A volumetric neuroimaging study of multigenerational schizophrenia families

CNST-funded summer research project with the Perelman School of Medicine’s Brain and Behavior Lab/Center for Clinical Neuroimaging in Psychiatry

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Schizophrenia

- Devastating mental illness
  - 1% prevalence worldwide
  - Of U.S. homeless, ~1/3 afflicted
  - ~10% commit suicide
- Highly heritable neurodevelopmental disorder
- Syndrome onset typically in early adulthood, often preceded by prodrome
- Characterized by Positive, Negative, and Cognitive symptoms
The experience of schizophrenia

This experience is much harder, and weirder, to describe than extreme fear or terror. Most people know what it is like to be seriously afraid. If they haven’t felt it themselves, they’ve at least seen a movie or read a book, or talked to a frightened friend—they can at least imagine it. But explaining what I’ve come to call “disorganization” is a different challenge altogether. Consciousness gradually loses its coherence. One’s center gives way. The center cannot hold. The “me” becomes a haze, and the solid center from which one experiences reality breaks up like a bad radio signal. There is no longer a sturdy vantage point from which to look out, take things in, assess what’s happening. No core holds things together, providing the lens through which to see the world, to make judgments and comprehend risk. Random moments of time follow one another. No organizing principle takes successive moments in time and puts them together in a coherent way from which sense can be made. And it’s all taking place in slow motion.
The objective of this multisite collaborative project is to combine 
*genetic* and *neurobiological* paradigms for understanding 
pathogenesis and detecting genes that modulate susceptibility to 
schizophrenia and related phenotypes.

Brain and Behavior Laboratory/Center for Clinical Imaging in Psychiatry
 PI's: Raquel Gur, MD, PhD and Ruben Gur, PhD, *Thanks to David Roalf for this slide!*
MGI protocol/available data

- Clinical assessment & follow-up
- Blood sample for genetic studies
- Neurobehavioral measures (computerized cognitive battery)
- Psychophysiological measures (ERP)
- Neuroanatomic MRI (**T1-weighted structural** and diffusion tensor imaging)
- Functional MRI
- Spectroscopy
Why study family members?

- Difficult to study disease pathophysiology in affected patients (confounders!)
  - Effects of medications
  - Effects of disease onset/acute psychosis?
  - Effects of co-morbid conditions
- Family members may possess similar or “intermediate” neurobehavioral phenotypes without manifesting the clinical disease.

Cannon & Keller, 2006
Volumetric differences in schizophrenia patients and family members

- Patients consistently show smaller total and regional brain volumes compared to normal controls in areas involved in higher cognition and emotional processing (Levitt, et al. 2010).
- Healthy first-degree relatives also frequently show volumetric reductions, most consistently in the hippocampus (Boos, et al. 2007).
Goals of this study

- Use two new, popular, fully automated methods (FreeSurfer and FSL’s FIRST tool) to analyze group differences in regional brain volume between patients, first degree relatives, and normal controls
- Assess validity of FIRST/FreeSurfer in this sample
- Other segmentation methods exist
  - Manual tracing by single expert in neuroanatomy = gold standard
  - Voxel Based Morphometry (VBM)
FSL/FIRST segmentation method

- 336 brains used as training data to create permissible models of 15 subcortical brain structures, each with a deformable mesh/vertex structure
  - Shape analyses are possible
  - Each region may be considered independently
  - Intensity data from input images then used to compute individual’s most likely shape configuration for each structure

Patenaude, et al. 2011
Possible shape configurations for each structure are limited by training data:

Table 1. Groups within the training data and their respective size, age range and resolutions. NC indicates normal controls, SZ indicates schizophrenia, AD indicates Alzheimer’s disease, ADHD indicates attention deficit disorder and PC indicates prenatal cocaine exposure. For the first group we do not have demographics for all the subjects.

