Huntington's Disease Society of America

Cognition and Huntington's Disease: HD 101

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Presenter Disclosures

Juan Sanchez-Ramos

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

No relationships to disclose or list

Huntington's Disease 101

- HD is a progressive hereditary neurological disorder that affects mind (cognitive function), mood (emotions, behavior) and control of movement
- It is inherited in a autosomal dominant pattern
  - Affects male and females equally
  - Each child of an affected parent has a 50% chance of inheriting the mutated gene
- Mutation on chromosome is an expansion of a polyglutamine repeat ($\geq$39 repeats of CAG)

Characteristics of the Movement Disorder

- Most often hyperkinetic, choreiform
- Dystonia, rigidity, akinesia supervene later in course
- Rigidity, bradykinesia, tremor can be prominent in juvenile onset HD (<20 yrs age)

Course and Prognosis

- Average age onset = 40 years
  - 10% <20, 10% >60
- Average survival 15-20 years although varies
- Initially, mood changes and subtle cognitive issues
- Chorea more prominent in middle stages
- Advanced stages with dementia and parkinsonism

Other clinical features: Incoordination

- Motor sequencing- fine motor
- Bradykinesia- slow movements
- Dysarthria/Dysphagia- speech/swallow
- Gait instability and falls
- These difficulties can be helped with PT/OT/ST

Psychiatric issues

- Mood disturbances
  - Depression
  - Anxiety
  - Mania
- OCD
  - Mild obessiveness can be seen
- Psychosis
  - Hallucination rare
  - Delusion more common but still rare

Depression

- Studies suggest about 40%
- 22 % of the 40 % meet criteria for major depression
- Not correlated with disease severity
- Can predate HD by years in “at risk” population but can occur at any stage of the disease
- Apathy is NOT depression
- Treat if necessary
- Suicidal attempt-7.3%-12%,
  - greater than average risk

Anxiety/OCD

- Anxiety
  - Excessive worry
  - Irritability
  - Poor sleep
  - Can respond to treatment
- OCD
  - SSRIs
  - Psychotherapy is difficult

Mania

- Small number of patients 4.8-10%
- Presents with
  - Elevated or irritable mood
  - Grandiosity
  - Impulsivity
- May be confused with bipolar illness
- Treatment: Avoid lithium, use valproate or carbamazepine

Cognition

- Decline in various domains of “thinking” or cognition
- Different from Alzheimer’s disease
- Testable by neuropsychological tests of memory, language ability, visual spatial skills, attention and concentration, and judgment

Early symptoms in pre-manifest HD

- A HD gene carrier can be completely normal for decades
- BUT changes in thinking and behavior (both subtle and not so subtle) are often recognized before the movement disorder appears

Two Important Questions

What are the earliest changes in cognitive function in HD gene carriers who have not yet reached a clinical diagnosis of HD?

When should we start medication to prevent or delay disease onset?

To answer these question, **longitudinal observational studies** have been performed including both pre-HD and HD subjects

TRACK-HD Study (An observational study)

- Subjects were recruited from Canada, France, UK, Netherlands
- Participants were thoroughly examined every year for 3 years
- Dozens of measurements were made on each subject that included:
  - Neuroimaging (MRI of brain)
  - Motor symptoms (including high tech eye movement tracking
  - Intellectual (cognitive) function
  - Emotional well being

