UNC Schizophrenia Research Center

an NIMH Silvio O. Conte Center for the Neuroscience of Mental Disorders

Early Brain Development in Normal and High Risk Children

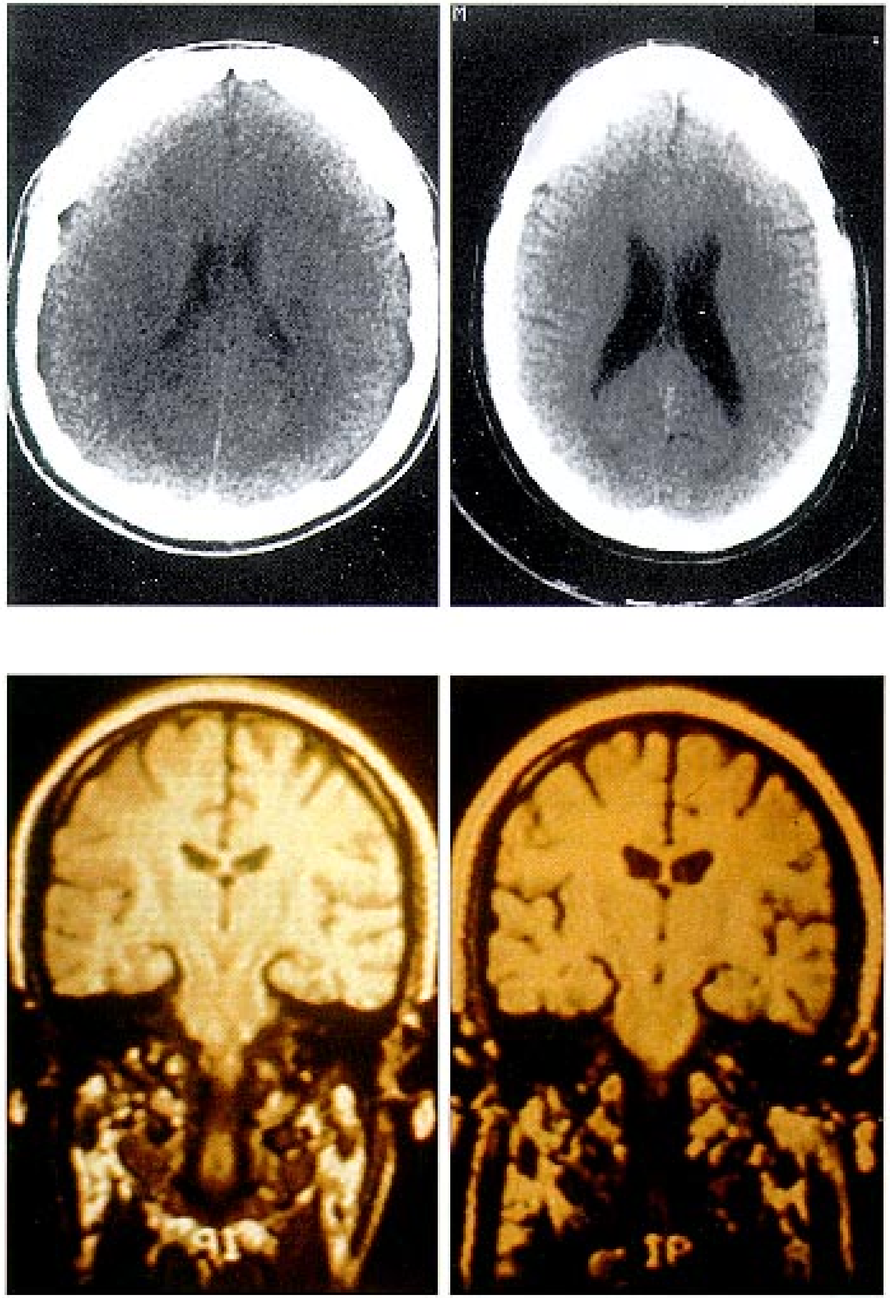
John H. Gilmore, MD

Department of Psychiatry

The University of North Carolina

Neurodevelopmental Hypothesis of Schizophrenia

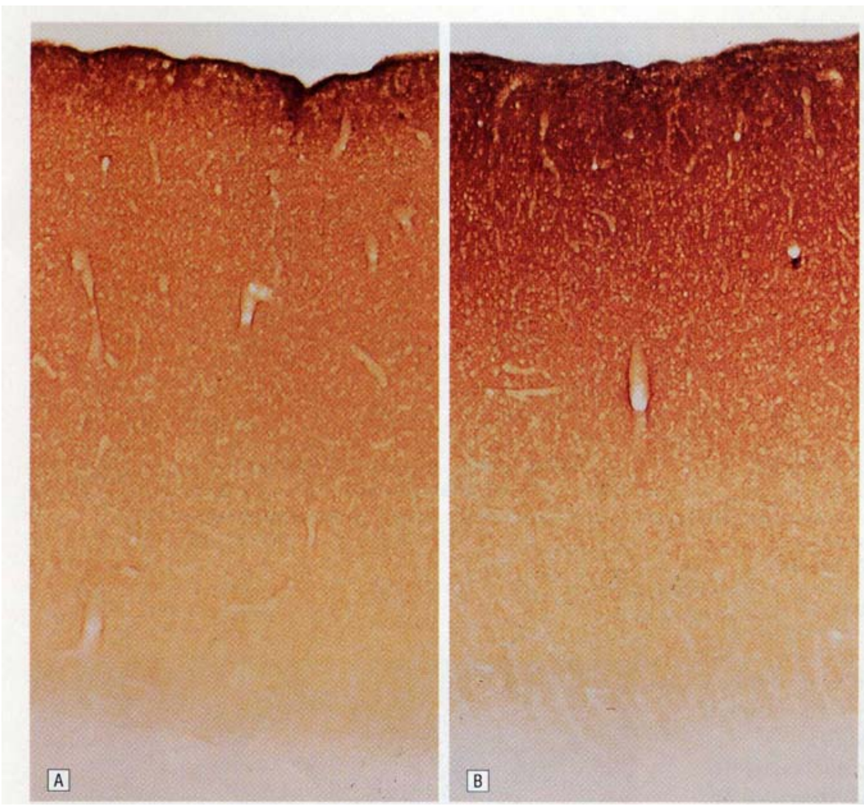
- Neurodevelopmental disorder with prenatal/perinatal origins
  - Pregnancy and birth complications (OR 2.0-4.0)
  - Subtle childhood neurodevelopmental abnormalities
  - Brain abnormalities on MRI are present at first episode



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

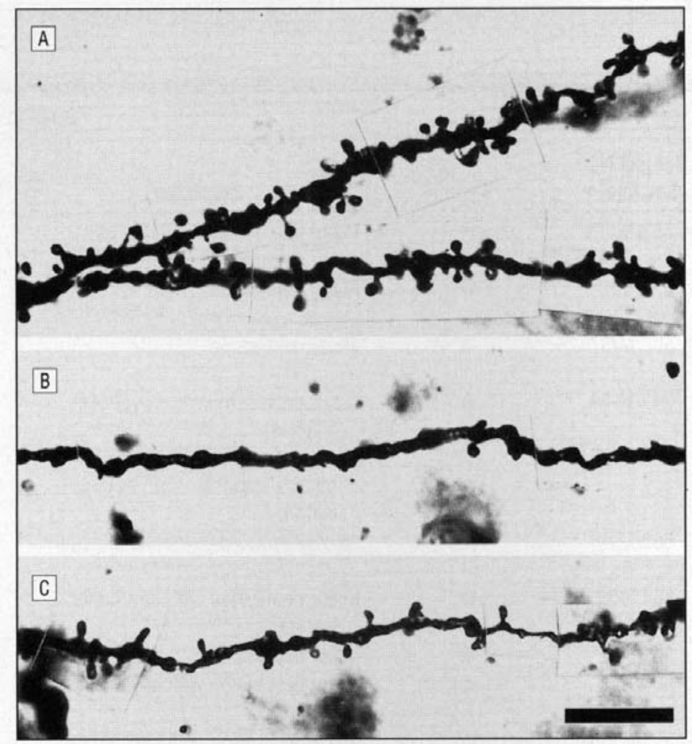
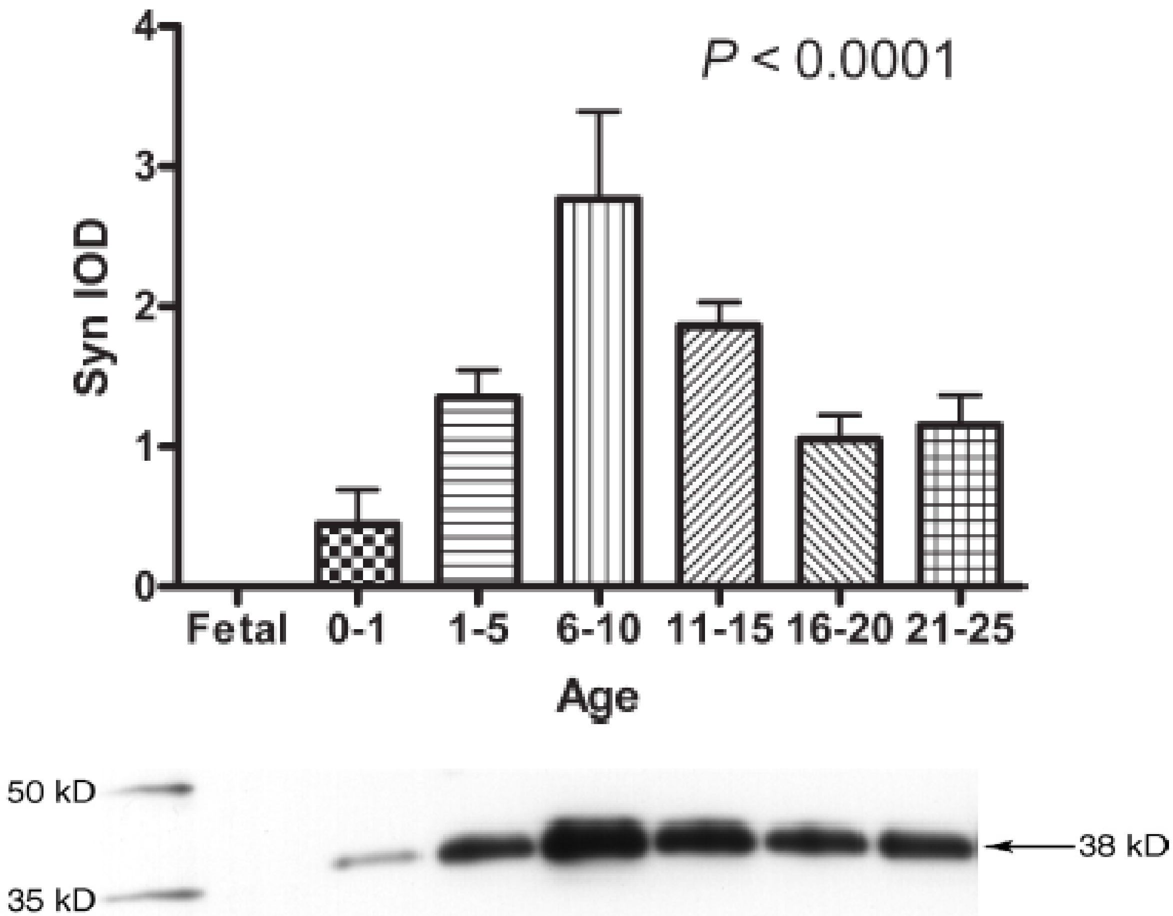


