Huntington's Disease
Psychiatry

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HDSA Convention

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--Many slides adapted from Adam Rosenblatt, MD

Huntington's Disease Society of America

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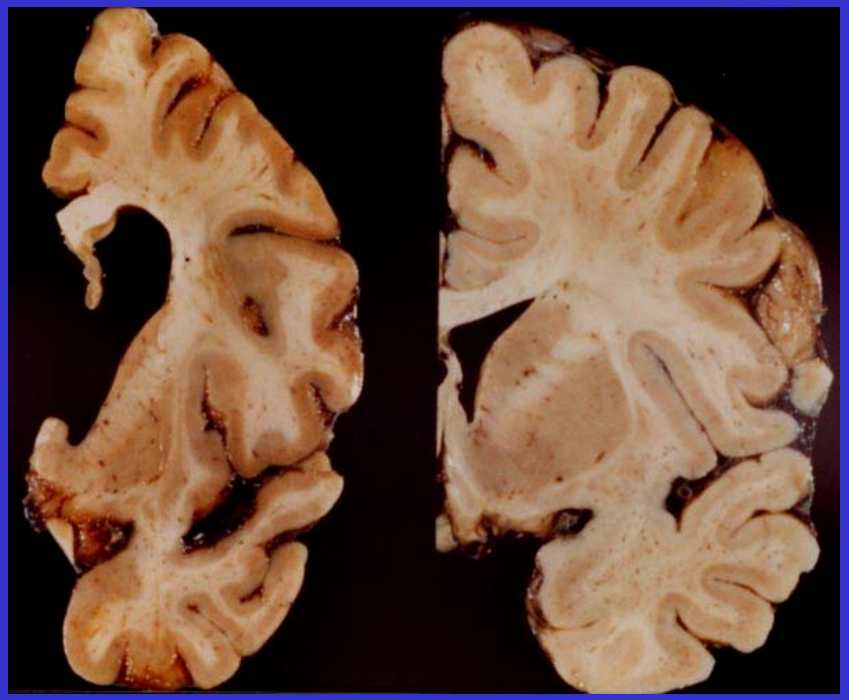
Huntington's Disease

- Selective neuronal degeneration in Basal Ganglia--Caudate and putamen, but also cerebral cortex and other regions
- CAG expansion mutation: longer CAG repeats have earlier onset and more widespead degeneration



CAG-CAG-CAG (DNA)

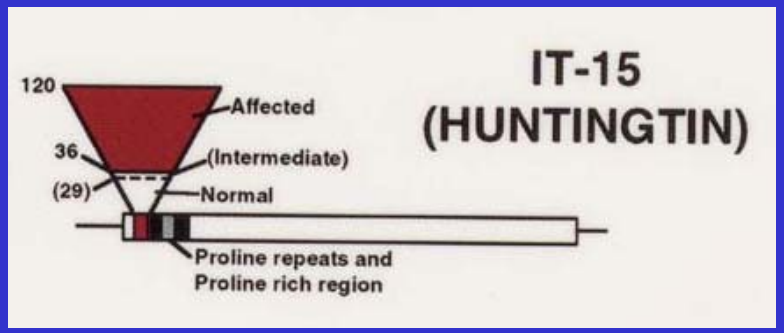
↓

CAG-CAG-CAG (RNA)

