Neuropsychiatric Aspects of Huntington's Disease

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What We'll Cover Today

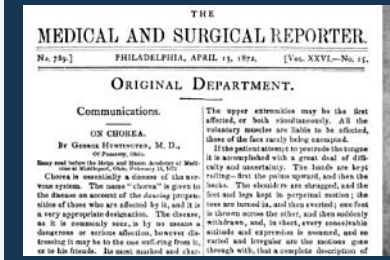
- How HD affects thinking and memory
- The emotional and behavioral changes in HD
- Depression, apathy, and irritability
- Less common but important symptoms
- When to worry: delirium warning signs
- Sleep and other quality-of-life concerns
- Treatment options and practical strategies

Please ask questions at any time!

A Disease Recognized Early

In 1872, Dr. George Huntington — at just 22 years old — wrote one of the most remarkable descriptions in all of medicine.

- It runs in families (hereditary nature)
- Symptoms typically emerge in adult life
- It causes both movement problems and changes in thinking
- Behavioral changes and emotional distress are part of the disease
- Suicide risk is elevated
- It gets worse over time


THE
MEDICAL AND SURGICAL REPORTER.
No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.
ORIGINAL DEPARTMENT.
Communications.
ON CHOREA.
By George Huntington, M. D.,
Of Pomeroy, Ohio.
Chorea is essentially a disease of the nervous system. 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 char-
The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.
If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of

George Huntington, MD (1850–1916)

Published "On Chorea" in the Medical and Surgical Reporter at age 22

"On Chorea" — Medical and Surgical Reporter, 1872

Huntington's Disease at a Glance

~30,000

Americans
living with HD

~200,000

At risk in
the U.S.

~40

Median age
at diagnosis

- Caused by a genetic change (expansion) in the HTT gene
- Each child of a parent with HD has a 50% chance of inheriting the gene
- Affects men and women equally
- The disease involves three domains: movement, thinking, and behavior