Figure 2. *Brightfield photomicrographs illustrating Golgi-impregnated basilar dendrites and spines on dorsolateral prefrontal cortex layer 3 pyramidal neurons from normal control subject 390 (A) and 2 subjects with schizophrenia (subjects 410 [B] and 466 [C]). The calibration bar equals 10 μm.*

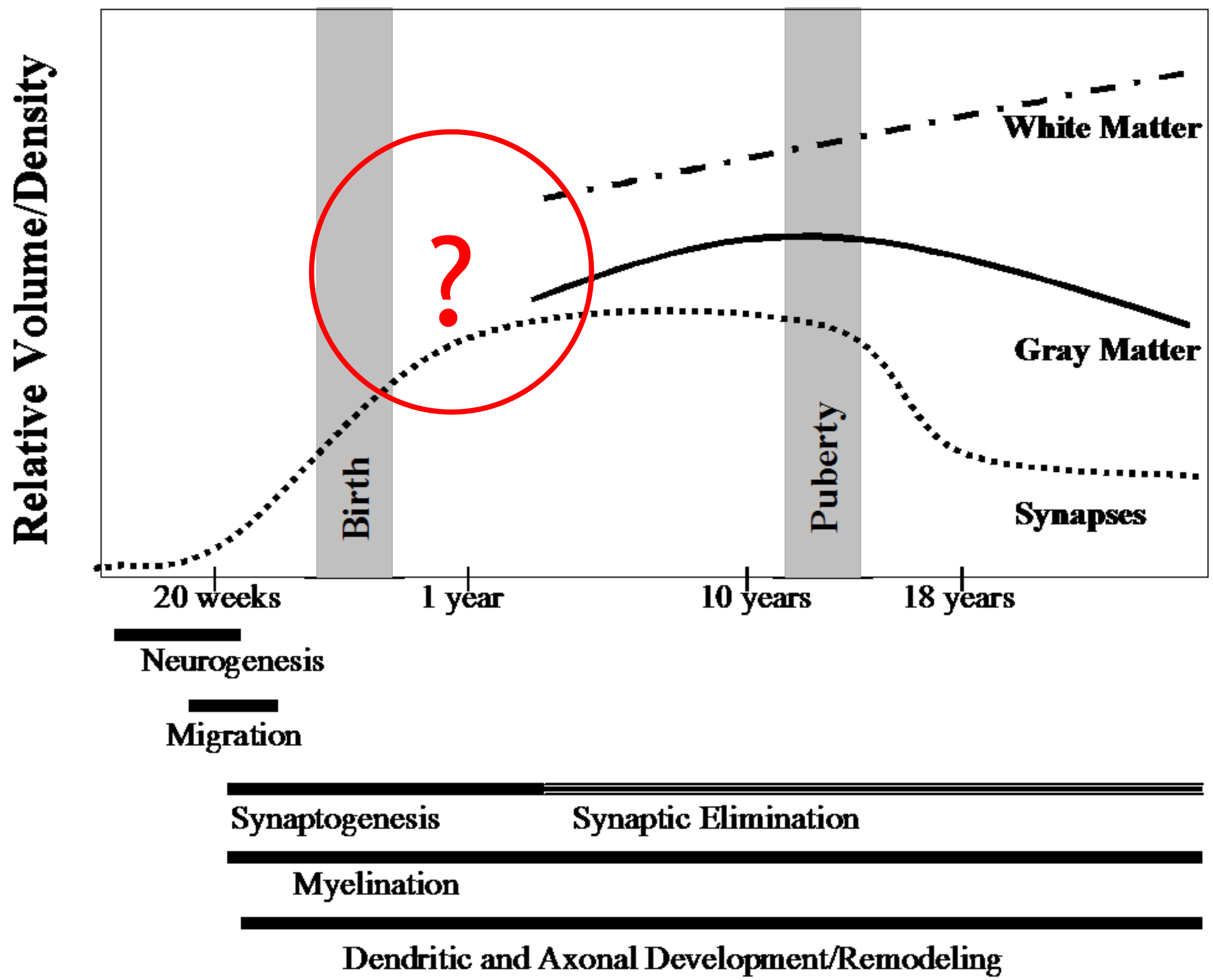
Glantz and Lewis, 2000

Synaptophysin Prefrontal Ctx

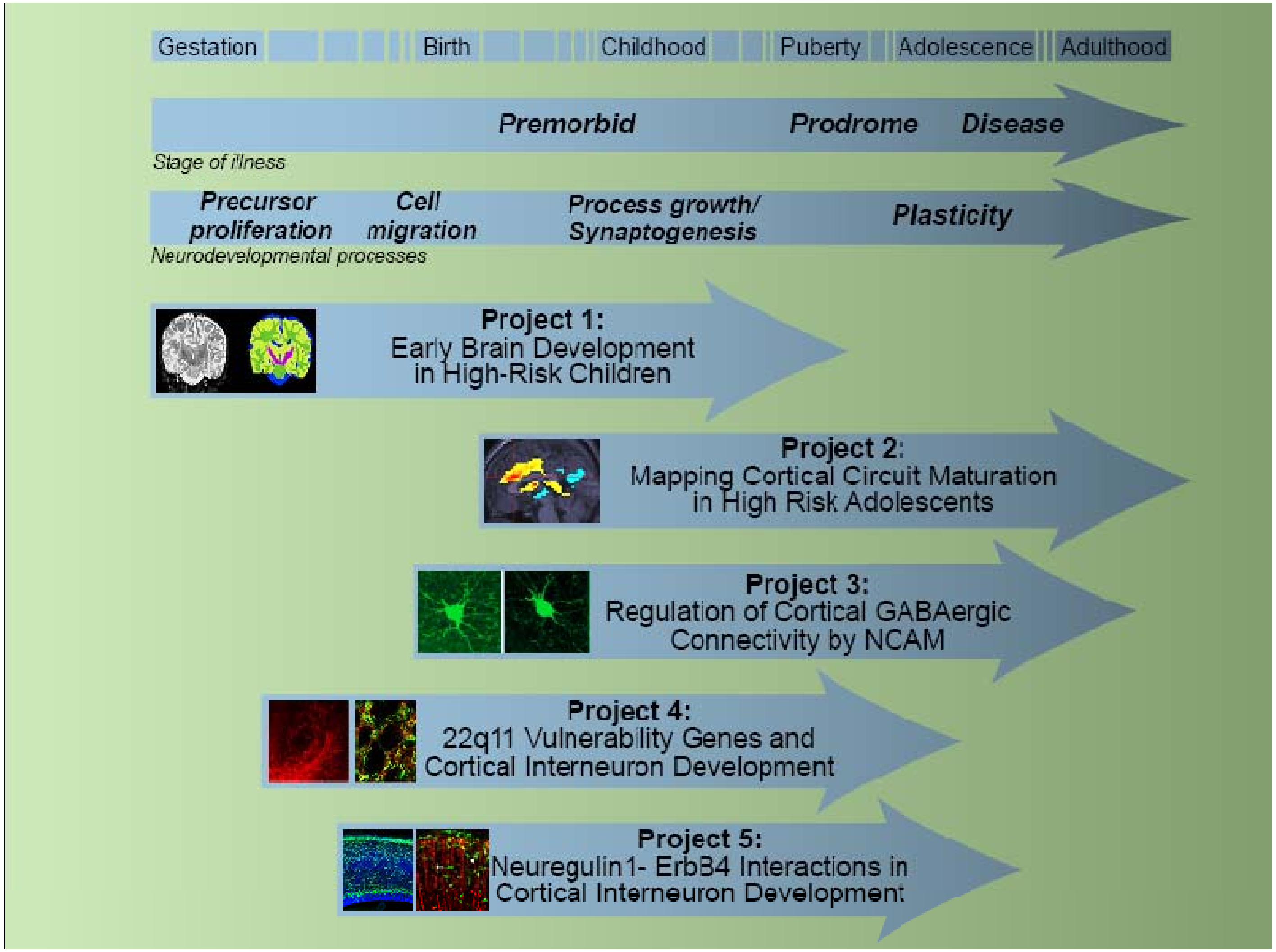


Glantz et al., 2007

Cortex Development



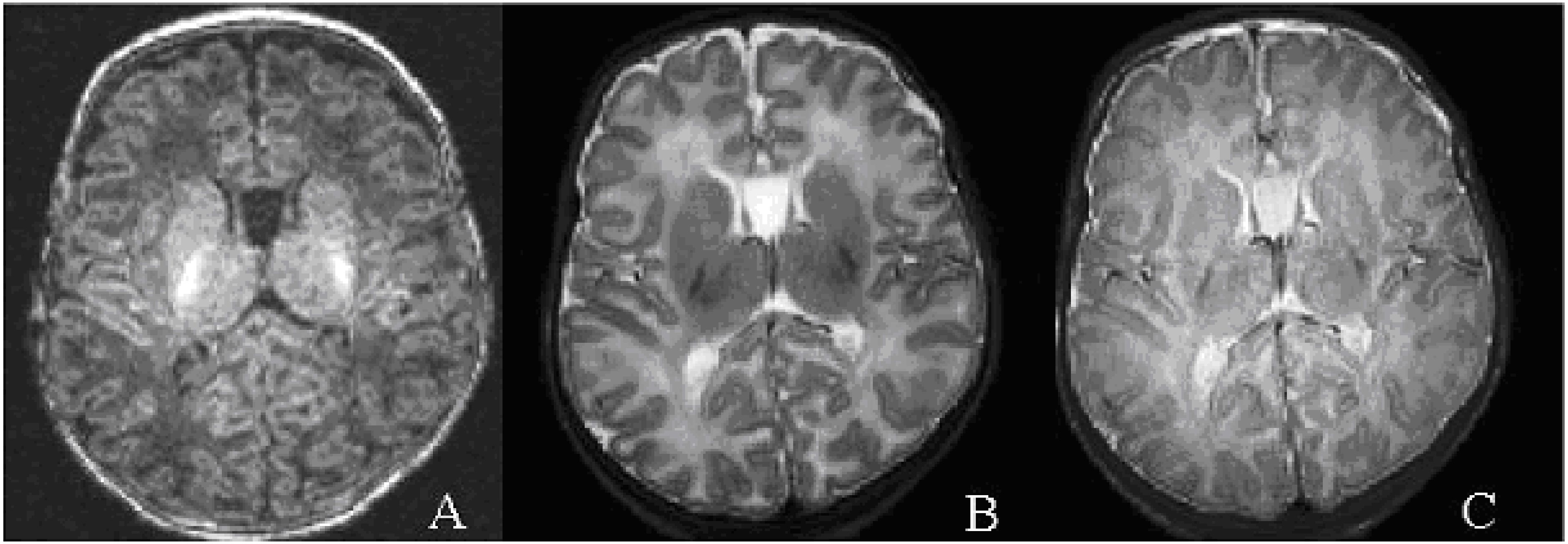
UNC Conte Center



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
$1.0 \times 0.9 \times 0.9\ mm^3$

FSE T2w
$1.25 \times 1.25 \times 1.95\ mm^3$

FSE PDw
$1.25 \times 1.25 \times 1.95\ mm^3$

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 ºC
  - Range 0.0-0.5 ºC
    - (Gilmore et al., Psych Res: Neuroimaging, 132, 2004)

Early Brain Development Studies

- John Gilmore, M.D.
  Principal Investigator
- Studies
- Investigators
- Image Analysis
- Progress/Publications
- Training Opportunities
- Links
- Contact Us

EDBS HOME

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

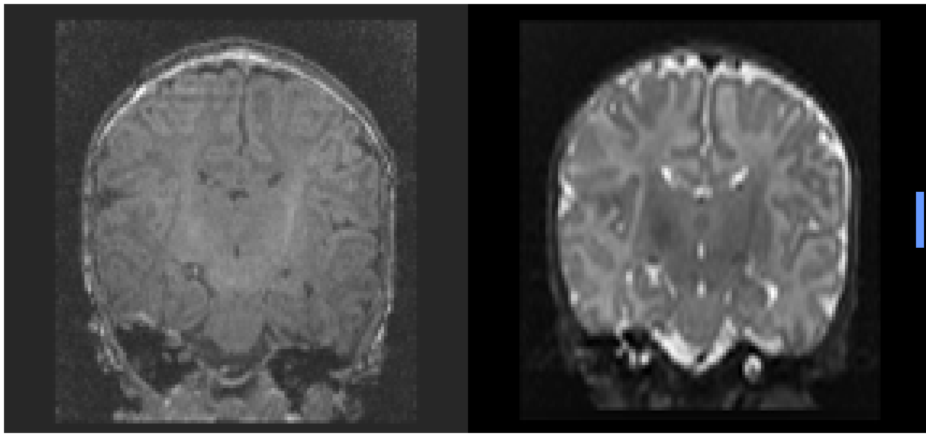
- Successful neonatal MRI’s to date

– Mothers with schizophrenia	29
– Fetuses with mild ventriculomegaly	37
– Controls	195
– Twins	110 pairs
– Bipolar	11

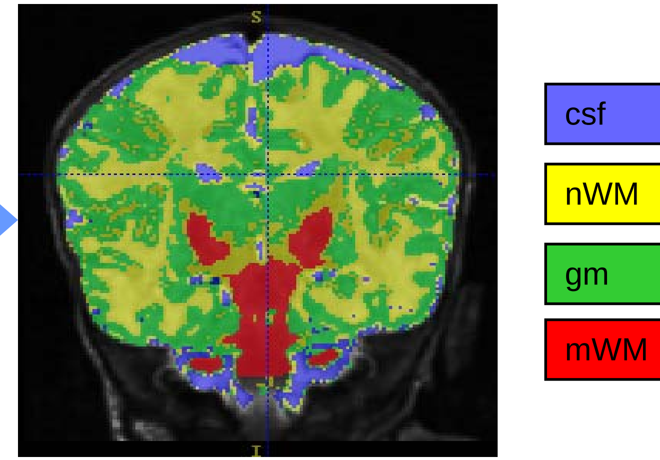
Challenges of Tissue Segmentation

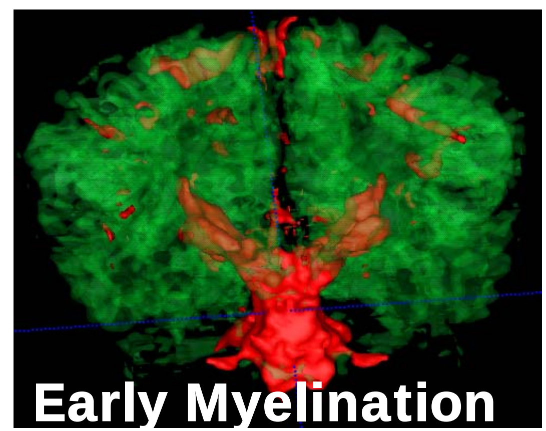
- Small head size
- Low contrast
- Bias field / intensity inhomogeneity
- Motion artifacts
- Ambiguous classification of white matter into myelinated and non-myelinated white matter