↓

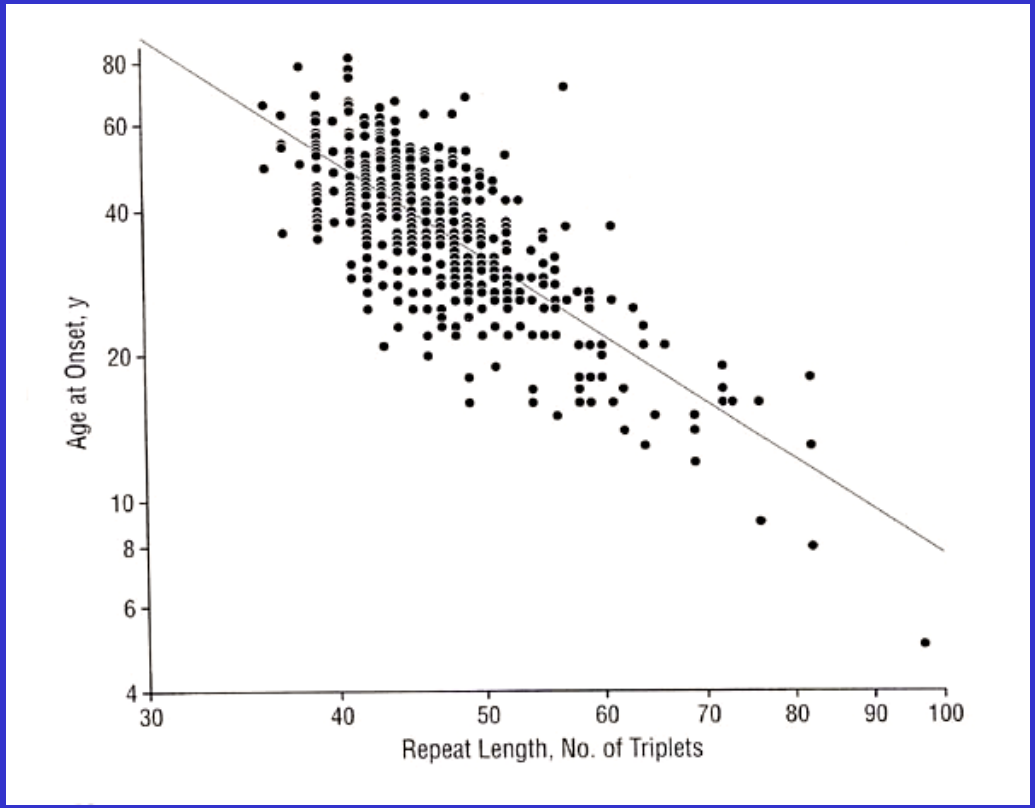
Gln---Gln---Gln (Protein)

(Q) (Q) (Q)



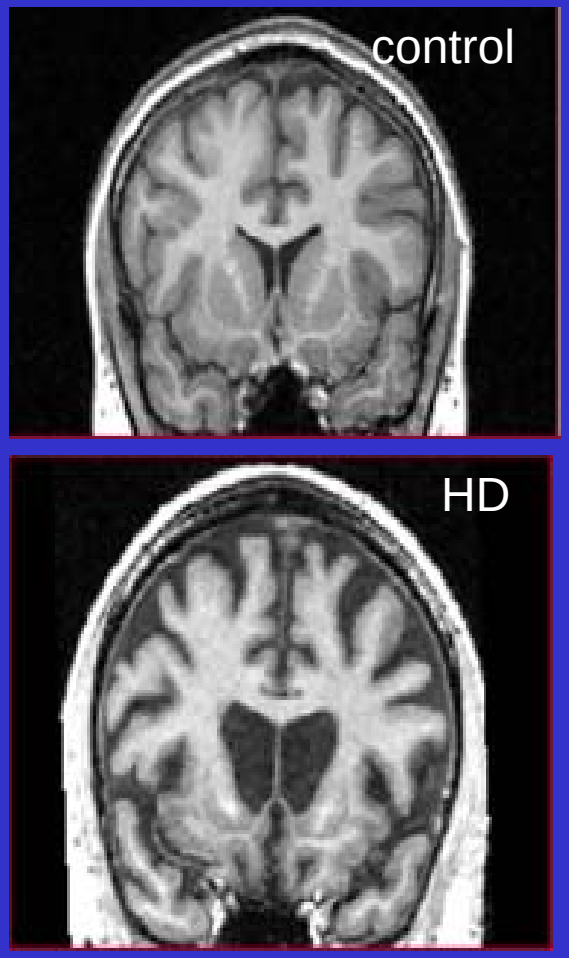
CAG Repeat length and Age of Onset of HD

