A Multimodal Imaging Analysis of Subcortical Gray Matter in Fragile X Premutation

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2012 International Fragile X Conference
Subcortical Gray Matter

- Main structures
  - Thalamus, putamen, caudate nucleus, globus pallidus
- Important for motor function
- High iron concentration
  - Risk of oxidative stress
- Likely affected in Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)
  - Progressive intention tremor and gait ataxia
  - Zinc and iron dysregulation causing mitochondrial dysfunction
  - Reduced gray matter density in the thalamus

A Multimodal Imaging Study of Subcortical Gray Matter

visualizing structures
T1-high resolution

structural organization
diffusion tensor imaging

water and iron content
diffusion weighted imaging (DWI)\(^1\)

Brain dissection of the white matter

Iron stain of the striatum

Fiber tracts

Control

FXTAS

A Multimodal Imaging Study of Subcortical Gray Matter

- Visualizing structures with T1-high resolution
- Structural organization with diffusion tensor imaging
- Fractional anisotropy (FA) increased
- Mean diffusivity (MD) decreased
- Water and iron content with diffusion weighted imaging (DWI)

**Control**
- Subcortical gray matter: $\text{FA} = 0.2-0.5$
- $\text{CSF}: \text{FA} = \sim 0$
- Internal capsule
- $\text{FA} > 0.5$
- *Control*

**FXTAS**
- High MD
- Low MD

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Methods

- Participants: 61 males, age 47-81 years
  - 14 controls
  - 11 non-FXTAS premutation
    - FXTAS stage 0-1
  - 36 FXTAS patients
    - FXTAS stage 2-5

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal function</td>
</tr>
<tr>
<td>1</td>
<td>Subtle tremor/balance problems with no interference in daily living</td>
</tr>
<tr>
<td>2</td>
<td>Minor tremor/balance problems with minor interference in daily living</td>
</tr>
<tr>
<td>3</td>
<td>Moderate tremor/balance problems with significant interference in daily living</td>
</tr>
<tr>
<td>4</td>
<td>Severe tremor/balance problems requiring a cane or walker</td>
</tr>
<tr>
<td>5</td>
<td>Use of a wheelchair on a daily basis</td>
</tr>
<tr>
<td>6</td>
<td>Bedridden</td>
</tr>
</tbody>
</table>

Methods

- **Image processing**
  - Automatic segmentations
    - FIRST
      - FMRIB’s Integrated Registration and Segmentation Tool
        - University of Oxford
  - FA, MD, and DWI generation
    - DTI Studio
      - Johns Hopkins Medical Institute
  - Register images to T1
    - Freesurfer
      - Martinos Center for Biomedical Imaging
  - Apply segmentations
Methods

- **Statistics**
  - Group comparisons and correlation with FXTAS stage
    - Multiple linear regression
    - Age and total cranial volume (for volume only) as covariates
  - Multiple comparisons
    - Corrected using false discovery rate (5%)
FXTAS: ↓ Volume & ↓ DWI

FXTAS vs. NC

<table>
<thead>
<tr>
<th></th>
<th>Thalamus</th>
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<th>Putamen</th>
<th>Pallidus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>*</td>
<td></td>
<td>*</td>
<td>*</td>
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<tr>
<td>DWI</td>
<td>*</td>
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**Volume, DWI, FA Showed High Correlation with FXTAS Stage**

**Partial $r^2 = 0.47$, $P < 0.001$**

**Partial $r^2 = 0.14$, $P = 0.011$**

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**With Stage**

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<tr>
<td>FA</td>
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* Negative correlation; * Positive correlation

* * * Why positive?
↑ FA in Caudate with FXTAS Stage

- Frontal-striatal pathway
  - In the head of the caudate
- Imaging measurements associated with ↑FA
  - ↓ volume, $r = -0.55$, $p < 0.001$
  - ↓ MD, $r = -0.49$, $p < 0.001$
  - ↓ DWI, $r = -0.29$, $p = 0.051$
- Preferential loss of cells, but relatively spared frontal-striatal pathway?

Iron stain of the striatum
Conclusions

- Involvement of all 4 structures in FXTAS
  - Volume atrophy and possibly iron deposition

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- Measurements correlated with FXTAS stage

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- Useful for tracking FXTAS progression
Acknowledgement

- Research participants and families
- Patrick Adams
  - Image and data collection
- Danielle Harvey
  - Statistical support

- NIH funding
  - TL1DA024854 to J.Y.W.
  - RL1AG032115 to R.J.H.
  - UL1DE0199583 to R.J.H.
  - HD036071 to R.J.H.
  - MH078041 to S.M.R.
  - NS062412 to S.M.R.