Early Brain Development in Normal and High Risk Children

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Neurodevelopmental Hypothesis of Schizophrenia

- Neurodevelopmental disorder with prenatal/perinatal origins
  - Pregnancy and birth complications (OR 2.0-4.0)
  - Subtle childhood neurodevelopmental abnormalities
  - Brain abnormalities on MRI are present at first episode
Abnormal Cortical Connectivity

- Postmortem studies
  - reduced neuropil
  - decreased synaptic markers
    - Synaptophysin, decreased spine numbers
  - no overall neuron loss
- Abnormal functional connectivity on fMRI
Reduced Synapses/Spines

Subject with schizophrenia

Matched normal control subject

Glantz and Lewis, 1997

Glantz and Lewis, 2000
Synaptophysin Prefrontal Ctx

Glantz et al., 2007
Schizophrenia as a neurodevelopmental disorder

- Hypothesized that the structural brain abnormalities associated with schizophrenia arise during very early brain development
- No direct evidence to support this hypothesis
- To understand the origins of schizophrenia and other neurodevelopmental disorders, it is critical to develop methodologies to study prenatal and neonatal brain structure
Neonatal MRI: 3T high resolution, high speed scans

T1 3D MPRage
1.0 x 0.9 x 0.9 mm³

FSE T2w
1.25 x 1.25 x 1.95 mm³

FSE PDw
1.25 x 1.25 x 1.95 mm³

3T Siemens Allegra
Scan Time: Structural MRI (T1, SpinEcho): 8min, DTI: 4min -> 12 Min tot
Neonatal MRI

- 3T (Siemens Allegra head-only)
- Unsedated, outpatient setting
- Neonates are fed prior to scanning, swaddled, fitted with ear protection; heads fixed in a vac-fix device
- A pulse oximeter monitored by a physician or research nurse
- Most neonates sleep during the scan
- Motion-free scans in approximately 83%
Safety Issues

• Scanner is FDA approved for use in all ages
• Scanner software and hardware limits specific absorption rates to safe levels based on infant weight
• Phantom study with scan sequences
  - Mean (SD) increase 0.19±0.20 °C
  - Range 0.0-0.5 °C
Early Brain Development Studies

Normal Controls

Twins

Mild Ventriculomegaly (MVM) (Brain)

Babies of Mothers with Schizophrenia

http://www.earlybrainresearch.org
Study Approach

- Prenatal ultrasound, neonatal MRI
- Neurostructural phenotype
  - Enlarged lateral ventricles
    - Gray matter, white matter development
- Two high risk groups
  - Genetic high risk: offspring of mothers with schizophrenia (10% develop schizophrenia)
  - Structural high risk: fetuses with isolated mild ventriculomegaly
Study Design

- Prenatal ultrasound at 22 and 32 weeks
- MRI at 2 weeks after birth
- Developmental assessments at 1 and 2 years of age
  - Mullen Scales of Early Learning
  - Working Memory, Attention
Early Brain Development Studies

- Recruiting to date
  - Mothers with schizophrenia: 47
  - Fetuses with mild ventriculomegaly: 50
  - Controls: 257
  - Twins: 158 pairs
  - Bipolar: 33

- Successful neonatal MRI’s to date
  - Mothers with schizophrenia: 29
  - Fetuses with mild ventriculomegaly: 37
  - Controls: 195
  - Twins: 110 pairs
  - Bipolar: 11
Challenges of Tissue Segmentation

• Small head size
• Low contrast
• Bias field / intensity inhomogeneity
• Motion artifacts
• Ambiguous classification of white matter into myelinated and non-myelinated white matter
Automated Tissue Segmentation

T1  T2
Prastawa M, Gilmore JH, Lin W, Gerig G
Med Image Anal 2005; 9: 457-466

Early Myelination
Parcellation
Myelinated White Matter
White Matter
Gray Matter
CSF

Overall homogeneity of slopes: $p < 0.001$
Gray Matter vs. White Matter: $p < 0.001$
Gray Matter vs. CSF: $p < 0.001$
Gray Matter vs. Umyelinated WM: $p < 0.001$
Regional Gray Matter