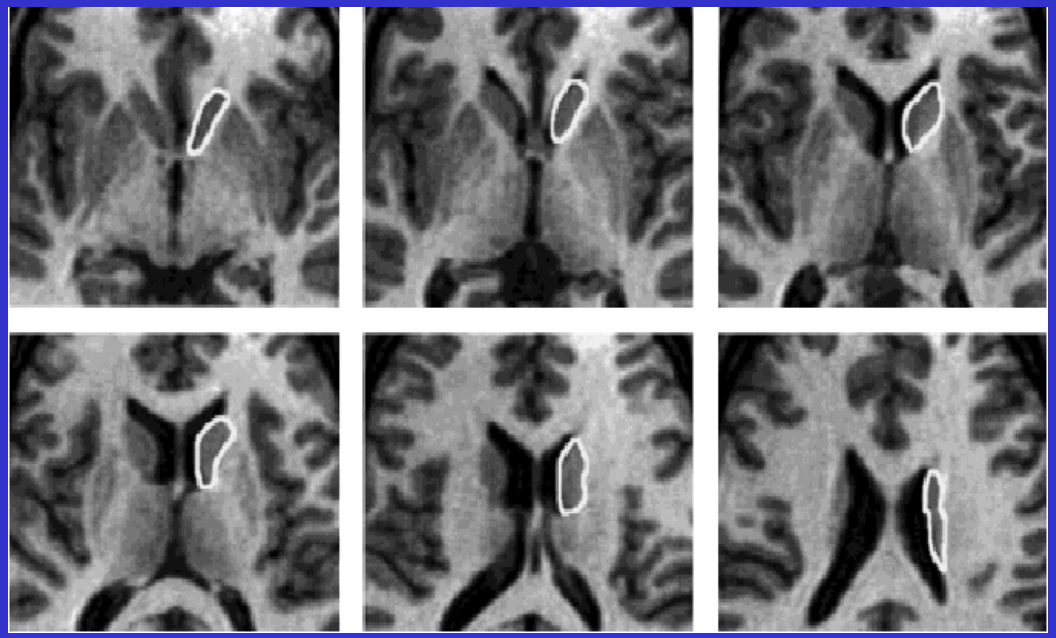
- CAG repeats of 35 or less do not cause HD
- Incomplete penetrance (delayed onset) for CAG 36 to 40
- Longer expansions result in earlier onset ages—thus can roughly predict onset age
- Determinants of the rate of progression are still unknown



--Ranen et al Am. J. Hum. Genet. 1995, and Margolis et al Arch. Gen. Psychiat. 1999

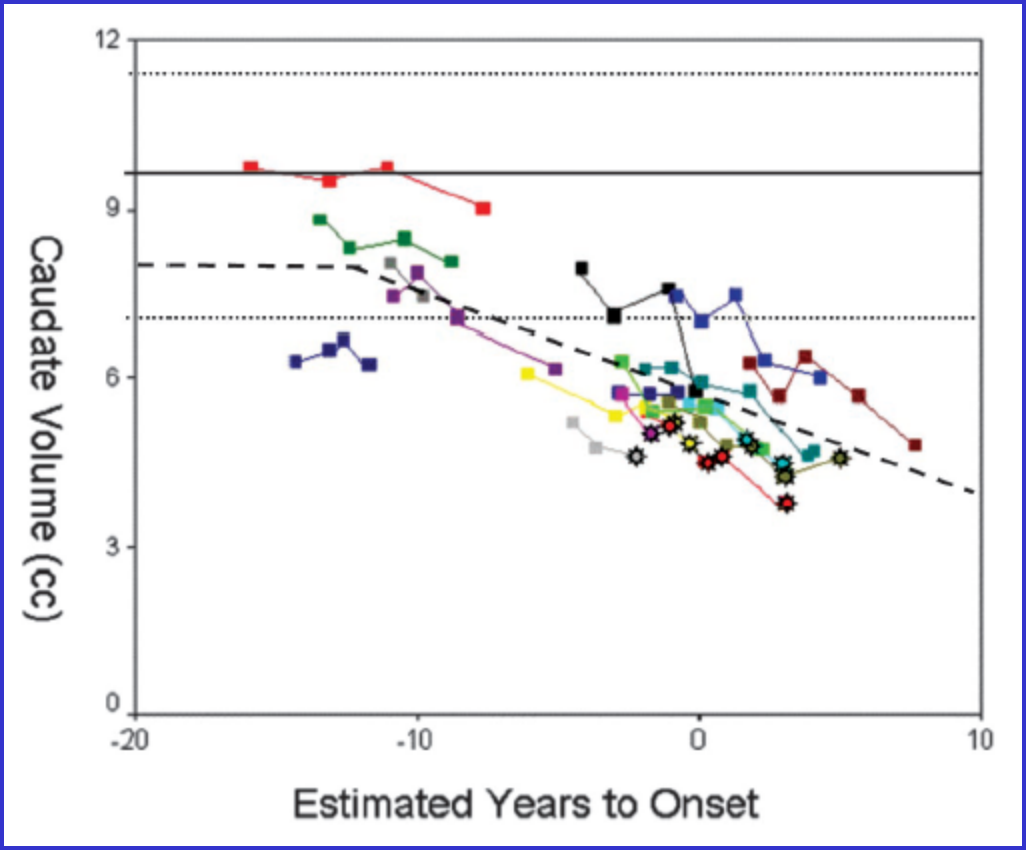
Quantification of Caudate Volumes: Regions of Interest