The CAG Repeat: What the Numbers Mean

10–26

Normal

No risk

27–35

Intermediate

Won't develop HD, but children may be at risk

36–39

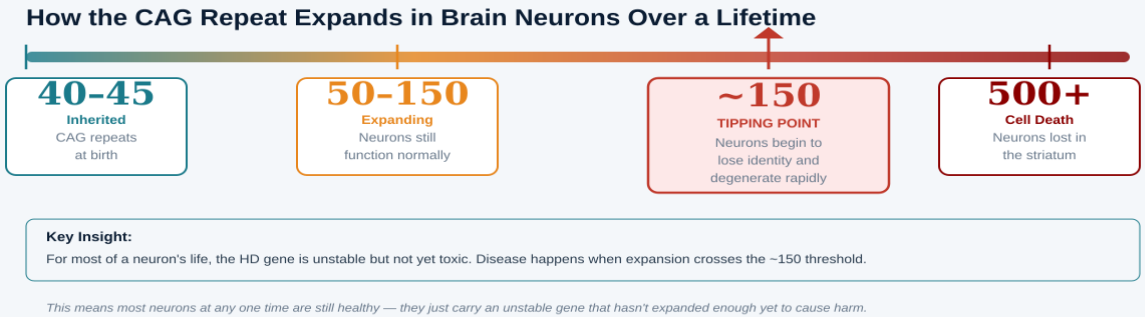
Reduced Penetrance

May or may not develop HD

40+

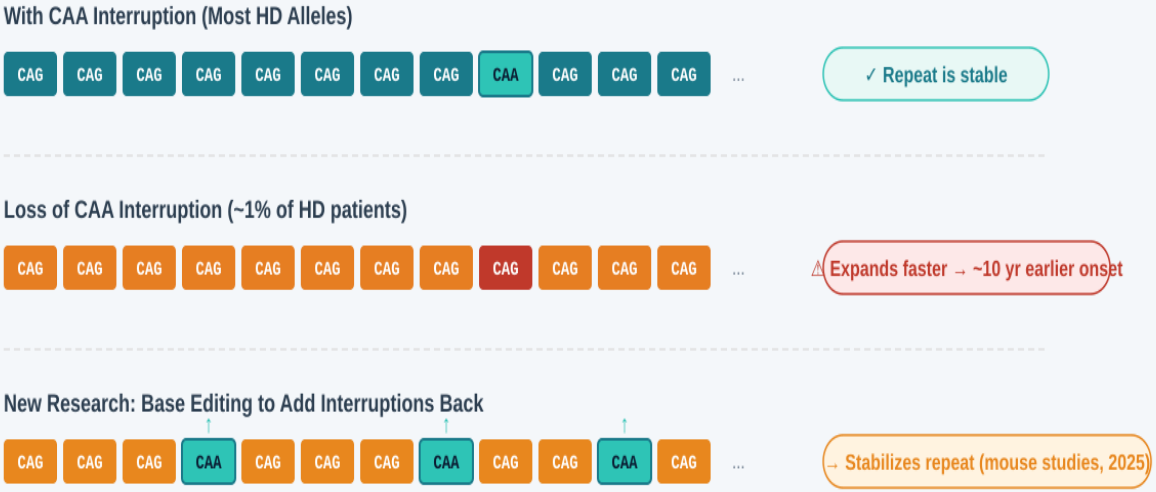
Full Penetrance

Will develop HD within a normal lifespan



Handsaker et al., Cell 2025

Why "Interrupted" Sequences Matter



This discovery has opened one of the most exciting potential therapeutic avenues in HD research today.

Wright et al., Genet Med 2020; Nature Genetics 2025

Rethinking How We Define HD: The HD-ISS

We now know the gene change is present from conception, with brain changes detectable before birth and cognitive/behavioral symptoms years before motor diagnosis. In 2022, experts proposed a new staging system based on this biological reality.

Stage 0

Gene Positive

Carry the HD gene
No detectable changes

Somatic CAG already expanding in blood (detectable by DNA test)

Stage 1

Biomarker Changes

↓ CSF PENK (MSN loss)
↑ CSF/blood NfL (nerve damage)
Caudate/putamen atrophy on MRI
~20+ yrs pre-diagnosis

Stage 2

Clinical Signs Appear

Cognitive, behavioral, or motor signs present

NfL & PENK worsen; striatal atrophy advancing; scales abnl

Stage 3

Functional Decline

Daily activities impaired

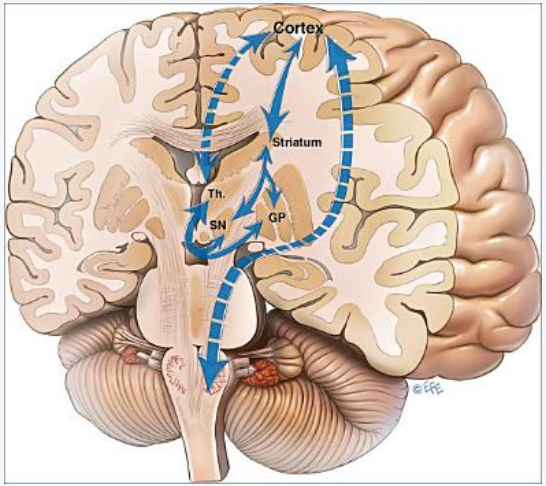
Work, finances & self-care declining; marked brain atrophy