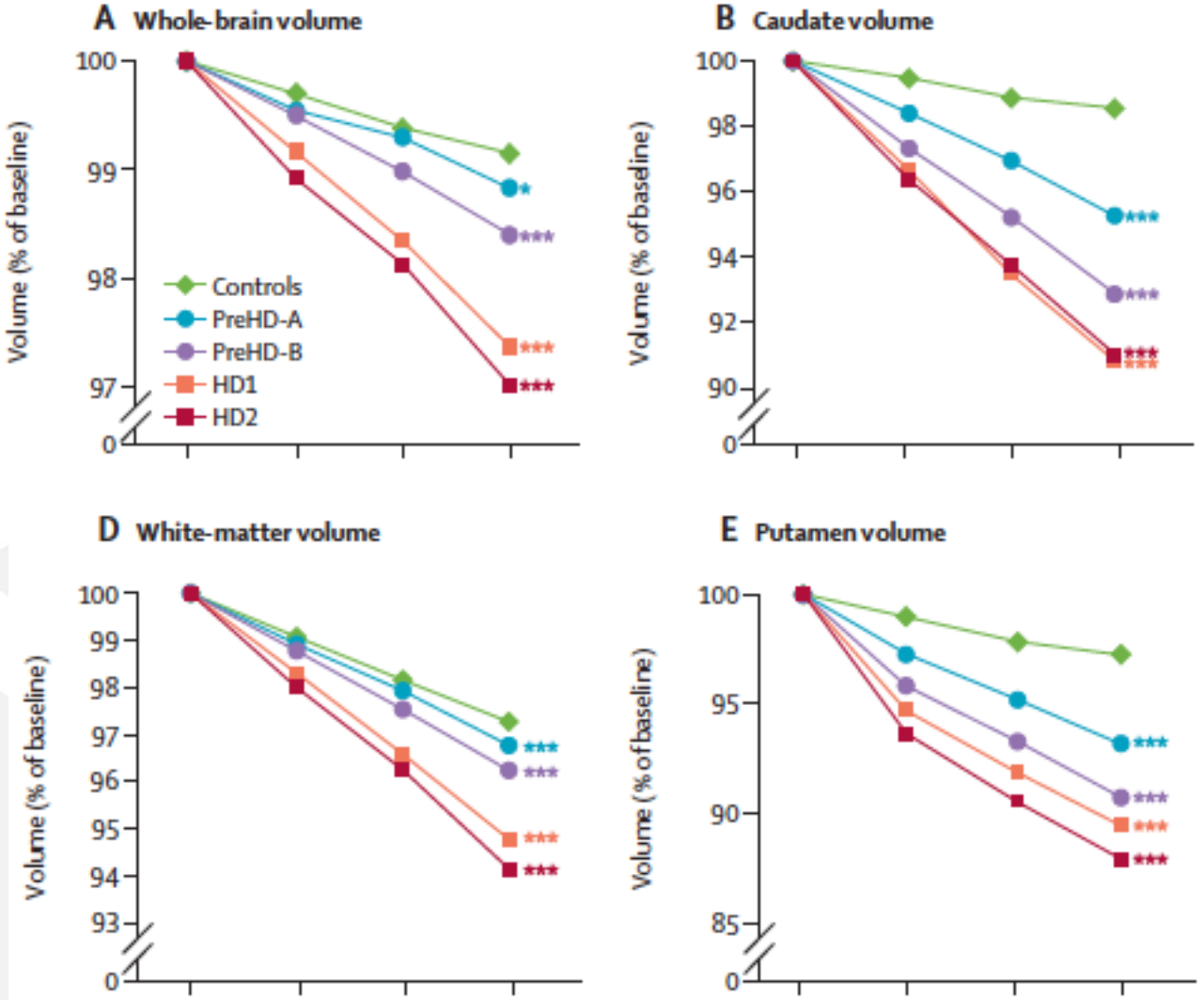
TRACK-HD Study

- Subjects without symptoms of HD (but gene carriers) were divided into two groups: those who were estimated to be close to or far from disease onset:
- Predicting how close subjects were to onset was based on a mathematical calculation that used # CAG repeats and age.
- A group of subjects in the early stages of HD and a control population that didn't carry the gene were also studied

Results: Neuroimaging Findings

- Whole brain volume decreases faster in people carrying the HD mutation than in control subjects
- Specific regions of brain (caudate and putamen) shrunk faster in people carrying the HD mutation
- White matter component of brain also exhibits early changes (the nerve fiber projections or “wiring”)