Automated Tissue Segmentation



T1 T2

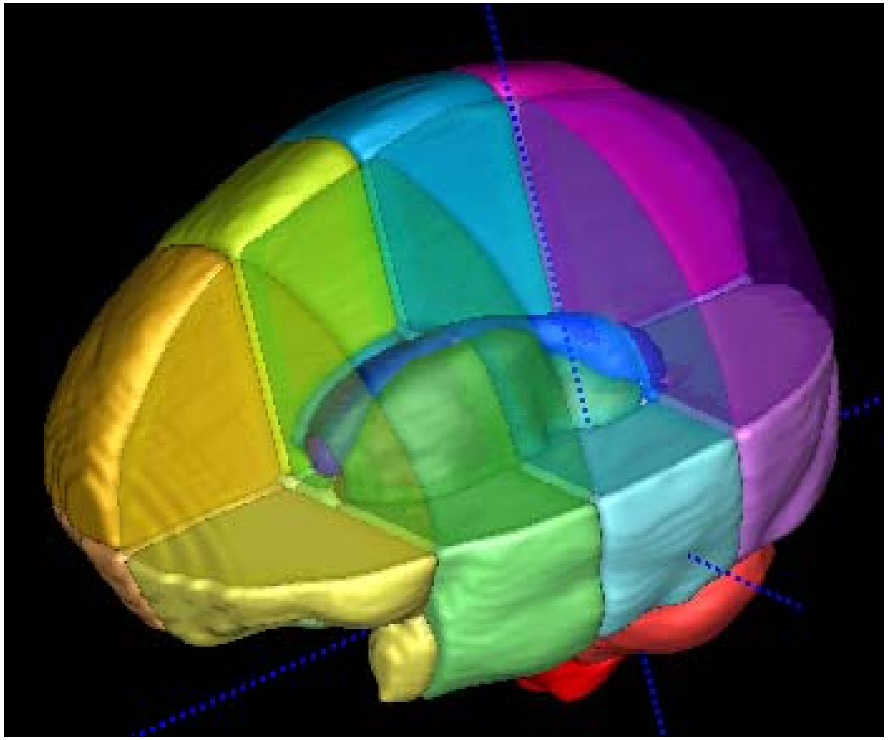




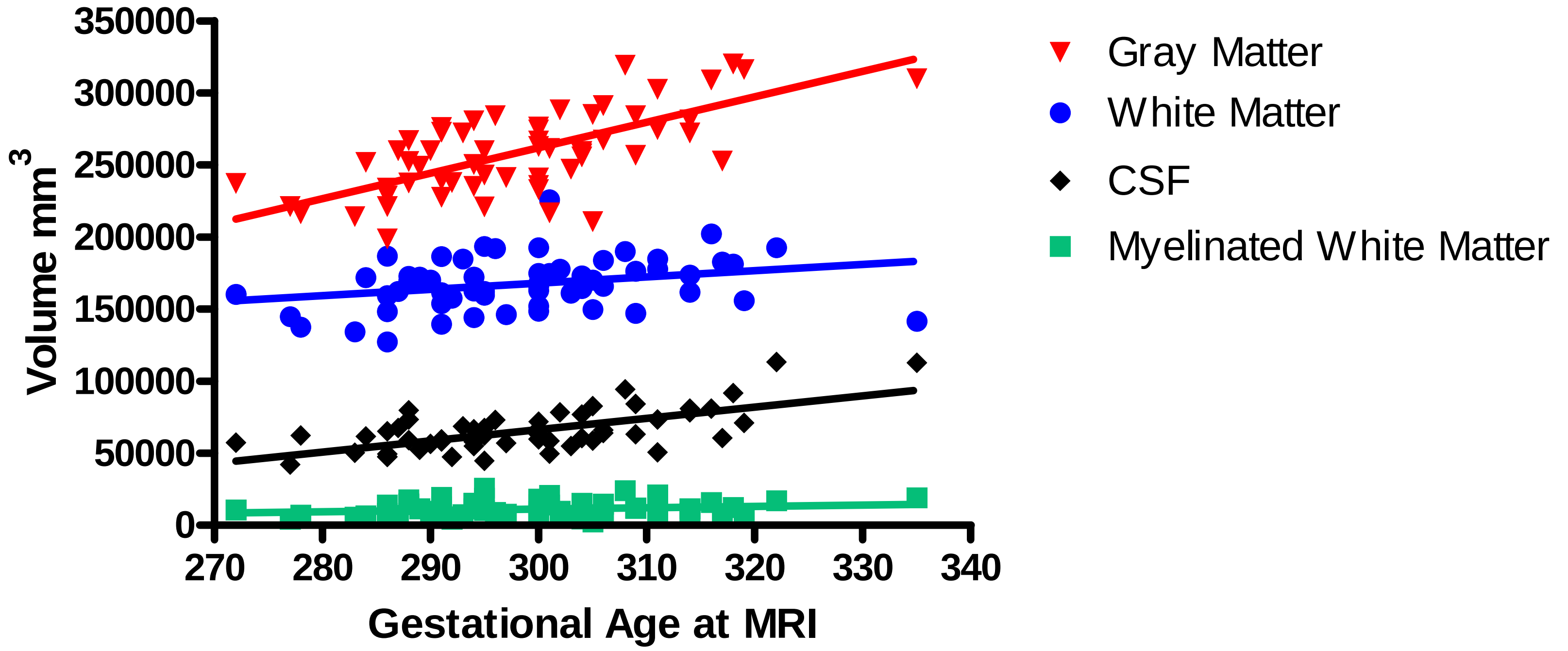
Prastawa M, Gilmore JH, Lin W, Gerig G

Med Image Anal 2005; 9: 457-466

Parcellation



Neonatal Brain Development



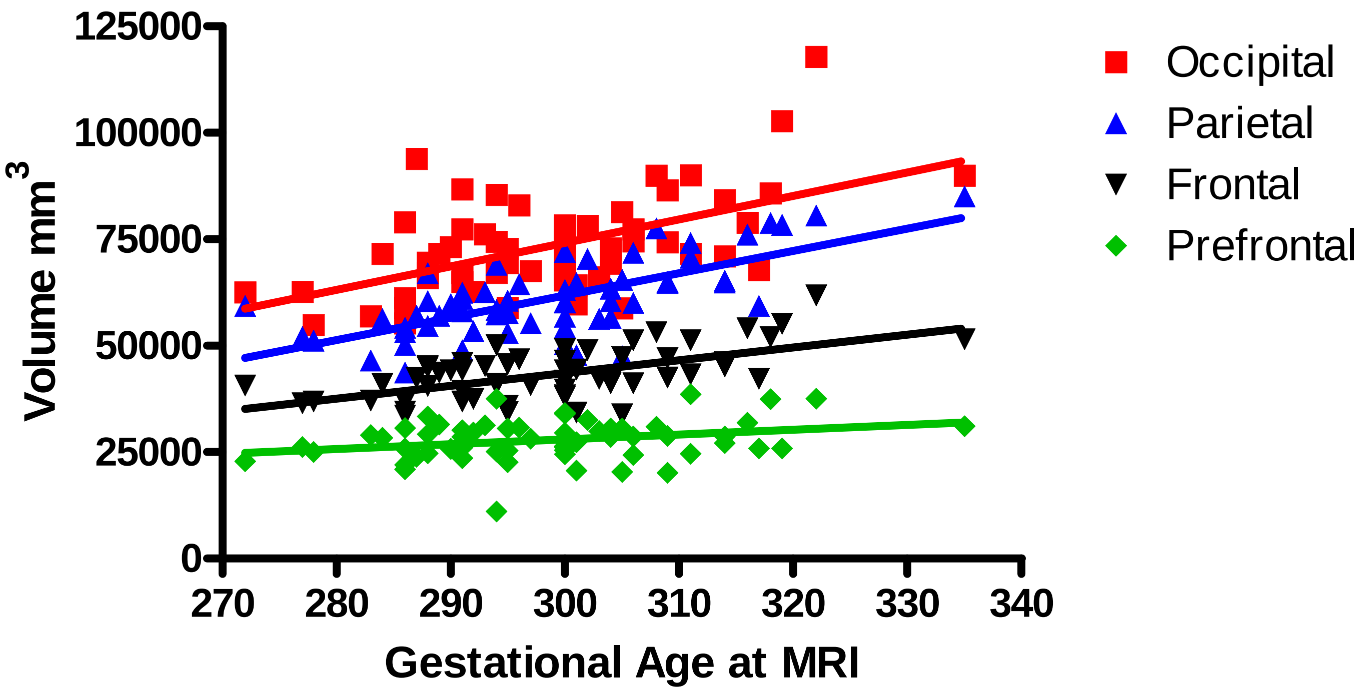
Overall homogeneity of slopes: $p < 0.001$

