Huntington's Disease Society of America

The Kids-HD and the Kids-JHD Program

Peg Nopoulos, MD
Professor of Psychiatry, Neurology, and Pediatrics

Huntington's Disease Society of America

The information provided by speakers in workshops, forums, sharing/networking sessions and any other educational presentation made as part of the 2018 HDSA Convention program is for informational use only.

HDSA encourages all attendees to consult with their primary care provider, neurologist or other healthcare provider about any advice, exercise, medication, treatment, nutritional supplement or regimen that may have been mentioned as part of any presentation.

Presenter Disclosures

Peg Nopoulos

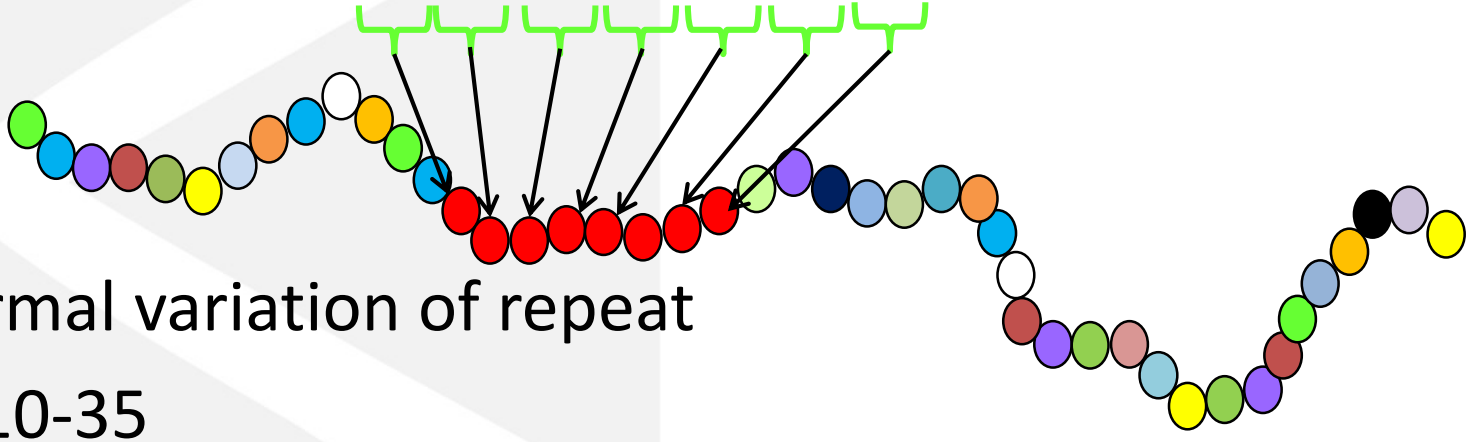
The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

No relationships to disclose
or list

The Huntington Gene

- Gene is Huntingtin or *HTT*
- Triplet repeat or trinucleotide repeat

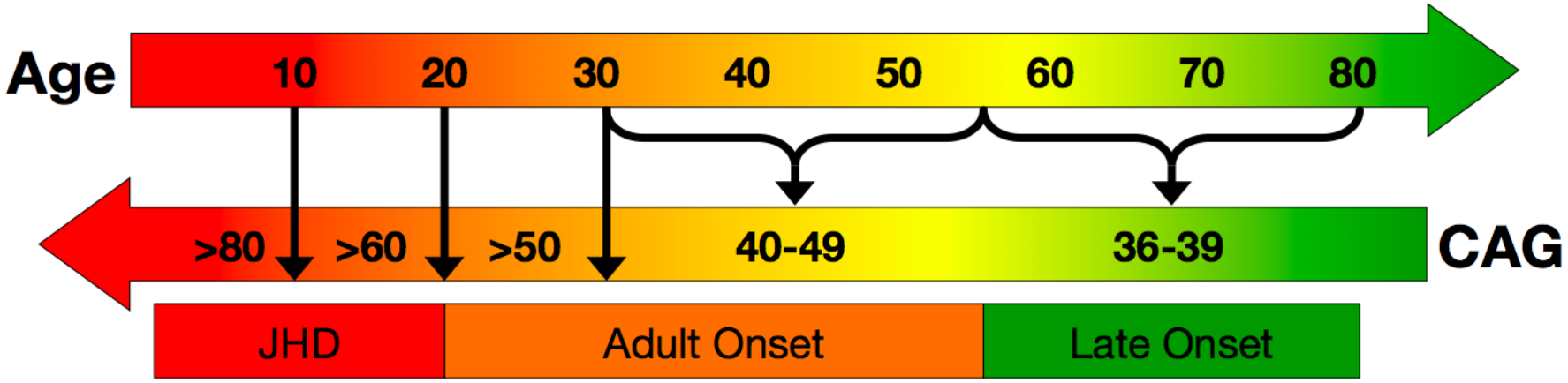
CGCCTAATCATGGCTCAGCAGCAGCAGCAGCAGCAGCAGGATATCCG



- Normal variation of repeat
  - 10-35
- >40, full penetration for disease
  - Mutant form = ***mHTT***

Huntington's Disease (HD)

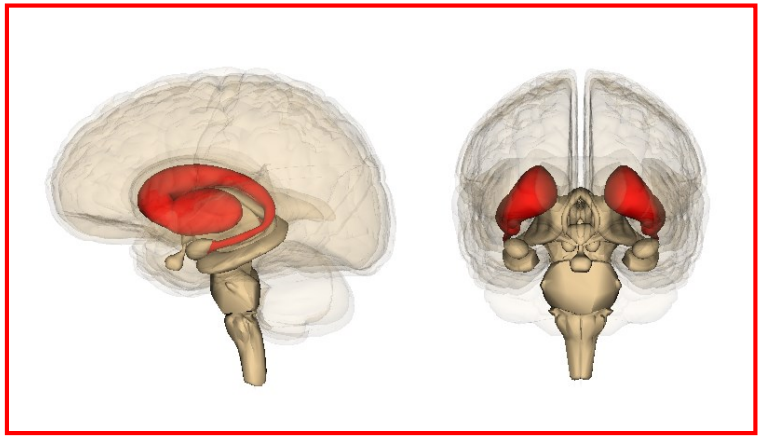
Longer CAG repeat → **earlier HD onset**



