Using Imaging to Understand the Brain and How to Translate to Therapeutics

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Introduction

- Neurogenetics – single gene disorders
- Biomarker development: Magnetic Resonance Imaging (MRI)

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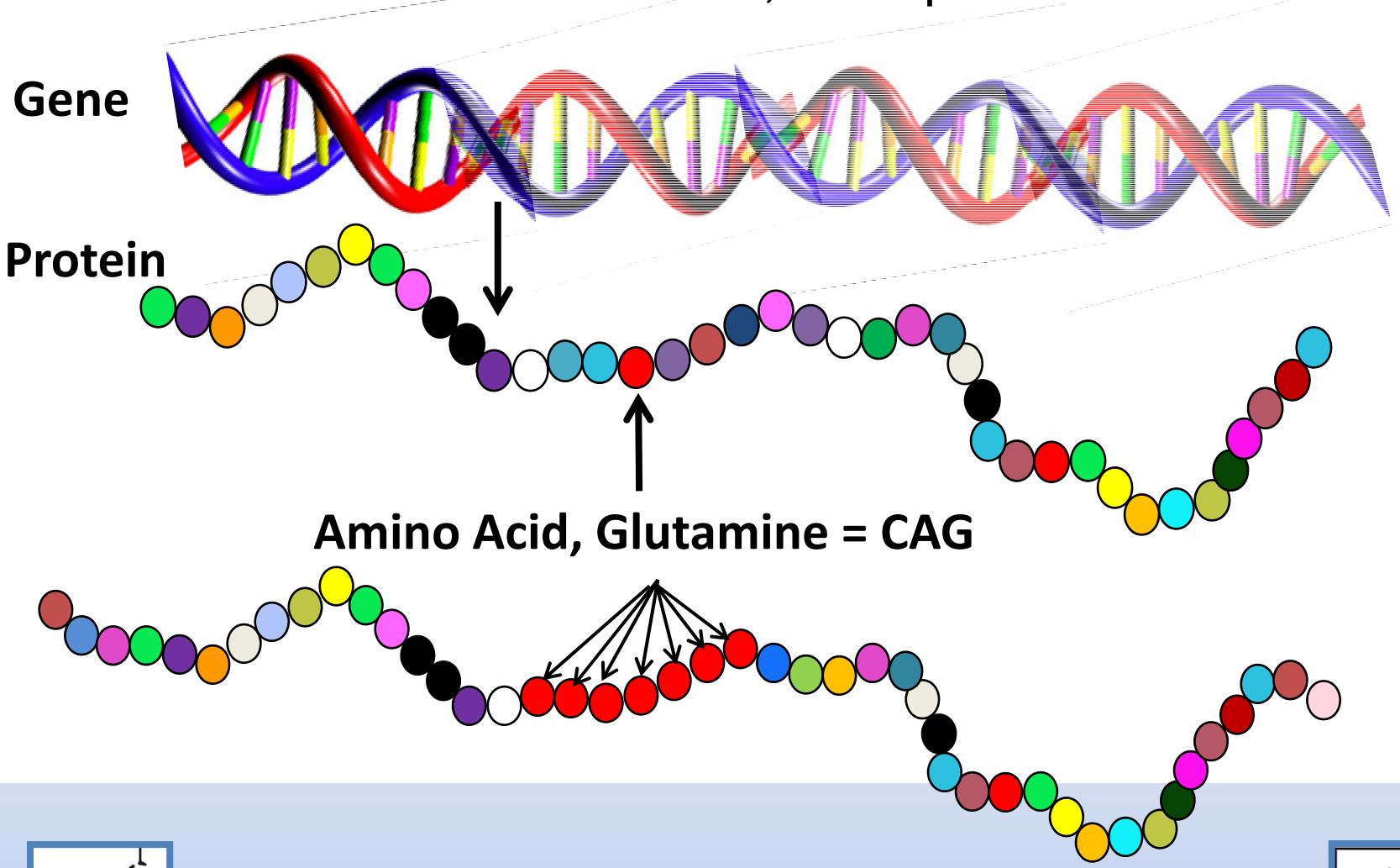
Trinucleotide (Triplet) Repeats

- Amino Acids = 3 nucleotides; example CAG = Glutamine



Triplet Repeat Genes Cause BRAIN DISEASE

- Autosomal Dominant
- These genes are highly polymorphic with a wide range of repeat numbers *in the normal population*
- Above a certain threshold = neurodegenerative disease
  - Huntington's Disease (HD)
  - Spinocerebellar Ataxia (SCA)
  - Spinobulbar muscular atrophy (SBMA)
  - Dentatorubropallidoluysian atrophy (DRPLA)
  - Fragile X Syndromes
  - Friedreich Ataxia (FRDA)
  - Myotonic Dystrophy

Single Gene Disorders: The Good and the Bad

- The Good: *SINGLE GENE = CURE*
- The Bad: not as simple as it sounds
  - ✓ Most of these genes were discovered in the early 1990's
  - ✓ Scientific discovery is focused almost exclusively on pathology rather than study of the normal gene
- The Good: Gene therapy IS HERE
  - ✓ For Huntington's Disease (HD), currently a phase 3 clinical trial
- The Bad: for some diseases, like Myotonic Dystrophy (DM1), the gene therapy hunt is further along than the basic understanding of the brain pathology
  - ✓ Trying to 'cure' something that we really don't know much about

Introduction

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Major Effects of Myotonic Dystrophy Type 1

www.myotonicdystrophy.com

Cognitive Function: *Intellectual impairment, behavioral and psychological disorders, excessive daytime sleepiness*

Vision: *Cataracts, retinal damage*

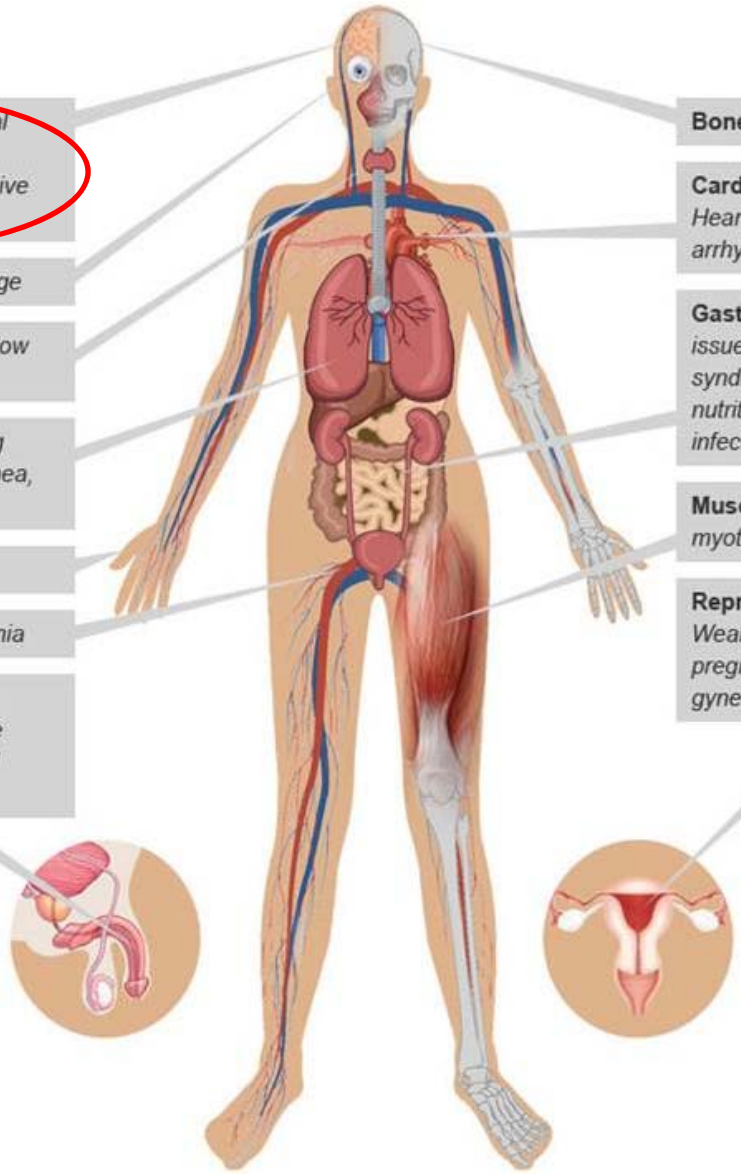
Endocrine System: *Diabetes, low thyroid hormone levels*

Respiratory System: *Breathing difficulties, aspiration, sleep apnea, high risk pneumonia*

Skin: *Pilomatrixomas*

Immune: *Hypogammalobulinemia*

Reproductive System in Men: *Low testosterone levels, erectile dysfuntion, testicular failure and gonadal altrophy.*



Bone: *Anomalies*

Cardiovascular System: *Heart condition abnormalities, arrhymias, cardiomyopathy*

Gastrointestinal Tract: *Swallowing issues, abdominal pain, irritable bowel syndrome, constipation/diarrhea, poor nutrition and weight loss, chronic infections*

Muscle: *Weakness, wasting (atropy), myotonia, pain*

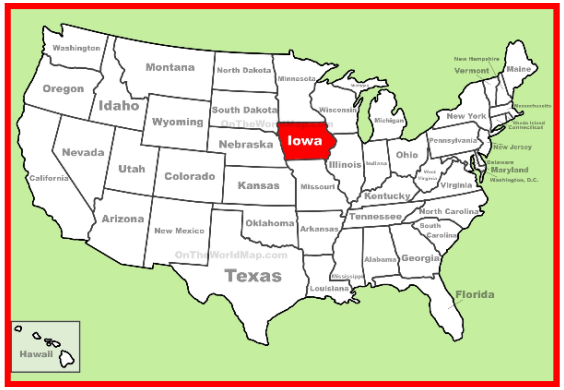
Reproductive System in Women: *Weakened uterine muscle, pregnancy-related complications, and gynecological problems.*

