Early Childhood Brain Development and Schizophrenia Risk

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UNC
SCHOOL OF MEDICINE

Disclosures

- John Gilmore, M.D., F.A.P.A., has no relevant financial relationships to disclose

Schizophrenia

- Heterogeneous chronic relapsing psychotic disorder
- Heterogeneous symptoms
- Heterogeneous course and outcome

Domains of Symptoms

- Positive Symptoms
  - Hallucinations, delusions
- Negative Symptoms
  - Amotivation, anhedonia, apathy
  - 25% have the “deficit syndrome”
- Cognitive Dysfunction
  - Executive function, attention, memory

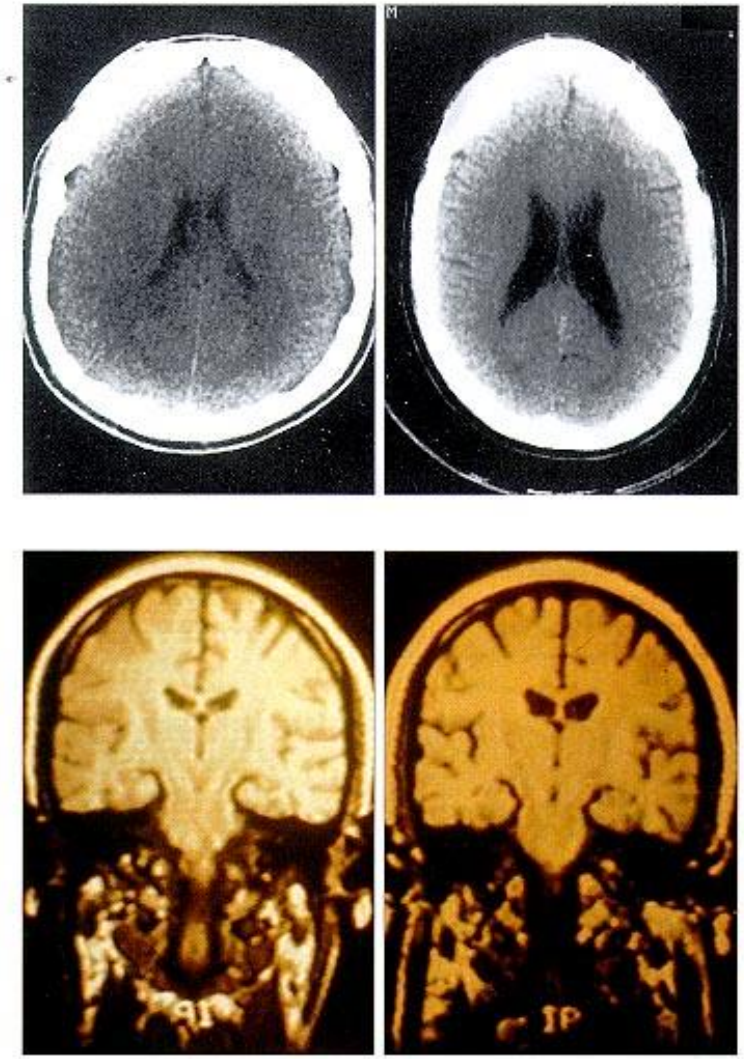
Course of illness

- Heterogeneous
  - about 25% have poor long-term outcome
- Remission rates are about 70-80%
  - Well controlled positive symptoms
- Recovery rates are 30-40 %
  - Independent living, meaningful social interactions, some work

Neurodevelopmental Hypothesis of Schizophrenia

- Neurodevelopmental disorder with prenatal/perinatal origins
  - Pregnancy and birth complications
  - Subtle childhood neurodevelopmental abnormalities
  - Brain abnormalities on MRI are present at first episode
  - Genes of risk play a role in brain development and plasticity

What is wrong in schizophrenia?



Structural Neuroimaging

- Enlargement of lateral ventricles
- Volume loss in frontal and temporal cortex, hippocampus
- Gray matter volume reductions
- Present in first-episode, never medicated patients
  - also in unaffected relatives
- Volumes losses progress over the course of the illness
  - may be due to antipsychotic medication

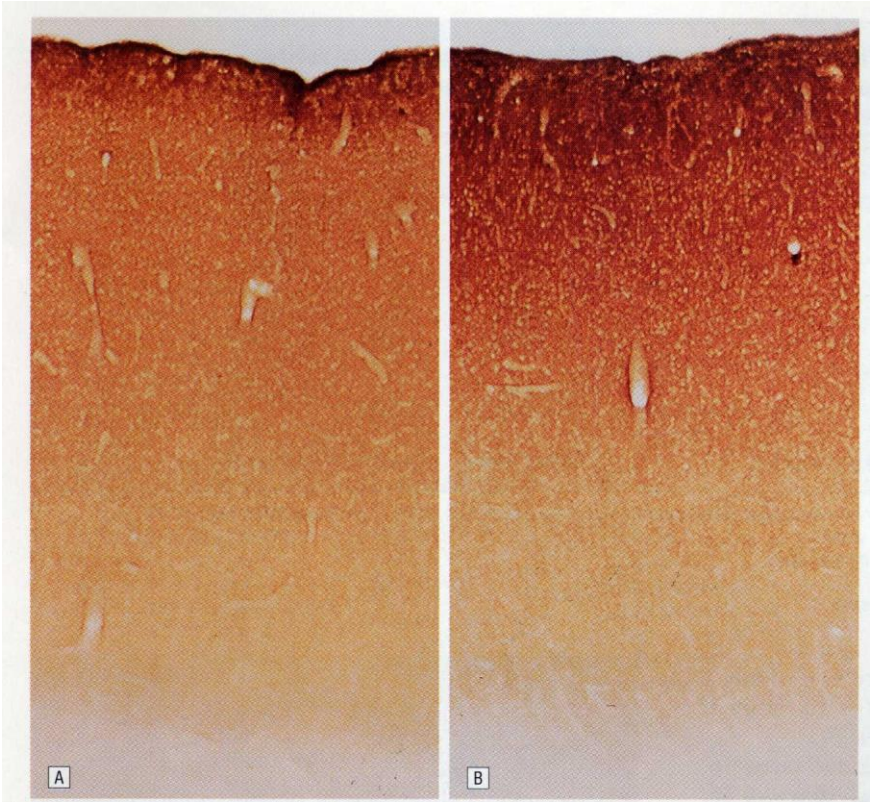
“Wiring” of the Brain

- Widespread abnormalities in white matter microstructure as measured with DWI

Functional Neuroimaging

- Task Based: broad abnormalities in circuits involved with executive function, learning and memory, social cognition
- Task independent resting state networks, esp. default mode networks
- Abnormal synchrony of cortical oscillatory networks on EEG

Reduced Synapses/Spines



Subject with schizophrenia

Matched normal control subject

Glantz and Lewis, 1997

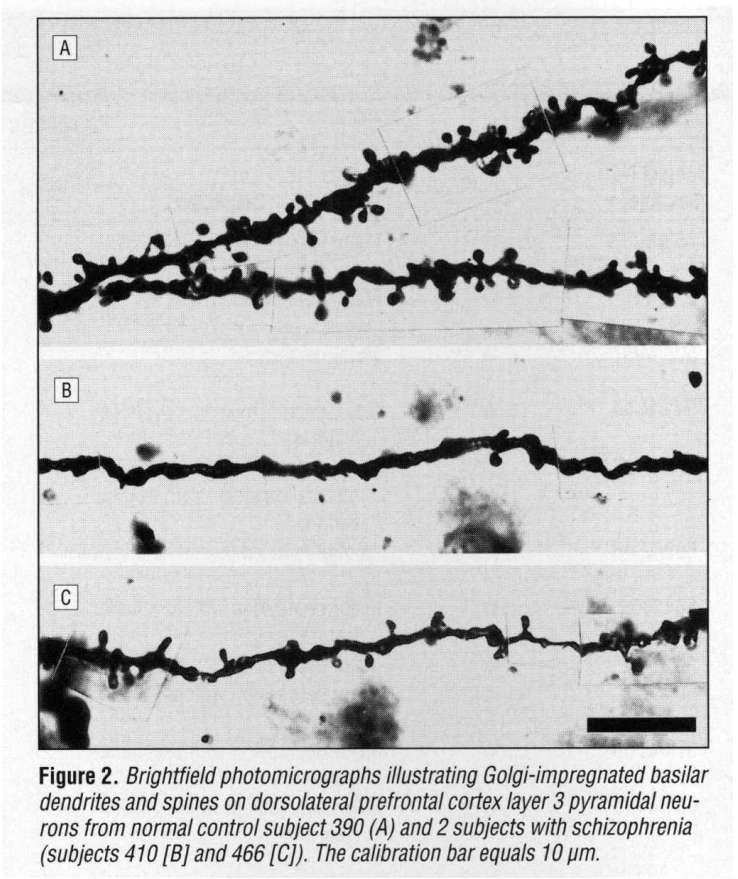


Figure 2. *Brightfield photomicrographs illustrating Golgi-impregnated basilar dendrites and spines on dorsolateral prefrontal cortex layer 3 pyramidal neurons from normal control subject 390 (A) and 2 subjects with schizophrenia (subjects 410 [B] and 466 [C]). The calibration bar equals 10 µm.*

Glantz and Lewis, 2000

Disorder of Connectivity

- Postmortem studies
  - no overall neuron loss; reduced neuropil
  - decreased synaptic markers
    - Synaptophysin, decreased spine numbers
  - abnormalities of GABA interneurons

Genetics of Schizophrenia

- **Family Studies** find a parent with schizophrenia increases risk in offspring to 10%
  - other first degree relative – 10%
- **Twin studies** estimate the heritability of schizophrenia to be approximately 50-75%
- Environmental factors account for the remaining 25-50% of liability

Genetics of Schizophrenia

- Rare Copy Number Variants – n=20
  - Duplications, deletions
  - Rare, but highly penetrate
  - Not disorder-specific
- GWAS: Common Variants – n=300
- “Taken together, these results suggest unexpected complexity in the mechanisms that drive schizophrenia, pointing to the involvement of ensembles of genes (polygenicity) rather than single-gene causation”
  - Sullivan et al., Nat Neurosci Reviews 2024

Environmental Risk - Exposome

- Prenatal/perinatal (OR 2.0-4.0)
  - Obstetrical complications
  - Maternal infection
  - Malnutrition
- Other – Socal Determinants of Mental Health
  - Early childhood adversity (OR=2.8; Zhou et al., 2025)
  - Urban birth/living, “deprived” residence, lack of green spaces, immigrant status,
  - Cannabis use

Non-specific; risk for multiple neuropsychiatric and neurodevelopemntal outcomes

Understanding What Causes Schizophrenia: A Developmental Perspective

- Schizophrenia is the end result of a complex interaction between thousands of genes and multiple environmental risk factors—none of which on their own causes schizophrenia
- Weinberger (1987), in his classic paper on brain development and schizophrenia entertained the "unlikely" possibility that schizophrenia is "not the result of a discrete event or illness process at all, but rather one end of the developmental spectrum that for genetic and/or other reasons 0.5% of the population will fall into."
- 30 years later, this "unlikely" possibility is looking more likely
- Schizophrenia may in fact be the tail end of a distribution of how the estimated 20 billion neurons and their trillions of synaptic connections in our brains are generated, eliminated, and maintained
- In the end, more or less by genetic and environmental chance, some of us get wired for psychosis

Am J Psychiatry 167:1, January 2010

Editorial

Understanding What Causes Schizophrenia: A Developmental Perspective

Schizophrenia is likely the result of an abnormal developmental trajectory of synapse and circuit formation that ultimately leads to a miswired brain and clinical symptoms. This abnormal developmental trajectory is contributed to by the interaction of thousands of risk genes and multiple environmental risk factors. Perhaps the best hope to understand and prevent schizophrenia is to focus not so much on the genes or risk factors but rather on the developmental trajectory itself, the final common pathway(s) to schizophrenia. We must understand the periods of human brain development that are important for synapse and circuit development. When do abnormalities in brain wiring actually occur in children at risk for schizophrenia? How do the known environmental and genetic risk factors alter normal developmental trajectories? What are the key transition periods in human brain development? Can we modify developmental trajectories during periods of enhanced plasticity? These and other issues critical to understanding

Am J Psychiatry 167:1, January 2010

JOHN H. GILMORE, M.D.

