Beyond Parkinson's: Exploring Cognitive Alterations in Other Movement Disorders

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Agenda

1. Hannah Combs, PhD, ABPP: Understanding Essential Tremor: Neuropsychological Insights
2. Samantha Henry, PhD: Cognition in Atypical Parkinsonism: A Neuropsychological Approach to PSP, MSA, and CBS
3. Hannah Combs, PhD, ABPP: Huntington's Disease: A Neuropsychological Perspective

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Understanding Essential Tremor: *Neuropsychological Insights*

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Disclosures

I have no actual or potential conflict of interest in relation to this program/presentation

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Objectives

1. Define Essential Tremor (ET)
2. Outline the underlying neurological mechanisms and brain regions involved in ET
3. Review cognitive features of ET
4. Outline treatment options for ET

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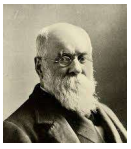
History of Essential Tremor (ET)

- **Ancient References:** Tremors documented in ancient India, Egypt, Israel, and Greece.
- **Historical Physicians**: Galen (130–200 AD), Sylvius de la Boe (1680), Van Swieten (1745), and Sauvages (1768) distinguished between kinetic and rest tremors.
- **19th Century:** The term "essential" applied to diseases with no known medical cause.
- **Charles Dana (1887):** Documented ET in several large families.



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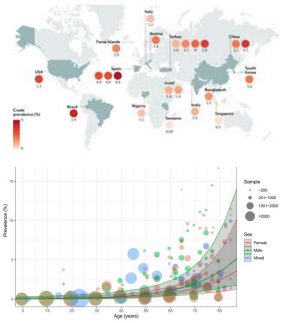
Essential Tremor

- Most common movement disorder encountered in neurology clinics.
- >60 million affected worldwide (Welton et al., 2021)
- Prevalence: 3.2 cases per 1000 individuals with ET globally 28.7 cases per 1000 over age 80



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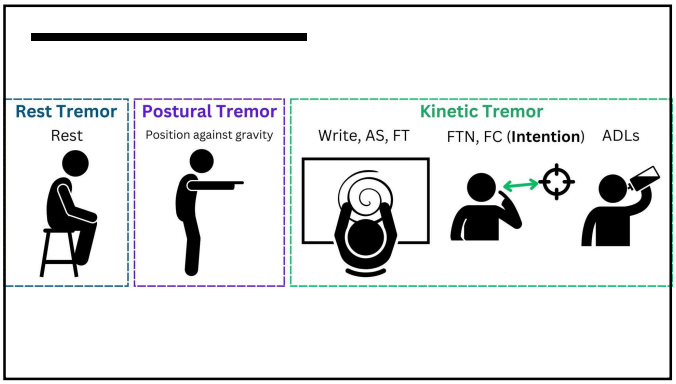

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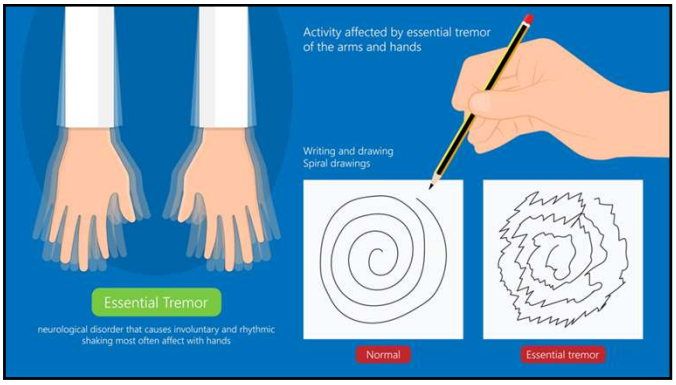

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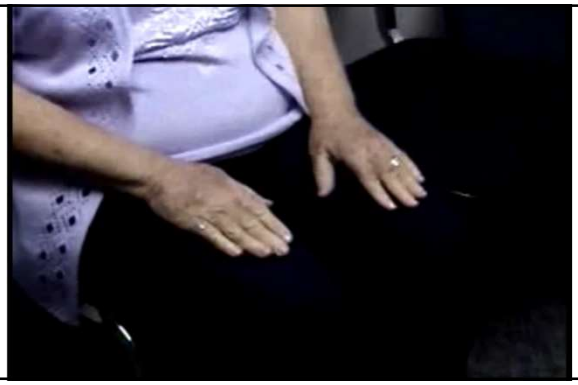

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“Benign” Essential Tremor?

“Benign”
- ET can be very mild
- Not life threatening or life shortening
- Slowly progressive disorder than can remain stable in some patients for decades

Term mostly dropped from diagnostic label
- Tremor severity varies, causing functional, social, and occupational impairment, reducing quality of life.

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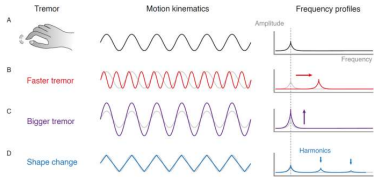
Tremor Characteristics

- As the illness progresses, tremor frequency decreases, but amplitude increases, leading to significant disability and impact on daily activities.
- ~20% of patients have impaired job performance and may require early retirement.
- Some patients experience embarrassment and social isolation.



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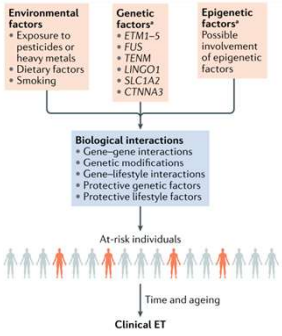
Causes of ET



Welton et al., 2021

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Cultural Differences in ET

Gender Differences:

- Women exhibit more frequent and more severe head or voice tremor than men.
- Men exhibit more severe postural hand tremor. (Hubble et al., 1997)

Ethnic Differences:

- Regional variability in the expression of tremor (e.g., "Head nodders" in New Guinea & tongue tremor in northern Sweden; Hornabrook, 1970; Larsson & Sjogren, 1960)
- Louis et al., 2000: White subjects exhibited the mildest form of tremor when compared to African American and Hispanic groups. Differences in severity of tremor were not the result of differences in age, disease duration, medications, or family history.

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Pathophysiology

- Not firmly established (see review by Welton et al., 2021)
- Neuroimaging:
  - Structural MRI: Inconsistent- Some show cerebellar atrophy
  - Functional MRI: Limited- Suggests altered metabolism, activity, and connectivity in the cerebellum
- Neuropathology: Loss and morphological changes in Purkinje cells and basket cells.
- GABA: Reduced GABA concentration and receptor expression.

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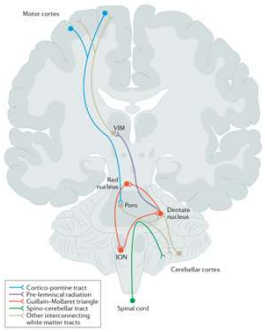
Pathways involved in ET



Welton et al., 2021

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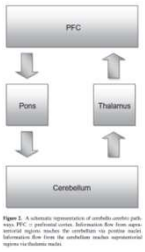
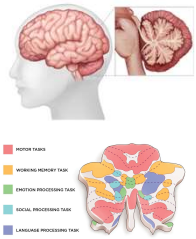
Cerebellum

- Research indicates the cerebellum is involved in visuospatial attention, language, learning, memory, and executive functions (Rudolph et al., 2023).
- The posterior cortex is linked to cognitive abilities, while the medial cerebellum is associated with emotional and neuropsychiatric issues.
- Cerebello-cerebral pathways may explain neuropsychological deficits and their recovery after cerebellar lesions.





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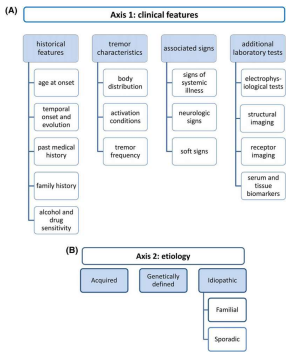
2018 Consensus Statement by the Task Force on Tremor of the International Parkinson and Movement Disorder Society (MDS)



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Expansion of the Clinical Phenotype of ET

Other types of tremor:

- Kinetic and Intention Tremors in the Limbs (primary)
- Postural tremors
- Resting tremors (without other PD signs)

Non-tremor motor signs:

- Gait ataxia (usually mild)
- Subclinical eye movement abnormalities
- Cerebellar motor signs: poor hand-eye coordination, greater variability in repetitive movements, and abnormalities in motor learning
- Dystonia

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Non-Motor Features

Psychiatric:
Increased rates of anxiety, social phobia, personality disorders, and depression
(Lorenz et al., 2006)

Sensory:
Olfactory and hearing deficits have been reported (Yilmaz et al., 2015).

Sleep:
Sleep abnormalities have been demonstrated
(Jimenez-Jimenez et al., 2020)

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Cognitive Features of ET

Cognitive deficits common in individuals with essential tremor (ET) and may precede movement symptoms (Janicki et al., 2013).

These deficits, along with neuropsychiatric symptoms, can cause functional impairment even after controlling for tremor severity.

ET is linked to an increased risk of mild cognitive impairment (MCI) and dementia, especially in those over 65.

ET patients with dementia often require home health assistance and have a higher risk of mortality.

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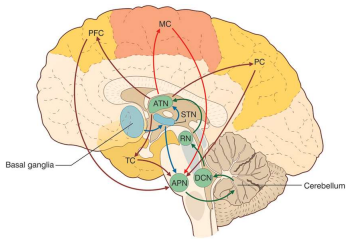
Cognitive Features of ET

- Cognitive impairments in ET include attention, working memory, episodic memory, language, visuoconstruction, and executive functioning (Bermejo-Pareja et al., 2011).
  - ET-related cognitive decline is associated with dysfunction in the cerebellar-thalamic-basal ganglia-cortical loop.



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Cognitive Features of ET

- Motor symptoms and reported neuroanatomical changes in ET are similar to changes observed in Parkinson's disease (PD; Tarakad & Jankovic, 2018).
- Individuals with ET have been shown to have similar cognitive profiles as PD (Higginson et al., 2008; Lacritz et al., 2002; Lombardi et al., 2011; Puertas-Martin et al., 2016).