The University of Iowa Myotonic Dystrophy Brain Study

Iowa DM1 Brain Study

- Funded by the NINDS 2015
- Single site (Iowa)
- Prospective, longitudinal study of ADULT ONSET DM1
  - Baseline, Year 1, Year 2 visits
  - Brain imaging
  - Assessments of cognition, behavior, and motor function

The University of Iowa
Myotonic Dystrophy
Brain Study

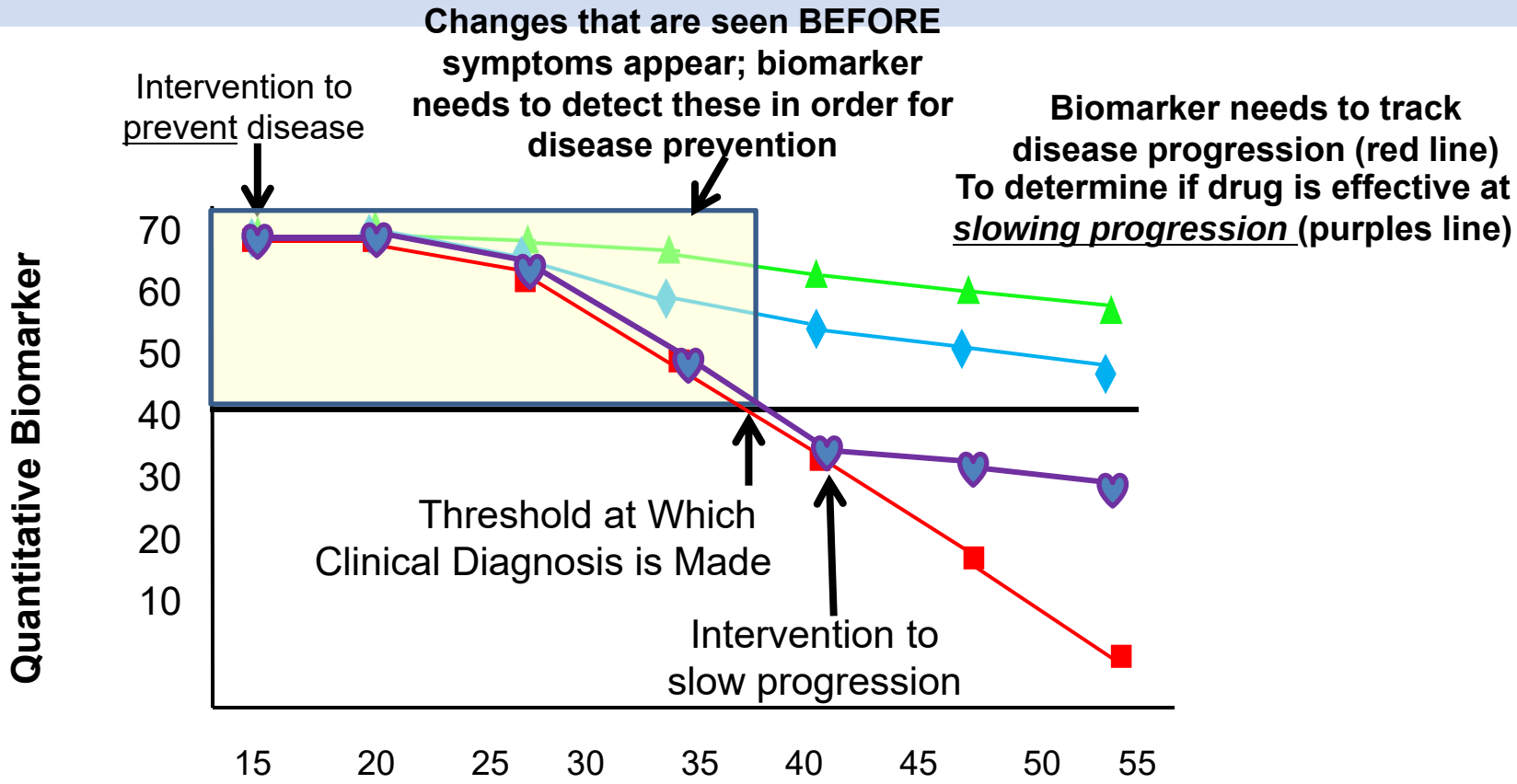


Introduction

- Gene therapy holds the promise for major impact in Myotonic Dystrophy Type 1 (DM1).
- Urgently needed for these trials is a biomarker that is: 1) Disease-specific ; 2) Clinically relevant and 3) Tracks disease progression
- Initial trials will be in affected patients, so goal will be *lack of disease progression*
  - ✓ Though symptom improvement is also possible
- For disease *prevention*, the biomarker will need to detect presymptomatic changes

Introduction

Model for DM1 Progression & Protective Treatment



- Normal Aging
- CTG > 50 Untreated
- CTG > 50 treated, successful *protection against progression*
- CTG >50 Treated with an effective *preventive treatment*

Outline

- **The overall aim of this study is to evaluate measures of brain structure using Magnetic Resonance Imaging (MRI)**

✓ Are there differences between patients and controls?

✓ Do the measures reflect symptoms?

✓ Do the measures reflect disease (CTG repeat)?

✓ Are there abnormalities PRIOR to disease onset?

✓ Do the measures change over time?

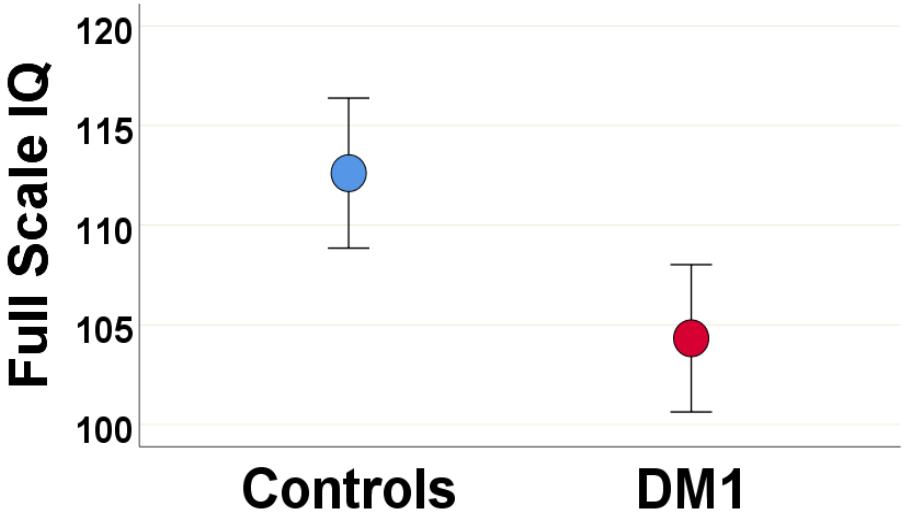
Methods

	n	M:F	Mean Age (sd)	Disease Duration (range)#	MIRS* (sd)	Mean CTG Repeats (range)
DM1	52	18:34	45.6 (11.1)	6.87 yr (0 - 28.5)	2.07 (0.85)	238 55-1000
Control	68	23:45	43.3 (12.2)	-	-	

- MIRS = Muscle Impairment Rating Scale ; 1 = normal function, 5 = severely affected (range in this sample was 1-4); mean of 2.07 = somewhat mildly affected group

Functional Findings

- IQ is lower in DM1 patients

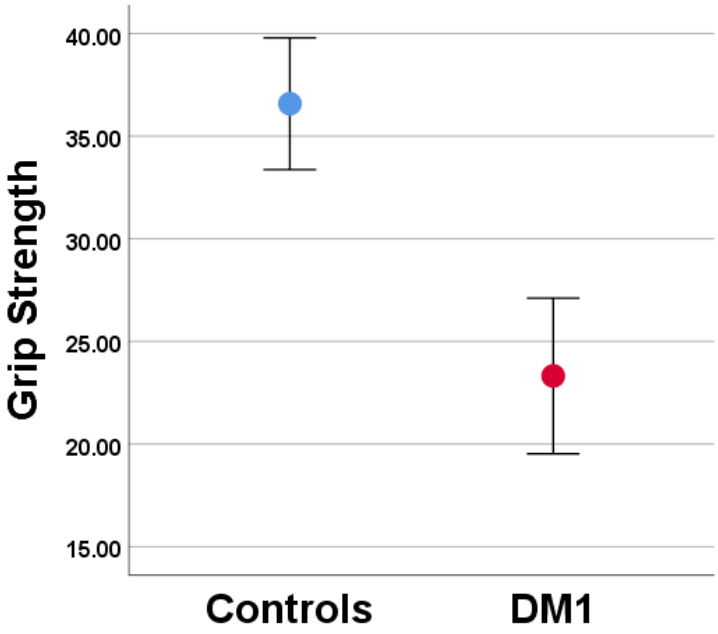


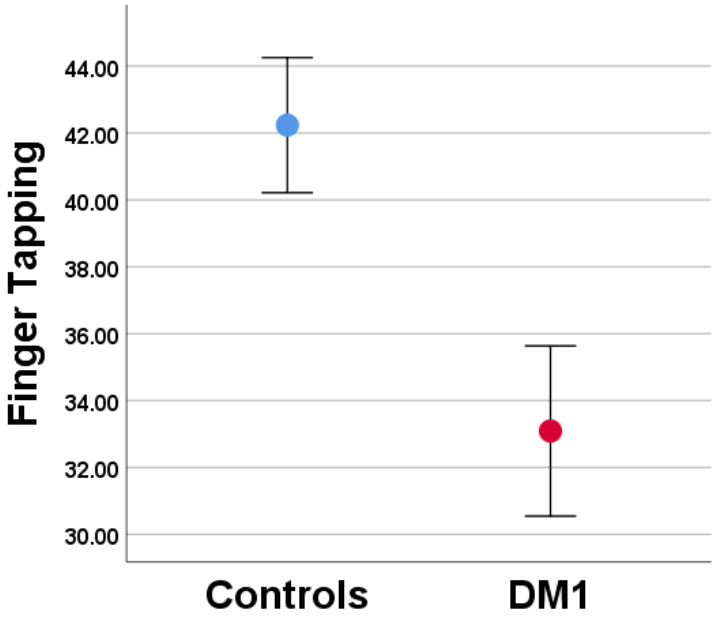
- Controls = 112.8
- DM1 = 104.5
- ANCOVA F = 7.58, p = 0.007
- Although in normal range, subjects with DM1 have substantially lower IQ scores compared to controls