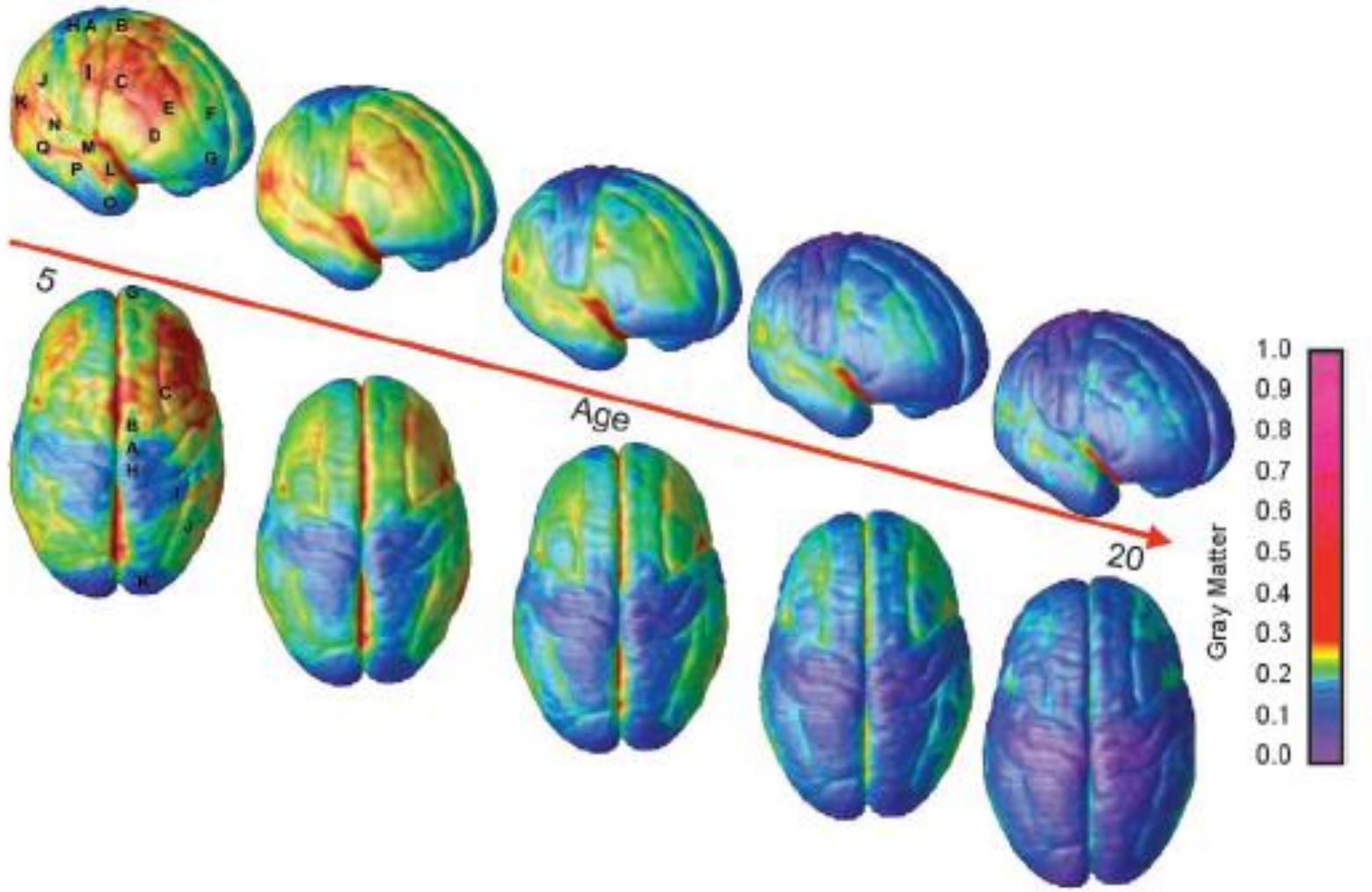
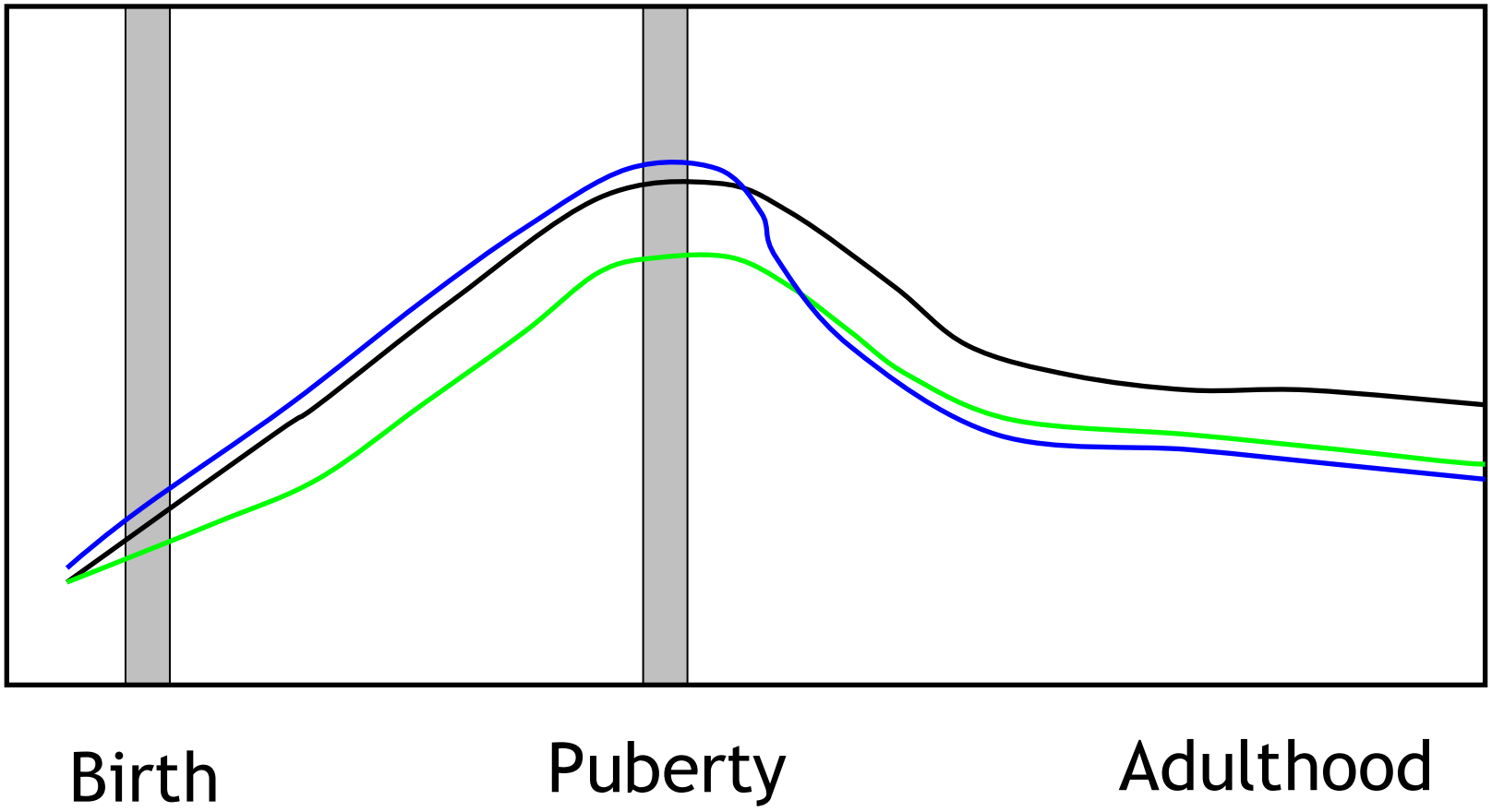
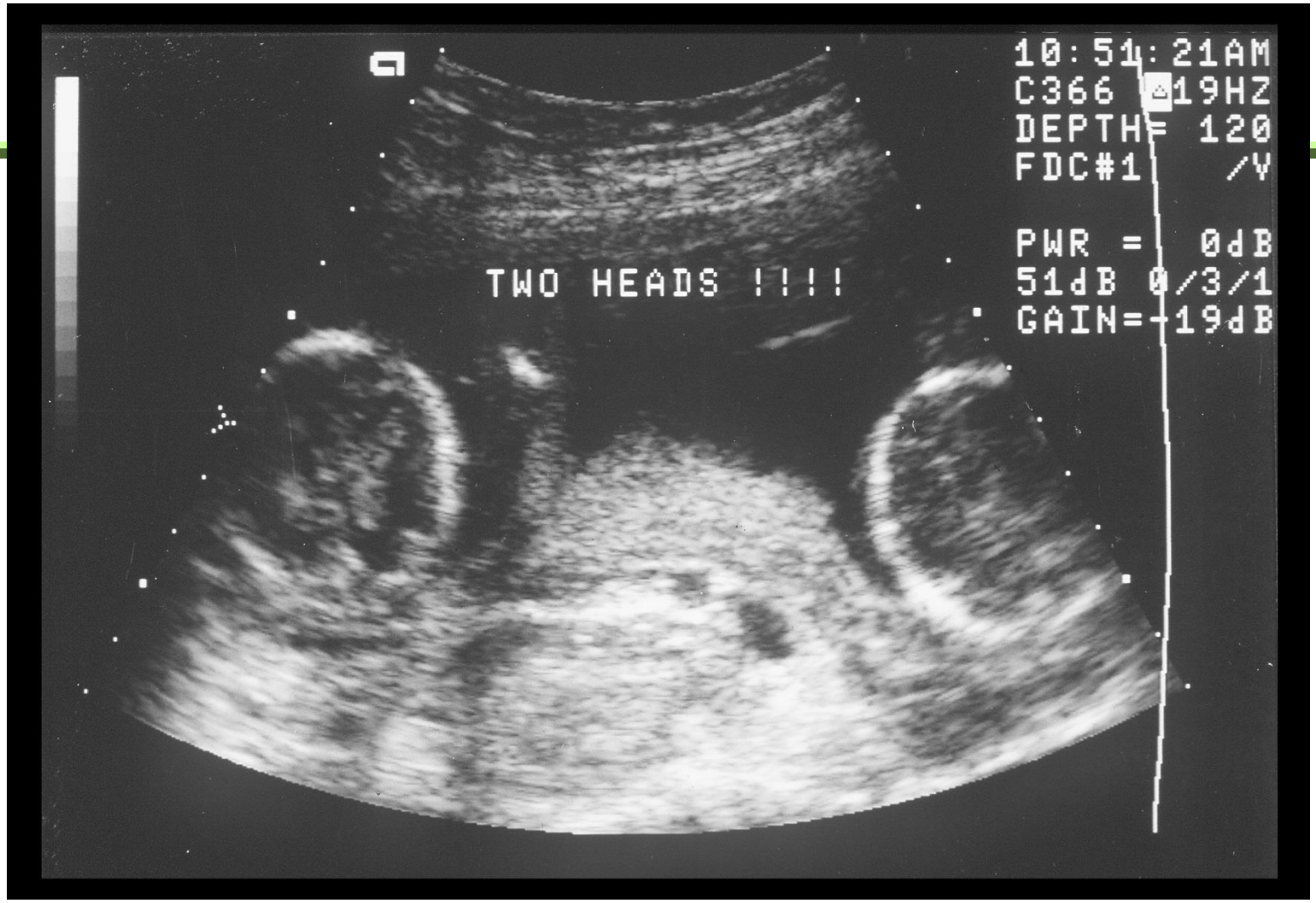


Fig. 3. Right lateral and top views of the dynamic sequence of GM maturation over the cortical surface. The side bar shows a color representation in units of GM volume. The initial frames depict regions of interest in the cortex as described for Fig. 1. This sequence is available in Movies 1–4 in the supporting information.

From Gogtay et al., 2004

Trajectories to Abnormal Synapses/Connectivity

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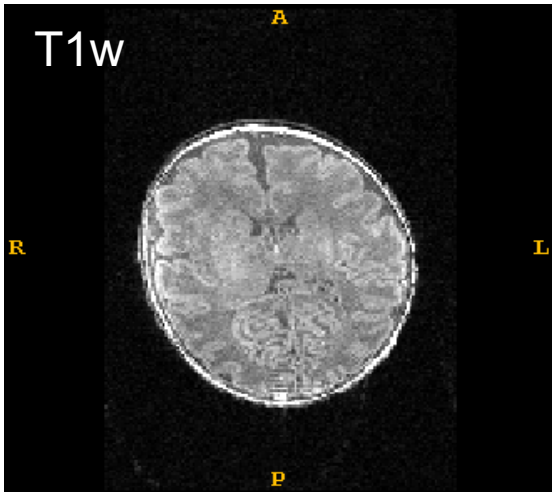
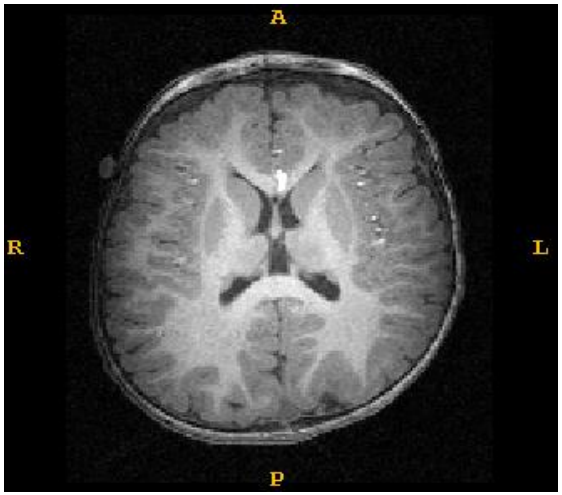
C366 19HZ
DEPTH= 120
FDC#1 /V
PWR = 0dB
51dB 0/3/1
GAIN=-19dB
TWO HEADS !!!!

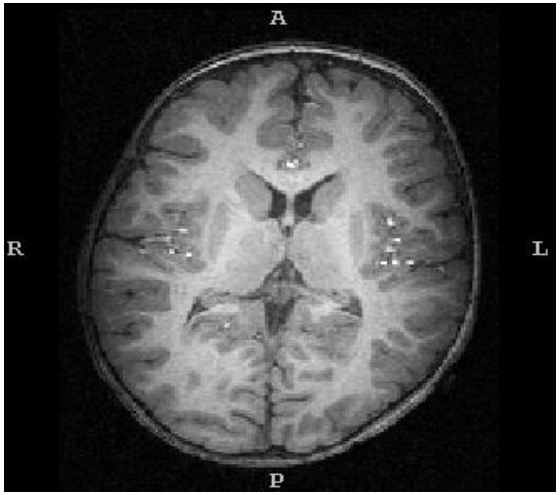
UNC Early Brain Development Studies

- **Singletons, twins, high risk**
  - Over 1000 children enrolled; First neonate scan- 2003
- **Recruited prenatally**
  - Prenatal ultrasound - 22 and 32 weeks
- **3T MRI (Siemens Allegra, TRIO, PRISMA)**
  - birth, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18 years
  - T1, T2, DWI, resting state fMRI
- **Assessments of Cognitive and Behavioral Development**
  - Mullen Scales of Early Learning
  - Working Memory, Attention, Language, IQ
  - BASC, BRIEF