Longer repeat = more severe mutation

The Huntington Gene

- Since the discovery of the gene, many studies
- What have we learned?
- An important region of the brain called the **Striatum** is particularly affected in HD
- Large studies of individuals subjects like PREDICT and Track have shown that the striatum is affected YEARS before the onset of the disease



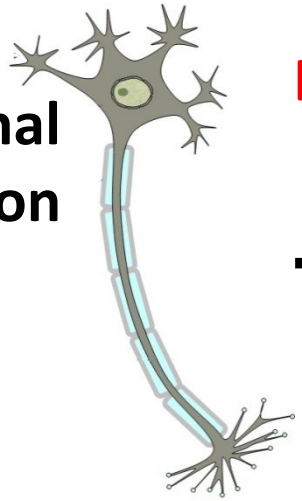
Questions that remain

- How far back does the abnormality in the striatum go? Is it possible that it didn't develop correctly?
- Why are there no symptoms until later in life even though the striatum is abnormal for years before that?
- We became interested in studying how the brain develops in people who have the expanded gene

Normal Neuron
Normal Development

Classical Concept: Gain of Function

Normal Neuron



Disease process
(toxic *mHTT*)

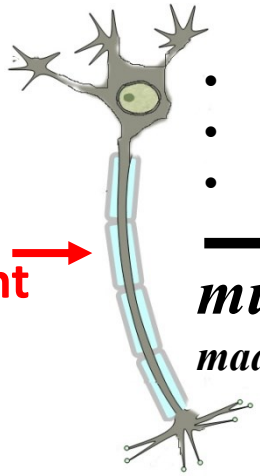
Degeneration

Cell Death

Mutant Neuron
Abnormal Development

Developmental Concept: Loss of Function

Disease process is abnormal development



- Maturational Processes
- Aging
- *mHTT*

mutant steady state
made possible by compensation

Degeneration

Cell Death

Kids-HD Program – Who is Eligible

- Subjects are children / young adults ages 6-25 years who
  - Have a parent (or grandparent)with HD (at-risk)
  - Healthy controls from the community=y
  - No symptoms of HD (no diagnosis of JHD)
- *For Research purposes only*, DNA from blood or saliva is used to measure CAG repeats in HTT; 2 groups:
  - Children at risk who are gene non-expanded (GNE)
  - Children at risk who are gene expanded (GE)

Kids-JHD Program – Who is Eligible

- Subjects are children / young adults ages 6-25 years who have already been diagnosed with JHD

Huntington's Disease Society of America

Kids HD + Kids JHD

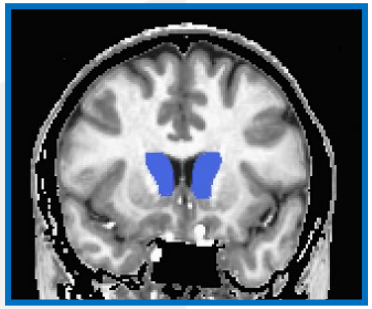
They come to Iowa City

Huntington's Disease Society of America

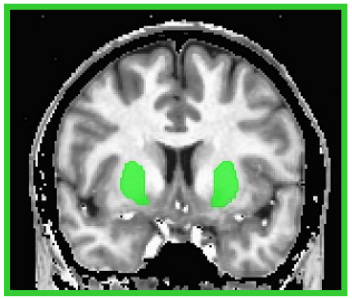
Kids HD + Kids JHD

Kids-HD and Kids-JHD Programs

- Magnetic Resonance Imaging (MRI) allows us to take a picture of a person's brain
- We get volumes of specific brain regions
- We call this assessment of brain structure



Caudate



Putamen

Caudate
+
Putamen
=
Striatum

- We look at brain function by looking at thinking skills tasks (memory, concentration, etc.) and motor function

Huntington's Disease Society of America

Kids HD + Kids JHD

The Kids-HD Program

	Combined Controls (CC) (n=356)	At-Risk GE (n-=125)
	Mean (s.d.) / Range	
Age	13.3 (3.8) 6-23	13.9 (4.0) 6-25
CAG Repeats	20.3 (4.1) 11-34	44.5 (5.1) 36-58