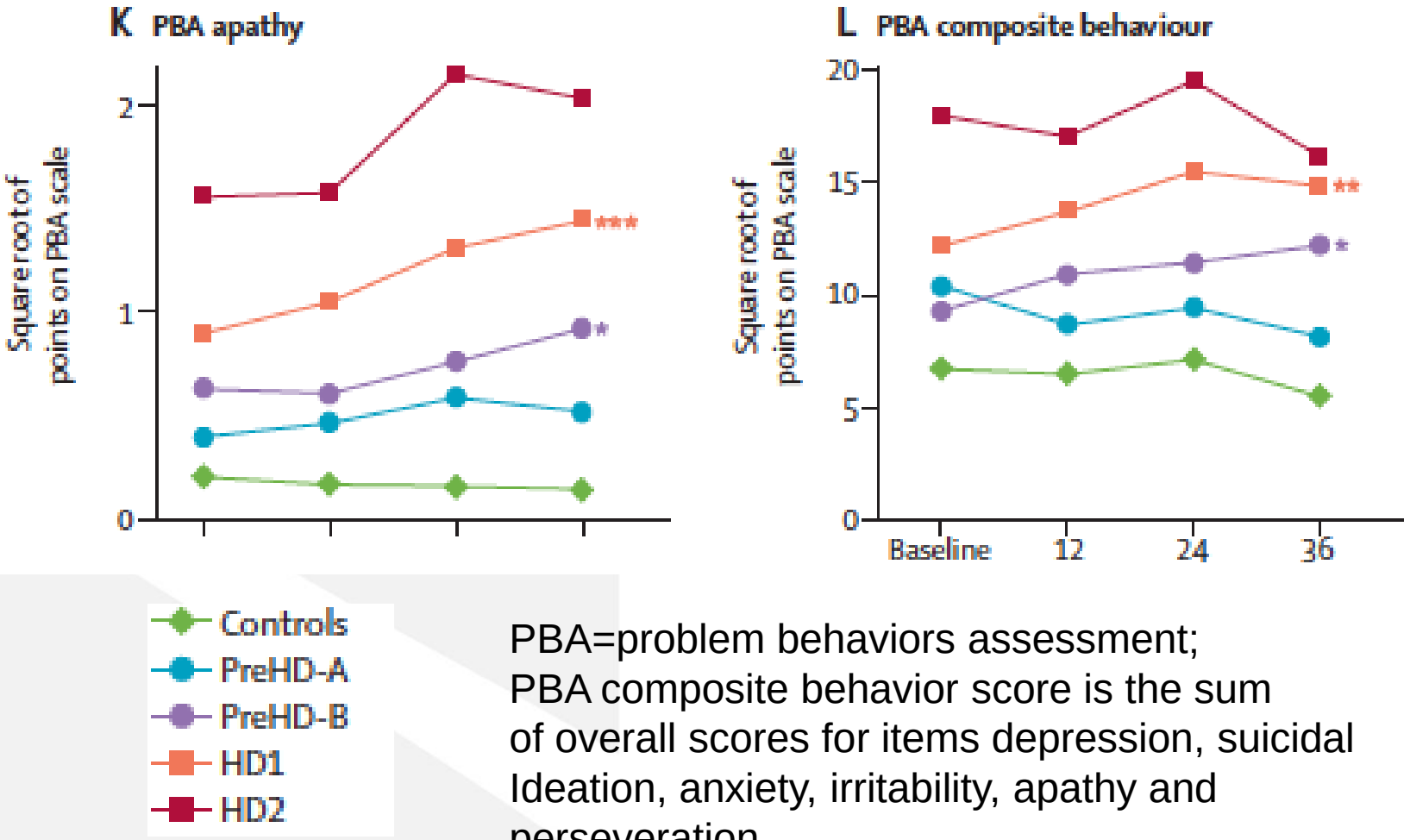
Neuroimaging Changes



Neuropsychiatric Changes

- Irritability and apathy was more frequent in HD mutation carriers at baseline than in non-gene carriers
- These symptoms did not change much over 3 years in those that were farther from onset
- But those gene carriers estimated to be near onset revealed changes in apathy and irritability scores by the 3rd year that approximated early manifest HD

Neuropsychiatric Assessments



PBA=problem behaviors assessment;
PBA composite behavior score is the sum of overall scores for items depression, suicidal Ideation, anxiety, irritability, apathy and perseveration