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Cognitive Functioning and Intraindividual Variability (IIV) in ET compared to Parkinson's Disease (PD)

- Combs, Henry, Webber, York, & Sober (under revision):
  - 188 PD, 53 ET, and 135 intact controls participants who underwent neuropsychological testing were reviewed.
  - Group comparisons on individual neuropsychological tests were examined.
  - IIV was calculated via the intraindividual standard deviation (iSD) across 13 neurocognitive test scores and the coefficient of variance (CoV).

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Group Differences on Neuropsychological Measures

	IC (n = 135) M (SD)	PD (n = 188) M (SD)	ET (n = 53) M (SD)	H	p	η^2
COWAT	49.46 (8.90)[c]	46.39 (10.57)	42.36 (9.33)[a]	21.63	<0.001*	0.06
Animal Fluency	51.36 (10.77)[b,c]	46.88 (11.89)[a]	45.25 (10.35)[a]	15.05	<0.001*	0.04
NAB Naming	54.36 (6.11)	52.05 (8.69)[c]	50.31 (5.67)[a]	15.07	<0.001*	0.04
Stroop Word Reading	42.45 (9.85)[b,c]	34.30 (10.48)[a]	32.26 (9.36)[a]	54.28	<0.001*	0.15
Stroop Color Naming	41.92 (9.53)[b,c]	35.74 (9.33)[a]	34.17 (9.28)[a]	37.89	<0.001*	0.10
Stroop Color Word Inhibition	46.69 (8.01)	42.80 (8.93)[a]	42.98 (8.68)	16.67	<0.001*	0.04
TMT A	49.72 (9.36)[b,c]	44.61 (9.16)[a]	43.72 (10.07)[a]	23.78	<0.001*	0.06
TMT B	51.99 (9.45)[b,c]	42.32 (11.15)[a]	42.42 (11.49)[a]	63.10	<0.001*	0.17
WAIS-IV Digit Span Forward	52.46 (8.82)[c]	49.81 (8.89)	46.06 (9.25)[a]	19.49	<0.001*	0.05
WAIS-IV Digit Span Backward	53.51 (9.92)[b]	49.78 (8.87)[a]	49.20 (10.11)	15.28	<0.001*	0.04
WAIS-IV Digit Span Sequencing	52.31 (8.77)	50.06 (9.15)	49.17 (9.66)	6.96	0.031	0.02
WMS-IV Logical Memory I	53.75 (9.02)[b]	48.53 (9.74)[a,c]	53.15 (10.28)[b]	24.15	<0.001*	0.06
WMS-IV Logical Memory II	51.48 (8.87)	48.16 (9.79)	49.43 (10.31)	8.21	0.016	0.02
Mean Composite	50.10 (4.87)[b,c]	45.49 (5.56)[a]	45.11 (5.05)[a]	58.82	<0.001*	0.16
CoV	0.18 (0.05)[b,c]	0.22 (0.07)[a]	0.24 (0.07)[a]	45.19	<0.001*	0.12
iSD	8.69 (2.14)[b,c]	9.69 (2.40)[a]	10.45 (2.45)[a]	23.79	<0.001*	0.06

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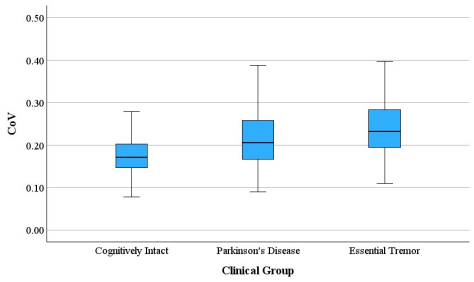
Group Differences in IIV (CoV)



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Study Takeaways

ET and PD demonstrated similar cognitive weaknesses on measures of attention/processing speed, and executive functioning, although PD was worse than ET on story learning and naming tasks.

PD and ET groups showed greater IIV than controls.

53% of PD and 46% of ET met criteria for MCI

When excluding MCI patients, PD no longer had greater IIV than controls. Greater IIV remained in the ET group.

Fronto-subcortical disruption has been proposed as the underlying mechanism for increased cognitive dispersion in PD (Jones et al., 2020). Frontal network compromise could also contribute to cognitive dispersion in ET.

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Essential Tremor- Plus (ET-Plus)

A newly suggested term coined in the 2018 consensus statement by the Movement Disorder Society on the classification of tremor (Bhatia et al., 2018).

Defined as an entity separate from ET and is characterized by the presence of neurological signs other than action tremor.

Studies suggest that 39-83% of ET patients could be reclassified as ET-plus (Prasad & Pal, 2019; Rajalingam, Lang, & Fasano, 2018).

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Controversy with ET-Plus

- Many argue that ET is a heterogeneous condition, making a second term unnecessary (Louis et al., 2020)
- The development of other clinical features (e.g., cognitive impairment) does not necessarily require a change in diagnosis; similar to Parkinson's disease.
- ET-plus may represent a disease stage, rather than a disease subtype (Louis, Huey, & Cosentino, 2021)
  - ET-plus is not defined on the basis of a difference in underlying cause or pathology, or an appreciable difference in prognosis or pharmacotherapeutic profile

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Treatments for ET

- No cure- Mild cases may not need treatment.
- 1st Line Medications: Propranolol and primidone tend to be the first-line treatments
  - Can be sedating and may be poorly tolerated in some elderly patients
  - Withdrawal from propranolol may result in a rebound increase in amplitude of the tremor, which may last longer than a week
- Alternative Medications: **Topiramate**, **gabapentin**, methazolamide, mirtazapine, and **clonazepam**
- Botulinum toxin injections: Disabling head or vocal cord tremor
- Neurosurgery: In severe cases- DBS, focused ultrasound thalamotomy, or radio-surgical gamma knife thalamotomy

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Thalamotomy

Stereotactic Thalamotomy for Essential Tremor (ET):

- Used since the 1950s
- Preference for targeting VIM nucleus over VL nucleus
- Tremor reduction: 75-95% from pre-surgical baseline (Schuurman et al., 2000)
- Adverse events: dysarthria, dysphagia, aphasia, seizures, etc.
- Largely replaced by DBS, but still an option for select patients

Surgical Criteria:

- Medication-refractory ET
- Intolerable side effects impacting quality of life

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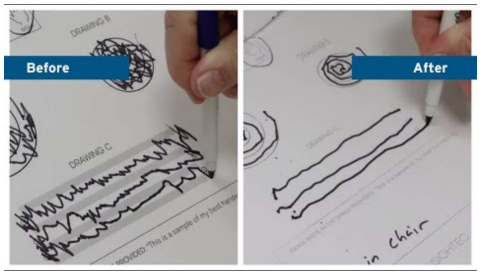
Focused Ultrasound for ET



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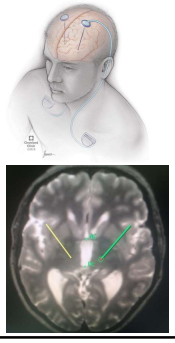
DBS for ET

- In the US, DBS for ET was approved by the FDA in 1997, five years before DBS was approved for PD
- DBS of the ventral intermediate nucleus of the thalamus (VIM) is effective for treating refractory ET

  1) Provides a nondestructive and potentially reversible technique

  2) Range of stimulation can be adjusted easily and safely postoperatively to maximize patient response, and

  3) Rate of neurological complications is lower for DBS than traditional ablative procedures



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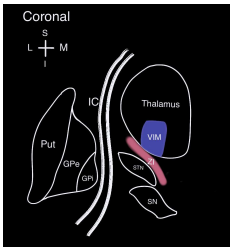
DBS for ET

- In most, unilateral VIM DBS may be sufficient to reduce disability by suppressing tremor within the dominant hand
  - However, in cases with disabling bilateral limb tremor or head, voice, and trunk tremor, a bilateral procedure may be indicated (Munhoz et al., 2016)
  - Some centers have adopted an approach that entails staging the procedures
- Average age of patients undergoing VIM DBS for the treatment of ET is in the 50s, but surgical patients range in age from 30s to the 90s



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Cognitive Outcomes in DBS for ET

- Neuropsychological evaluation has been recommended as part of the minimum standard of the pre-DBS workup in ET
- Generally considered cognitively safe.
- Ali and colleagues (2024): Systematic review of cognitive outcomes in DBS for ET
  - 20 studies (13 prospective, 7 retrospective) that examined cognition in patients with ET who underwent VIM, VL/VLp, or cZi/PSA
  - Most studies were small with a median number of 22 ET patients per study
  - Only one prospective randomized clinical trial
- Mild cognitive decline more likely to occur among persons with tremor onset after age 37 years and when pulse widths of 120 µs or greater are used in stimulation

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Neurobehavioral Outcomes in DBS for ET

Neurobehavioral adverse event rates in clinical trials are difficult to interpret

- Studies differ in how systematically and by which methods the data were collected

Bishay et al. 2025: Effect of DBS on nonmotor symptoms of ET in 139 patients

- BDI-II scores decreased postoperatively ($p<0.001$; $d = 0.176$)
- BAI scores were unchanged

Gupta et al., 2023: Depression following VIM-DBS for ET Meta-Analysis

- VIM DBS improves depression postoperatively.

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Take-Aways

ET is the most common movement disorder and involves more than action tremor.

Cognitive dysfunction is common in ET, likely related to dysfunction in frontal-cerebellar circuits.

Neuropsychological evaluation is important to aid in differential diagnosis of ET-related cognitive dysfunction as well as in determining candidacy for DBS or FUS.

