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Association of CAG Repeats With Long-term Progression in Huntington Disease

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Langbehn, D. R., Stout, J. C., Gregory, S., Mills, J.A., Durr, A., Leavitt, B. R., Roos, R. A. C., Long, J. D., Owen, G., Johnson, H. J., Borowsky, B., Craufurd, D., Reilmann, R., Landwehrmeyer, B., Scahill, R. I., & Tabrizi, S. J.

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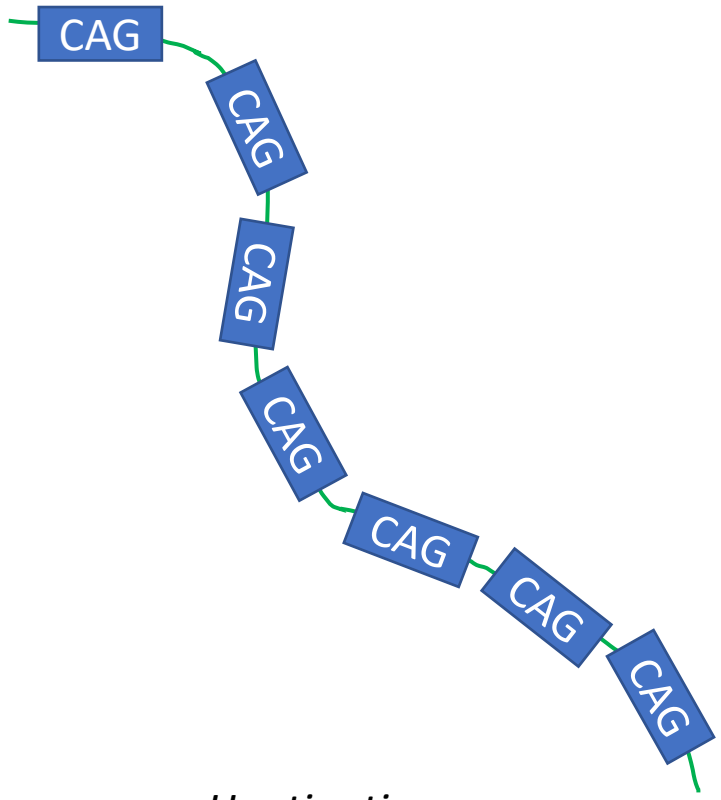
Abstract Abstracted

- Huntington’s disease is neurodegenerative disease caused by a single mutation in the Huntingtin gene
- The number of CAG repeats can be used to predict the severity of degeneration in the brain as well the age of disease onset
- Disease progression can be defined in terms of a number of variables (including performance on tests and brain volume), but the most basic one is time
- Langbehn et al. found that putamen and caudate volumes best tracked disease progression at any given time

Introduction

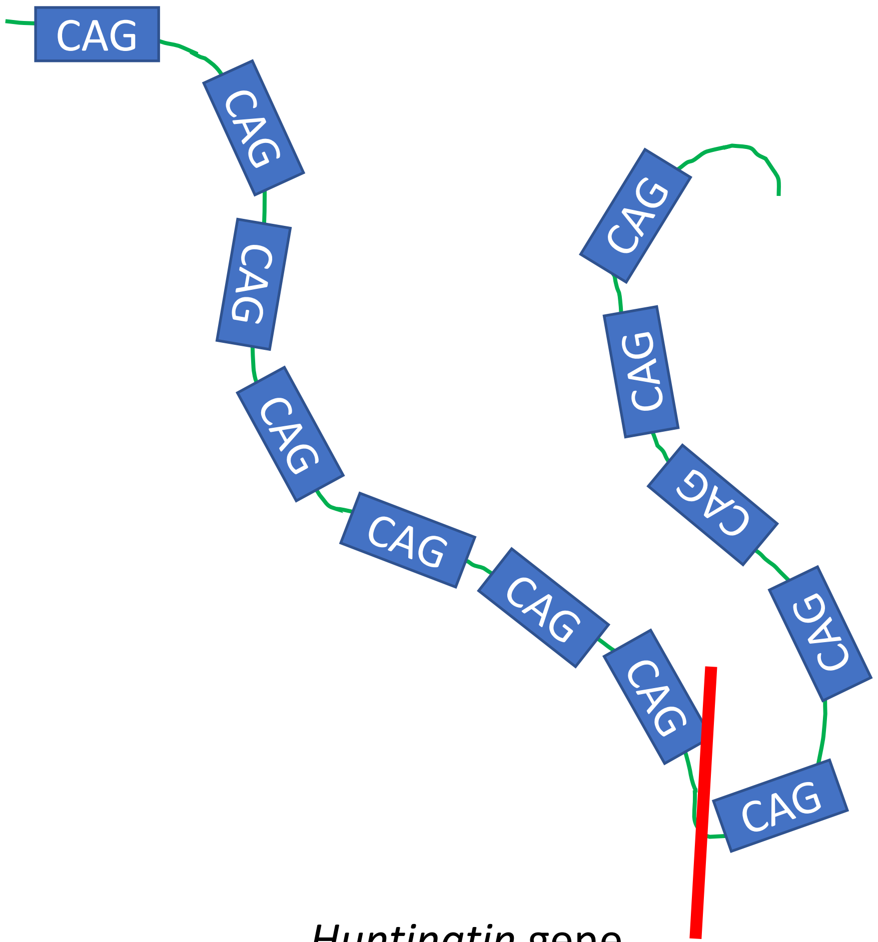
- Huntington's disease is a neurodegenerative disease characterized by expansion of the CAG trinucleotide sequence in the *huntingtin* gene of chromosome 4