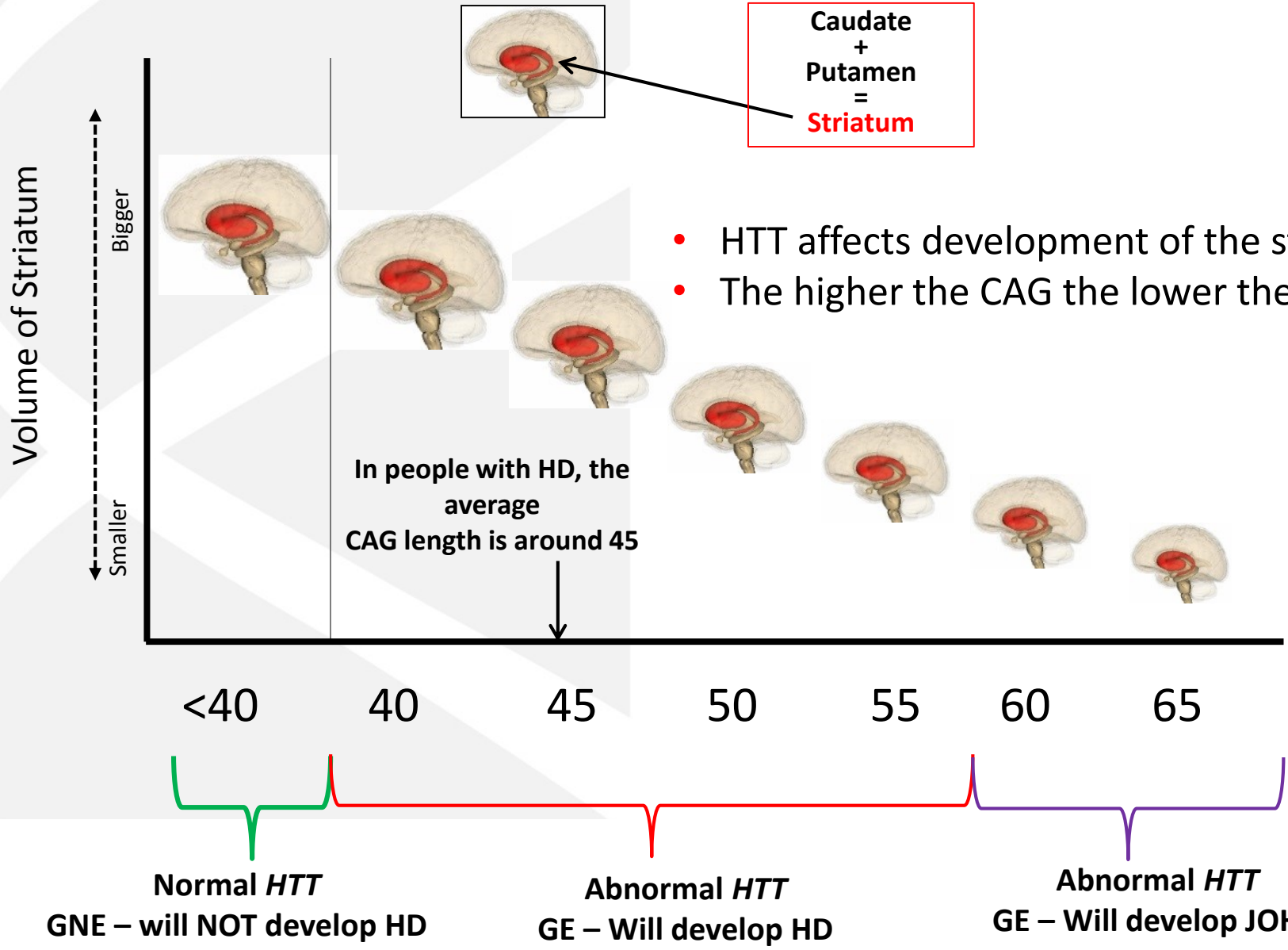
CC= healthy controls and GNE

Sonia Slevisnski

Jennifer Henderson

Jordan Harrelson

Effects of GE on Brain Development

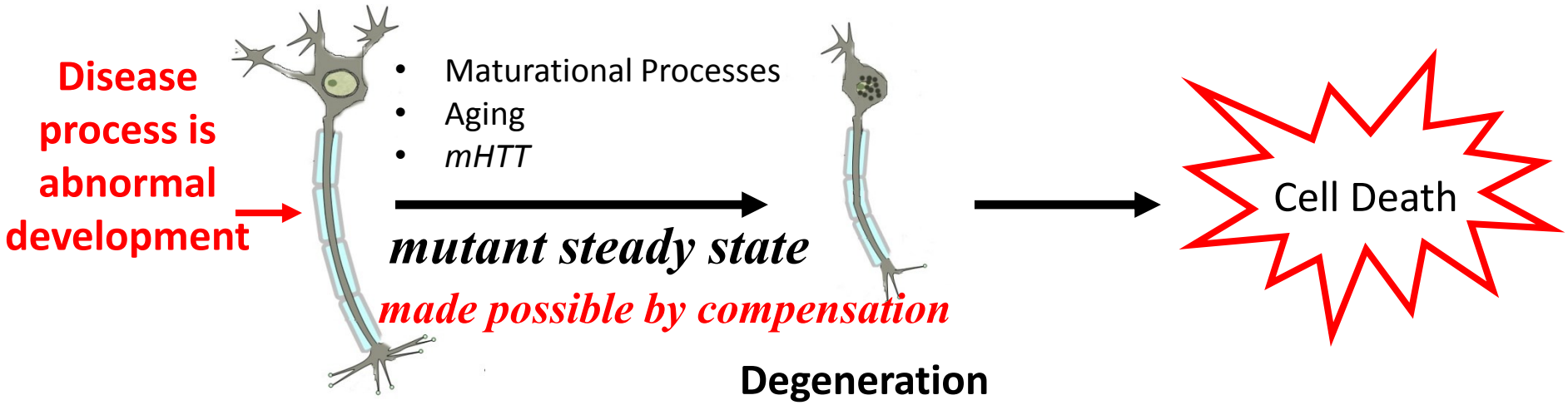


- HTT affects development of the striatum
- The higher the CAG the lower the volume

The Kids-HD Program

- So if the striatum is abnormal, why are these kids not having any symptoms?

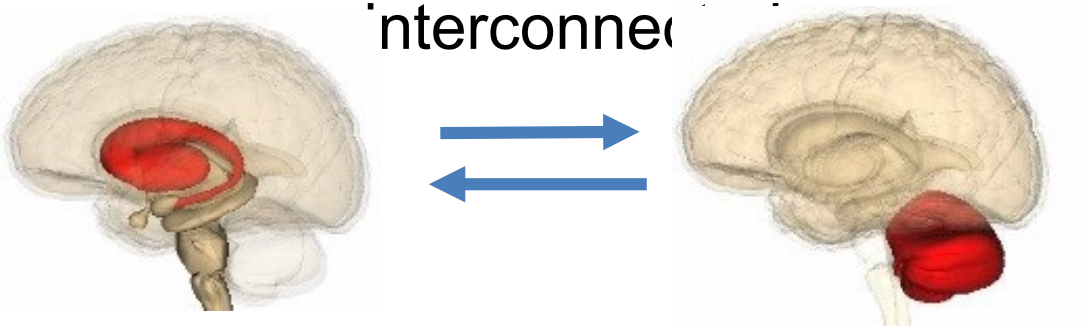
Developmental Concept: Loss of Function



What other parts of the brain might be responsible?
Invokes one of the most important advances in neuroscience: circuitry

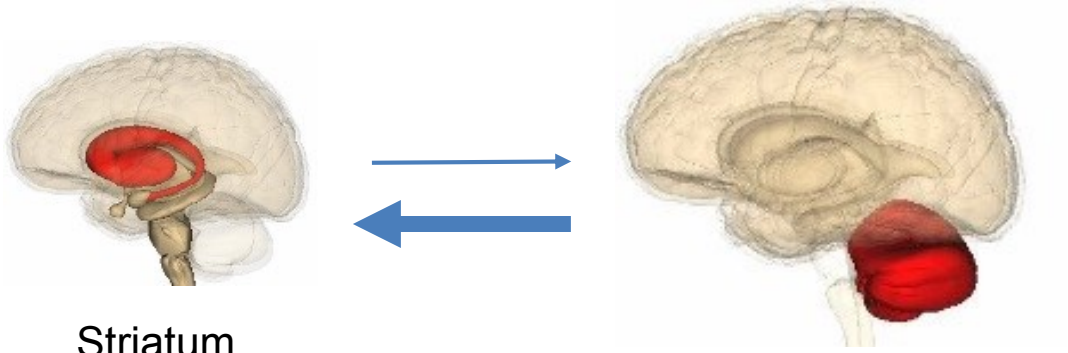
What happens when your striatum doesn't develop properly?