<table>
<thead>
<tr>
<th>Group</th>
<th>Size</th>
<th>Age range</th>
<th>Resolution (mm)</th>
<th>Patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>16 to 72</td>
<td>1.0 × 1.5 × 1.0</td>
<td>NC and SZ</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>18 to 87</td>
<td>1.0 × 1.0 × 1.0</td>
<td>NC and AD</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>85 to 83</td>
<td>0.9375 × 1.5 × 0.9375</td>
<td>NC and AD</td>
</tr>
<tr>
<td>4</td>
<td>87</td>
<td>23 to 66</td>
<td>0.9375 × 3.0 × 0.9375</td>
<td>NC and SZ</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>9 to 11</td>
<td>1.0 × 1.0 × 1.0</td>
<td>NC and PC</td>
</tr>
<tr>
<td>6</td>
<td>139</td>
<td>4.2 to 16.9</td>
<td>0.9375 × 1.5 × 0.9375</td>
<td>NC and ADHD and SZ</td>
</tr>
</tbody>
</table>

Patenaude, et al. 2011
**Example segmentation:** 40 yr old male nc

15 labels assigned: L, R Thalamus; L, R Caudate; L, R Putamen; L, R Pallidum; BrStem; L, R Hippocampus; L, R Amygdala; L, R Accumbens
Example hippocampal segmentation:
29 yr old male scz with larger hippocampus
Example hippocampal segmentation:
60 yr old male scz with smaller hippocampus

(115, 112, 55)
Subjects and exclusions for FSL/FIRST analysis

270 total MPRAGE scans

257 diagnostic includes

13 diagnostic excludes

27 schizophrenia patients (sch)

355 normal controls (NC)

18 excluded

3 MNI study excludes

6 bad MPRAGE scans

9 excluded for >25% of segmented regions, 4 or more subjects below mean

21 sch FSL/FIRST segmentation includes

6 excluded

6 MNI study excludes

29 fam1 FSL/FIRST segmentation includes

1 excluded

1 excluded for 7 regions > 2 std dev from mean

44 fam2 FSL/FIRST segmentation includes

1 excluded

1 MNI study exclude
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Number of subjects (males, females)</th>
<th>Average age (range, sd)</th>
<th>Average yrs education (range, sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large sample</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia patients (scz)</td>
<td>21 (13, 8)</td>
<td>48.9 (25-61, 10.8)</td>
<td>12.7 (10-16, 1.9)</td>
</tr>
<tr>
<td>Unaffected 1st degree family members (fam)</td>
<td>29 (12, 17)</td>
<td>52.5 (27-84, 17.7)</td>
<td>14.1 (10-18, 2.4)</td>
</tr>
<tr>
<td>Normal controls (nc)</td>
<td>139 (62, 77)</td>
<td>38.3 (16-85, 16.3)</td>
<td>15.4 (10-20, 2.3)</td>
</tr>
<tr>
<td><strong>Group differences</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ns</td>
<td>nc&lt;scz***</td>
<td></td>
<td>nc&lt;scz***</td>
</tr>
<tr>
<td></td>
<td>nc=fam***</td>
<td></td>
<td>nc=fam***</td>
</tr>
<tr>
<td></td>
<td>scz vs fam, ns</td>
<td></td>
<td>fam=scz*</td>
</tr>
<tr>
<td><strong>Matched sub-sample</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Normal controls (nc)</td>
<td>48 (24, 24)</td>
<td>47.8 (25-80, 14.9)</td>
<td>14.4 (12-18, 1.9)</td>
</tr>
<tr>
<td><strong>Group differences</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ns</td>
<td>/ns</td>
<td></td>
<td>nc&lt;scz**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>fam&gt;scz*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nc vs fam, ns</td>
</tr>
</tbody>
</table>
Total GM Results: **NC>SCZ**