Overall homogeneity of slopes: $p < 0.001$
Occipital vs. Prefrontal: $p < 0.001$
Parietal vs. Prefrontal: $p < 0.001$
Regional White Matter

Overall homogeneity of slopes: \( p = 0.12 \)
Regional differences in synapse development

P.R. HUTTENLOCHER AND A.S. DABHOLKAR

Fig. 2. Mean synaptic density in synapses/100 μm² in auditory, calcarine, and prefrontal cortex at various ages. Open circles, visual cortex (area 17); filled circles, auditory cortex; x, prefrontal cortex (middle frontal gyrus).
Conclusions

- Early neonatal brain development is characterized by rapid increases in gray matter compared to white matter.
- Regional specificity of gray matter development: posterior faster than anterior.
- Gender differences in ICV, gray matter volumes present at birth; arise during prenatal brain development.
- Asymmetries present at birth, L>R; adult pattern develop after birth.
Isolated Mild Ventriculomegaly

- Atrial width $\geq 10$mm
- No associated CNS abnormalities
- Up to 0.7% of pregnancies
- Associated with older maternal age, lower gestational age at birth, and maternal infection
  - Gilmore et al., 1998; Dommergues et al., 1996
- Outcome
  - 33% have developmental delays (Bloom et al., 1997)
  - Autism, ADHD, learning disorders (Gilmore et al., 2001)
MVM study

- 34 children with isolated MVM
- 34 age and gender matched controls
- Children in the MVM group had significantly larger prenatal maximum lateral ventricle width
  - $1.15 \pm 0.03$ vs. $0.59 \pm 0.03$; $p < 0.0001$
Mild Ventriculomegaly
<table>
<thead>
<tr>
<th></th>
<th><strong>Control</strong> LS mean (SE)</th>
<th><strong>MVM</strong> LS mean (SE)</th>
<th><strong>% difference</strong></th>
<th><strong>F-value (DF)</strong></th>
<th><strong>P value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial Volume (mm³)</td>
<td>475,757 (8,207)</td>
<td>509,615 (8,207)</td>
<td>7.1%</td>
<td>8.51 (1,33)</td>
<td>0.0063</td>
</tr>
<tr>
<td>Lateral Ventricle (mm³)</td>
<td>1,701 (585)</td>
<td>6,572 (585)</td>
<td>286.4%</td>
<td>34.64 (1,33)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Cortical Gray Matter (mm³)</td>
<td>197,625 (3,839)</td>
<td>219156 (3,839)</td>
<td>10.9%</td>
<td>15.72 (1,33)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Cortical White Matter (mm³)</td>
<td>152,426 (2,962)</td>
<td>158,680 (2,962)</td>
<td>4.1%</td>
<td>2.23 (1,33)</td>
<td>0.1449</td>
</tr>
<tr>
<td>Cerebellum (mm³)</td>
<td>27361 (547)</td>
<td>27181 (547)</td>
<td>-0.06%</td>
<td>0.05 (1,33)</td>
<td>0.8184</td>
</tr>
</tbody>
</table>
A. Maximum lateral ventricle width in controls and MVM cases (n= 34/ group; p < 0.0001)

B. Neonates with prenatal MVM have significantly larger lateral ventricle volumes than matched controls (n= 34/ group; p < 0.0001).
There was a significant correlation between the prenatal maximum lateral ventricle width on ultrasound and neonatal lateral ventricle volume on MRI for both the normal control (Pearson r = 0.3563; p = 0.0386) and the MVM groups (Pearson r = 0.7482, p < 0.0001)
There is a significant difference in the relationship between ICV and cortical gray matter volume in MVM cases compared to controls (homogeneity of slope $F=13.15$ $(1,31); p=0.0010$)

There is a significant difference in the relationship between ICV and cortical white matter volume in MVM cases compared to controls (homogeneity of slope $F= 7.04$ $(1,31); p=0.0125$)
DTI Tractography
General Principles