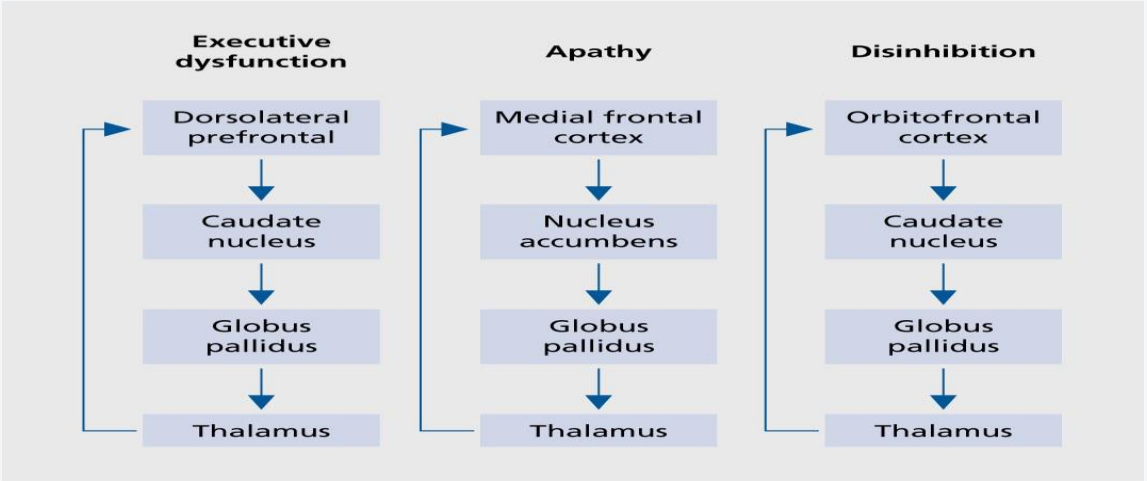
Why this matters for you: It formally recognizes what families have always known — the disease is present long before the movement disorder is diagnosed. Future treatments will aim to intervene at Stages 0–1, before significant damage occurs.

Tabrizi et al., Lancet Neurol 2022; Farag et al., Mov Disord 2025; Scahill et al., Nat Med 2025; Barnat et al., Science 2020

What Happens in the Brain

> The caudate and putamen (the "striatum") are hit hardest and earliest. They are part of circuits that loop through the frontal lobes — the brain's center for planning, judgment, motivation, and emotional control. When these circuits break down, thinking, mood, and behavior all change.





Left: The cortico-striato-pallido-thalamo-cortical loop. Right: Three parallel frontal-subcortical circuits affected in HD.

The Three Domains of HD

Movement

Chorea, coordination problems, swallowing difficulties

Thinking

Slower processing, planning difficulty, memory changes

Behavior & Emotions

Depression, apathy, irritability, sleep problems

Today's focus: the thinking, behavioral, and emotional changes

Cognitive Changes

How HD affects thinking

Slower Thinking and Planning Difficulty

Processing Speed

The brain takes longer to process information. This shows up as:

- Slower responses in conversation
- Difficulty keeping up with group discussions
- Needing more time to make decisions

Executive Function

The ability to plan, organize, and switch between tasks declines:

- Trouble organizing steps of a task
- Difficulty multitasking
- Reduced mental flexibility
- Problems with judgment and planning

Tip: Give extra time for responses. Slower processing ≠ less understanding.

What Families Often Notice

"They won't do anything"

People with HD often have difficulty starting tasks — but once started, they can follow through. This is a problem with initiation, not laziness or refusal.

"They get stuck on things"

Perseveration — getting fixated on a thought, topic, or behavior — is common. The person may repeat questions, dwell on a concern, or have difficulty shifting to a new activity.

Both are brain-based symptoms, not character flaws. Gentle cueing and structured routines help.

Losing Well-Practiced Skills

Unlike Alzheimer's disease, where well-practiced routines are preserved until late, HD affects "procedural" or "muscle memory" early.

- Activities like riding a bike, driving, or playing an instrument gradually decline
- Eventually, even chewing and swallowing can be affected
- This is a key difference from Alzheimer's disease

Alzheimer's Disease

Forgets facts and events first;
practiced skills preserved longer

Huntington's Disease

Practiced skills decline early;
recognition memory preserved longer

Changes in Perception and Awareness

Emotion Recognition

Difficulty reading facial expressions, especially disgust and anger. Can lead to social misunderstandings.

Time Perception

The internal clock becomes unreliable. People who were punctual may become consistently late.

