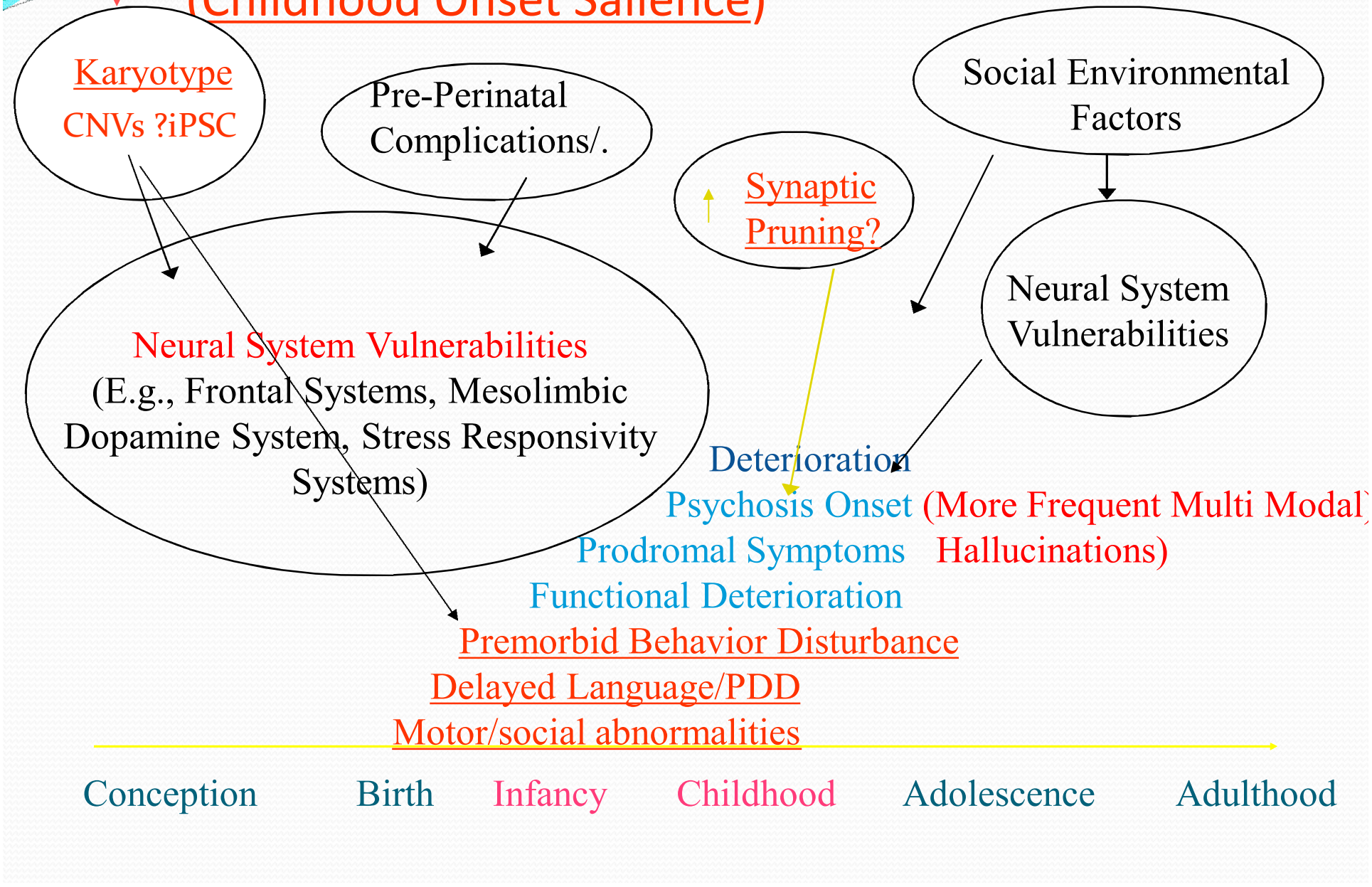
Childhood Onset Schizophrenia: Rare but worth studying