- Mean Diffusivity decreases with age
- Fractional Anisotropy increases with age
- Mean Diffusivity a more sensitive marker of myelination in neonates
<table>
<thead>
<tr>
<th>Location/ track</th>
<th>LSMean (SE) Normal Control</th>
<th>MVM</th>
<th>F-Test for difference: Normal Control vs MVM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genu (-21)</td>
<td>14.58 (0.16)</td>
<td>15.63 (0.17)</td>
<td>20.46 (1,24)</td>
</tr>
<tr>
<td>Genu (0)</td>
<td>13.71 (0.28)</td>
<td>14.28 (0.30)</td>
<td>1.92 (1,24)</td>
</tr>
<tr>
<td>Genu (21)</td>
<td>13.61 (0.44)</td>
<td>15.31 (0.48)</td>
<td>6.79 (1,24)</td>
</tr>
<tr>
<td>Splenium (-24)</td>
<td>15.01 (0.33)</td>
<td>16.70 (0.35)</td>
<td>12.12 (1,24)</td>
</tr>
<tr>
<td>Splenium (0)</td>
<td>14.23 (0.21)</td>
<td>14.91 (0.22)</td>
<td>4.88 (1,24)</td>
</tr>
<tr>
<td>Splenium (24)</td>
<td>14.59 (0.24)</td>
<td>16.26 (0.26)</td>
<td>22.47 (1,24)</td>
</tr>
<tr>
<td>Left Cortico-spinal (-12)</td>
<td>10.08 (0.08)</td>
<td>10.41 (0.08)</td>
<td>8.55 (1,23)</td>
</tr>
<tr>
<td>Left Cortico-spinal (9)</td>
<td>12.43 (0.18)</td>
<td>13.22 (0.20)</td>
<td>8.92 (1,23)</td>
</tr>
<tr>
<td>Right Cortico-spinal (-12)</td>
<td>10.06 (0.07)</td>
<td>10.54 (0.08)</td>
<td>20.37 (1,23)</td>
</tr>
<tr>
<td>Right Cortico-spinal (9)</td>
<td>12.45 (0.21)</td>
<td>13.10 (0.23)</td>
<td>4.42 (1,23)</td>
</tr>
<tr>
<td>Fractional Anisotropy</td>
<td>Location/ track</td>
<td>LSMean (SE) Normal Control</td>
<td>LSMean (SE) MVM</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F-value (DF)</td>
<td>P-Value</td>
</tr>
<tr>
<td>Genu (-21)</td>
<td>0.23 (0.01)</td>
<td>0.21 (0.01)</td>
<td>3.08 (1,24)</td>
</tr>
<tr>
<td>Genu (0)</td>
<td>0.50 (0.01)</td>
<td>0.47 (0.01)</td>
<td>2.22 (1,24)</td>
</tr>
<tr>
<td>Genu (21)</td>
<td>0.23 (0.01)</td>
<td>0.22 (0.01)</td>
<td>0.74 (1,24)</td>
</tr>
<tr>
<td>Splenium (-24)</td>
<td>0.29 (0.01)</td>
<td>0.29 (0.01)</td>
<td>0.04 (1,24)</td>
</tr>
<tr>
<td>Splenium (0)</td>
<td>0.56 (0.01)</td>
<td>0.49 (0.02)</td>
<td>10.59 (1,24)</td>
</tr>
<tr>
<td>Splenium (24)</td>
<td>0.28 (0.01)</td>
<td>0.25 (0.01)</td>
<td>4.27 (1,24)</td>
</tr>
<tr>
<td>Left Cortico-spinal (-12)</td>
<td>0.51 (0.01)</td>
<td>0.50 (0.01)</td>
<td>1.24 (1,23)</td>
</tr>
<tr>
<td>Left Cortico-spinal (9)</td>
<td>0.31 (0.01)</td>
<td>0.28 (0.01)</td>
<td>4.29 (1,23)</td>
</tr>
<tr>
<td>Right Cortico-spinal (-12)</td>
<td>0.54 (0.01)</td>
<td>0.50 (0.01)</td>
<td>5.20 (1,23)</td>
</tr>
<tr>
<td>Right Cortico-spinal (9)</td>
<td>0.28 (0.01)</td>
<td>0.28 (0.01)</td>
<td>0.03 (1,23)</td>
</tr>
</tbody>
</table>
MVM Conclusions