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Cognition in Atypical Parkinsonism

A Neuropsychological Approach to MSA, PSP, and CBS

AACN 2025

1

Learning Objectives

- Describe the neuropsychological and neuropsychiatric profiles commonly observed in Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP), and Corticobasal Syndrome (CBS)
- Review the latest advancements in the neuropsychological assessment of atypical parkinsonian syndromes
- Discuss cultural considerations and health disparities relevant to atypical parkinsonisms
- Identify key diagnostic challenges in differentiating atypical parkinsonisms from other neurodegenerative conditions using a neuropsychological approach

AACN 2025

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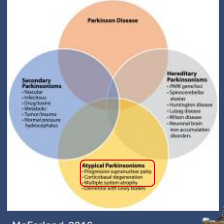
Beyond Parkinson's



McFarland, 2016

AACN 2025

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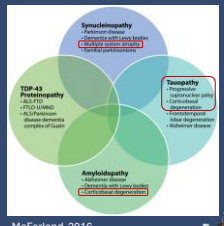
Proteinopathy



McFarland, 2016

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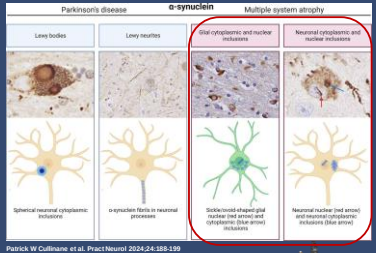
Morphology of α-synuclein inclusions in Parkinson's disease and multiple system atrophy.



Patrick W Cullinane et al. Pract Neurol 2024;24:188-199

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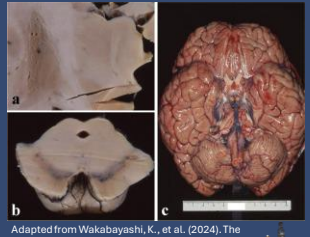
Macroscopic Findings in MSA



Adapted from Wakabayashi, K., et al. (2024). The Cerebellum, 23(1), 2–12.

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Wenning et al. (2022). The movement disorder society criteria for the diagnosis of multiple system atrophy. *Movement Disorders, 37*(6), 1131-1148.

TABLE 1 *Diagnostic criteria for clinically established and clinically probable multiple system atrophy*

Division into clinically established MSA-P or MSA-C according to predominant motor syndrome

Essential features	A sporadic, progressive adult (>30 years) onset disease	
	Clinically established MSA	**Clinically probable MSA**
Core clinical features	1. Autonomic dysfunction defined as (at least one is required) ○ Unexplained voiding difficulties with post-void urinary residual volume ≥100 mL ○ Unexplained urinary urge incontinence ○ Neurogenic OH (≥20/10 mmHg blood pressure drop) within 3 minutes of standing or head-up tilt test and at least one of 1. Poorly L-dopa-responsive parkinsonism 2. Cerebellar syndrome (at least two of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features)	At least two of: 1. Autonomic dysfunction defined as (at least one is required): ○ Unexplained voiding difficulties with post-void urinary residual volume ○ Unexplained urinary urge incontinence ○ Neurogenic OH (≥20/10 mmHg blood pressure drop) within 10 minutes of standing or head-up tilt test 2. Parkinsonism 3. Cerebellar syndrome (at least one of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features)
Supportive clinical (motor or non-motor) features	At least two	At least one[a]
MRI marker	At least one	Not required

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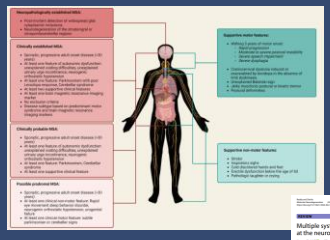

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MSA Phenotypes

- **Multiple System Atrophy- Parkinsonian Type (MSA-P)**
  - Symmetrical onset
  - Rapid progression
  - Tremor (distal, myoclonic)
  - Frequent rigidity, hypokinesia
  - Dystonia (axial), antecollis (drooped head)
  - Early falls
  - Dysarthria, dysphonia
  - Sleep apnea, rapid eye movement (REM) sleep behavior disorder
  - Respiratory/laryngeal stridor
  - Hyperreflexia, Babinski signs
  - Dysautonomia (89% versus 5% in Parkinson disease)
  - Poor/unsustained levodopa response (~30%)
  - Dyskinesia (orofacial common)
- **Multiple System Atrophy- Cerebellar Type (MSA-C)**
  - Cerebellar limb and gait ataxia
  - Early falls
  - Dysarthria (scanning, ataxic)
  - Dysphagia
  - Gaze impairment (hypokinetic/hyperkinetic saccades)
  - Lower and upper motor neuron signs
  - Emotionality, depression, anxiety
  - Progressive dementia

Clinical Presentation	Features[a]
Multiple system atrophy-parkinsonian type (MSA-P) (previously referred to as Shy-Drager syndrome or striatonigral degeneration)	Onset <40 years, duration ~10 years, progressive parkinsonism poorly responsive to levodopa, with autonomic failure (including orthostatic hypotension, impotence, bladder dysfunction)
Multiple system atrophy-cerebellar type (MSA-C) (previously referred to as olivopontocerebellar atrophy)	Ataxia, degeneration of ventral pons, olives, cerebellum; mild parkinsonism and cognitive decline

[a] Autonomic dysfunction, respiratory symptoms, and sleep disturbance can precede motor signs by months to years.

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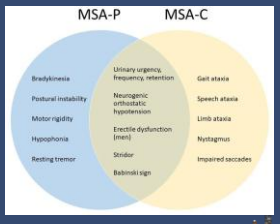
MSA Phenotypes



Goolla, Cheshire, Ross, & Kondru (2023)

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Sex Differences in MSA

- Disease characteristics
  - Women are diagnosed earlier, live slightly longer, and experience greater disease severity than men (Coon et al., 2019; Cuoco et al., 2020)
  - Men more often present with autonomic symptoms; women with motor symptoms and early falls (Coon et al., 2019; Leys et al., 2024)
    - Sexual dysfunction prominent in males but not females (Coon et al., 2019)
- Non-motor symptoms
  - Men perform better on MoCA, especially in language and attention, and JLO (Cuoco et al., 2020)
  - Women more likely to meet criteria for single-domain MCI (Cuoco et al., 2020)
  - Depression more frequent in women at baseline and follow-up (Leys et al., 2024)

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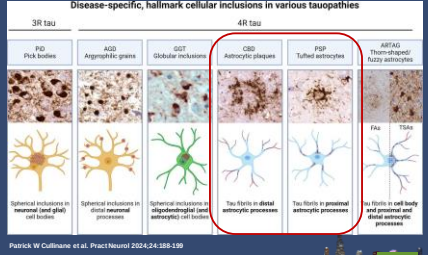
Morphology of cellular inclusions in various tauopathies.



Patrick W Cullinane et al. Pract Neurol 2024;24:188-199

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PN

12

Höglinger, G. U., Respondek, G., Stamelou, M., Kurz, C., Josephs, K. A., Lang, A. E., ... & Bordelon, Y. (2017). Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Movement Disorders*, 32(6), 853-864.

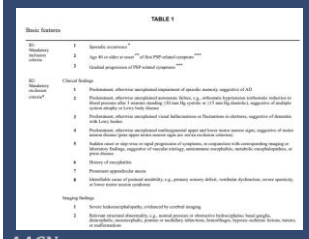
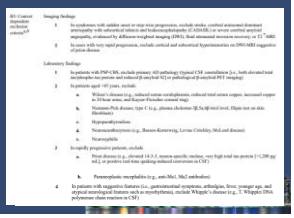


TABLE 1

Basic features

MI: Mandatory inclusion criteria	1	Sporadic occurrence [1]
	2	Age 40 or older at onset [2] of first PSP-related symptoms [3,4]
	3	Gradual progression of PSP-related symptoms [5,6]
MI: Mandatory inclusion criteria[1]	Clinical findings	
	1	Predominant, otherwise unexplained impairment of episodic memory, suggestive of AD
	2	Predominant, otherwise unexplained autonomic failure, e.g., orthostatic hypotension (orthostatic reduction in blood pressure after 3 minutes standing ≥30 mm Hg systolic or ≥15 mm Hg diastolic), suggestive of multiple system atrophy or Lewy body disease
	3	Predominant, otherwise unexplained visual hallucinations or fluctuations in alertness, suggestive of dementia with Lewy bodies
	4	Predominant, otherwise unexplained cerebellargenital upper and lower motor neuron signs, suggestive of motor neuron disease (pure upper motor neuron signs are not mechanism criterium)
	5	Sudden onset or step-wise or rapid progression of symptoms, in conjunction with corresponding imaging or laboratory findings, suggestive of vascular etiology, autoimmune encephalitis, metabolic encephalopathies, or prion disease
	6	History of encephalitis
	7	Prominent appendicular ataxia
	8	Identifiable cause of postural instability, e.g., primary sensory deficit, vestibular dysfunction, severe spasticity, or lower motor neuron syndrome
	Imaging findings	
	1	Severe leukoencephalopathy, evidenced by cerebral imaging
	2	Relevant structural abnormality, e.g., ventral pontine or obstructive hydrocephalus, basal ganglia, thalamic, mesencephalic, pontine or medullary infarctions, hemorrhages, hypoxic-ischemic lesions, tumors, or malformations



RC: Context dependent exclusion criteria[1,5]	Imaging findings	
	1	In syndromes with sudden onset or step-wise progression, exclude stroke, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or severe cerebral amyloid angiopathy, evidenced by diffusion-weighted imaging (DWI), fluid attenuated inversion recovery, or T2*-MRI
	2	In cases with very rapid progression, exclude cortical and subcortical hyperintensities on DWI-MRI suggestive of prion disease
	Laboratory findings	
	1	In patients with PSP-CBS, exclude primary AD pathology (typical CSF constellation [i.e., both elevated total tau/phospho-tau proteins and reduced β-amyloid 1-42] or pathological β-amyloid PET imaging)
	2	In patients aged <65 years, exclude:
		a. Wilson's disease (e.g., reduced serum ceruloplasmin, reduced total serum copper, increased copper in 24-hour urine, and Kayser-Fleischer corneal ring)
		b. Niemann-Pick disease, type C (e.g., plasma cholestan-3β,5α,6β-triol level, filipin test on skin fibroblasts)
		c. Hyperuricemia/gout
		d. Neuroacanthocytosis (e.g., Bassen-Kornzweig, Levine-Critchley, McLeod disease)
		e. Neuropathia
	3	In rapidly progressive patients, exclude
		a. Prion disease (e.g., elevated 14-3-3, neuron-specific enolase, very high total tau protein [>1,200 pg/mL], or positive real-time quaking-induced conversion in CSF)
		b. Paraneoplastic encephalitis (e.g., anti-Ma2, Ma2 antibodies)
	4	In patients with suggestive features (i.e., gastrointestinal symptoms, arthralgias, fever, younger age, and atypical neurological features such as myorhythmia), exclude Whipple's disease (e.g., T. Whipplei DNA polymerase chain reaction in CSF)

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Höglinger, G. U., Respondek, G., Stamelou, M., Kurz, C., Josephs, K. A., Lang, A. E., ... & Bordelon, Y. (2017). Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Movement Disorders*, 32(6), 853-864.

