The Effect of Cognitive Functioning, Age, and Molecular Variables on Brain Structure Among Carriers of the Fragile X Premutation: Deformation Based Morphometry Study

Naomi J. Goodrich-Hunsaker*, Ling M. Wong, Yingratana McLennan, Flora Tassone, Danielle Harvey, Johnson GadElkarim, Liang Zhan, Olusola Ajilore, Alex Leow, Susan M. Rivera, Tony J. Simon

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Talk Overview

1. Neurocognitive phenotype in fragile X premutation carriers (fXPCs)

2. Deformation based morphometry analysis

3. Implications and future plans
FMR1 Gene Variation

Normal: < 45 CGG Repeats
- Clinical: Normal
- mRNA: Normal
- FMRP: Normal

Premutation: 55 - 200 CGG Repeats
- Clinical: Fragile X-associated tremor ataxia syndrome (FXTAS)
- mRNA: Premutation
- FMRP: Reduced

Full Mutation: > 200 CGG Repeats
- Clinical: Fragile X syndrome
- mRNA: Full Mutation
- FMRP: No expression
Psychomotor Speed

- Male and female HCs replicate published population values, as do male fXPCs\(^1\)

- Adult female fXPCs show faster psychomotor speed compared to HCs\(^2\)

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Numerical Spatial Attention

- Male fXPCs **impaired** compared to male HCs\(^1\)
- No difference between female fXPCs and HCs\(^2\)
- We see similar results on a magnitude\(^1,3\) comparison task!


**Adult Males\(^*\)**

**Adult Females**
Aim of the Current Study

- We wanted to investigate structural brain deformation in the same unaffected male and female fXPCs.

- Results might provide a bases for the aforementioned cognitive impairments and/or be a biomarker for later neurodegeneration.

- We also examined the possibility that genetic “dosage” (e.g. CGG repeat length, *FMR1* mRNA levels) might modulate brain changes.
Brain Features

- MRI studies have shown in older male fXPCs
  - T2 hyperintensities in the middle cerebellar peduncle\(^1\)
  - Reduced volume in amygdala-hippocampal complex, thalamus, caudate, insula, cerebellum, and brainstem\(^2,3\)
  - White matter abnormalities in the middle cerebellar peduncle, superior cerebellar peduncle, and fornix / stria terminalis\(^4\)
- Female fXPCs with FXTAS demonstrate milder brain changes than affected male fXPCs\(^5,6\)
- Intranuclear inclusions are found throughout the CNS in neurons and glial cells: cortex, basal ganglia, thalamus, hippocampus, and cerebellum\(^7,8\)

Study Design

- Participants included 102 adults (aged 18 - 45)
  - 48 HCs (24 males, 24 females)
  - 34 female fXPCs
  - 20 male fXPCs

- 3T MRI using a Siemens Trio 3T scanner at the UCDIRC

- DBM analysis consisted of preprocessing, spatial normalization, and Jacobian calculation
  - ART acpcdetect (http://www.nitrc.org/projects/art/)
  - ANTs (http://www.picsl.upenn.edu/ANTS/)
  - VBM toolbox SPM8 (http://dbm.neuro.uni-jena.de/vbm/)
Deformation Based Morphometry

- Sensitive technique for investigating anatomical variations in brain shape, because it provides an unbiased voxel-wise comparison across the entire brain

Moving: Participant

Fixed: Template

Non-linear Moving to Fixed
Shown is the log of Jacobian matrix from a participant image with respect to template.

- Volume decrease
- Volume increase
Statistical Analyses

- Using SPM8, performed ANCOVA with age as covariate on smoothed (4-mm Gaussian kernel) log Jacobian maps
- We report clusters exceed threshold of 100 voxels & FDR-corrected cluster level $p < 0.05$
- Contrasts:
  - Female fXPCs versus HC
  - Male fXPCs versus HC
  - Male fXPCs versus female fXPCs
- Correlated the mean log Jacobian with:
  - Age, IQ, CGG repeat length, $FMR1$ mRNA levels
  - Basic psychomotor speed performance
  - Enumeration & magnitude comparison task performance
Female fXPCs compared to HCs

- Showed significant regional volume enlargement in:
  - Supplementary motor, precentral & postcentral gyrus
  - Orbital part of frontal lobe
  - Anterior cingulate gyrus
  - Frontal lobe white matter regions (e.g. anterior corona radiata, superior longitudinal fasciculus)

- **No significant** clusters for volume reduction in female fXPCs compared to HCs
Male fXPCs compared to HCs

- Showed significant regional volume reduction in:
  - Cerebellar lobule VIIb
  - Middle cerebellar peduncle
- Similar findings reported in older male carriers with and without FXTAS\(^1,2\)

- **No significant** clusters for volume enlargement in male fXPCs compared to HCs

Male fXPCs compared to Female fXPCs

- Showed significant regional volume reduction in:
  - Cerebellar lobule VIIb
  - Middle cerebellar peduncle
  - Orbital part of frontal lobe
  - Middle temporal gyrus
  - Inferior parietal lobule
  - Superior longitudinal fasciculus
  - Thalamus

- No significant clusters for volume enlargement in male fXPCs compared to female fXPCs
Summary of Results

- Female and male fXPCs showed significant morphometric changes in OFC, ACC, and thalamus, which are part of the network for decision-making and emotional processing.
  - Relevant to clinical features of anxiety in female fXPCs and/or to the psychiatric symptoms of FXTAS like disinhibition, obsessive-compulsiveness, and apathy.
- Female fXPCs compared to HCs had enlarged volumes in sensory and motor cortical areas, which may underlie enhanced basic psychomotor speed in female fXPCs.
- Male fXPCs compared to HCs and female fXPCs had reduced cerebellum and MCP volume, regions implicated in the symptomatology of FXTAS.
- Male fXPCs compared to female fXPCs also showed reduced volume in IPL, a region involved in processing cognitive domains like space, time, and number.
  - Recall these same male fXPCs, but not female fXPCs were impaired on an enumeration task & a magnitude comparison task.
- Correlation analyses revealed no significant associations.
Implications & Future Plans

‣ First study to demonstrate brain deformation differences in young adult male and female fXPCs using deformation-based morphometry

‣ Longitudinal studies needed to determine...
  ▶ Whether the morphological brain changes are present in children with premutation allele (i.e., stable phenotype)
  ▶ Whether these anatomical variations relate to risk of neurodegeneration (i.e., biomarker)
Thanks

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