- Prenatal enlargement of the lateral ventricle detected by ultrasound is associated with significant enlargement of the lateral ventricles after birth.
- Increased gray matter volumes.
- Reduced white matter volumes, and delayed or abnormal maturation of DTI properties in the splenium of the corpus callosum.
- It is suggested that prenatal ventricle volume may be an early structural marker of subsequent dysmaturation of the cerebral cortex after birth.
Offspring of Mothers with Schizophrenia

- Neonatal MRIs on 19 high risk children and 19 matched controls
- Mothers with schizophrenia, schizoaffective DO
- Controls without psychiatric illness
- Matched on gender, maternal age, gestational age at birth, ethnicity
- 9 males and 10 females
- mean gestational age at MRI 42.7 ± 3.0 weeks
Neonatal brain structure in high risk children

- High risk children had approximately 2.6% less total gray matter ($p = 0.077$)

\[ \text{Occipital Gray Matter} \]

\[ \begin{align*}
\text{Schiz-Off} & \quad \text{Control} \\
0 & \quad 0 \\
10,000 & \quad 10,000 \\
20,000 & \quad 20,000 \\
30,000 & \quad 30,000 \\
40,000 & \quad 40,000 \\
50,000 & \quad 50,000 \\
60,000 & \quad 60,000 \\
70,000 & \quad 70,000 \\
80,000 & \quad 80,000 \\
\end{align*} \]

\[ \text{Myelinated White Matter} \]

\[ \begin{align*}
\text{Schiz-Off} & \quad \text{Control} \\
0 & \quad 0 \\
2,500 & \quad 2,500 \\
5,000 & \quad 5,000 \\
7,500 & \quad 7,500 \\
10,000 & \quad 10,000 \\
12,500 & \quad 12,500 \\
15,000 & \quad 15,000 \\
\end{align*} \]

\[ \text{p} = 0.0325 \quad \text{p} = 0.083 \]
Lateral Ventricle Size

Fetal Lateral Ventricle

Neonatal Lateral Ventricle

Width (mm)

Volume (mm³)
Conclusions

- Early results indicates that the offspring of mothers with schizophrenia have reduced cortical gray matter volumes in the rapidly developing occipital region
- May reflect genetically mediated impairment of cortical synapse development that would be most apparent in the rapidly growing cortical region
- There is a suggestion of altered white matter development
- No difference in lateral ventricle volumes
  - Lateral ventricle volumes increase rapidly in the first year of life – the enlargement may arise after birth
- These results focus the time-frame of candidate neurodevelopmental processes that contribute to risk for schizophrenia
- Limitations
  - Medications during pregnancy
  - Mothers with schizophrenia have high rates of prenatal/perinatal complications
Early Brain Development in 1 and 2 year Olds

- **Singleton Controls**
  - 59 one year olds (68% success rate)
  - 44 two year olds (60% success rate)

- **Twins**
  - 51 pairs at age 1 (90% success rate)
  - 37 pairs at age 2 (76% success rate)
Subject with follow-up scans

T1w

2 weeks

1 year

2 years

T2w
TBV grows 101% in first year, 15% in second year
2-4 weeks: 36% of adult volume; 72% at 1 year and 83% at 2 years
Brain development birth to age 2

Cortical Gray and White Matter

Cortical GM:  149% in the first year; 14% in the second year
Cortical WM:
Brain development birth to age 2

Lateral Ventricles

Volume (mm$^3$)

<table>
<thead>
<tr>
<th>Age</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>2500</td>
</tr>
<tr>
<td>1 year</td>
<td>7500</td>
</tr>
<tr>
<td>2 years</td>
<td>7500</td>
</tr>
</tbody>
</table>
Future Directions

- Collecting DNA to study gene-brain structure relationships in early childhood
- Developmental assessments at age one and two years to study structure-function relationships
- Develop age specific head coils to improve resolution and contrast (W. Lin)
- Resting State Networks (W. Lin)
- Apply to other high risk groups
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  - Weili Lin PhD, Keith Smith MD, Kathy Wilber

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  - Dianne Evans MA