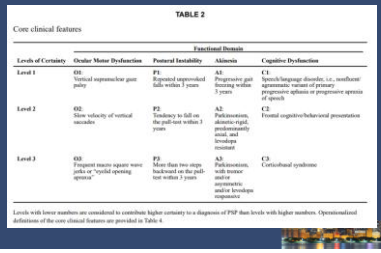

TABLE 2

Core clinical features

	Functional Domain			
Levels of Certainty	**Ocular Motor Dysfunction**	**Postural Instability**	**Akinesia**	**Cognitive Dysfunction**
Level 1	O1: Vertical supranuclear gaze palsy	P1: Repented unprovoked falls within 3 years	A1: Progressive gait freezing within 3 years	C1: Speech/language disorder, i.e., nonfluent/ agrammatic variant of primary progressive aphasia or progressive apraxia of speech
Level 2	O2: Slow velocity of vertical saccades	P2: Tendency to fall on the pull-test within 3 years	A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	C2: Frontal cognitive/behavioral presentation
Level 3	O3: Frequent macro square wave jerks or "eyelid opening apraxia"	P3: More than two steps backward on the pull-test within 3 years	A3: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	C3: Corticobasal syndrome

Levels with lower numbers are considered to contribute higher certainty to a diagnosis of PSP than levels with higher numbers. Operationalized definitions of the core clinical features are provided in Table 4.

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PSP Diagnosis

- Four levels of diagnostic certainty
  - Definite PSP
  - Probable PSP
  - Possible PSP
  - "Suggestive of PSP"
- Clinical phenotypes
  - PSP-RS
  - PSP-P
  - PSP-OM
  - PSP-F
  - PSP-PGF
  - PSP-CBS
  - PSP-PI
  - PSP-SL
  - *PSP-PLS, PSP-C acknowledged but no criteria

Progressive Supranuclear Palsy (PSP) Syndrome	Clinical Features	Regional Pathology
Classic PSP (Richardson syndrome)	Early gait instability, falls, supranuclear gaze palsy, axial rigidity, dysarthria, dysphagia, progressive dementia	Dentate nucleus, globus pallidus, subthalamic nucleus, red nucleus, and superior cerebellar peduncle
PSP-parkinsonism	Tremor, rigid bradykinesia, levodopa responsive,* late cognitive decline, longer life expectancy (9 years)	Substantia nigra, subthalamic nucleus
PSP-pure akinesia with gait freezing	Early gait difficulty, freezing of gait/motor block, micrographia, speech impairment, hypophonia, longer disease duration (11-16 years)	Motor cortex, pons, cerebellum
PSP-corticobasal syndrome	Dystonia, dyspraxia, cortical sensory loss, apraxia of speech	Frontal and parietal cortex
PSP-behavioral variant of frontotemporal dementia	Predominant cognitive, personality change, late parkinsonism	Frontotemporal cortex
PSP-primary lateral sclerosis	Bulbar, limb weakness, upper motor neuron signs/spasticity	Frontal predominant, corticospinal tract
PSP-cerebellar	Cerebellar ataxia	Deep cerebellar nuclei

*Levodopa response for PSP-parkinsonism varies less in disease.

McFarland, 2016

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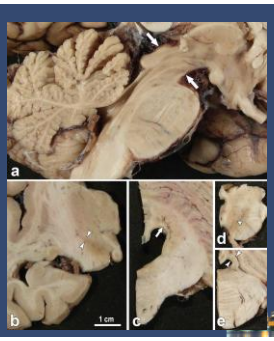
Macroscopic Findings in PSP



Adapted from Coughlin, D. G., Dickson, D. W., Josephs, K. A., & Litvan, I. (2021). In Frontotemporal Dementias (Ghetti et al., Eds., Vol. 1281, Springer).

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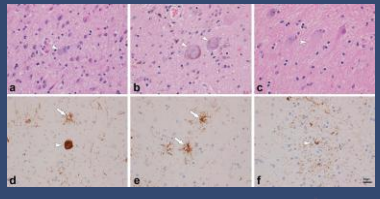
Microscopic Findings in PSP



Adapted from Coughlin, D. G., Dickson, D. W., Josephs, K. A., & Litvan, I. (2021). In Frontotemporal Dementias (Ghetti et al., Eds., Vol. 1281, Springer).

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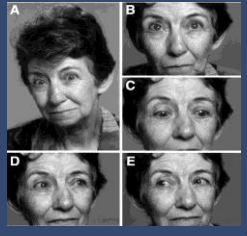
Comparison of motor, cognitive, and behavioral features in progressive supranuclear palsy and Parkinson's disease



Movement Disorders, Volume: 21, Issue: 5, Pages: 632-638, First published: 13 December 2005, DOI: (10.1002/mds.20779)

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Age of Onset in PSP

- Age of onset of PSP ranges from 45 to 73
- Clinical implications of young-onset vs late-onset PSP remain unclear
  - AlWazan et al. (2023): Speech/language symptoms (dysarthria and aphasia) were more common at onset in YO PSP
    - PSP-RS is the most common phenotype in both YO and LO groups
  - In CBS presentations, PSP pathology is more common in early-onset cases; AD pathology predominates in late-onset (Seo et al., 2018)

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Sex Differences in PSP

- Greater male prevalence in PSP (Fs et al., 2023; Nasri et al., 2024; Stang et al., 2020; Zella et al., 2020)
  - May not hold true for all phenotypes (Williams et al., 2005)
- Conflicting findings
  - Sex largely unrelated to multiple disease variables such as disease duration and severity, initial motor presentation, and medication use (Baba et al., 2005)
  - Men experienced faster cognitive decline than women on category fluency (Digma et al., 2023)
- Park and colleagues (2018) investigated whether estrogen was neuroprotective in PSP (n=350 PSP cases, 300 HC)
  - No relationship found between duration of estrogen exposure and PSP
  - ERT use associated with lower risk of PSP

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CBS Phenotypes

Armstrong et al. (2013). Criteria for the diagnosis of corticobasal degeneration. *Neurology*, *80*(5), 496-503.

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CBS Phenotypes

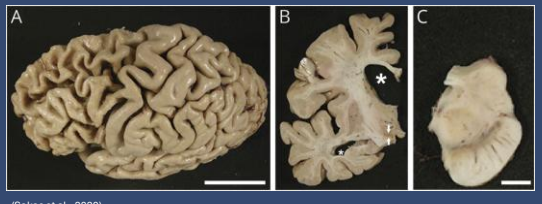
TABLE 5-1 Corticobasal Syndrome Phenotypes*

Syndrome	Key Features
Corticobasal syndrome (CBS) (classic corticobasal degeneration)	Asymmetric limb rigidity, akinesia, dystonia, or myoclonus AND Orobuccal or limb apraxia, cortical sensory deficit, or alien limb phenomenon Probable CBS is two features in each of the categories above; possible CBS is one feature in each of the categories above and may be symmetric
Frontal behavioral (frontotemporal dementia) variant	Executive dysfunction, behavioral or personality changes
Posterior cortical atrophy syndrome	Visuospatial disturbance, apraxia, myoclonus, association with Alzheimer disease pathology
Progressive nonfluent/agrammatic aphasia	Effortful, agrammatic speech; impaired grammar; relative comprehension of meaning; or distorted speech production (apraxia of speech)
Progressive supranuclear palsy syndrome	Axial or symmetric limb rigidity/akinesia, postural instability, falls, urinary incontinence, behavioral changes, supranuclear vertical gaze palsy

*Modified with permission from Armstrong MJ, et al, Neurology.™ © 2013 American Academy of Neurology. www.neurology.org/content/80/5/496.short

McFarland, 2016

22



(Sakae et al., 2020)

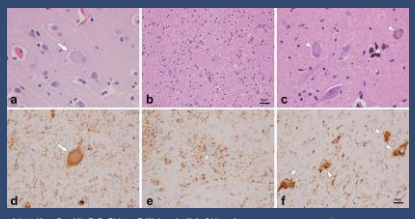
23

Macroscopic Findings in CBD

Adapted from Coughlin, D. G., Dickson, D. W., Josephs, K. A., & Litvan, I. (2021). In Frontotemporal Dementias (Ghetti et al., Eds., Vol. 1281, Springer).

24

Microscopic Findings in CBD



Adapted from Coughlin, D. G., Dickson, D. W., Josephs, K. A., & Litvan, I. (2021). In Frontotemporal Dementias (Ghetti et al., Eds., Vol. 1281, Springer).

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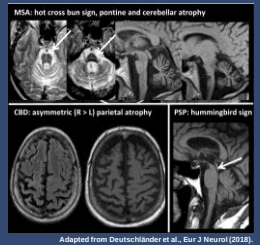
MRI Findings



Adapted from Deutschländer et al., Eur J Neurol (2018).

Table 3 Neuroimaging

	Characteristic MRI findings
MSA	'Hot-cross bun' sign (pontine T2 hyperintensity) Putaminal rim sign (T2 hyperintense rim of dorsolateral putaminal border) Atrophy of pons, cerebellum, middle cerebellar peduncle
PSP	'Hummingbird sign' (more severe midbrain than pontine atrophy) 'Morning glory sign' (atrophy of midbrain tegmentum) Atrophy of midbrain, tegmentum, superior cerebellar peduncles
CBS	Asymmetric atrophy in parietal and (pre)frontal cortices

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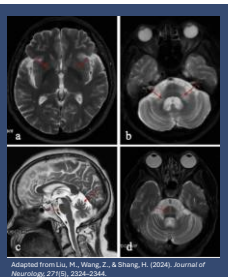
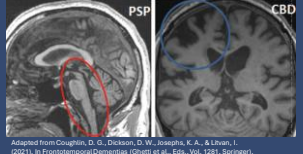


Adapted from Liu, M., Wang, Z., & Shang, H. (2024). *Journal of Neurology, 271*(5), 2334–2344.