Awareness of Illness

Many people with HD don't fully recognize their own symptoms. This is called anosognosia — a neurological symptom, not denial.

Anosognosia is not stubbornness — it's the brain's inability to see its own deficits.

Neuropsychiatric Symptoms

The emotional and behavioral side of HD

Behavioral Symptoms: Often the First Sign

Neuropsychiatric symptoms can appear years — even decades — before the movement problems.

Apathy Factor

Reduced activity
Low initiative
Emotional blunting
Worsens over time

Depression Factor

Low mood
Anxiety
Low self-esteem
Present at all stages

Irritability Factor

Poor temper control
Verbal/physical aggression
Impulsivity
Peaks early in disease

Rickards et al., 2011; van Duijn et al., JNNP 2014

Apathy: The Most Common Symptom

Apathy is the single most common neuropsychiatric symptom across all stages of HD.

- Loss of motivation, interest, and emotional responsiveness
- Worsens steadily as the disease progresses
- Different from depression — a person with apathy may not feel sad, just "empty"
- Strongly associated with declining functional capacity
- One of the most distressing symptoms for caregivers

Apathy ≠ Depression. They look similar but have different causes. Apathy responds poorly to antidepressants. Structured activities and routines help most.

van Duijn et al., JNNP 2014; Ruiz-Idiago et al., Parkinsonism Relat Disord 2023

Depression in HD

38%

overall frequency of depression in manifest HD

- Can occur at any stage — and can be the first symptom
- Depression in HD may have different biology than typical major depression
- Suicide rate is 4–12x that of the general population
- Severe cases may include psychotic features

What We Know About Treatment

- Standard antidepressants are used but high-quality HD-specific evidence is limited
- People with HD may be more sensitive to medication side effects
- ECT (electroconvulsive therapy) can be effective for severe depression
- Psychotherapy and multidisciplinary rehabilitation also have roles

Zadegan et al., J Neuropsychiatry Clin Neurosci 2024; 2025 meta-analysis

Suicide Risk in HD

Suicide rates in HD are 4 to 12 times higher than the general population.

There are two critical high-risk periods:

At the time of diagnosis

When the reality of the diagnosis sinks in and future fears are highest.

When independence is lost

When driving, working, or managing daily life is no longer possible.

Risk Factors

Depression, hopelessness, social withdrawal, fear of future suffering

What You Can Do

Screen routinely for depression.
Ask about suicidal thoughts directly.
Connect with HD support services.

Irritability and Impulsivity

Irritability

- Among the earliest behavioral symptoms — 52% report it before diagnosis
- Temper outbursts come from loss of impulse control, confusion, and being overwhelmed
- The person may become violent but often forgets the incident, while the family doesn't
- Tends to peak in early-to-moderate stages

Impulsivity

- Poor self-control leading to risky behaviors
- May include reckless spending, gambling, or inappropriate sexual remarks
- Related to breakdown in frontal circuits that normally act as a "brake"
- Not done intentionally — the filter is broken

Reduce environmental triggers: noise, chaos, time pressure, and over-stimulation.

Anxiety: The Most Underrecognized Symptom

78%

of HD patients report current anxiety

40%

have never been prescribed treatment

Anxiety was associated with poorer quality of life

- Anxiety can appear years before motor diagnosis — among the earliest symptoms
- Often co-occurs with depression but can exist independently
- May present as social anxiety, generalized worry, or panic-like episodes
- SSRIs are first-line; buspirone is an option; benzodiazepines should generally be avoided in HD
- Simple interventions: structured routine, reducing uncertainty, clear communication

Sellers Gibson et al., Arch Psychiatr Nurs 2021

Mania and Elevated Mood States

Mania or bipolar-like episodes occur in 5–10% of people with HD — higher than in the general population.

Like depression, mania can be the very first sign of HD.

True Mania Includes:

- Elevated or irritable mood
- Grandiose or paranoid thinking
- Racing thoughts, pressured speech
- Decreased need for sleep

Disinhibition (Not Mania):

- Inappropriate comments or jokes
- Social boundary violations
- Impulsive behavior
- Lacks the grandiosity and mood elevation of true mania

Repetitive Behaviors: OCD or Perseveration?

