The Potential of Non-Invasive Brain Imaging in Understanding CAS

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Diagnostic Criteria

- Increased speech sound durations
- Increased duration of intervals between sounds and syllables
- Speech sound distortions (any substitutions are distorted)
- Abnormal sentence and lexical stress and prosodic patterns
- Speech segmentation (staccato-like speech)

Non-Differential Features

- Severe intelligibility reduction
- Inconsistency
- Increasing errors as length of utterance increases
- Groping
- Increased errors on more complex phonemes
- Speech initiation difficulties
- Awareness of errors (e.g., self-corrections)
- Automatic speech better than propositional speech
- Perseveration errors

Features Differential for other Speech Sound Disorders

- Anticipatory errors
- Transposition errors
- Weakness of the oral structures

Exclusionary Criteria

- Fast speech rate
- Normal speech rate
- Normal stress and prosody
- Smooth transitions (no segmentation)

This Talk

- Overview Methods (BRIEFLY)
- Review the very small literature
- Offer a proposal to use Genomic imaging to better understand CAS (and other speech disorders)

Non-Invasive Imaging Methods

- Structural MRI
- Functional MRI
- Positron Emission Tomography (PET)
- Image guided, robotic Transcranial Magnetic Stimulation

FOXP2 (Watkins, Vargha-Khadem et al., 2002)

- VBM with T1-weighted MRI scans in 17 family members (7 of whom had AOS)
  - AOS associated with reduced gray matter in caudate nucleus, bilaterally
  - AOS also may be associated with reduced gray matter in dorsal inferior and precentral frontal gyri

Adult Stroke-Induced AOS

- Regions of interest include Left Dorsal Pre-frontal cortex, Broca’s area, insula

Genomic Imaging-A Proposal for CAS (with thanks to Dr. David Glahn)

- "Neuroimaging offers a powerful way to bridge the gaps between genes, neurobiology and behavior" (Bearden, Glahn et al, 2008)
- Neuroanatomic markers from *high resolution* MRI are strong candidates for neurophenotypes (endophenotypes)

What’s to Follow

- Overview of converging methodologies to examine genetic influenced on brain structure
- Examples of approach and methods in various genetic syndromes
- Including some astounding pictures of brain structures
- First, a digression into evolution (courtesy of Dr. Peter Kochonov)