--Aylward et al Neurology 2004

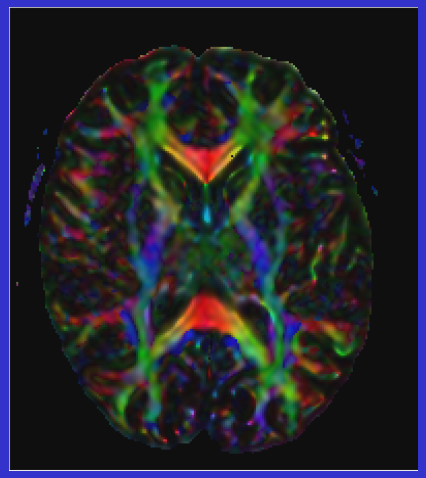
Caudate Atrophy in Pre-Symptomatic HD: Longitudinal Study in Hopkins Cohort

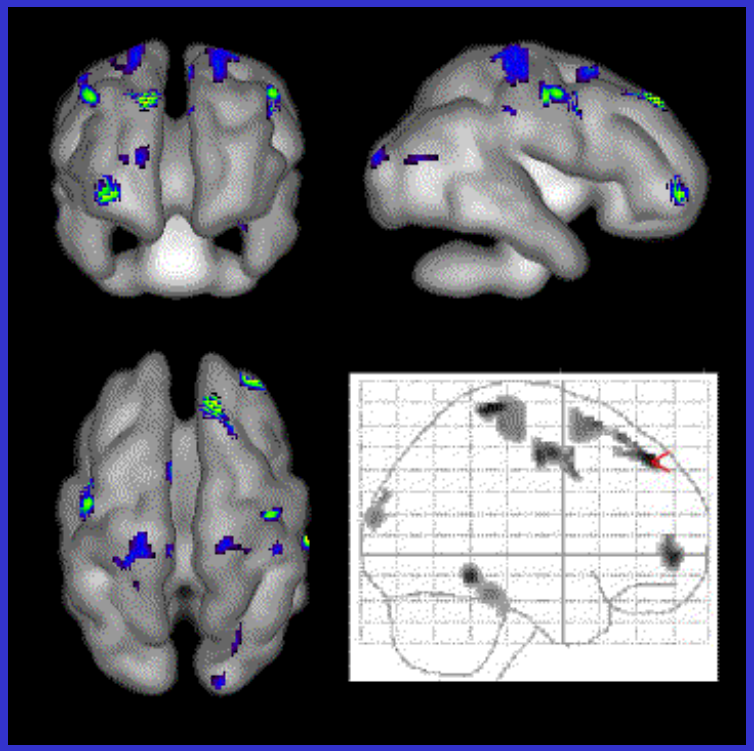


--Aylward et al, Neurology 2004

White Matter Alterations in HD Mutation-Positive Pre-Symptomatic Individuals

- DTI: Water diiffusion for fiber tract directionality



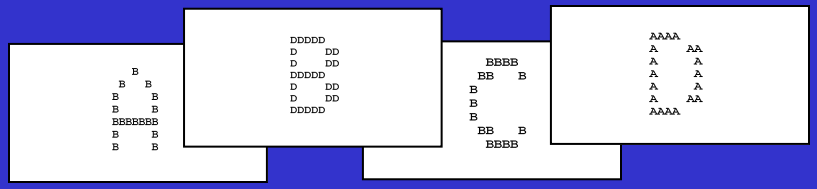


  - Fractional anisotropy measure of white matter integrity
  - SPM map of significant differences—blue and green represent HD Pre-Sx less than control

