of items in home, time of day/medication administration
- Discuss behavioral management with carepartners (validate, redirect, depersonalize)
- Medication review
  - New medications, increase in dosage
  - Most classes of PD medications can contribute, even if on therapy for many years
    - Anticholinergics, amantadine, dopamine agonists, and levodopa

Psychosis Treatment

If no external cause can be identified, distressing psychotic symptoms should be treated with medications

- Pimavanserin is the only atypical antipsychotic approved for treatment of Parkinson's disease psychosis
  - First line, requires specialty pharmacy dispensing
  - Ideal for milder symptoms not requiring rapid response

- Off label use
  - Clozapine - strongest evidence for efficacy (specifically paranoid delusions) but weekly monitoring for neutropenia limits use
    - Utilized more in inpatient/SNF settings or treatment-refractory cases
  - Quetiapine – widely available, commonly prescribed due to ease of obtaining/titrating
  - Some evidence for cholinesterase inhibitors (rivastigmine, donepezil) for visual hallucinations without dementia, but randomized trial data is limited (Foltynie et al., 2024)

Treatment Considerations

- Haloperidol is grossly contraindicated in Parkinson's disease
  - Dopamine blocking and can cause incapacitation/irreversible motor worsening
  - Consider parenteral benzodiazepines

- Other antipsychotics also have limited use due to potential for dopamine blockade

Safe & Contraindicated Medications

	Safe Medications	Medications to Avoid
Antipsychotics	Pimavanserin (Nuplazid) Quetiapine (Seroquel) Clozapine (Clozaril) After non-drug de-escalation or re-direction and addressing underlying causes: **For acute agitation:** A low dose of benzodiazepine may be needed. **For hyperactive delirium:** Stop unnecessary deliriogenic medications, consider quetiapine. Parenteral benzodiazepines may be needed for safety. Limit repeat use to avoid worsening confusion.	Haloperidol (Haldol) and other typical antipsychotics. Atypical antipsychotics not listed in the "safe" column, such as olanzapine (Zyprexa), risperidone (Risperdal) and aripiprazole (Abilify).

Parkinson's Foundation: Hospital Safety Guide, 2025. Parkinson.org/hospitalsafety

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