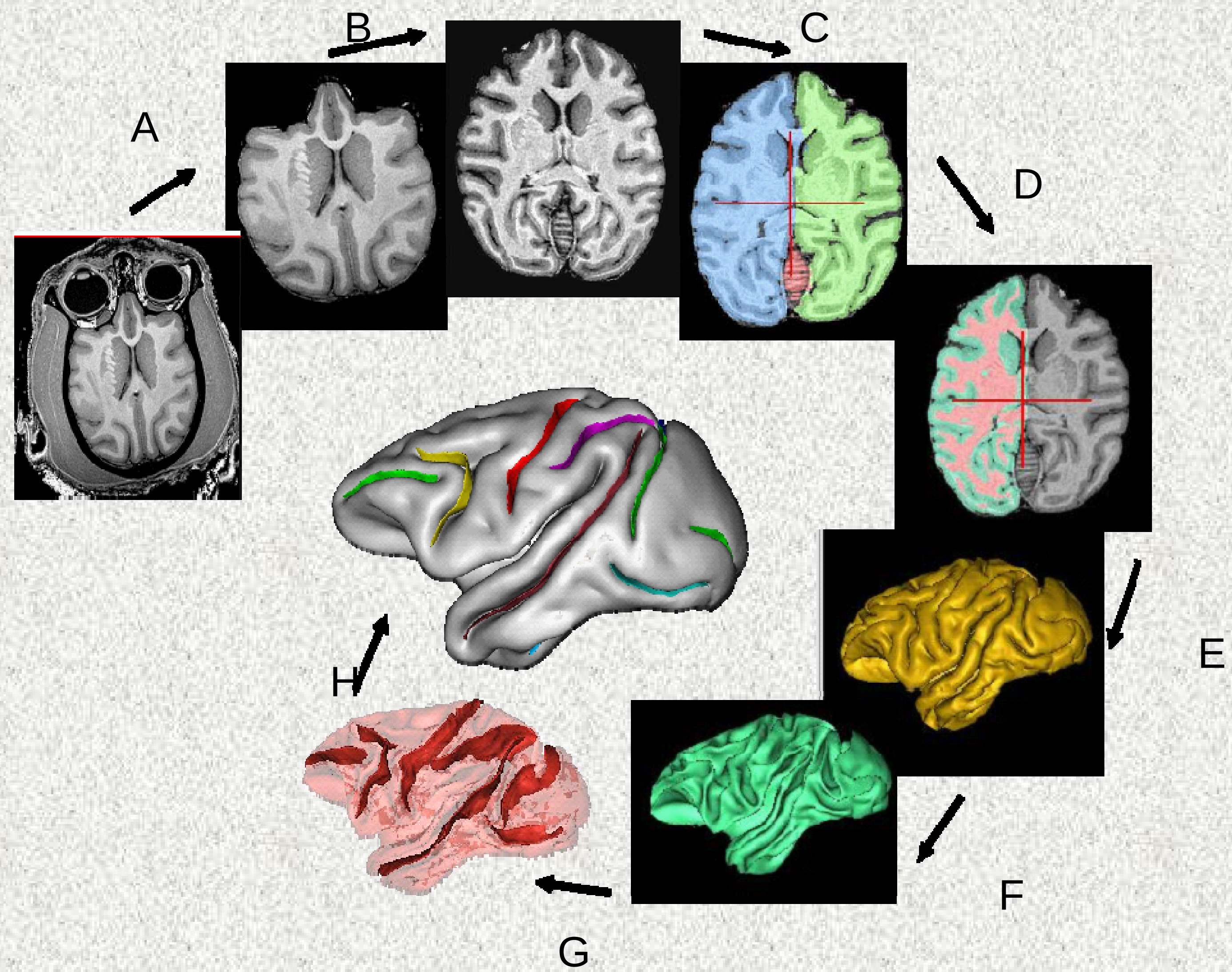


Figure 2. Structural MRI data were processed using object-based-morphometry pipeline. Brain images were processed with the following steps: skull-stripping (A); RF-homogeneity correction and spatial normalization (B); hemispheric and tissue segmentation (C,D), extraction of GM and WM surfaces (E,F); Identification of sulcal surfaces using crevasse detector (G); Identification and labeling of sulcal structures (H).