Repetitive, rigid behaviors are common in HD — but they are usually perseveration (a frontal symptom), not true OCD.

Perseveration (Common)

- Getting "stuck" on a topic
- Repeating the same question
- Inflexible routines
- Part of executive dysfunction
- Related to frontal circuit damage

True OCD (Less Common)

- Intrusive, distressing thoughts
- Rituals performed to reduce anxiety
- The person recognizes it's irrational
- Causes significant distress
- May respond to SSRIs or CBT

Psychosis in HD

More common than previously thought — and may represent a unique phenotype

- Prevalence estimates range from 3% to 11% — higher than previously reported; psychotic symptoms can start 4–11 years before motor diagnosis
- Typically presents with paranoid delusions and/or hallucinations; formal thought disorder is less frequent
- Associated with lower CAG repeats and younger age at diagnosis, suggesting a unique phenotype within the HD spectrum
- Shared genetic vulnerability with schizophrenia — polygenic risk scores for schizophrenia predict psychosis risk in HD
- Familial aggregation is well documented: 23.8% of HD patients with psychosis have a first-degree relative with psychosis
- Treatment: second-generation antipsychotics preferred (risperidone, olanzapine, aripiprazole); ECT effective for refractory cases (used in ~20%, with 93% improvement)

Jellinger, J Neural Transm 2026; Badenoch et al., Schizophr Res 2025; Yakubu et al., BJPsych Open 2025

Other Important Concerns

Delirium, sleep, and daily life

Delirium: The Red Flag

Rule of thumb: Nothing changes rapidly in HD.
A sudden change in behavior or thinking = look for delirium.

Common Causes

- Dehydration and poor nutrition
- Urinary tract or lung infections
- Medication side effects
- Falls with head injury (subdural hematoma)
- Metabolic disturbances

What To Do

- Seek medical evaluation promptly
- Review all medications with the doctor
- Check for infections (UTI, pneumonia)
- Ask about head injuries from falls
- The cure is finding and fixing the cause

Sleep Problems

~90%
report sleep problems

Sleep problems can appear early, even in the premanifest stage, and may be tied to mood and anxiety disorders.

Causes & Factors

- Involuntary movements at bedtime
- Depression and anxiety
- Disrupted sleep-wake cycle
- Medication side effects (tetrabenazine, amantadine, others)
- Lack of daytime activity (apathy-related)

What Helps

- Keep a consistent daily schedule
- Maximize daytime activity
- Treat chorea if it disrupts sleep
- Avoid benzodiazepines (usually unhelpful in HD)
- Consider sedating antidepressants cautiously

Sexual Changes

Sexual function changes are common but underreported in HD.

- Can involve decreased interest (often linked to apathy or depression), or increased/inappropriate sexual behavior (linked to disinhibition)
- Medication effects — particularly antidepressants and antipsychotics — can reduce sexual function
- Involuntary movements may create physical difficulties
- Communication about these issues is often limited because of embarrassment or cognitive changes
- These are legitimate medical concerns — talk to your HD care team

Sex Differences in HD Neuropsychiatry

Although HD confers equal genetic risk to men and women, a 2026 scoping review of 44 studies found consistent sex differences in how neuropsychiatric symptoms present.

Women with HD

- More frequent depression and irritability
- Greater functional impairment and decline in daily activities
- More likely to receive antidepressants and anxiolytics
- Lower rates of full-time employment
- Motor symptoms drive functional decline

Men with HD

- More frequent apathy and substance misuse
- More psychotic symptoms and suicidal ideation over time
- More likely to receive antipsychotics and tetrabenazine
- Cognitive symptoms drive functional decline
- More pronounced cortical thinning on imaging

Recognizing sex-specific patterns helps with earlier detection, more targeted treatment, and better genetic counseling.