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

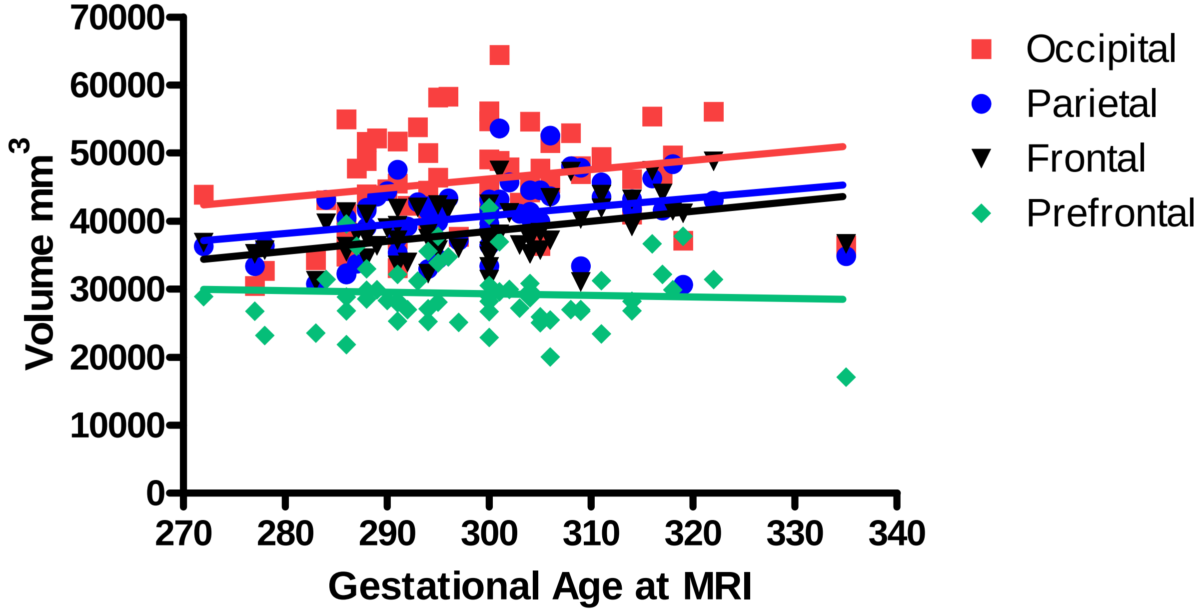


Overall homogeneity of slopes: $p < 0.001$

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

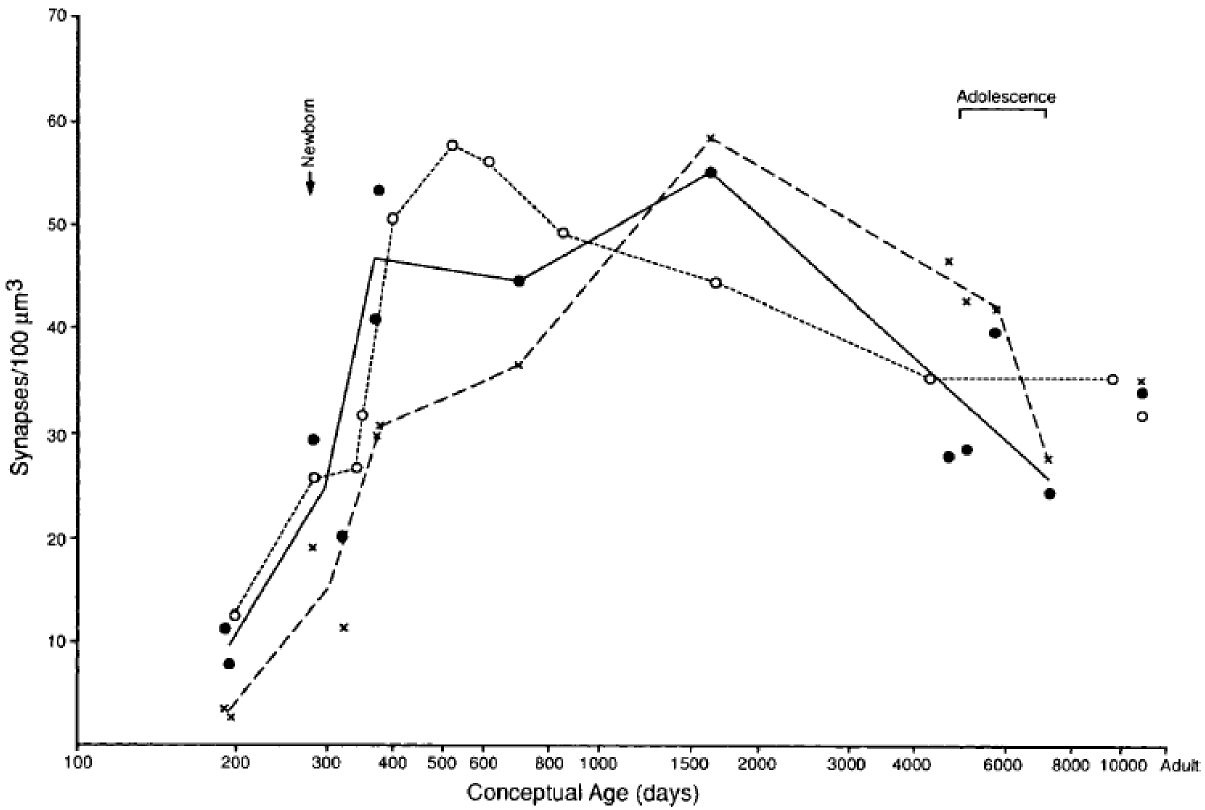


Fig. 2. Mean synaptic density in synapses/100 µm³ in auditory, calcarine, and prefrontal cortex at various ages. Open circles, visual cortex (area 17); filled circles, auditory cortex; x, prefrontal cortex (middle frontal gyrus).

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

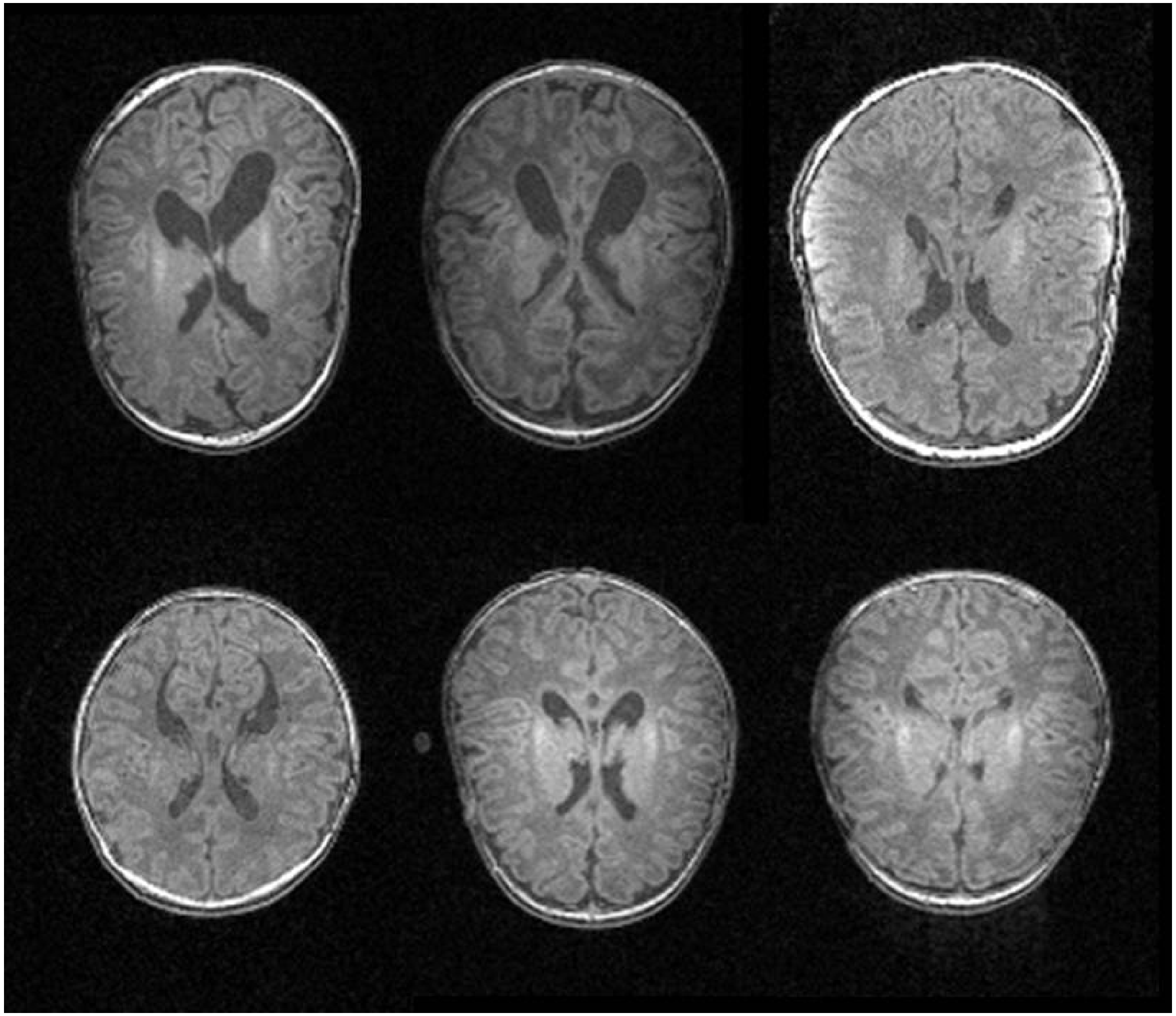
Isolated Mild Ventriculomegaly

- Atrial width ≥ 10mm
- 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 ± 0.03 vs. 0.59 ± 0.03; $p < 0.0001$

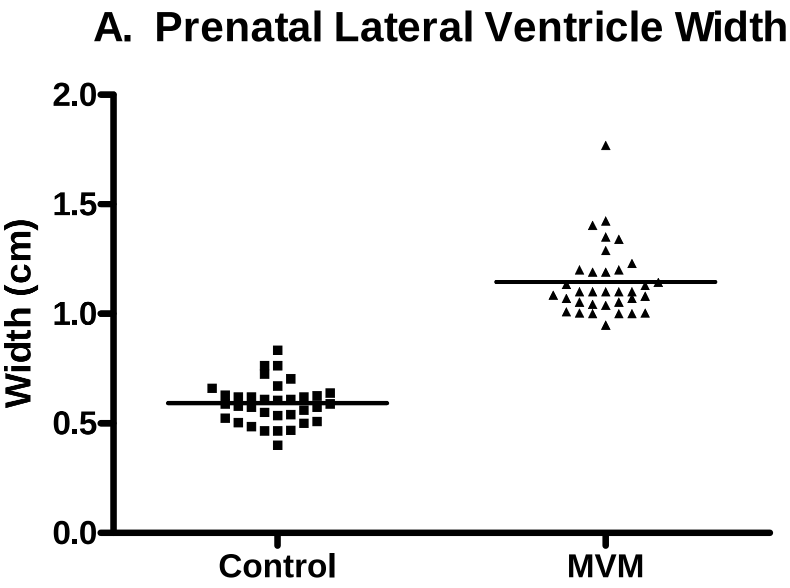
Mild Ventriculomegaly

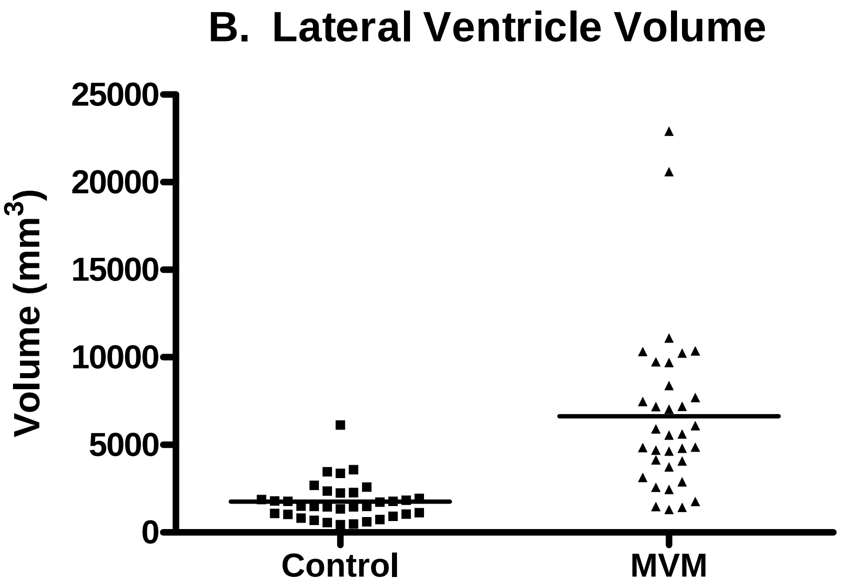


Neonatal Brain Structure

	Control LS mean (SE)	**MVM** LS mean (SE)	**% difference**	**F-value** (DF)	**P value**
Intracranial Volume (mm^3)	475,757 (8,207)	509,615 (8,207)	7.1%	8.51 (1,33)	**0.0063**
Lateral Ventricle (mm^3)	1,701 (585)	6,572 (585)	286.4%	34.64 (1,33)	< **0.0001**
Cortical Gray Matter (mm^3)	197,625 (3,839)	219156 (3,839)	10.9%	15.72 (1,33)	**0.0004**
Cortical White Matter (mm^3)	152,426 (2,962)	158,680 (2,962)	4.1%	2.23 (1,33)	0.1449
Cerebellum (mm^3)	27361 (547)	27181 (547)	- 0.06%	0.05 (1,33)	0.8184