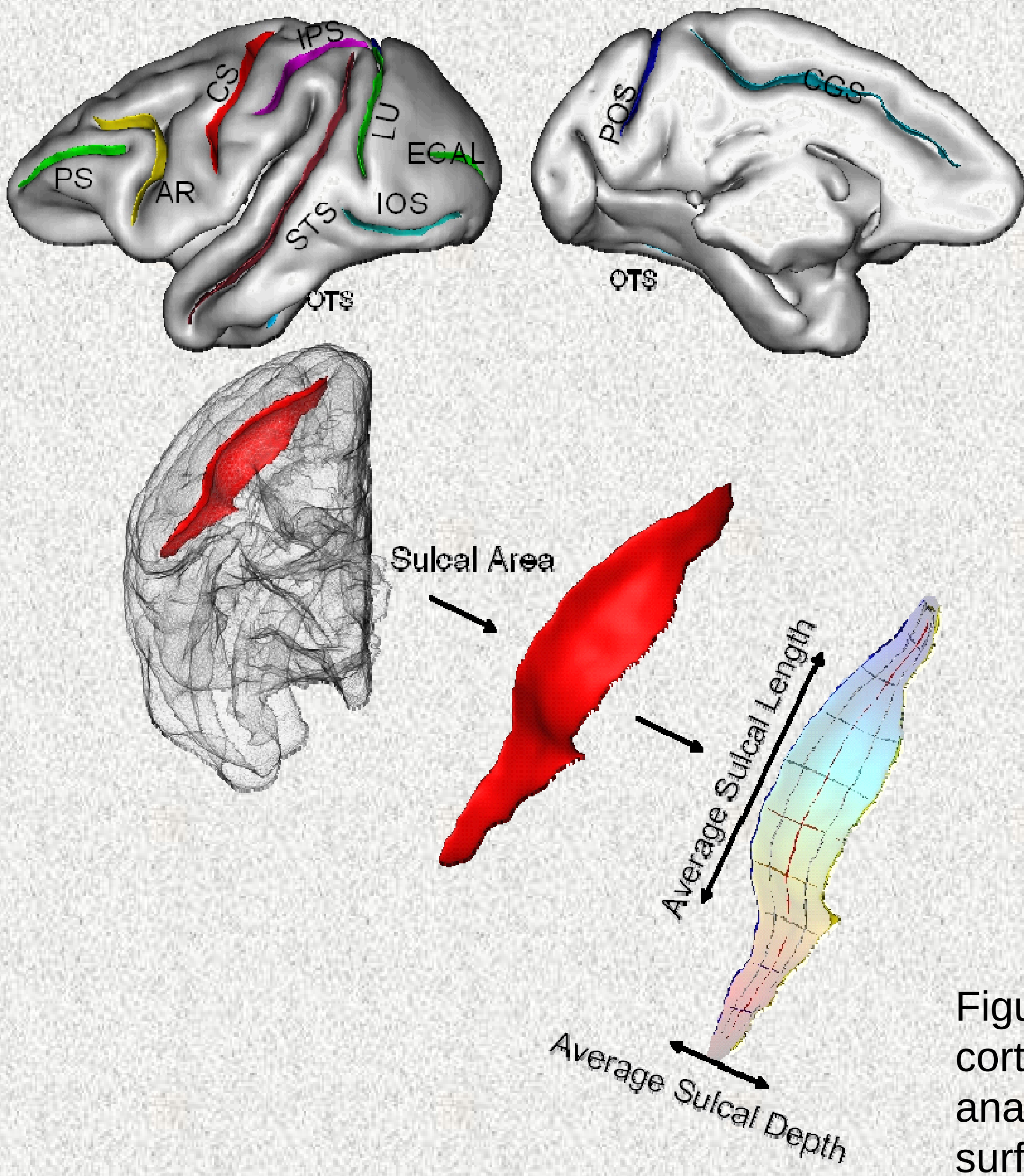