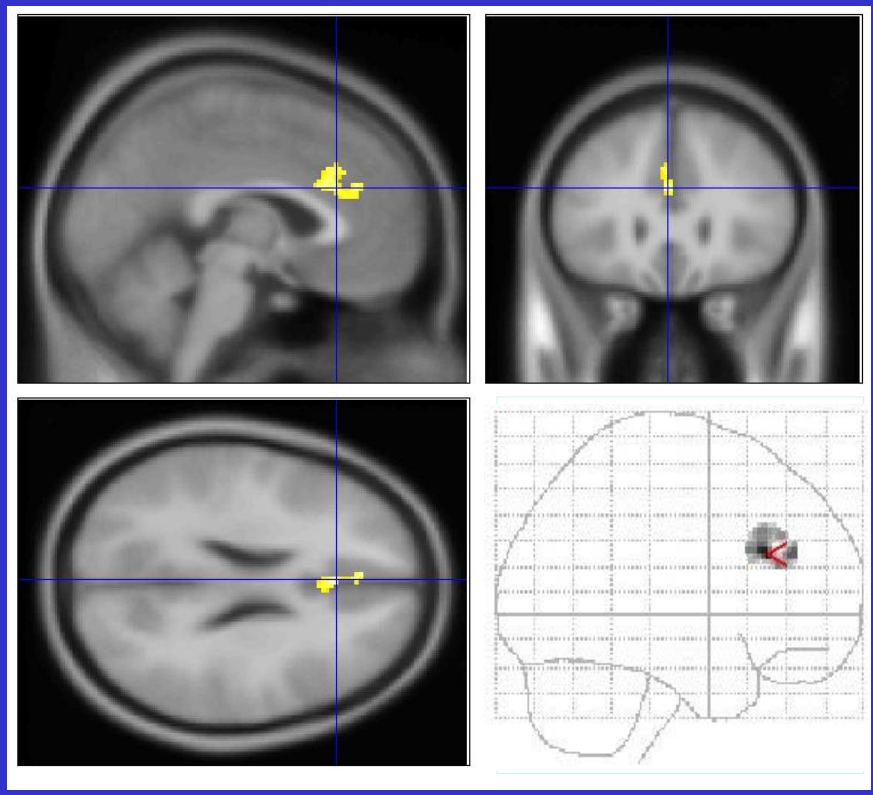
--Reading, Mori et al 2005

fMRI Alterations in HD Mutation-Positive Pre-Symptomatic Individuals

- 7 Pre-Symptomatic HD
- 7 controls
- Stroop interference type task



- SPM subtractive analysis
  - Baseline from active (by group)
  - Pre-Sx from controls



Between-group differences of BOLD response with the “active” condition of the task

--Reading et al Ann Neurol 2004

Movement Disorder

- Involuntary movements- chorea
  - Begins with distal extremities
  - May also include vocal tics
- Impaired voluntary movements
  - Clumsiness, falls, swallowing, dysarthria
  - Eventually eclipses the chorea
  - Also “apraxia” difficulty organizing movements in space
- Sometimes treated with antidopaminergic drugs
  - Neuroleptics, benzodiazepines, reserpine/tetrabenazine

Dementia

- “Subcortical” dementia (vs Alzheimer’s disease)
  - Losses in speed, attention, and flexibility
  - Orientation, memory, language relatively preserved
  - May be more impaired than is obvious
- Impaired judgement is a big problem
  - Makes advance planning very important

Types of Psychiatric Disturbances

- Mood disorders
  - Depression and mania
- Obsessive-Compulsive symptoms
- Psychosis
- “Frontal” symptoms/ Personality change
  - Irritability, apathy, disinhibition
- Sexual disorders
- Delirium

Depression

- High prevalence
  - ~40% in HD by various estimates
  - Suicide rate 4-6x higher than normal
- Commonly underdiagnosed
  - Poor communication, atypical presentation
  - “Explained away” by clinicians
- Overdiagnosis is also a problem
  - Misinterpretation of symptoms, unnecessary meds
    - Differential includes apathy, abulia, akinesia, delirium, dementia
- Severity trumps other considerations