- More specific Cognitive Skills
  - Verbal skills more preserved than visual-spatial skills
  - Executive functions – planning, organizing, shifting – lower in DM1
- Behavior / Sleepiness
  - No significant increase in depression however APATHY higher in DM1
  - Daytime sleepiness higher in DM1

Functional Findings

- Fine Motor Skill





Methods

- Structural MRI – provides volumes of brain regions
- Focus on White Matter
  - Diffusion Tensor Imaging or DTI

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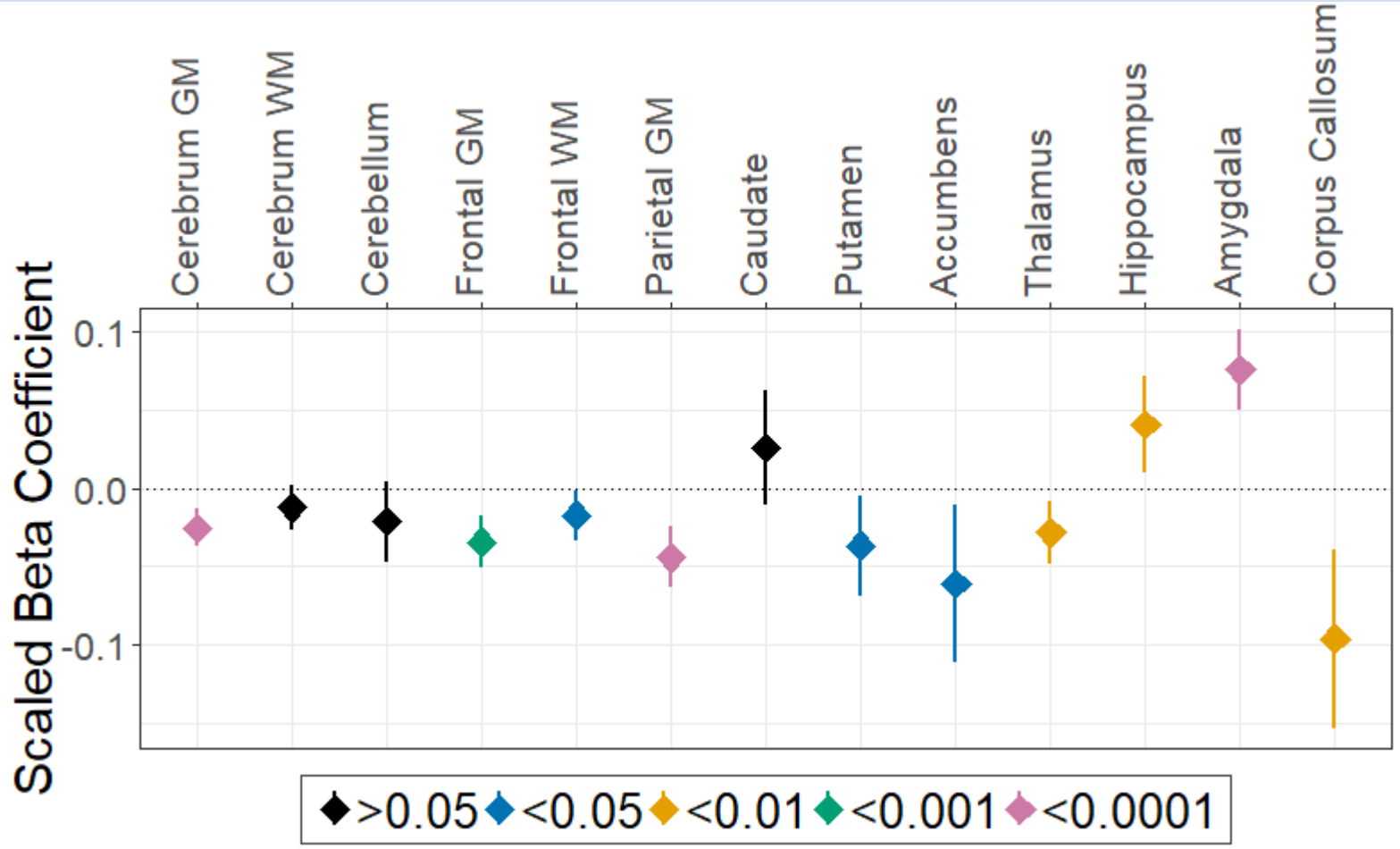
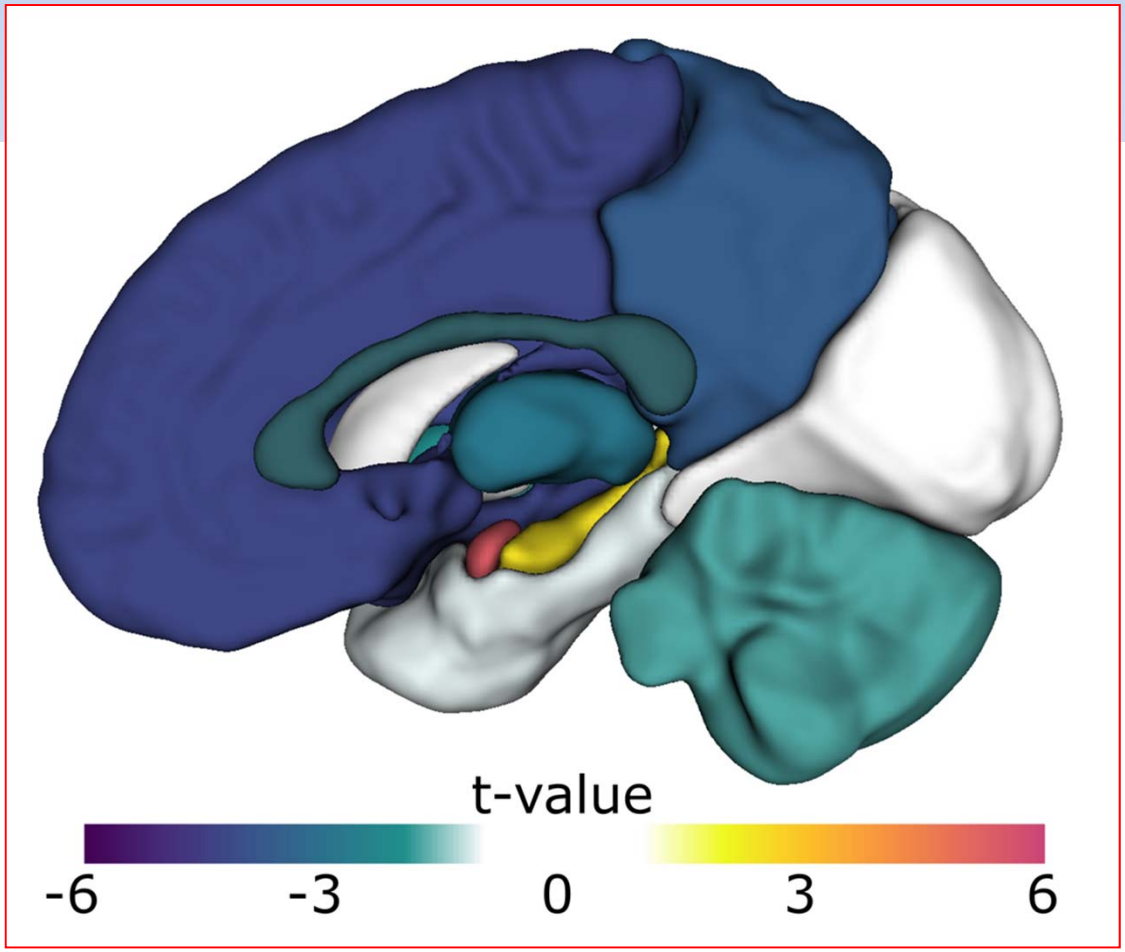
Results