- Therefore, Huntington's disease is inherently a genetic disease

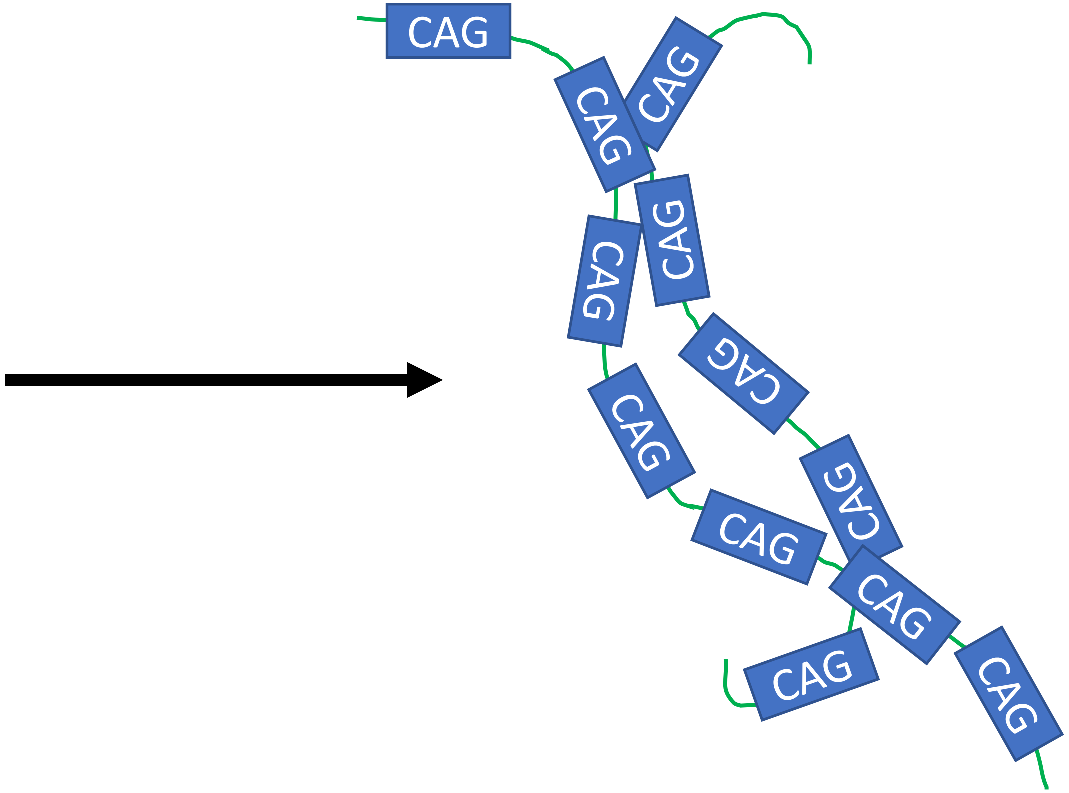


Huntingtin gene

Introduction

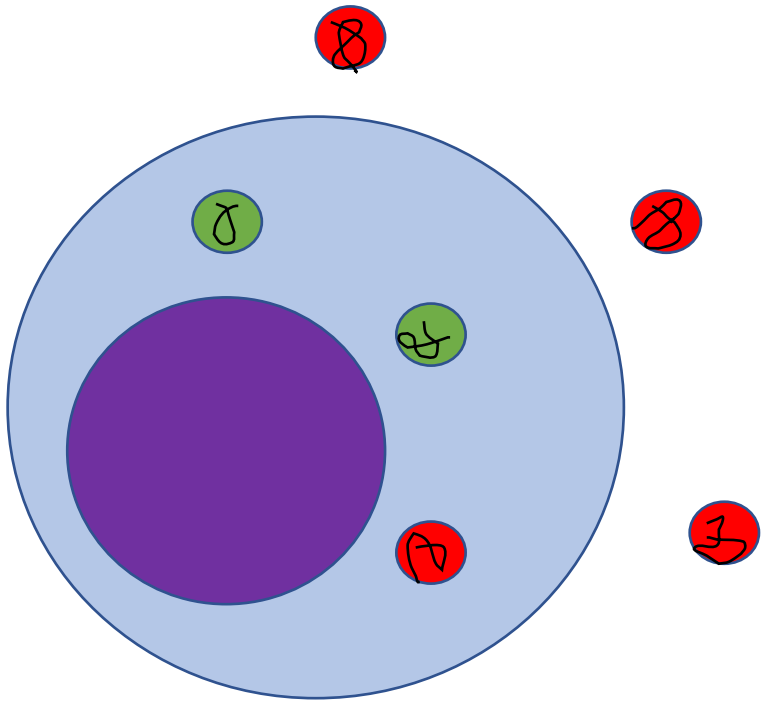


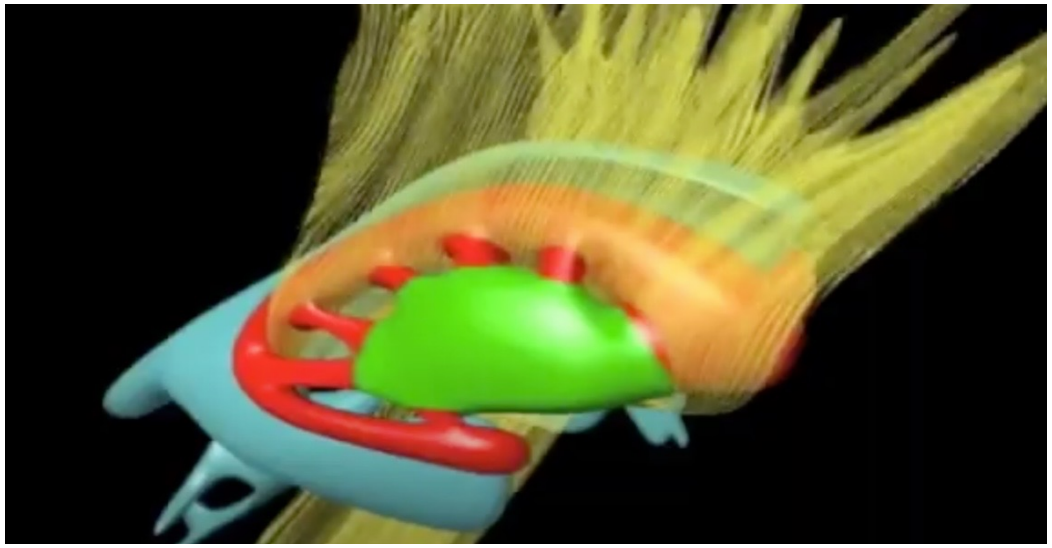
Huntingtin gene



Htt pools/inclusions

Introduction





Intracellular and extracellular inclusions develop (Jimenez-Sanchez et al., 2017)

↓ brain volume in the striatum (Alila Medical, 2021)

Introduction

- The primary clinical markers of the disease are cognitive and motor deficits
  - Perform worse on a tapping task
  - Perform worse on a Stroop word reading task
- The expression of the disease symptomatically based on the genetic underpinning is known as *penetrance*
  - 10-26 repeats → no penetrance
  - 26-25 repeats → intermediate penetrance
  - 39-39 repeats → reduced penetrance
  - 40+ repeats → full penetrance

Introduction

- Langbehn et al. claim that few disease characteristics can be determined using just the CAG repeat length and age
- The goal of the research was to determine the clinical and morphometric implications of CAG repeat length
- Hopefully, the results would help determine:
  - 1. Which variables are best associated with CAG repeat length and age (highest R^2)
  - 2. How the progression of Huntington's disease looks like (Quadratic? Linear? Flat?)