The Cerebellum and Striatum are interconnected



Striatum Cerebellum

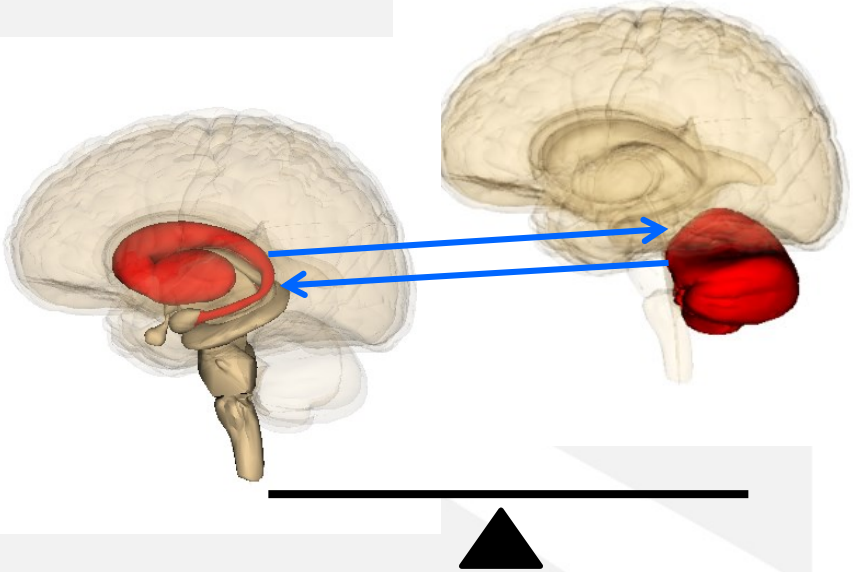
- They develop as a balanced circuit
- When one part is weak, the other part helps out or 'compensates'



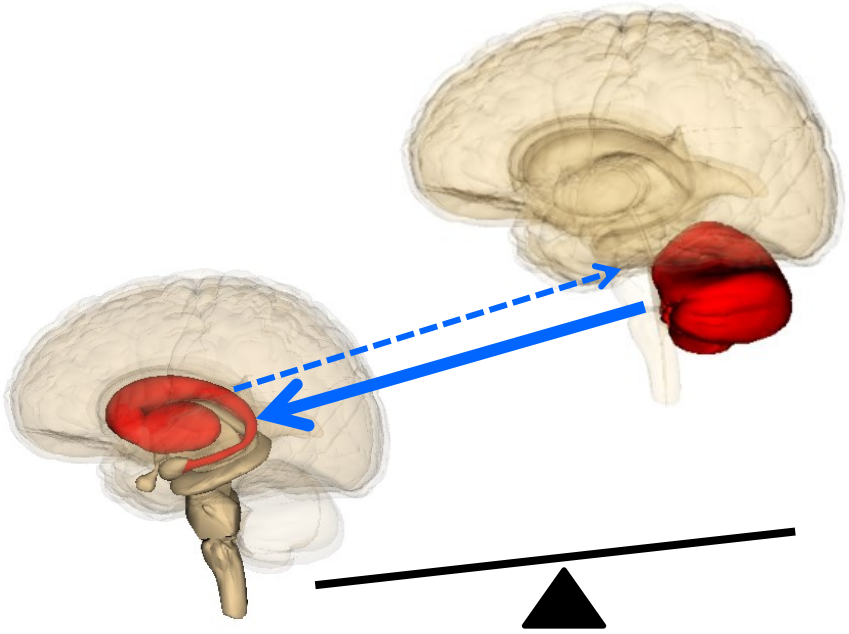
Striatum Cerebellum

Circuitry

- Theory – abnormal growth of the striatum is compensated for by the cerebellum



Normal Growth balanced circuit

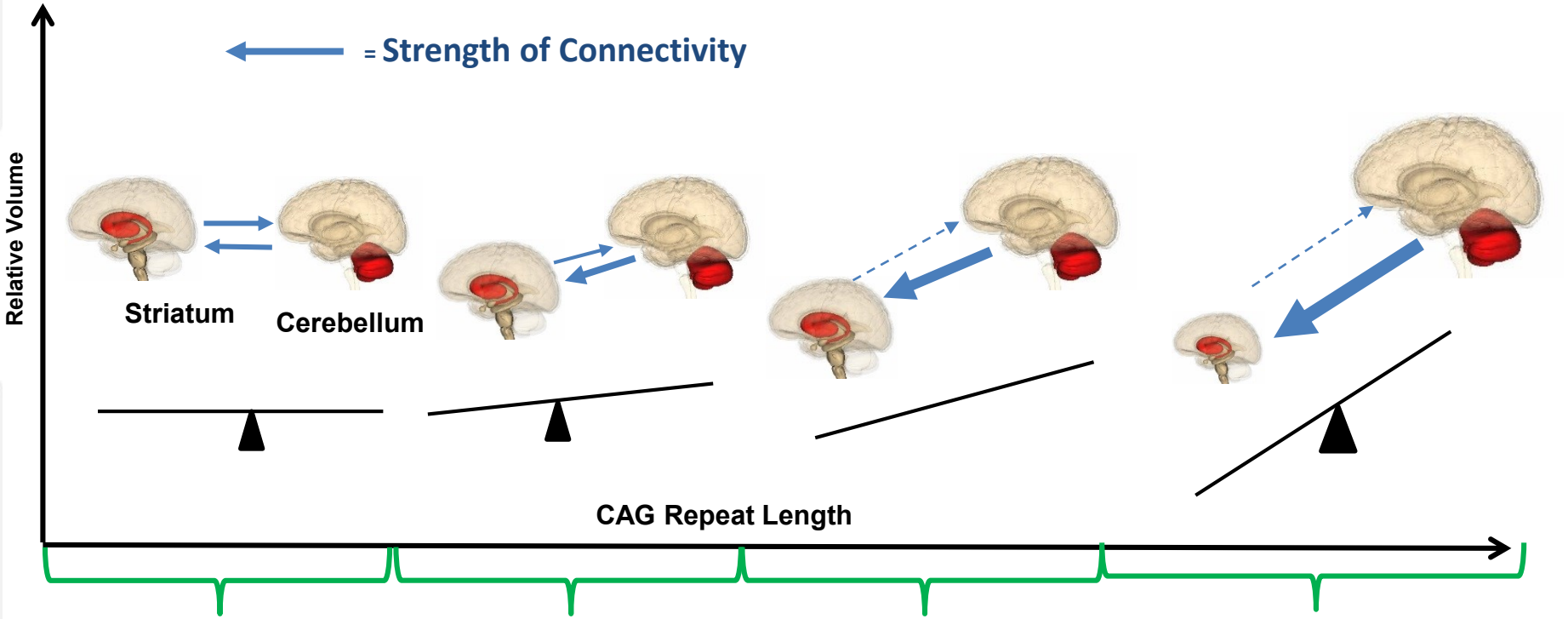


Abnormal growth, Cerebellar compensation

Circuitry

- Whhaaaa? The cerebellum involved in HD?
  - the one area of the brain discussed the least in all literature
  - considered to be ‘spared’ by HD disease pathology