MRI Findings



Adapted from Coughlin, D. G., Dickson, D. W., Josephs, K. A., & Litvan, I. (2021). In Frontotemporal Dementias (Ghetti et al., Eds., Vol. 1281, Springer).

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Race/Ethnicity in Atypical Parkinsonisms

- Racial and ethnic diversity not well represented in studies
- Regional differences in MSA presentation exist, with MSA-P more common in Europe and the US, and MSA-C more frequently seen in Japan (Ozawa & Onodera, 2017)
  - Emerging info suggests MSA-C more prevalent in Mestizo groups in North and Latin America (Gatto et al., 2014)
- Couto et al. (2024) found higher proportion of PSP among South Asian patients in Toronto area
  - Lower proportion of PSP in African Americans but overall disease severity was worse
- Among South Asian patients in the UK (n=27; Balint et al., 2024):
  - A significant portion had early-onset disease (<60 y) and/or family history of parkinsonism
  - Cortical features were more common at presentation
  - Parkinsonism was the most common initial clinical presentation, and
  - Atypical features like visual hallucinations and levodopa-induced dyskinesia were evident in a proportion
- Native Hawaiians and Pacific Islanders were significantly younger at diagnosis, had higher BMIs, and shorter survival time from PSP diagnosis to death (2 y vs. 6 y) (Kanman et al., 2023)

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The Neuropsychology of Atypical Parkinsonisms Revisited

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MSA: Clarifying the Cognitive Phenotype

- Overall cognition
  - Dementia is not a formal diagnostic criterion, but MCI is common
    - Limitations of DSM-IV criteria and MMSE
    - Recent studies report CI in 30-85% of MSA patients, with MCI far more common than dementia (Eschlböck et al., 2020; Nasri et al., 2022; Sambati et al., 2020)
  - Cognitive changes viewed as less severe than PSP or CBS
    - CI profiles are heterogeneous—some patients remain stable while others decline within 16 months (Sambati et al., 2020)
- Mixed phenotypic differences
  - MSA-C > MSA-P in cognitive severity (Gerstenecker, 2017)
  - MSA-P is more cognitively vulnerable than MSA-C, especially in executive and language domains (Nasri et al., 2022; Eschlböck et al., 2020)
- APOE ε4 carrier status is associated with increased risk and severity of CI in MSA, particularly in executive and language domains (Nasri et al., 2022)
- CI correlates with neuronal cytoplasmic inclusion burden in the dentate gyrus, not with Alzheimer-type pathology (Koga et al., 2017)

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MSA: Clarifying the Cognitive Phenotype

- Executive dysfunction and slowed processing were considered the core deficits in MSA, typically mild, with relative preservation of memory and language (Gerstenecker, 2017)
  - Stroop and TMT-B performance worse compared to PD and HC across phenotypes
  - EF dysfunction MSA-C > MSA-P
- Recent studies suggest attention, executive function, and verbal memory are the most commonly impaired domains (Koga et al., 2017; Sambati et al., 2020)
- Attention variable
  - Processing speed often slowed
  - Basic auditory attention relatively spared
  - Working memory can be impaired

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MSA: Clarifying the Cognitive Phenotype

- Language
  - Dysarthria common
  - Verbal fluency impairments are common
    - Category fluency often worse than phonemic fluency
    - Noun fluency worse in MSA-C
  - Naming intact
- Memory similar to PD patients
  - Immediate and delayed recall worse in MSA-C > MSA-P
- Visuospatial ability variable across studies

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PSP: An Evolving Cognitive Profile

- Cognitive impairment recognized as a core diagnostic criterion (MDS 2017 criteria), affecting the majority of patients (Nasri et al., 2024)
  - PSP consistently performs worse than MSA and PD, and is comparable to CBS, particularly in executive and global cognitive domains (Raimo et al., 2023)
- Longitudinal insights confirm a relatively rapid cognitive decline compared to PD
  - PSP patients declined across multiple domains over 12 months while PD patients remained stable (Tsuboi et al., 2024)
  - Within 15 months, PSP-RS showed statistically significant declines in semantic fluency, working memory (Digit Span Sequencing), and visuospatial processing (Benton's JLO), while PD and MSA remained stable (Fiorenzato et al., 2019)
- Phenotypic variability has emerged
  - Pavone et al. (2024) found that PSP-Cortical presents with greater cognitive impairment than PSP-Subcortical, consistent with divergent tau pathology distribution

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PSP: An Evolving Cognitive Profile

- Executive dysfunction remains the hallmark cognitive feature, consistent with Gerstenecker's review (2017), particularly deficits in initiation, set-shifting, and verbal fluency
  - Koga et al., 2024 found executive dysfunction correlates with total PSP tau burden, especially in pontine base and cerebellar white matter
  - A recent meta-analysis across 74 studies shows PSP has the most severe executive dysfunction and global cognitive impairment among atypical parkinsonisms (Raimo et al., 2023)
    - More than MSA and comparable to CBS

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PSP: An Evolving Cognitive Profile

- Verbal fluency remains disproportionately impaired (letter > semantic), and action naming deficits are prominent (Fiorenzato et al., 2019; Pellicano et al., 2017; Raimo et al., 2023)
  - Early deficits in phonemic verbal fluency distinguish PSP-RS from PD and PSP-P, while apathy is more predictive of PSP-P diagnosis (Pellicano et al., 2017)
    - These findings emerged within 24 months of symptom onset, supporting fluency and apathy as early discriminators
  - PSP-RS show significantly greater baseline impairment in verbal fluency, visuospatial skills, and processing speed compared to PD and MSA (Fiorenzato et al., 2019)
- Memory remains relatively preserved in encoding but impaired in retrieval
  - Macedo et al. (2024) found episodic memory impairments in both verbal and visual modalities in PSP versus HC
    - PSP performance better than AD or SD
    - Performance comparable to PD, MSA, and CBS
- Visuospatial and complex attention impairments noted in earlier work remain robust findings, with newer studies confirming their progressive nature (Fiorenzato et al., 2019; Tsuboi et al., 2024)

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PSP: An Evolving Cognitive Profile

- Comorbid pathology reconsidered
  - Mixed findings
    - Koga et al. (2017) found AD co-pathology does not significantly worsen cognitive outcomes in PSP
      - Total PSP-related tau burden is the primary driver of impairment
    - APOE ε4 status not associated with increased risk of CI (Koga et al., 2017)
    - APOE ε4 carriers exhibited greater impairment on cognitive tasks, esp. memory and executive functioning, and demonstrated early language involvement in a North African sample (Nasri et al., 2024)
      - 40% of PSP patients heterozygous for ApoE ε4

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Santangelo, G., Cuoco, S., Pellecchia, M. T., Erro, R., Barone, P., & Picillo, M. (2018). Comparative cognitive and neuropsychiatric profiles between Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. *Journal of Neurology, 265*, 2602-2613.

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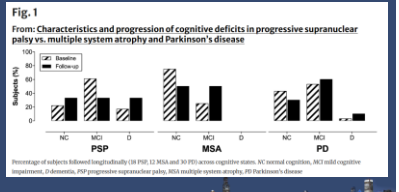

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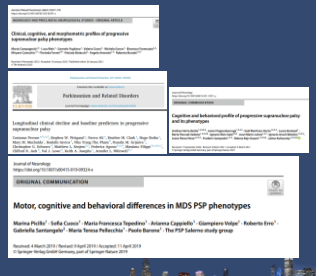
Cognitive Phenotypes in PSP?

- PSP-RS associated with greater impairment in verbal fluency and memory (Horta-Barba et al., 2021; Picillo et al., 2019)
- PSP-Cog patients show greater cognitive and functional decline, including more iADL impairment, lower MoCA scores, and higher dementia prevalence (Compagnolo et al., 2023)
- PSP-SL shows selective semantic fluency impairment with preserved phonemic fluency and naming, alongside predominant apraxia of speech (Horta-Barba et al., 2021)
- PSP-Subcortical phenotypes displayed a slower rate of disease progression in overall PSP severity and in motor scales, and milder ocular motor impairment, while PSP-Cortical was characterized by greater cognitive impairment (Pavone et al., 2023)
- PSP-PGF demonstrated a slower progression than PSP-RS (Tsuboi et al., 2025)



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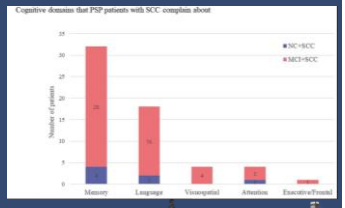
Subjective Cognition in PSP



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The Neuropsychology of CBS Refined

- Few studies with pathologically-confirmed CBD
  - Cognitive impairment and dementia are central features and may precede onset of motor symptoms (Constantinides et al., 2023; Day et al., 2023)
- Cognitive profile involves executive dysfunction, impaired verbal fluency, and orobuccal apraxia with relative preservation of naming and comprehension early on (Gerstenecker, 2017)

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The Neuropsychology of CBS Refined

- Phenotypic heterogeneity as CBS may result from various pathologies (e.g., CBD, AD, PSP)
  - Up to 50% of CBS cases show AD co-pathology (Constantinides et al., 2023; Ghirelli et al., 2025)
    - CBS-AD is more amnestic, while CBS-CBD features more executive and visuospatial deficits (Constantinides et al., 2023; Jabbari et al., 2020; Ghirelli et al., 2025)
  - Sakae et al. (2020) identified a CBD-Cog variant marked by apathy, visuospatial and executive dysfunction, and minimal motor symptoms
    - Pathology showed greater temporal tau burden than perirolandic
- FDG-PET studies reveal lateralized hypometabolism with left-hemisphere disease linked to verbal memory deficits and right-hemisphere disease to visuospatial neglect (Isella et al., 2024)
- Emerging evidence shows cerebellar atrophy contributes to executive dysfunction (Tse et al., 2020)