Lateral Ventricles

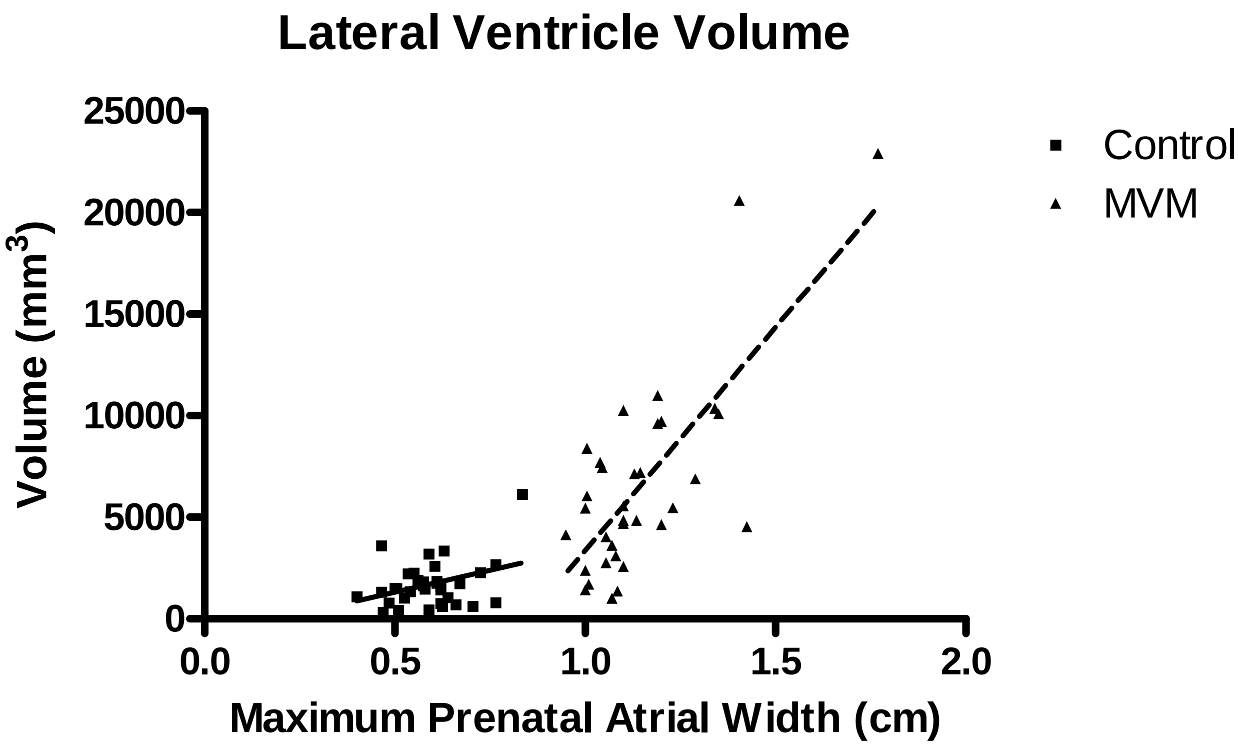




A. Maximum lateral ventricle width in controls and MVM cases (n= 34/ group; $p < 0.0001$)

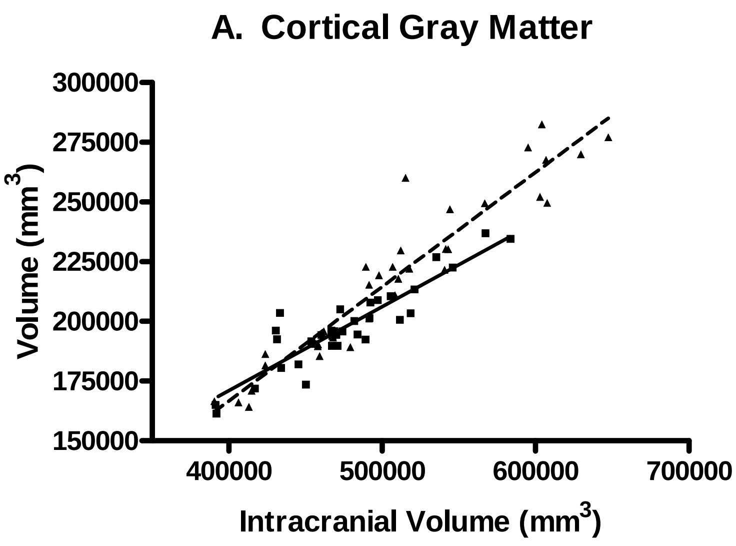
B. Neonates with prenatal MVM have significantly larger lateral ventricle volumes than matched controls (n= 34/ group; $p < 0.0001$).

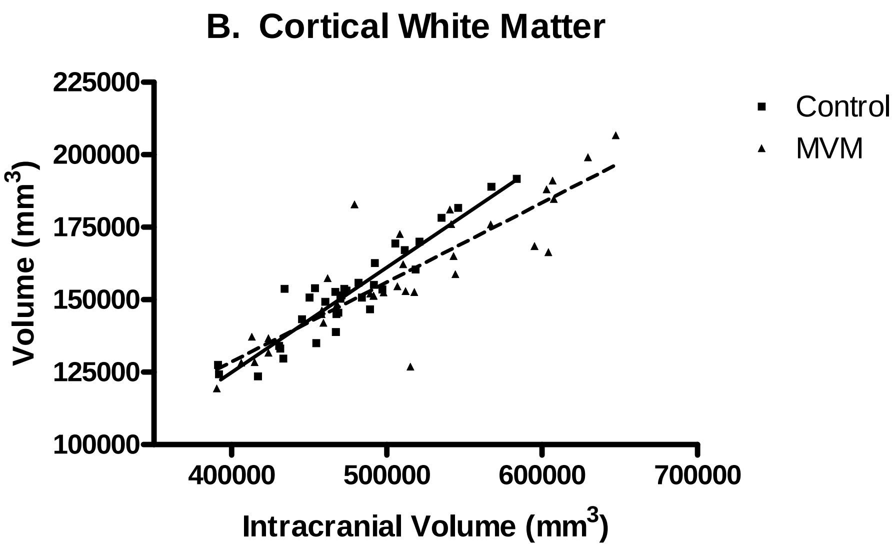
Prenatal/Neonatal Relationship



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)

Gray and White Matter Volume



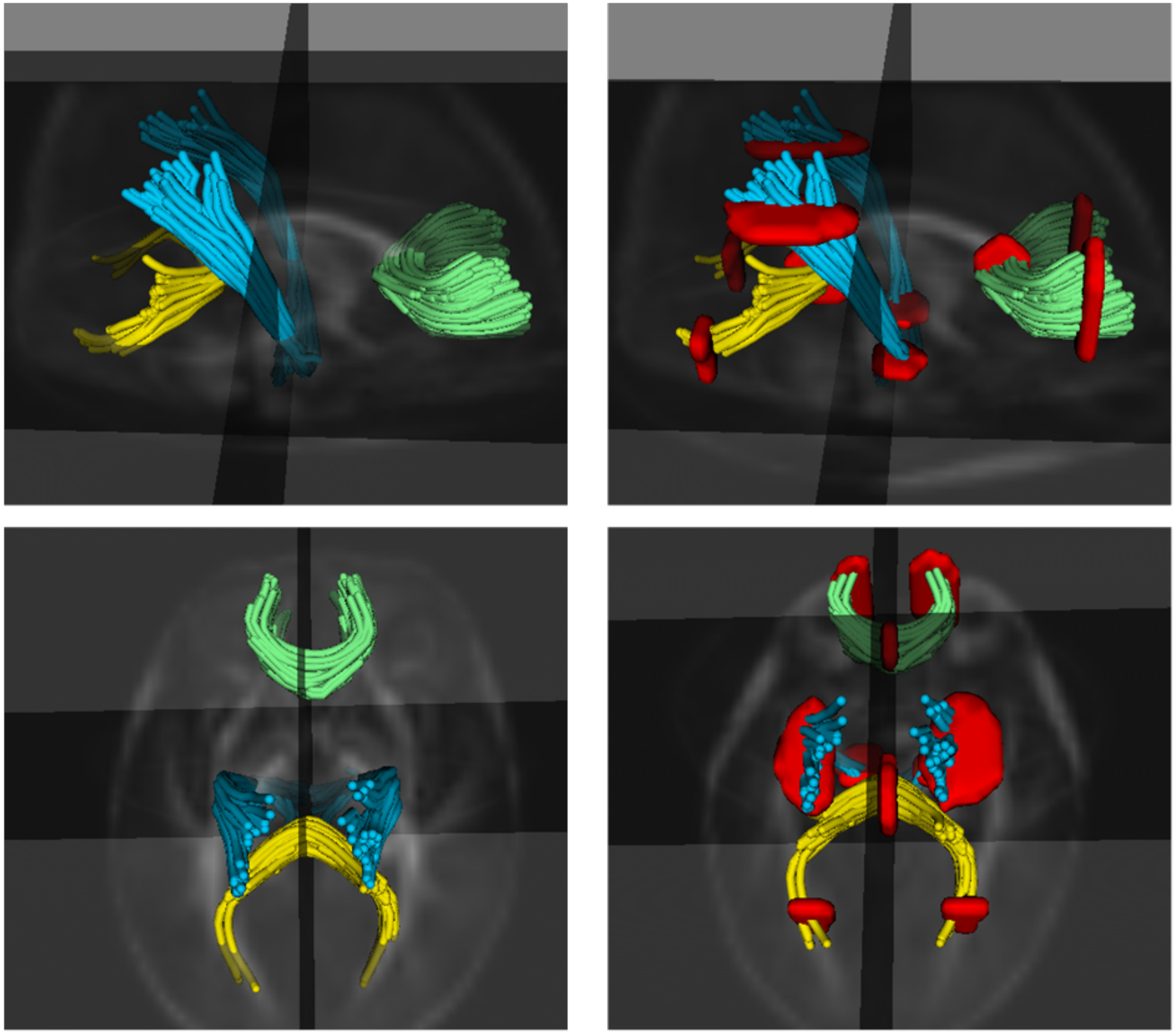


There is a significant difference in the relationship between ICV and cortical gray matter volume in MVM cases compared to controls (homogeneity of slope F=13.15 (1,31); p=0.0010)