Treatment of Depression

- There is little evidence from research
  - Have used all classes of antidepressants with success
- Vulnerable to side effects
  - Sedation, falls, cognitive impairment
  - Similar to geriatric patients
- SSRI's offer several advantages
  - May treat other "frontal" symptoms
- ECT effective and well tolerated

Mania

- Prevalence estimates for HD 4-10%
  - Small number of bipolar conditions
- HD “mania” may not be the usual type
  - Chronic disinhibition, irritability
- Conventional wisdom is not to use Lithium
  - Divalproex, carbamazepine, neuroleptics

Obsessive-Compulsive Symptoms

- Reported in HD and common in Tourette's
- True OCD is relatively uncommon in HD
  - vs perseverative behavior
  - Also hoarding and other behaviors
- Both conditions may respond to medicine
  - Serotonergic antidepressants
  - Cognitive impairment limits psychotherapy
- Education of families is very important

Psychosis

- Prevalence in HD 3-12%
  - May result from a hyperdopaminergic state
- New onset prompts a search for causes
- Neuroleptics complicate movement disorder
  - Tend to favor “atypicals” for that reason
  - Tardive dyskinesia will be hard to spot

The “frontal” syndrome of HD

- “Frontal” is a pseudoanatomical term
- Name derives from similarity to other conditions
  - Often involving “subcortical” dementia
    - Parkinson’s disease
    - Fronto-temporal dementia
    - Traumatic brain injury
    - CVA
    - HIV
- Disorders of “executive” function

Personality Change or “Frontal” Behaviors

- “Frontal” disorders hard to define, characterize, treat
- Probably among the most common problems in HD
  - Rarely lead to a specific diagnosis
  - Significant cause of morbidity, institutionalization
- Often regarded as personality change
  - Apathetic
  - Irritable
  - Disinhibited
  - Impulsive
  - Obsessional
  - Perseverative

Apathy

- Emotional and cognitive aspects
  - Failure to initiate activities
  - Internal feeling of lack of interest
- Common in HD clinical practice
  - HD may be more apathetic that AD with similar cognition
  - Distressing to caregivers
- Large differential diagnosis
  - Mood, cognitive, Neurologic
- May not segregate with depression, aggression, irritability

Treatment of Apathy

- Is treatment necessary?
  - Often more distressing to caregivers than patient
  - Education and appropriate expectations
- Non-pharmacologic approaches
  - Schedule, stimulation, cueing, reinforcement
- Drug therapy
  - Stimulants: amphetamine, methylphenidate, pemoline
  - Non-sedating SSRI: fluoxetine, sertraline, citalopram
  - Dopaminergic: amantadine, selegiline, bromocriptine

Irritibility, Disinhibition, Perseveration

- May take the form of a personality change
  - Very distressing to caregivers
  - A cause of morbidity, institutionalization
  - Disinhibition and rigidity lead to explosions
- Behavioral management is vital
  - Place events in context
  - Identify and avoid precipitants

“Frontal” Pharmacotherapy

- Antidepressants
  - SSRI’s are among the most helpful
- Neuroleptics
  - Newer agents, if not needed for chorea
- “Mood stabilizers”
- Amphetamines
- Dopaminergic agents
- Others—amantadine, memantine

Sexual Disorders

- Most common problem is loss of libido
  - high prevalence in HD
- Some problems arise from disinhibition-rare
  - Voyeurism, paraphilias
- Situational problems
  - Changing relationships
- Antiandrogens may help truly hypersexual