Cognitive Function

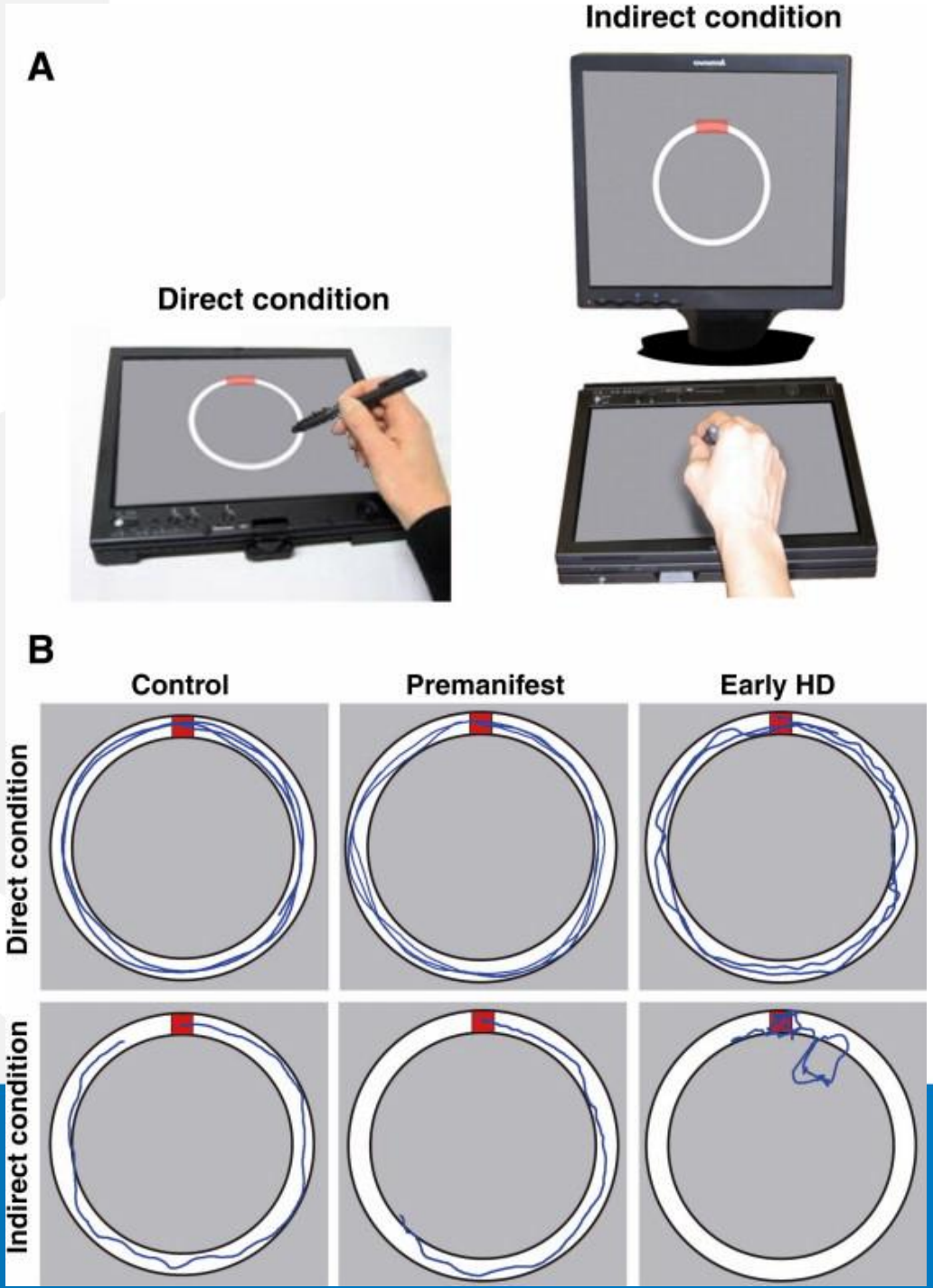
- Some (but not all) tests of intellectual function were worse in HD gene carriers
- Performance was worst in ability to trace a circle on a computer screen (test of visuo-motor integration)
- Over time this performance worsened
- A number of other cognitive tests didn't change enough over the course of a year to be useful in a short drug trial in pre-symptomatic HD gene carriers