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

Mean Diffusivity	LSMean (SE)		F-Test for difference: Normal Control vs MVM	
Location/ track	**Normal Control**	**MVM**	**F-value (DF)**	**P-Value**
Genu (-21)	14.58 (0.16)	15.63 (0.17)	20.46 (1,24)	**0.0001**
Genu (0)	13.71 (0.28)	14.28 (0.30)	1.92 (1,24)	0.1782
Genu (21)	13.61 (0.44)	15.31 (0.48)	6.79 (1,24)	**0.0155**
Splenium (-24)	15.01 (0.33)	16.70 (0.35)	12.12 (1,24)	**0.0019**
Splenium (0)	14.23 (0.21)	14.91 (0.22)	4.88 (1,24)	**0.0370**
Splenium (24)	14.59 (0.24)	16.26 (0.26)	22.47 (1,24)	**<0.0001**
Left Cortico-spinal (-12)	10.08 (0.08)	10.41 (0.08)	8.55 (1,23)	**0.0076**
Left Cortico-spinal (9)	12.43 (0.18)	13.22 (0.20)	8.92 (1,23)	**0.0066**
Right Cortico-spinal (-12)	10.06 (0.07)	10.54 (0.08)	20.37 (1,23)	**0.0002**
Right Cortico-spinal (9)	12.45 (0.21)	13.10 (0.23)	4.42 (1,23)	**0.0466**

Fractional Anisotropy	LSMean (SE)		F-Test for difference: Normal Control vs MVM	
Location/ track	Normal Control	MVM	F-value (DF)	P-Value
Genu (-21)	0.23 (0.01)	0.21 (0.01)	3.08 (1,24)	0.0920
Genu (0)	0.50 (0.01)	0.47 (0.01)	2.22 (1,24)	0.1493
Genu (21)	0.23 (0.01)	0.22 (0.01)	0.74 (1,24)	0.3972
Splenium (-24)	0.29 (0.01)	0.29 (0.01)	0.04 (1,24)	0.8448
Splenium (0)	0.56 (0.01)	0.49 (0.02)	10.59 (1,24)	**0.0034**
Splenium (24)	0.28 (0.01)	0.25 (0.01)	4.27 (1,24)	**0.0498**
Left Cortico-spinal (-12)	0.51 (0.01)	0.50 (0.01)	1.24 (1,23)	0.2763
Left Cortico-spinal (9)	0.31 (0.01)	0.28 (0.01)	4.29 (1,23)	**0.0497**
Right Cortico-spinal (-12)	0.54 (0.01)	0.50 (0.01)	5.20 (1,23)	**0.0322**
Right Cortico-spinal (9)	0.28 (0.01)	0.28 (0.01)	0.03 (1,23)	0.8629