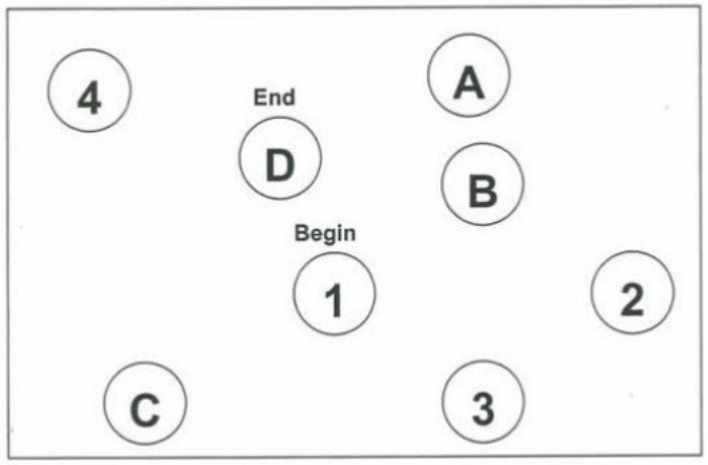
Methods

- The researchers did not sample individuals themselves
- Rather, they obtained data through the TRACK-HD/TRACK-ON studies

TRACK-HD	TRACK-ON
• four academic institutions first recruited 123 healthy controls, 120 pre-HD carriers, and 123 with early HD subjects	• a follow up of TRACK • still occurring • maximum time of consideration: 6 years
Combined	
• 2065 patient visits • 443 participants • Used UHDRS variables + morphometric data	

Methods

- UHDRS – Clinical
  - A clinical battery of tests used to assess disease severity
  - Involves motor, cognitive, and neuropsychiatric tasks/tests
  - 74 total items



- Morphometric data (MRI)
  - Brain volumes (caudate and putamen, total brain volume)
  - Given that people naturally have different-sized heads, the **ratios** of these volumes to the total intracranial volume

$$Volume\ Considered = \frac{Actual\ Volume}{Total\ Intracranial\ Volume}$$

Methods

- Principal component analysis was used to derive summary scores for clinical and morphometric data
  - *“the weighted sum of the original set of variables that has the highest possible mean correlation with those same variables”*
  - That statistics themselves are described using linear algebra

$$\mathbf{w}_{(1)} = \arg\max_{\|\mathbf{w}\|=1} \left\{ \sum_i (t_1)^2_{(i)} \right\} = \arg\max_{\|\mathbf{w}\|=1} \left\{ \sum_i \left(\mathbf{x}_{(i)} \cdot \mathbf{w} \right)^2 \right\}$$

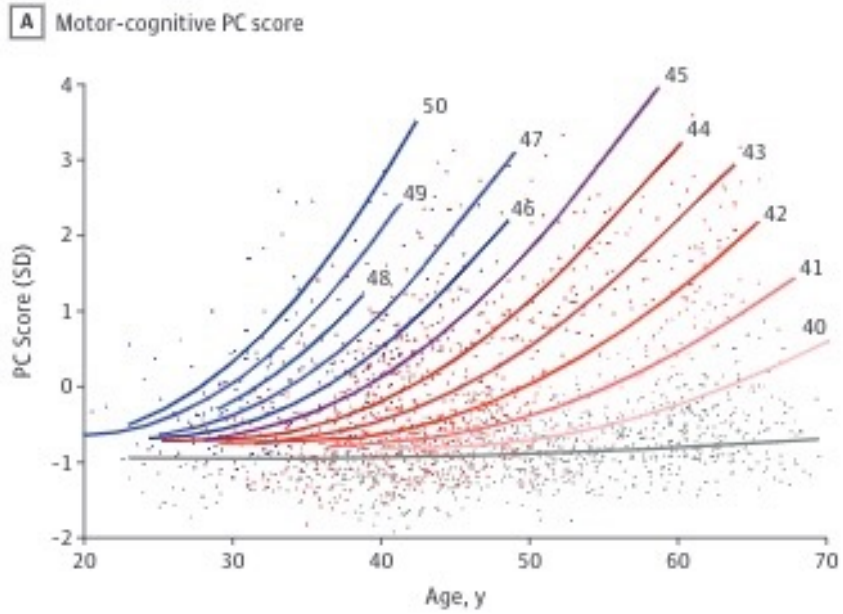
$$\mathbf{w}_{(1)} = \arg\max_{\|\mathbf{w}\|=1} \left\{ \|\mathbf{X}\mathbf{w}\|^2 \right\} = \arg\max_{\|\mathbf{w}\|=1} \left\{ \mathbf{w}^\mathsf{T} \mathbf{X}^\mathsf{T} \mathbf{X} \mathbf{w} \right\}$$