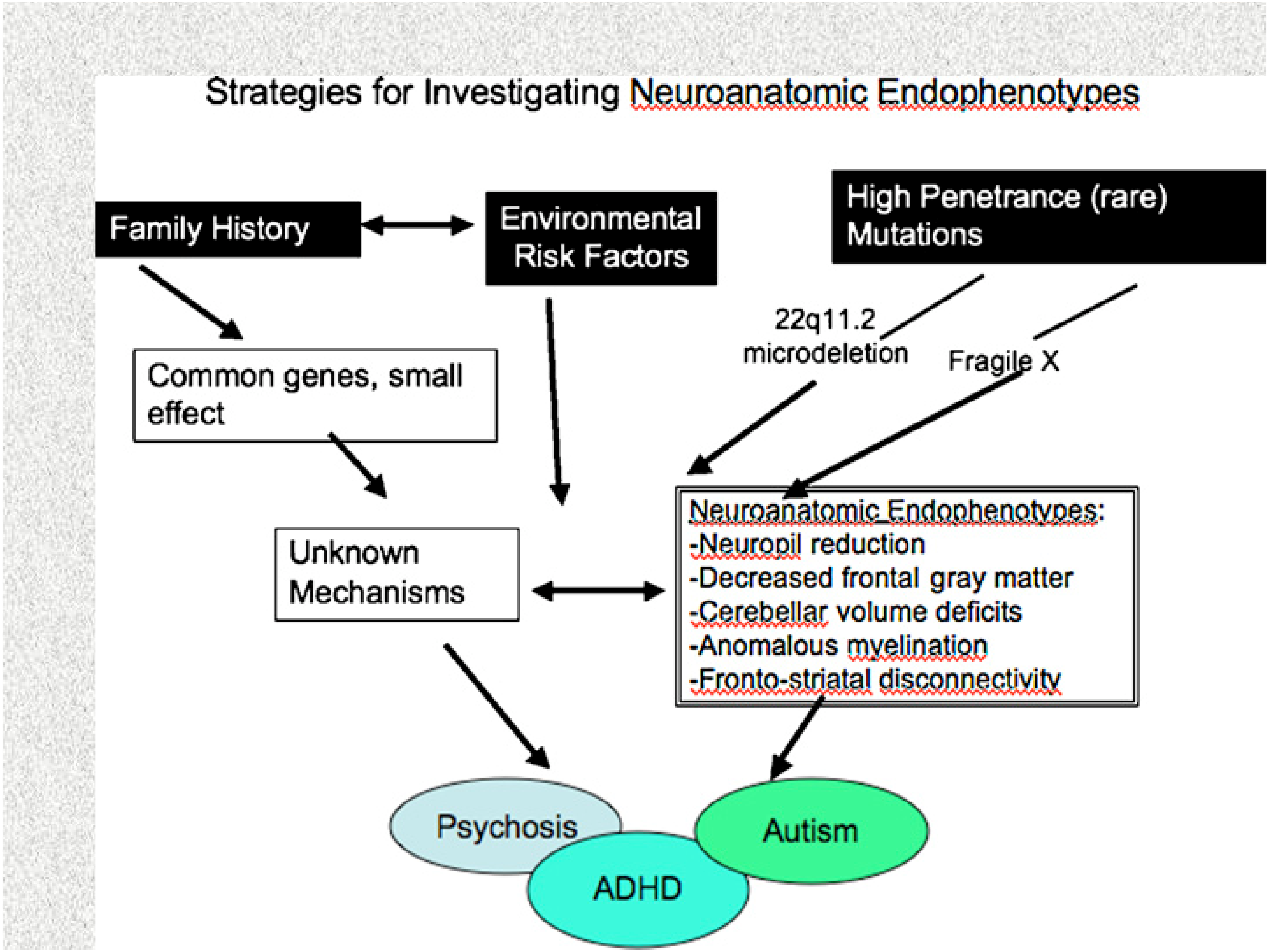