Direct and Indirect Circle Tracing Test

An earlier study had reported the circle tracing task as a very sensitive marker in pre-HD subjects

“Visuomotor integration deficits precede clinical onset in Huntington's disease”

Neuropsychologia Volume 49, Issue 2, January 2011, Pages 264–270



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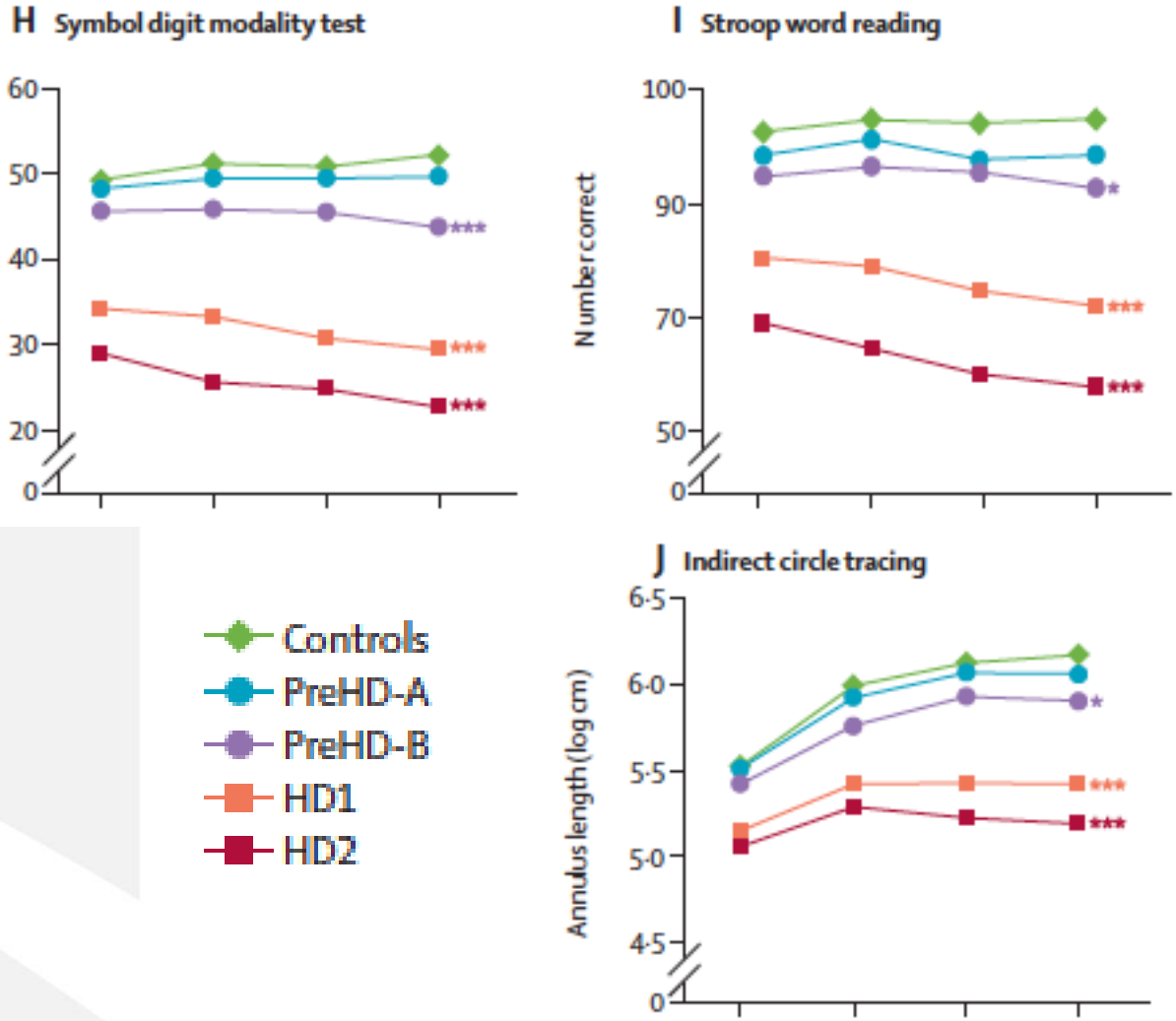
Cognitive Assessments in the TRACK-HD Study