***p<0.001; **p<0.01; *p<0.05; ns p>0.05***
Thalamus, Dorsal and Ventral Striatum:

NC>SCZ, NC>FAM

*** p<0.001; ** p<0.01; * p<0.05; ns p>0.05
**Hippocampus: NC>FAM>SCZ**

***p<0.001; **p<0.01; *p<0.05; ns p>0.05**

- Normalized volume
- SCZ
- Fam
- NC

*Hippocampus*
Pallidum & Amygdala: No differences

*** p<0.001; ** p<0.01; * p<0.05; ns p>0.05
Preliminary conclusions

- FSL’s FIRST tool is capable of obtaining **specific regional volume differences** between controls, patients, and unaffected healthy family members.
- Our results replicate previously reported volume reductions in schizophrenia patients in total gray matter, hippocampus, thalamus, and dorsal and ventral striatum.
- Healthy first degree relatives in this study also show specific volumetric differences.
Future directions

- Account for family relationships
- Explore volumetric relationships with behavioral performance, other neuroimaging measures (fMRI, DTI, spectroscopy), clinical symptoms, and genetic data
- More subjects!
- Vertex analyses: examine anatomical shape differences in specific structures
- FreeSurfer: segmented cortical thickness and volume
Preliminary vertex (shape) analysis:

based on FIRST segmentation

Hippocampal shape analysis: nc vs. scz

Right Posterior Superior
Left Posterior Superior

Right Anterior Superior
Left Anterior Superior

Uncorrected comparison between patients and controls
Data still being processed, almost finished
Cortical parcellation is unique/advantageous because registration to sphere is based on alignment of cortical folding patterns; method is sensitive to individual differences in gyrification
Acknowledgments

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Supplemental Slides
Obtaining scaling factor and brain/gray/white matter volumes

- Brain tissue volume, normalized for subject head size, was estimated using FSL’s SIENAX tool (Smith 2001, Smith 2004).
- This method provides estimations of total brain tissue volume as well as gray matter, white matter, peripheral gray matter and ventricular CSF.
- It also provides a scaling factor that may be used to normalize volumetric data for brain size; all extracted FIRST data presented here has been normalized in this manner.
Laterality effects

• No main effect of hemisphere across all regions
• Each region (left and right) significantly correlated with itself
  – Thalamus: $r=0.92$
  – Caudate: $r=0.90$
  – Putamen: $r=0.84$
  – Pallidum: $r=0.73$
  – Hippocampus: $r=0.63$
  – Amygdala: $r=0.46$
  – Accumbens: $r=0.56$
• Average from both hemispheres used for remaining analyses
Age-related effects

• Found main effect of age across regions on volume and an age x region interaction
• Main effect of age by group, with nc younger than scz and fam
• We therefore excluded nc’s to create a sub-sample matched for age across all three groups (and education for nc and fam)
Data exclusion criteria

- Bad MPRAGE scans (6 nc’s excluded)
- For nc’s, whole subject excluded if >25% of regions \( \pm 2 \text{ sd’s} \) outside of mean (n=7), individual data points excluded if \( \pm 2 \text{ sd’s} \) of mean
- 1 fam excluded for 50% of regions > 2 sd from mean
- Additional exclusions by MGI study criteria and family relationship/diagnosis
## FSL/FIRST Results: matched sub-sample

<table>
<thead>
<tr>
<th>Region</th>
<th>Average volume (ad) in mm$^3$ (# voxels)</th>
<th>Post-hoc t-tests (T, P values)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>scg, fam</td>
<td>ne</td>
</tr>
<tr>
<td>Thalamus</td>
<td>9918 (933)</td>
<td>10676 (813)</td>
</tr>
<tr>
<td>Caudate</td>
<td>4162 (439)</td>
<td>4277 (489)</td>
</tr>
<tr>
<td>Putamen</td>
<td>5935 (584)</td>
<td>5576 (703)</td>
</tr>
<tr>
<td>Pallidum</td>
<td>2397 (407)</td>
<td>2302 (266)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>4316 (543)</td>
<td>4596 (483)</td>
</tr>
<tr>
<td>Amygala</td>
<td>1589 (175)</td>
<td>1577 (253)</td>
</tr>
<tr>
<td>Accumbens</td>
<td>475 (125)</td>
<td>545 (118)</td>
</tr>
<tr>
<td>Total gray</td>
<td>712082 (53452)</td>
<td>746676 (69246)</td>
</tr>
<tr>
<td>Total white</td>
<td>734754 (36312)</td>
<td>731626 (45079)</td>
</tr>
<tr>
<td>Total brain</td>
<td>1447636 (69722)</td>
<td>1478002 (97498)</td>
</tr>
</tbody>
</table>
FSL/FIRST Results: matched sub-sample