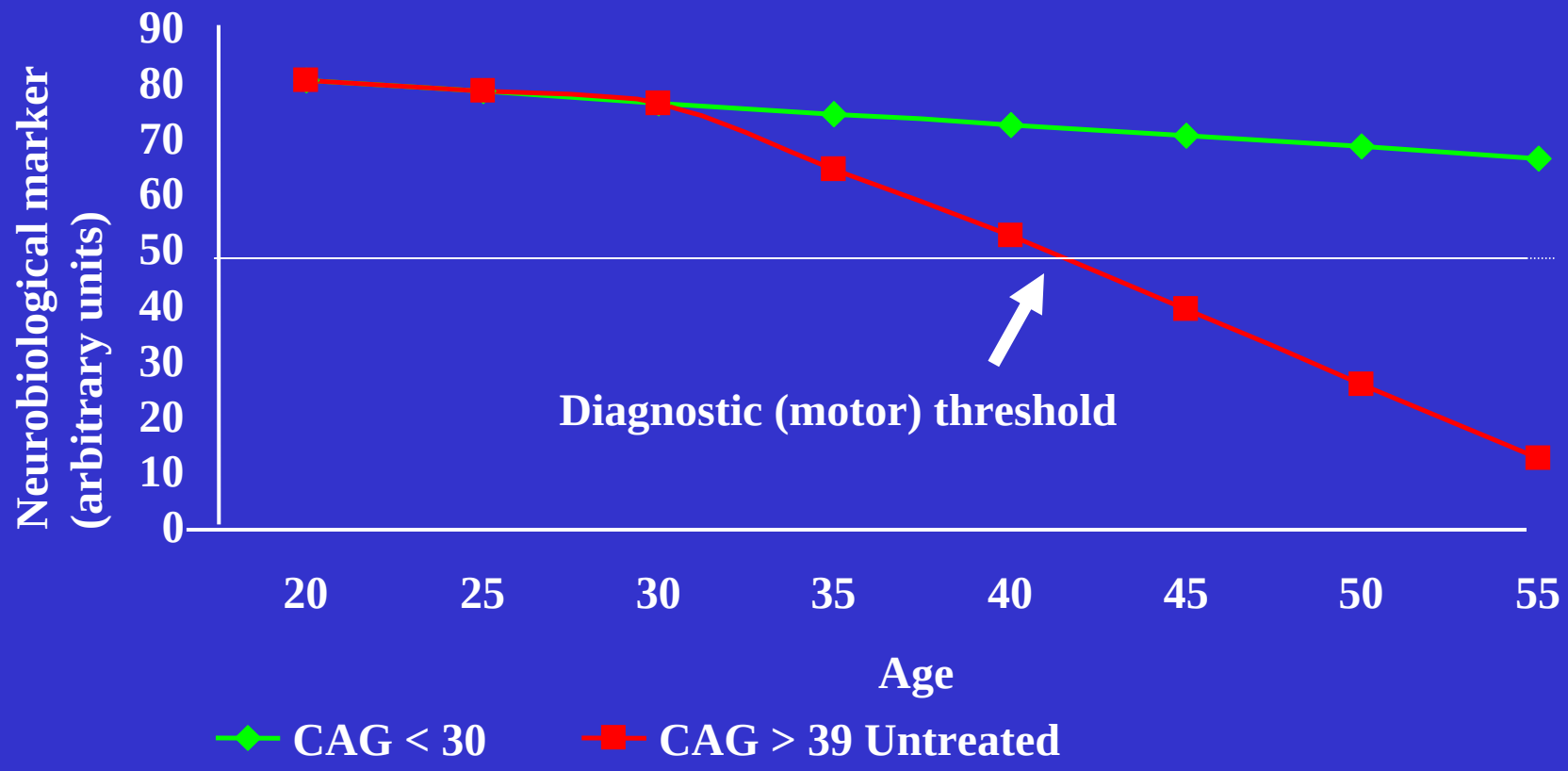
Delirium

- Patients are extremely vulnerable
  - Loss of brain tissue
  - Susceptible to falls, dehydration, polypharmacy
- Delirium may mimic other psychiatric problems
  - Obtundation, arousal, lability, hallucinosis
- Nothing changes rapidly in HD
  - Always suspect delirium with new symptoms
  - IF FALL WITH HEAD INJURY CONSIDER SUBDURAL HEMATOMA

Conclusions

- HD is a neuropsychiatric condition
  - Amenable to rational treatment
- Obstacles must be overcome at every step
  - Difficulties in diagnosis, treatment, assessment
- Problems with attitude are often the worst
  - Do not regard these cases as hopeless
  - Do not regard depression as “normal”
- Many (?most) individuals with HD do just fine

HD Over the Lifetime



Design of Therapeutic Trials for Pre-Symptomatic HD