Abnormal Development of Striatum



CAG = 10- 39

Normal Function

CAG = 40 – 44

Abnormal development with initial cerebellar compensation

CAG 40-44, well compensated; very subtle abnormalities in childhood

Adult onset of symptoms

CAG = 45 – 59

Abnormal development

Cerebellum doesn't compensate 100%

abnormalities in thinking and motor skills during childhood; the higher the CAG the worse the skills

Adult onset of symptoms, but earlier

CAG > 60 (JHD)

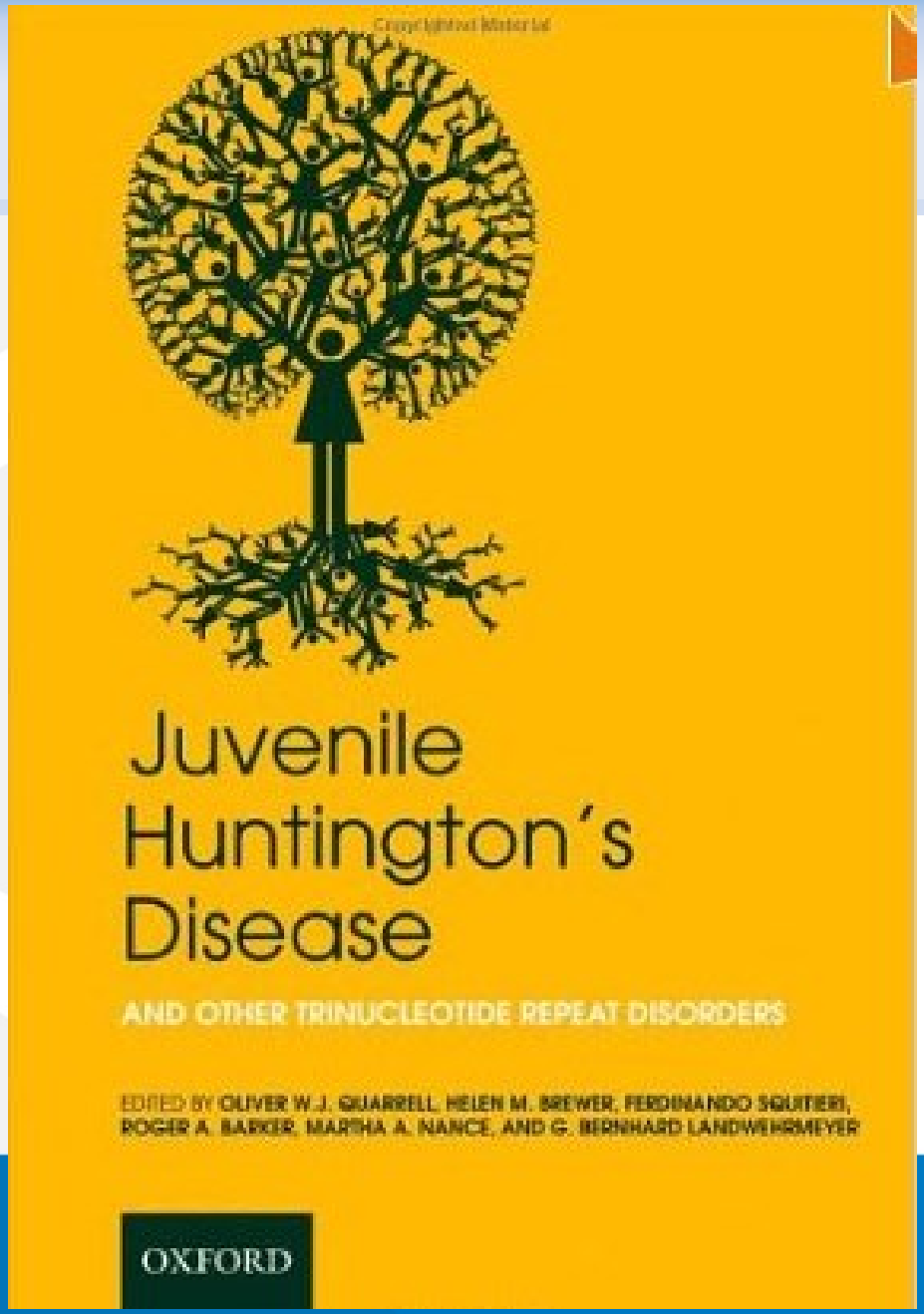
Severe abnormal development

cerebellum **<u>enlarged</u>**

Cerebellum instead of helping, is now 'over-active'

An over-active cerebellum leads to the hypokinetic symptoms of JHD (slowing, stiffness)