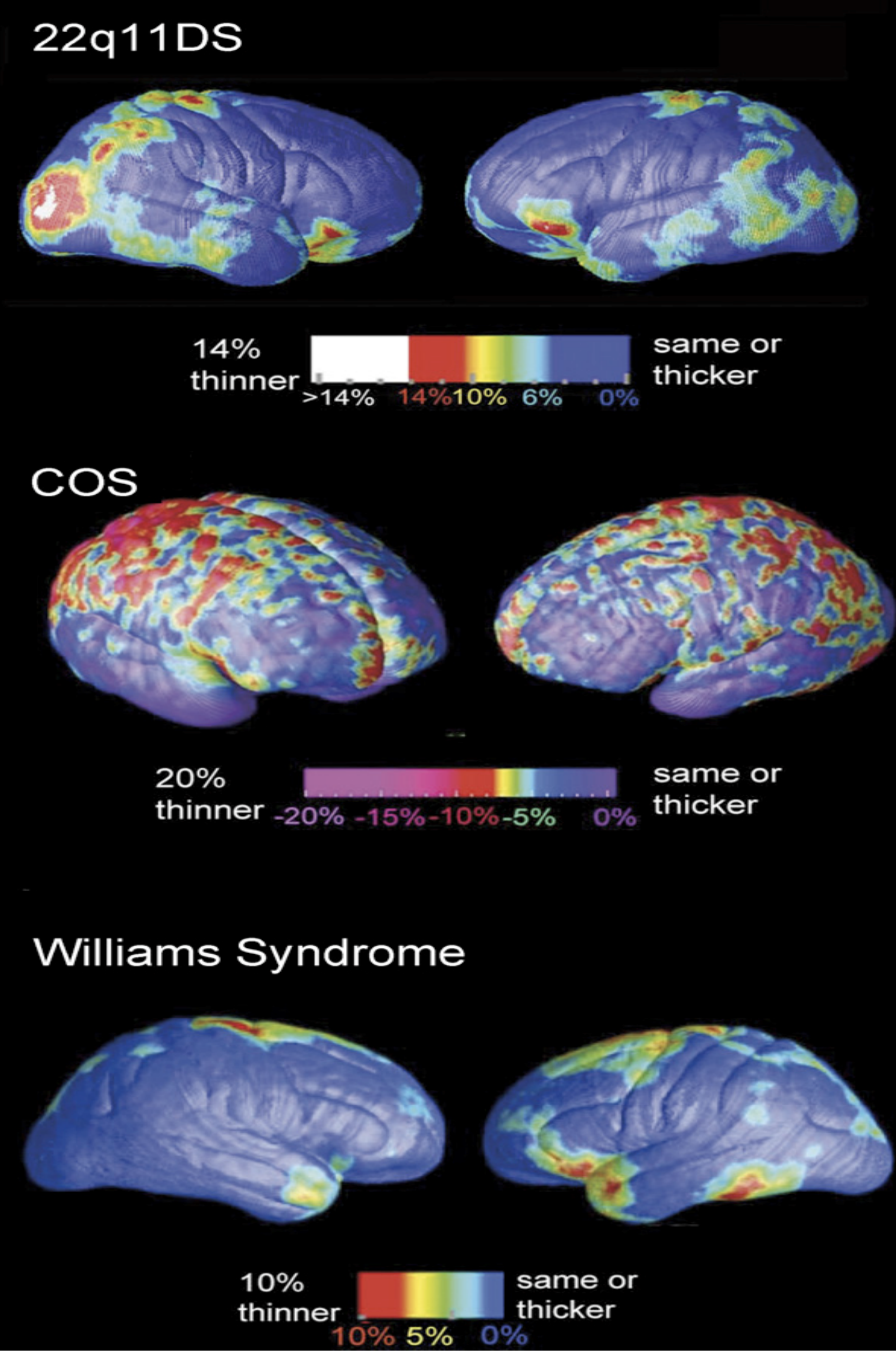