Brain & Behavior Research Foundation Webinar, September 9, 2013

Judith L. Rapoport MD

NIMH, Bethesda MD

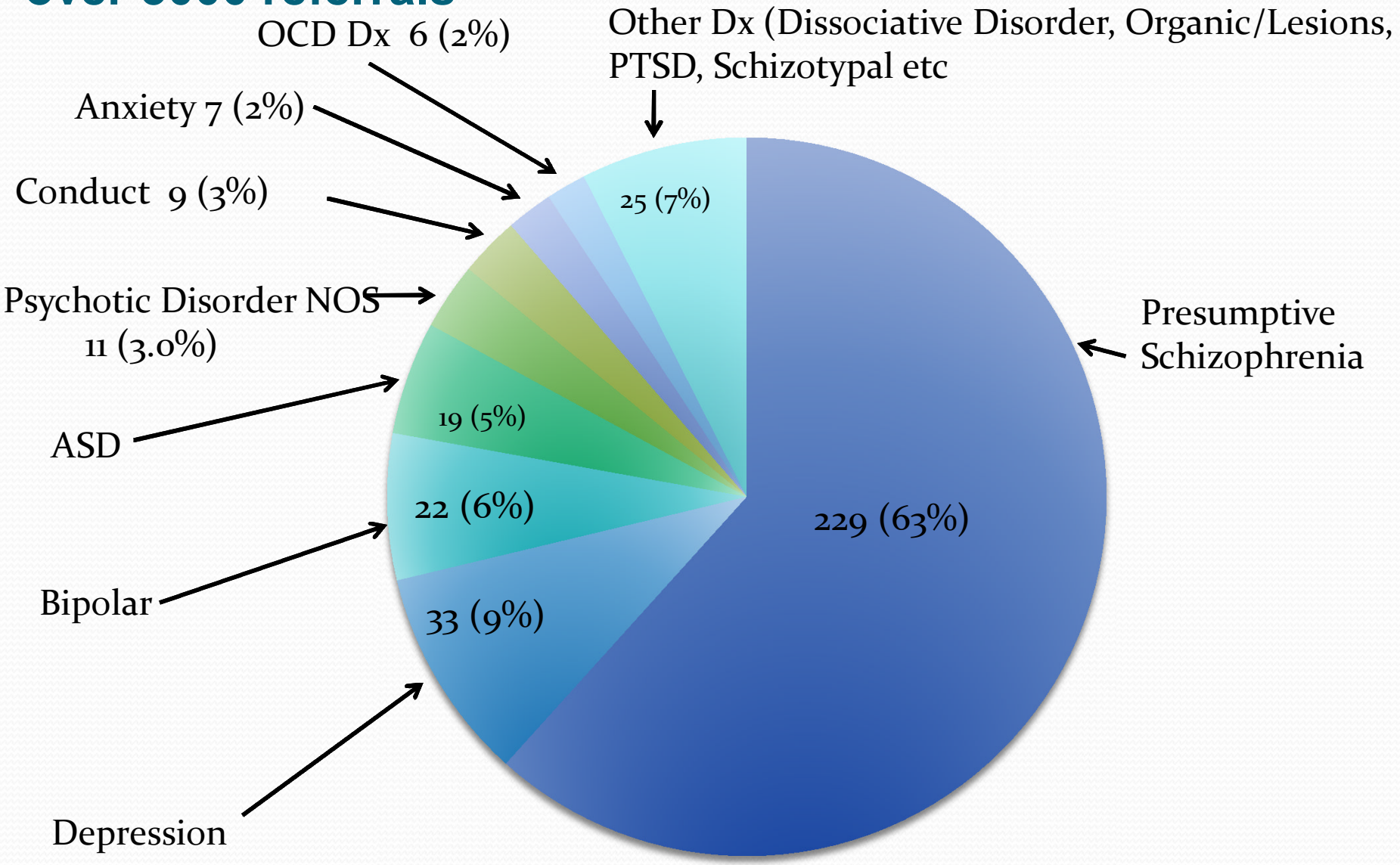
Schizophrenia:Theoretical Framework (Childhood Onset Salience)