Brain Development birth to 2 years



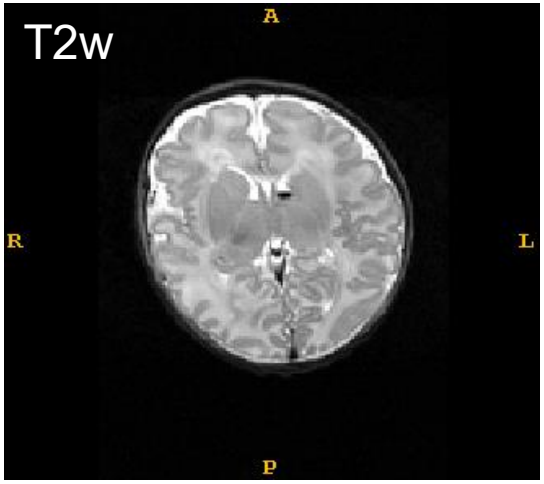


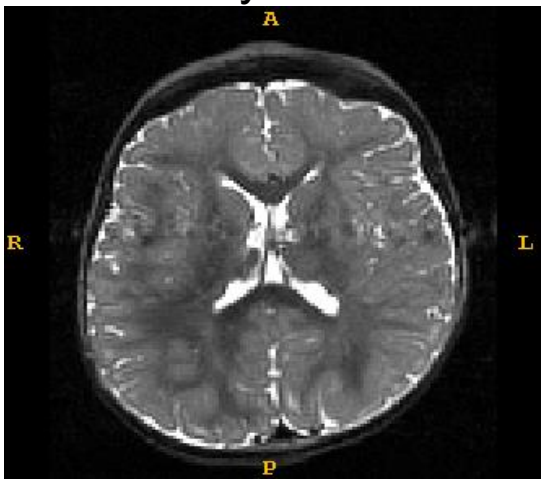


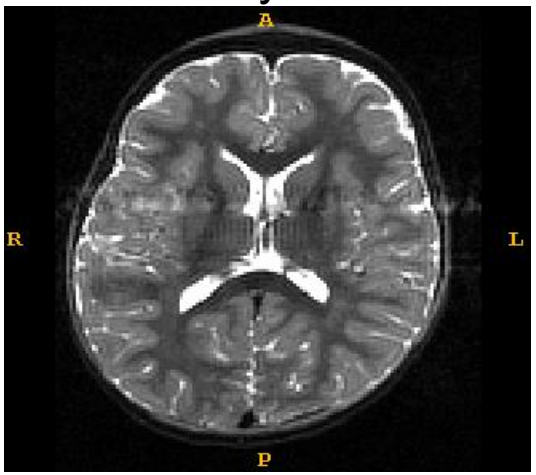
2 weeks

1 year

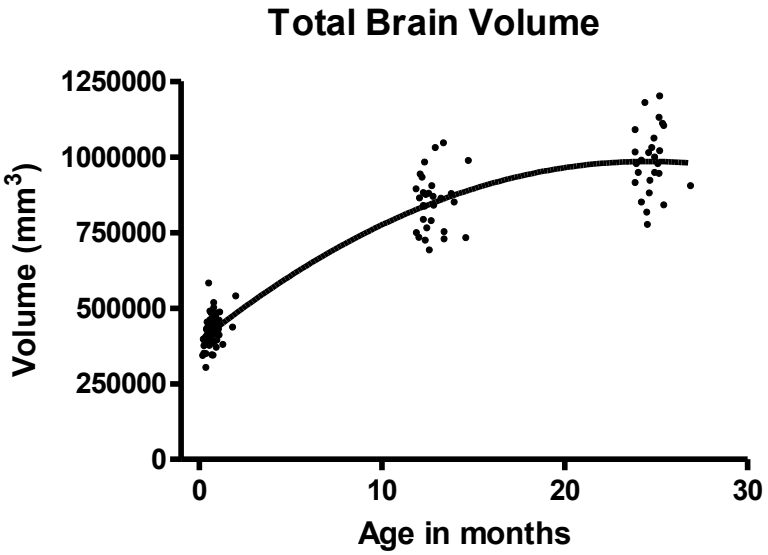
2 years

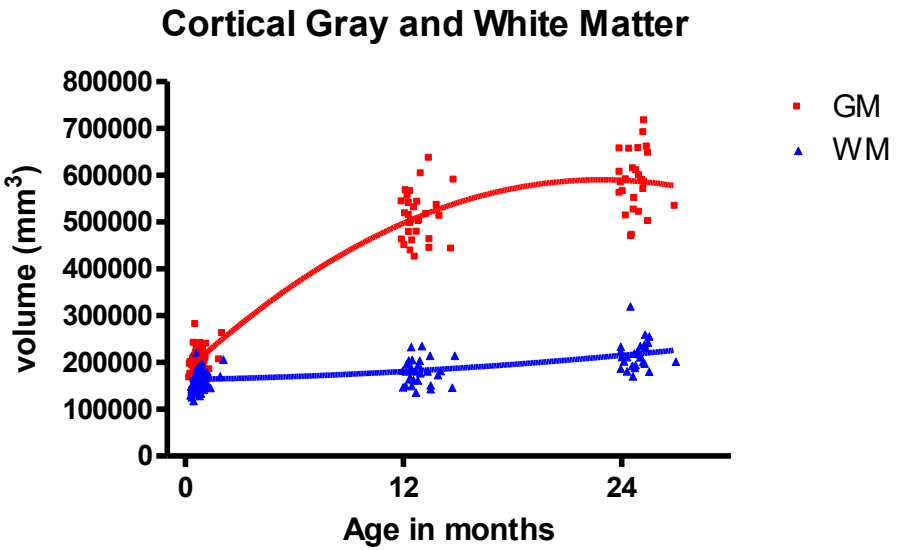






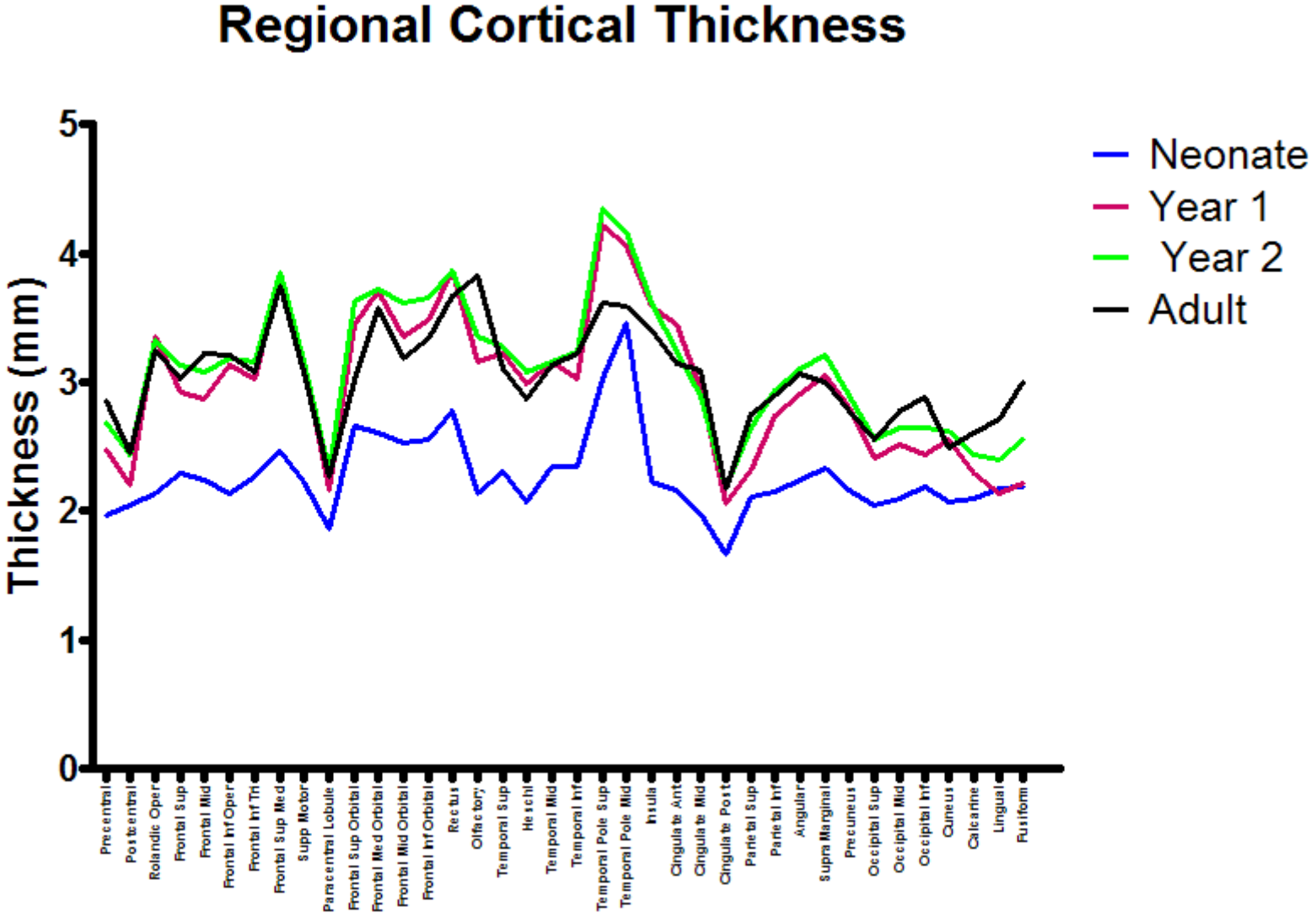
Brain development birth to 2 years



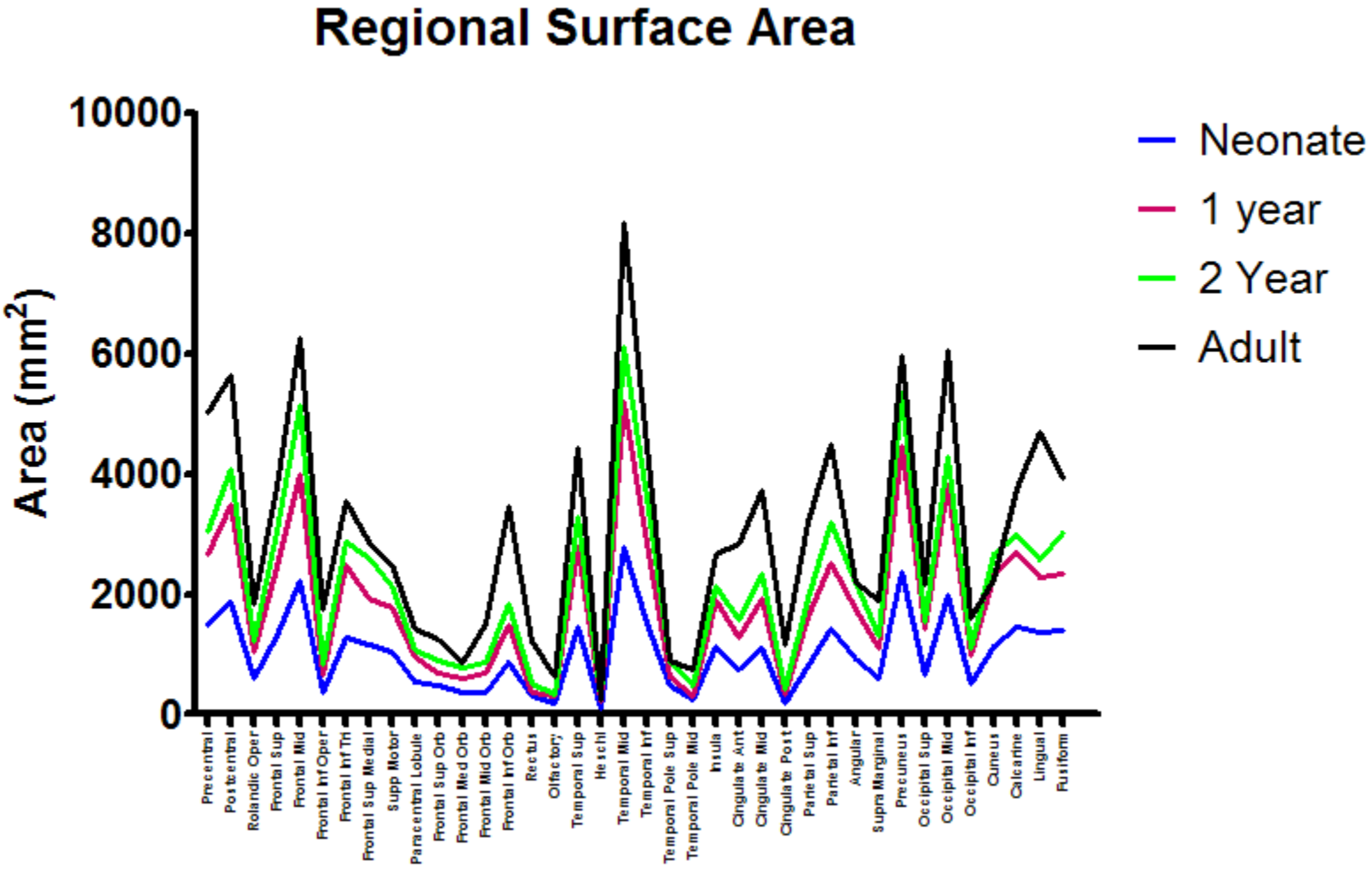


- Total brain volume grows 101% in first year, 15% in second year
- 2-4 weeks: 36% of adult volume; 72% at 1 year and 83% at 2 years
- Cortical GM: 149% in the first year; 14% in second
- Cortical WM: 11% in the first year; 19% in second

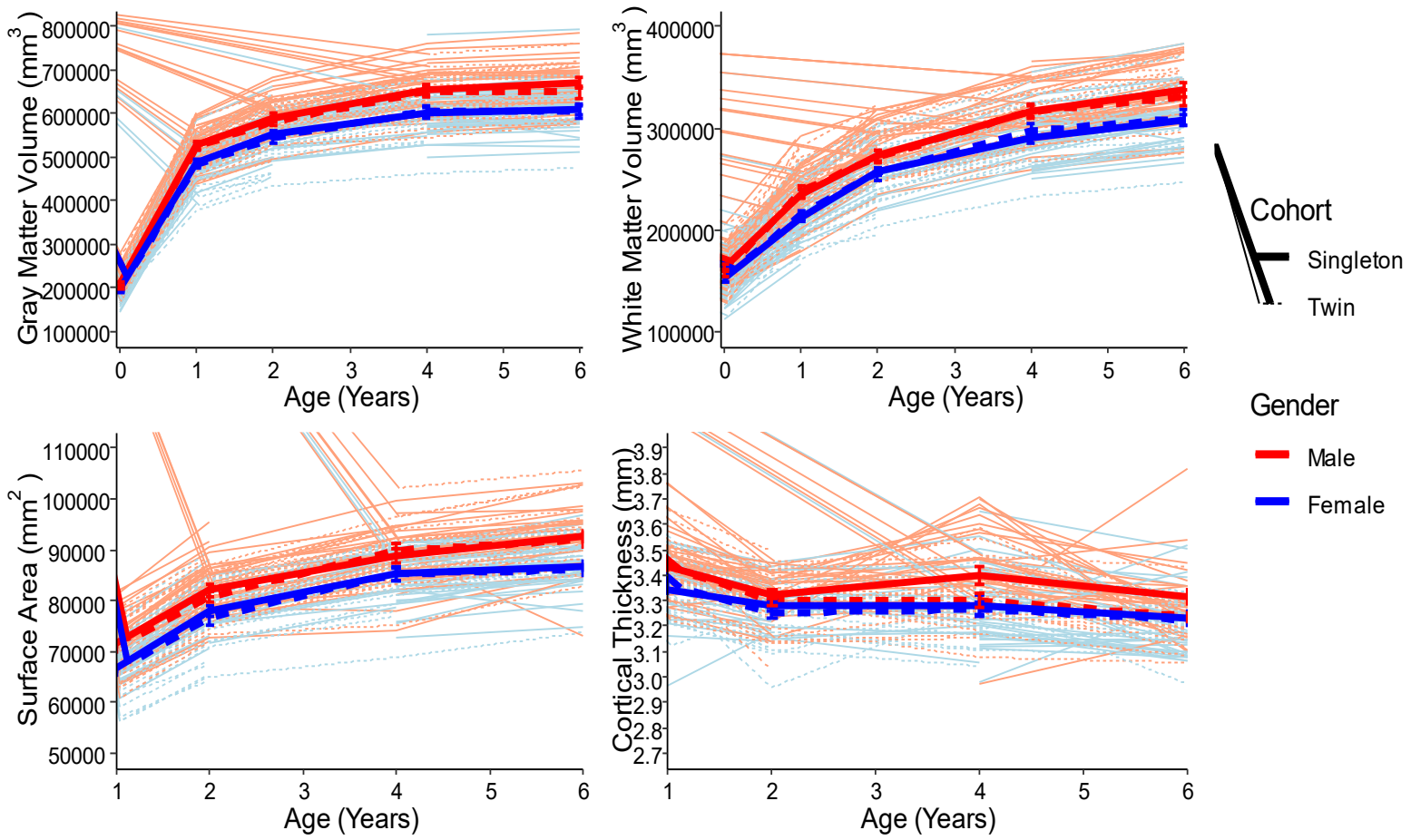
Knickmeyer et al., J Neurosci 2008



- Birth to 1 year: 35% (range: 3-67%)
- 1 to 2 years: 4% (range: -7 – 18%)
- 2 year: 97% of adult value (range 76-127%)