$$\mathbf{w}_{(1)} = \arg\max \left\{ \frac{\mathbf{w}^\mathsf{T} \mathbf{X}^\mathsf{T} \mathbf{X} \mathbf{w}}{\mathbf{w}^\mathsf{T} \mathbf{w}} \right\}$$

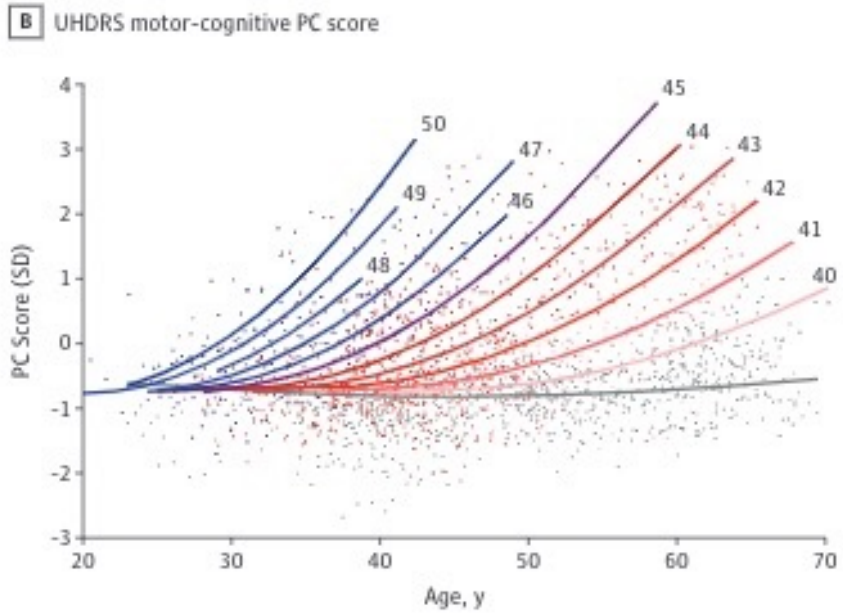
Results

Variable	Motor-Cognitive Score	UHDRS Motor-Cognitive Score	White Matter-Ventricle Score	Caudate-Putamen Score
Symbol Digit Modalities Test, No. correct	−0.795	−0.903	NA	NA
Stroop word reading, No. correct	−0.770	−0.879	NA	NA
Spot the Change 5 s, corrected for guessing	−0.582	NA	NA	NA
UHDRS total motor score	0.872	0.891	NA	NA
Paced tapping 3-Hz SD of intertap intervals, log	0.808	NA	NA	NA
Q-Motor speeded tapping intertap interval, mean	0.829	NA	NA	NA
Q-Motor speeded tapping interonset interval, log SD	0.885	NA	NA	NA
Q-Motor speeded tapping tap duration, log SD	0.889	NA	NA	NA
Q-Motor speeded tapping interonset interval, log mean	0.918	NA	NA	NA
Putamen volume, ratio to ICV	NA	NA	NA	−0.947
Caudate volume, ratio to ICV	NA	NA	NA	−0.947
Total brain volume, ratio to ICV	NA	NA	−0.926	NA
Ventricle volume, ratio to ICV	NA	NA	0.818	NA
White matter volume, ratio to ICV	NA	NA	−0.870	NA
Gray matter volume, ratio to ICV[b]	NA	NA	NA	NA
Variance explained by the first PC, %	67.6	79.4	76.1	89.7