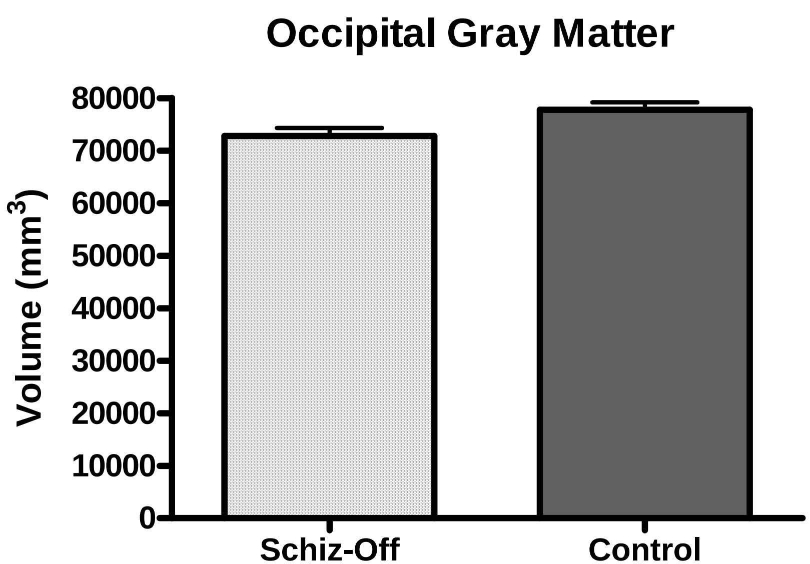
MVM Conclusions

- 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

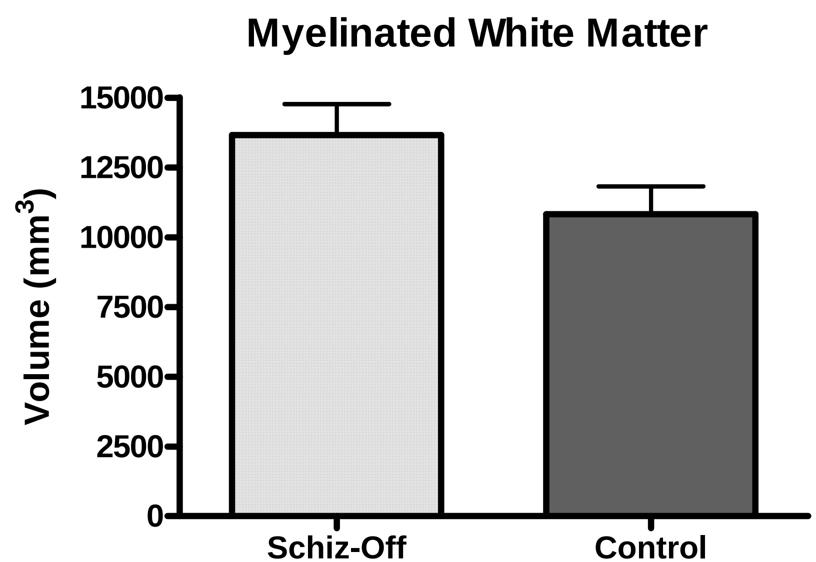
Offspring of Mothers with Schizophrenia

- 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



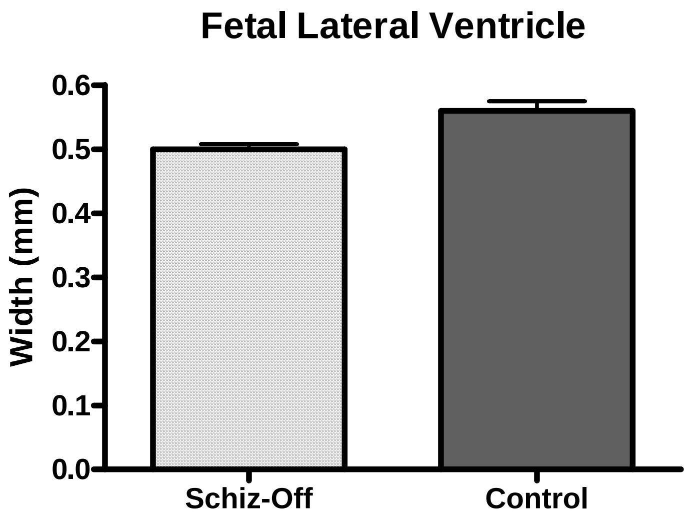
p = 0.0325

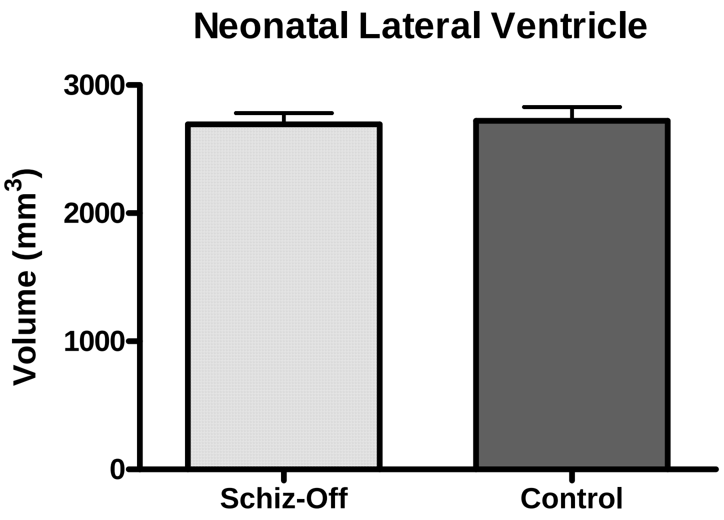


p = 0.083

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

Lateral Ventricle Size





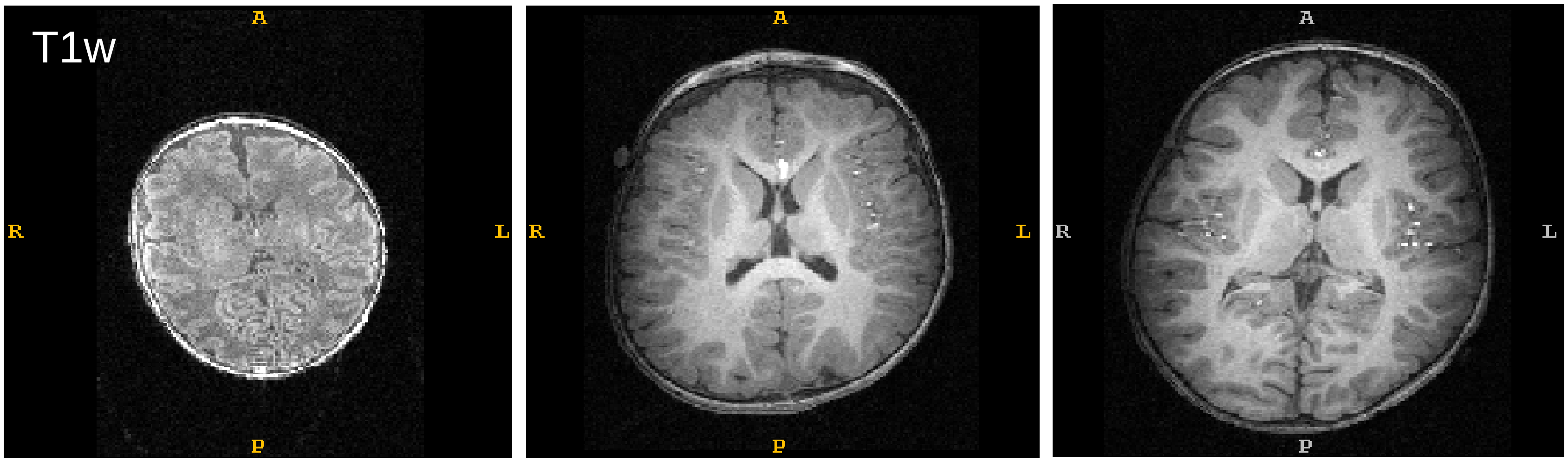
Conclusions

- 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

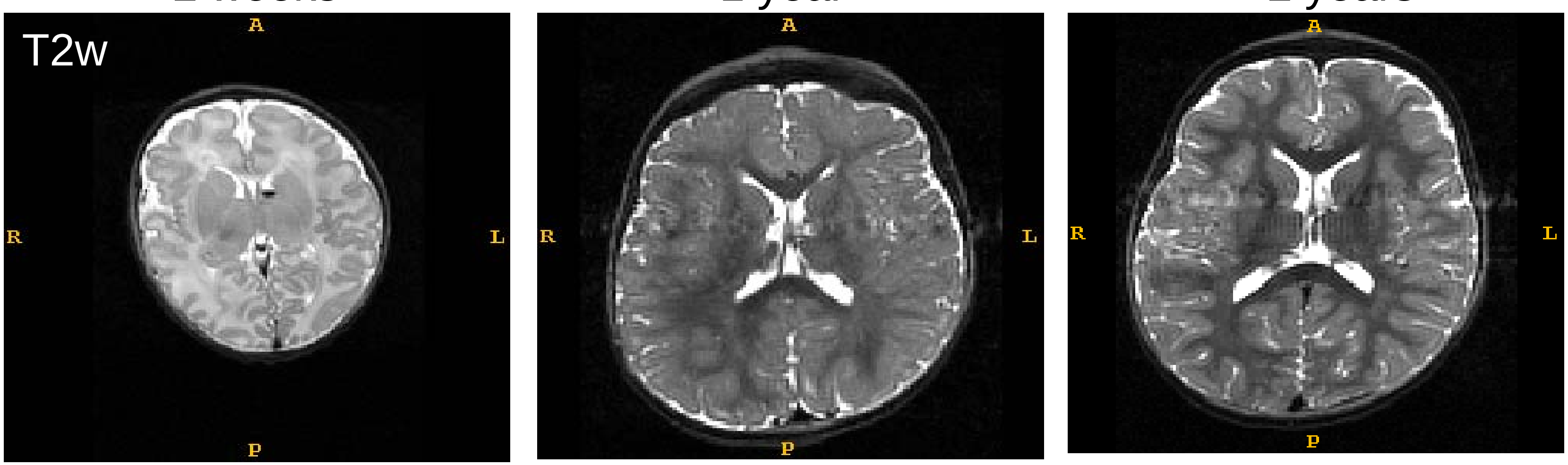