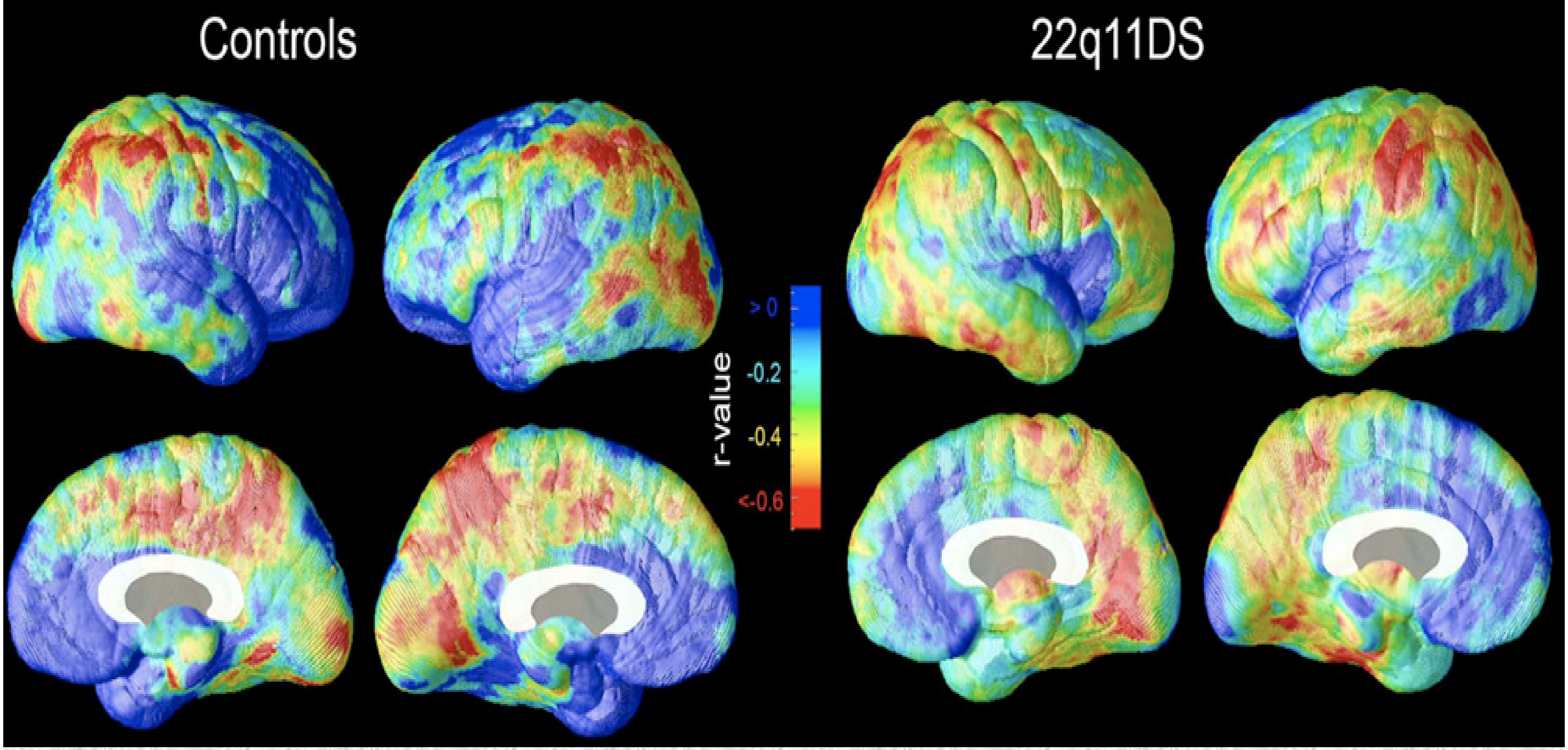
Figure 3. Top part: eleven cortical sulci were used in this analysis. Bottom part: sulcal surface area, depth and length were computer for each structure