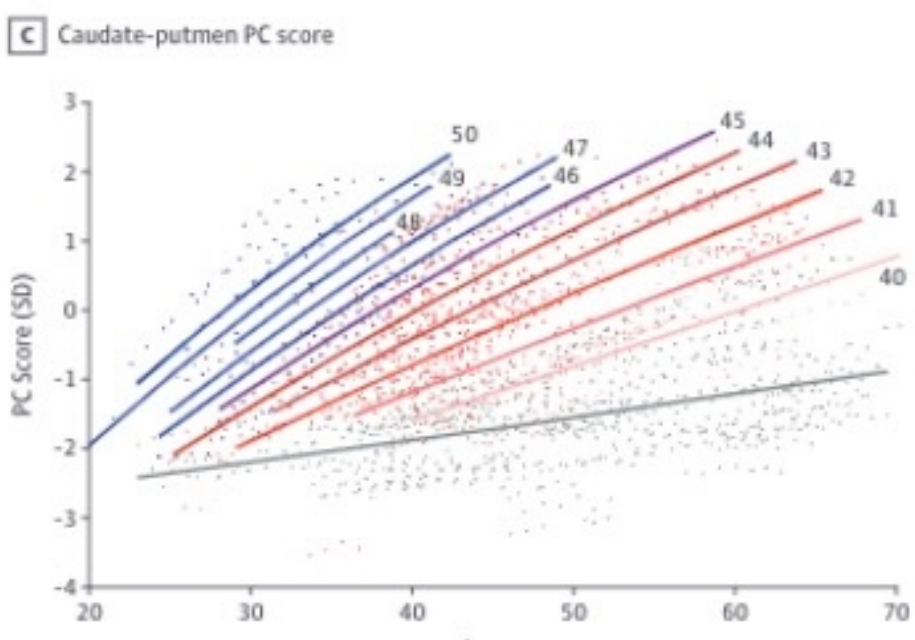
Results



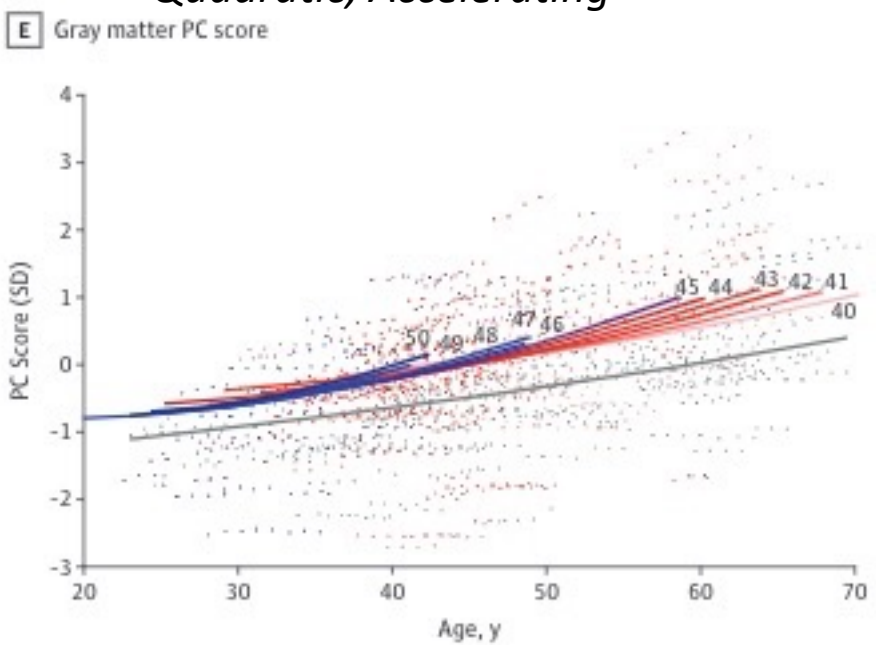
Quadratic, Accelerating



Quadratic, Accelerating

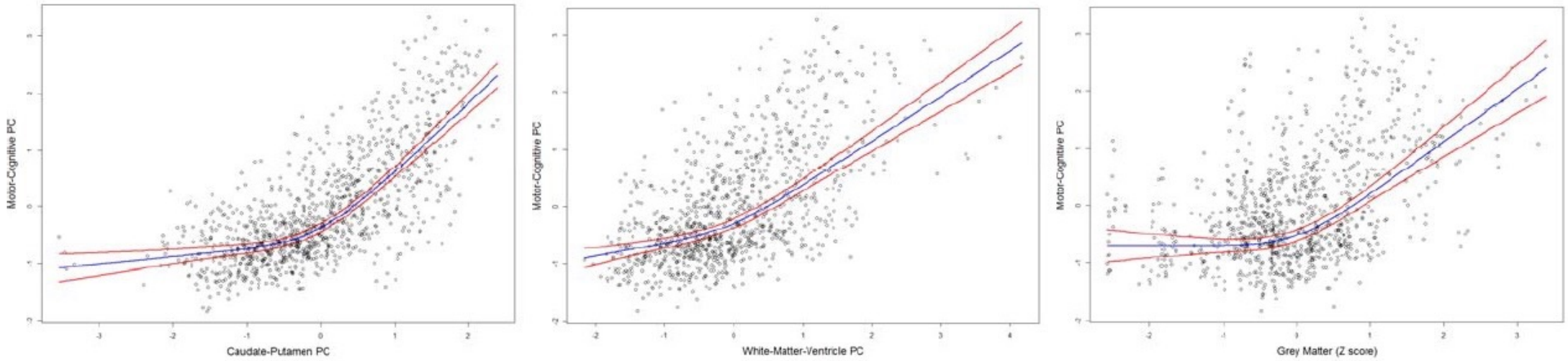


Quadratic, Accelerating



Non-linear, low slope

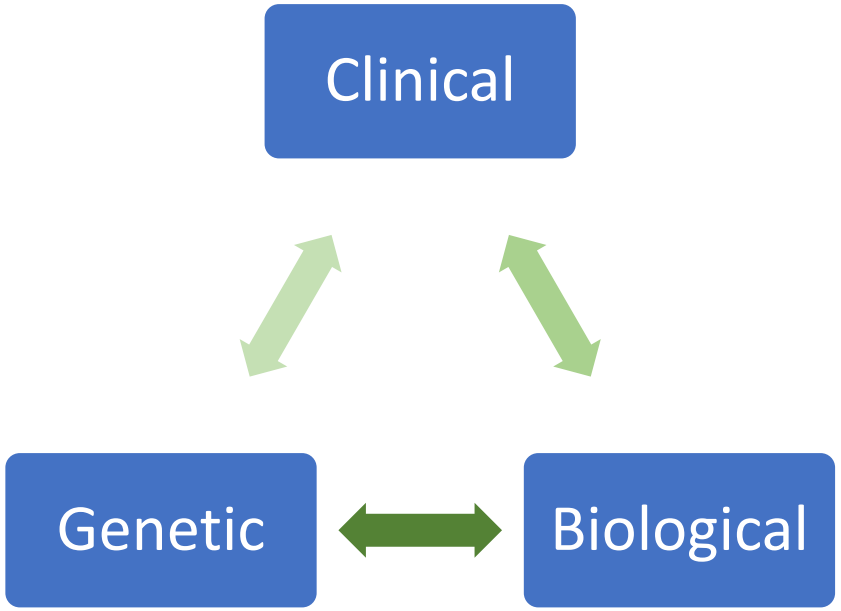
Results



- Previous graphs depicted motor-cognitive, caudate-putamen, and gray matter scores as a function of time
- These graphs indicate the relationship between the PCs themselves
- The inflection point at PC = 0 indicates shift from healthy to HD subjects

Conclusion

- Phenotype declines in a CAG-dependent manner
  - However, different acceleration rates between CAG repeat lengths indicate that a relationship is present
- Clinical predictors do not as strongly track disease progression as morphometric predictors do
- Variance can be decreased using a smaller subset of variables
- Neurodegeneration in the caudate and putamen is linear over time



Discussion Questions

- Why do you think brain matter volume tracked age in a quadratic manner?
- Why do you think neurodegenerative diseases have no cure? (Keep in mind genetics)
- What directions do think neuroscience/neurology should take in the future?

References

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