Kids HD + Kids JHD



Huntington's Disease Society of America

Juvenile Huntington's Disease

- Prevalence – How Common is it?
- Clinical features
- The diagnostic challenge

Juvenile Huntington's Disease

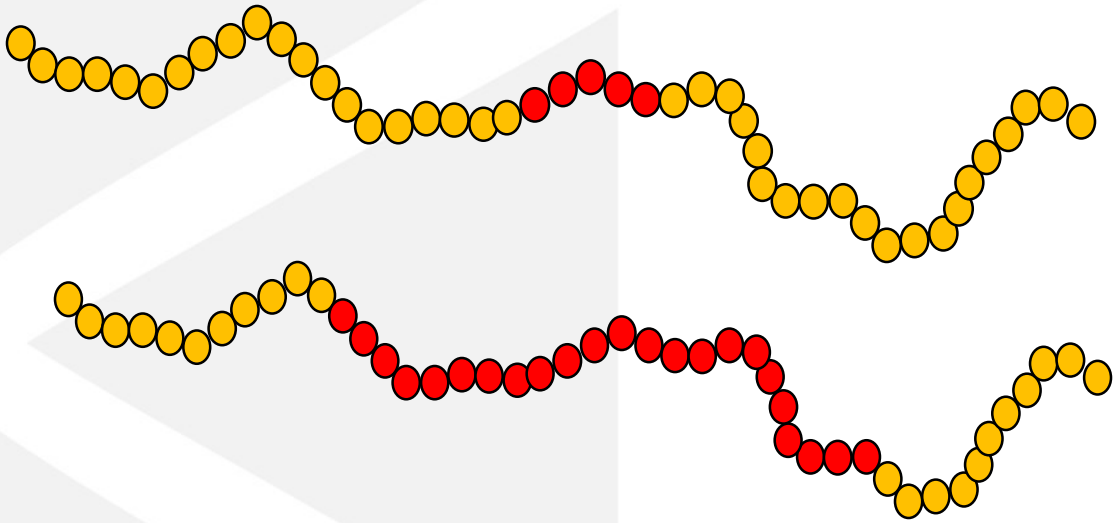
- Prevalence – How Common is it?
- Clinical features
- The diagnostic challenge

Juvenile Huntington's Disease

- Rare
  - Best estimate is around 5% of all HD cases
  - Even more rare for childhood onset

Genetic Anticipation

child, there is a chance it will expand



Example:
Parent
CAG = 43

Example:
Child
CAG = 65

- **This expansion is more likely to happen when the parent is MALE**
  - **Most JHD cases (up to 90%) have a father with HD**
  - **Converse – vast majority of fathers with HD will NOT have a child with JHD**

Juvenile Huntington's Disease

- Prevalence
- Clinical features
- The diagnostic challenge

Clinical Features

- Like all forms of HD, symptoms cluster in 3 main categories
  - Motor symptoms
  - Cognitive symptoms
  - Behavioral symptoms

Motor Symptoms

- Rigidity – stiff muscles
- Dystonia – muscles contract in abnormal position
- Ataxia – slow, shuffling, stooped walk
- Dysarthria – slurred speech
- Tremor
- Masked face – lack of movement in face
- Chorea – dance-like movements

Motor Symptoms

- These symptoms are often referred to as ‘Parkinsonian’ as they are similar to features of Parkinson’s disease.
- Chorea is much less common than is seen in adult onset HD, and often comes later in the disease

Cognitive Symptoms

  - Everything from general intelligence (IQ) to specific functions such as memory, attention, language and visuospatial skills

- For children with childhood onset (before the age of 10), this may be a failure of thinking skills development
- For JHD it is often seen as declining school or academic performance
- Like Adult onset, these thinking skills deficits will progress over time

Behavioral / Psychiatric Symptoms

- Behavior can be divided into 2 main categories:
  - Externalizing Behaviors – behavior that other people can see
    - Hyperactivity
    - Inattention
    - Opposition (not wanting to follow rules, talking back)
    - Aggression
  - Internalizing Behaviors – what people feel inside
    - Sad or depressed
    - Anxious
    - Obsessions

Behavioral /Psychiatric Symptoms

- Externalizing – the most common
  - Attention Deficit Hyperactivity Disorder (ADHD) may be diagnosed
  - Aggression may come on quickly, with unclear triggers
- Psychosis: hallucinations and delusions
    - More common in onset in teens and 20's

Presenting Symptoms

- In a large study of 53 cases *(Siesling et al.)*
  - 70% presented with Behavior symptoms
  - 48% with motor symptoms
  - 27% with cognitive symptoms
  - During the course, the number of cases that experienced behavioral disturbances:
    - Males: 93%
    - Females: 81%

Other Accompanying Features

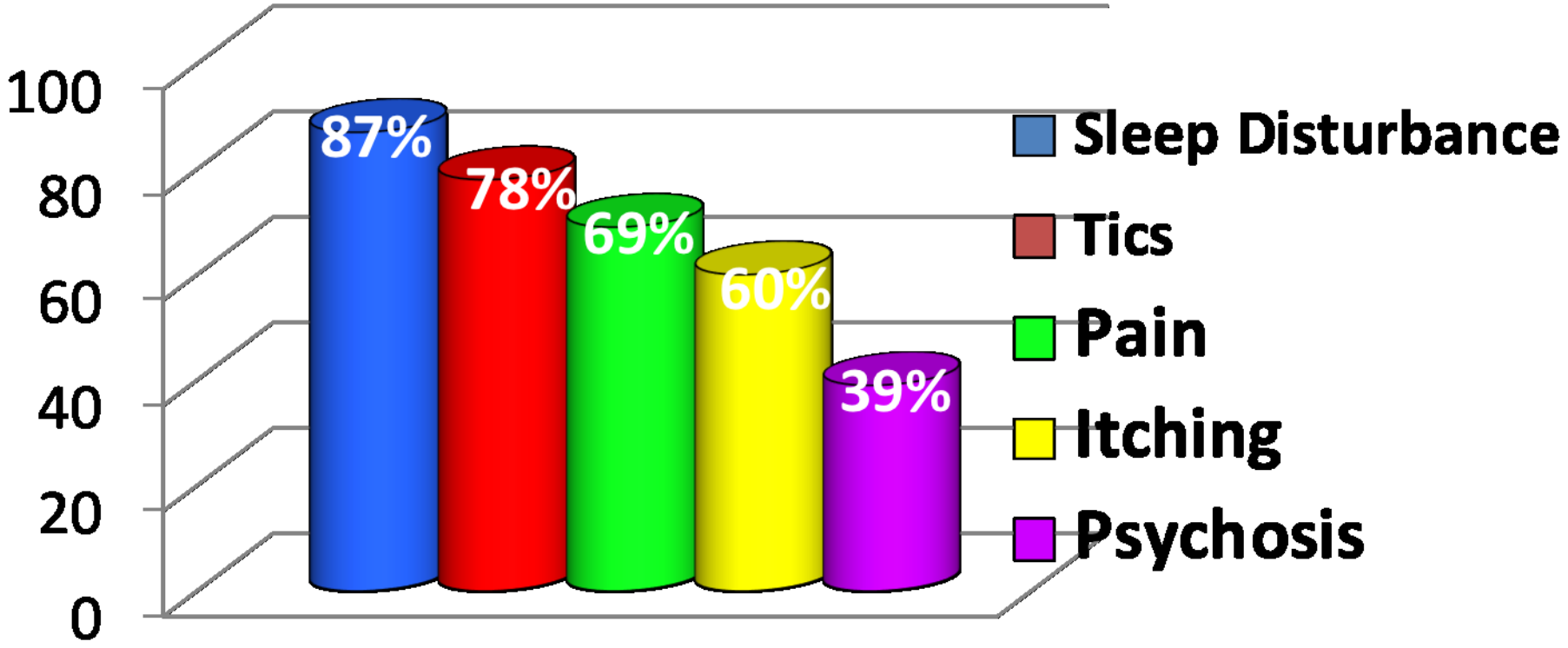
- Seizures
  - Up to 30-40% of cases
    - Generalized or tonic-clonic - ‘’grand mal”
      - Lose consciousness; entire brain involved
    - Partial complex
      - Impaired consciousness; parts of the brain involved
    - myoclonic epilepsy
      - Muscle jerks, no impairment of consciousness
  - Tend to be more common in the earliest onset cases and can be a presenting symptom