Hemicker et al., Biol Sex Differ 2026 (scoping review, 44 studies)

Treatment and Support

What we can do

Treatment Overview

High-quality clinical trial evidence for treating neuropsychiatric symptoms in HD is very limited. Treatment is guided by clinical expertise and extrapolation from other conditions.

Depression	SSRIs, SNRIs, mirtazapine, ECT for severe cases
Irritability	SSRIs; antipsychotics if severe; reduce triggers
Apathy	Structured activities, routine; limited medication benefit
Psychosis	Olanzapine, aripiprazole; also help with chorea
Mania	Valproate, antipsychotics; lithium with caution
Anxiety	SSRIs preferred; buspirone; avoid benzodiazepines

Important: People with HD are more sensitive to medication side effects, especially delirium and sedation.

Andriessen et al., Mov Disord Clin Pract 2025; Anderson et al., J Huntingtons Dis 2018

Research on the Horizon

The most promising oral disease-modifying data yet — and a new understanding of what makes the huntingtin protein toxic.

Huntingtin Lowering

★ Votoplam (Novartis/PTC)
Oral daily pill, 52% slowing at 24 mo. Phase 3 (INVEST-HD), ~770 pts, initiated 2026

AMT-130 (uniQure)
Gene therapy; 75% slowing at 3 yrs. FDA needs Ph.3; UK MHRA filing Q3 2026

Tominersen (Roche)
100mg only (60mg dropped Mar 2026); 301 pts enrolled; completing 2026

WVE-003 (Wave) — allele-selective ASO; 46% mHTT↓

Targeting Somatic Expansion

MSH3-lowering ASOs — stalled CAG expansion in human neurons

Oral MSH3 inhibitors (Pfizer, LoQus23)

Base editing to add CAA interruptions (mouse studies, 2025)

Other Approaches

SKY-0515 (Skyhawk) — oral RNA splicing, Phase 3 underway

CRISPR — early promise in mouse models (2026)

Branaplam — terminated due to neurotoxicity (VIBRANT-HD, 2026)

Votoplam data (April 2026) represents the most encouraging disease-modification signal yet in HD. No therapy is approved as disease-modifying, but Phase 3 results are expected by 2029.

Non-Medication Approaches

Structure & Routine

Consistent daily schedules, structured activities, day programs. The single most effective non-medication strategy.

Communication

Speak simply and directly. Allow extra response time. Avoid 'talking over' the patient — comprehension is often better than it appears.

Environment

Reduce noise and chaos. Minimize time pressure. Create a calm, predictable environment.

Caregiver Support

HD places enormous burden on caregivers. Support groups, respite care, and your own mental health matter.

Key Takeaways

1. Behavioral and emotional symptoms are core features of HD — not just side effects
2. These symptoms can appear years before movement problems
3. Apathy, depression, and irritability are the "big three" neuropsychiatric symptoms
4. A sudden change in behavior = look for delirium, not just disease progression
5. Treatments are available — start low, go slow, and use a team approach
6. Don't forget the caregiver — you need support too

Recommended Reading

Can You Help Me?

Inside the Turbulent World of Huntington Disease

Thomas D. Bird, MD

Professor of Neurology & Medical Genetics, University of Washington

Drawing on more than 40 years of caring for over 1,000 HD families, Dr. Bird shares the real human stories behind the disease — the challenges, the surprising moments, and the resilience of patients and families. Written for a general audience, it is one of the best resources available for understanding what it is like to live with Huntington's disease.

Highly recommended for patients, families, and anyone who wants to understand HD.

Resources

HDSA (Huntington's Disease Society of America)

hdsa.org — Information, support groups, Centers of Excellence

988 Suicide & Crisis Lifeline

Call or text 988 — 24/7 free, confidential support

HDSA Center of Excellence Network

Multidisciplinary HD clinics across the country

Your HD Care Team

Neurologist, psychiatrist, social worker, genetic counselor

Questions?

Thank you for your time and your advocacy for people living with Huntington's disease.

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