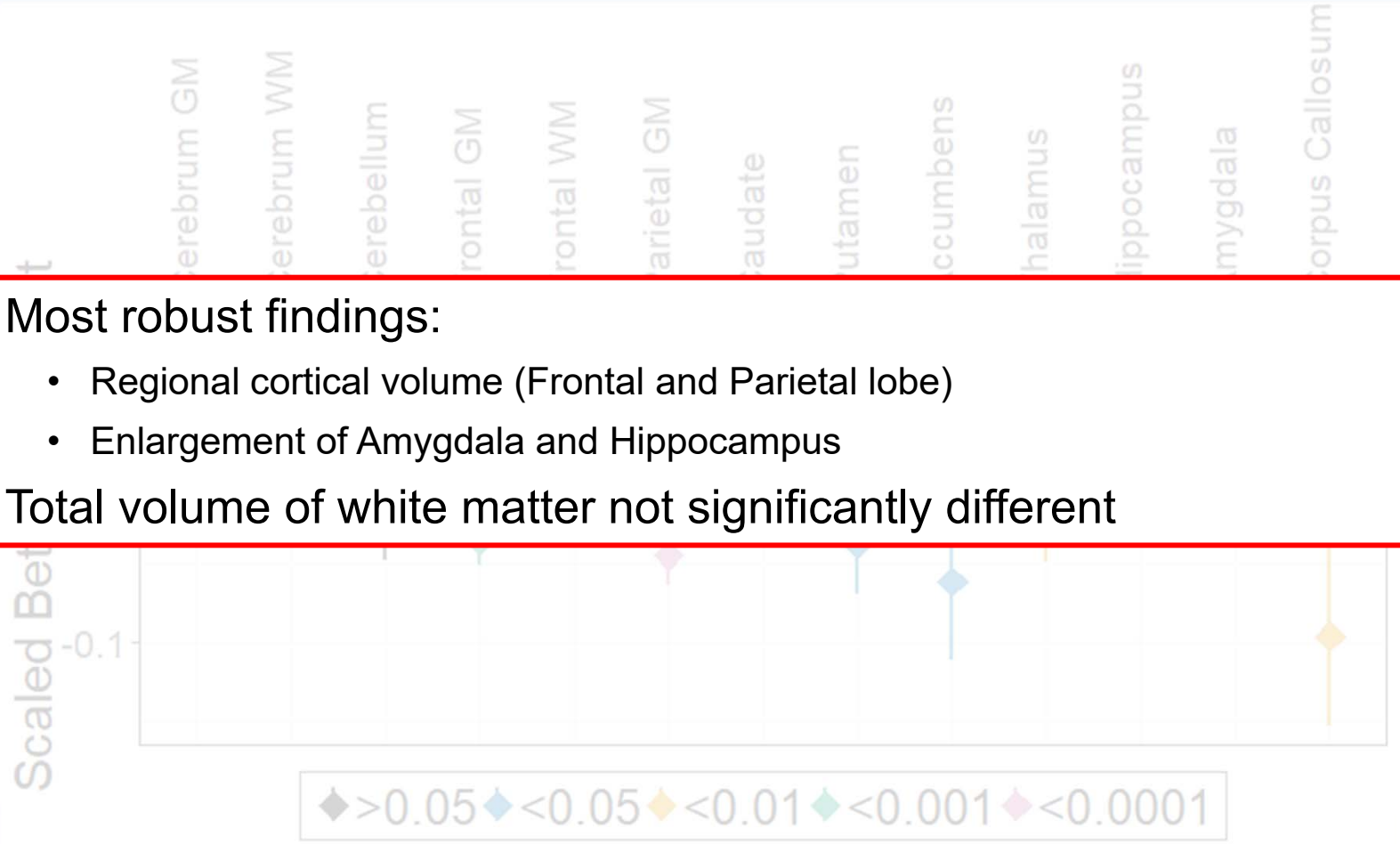
- GM = Gray matter (cortex)
- WM = White Matter

Results



Summary of group differences in regional volumes between individuals with and without DM1. The colors correspond with the magnitude of the t-values of group differences (see color scale). Cool colors indicate that the DM1 group had lower volume than the unaffected group, while hot colors indicate the opposite pattern.

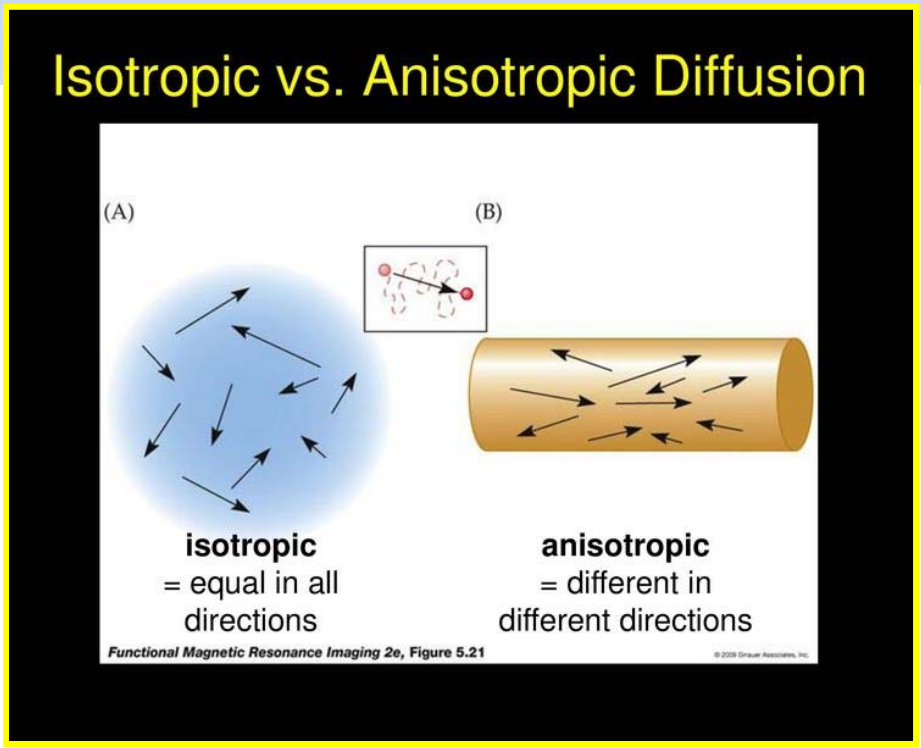
Results

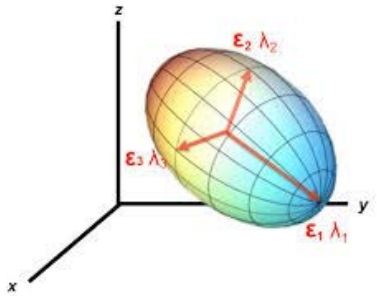


- Most robust findings:
  - Regional cortical volume (Frontal and Parietal lobe)
  - Enlargement of Amygdala and Hippocampus
- Total volume of white matter not significantly different

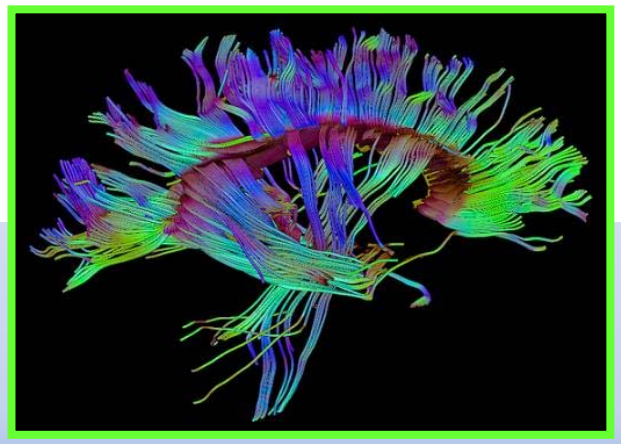
- GM = Gray matter (cortex)
- WM = White Matter

Diffusion Tensor Imaging (DTI)

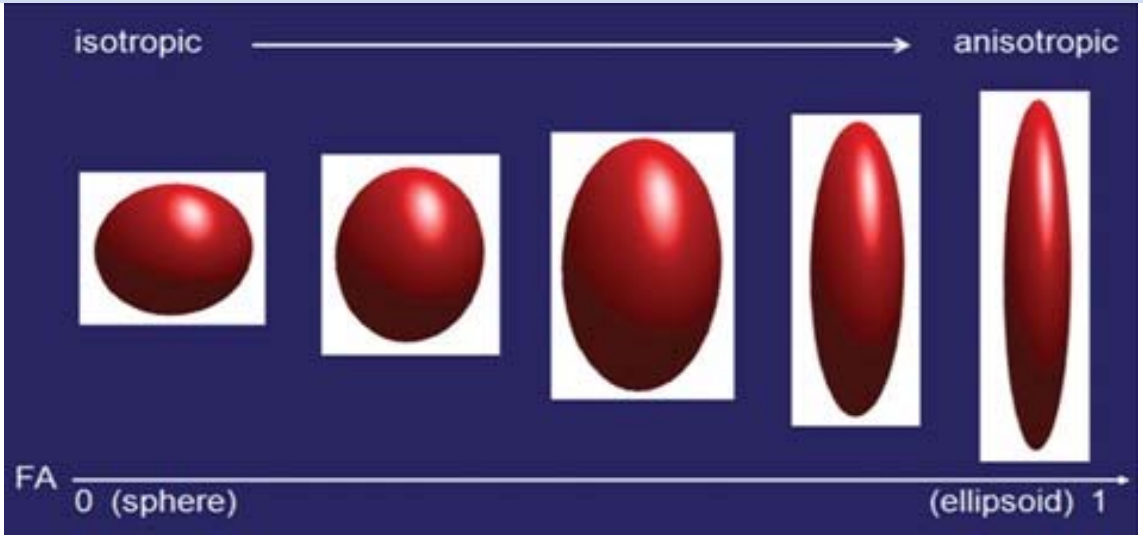




- DTI measures the *direction* of motion of water molecules
- In white matter, nicely organized fiber bundles allow water to move in specific directions
- **Fractional Anisotropy (FA)**