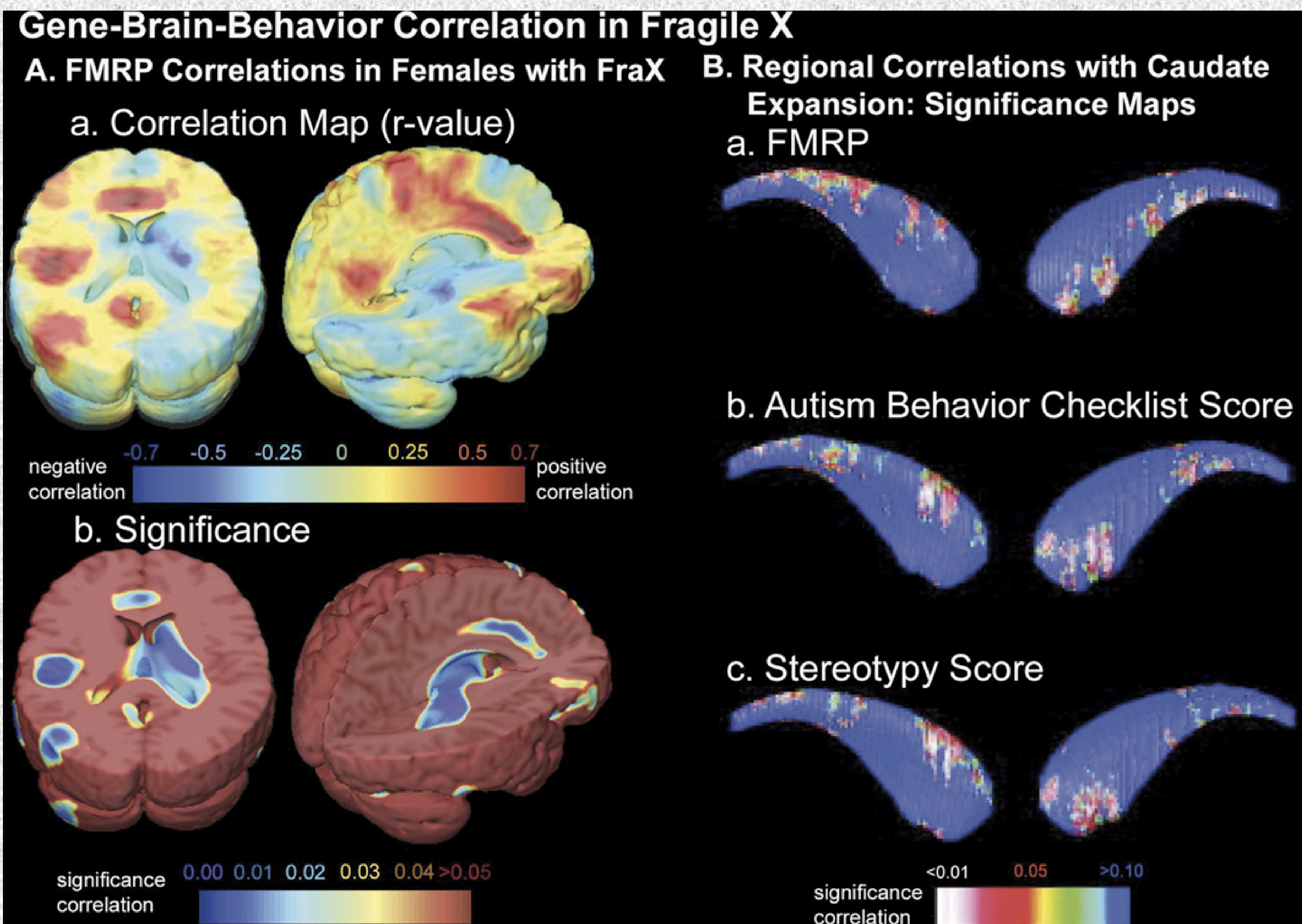

Strategies for Investigating Neuroanatomic Endophenotypes
Family History
Environmental Risk Factors
High Penetrance (rare) Mutations
22q11.2 microdeletion
Fragile X
Common genes, small effect
Unknown Mechanisms
Neuroanatomic Endophenotypes:
-Neuropil reduction
-Decreased frontal gray matter
-Cerebellar volume deficits
-Anomalous myelination
-Fronto-striatal disconnectivity
Psychosis
ADHD
Autism