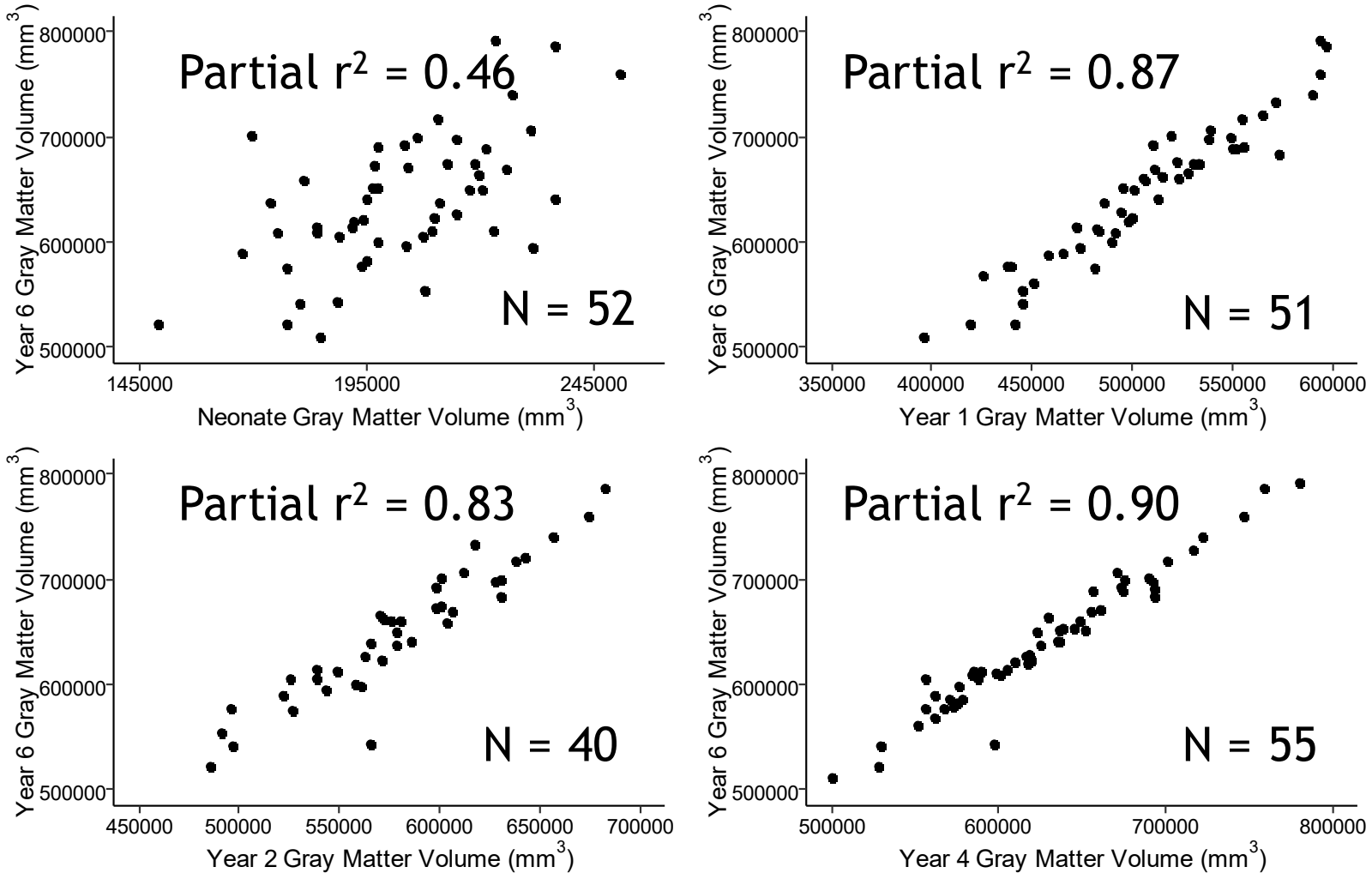


- Birth to 1 year: 75% (range: 12-120%)
- 1 to 2 years: 21% (range: 8-63%)
- 2 year: 69% of adult value (range 22.5-117%)



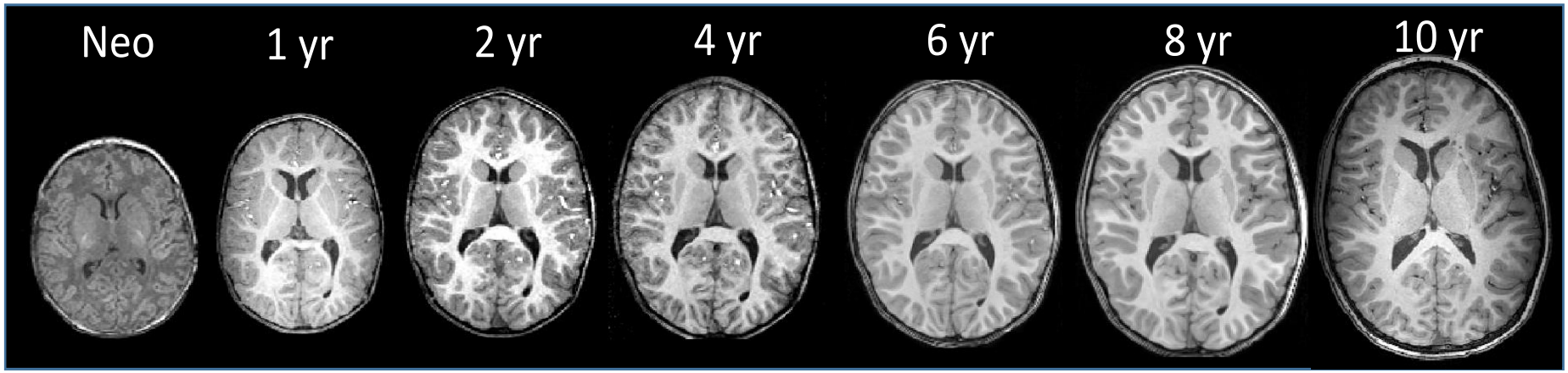
Gilmore et al, Biol Psych: CNNI 2021

Individual differences in gray matter volume set up very early

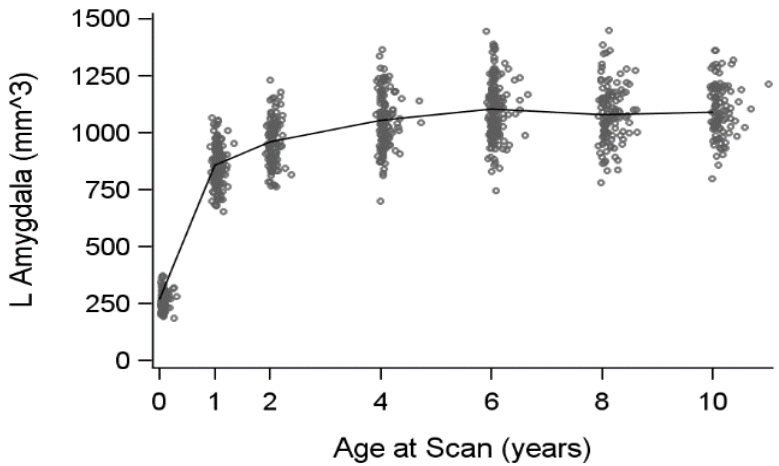


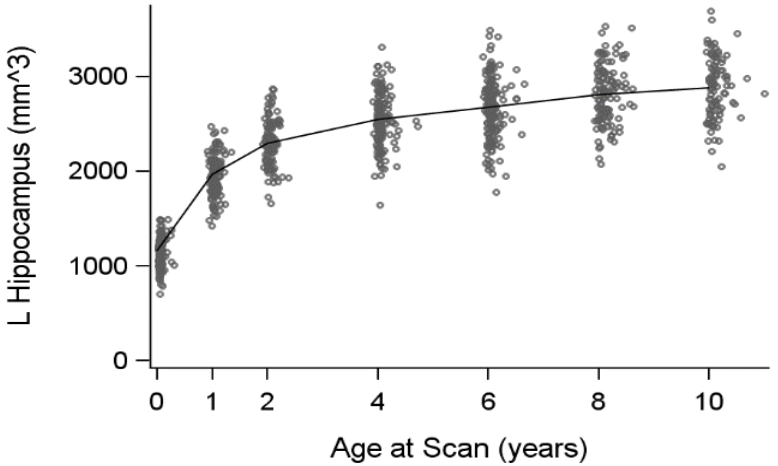
Gilmore et al, Biol Psych: CNNI 2021

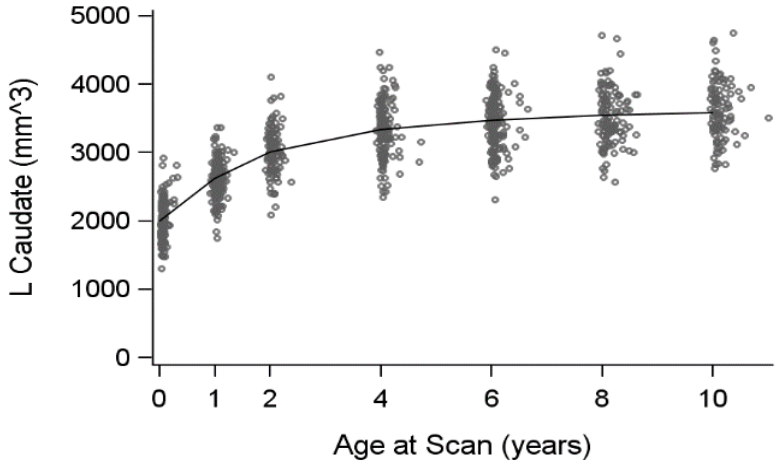
Birth to 10 years

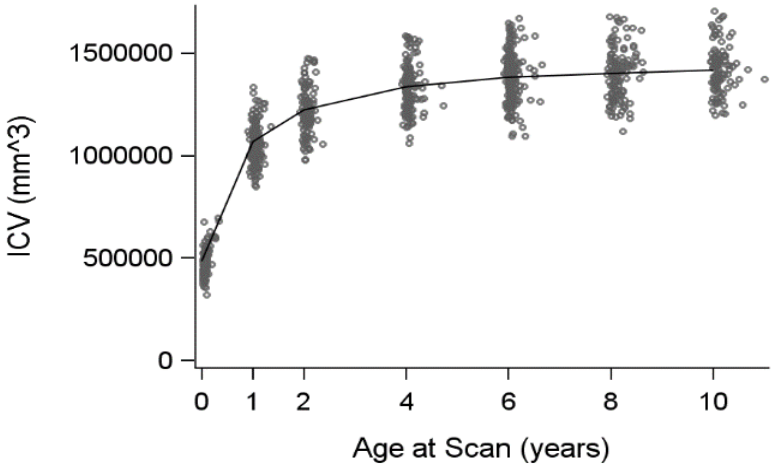


Subcortical development 0-10 years



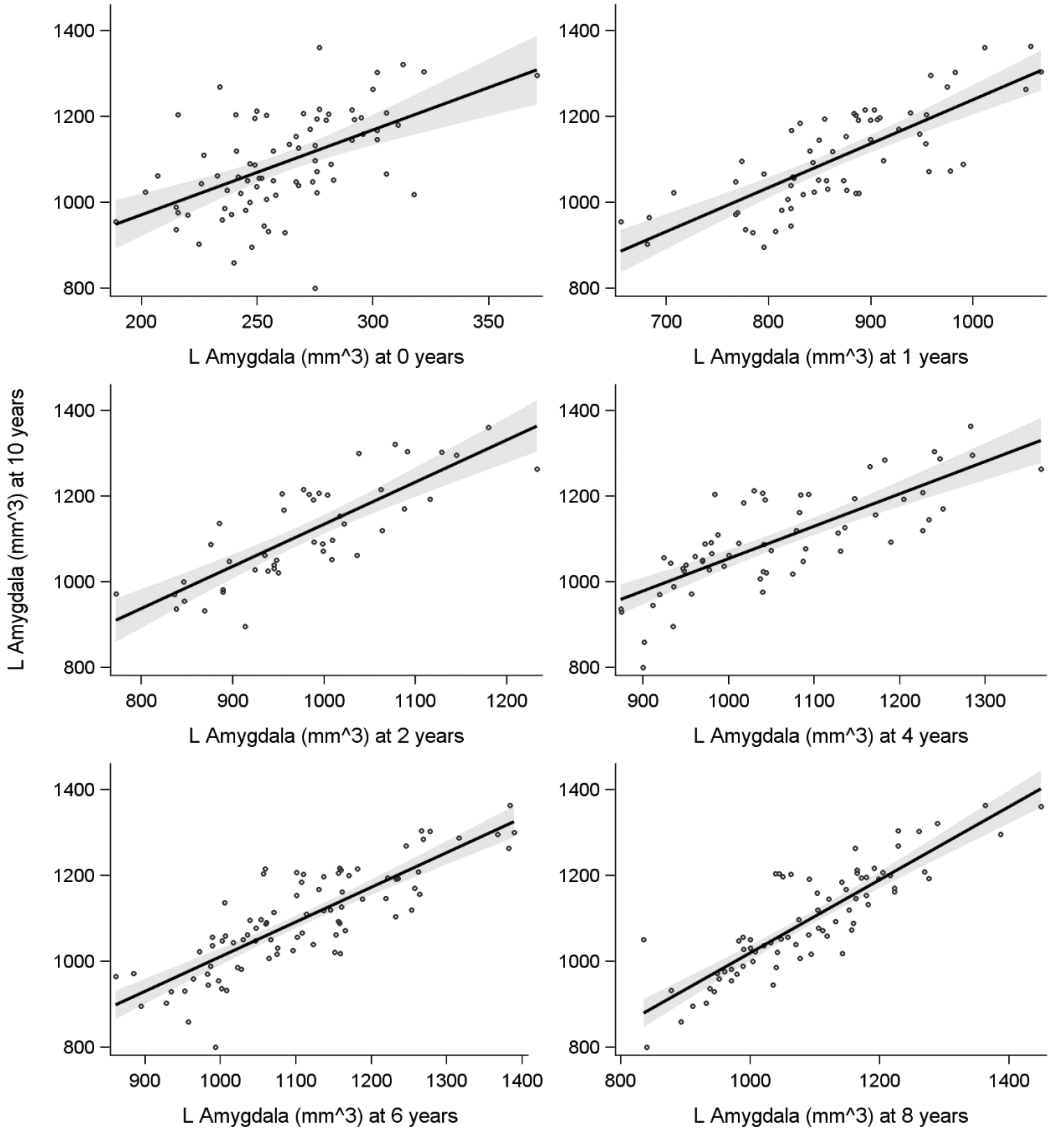






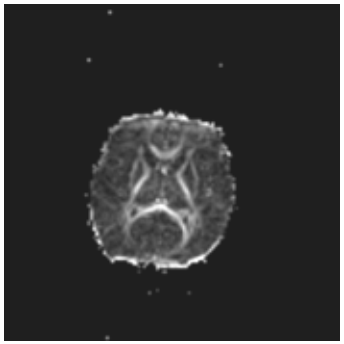
Stephens et al., Submitted

Individual differences in age 10 amygdala volume arise very early in life

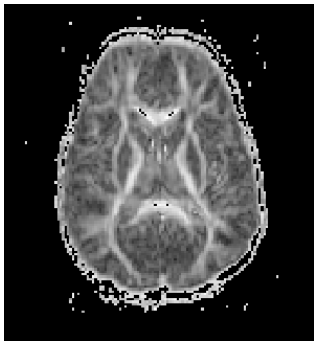


Stephens et al., Submitted

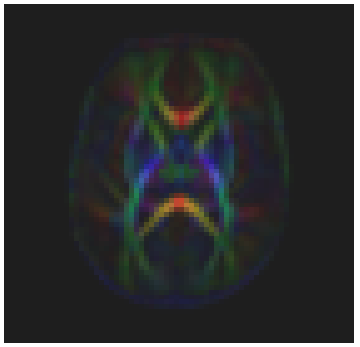
Diffusion Tensor Imaging of White Matter Tracts