Common but unrecognized

- Through social media, we administered a survey designed to quantify identified symptoms often mentioned by JHD caretakers, but not part of the classic triad motor, cognitive, behavioral symptoms
    1. **Sleep Disturbance**
    2. **Pain**
    3. **‘Itching’**
    4. **Tics**
    5. **Psychosis**

Common but unrecognized

Demographic Info N=33	Mean	Range
Age at Diagnosis (yr)	12.21	3-21
Current Age (years)	15.75	4-27



Duration of Disease

- Somewhat controversial
- Duration of disease in JHD does NOT seem to be any different than duration of disease in adult onset
  - Average 15-20 years from diagnosis to death
- Thus even though CAG repeat can predict age of onset, it does NOT seem to predict duration of disease

Juvenile Huntington's Disease

- Prevalence
- Clinical features
- The diagnostic challenge

Juvenile Huntington's Disease

- Onset
  - The presence of unmistakable (not subtle) neurologic (**motor**) signs

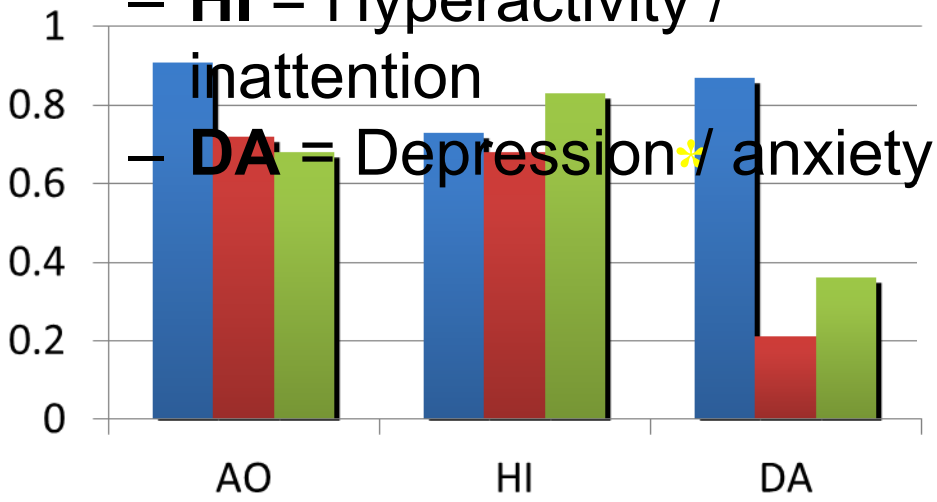
The Diagnostic Challenge

- Average length of time from first symptom to diagnosis – NINE YEARS *(Ribai et al)*
- *Most common presenting symptom is behavior

Behavior is a non-specific symptom

- Data from Kids-HD study
- Parent ratings of behavior
  - **AO** = aggression / opposition
  - **HI** = Hyperactivity / inattention
  - **DA** = Depression / anxiety

The higher the score, the worse the behavior



GNE = at risk, Gene Non-Expanded

GE = at risk, Gene Expanded SHORT CAG 40-49

GE = at risk, Gene Expanded LONG CAG 50-73

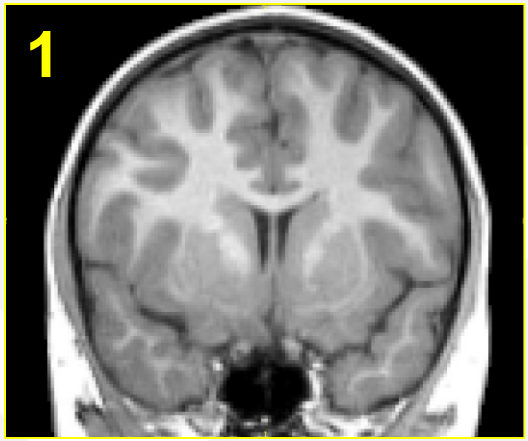
- Behavior does NOT distinguish groups
  - Exception being more depression in the gene non-expanded group

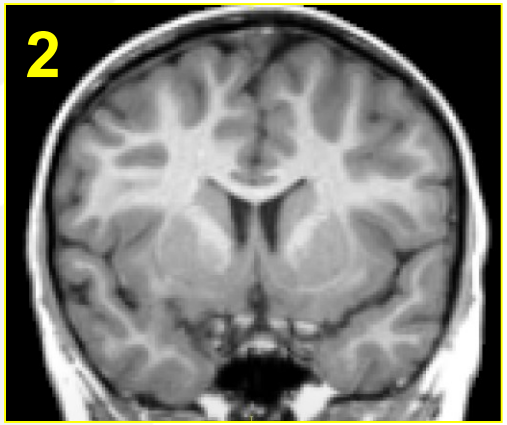
The Diagnostic Challenge

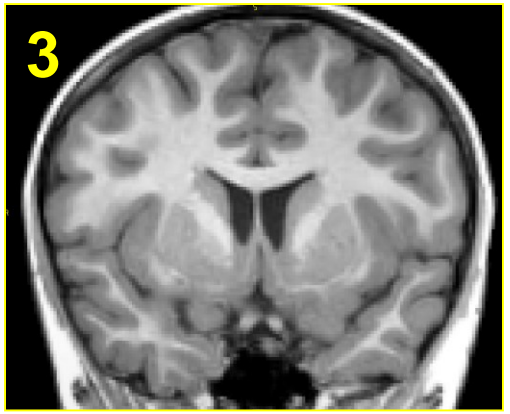
- What is the risk of getting a genetic test based on a non-specific symptom?
  - That symptom may not be related to HD
  - Analogy – making diagnosis of pneumonia for every patient that presents with a cough
- Example, child with ADHD
  - Genetic test: CAG=43
  - What if motor symptoms do not develop
    - And behavioral symptoms ameliorate
    - May have gotten ‘presymptomatic’ testing on a child who did not have the chance to make that decision for themselves