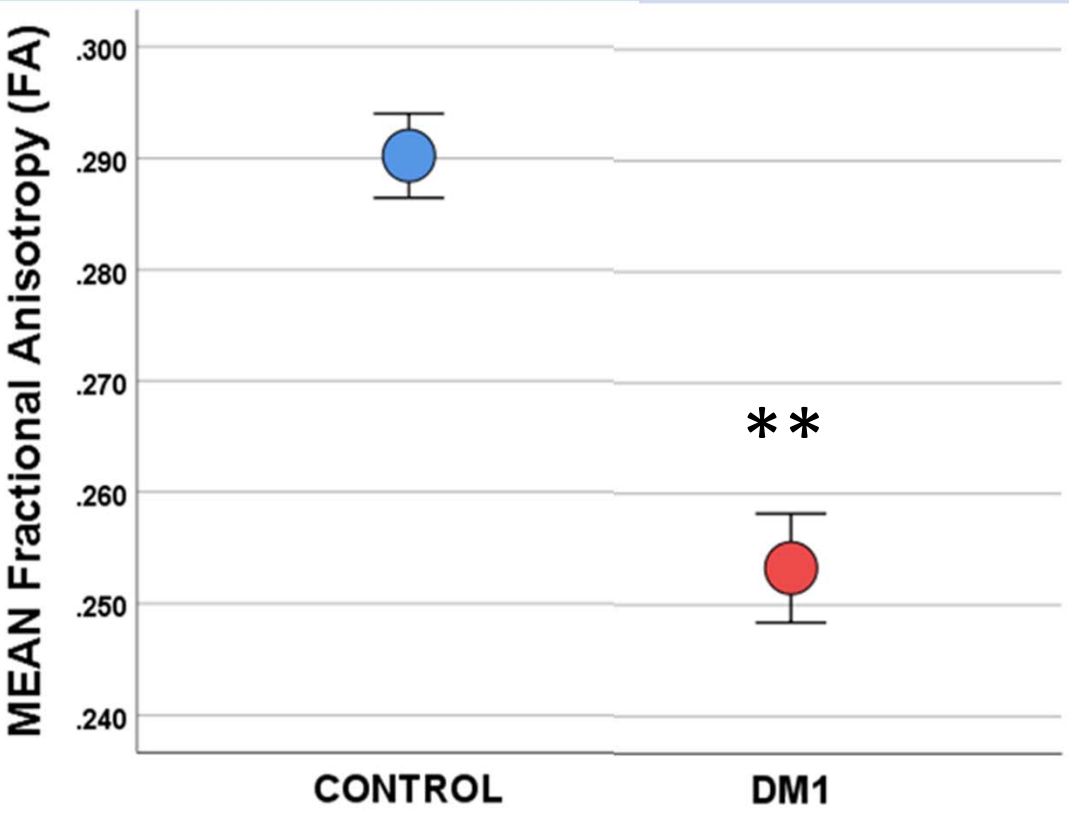


Diffusion Tensor Imaging



- The higher the FA, the more ‘healthy’ the white matter

Results



** p <0.001

FA is Significantly abnormal in patients with DM1

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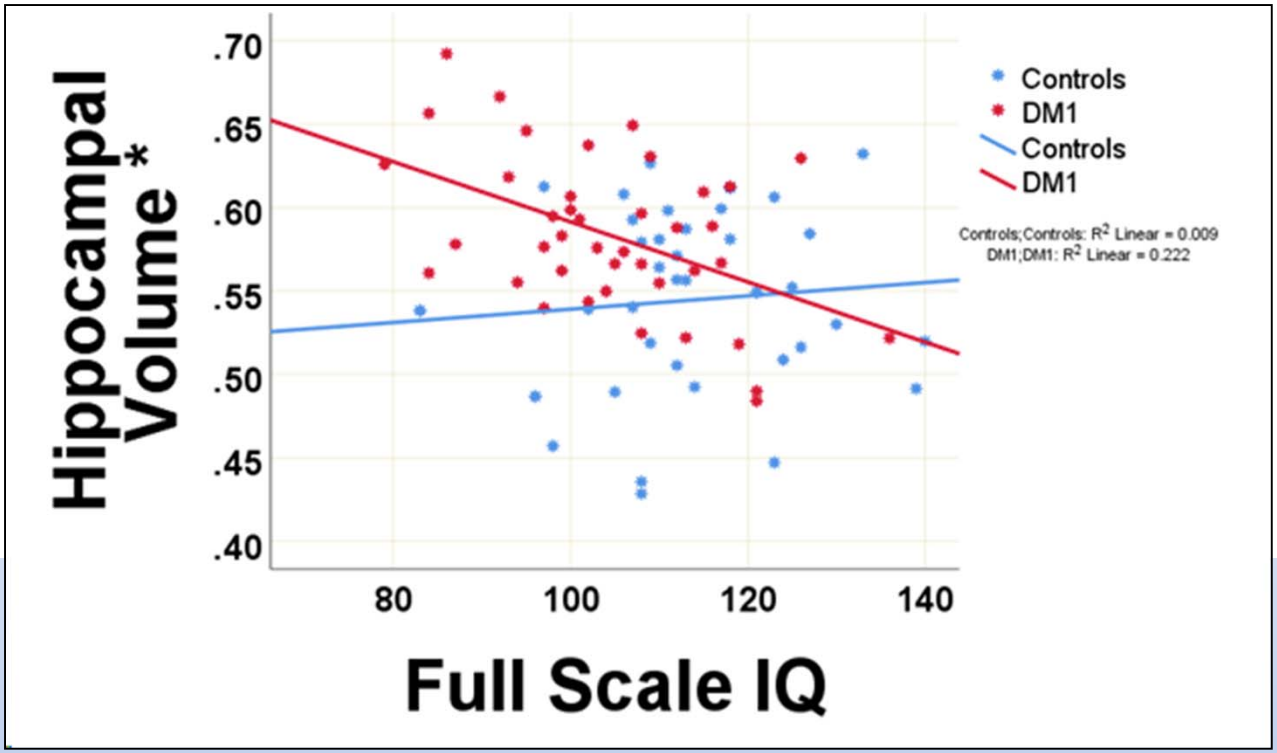
Results

- The enlargement of the amygdala and hippocampus is likely pathological
  - The larger the amygdala, the greater the apathy
  - The larger the hippocampus the lower the IQ



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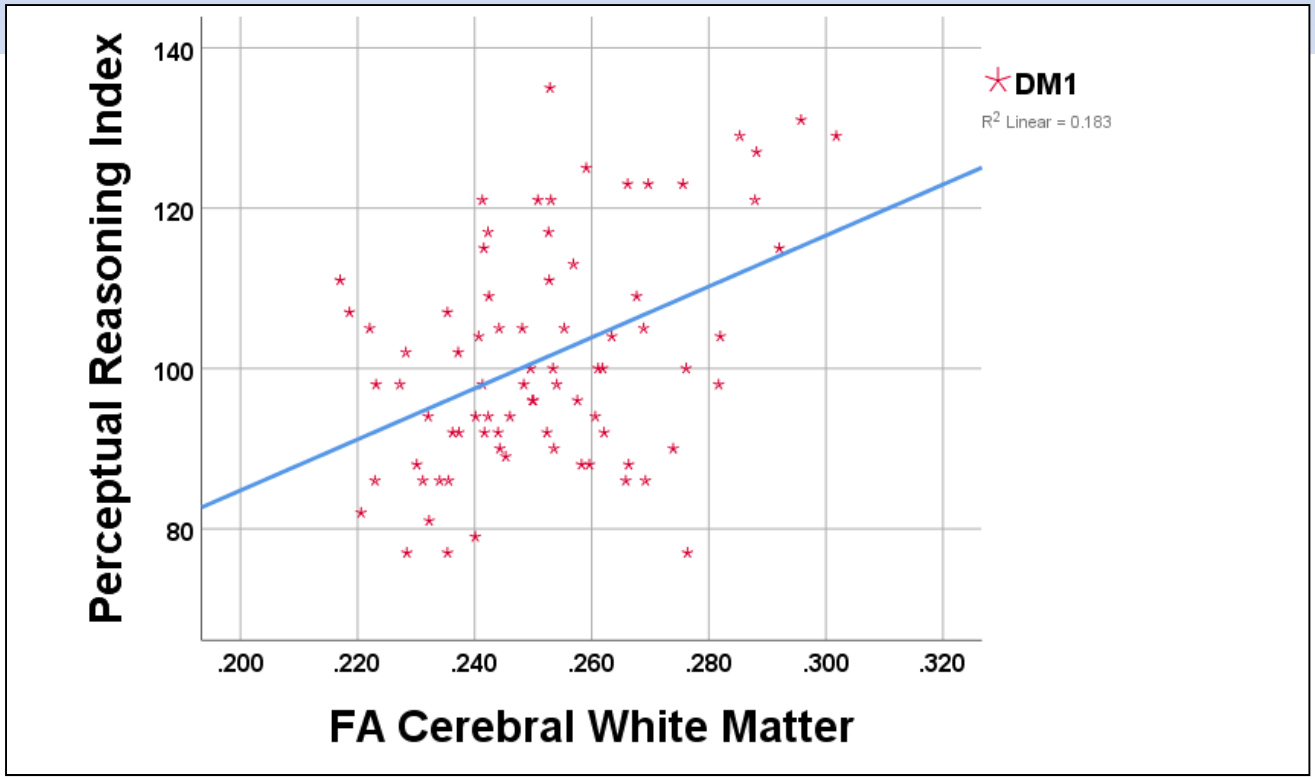
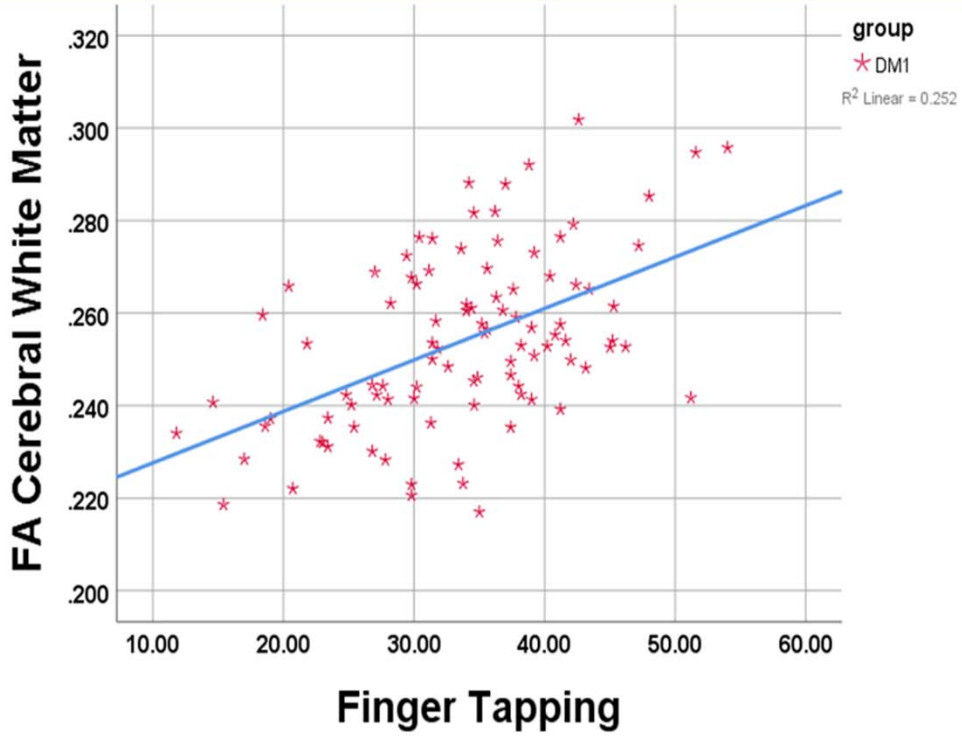
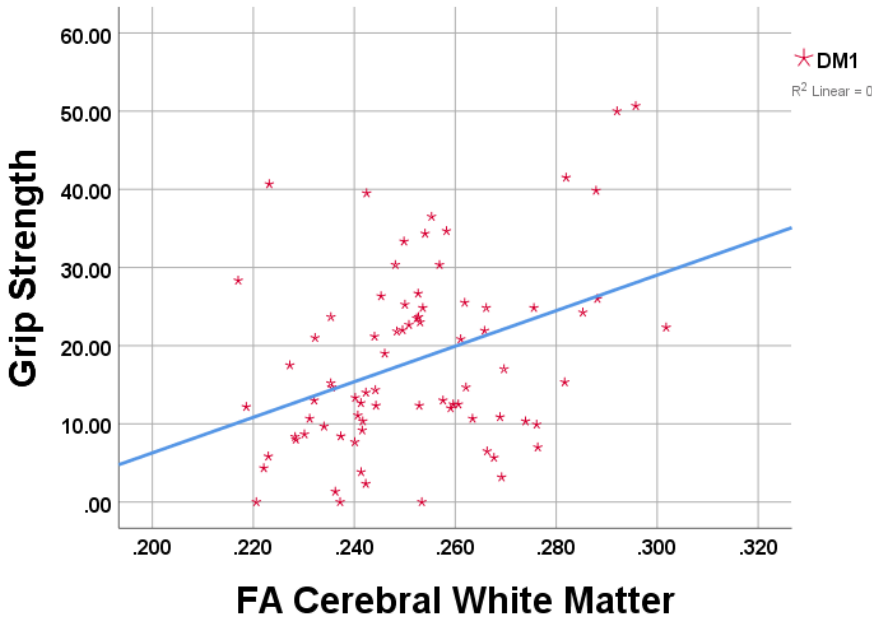