Cortical Thinning Maps

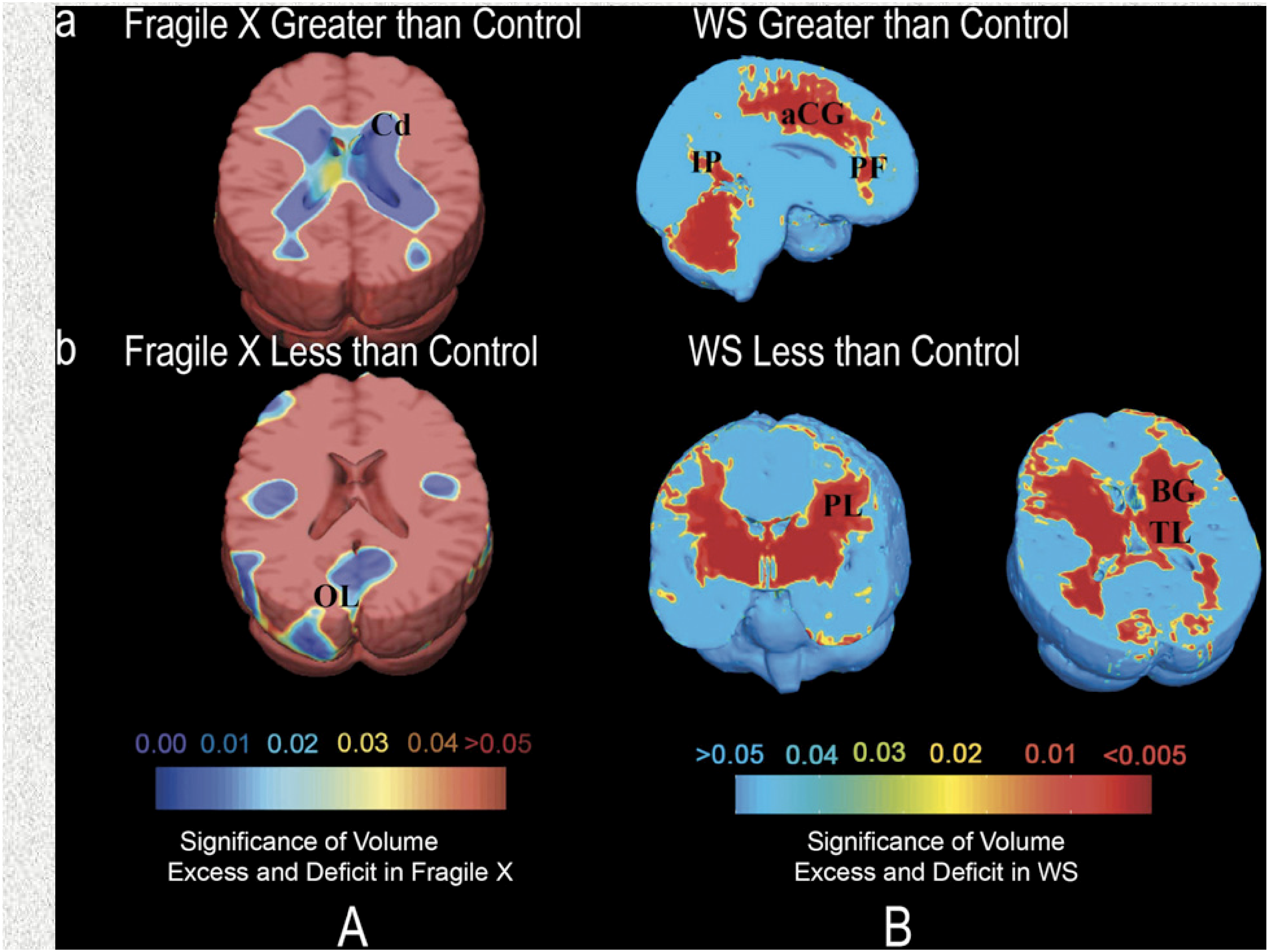


Correlation Maps





Gene-Brain-Behavior Correlation in Fragile X
A. FMRP Correlations in Females with FraX
a. Correlation Map (r-value)
negative correlation
-0.7 -0.5 -0.25 0 0.25 0.5 0.7
positive correlation
b. Significance
significance correlation
0.00 0.01 0.02 0.03 0.04 >0.05
B. Regional Correlations with Caudate Expansion: Significance Maps
a. FMRP
b. Autism Behavior Checklist Score
c. Stereotypy Score
significance correlation
<0.01 0.05 >0.10



a
Fragile X Greater than Control
WS Greater than Control
Cd
aCG
IP
PF
b
Fragile X Less than Control
WS Less than Control
OL
PL
BG
TL
0.00 0.01 0.02 0.03 0.04 >0.05
Significance of Volume Excess and Deficit in Fragile X
>0.05 0.04 0.03 0.02 0.01 <0.005
Significance of Volume Excess and Deficit in WS
A
B

Conclusions

- Using Non-Invasive Imaging has great potential as an endophenotype in speech disorders
- CAS likely has a genetic basis that remains unknown
- Structural Imaging is likely the way to go (e.g. DTI), functional Imaging should be useful in older children and adults with CAS