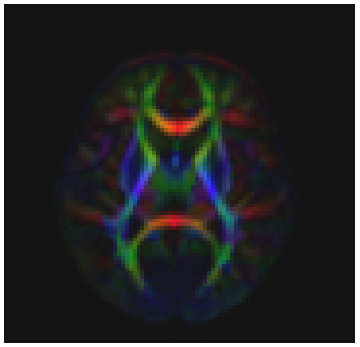
Neonate



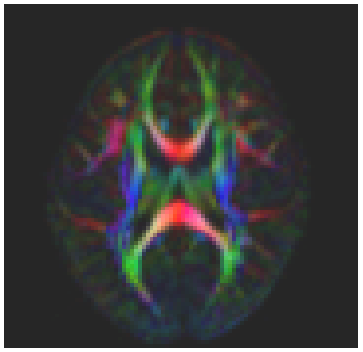
Adult



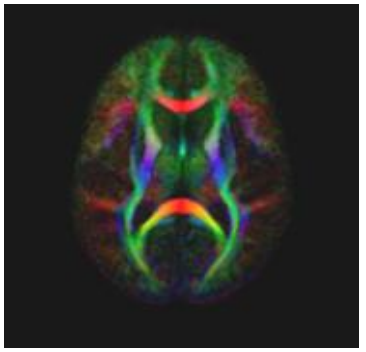
Neonate (N=95)



1 year (N=25)



2 year (N=25)



Adult (N=24)

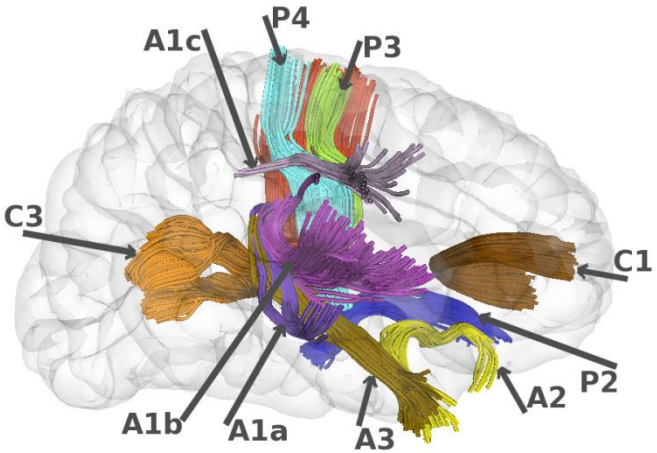
In General: diffusion properties reflects degree of maturation (myelination) and structure of fiber tracts

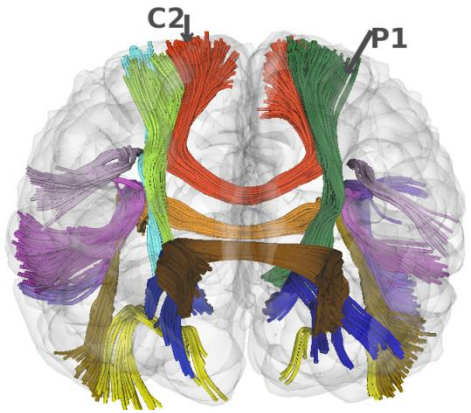
With maturation/organization

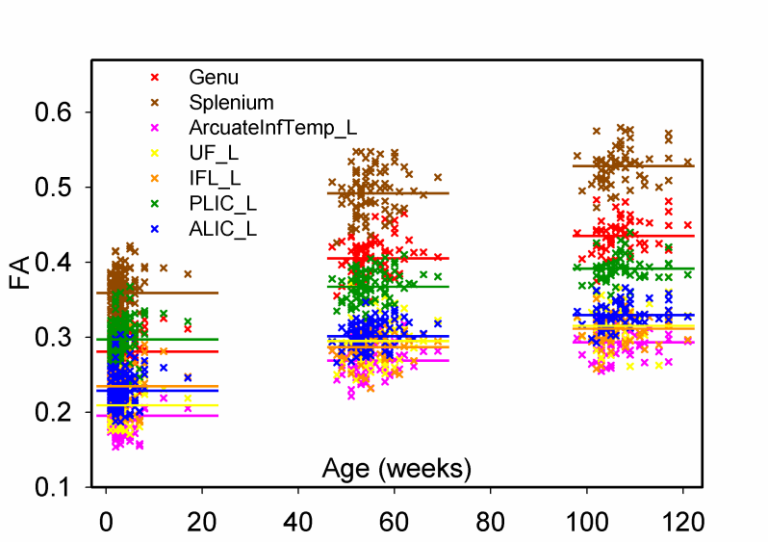
- MD **decreases**
- FA **increases**

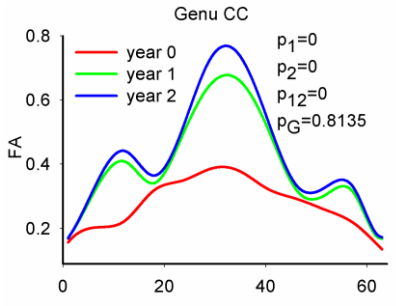
Major white matter reacts are present at birth

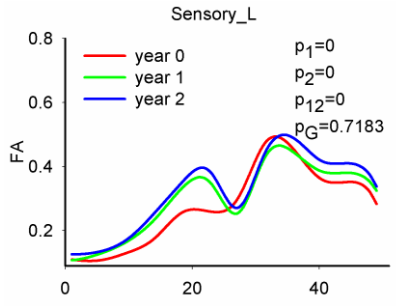
White Matter Tract Development









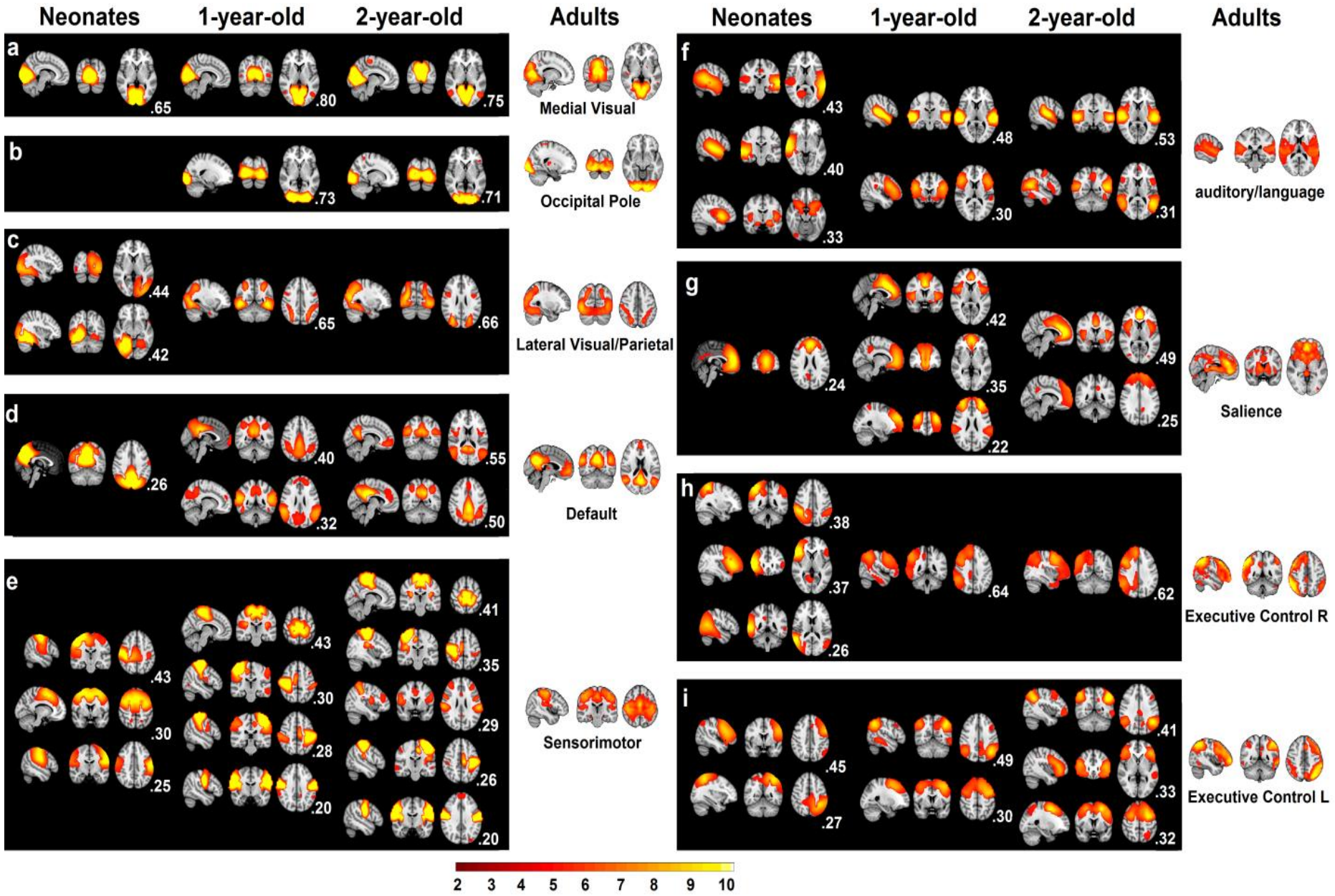


Geng et al., NeuroImage, 2012

Individual differences in white matter microstructure slower to establish

	AD				RD				FA			
	neo	1yr	2yr	4yr	neo	1yr	2yr	4yr	neo	1yr	2yr	4yr
ARCFP-L	.03	.33	.20	**.49**	.16	**.47**	.32	**.56**	.06	**.53**	**.62**	**.74**
ARCFP-R	.16	.09	.21	**.46**	.05	**.43**	**.58**	**.46**	.00	**.44**	**.55**	**.62**
ARCFT-L	.05	.23	.39	**.39**	.21	**.49**	**.73**	**.61**	.21	**.61**	**.81**	**.74**
ARCFT-R	.10	.33	.44	**.34**	.19	**.51**	**.65**	**.51**	.16	**.54**	**.58**	**.60**
ARCTP-L	.02	.31	**.48**	**.46**	.09	**.39**	**.64**	**.63**	.01	**.62**	**.66**	**.65**
ARCTP-R	.03	.12	**.65**	**.50**	.23	**.52**	**.68**	**.42**	.15	**.35**	.47	**.58**
CGC-L	.03	**.36**	.44	**.38**	.19	**.36**	.28	**.44**	.14	**.63**	**.50**	**.48**
CGC-R	.01	**.41**	.43	**.39**	**.32**	**.45**	**.59**	**.45**	.21	**.60**	**.64**	**.50**
CTPF-L	.03	.30	**.60**	**.54**	.12	.35	**.70**	**.75**	.25	**.45**	.35	**.65**
CTPF-R	.10	**.44**	**.46**	**.62**	.11	**.53**	**.65**	**.54**	.20	**.54**	.40	**.41**
Genu	.02	.26	.28	**.39**	.15	**.40**	**.49**	**.43**	.21	**.49**	**.48**	**.54**
IFOF-L	.25	**.50**	**.60**	**.68**	.24	**.52**	**.59**	**.68**	.18	**.59**	**.63**	**.70**
IFOF-R	.11	**.38**	.35	**.54**	.21	**.46**	.19	**.53**	.11	**.44**	.12	**.55**
ILF-L	.27	**.54**	**.72**	**.80**	.24	**.54**	**.63**	**.67**	**.29**	**.58**	**.67**	**.65**
ILF-R	.15	**.53**	**.48**	**.62**	.18	**.55**	.44	**.64**	.11	**.54**	.20	**.48**
SLF-L	.09	.16	.43	**.37**	.14	**.40**	**.63**	**.56**	.04	**.42**	**.61**	**.64**
SLF-R	.15	.20	.43	**.54**	.00	**.57**	**.59**	**.73**	.19	**.68**	.33	**.77**
Splenium	.15	.15	.28	**.51**	.07	.28	**.45**	**.67**	.00	**.35**	.43	**.58**
UNC-L	.07	.31	.26	**.48**	.18	**.40**	**.51**	**.59**	.07	**.55**	**.53**	**.57**
UNC-R	.04	.30	**.56**	**.40**	.20	**.55**	.43	**.63**	.10	**.64**	**.57**	**.61**
Average	.09	.31	.43	.50	.16	.46	.54	.57	.14	.53	.51	.60

Stephens et al., 2020



Gao et al., Brain Struct Funct, 2014

Functional Network Architecture Birth to 2 years

- Primary sensorimotor and medial visual networks are adult-like at birth
- Higher order networks are incomplete and isolated at birth, with rapid increase in connectivity by 1 year
- 2-year-old networks are refined somewhat compared to 1 year, but overall consistent