- Brain FA is associated with cognitive function
  - Lower the FA, lower the skill

Results





- Brain FA is associated with MOTOR FUNCTION
  - **Muscle weakness in DM1 is due to primary muscle pathology**
  - ***May*** **be a secondary factor of brain health in muscle weakness**

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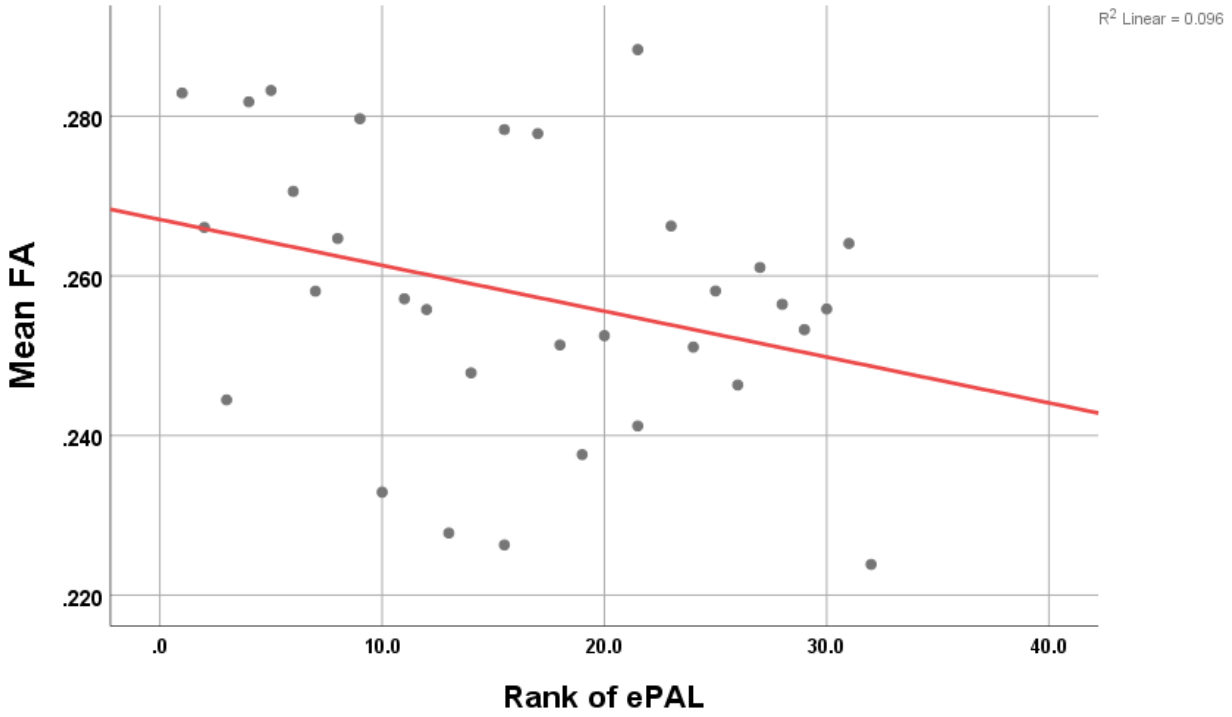

- Brain FA is associated CTG repeat
  - ePal = estimated progenitor allele length
  - The higher the CTG, the lower the FA

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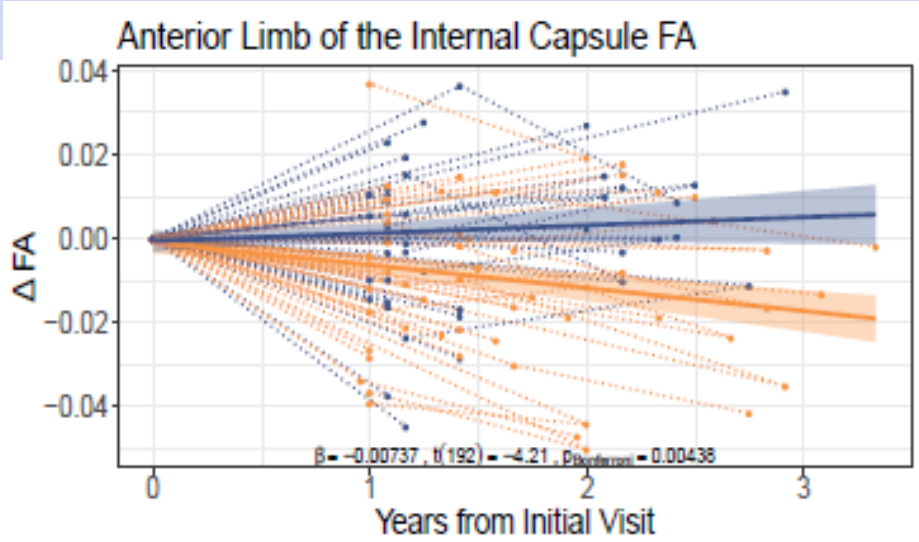
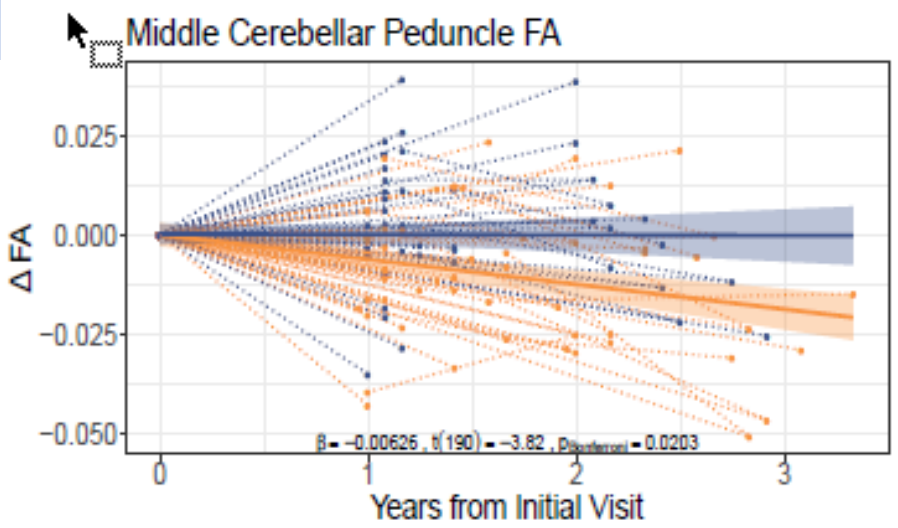
Change Over Time