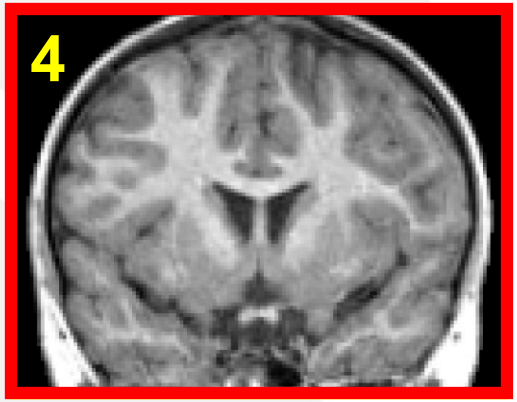
Can MRI imaging help the diagnosis of JHD?

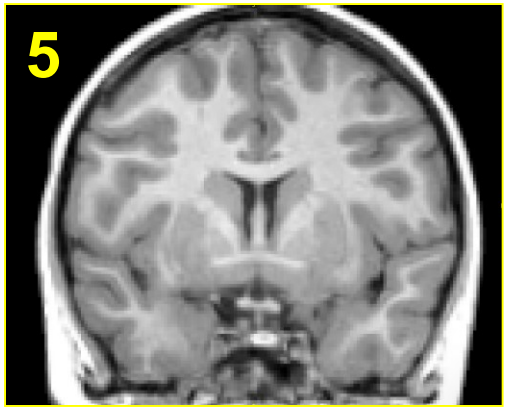
- Here are 5 Seven year old females
- Which one has JHD, age onset 6, CAG 101?









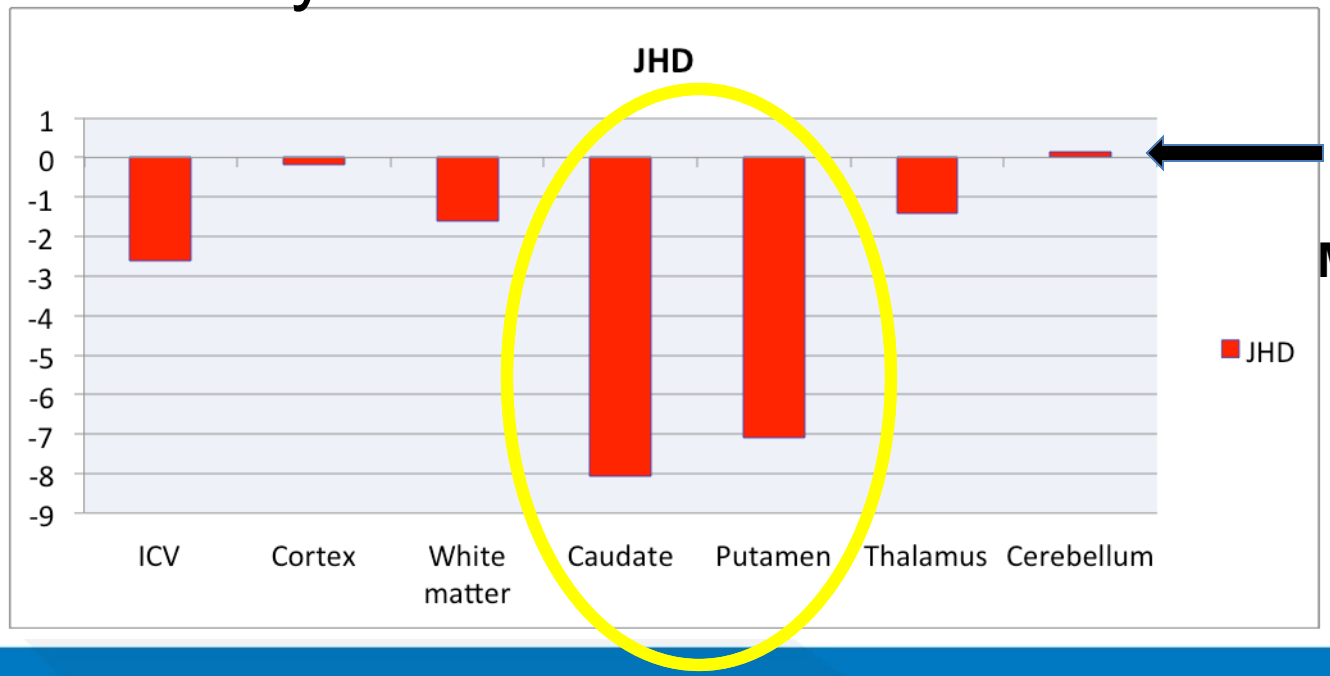


A 'clinical' scan, read by a radiologist – qualitative assessment: does this brain 'look' different?

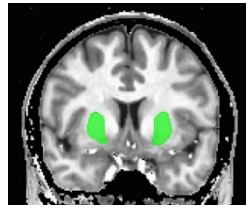
No – this will not help diagnosis

QUANTITATIVE MRI

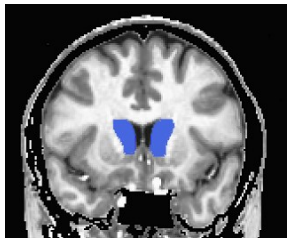
- Computer program calculates volumes
- JHD case compared to 7 age matched females, healthy controls



Healthy Control Mean = 0



Putamen



Caudate

Acknowledgements – Nopoulos Lab

Front: Amanda Benavides, Joel Bruss, Corinne Hamlin, Jessica Lee, Stephen Cross, Lynsday Harshman, Gail Harmata, Jon Goodwin

Back: Sasha Tereshchenko, Eric Axelson, Ian DeVolder, Peg Nopoulos, Jennifer Henderson, Jordan Harrelson, Sonia Slevinski

Not shown: Vince Magnotta,

Huntington's Disease Society of America

Kids HD+Kids JHD

Thank You to the kids and families

Huntington's Disease Society of America

Kids HD + Kids JHD