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Neuropsychiatric Features of MSA

- Affective and behavioral disturbances
  - Depression is common
    - Sometimes the presenting symptom
  - Anxiety and apathy also elevated
  - Irritability, hallucinations, agitation, disinhibition, appetite and eating changes, and repetitive motor behaviors also present in a minority
    - Less prone to hallucinations
    - Pseudobulbar affect may be present
- Sleep disorders are common
  - REM sleep behavior disorder common and may be initial presenting symptom
  - Vivid dreaming also frequently occurring
  - Excessive daytime sleepiness is common and may be a function of:
    - Disordered breathing (nocturnal stridor)
    - RLS

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Neuropsychiatric Features of PSP

- Affective and behavioral
  - Apathy is highly prevalent
    - May be a key differentiator between PSP and AD in context of low agitation and anxiety
  - Depression is common, though less so than in PD
  - Sizeable minority exhibit disinhibition, agitation, irritability, disrupted eating patterns, or pseudobulbar affect
  - Less frequently, anxiety and elation or euphoria also seen
  - Hallucinations and delusions are rare

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Neuropsychiatric Features of PSP

- Sleep
  - Sleep disorders are common, perhaps more so than in PD
    - Increased sleep latency
    - RLS
    - OSA
    - Excessive daytime sleepiness that worsens with disease progression
  - Less prone to REM sleep behavior disorder
- Neuropsychiatric features are not strongly linked to cognitive performance, suggesting parallel but independent circuits
- No specific behavioral or neuropsychiatric complications that were more frequent in any specific PSP predominant phenotype (Horta-Barba et al., 2021)

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Neuropsychiatric Features of CBD

- Studies are rare
- Neurobehavioral issues may be underestimated
  - Apathy, irritability, and disinhibition are most common
  - Behavioral features may resemble those of FTLD (compulsive behaviors, impulsivity, disinhibition)
  - Depression may be present
- Neurobehavioral features may depend on clinical phenotype
  - Symptoms uncommon initially in CBD-PPA/FTD but may develop inappropriate social behaviors and disinhibition later on
  - Irritability, indecision, and somnolence were present early on in CBD-FTD group with impulsivity, impaired judgment, and aggression becoming more severe later on
  - CBD-CBS exhibited depressive and compulsive features
- Visual hallucinations are rare and may help distinguish from other syndromes
- Limited info on sleep

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Caregiving

- Kellermair and colleagues (2021) studied 62 patient-caregiver dyads affected by either PSP or CBS
  - Caregiver burden was initially correlated with motor symptoms at baseline but not later on and increased with disease duration
  - Most caregivers were women but there was no significant difference in caregiver burden between male and female caregivers
    - However, female caregivers endorsed more depressive experiences
  - In comparison to CBS, caregiver burden was higher for carers of patients with PSP (although majority were PSP-RS)
    - Greater caregiver burden was possibly related to greater ADL impairment and greater frontal lobe-mediated neuropsychiatric issues
- Caregiver burden was high across PSP phenotypes (Pillas et al., 2022)

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Practical Applications in Differential Diagnosis

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Red Flags in Movement Disorders

- Features Suggestive of Atypical Parkinsonism
  - Rapid disease progression or prominent CI
  - Early gait instability, falls
  - Absence or paucity of tremor
    - Irregular jerky tremor, myoclonus
  - Poor/absent response to levodopa
  - Marked dysarthria/dysphagia in first year
  - Abnormal eye movements (supranuclear gaze palsy, slow vertical saccades)
  - Inspiratory stridor
  - Early autonomic dysfunction (early orthostatic hypotension, urinary incontinence, ED)
  - Visual hallucinations
  - Apraxia


Review Article continuum
Diagnostic Approach to Atypical Parkinsonian Syndromes

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Red Flags in Movement Disorders

- Cognitive
  - Presence of severe cognitive impairment or profound dementia early in the disease
  - Prominent executive dysfunction within the first 3 years
  - Presence of language involvement, such as apraxia of speech or non-fluent aphasia
  - Limb apraxia, esp. ideomotor apraxia
- Behavioral
  - Motor impulsivity
- Mood/Neuropsychiatric Symptoms
  - Visual or auditory hallucinations
  - Apathy
  - Emotional incontinence

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Distinguishing MSA, PSP, CBS

- Distinguishing PSP vs MSA
  - Emotional incontinence occurs in both, but is more suggestive of PSP when paired with apathy or impulsivity
  - Inspiratory stridor and nocturnal breathing abnormalities tend to occur only in MSA
- Distinguishing CBS/CBD from MSA and PSP
  - Limb apraxia, alien limb phenomena, and nonfluent/agrammatic speech support CBS/CBD diagnosis
  - Apraxia more prominent in CBS than PSP or MSA
  - Autonomic failure and cerebellar signs are not features of CBS but are key in MSA
  - Milder cognitive symptoms in MSA

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Biomarkers & Imaging

Adapted from Bruno et al., 2024, Neurology: Clinical Practice

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Language Involvement

- A function of…
  - Slowed processing speed?
  - Oculomotor or vocal motor abnormalities?
  - Frontal lobe involvement or executive dysfunction?
  - Temporoparietal involvement or semantic network degradation?

Language impairment in progressive supranuclear palsy and corticobasal syndrome

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Clinical Language Phenotypes

- PSP:
  - Non-fluent/agrammatic speech
  - Apraxia of speech and dysarthria
  - Impaired prosody
- CBS:
  - Agrammatism and apraxia of speech
  - Word-finding difficulty and impaired sentence comprehension
- Overlaps with primary progressive aphasia (PPA) profiles
  - CBS → May overlap with logopenic or mixed aphasia profiles
  - PSP → Similar to nfvPPA

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Diagnostic Challenges

- Overlap with PPA syndromes—especially nfvPPA
- Distinguishing features:
  - PPA: Language as primary deficit for first 2 years
  - PSP/CBS: Language + motor/executive dysfunction early
- Clinical evolution of disease is important
  - Language impairment may precede motor symptoms in atypical parkinsonisms
  - Easier to distinguish between nfvPPA from PSP-SL as the disease progresses and ocular symptoms emerge
  - nfvPPA has an earlier age of onset than PSP-SL (Gazzina et al., 2019)

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Differential Diagnosis of Language Disorders

- Red flags:
  - Apraxia of speech
  - Effortful, halting speech
  - Agrammatism without frank aphasia
  - Sentence repetition errors
  - Presence of falls and oculomotor dysfunction significantly more common in PSP-SL (Gazzina et al., 2019)

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Clinical Takeaways

- Language screening is essential even in patients referred for motor complaints
- Speech-language assessments + neuroimaging = critical for differential diagnosis
- Implications for Neuropsychologists
  - Tailor batteries to include:
    - Sentence repetition
    - Grammaticality judgment
    - Motor speech examination (if feasible)
    - Maybe even action fluency
  - Interpret fluency scores in context of motor speech capacity
  - Monitor language trajectory for early signs of decline or transition to mutism

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Take Home Message

- Cognitive profiles in MSA, PSP, and CBS are heterogeneous but clinically meaningful
- Biomarkers and imaging aid but do not replace clinical acumen
  - Interpretation must be anchored in a cognitive-behavioral framework
  - Neuropsychology can play a critical role in differential diagnosis
- Sex and racial/ethnic differences in presentation and progression are emerging but under-investigated
- Caregiver burden is high and begins early because of neuropsychiatric symptoms and iADL dependence
- Interdisciplinary diagnosis is both possible and necessary
  - Neuropsychologists can help identify early red flags, clarify mixed presentations, and advocate for access to diagnostic and support resources

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- *Full reference list available upon request*

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Huntington's Disease:
A Neuropsychological Perspective

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1

Disclosures

I have no actual or potential conflicts of interest in relation to this program/presentation

2

Objectives

1. Review the history of Huntington's disease (HD)
2. Identify the neuropathology/genetics involved in HD
3. Discuss the clinical features, including cognitive changes, in HD
4. Review Huntington Study Group (HSG) Neuropsychology Working Group Practice Recommendations

3

Huntington's Disease

Hyperkinetic Movement Disorder

Progressive neurodegenerative condition characterized by:

- Chorea
- Cognitive Impairment
- Psychiatric/Neurobehavioral disturbance
- Symptom onset – 30-50 years of age
- 15-20 year life expectancy following onset

Fatal

4

Brief History of HD

THE
MEDICAL AND SURGICAL REPORTER.
No. 17.] PHILADELPHIA, APRIL 15, 1871. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications

ON CHOREA.

By George Huntington, M. D.,
Of Pomeroy, Ohio.