- **Conundrum: neurodegenerative diseases typically progress slowly**
  - Good for the patient
  - Bad for clinical trial design
    - Don’t want to have to wait 1- 2 years to see if the drug is neuroprotective (slows progression)

Results





BLUE = Controls

Orange = DM1

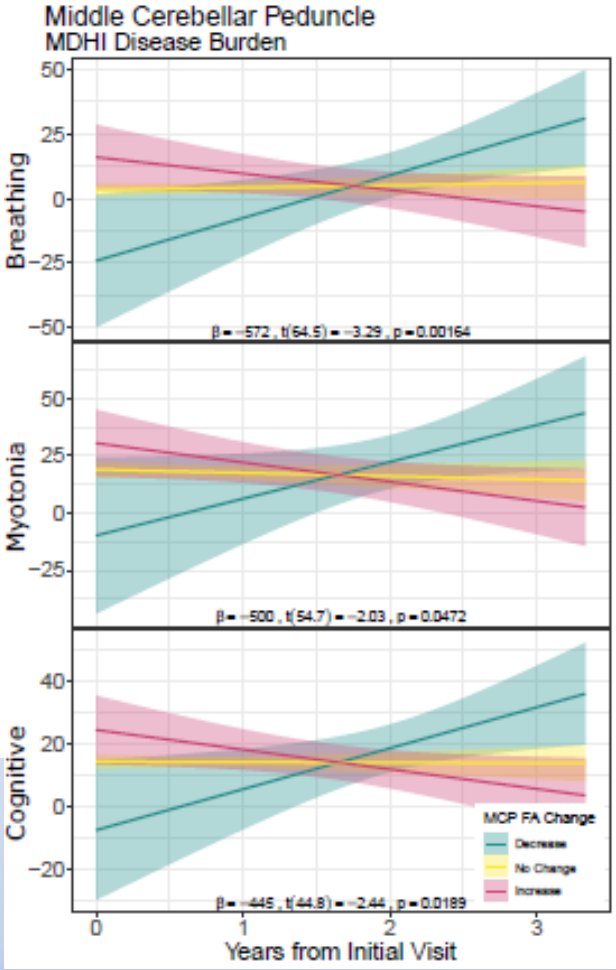
- Decreases in FA in these two regions can be seen within 6 months

Change Over Time

- **Conundrum: do the brain changes reflect changes in clinical symptoms?**
  - Although we can measure brain change within 6 month, our clinical measures (cognitive function, muscle strength, etc), do NOT change within 6 months

Change Over Time

- However, we did see a relationship with Patient reported symptoms



- In patients who had a decrease in FA, there was a related increase in patient-reported disease burden for
  - Breathing
  - Myotonia
  - Cognitive skills

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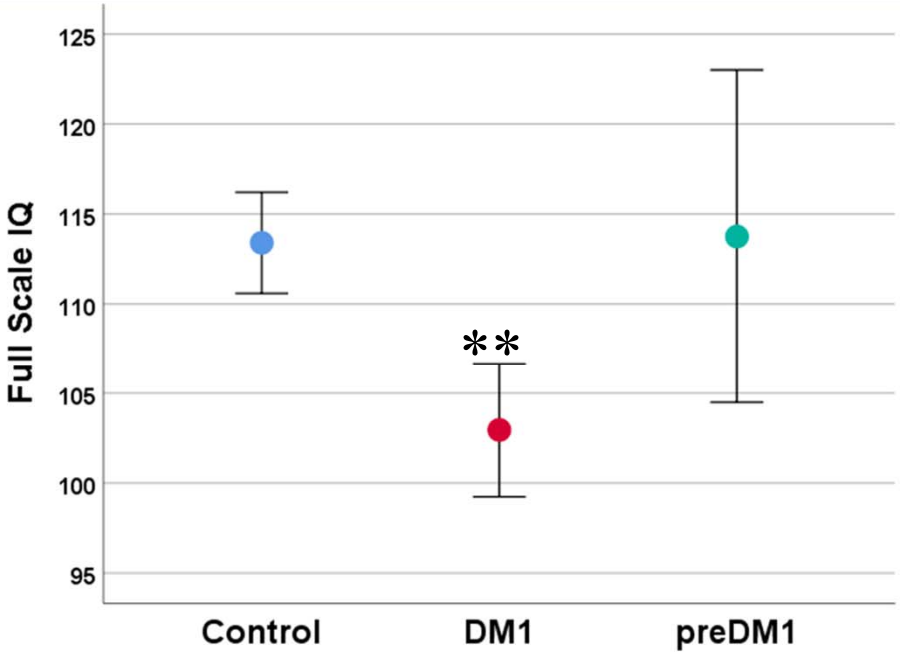
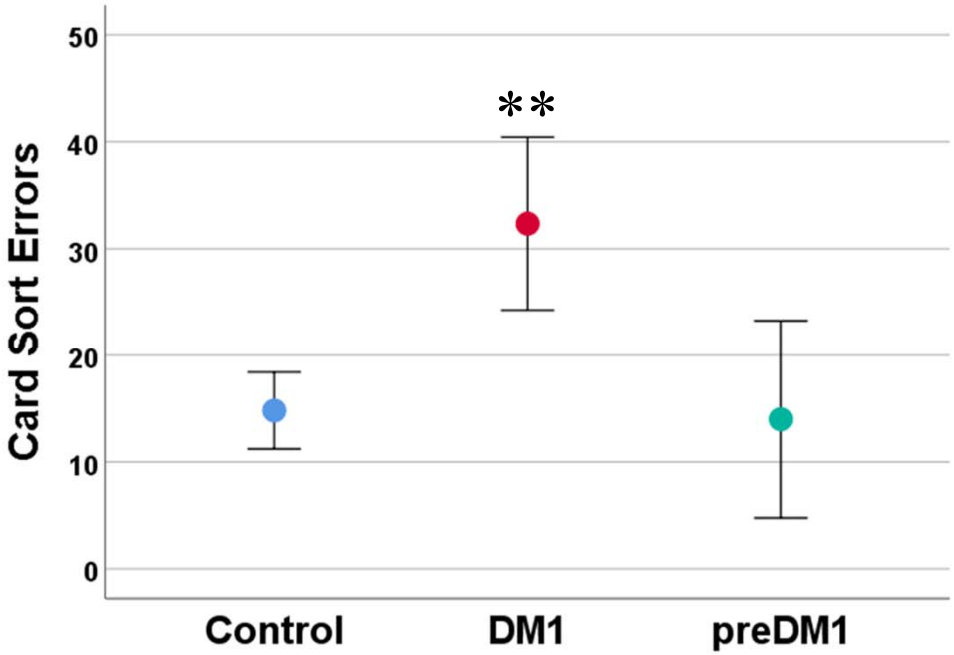
Methods

			Age (sd)	Duration (range)#	(sd)	Repeats (range)
DM1	44	13:31	45.6 (11.1)	6.87 yr (0 - 28.5)	2.07 (0.85)	238 55-1000
PreDM1	8	5:3	43.5 (19.0)	0	1.0	122 55-375