Summary: Normal Development

- Enormous growth of gray matter in first two years of life, cortical thickness reaches adult-like values by age 1
  - Period of risk for schizophrenia? – cortical thinning
  - Timing of “overgrowth” in autism? – increased surface area
- Major white matter tracts evident at birth
  - less overall growth of volume
  - though rapid maturation of myelin, “organization”
- Resting state functional networks have adult-like form by age 2 years
- White matter connectome is fairly mature by age 1
- Structure-function coupling is also fairly mature by age 1

Early Imaging Biomarkers

- Most psychiatric disorders have origins in early brain development
- Cognitive and behavioral domains also have early childhood precursors
- Can we identify structural or functional predictors or brain biomarkers of risk, cognition, behavior?
- Can we use brain biomarkers to identify “sensitive periods” in early development that can be targeted for early intervention?
- Early childhood biomarkers of risk and sub-optimal outcomes would allow early identification and early intervention that would reduce risk or mitigate severity (Gabrieli et al., 2015; Woo et al., 2017; Sui et al., 2020)

High Risk Brain Development

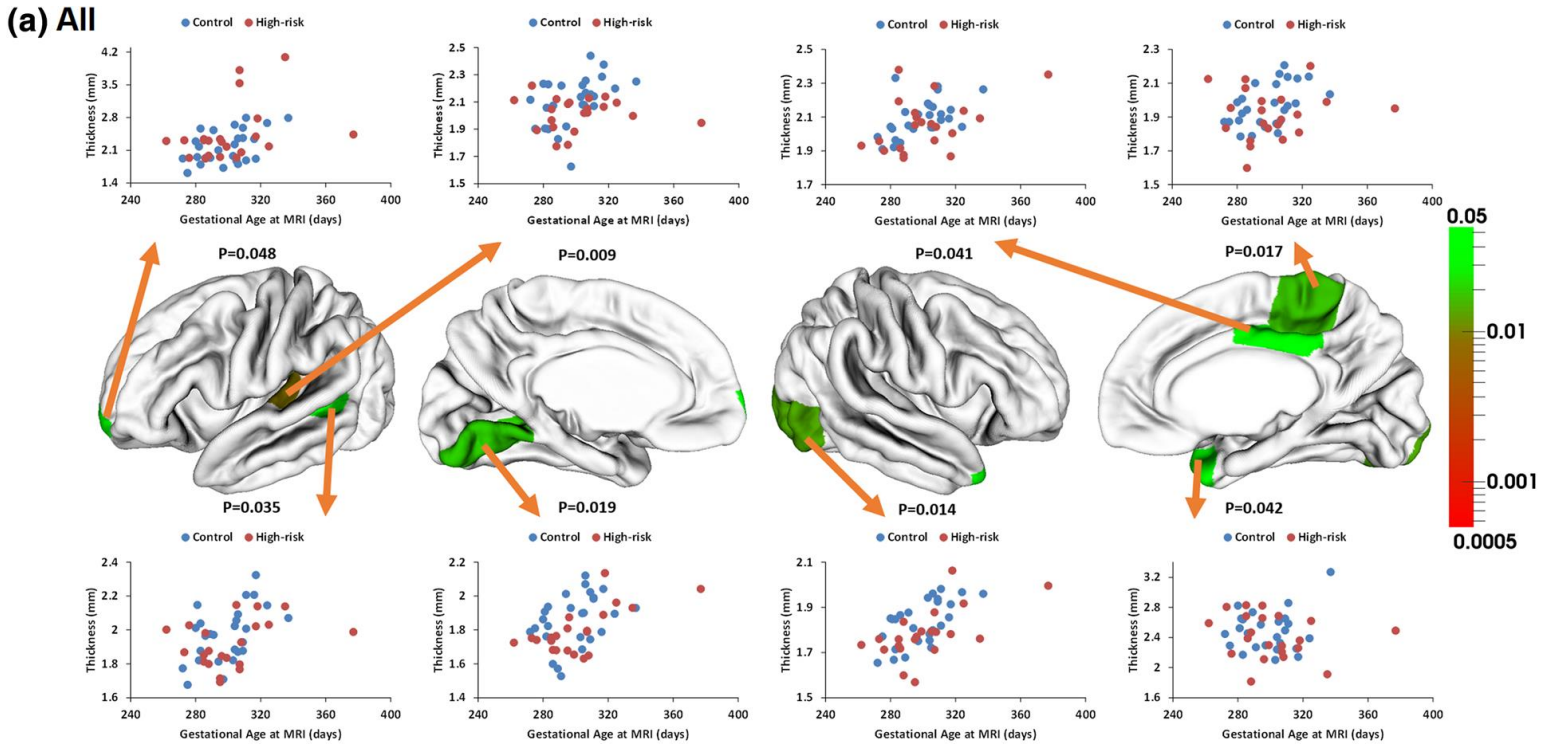
TABLE 4. Brain Volumes of Male and Female Infants at High Genetic Risk for Schizophrenia and Comparison Infants[a]

	Volume (mm^3)							
	Comparison Infants		High-Risk Infants			F Test for Difference		
Gender and Tissue Type	Least Squares Mean	SE	Least Squares Mean	SE	% Difference	F	df	p
Male (N=24)								
Intracranial	497,216	19,111	533,850	19,111	7.4	5.88	1, 11	0.04
Total gray matter	262,836	10,726	276,743	10,726	5.3	6.38	1, 11	0.03
Total unmyelinated white matter	162,379	8,294	178,051	8,294	9.7	2.65	1, 11	0.14
Total myelinated white matter	9,342	1,288	8,687	1,288	–7.0	0.22	1, 11	0.65
Total CSF	62,658	3,438	70,368	3,438	12.3	5.51	1, 11	0.04
Lateral ventricle	4,305	452	5,219	452	21.2	5.11	1, 11	0.05
Cortical gray matter	216,741	9,283	229,592	9,283	5.9	5.55	1, 11	0.04
Cortical white matter	160,887	5,193	166,817	5,193	3.7	1.62	1, 11	0.23
Cerebellum	27,122	1,560	27,897	1,560	2.9	0.54	1, 11	0.48
Female (N=28)								
Intracranial	463,953	17,233	470,249	17,233	1.4	0.10	1, 13	0.76
Total gray matter	238,544	8,079	240,032	8,079	0.6	0.03	1, 13	0.88
Total unmyelinated white matter	158,632	5,801	159,595	5,801	0.6	0.02	1, 13	0.90
Total myelinated white matter	9,561	1,235	10,188	1,235	6.6	0.18	1, 13	0.69
Total CSF	57,216	4,276	60,435	4,276	5.6	0.51	1, 13	0.49
Lateral ventricle	4,063	439	4,151	439	2.2	0.03	1, 13	0.86
Cortical gray matter	197,085	6,765	197,839	6,765	0.4	0.01	1, 13	0.93
Cortical white matter	148,689	5,125	148,928	5,125	0.2	0.00	1, 13	0.97
Cerebellum	24,123	918	24,022	918	–0.4	0.02	1, 13	0.91

[a] Not adjusted for intracranial volume. After adjustment for intracranial volume, all tests were nonsignificant. There were no group differences for intracranial volume or any other tissue volume in the female infants.

Gilmore et al., Am J Psychiatry, 2010

High Risk Brain Development



Neonates – regions of reduced cortical thickness; Not significant after FDR

Li et al., Brain Struct Funct, 2016

High Risk Brain Development

Table 6
Comparison of two general linear models in significant least square mean difference between neonates at high risk for schizophrenia and healthy control. The model 1 was adjusted for gestational age at birth, gender, postnatal age at MRI, and MRI scanner type. Model 2 was adjusted by model 1 covariate plus maternal education. Non-significant tracts are not shown.

	Model 1						Model 1 + maternal education					
	Neonates		One year		Two year		Neonates		One year		Two year	
Tract	V	P-value	V	P-value	V	P-value	V	P-value	V	P-value	V	P-value
Arc_FT_L	FA	0.36	FA	0.03*	FA	0.03*	FA	0.80	FA	0.14	FA	0.36
	AD	0.86	AD	0.08	AD	0.42	AD	0.46	AD	0.13	AD	0.63
	RD	0.43	RD	0.13	RD	0.09	RD	0.83	RD	0.21	RD	0.66
Cing_G_L	FA	0.03*	FA	0.42	FA	0.13	FA	0.02*	FA	0.96	FA	0.06
	AD	0.20	AD	0.25	AD	0.42	AD	0.03*	AD	0.42	AD	0.46
	RD	0.99	RD	0.95	RD	0.22	RD	0.56	RD	0.54	RD	0.11
Cing_H_L	FA	0.05	FA	<0.01**	FA	0.01*	FA	0.22	FA	<0.01**	FA	0.09
	AD	0.13	AD	0.02*	AD	0.30	AD	0.30	AD	0.02*	AD	0.28
	RD	<0.01**	RD	0.17	RD	0.08	RD	0.04*	RD	0.22	RD	0.53
CT_PreF_L	FA	0.53	FA	0.83	FA	<0.01**	FA	0.62	FA	0.56	FA	0.04*
	AD	0.23	AD	0.51	AD	0.92	AD	0.63	AD	0.69	AD	0.91
	RD	0.27	RD	0.80	RD	0.15	RD	0.89	RD	0.79	RD	0.25
SLF_L	FA	0.85	FA	0.67	FA	0.04*	FA	0.80	FA	0.57	FA	0.08
	AD	0.74	AD	0.36	AD	0.69	AD	0.73	AD	0.95	AD	0.89
	RD	0.72	RD	0.36	RD	0.02*	RD	0.77	RD	0.59	RD	0.07
SLF_R	FA	0.51	FA	0.40	FA	0.04*	FA	0.79	FA	0.96	FA	0.19
	AD	0.52	AD	0.87	AD	0.81	AD	0.12	AD	0.70	AD	0.61
	RD	0.69	RD	0.31	RD	0.03*	RD	0.18	RD	0.68	RD	0.12
UCN_R	FA	0.03*	FA	0.48	FA	0.28	FA	0.60	FA	0.63	FA	0.30
	AD	0.25	AD	0.25	AD	0.21	AD	0.74	AD	0.56	AD	0.31
	RD	0.10	RD	0.16	RD	0.07	RD	0.74	RD	0.43	RD	0.04*

V, variable; Arc_FT_L, left arcuate front-temporal fasciculus; Cing_G_L, left cingulate superior segment; Cing_H_L, left cingulate hippocampal segment; CT_PreF_L, left prefronal cortico-thalamic tract; SLF_L, left superior longitudinal fasciculus; SLF_R, right superior longitudinal fasciculus; UNC_R, right uncinated fasciculus. *$p < 0.05$; **$p < 0.01$.

Reduced FA, Higher RD-less organized

Ahn et al., Schiz Res 2019

Cognitive functioning in schizophrenia

- Cognitive abnormalities associated with schizophrenia are evident in very early childhood and tend to progress through childhood and adolescence
- Deviations from normal cognitive and motor developmental trajectories are present very early in childhood (Fish et al., 1992; Hameed et al., 2016; Filatova et al., 2017)
- Children who go on to develop schizophrenia tend to score lower on cognitive testing as early as age 4 years (Mollon et al., 2018)
- There appears to be cognitive decline in late childhood and early adolescence prior to onset of symptoms
- Cognitive function is typically stable after first episode
- May have higher rates of dementia, but many confounding variables (RR 2.3; Cai and Huang, 2018)

Children at Genetic Risk for Schizophrenia

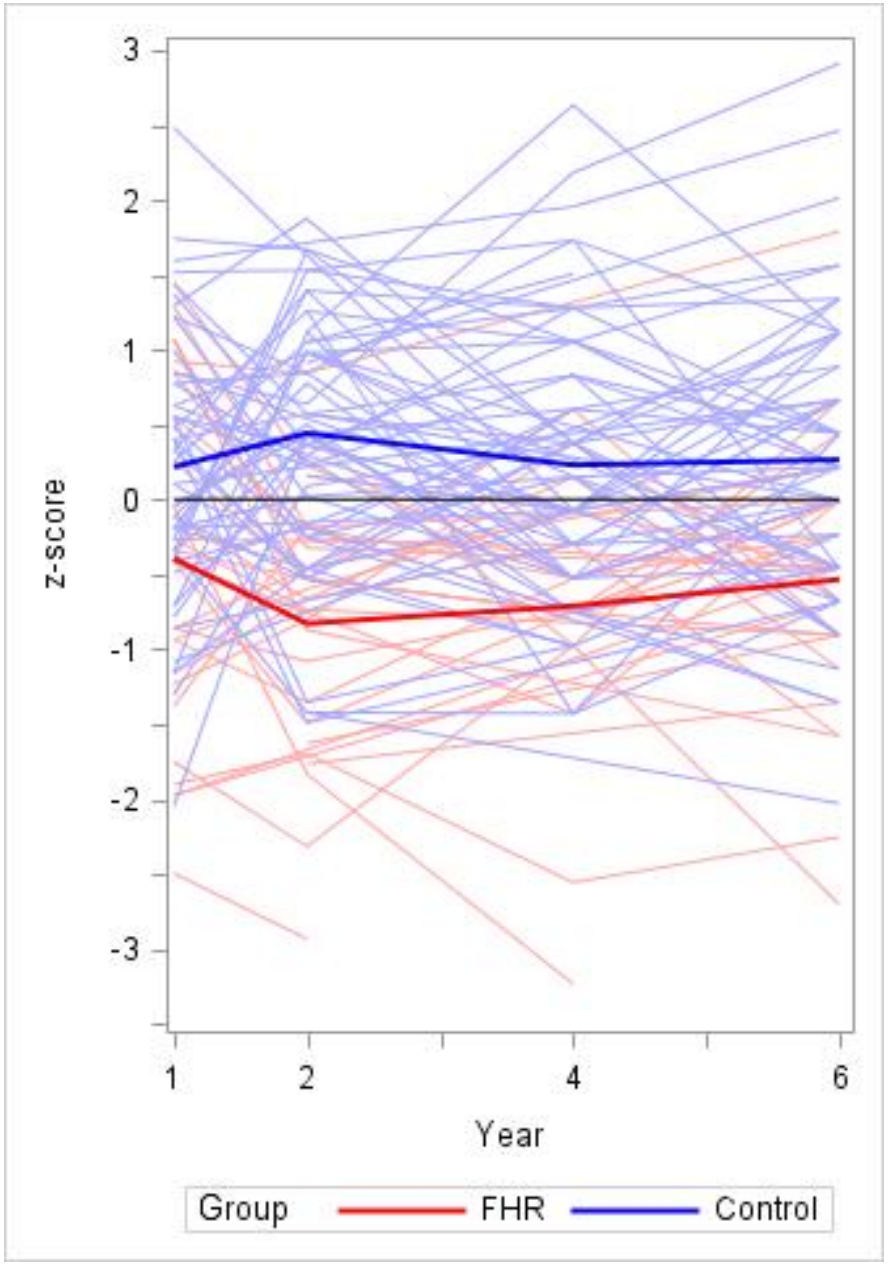
- Subjects:
  - Pregnant mothers with schizophrenia/schizoaffective DO
    - No active substance use
  - Comparison group of mothers with bipolar illness
  - Control mothers with no psychiatric illness
- 3T MRI (Siemens Allegra, TRIO) at birth, 1, and 2 years
- Developmental assessments
  - Mullen Scales of Early Learning
- Multiple assessments at 4 and 6 years targeting executive function, attention problems and anxiety