Symbol Digit Modalities Test (SDMT) is a test of visuomotor integration, measuring visual attention and motor speed

Stroop Test - word reading condition is a test of processing speed (subject must read as many words as possible in 45 seconds from a list of the names of colours printed in black ink and the number of words read correctly is the primary variable

Circle Tracing –subject traces a circle as quickly and accurately as possible, aiming to stay within the ring, using a stylus on the horizontally-placed tablet PC



Processing speed

- Processsing speed was most commonly affected in pre-HD persons
  - PS was assessed using the Symbol Digit Modalities Test (SDMT). Participants have 90 seconds to use a reference key to pair as many numeric digits with corresponding geometric figures. The number of correctly paired items was used to score results

≥	±	«	∏	ж	ψ	Δ	o	↑
1	2	3	4	5	6	7	8	9

ψ	±	∏	ψ	±	o	≥	Δ	↑	ж	±	«	±	≥	Δ
6	2	4												

ж	Δ	↑	o	∏	«	Δ	↑	ж	±	«	«	«	ж	ψ

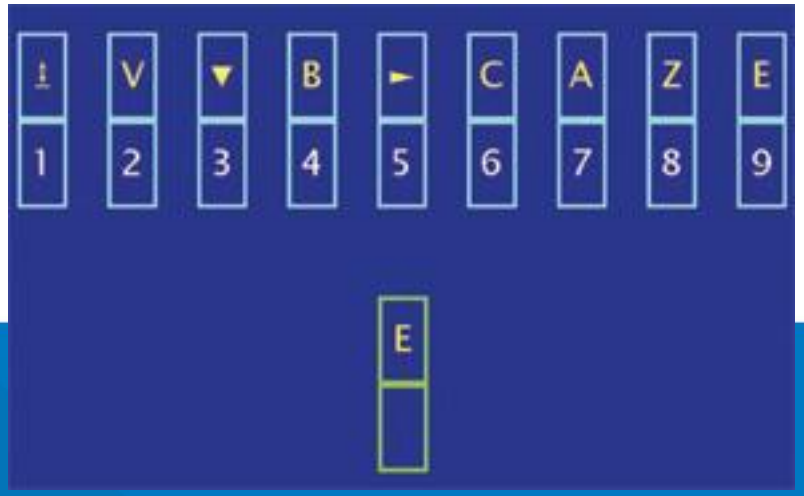
o	±	«	∏	ж	ψ	≥	o	±	≥	±	«	«	ψ	o

≥	∏	«	ψ	ж	±	Δ	o	↑	o	±	«	∏	ж	«

±	±	«	∏	ж	ψ	o	±	o	≥	±	«	∏	o	ψ

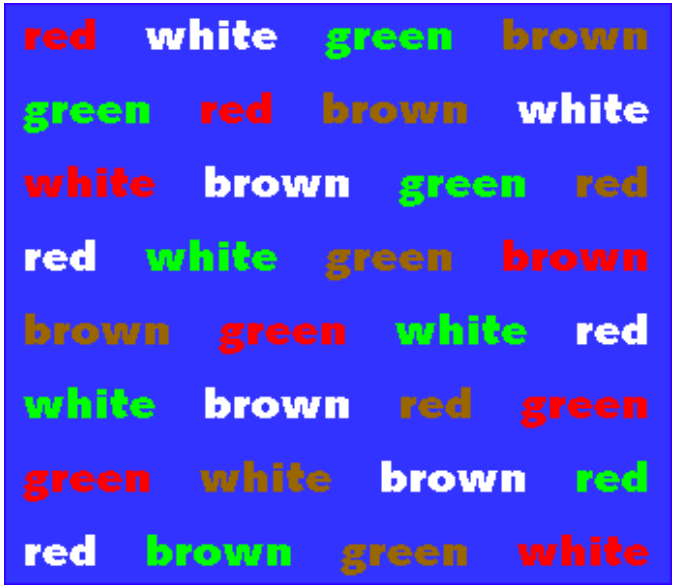
«	∏	«	Δ	«	∏	Δ	o	↑	Δ	«	«	Δ	ж	ψ

≥	±	«	±	ж	«	±	o	«	≥	±	±	∏	Δ	ψ



Executive function

- Percentage of subjects with executive dysfunction (3.1%) was the lowest of the 4 domain subtypes examined, irrespective of the estimated time to HD diagnosis.
- The test used was Stroop Color Word Test (SCWT)
- Response inhibition on the SCWT does not fully capture the multifaceted domain of executive functioning.