Age	CTG
57	55
61	100
64	59
21	375
19	125
20	120
54	88
50	56

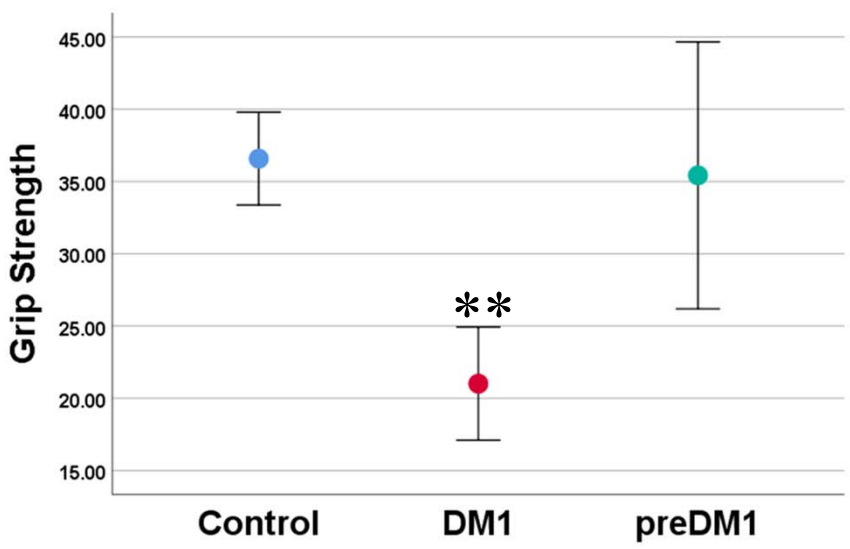
Results

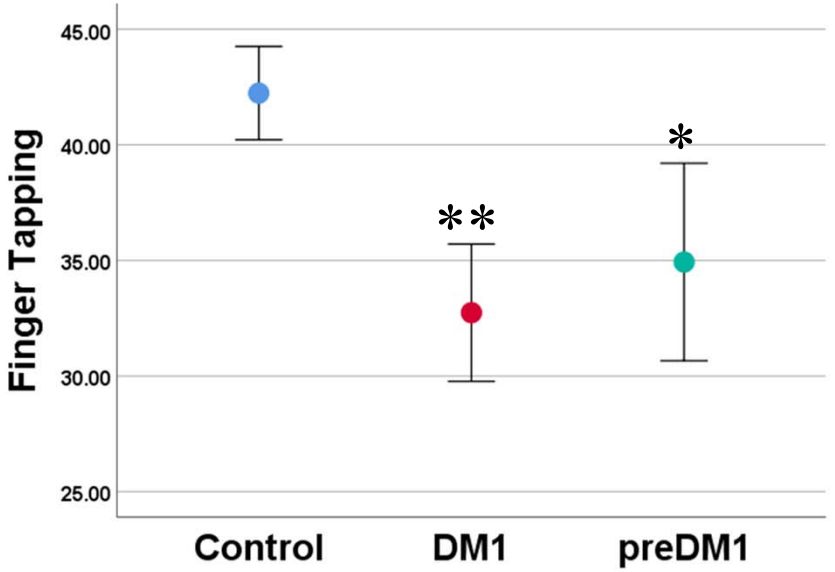




PreDM1 have no significant cognitive deficits

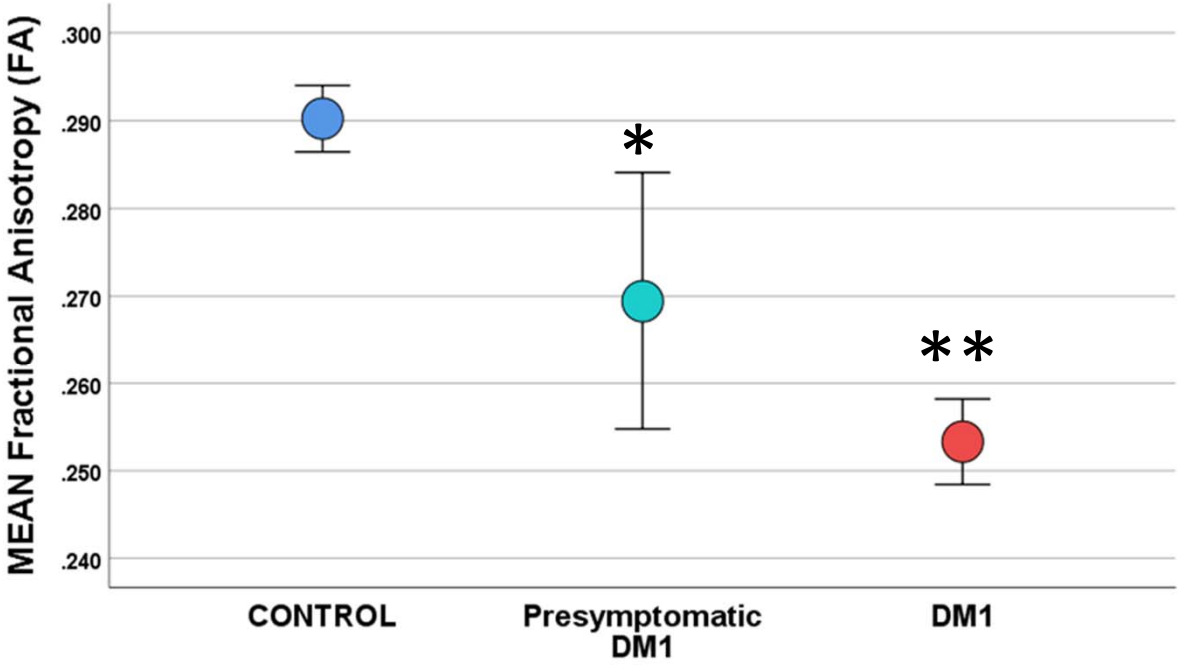
Results





PreDM1 have normal grip strength but ABNORMAL Finger Tapping Scores

Results



* p <0.01

** p <0.001

FA is abnormal *prior to symptom manifestation*

Conclusion

- Brain FA holds promise for being a useful biomarker for gene therapy trials

1. Disease-specific (correlates with CTG)
2. Clinically relevant (correlates to symptoms)
   - ✓ Correlates to muscle function; also to other CNS functions (apathy, cognitive function)
3. Tracks disease progression
4. Present prior to disease onset (important in trials evaluating *disease prevention*)

Acknowledgements – Nopoulos Lab

Front row: Tim Koscik, Ellen Van der Plas, Kathleen Langbehn, Stephen Cross, Mickey Sloat, Liza Casella

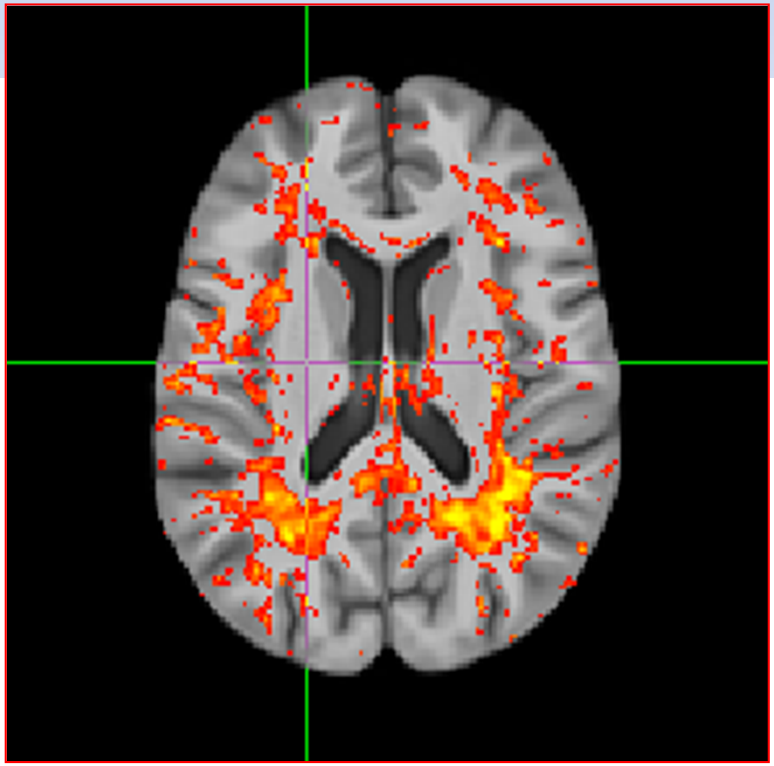
Second row: Marci Novak, Lyndsay Harshman, Joel Bruss, Zoe Carlson-Stadler, Amy Conrad, Emily Laing, Ansley Kunath

Third row: Matt McIlrath, Sasha Tereshchenko, Ashley Cochran, Claire Johnson, Jordan Schultz, Peg Nopoulos, Eric Axelson, Sonia Slevinski, Jennifer Henderson

Special Thanks to all of the patients, families, and controls who donated their time and efforts to travel to Iowa and participate in our study

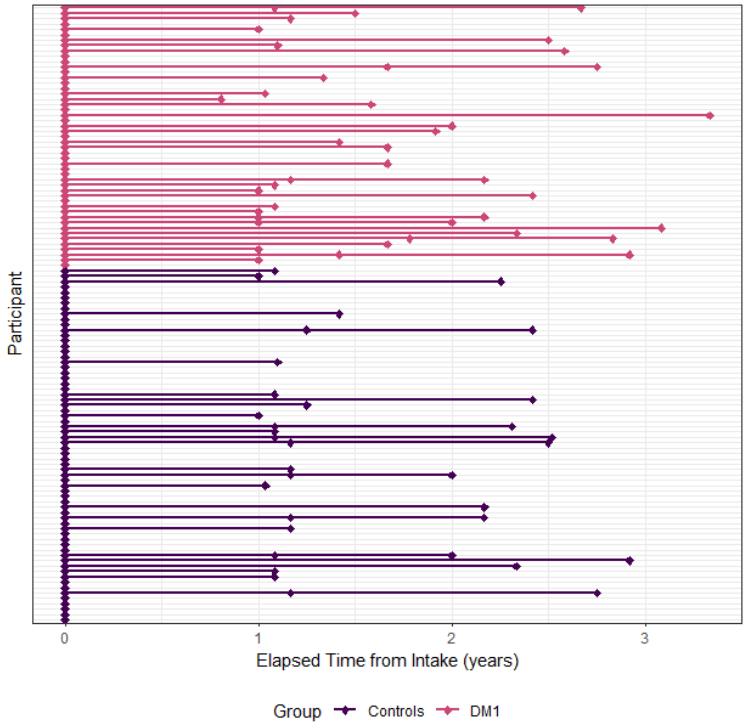
Study Funded by NINDS

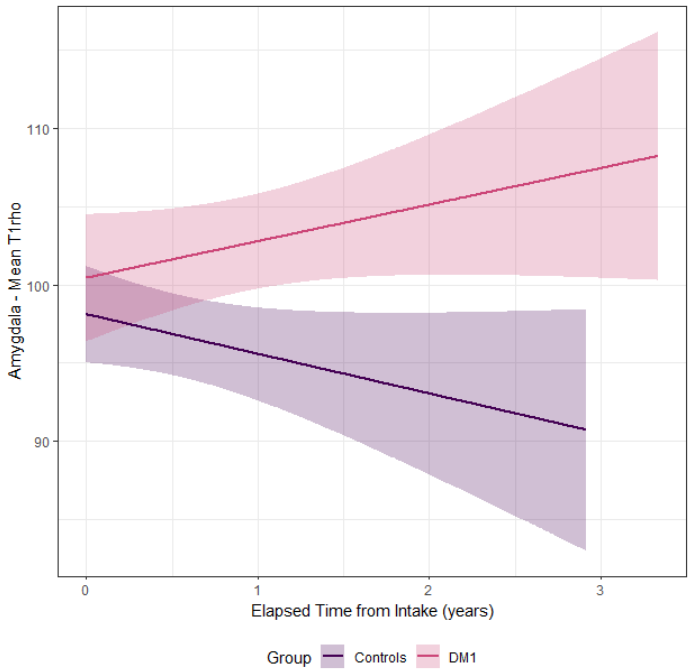
T1rho – pH imaging



- Comparison map – DM1 patients compared to controls; red and yellow where T1rho is higher
- **most sensitive marker
  - CHANGE IN ONE YEAR (amygdala)

T1rho – pH imaging





- **most sensitive marker
  - Abnormal prior to disease onset
  - CHANGE IN ONE YEAR (amygdala)