1859 – Norway by Johan Christian Lund

- "setesdal rykkja"

1872 – George Huntington published "on Chorea"

Bhattacharrya, 2016

5

Brief History of HD

- Observed families afflicted by chorea as a child in family-run clinic
  - East Hampton, New York
- Ancestors of Jeffrey Francis, who emigrated from England in 1645, carrying the gene

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"The name 'chorea' is given to the disease on account of the dancing propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and characteristic feature is a clonic spasm affecting the voluntary muscles... The disease commonly begins by slight twitchings in the muscles of the face, which gradually increase in violence and variety. The eyelids are kept winking, the brows are corrugated, and then elevated, the nose is screwed first to the one side and then to the other, and the mouth is drawn in various directions, giving the patient the most ludicrous appearance imaginable. The upper extremities may be the first affected, or both simultaneously… As the disease progresses the mind becomes more or less impaired, in many amounting to insanity, while in others mind and body gradually fail until death relieves them of their suffering. When either or both the parents have shown manifestations of the disease, one or more of the offsprings invariably suffers from the condition... Unstable and whimsical as the disease may be in other respects, in this it is firm; It never skips a generation to again manifest itself in another, once having yielded its claims, it never regains them…"

– George Huntington

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Brief History of HD

Americo Negrette – Maracaibo, Venezuela

1950s

1979

Nancy Wexler – US-Venezuela Collaborative Research Project

Location of HD marker on chromosome 4 was discovered

1983

1993

HD gene was discovered

Moscovitch et al., 2011

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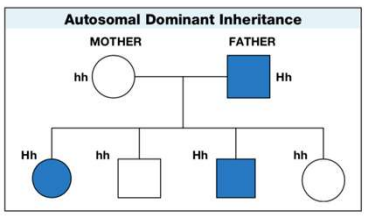
The Pattern of Inheritance in HD



Genetics

Autosomal dominant disorder
- 50:50 chance of inheritance
- Men and women are equally affected

HTT gene – huntingtin protein

Abnormal polyglutamine stretch in HTT protein

CAG – trinucleotide repeat in chromosome 4

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HD Status	Predictive Test Result	CAG Repeat Length
Unaffected	Normal	10-26
	Intermediate	27-35
Affected	Reduced Penetrance	36-39
	Full Penetrance	40-Above

Genetics

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Genetics

Meiotic Instability

- CAG repeats in abnormal range are unstable
- CAG repeats tend to change during meiosis in sperm and egg
  - HD parent 17 CAG repeats -> child with 17 CAG repeats
  - HD parent with 45 CAG repeats -> child with 44,46,47 or more CAG repeats
- Paternal side & father's age

Wright et al., 2019

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Genetics

CAA Interruptions – findings from GEM-HD and UBC (2019/2020)

- CAG – glutamine & CAA – glutamine
- CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAG-CAA-CAG

GEM-HD study

- 1 in 300 were missing the CAA interruption - earlier onset of HD symptoms
- 1 in 100 had an extra CAA interruption - delayed onset of symptoms

University of British-Columbia - Michael Hayden

- 16 people without CAA interruption - earlier onset of symptoms
- 36-38 CAG repeats w/ symptoms - majority were missing CAA interruption

Lee et al., 2019

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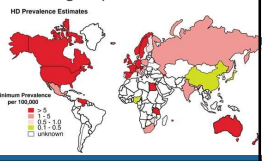
Epidemiology

- Sources usually state that 30,000 individuals in the US have HD with another 200,000 at risk
- Recent study by Yohrling et al., 2020 looked at prevalence in US and Canada
  - HD prevalence in the US to be 41,467, while the number of persons currently diagnosed to be at least 21,331 (not accounting for prevalence in uninsured)
- Worldwide:
  - 2.71 per 100, 000 Worldwide incidence per meta- analysis/systematic review (Pringsheim et al., 2012)
  - Higher prevalence in Europe, North America, and Australia
  - Lower prevalence in Asia



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Cultural Considerations

Nguyen et al., 2022:

- Medicare beneficiaries ≥ 65 yrs old with HD
- Limited access to HDSA COEs related to geographical factors rather than socioeconomic factors
  - Most underserved states were in the Mountain and West Central US

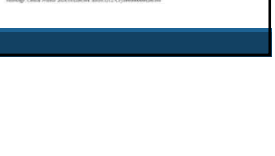
Mendizabal et al., 2024:

- 4,717 HD patients. Black participants were diagnosed with HD 1 year later than White participants.
- Clinical factors suggesting delay:
  - Psychiatric symptoms at disease onset
  - Negative family history of HD
  - Unemployment during baseline visit


Geographic Barriers Drive Disparities in Specialty Center Access for Older Adults with Huntington's Disease

Thanh Phuong Pham Nguyen[1,2,3,4,*], Licia Bravo[5,6], Pedro Gonzalez-Alegre[1,7] and Allison W. Willis[1,2,3,8]

*Center for Pharmacoepidemiology Research and Training, Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.


Racial Disparities in Time to Huntington Disease Diagnosis in North America

An ENROLL-HD Analysis

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HD Variation by Cultural Factors

- Bruzelius et al., 2019: 3,707 individuals diagnosed with Huntington's disease between 2003–2016
  - Cumulative incidence: 1.22 per 100,000
  - Asian Americans- 2.08 per 100,000, over twice as large as those that have been reported in studies conducted in Asian countries
  - Hispanic or Latino Americans, crude diagnostic frequency per 100,000 persons was 2.93
- Identified inverse relationship between income and HD diagnosis
  - Social selection
  - Environmental factors as modifiers of disease experience
  - Intergenerational transmission of income
  - Disclosure and treatment


Huntington's Disease in the United States: Variation by demographic and socioeconomic factors

Emilie Bruzelius[1,2], Joseph Scarpa, MD, PhD[1], Yiyi Zhao, BS[1,2], Sanjay Basu, MD, PhD[3], James H. Faghmous, PhD[1], and Aaron Baum, PhD[1]

[1]Icahn School of Medicine at Mount Sinai
[2]Mailman School of Public Health, Columbia University
[3]Stanford University School of Medicine

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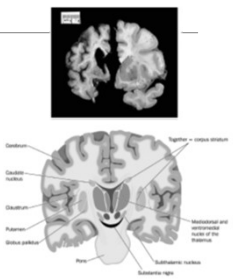
Neuropathology

- Striatal atrophy (putamen and caudate)
  - Neuronal loss
  - Astrogliosis
  - Reactive microgliosis
- Putamen volume in mild HD
- Caudate volume in moderate HD
- Medium spiny neurons – 80% of striatal neurons and are inhibitory projections neurons (GABA)
- Chorea - loss of MSN projecting to GPe



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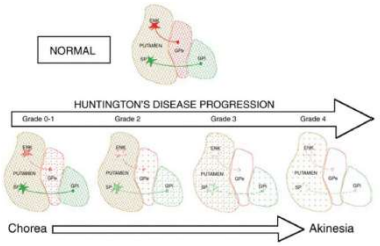
Neuropathology



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Clinical Features of HD

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Clinical Features

Triad of **MOTOR**, COGNITIVE, and PSYCHIATRIC symptoms

- Emergence of involuntary movements
  - Chorea - Progresses through middle stages but declines as rigidity increases
- Impaired voluntary movements
  - Bradykinesia, slurred speech, manual dexterity, dysphagia, balance problems, falls
- Other movement disorders
  - Dystonia, tics, myoclonus, tremors

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Diagnostic Criteria

Current accepted criteria (Reilmann, Leavitt, & Ross, 2014):

1. Carries a known CAG-expanded allele of the HD gene or has a family history of HD
2. Develops motor symptoms that are "unequivocal signs of HD" as defined in the "Diagnostic Confidence Level" (DCL) of the Unified Huntington's Disease Rating Scale (UHDRS)

*Cognitive and psych symptoms are not used for current diagnostic criteria

Biglan et al., 2013

Table 1 | The Unified Huntington Disease Rating Scale diagnostic confidence level and CAG diagnostic criteria.

A. Diagnostic confidence level

To what degree are you confident that this person meets the operational definition of the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder (e.g., chorea, dystonia, bradykinesia, rigidity) in a subject at risk for HD?

0 – normal (no abnormalities)
1 – non-specific motor abnormalities (less than 50% confidence)
2 – motor abnormalities that may be signs of HD (50–89% confidence)
3 – motor abnormalities that are likely signs of HD (90–98% confidence)
4 – motor abnormalities that are unequivocal signs of HD (≥99% confidence)

B. CAG diagnostic criteria

Based on the entire UHDRS (Motor, Cognitive, Behavioral, and Functional components) do you believe with a confidence level ≥99% that this participant has manifest HD? (0 – No, 1 – Yes)

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Unified Huntington's Disease Rating Scale Motor Assessment Chorea Scale

Body Region	Severity	
Face	0	Absent
Bucco-oral-lingual	1	Slight/intermittent
Trunk	2	Mild/common or moderate/intermittent
Right upper extremity	3	Moderate/common
Left upper extremity	4	Marked/prolonged
Right lower extremity	Total score: Sum of scores for each body region Range = 0 - 28	
Left lower extremity		

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Stages of HD

Prodromal (7-10 years before motor symptoms) → **Early HD** (Stages 1-2) → **Mid-stage HD** (Stage 3) → **Late Stage HD** (Stage 4-5)

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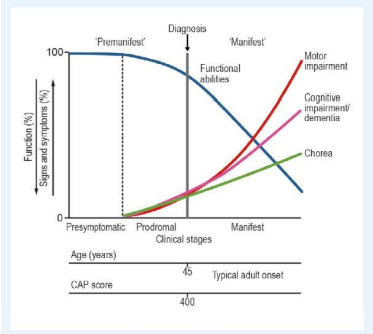

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TABLE 1 *Criteria for diagnoses in individuals with a CAG-repeat expansion in Huntingtin*

Diagnosis	Motor	Cognitive	Potential Treatment
(1) Presymptomatic HD	Dx conf 0–2	Normal	(1) Disease modifying
(2) Prodromal HD	A) Dx conf 2	(A) + Minor or major neurocognitive changes	(2A or B) Symptomatic or disease modifying
(either A or B)	B) Dx conf 3	(B) With normal (unchanged) cognition	
(3) Manifest HD	A) Dx conf 3	(A) + Minor or major neurocognitive changes	(3A or B) Symptomatic or disease modifying
(either A or B)	B) Dx conf 4	(B) With normal (unchanged) cognition	

Potential treatments apply to each of the 3 diagnoses regardless of the criteria for meeting the diagnosis. It is expected that the ability to define signs and symptoms would be enhanced by longitudinal follow-up and assessments.
Dx conf, Diagnostic Confidence; HD, Huntington's disease.