Early Brain Development in 1 and 2 year Olds

- 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)

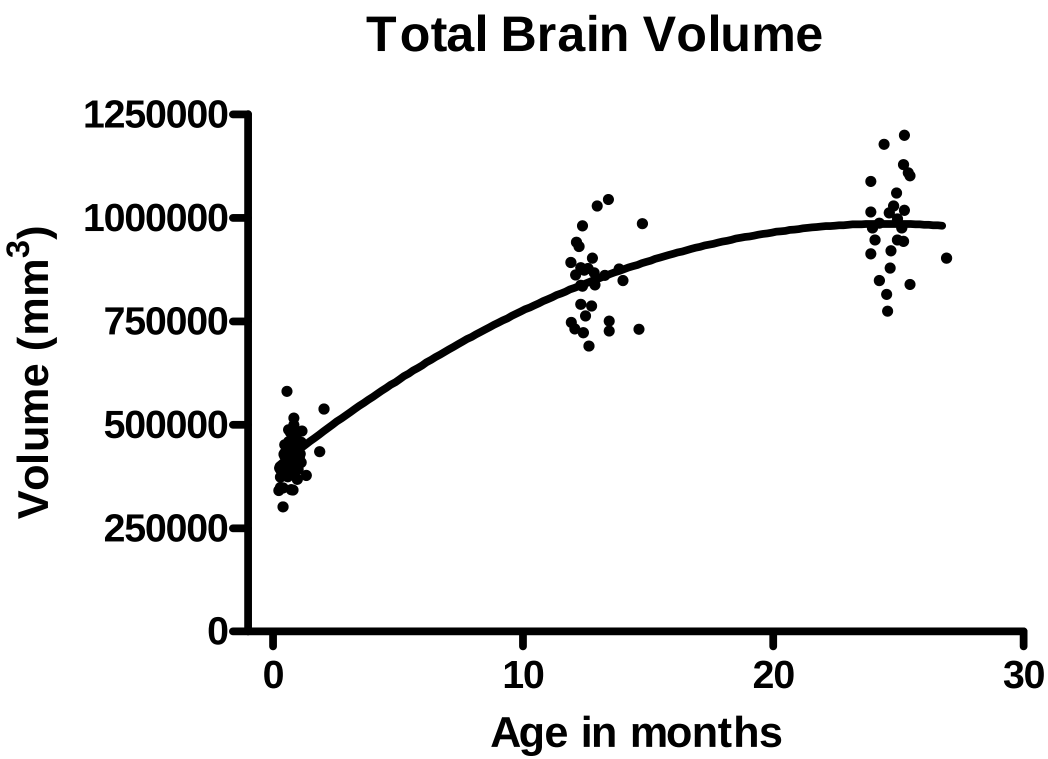
Subject with follow-up scans



2 weeks 1 year 2 years



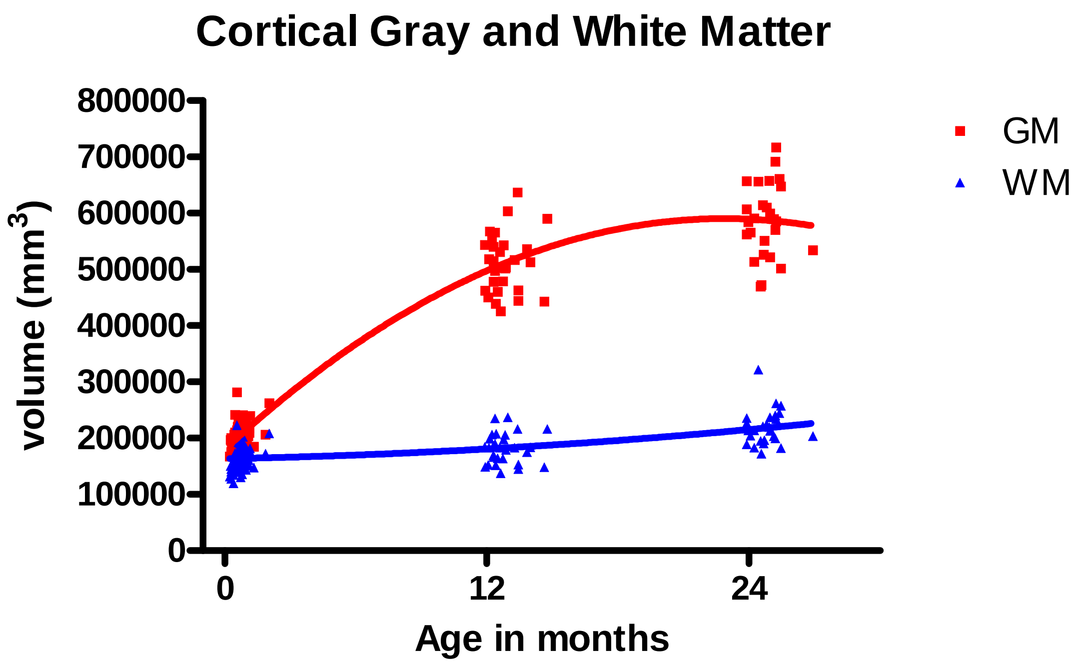
Brain development birth to age 2



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

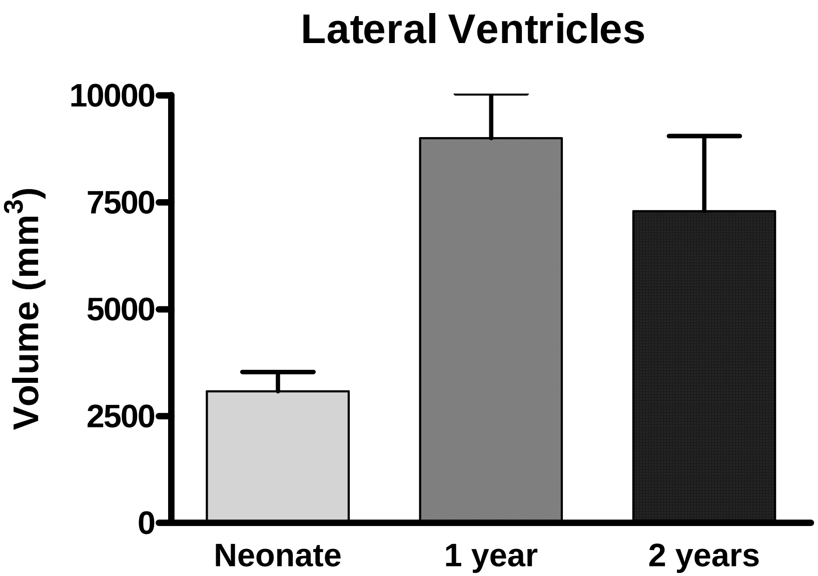
Brain development birth to age 2



Cortical GM: 149% in the first year; 14% in the second year

Cortical WM:

Brain development birth to age 2



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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