Stephens et al., Schiz Res 2024

Cognitive Outcomes

Stephens et al., Schiz Res 2024

	High-Risk		Control		
	N	LSM (SE)	N	LSM (SE)	*p*-value
1-year Mullen scores					
Verbal Developmental Quotient	29	101.4 (2.4)	53	107.6 (1.9)	0.063
Nonverbal Developmental Quotient	29	116.7 (2.5)	53	119.7 (1.9)	0.376
Mullen Composite	29	113.5 (2.3)	53	119.1 (1.8)	0.082
2-year Mullen scores					
Verbal Developmental Quotient	29	98.0 (2.6)	54	111.2 (2.0)	**<.001**
Nonverbal Developmental Quotient	30	93.9 (1.9)	55	103.9 (1.4)	**<.001**
Mullen Composite	29	97.5 (2.4)	54	112.7 (1.9)	**<.001**
4-year cognitive scores					
Stanford-Binet					
Abbreviated IQ	21	99.7 (2.8)	55	109.9 (1.8)	**0.005**
Fluid Reasoning	20	104.4 (3.7)	56	114.5 (2.2)	**0.025**
Working Memory	18	97.6 (3.1)	48	115.9 (1.8)	**<.001**
BRIEF-P					
Working Memory	26	65.6 (2.3)	56	51.3 (1.5)	**<.001**
Emerging Metacognition Index	26	63.5 (2.3)	56	50.2 (1.6)	**<.001**
Global Executive Composite	26	60.5 (2.4)	56	48.7 (1.6)	**<.001**
6-year cognitive scores					
Stanford-Binet					
Abbreviated IQ	29	99.9 (2.5)	58	109.2 (1.8)	**0.006**
Fluid Reasoning	28	105.2 (2.6)	58	115.5 (1.8)	**0.003**
Working Memory	12	102.9 (3.9)	43	114.5 (2.0)	**0.013**
BRIEF					
Working Memory	27	60.6 (2.5)	58	50.8 (1.7)	**0.003**
Metacognition Index	26	58.3 (2.0)	57	48.7 (1.3)	**<.001**
Global Executive Composite	26	59.2 (2.0)	57	48.8 (1.4)	**<.001**
CANTAB					
RVP A'	27	0.9 (0.0)	58	0.9	**0.001**
SOC	25	4.4 (0.4)	56	5.6	**0.020**
SSP	28	3.1 (0.2)	57	3.8	**0.004**



Stephens et al., Schiz Res 2024

Psychopathology

	FHR, *n* = 26 LSM (SE)	Control, *n* = 56 LSM (SE)	*p*-value
4-year BASC-2 scores			
Anxiety	53.9 (2.4)	47.1 (1.6)	**0.031**
Depression	50.7 (2.4)	47.9 (1.6)	0.355
Somatization	51.2 (2.5)	46.5 (1.7)	0.155
Atypicality	60.4 (2.1)	49.5 (1.4)	**<.001**
Attention Problems	54.9 (1.9)	49.6 (1.2)	**0.029**
Hyperactivity	58.4 (2.1)	48.8 (1.4)	**<.001**
Withdrawal	51.1 (2.3)	46.4 (1.5)	0.114
Developmental Social Disorders	56.8 (2.0)	46.6 (1.4)	**<.001**
Executive Functioning	55.9 (2.3)	48.5 (1.5)	**0.015**
Externalizing Problems	55.0 (2.1)	48.1 (1.4)	**0.012**
Internalizing Problems	52.6 (2.6)	46.2 (1.7)	0.062
Behavioral Symptoms Index	55.9 (2.1)	47.8 (1.4)	**0.003**
	FHR, *n* = 27 LSM (SE)	Control, *n* = 58 LSM (SE)	*p*-value
6-year BASC-2 scores			
Anxiety	52.2 (2.1)	46.1 (1.4)	**0.025**
Depression	53.3 (1.6)	45.7 (1.1)	**<.001**
Somatization	48.7 (2.1)	45.6 (1.4)	0.257
Atypicality	56.0 (2.0)	47.7 (1.3)	**0.001**
Attention Problems	57.3 (1.9)	47.3 (1.3)	**<.001**
Hyperactivity	57.1 (2.0)	49.0 (1.4)	**0.003**
Withdrawal	52.6 (2.3)	47.4 (1.6)	0.088
Developmental Social Disorders	55.4 (1.9)	45.4 (1.3)	**<.001**
Executive Functioning	55.9 (1.9)	46.6 (1.3)	**<.001**
Externalizing Problems	55.9 (1.8)	47.9 (1.2)	**<.001**
Internalizing Problems	51.8 (1.8)	44.7 (1.3)	**0.004**
Behavioral Symptoms Index	56.2 (1.8)	46.4 (1.2)	**<.001**

Stephens et al., Schiz Res 2024

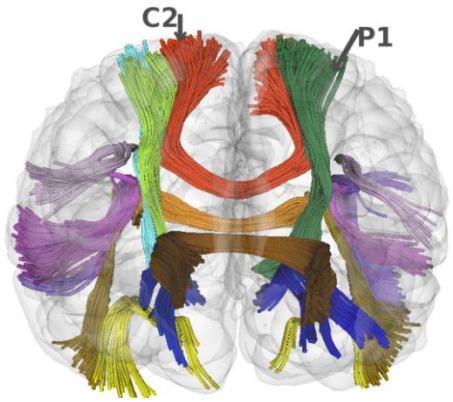
Children at High Risk for Schizophrenia

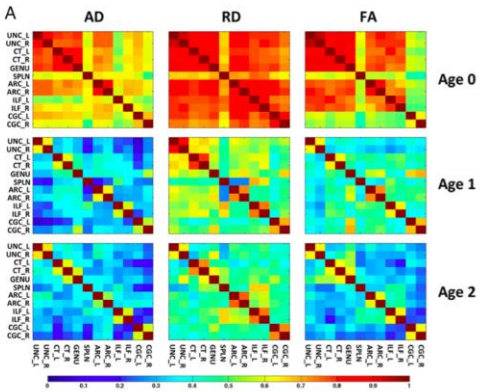
- Significant delays in cognitive development at 1 and 2 years
- Continue to exhibit deficits in IQ and executive function at 4 and 6 years – no clear progression
- Have abnormalities of attention, anxiety and other psychopathology at 4 and 6 years
- Consistent with the early origins of risk for schizophrenia and the complex, heterogeneous relationships between risk and psychiatric disorders

WM Integrity & Cognitive Ability

Common and heritable components of white matter microstructure predict cognitive function at 1 and 2 y

Seung Jae Lee[a,b], Rachel J. Steiner[a], Yang Yu[c], Sarah J. Short[a], Michael C. Neale[d], Martin Andreas Styner[a,e], Hongtu Zhu[f,g], and John H. Gilmore[a,g,1]





- Early white matter properties across tracts are correlated.
- "Global" white matter properties related to future and present cognition at ages 1 and 2 years.

Table 1 Distance correlation coefficients between Mullen ELC and factors of DTI parameters

Age group	DTI value & factor	ELC at age 1		ELC at age 2	
		dCor	FDR-p	dCor	FDR-p
Neonates	FA_F1	0.10	0.446	0.12	0.243
	AD_F1	**0.13**	**0.019**	0.12	0.352
	RD_F1	0.11	0.243	0.12	0.243
1-year-olds	FA_F1	**0.20**	**<0.00001**	0.10	0.710
	AD_F1	0.11	0.446	**0.20**	**<0.00005**
	AD_F2	0.10	0.745	0.09	0.778
	RD_F1	**0.20**	**<0.00001**	0.12	0.446
2-year-olds	FA_F1		–	0.12	0.564
	FA_F2		–	0.12	0.518
	FA_F3		–	0.13	0.446
	AD_F1		–	**0.19**	**0.001**
	AD_F2		–	0.11	0.710
	AD_F3		–	0.16	0.170
	RD_F1		–	0.11	0.628
	RD_F2		–	0.10	0.392
	RD_F3		–	0.13	0.778

FDR-p, false discovery rate *P*-value

Lee et al., PNAS 2017

Amygdala-Anxiety Relationships

Table 8. Partial correlations between amygdala volumes and 10-year anxiety scores – main sample

	Predicting age	Full sample		Girls		Boys	
		n	*r*	*n*	*r*	*n*	*r*
L amygdala	Neonate	84	-.19	46	-.20	38	-.13
	1-year	68	-.11	33	-.07	35	-.20
	2-year	50	-.10	22	.39	28	-.23
	4-year	67	-.01	34	-.08	33	-.04
	6-year	93	.05	46	.14	47	-.06
	8-year	85	.05	42	.18	43	-.05
	10-year	100	-.10	51	.004	49	-.22
R amygdala	Neonate	84	-.12	46	-.07	38	-.19
	1-year	68	-.14	33	-.02	35	-.32
	2-year	50	-.23	22	.19	28	-.34
	4-year	67	.01	34	.12	33	-.14
	6-year	94	-.10	46	.03	48	-.25
	8-year	84	-.09	41	.23	43	-.31*
	10-year	97	-.13	50	-.01	47	-.21

Notes. *$p < .05$; no correlations were statistically significant after FDR correction for multiple comparisons. Covariates include age at MRI, age at 10-year BASC, gestational age at birth, motion score, and sex (for full sample analyses only).

Stephens et al., Submitted

Lessons learned – brain development

- There is rapid maturation of brain structure and its white matter and resting state functional networks in the first year or two of life
- Individual differences in structure and white matter networks are evident at birth and are in place by age 1
- Structural brain development is largely complete and the fundamental architecture of the brain is set up by 1-2 years
- Connectivity - white matter and resting state functional networks - is near adult form
- The stage is set for learning, plasticity and fine tuning of connections

Lessons learned – brain biomarkers

- Modest, inconsistent relationships of brain structure with high-risk status
- Structure/cognition relationships are also modest and inconsistent in early childhood, similar to those found in adults
- Structure/cognition relationships are age dependent in early childhood – state vs trait
- Structure/psychopathology relationships are also modest and inconsistent
- Not clinically informative

The challenge of complexity

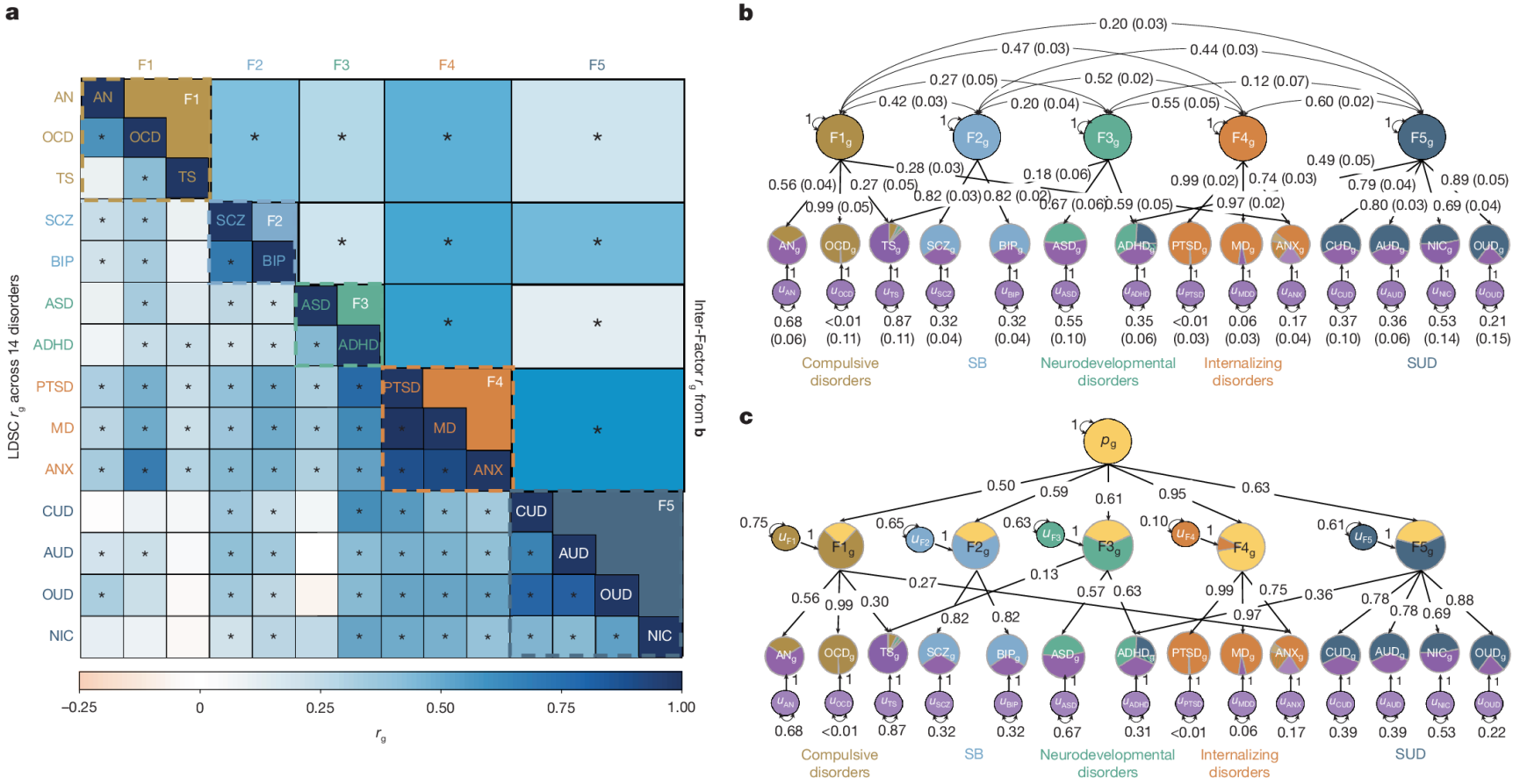
- Schizophrenia and other psychiatric disorders are very heterogeneous and complex – difficult to study using genetics and imaging
- Co-morbidity
- Non-specificity of risk genes
- Non-specificity of imaging phenotypes

Co-morbidity in Schizophrenia

- Depression - 50%
- Posttraumatic stress disorder - 29%
- Obsessive-compulsive disorder – 23%
- Panic disorder 15%
- Substance abuse 47%