Thalamus

Volume

Age

SGZ
fam
nc
FSL/FIRST Results: matched sub-sample

Caudate

Volume

Age
FSL/FIRST Results: matched sub-sample

Putamen

Volume

Age

4000 4500 5000 5500 6000 6500 7000 7500 8000

20 30 40 50 60 70 80 90
FSL/FIRST Results: matched sub-sample

Pallidum

Volume

Age

1500 2000 2500 3000 3500 4000
20 30 40 50 60 70 80 90
FSL/FIRST Results: matched sub-sample

Hippocampus

Volume

Age

3000 3500 4000 4500 5000 5500 6000 6500

20 30 40 50 60 70 80 90
FSL/FIRST Results: matched sub-sample

Amygdala

Volume

Age
FSL/FIRST Results: matched sub-sample

Accumbens

Volume

Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>30</td>
<td>200</td>
</tr>
<tr>
<td>40</td>
<td>300</td>
</tr>
<tr>
<td>50</td>
<td>400</td>
</tr>
<tr>
<td>60</td>
<td>500</td>
</tr>
<tr>
<td>70</td>
<td>600</td>
</tr>
<tr>
<td>80</td>
<td>700</td>
</tr>
<tr>
<td>90</td>
<td>800</td>
</tr>
</tbody>
</table>

- **red**: not
- **blue**: fam
- **green**: inc
Family members look like controls except in response time for emotion recognition.
Future directions: FreeSurfer

- “Surface stream”: constructs surfaces for gray-white matter boundary and pial surface.
  - From this, cortical thickness, volume, curvature, and surface normal may be measured
  - Sensitive to variation in folding patterns (unlike VBM); registration is based on aligning cortical folding patterns to a sphere

- “Volume stream”:
  - Uses different method, and may perform better than FIRST on segmentation (see Morey, et al. 2009)

- Cortical parcellation and subcortical segmentation/labeling
  - Both use probabilistic atlases constructed by training data and subject specific values all mapped onto common space (spherical for surface/cortical and Talairach for volume/subcortical)
Volume and cortical thickness data can be separated into these regions.

-Freesurfer labels-
- Sementation ID's: 3\textsuperscript{rd} ventricle, 4\textsuperscript{th} ventricle, brain-stem, csf, 5\textsuperscript{th} ventricle, wm hypointensities, optic chiasm, CC posterior, CC\_mid\_posterior, CC\_central, CC\_mid\_anterior, CC\_anterior, and Left and Right Lateral-Ventricle, Inf-Lat-Vent, Cerebellum-White-Matter, Cerebellum-Cortex, Thalamus-Proper, Caudate, Putamen, Pallidum, Hippocampus, Amygdala, Accumbens-area, VentralDC, vessel, choroid-plexus
- Parcellation ID's (for left and right hemispheres): caudal anterior cingulate, caudal middle frontal, cuneus, entorhinal, fusiform, inferior parietal, inferior temporal, isthmus cingulate, lateral occipital, lingual, medial orbito frontal, middle temporal, parahippocampal, paracentral, parsopercularis, parsorbitalis, parstriangularis, pericalcarine, postcentral, posterior cingulate, precentral, precuneus, rostral anterior cingulate, rostral middle frontal, superior frontal, superior parietal, superior temporal, supramarginal, frontal pole, temporal pole, transverse temporal, and insula.
Schizophrenia patients perform poorly in most neurocognitive tasks; Neurocognitive measures and neurophysiologic measures show heritability and represent an endophenotype/intermediate phenotype for schizophrenia (rationale behind studying siblings); there have also been efforts to correlate these phenotypes with genetic markers; might the same be true for brain volume?
Early analyses have linked SNPs to neurocognitive phenotypes in this family study.