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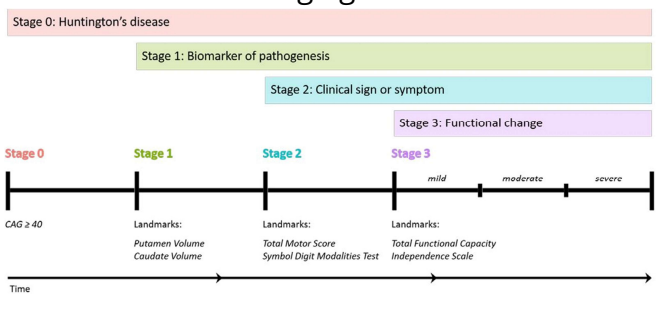
HD-ISS Staging Framework



Tabrizi et al., 2022

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Clinical Features

Triad of MOTOR, **COGNITIVE**, and PSYCHIATRIC symptoms
- 15 years prior to motor symptoms
- Cognitive and psychiatric changes most debilitating
- Impairments:
  - Psychomotor speed, executive functioning, implicit memory, emotion processing/social cognition

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Cognition: Processing Speed

Processing/psychomotor speed
- Earliest changes
- Predictor of disease progression
- Stroop, SDMT, Trail Making Test
- Predictor of functional abilities
  - Driving cessation

Snowden, 2017

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Cognition: Executive Functions

Executive Functioning
- Planning
- Organization and sequencing
- Multi-tasking
- Working Memory
- WCST, Trail Making Test Part B, Lexical Fluency, WAIS-IV Digit Span

Snowden, 2017

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Cognition: Memory

Memory
- Explicit
  - Learning difficulties
  - Retrieval deficits
  - Non-amnestic
- Implicit memory/procedural
  - Coordinated movement and skills

Snowden, 2017

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Cognition: Social Cog./Emotional Processing

Emotion Processing & Social Cognition
- Difficulty processing facial expressions
  - Earlier changes
  - Negative emotions
  - ACS Affect Recognition
- Recognition of socially inappropriate behaviors, "theory of mind" tests, sarcasm

Snowden, 2017

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Cognition: Other Domains

Other cognitive domains
- No frank aphasia, apraxia, agnosia
- Speech change due to motor impairment
- Language impacted by other cognitive deficits
- Visuospatial deficits
  - Construction tasks with executive demands
  - Perceptual Integration

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Clinical Features

Triad of MOTOR, COGNITIVE, and **PSYCHIATRIC** symptoms
- Apathy
- Depression/suicide
- Irritability, frustration, anger
- Impulsivity/disinhibition
- Perseveration
- Anosognosia

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HSG NPWG Practice Recommendations

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HSG NPWG: NP Practice Recommendations

NP Evaluation should be considered an essential component for clinical diagnosis of a suspected cognitive-phenotype HD manifest diagnosis.

- Early intervention, eligibility for clinical research, and establishing cognitive baselines that may impact patients subsequently

1. Clinical History
2. Neuropsychological Test Battery
3. Diagnosis

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Routledge
Taylor & Francis Group

Check for updates

Huntington study group's neuropsychology working group position on best practice recommendations for the clinical neuropsychological evaluation of patients with Huntington disease

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HSG NPWG: NP Practice Recommendations

Part 1. Clinical History: Onset and course of signs and symptoms (motor and non-motor)

- Depending on clinic setting, may involve thorough psychiatric history and review of current emotional functioning.
- Collateral report via interview and informant questionnaires
- Review of functional status
- Detailed family medical history should include questions about behavioral and motor signs in relatives who are at-risk for HD

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HSG NPWG: NP Practice Recommendations

Part 2. Neuropsychological Test Battery

Domain of Functioning	Inclusion Advice	Exemplars	Alternatives and Additions
Global Cognitive	Encouraged	• MoCA • PD-CRS	• MMSE
Premorbid Intellectual Attention & Processing Speed	Recommended Recommended	• TOPF • TMT-A • WAIS-4 – Digit Span Forward • SDMT – written + oral • Stroop – word + color	• WRAT-4 Reading • CPT-3 • DKEFS – Trails forms 1-3
Visuoperception & Visuoconstruction	Encouraged	• RCFT Copy • BBANS Line Orientation	• HVOT
Language	Recommended	• NAB – Naming • Animal Fluency	• DKEFS-Category Fluency • BNT
Auditory-Verbal Memory	Recommended	• HVLT-R	• RAVLT • CVLT-3 • WMS-4 AMI • NAB Memory module

Domain of Functioning	Inclusion Advice	Exemplars	Alternatives and Additions
Visuospatial Memory	Encouraged	• BVMT-R	• RCFT • WMS-4 VMI • NAB Spatial Memory
Executive (cognitive-control)	Recommended	• TMT-B • Stroop – Color/Word • CONAT/FAS • WAIS-4 – Digit Span Backwards	• DKEFS – Trails form 4 • DKEFS – Letter Fluency • DKEFS – C/WT
Executive (problem-solving)	Encouraged	• DKEFS – Towers (achievement score) • WCST	• WAIS-4 – Similarities • WAIS-4 – Matrix Reasoning
Socio-emotional	Encouraged	• ACS – Affect Recognition	• ACS other social perception subtests • Cambridge Emotion Recognition Task
Motor	Recommended	• Grooved Pegboard	• Finger Tapping Test
Sensory	Encouraged	• BSIT	• Sniffin' Sticks

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HSG NPWG: NP Practice Recommendations

Self & Informant Report	Depression / Suicide Risk	Recommended	• PHQ-9 • (note suicide item #9)	• PROMIS – Depression • BDI-2
	Anxiety	Recommended	• GAD-7	• PROMIS – Anxiety • BAI
	Sleep-wake	Encouraged	• ESS • PSQI	• PROMIS – Sleep Disturbance • PROMIS – Sleepiness-related Impairment
	Frontal-Behavioral Syndrome	Encouraged	• FrSBE (informant) • FrSBE (patient)	• b-DAS (informant)
	Anosognosia	Encouraged	• Anosognosia Scale	• FrSBE (patient v. informant)
	Neuropsychiatric Symptoms	Recommended	• PBA-s • NPI-Q (informant)	• BIS-11 • BVC
	Functional Status	Recommended	• HD-CFRS	• FAQ • WHODAS 2.0

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HSG NPWG: NP Practice Recommendations

Part 2. Neuropsychological Test Battery
- Assess Effort & Performance Validity
- Test battery duration
- Minimize or limit motor tasks

Part 3. Diagnosis
- DSM-5 includes Mild and Major Neurocognitive Disorder due to Huntington's disease

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Table 2. DSM-5 Mild and Major Neurocognitive disorder due to Huntington disease.

DSM-5 Syndrome	DSM-5 Criteria	Diagnostic Feature	Associated Features	Functional Consequences
Mild or Major Neurocognitive Disorder Due to HD	• Criteria for mild or major neurocognitive disorder was met (see below) • Insidious onset and gradual progression • Clinically established HD or risk for HD based on family history or genetic testing • Neurocognitive disorder is not attributable to another medical condition and is not better explained by another mental disorder	• Progressive cognitive impairment is a core feature of HD, with early changes in executive function (i.e. processing speed, organization, and planning) rather than learning and memory • Cognitive and behavioral changes often precede the emergence of typical motor abnormalities of bradykinesia • Diagnosis of definite HD given in the presence of unequivocal, extrapyramidal motor abnormalities in an individual with a family history of HD, or genetic testing showing a CG trinucleotide repeat expansion in the HTT gene (chromosome 4)	• Frequent • Depression • Irritability • Anxiety • Apathy • Obsessive-compulsive symptoms • Sleep disorder • Rare • Psychosis	• In prodromal stage and early illness, occupational decline is most common • Emotional, behavioral, and cognitive aspects of HD (e.g. disinhibition and personality changes) are highly associated with functional decline • Cognitive deficits that contribute to most functional decline include processing speed declines, inattention, and initiation difficulties • Given the age of onset, HD can greatly affect social, occupational, and family life • As the disease progresses, disability from motor symptoms becomes more apparent, as well as disability from continued cognitive impairment

Differential Diagnosis
- **Criteria for a mild neurocognitive disorder:**
  - Modest cognitive decline from prior level of performance in one or more cognitive domains based on 1) concern from the individual, informant, or clinician; or 2) modest impairment on neuropsychological assessment.
  - The cognitive deficits do not interfere with everyday independence.
- **Criteria for a major neurocognitive disorder:**
  - Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domain based on 1) concern from the individual, informant, or clinician; or 2) substantial impairment on neuropsychological assessment.
  - The cognitive deficits are functionally limiting (i.e. at a minimum, requiring assistance with complex instrumental activities of daily living).
- For both a major or mild neurocognitive disorder diagnosis, these cognitive symptoms do not occur in the context of a delirium and are not better explained by another mental disorder.
- Early symptoms of HD may include emotional lability, irritability, or compulsive behaviors that may initially suggest another mental disorder. Genetic testing or developmental of motor symptoms will increase diagnostic clarity.
- Early HD symptoms, such as executive dysfunction and impaired psychomotor processing speed, can resemble other underlying etiologies for cognitive disorders (e.g. Parkinson's disease, vascular dementia).
- HD is not the only consideration in the context of chorea, such as Wilson's disease or drug-induced tardive dyskinesia.

Note. Adapted from DSM-5.

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HSG NPWG: NP Practice Recommendations

Part 4. Clinical Recommendations

- Pharmacological interventions
  - Cognition: SAGE-718- Dalzanemdor for the treatment of cognitive impairment in HD did not meet primary endpoints
    - Stimulants: No evidence of benefit, may worsen irritability, sleep, and motor agitation
  - Psychosis: Aripiprazole (off-label) has been found to be beneficial, and may improve concentration (Brusa et al., 2009; Patrick & Ritchie, 2020)
- Nonpharmacologic interventions
  - Multidisciplinary interventions (cognitive training, exercise, social interactions) have shown promise (Zinzi et al., 2007; Barlett et al., 2020).

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HSG NPWG: NP Practice Recommendations

Part 4. Clinical Recommendations

- Psychosocial and safety considerations
  - Evaluating patient's ability to manage affairs, live independently, and drive safely
  - Referrals to PT, OT, and SW
  - Decision-making capacity
  - Work/School accommodations
  - Disability status
  - Psychosocial education
  - Referrals to support groups

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Giving Back

Factor H: Not-for-profit organization

- Improve the quality of life and dimmish suffering of people affected with Huntington disease living in extreme conditions of poverty and social neglect
- www.factor-h.org

Huntington's Gratitude Day (3/23)

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