Buckley et al., 2009, Schiz Bull

Shared genetic risk across psychiatric disorders



Grotzinger et al., Nature 2026

Pre-clinical lessons

Neuron
Report

Genetic Background Limits Generalizability of Genotype-Phenotype Relationships

Laura J. Sittig,[1,2] Peter Carbonetto,[1] Kyle A. Engel,[1] Kathleen S. Krauss,[1] Camila M. Barrios-Camacho,[1] and Abraham A. Palmer[1,2,3,*]
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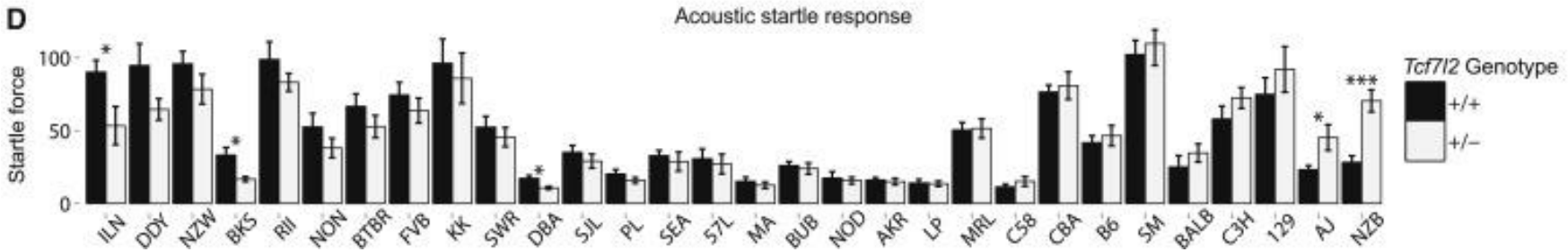
http://dx.doi.org/10.1016/j.neuron.2016.08.013

TCF7L2 – diabetes, schizophrenia, bipolar illness



Sittig et al., Neuron 2016

Epistasis dominates the genetic architecture of *Drosophila* quantitative traits

2012

Wen Huang[a], Stephen Richards[b], Mary Anna Carbone[a], Dianhui Zhu[b], Robert R. H. Anholt[c], Julien F. Ayroles[a,1], Laura Duncan[a], Katherine W. Jordan[a], Faye Lawrence[a], Michael M. Magwire[a], Crystal B. Warner[b,2], Kerstin Blankenburg[b], Yi Han[b], Mehwish Javaid[b], Joy Jayaseelan[b], Shalini N. Jhangiani[b], Donna Muzny[b], Fiona Ongeri[b], Lora Perales[b], Yuan-Qing Wu[b,3], Yiqing Zhang[b], Xiaoyan Zou[b], Eric A. Stone[a], Richard A. Gibbs[b], and Trudy F. C. Mackay[a,4]

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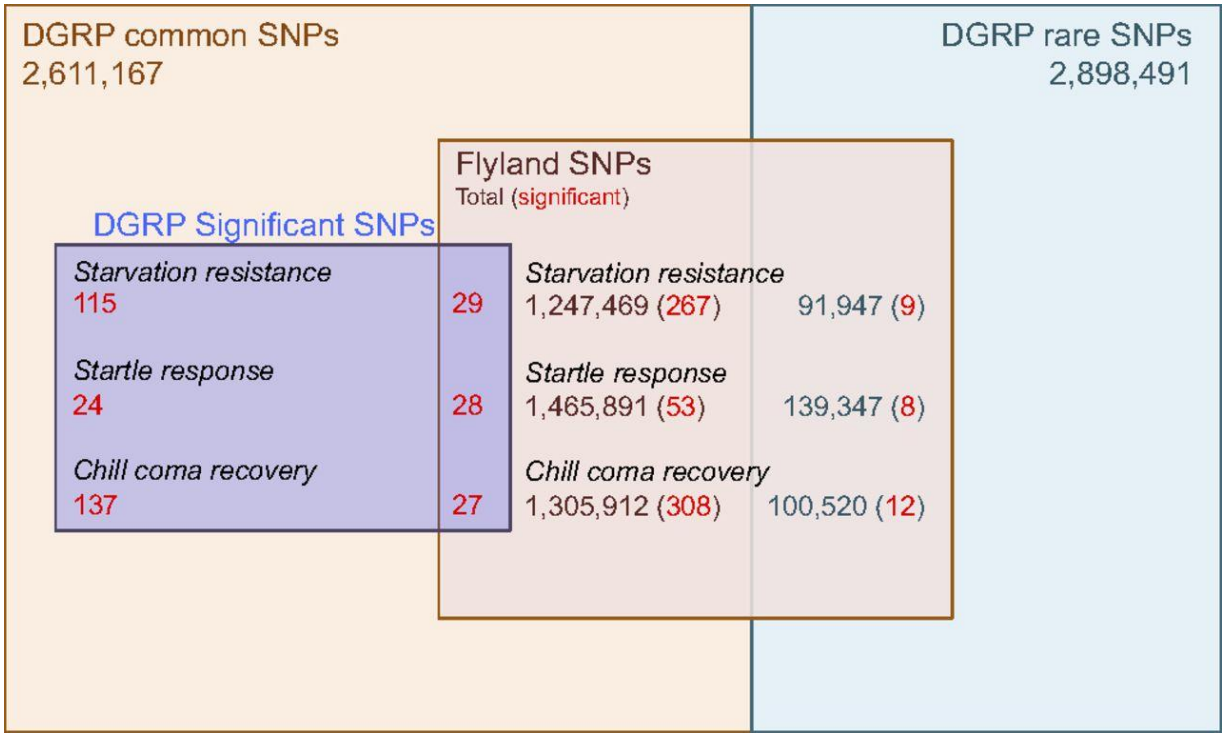


No overlap between significant SNPs in Flyland and the DGRP. Numbers of SNPs overlapping between different categories of SNPs are shown in boxes. Numbers within each box are for SNPs in the corresponding category. SNPs belonging to multiple categories are indicated by overlaps between boxes.

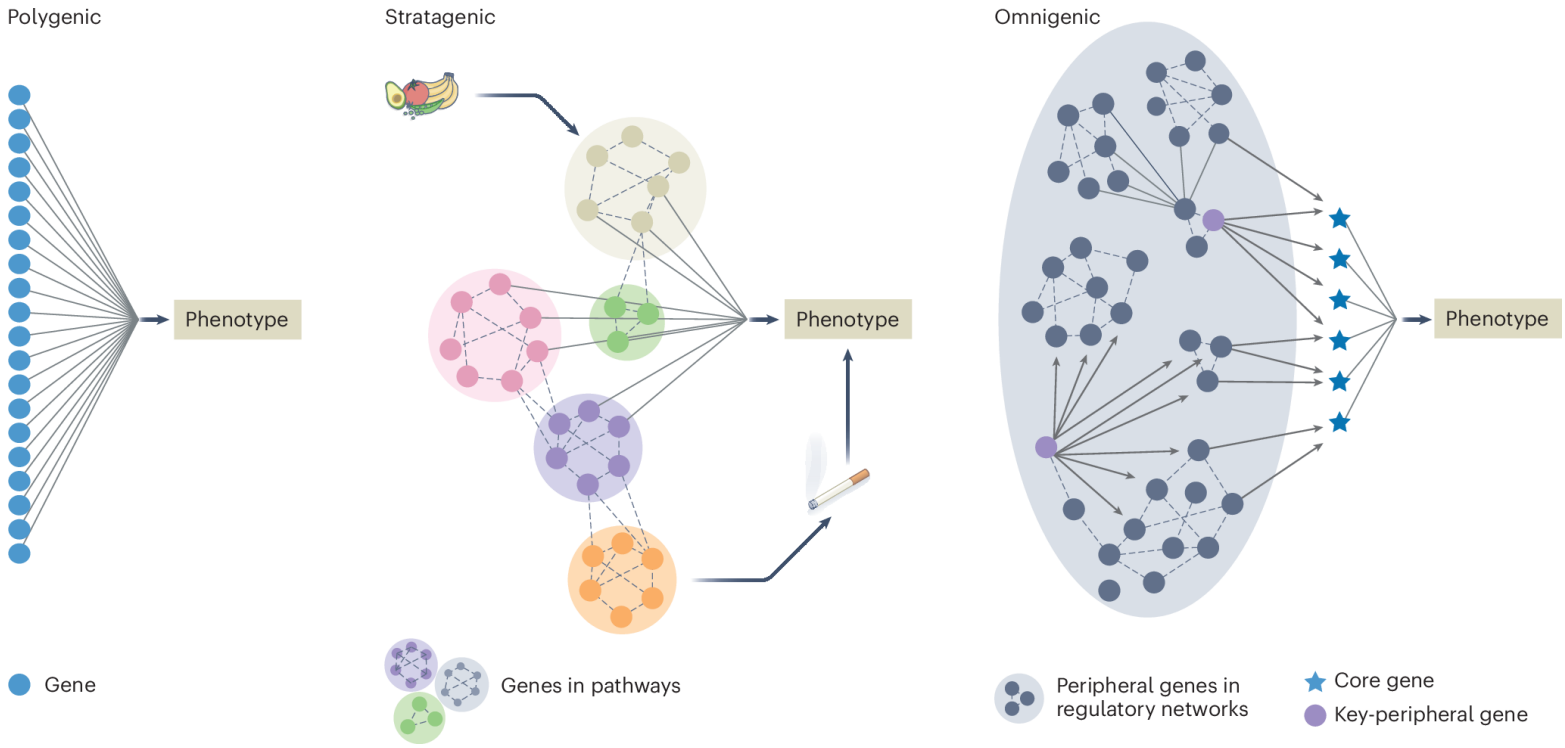
Hidden in plan view: degeneracy in complex systems

Mason et al., BioSystems 2015

- **Degeneracy** – dissimilar gene networks or structures that are functionally similar
- Causality is diverse and distributed
- Different from the scientific view that dominated imaging and genetic studies of schizophrenia

The polygenic, omnigenic and stratagenic models of complex disease risk

Garcia-Gonzales & O'Reilly, Nat Genetics 2026



Common Brain Substrates of Psychiatric Disorders

- Emerging studies indicate that psychiatric disorders share many imaging phenotypes
- Transdiagnostic brain mapping in developmental disorders
  - Siugzdaite et al., Current Biology 2020
- A shared neural basis underlying psychiatric co-morbidity
  - Xie et al., Nat Medicine 2023
- Regional, circuit and network heterogeneity of brain abnormalities in psychiatric disorders
  - Segal et al., Nat Neurosci 2023

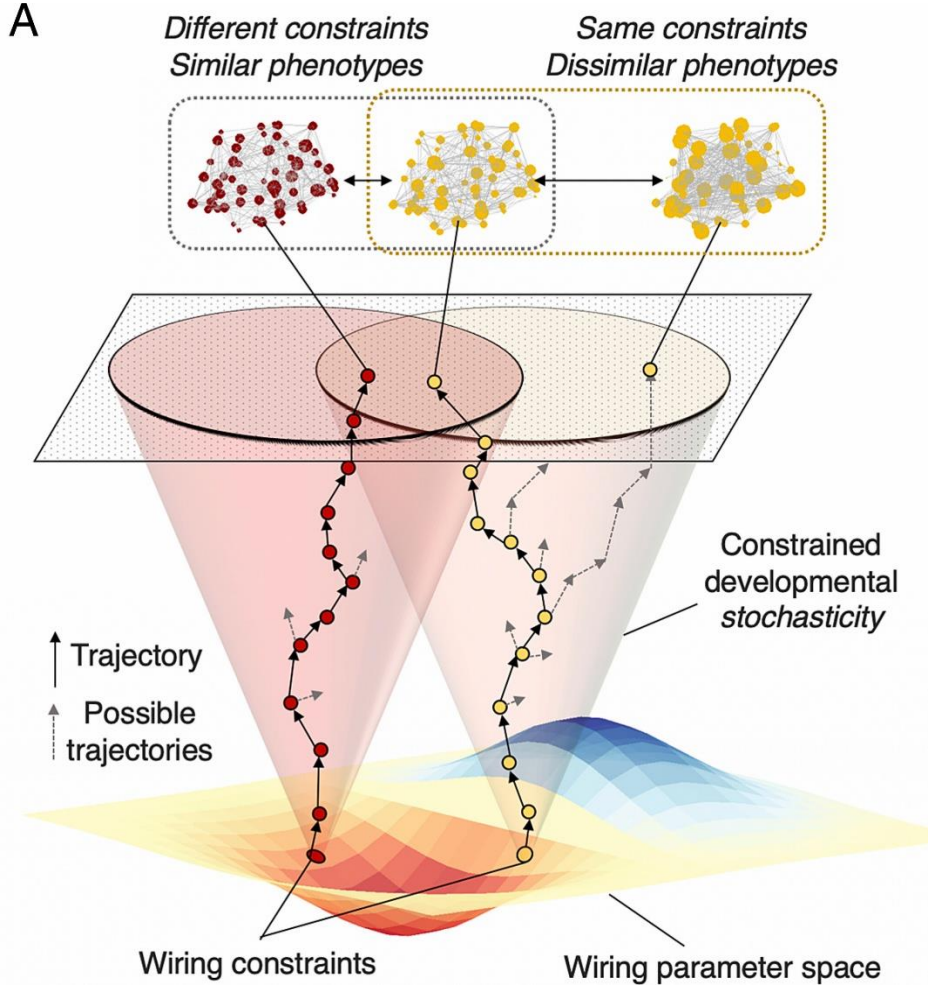
Stochasticity

- Brain development is **probabilistic**, not deterministic
  - Randomness or noise
  - Phenotypes that cannot be predicted by measurable variables
- Stochastic processes occur at multiple levels
  - Transcription and translation of proteins
  - Protein-protein interactions-i.e. receptors, cell adhesion molecules
  - Axon/dendrite growth and synapse formation (neuronal filapodia)
  - Neuronal firing and synaptic transmission

PNAS RESEARCH ARTICLE | DEVELOPMENTAL BIOLOGY OPEN ACCESS

The adaptive stochasticity hypothesis: Modeling equifinality, multifinality, and adaptation to adversity

Sofia Carozza[a,b,c,1], Danyal Akarca[a,1], and Duncan Astle[a,d]



- Modeled white matter network development based on childhood MRIs
- Children from low SES family (high stress) showed higher stochasticity in network development
- More stochasticity in the setting of environmental stressors allows more adaptive/resilient phenotypes to emerge

Carozza et al., PNAS 2023

The challenge of complexity

- Have entered a post-imaging, post-genomic era of psychiatric research
- Individuals are unique; do patients have unique forms of psychiatric illness?
  - Some shared risk factors and to illness
- Implications for Precision Psychiatry

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