Mild Cognitive Impairment (MCI) in pre-HD

- Mild cognitive impairment (MCI) is a transitional stage between “normal” cognition and dementia
- Assessment of MCI is valuable since it identifies individuals who will progress to dementia more quickly than cognitively normal peers
- There are multiple domains of cognition that are affected to different degrees in manifest HD:
  - attention, verbal fluency, psychomotor speed, executive function, memory and visuospatial function
- Cognitive changes develop very slowly in HD, with some appearing 15 years before motor manifestations are observed

PREDICT-HD (An observational study)

- **Prospective observational investigation of the earliest signs and symptoms of HD** conducted by a multi-center consortium of HD clinics (HSG).
- Study participants included 160 non–gene-expanded and 575 gene-expanded individuals
- Goal was to identity early cognitive changes in subjects who were gene positive (expanded CAG-repeats) who did not yet show sufficient motor signs to be diagnosed with HD (ie pre-HD)

Neurology 75 August 10, 2010

Mild Cognitive Impairment (MCI) in pre-HD

- In a large cohort of individuals who were estimated to be over 14 years from a motor diagnosis, nearly **40%** displayed mild impairments in
  - episodic memory,
  - processing speed,
  - executive functioning, and/or
  - visuospatial perception
- These pre-HD individuals met existing criteria for MCI:
  - did not have dementia
  - were not experiencing functional decline and
  - showed cognitive deterioration using standard criteria for MCI

Neurology 75 August 10, 2010

MCI in pre-HD (overall results)

- Nearly 40% of pre-HD individuals met criteria for MCI
- Individuals closer to HD diagnosis had higher rates of MCI.
- Non-amnestic MCI (ie with no deficit in memory) was more common than amnestic MCI (ie those with memory problems).
- Single domain MCI was more common than multiple-domain
  - Single domain deficits may reflect an earlier point in transition from normal cognition and dementia and multiple domain MCI represents a later point in the progression of cognitive dysfunction
- Within the non-amnestic single-domain subtype, **impairments in processing spee**d were most frequent.

Neurology 75 August 10, 2010

Summary: MCI in pre-HD

- MCI is relatively common in pre-HD
- MCI appears associated with onset of HD
  - As more motor abnormalities were observed in these patients, MCI rates increased. For example, ***33.8%*** of individuals rated as motorically normal were classified with some type of MCI, whereas **64%** of individuals with motor signs likely to be HD had MCI.
- MCI risk also appears related to genetic risk of HD, as individuals approaching estimated diagnosis (based on CAG repeat length and current age) had double the rates of MCI (e.g., **27.3%** and **54.1%** of the far and near participants).
- These findings indicate that MCI represents a prodromal period in HD, similar to the transitional stage in AD and other neurodegenerative conditions

Clinical and Research Implications

- For health care providers, greater attention needs to be directed toward MCI in pre-HD.
- Despite being “presymptomatic,” a sizable minority of this relatively young cohort is falling well below expectations in a broad range of cognitive domains
- The need for early identification of MCI is partly driven by the development of neuroprotective agents that ideally would be administered when pathology is first detected (perhaps when one domain of MCI is found to be abnormal?)
- many pre-HD individuals who are working and raising families may actually be experiencing some mild functional difficulties in daily life that are not captured by the functional capacity scale of the UHDRS.

Thank You for Your Attention

Key Staff at the HDSA Center of Excellence at University of South Florida

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Resources

- HDSA Website: www.hdsa.org
- HD Buzz: www.hdbuzz.net
- TRACK-HD study:

  Lancet Neurology Vol 12 July 2013
- PREDICT-HD study:

  Neurology Journal Vol 75 August 10, 2010