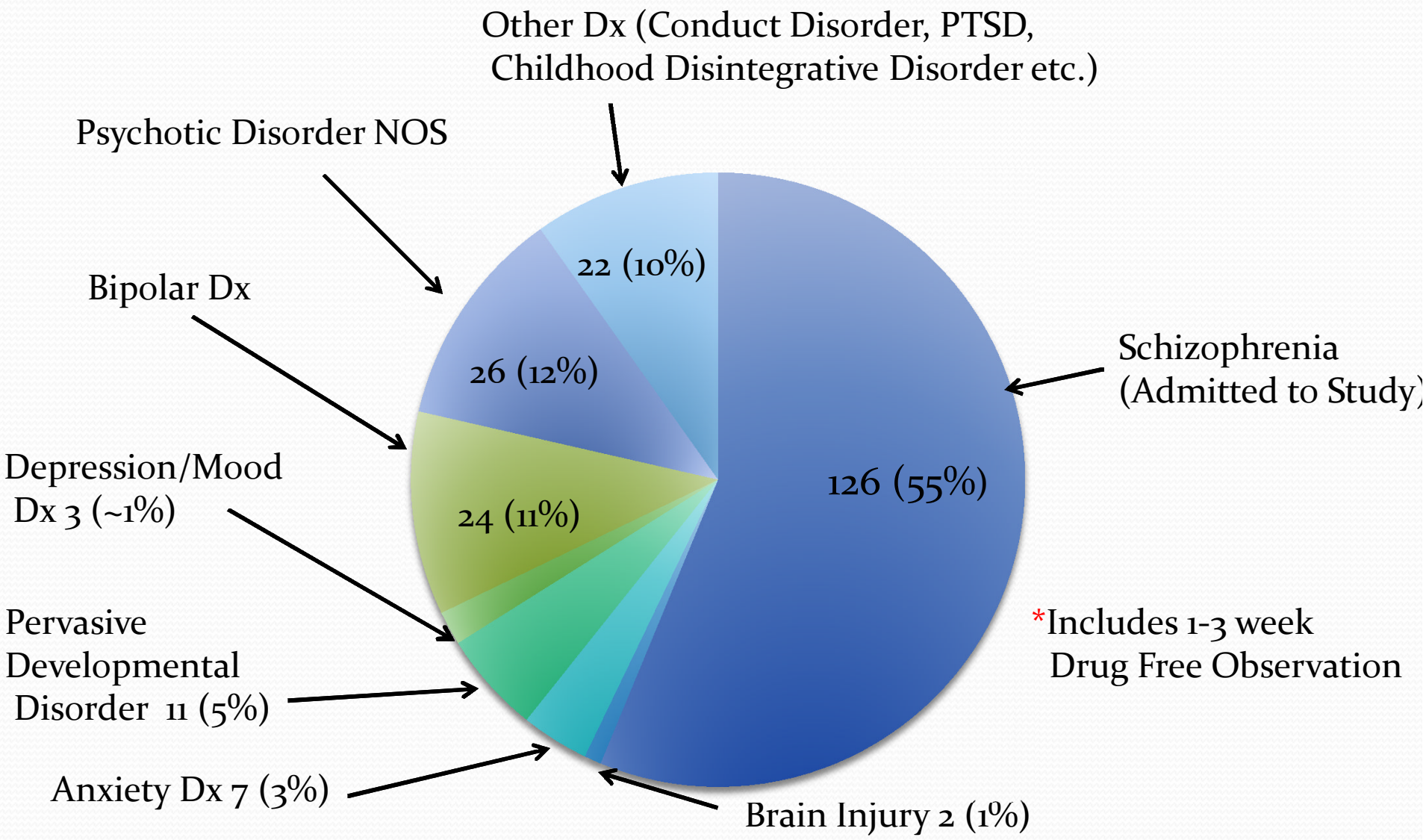
Childhood Onset Schizophrenia

- Defined as Onset before 13
- Very rare – but over diagnosed in children
- Observation off medication important for diagnosis
- NIMH study has been ongoing since 1990
- Early onset illness has been helpful in understanding genetics and biology of many disorders (e.g. breast cancer, Alzheimers) throughout medicine

Over-diagnosis of Childhood-Onset Schizophrenia: Primary Diagnosis after initial Two-day Out-Patient Screenings (N = 361) national recruiting – selected from over 3000 referrals

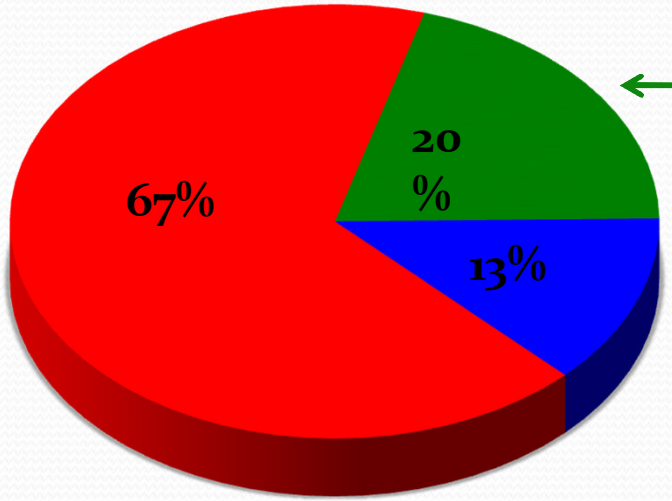


Childhood-Onset Schizophrenia:
Discharge Diagnosis after 228 In-Patient Admissions*



High Rates of Pre- Psychotic Neurodevelopmental Impairment for Childhood Onset Schizophrenia Probands (January, 2013)

Pervasive Developmental Disorder (PDD) ←



Educational, language, social, and/or motor difficulties →

No Earlier Developmental Impairments

Genetic/familial risk? Not a high rate of sibling neurodevelopmental impairment
Model: our patients have some higher rare genetic risk and lack protective factors.

Previous clinical studies

Risk: no strong indication of:

- Obstetrical risk (obstetrical record comparison vs. siblings)
- Early puberty
- Paternal age
- Season of birth
- Trauma
- Sibling neurodevelopmental impairment

Continuity with AOS

- Unmodified DSM IV Diagnosis
- Neuropsychological Profile
- Skin conductance
- SPEM (eye movements)
- Anatomic brain MRI (increased ventricular and decreased hippocampal volumes)

Treatment

- Double blind superiority of clozapine vs haloperidol
- Double blind superiority of clozapine vs olanzapine
- Safety study of TDCS

Ongoing Clinical Studies

TDCS
(transcranial direct current stimulation)

- Double blind, (sham control), parallel design
- New very small brain stimulator (can be carried in pocket)
- Testing for treatment of cognitive deficits and for psychotic symptoms

Intranasal Oxytocin

- Double blind study with measures of social interaction

Has been shown to increase social interaction in autism

- Pre-post Imaging with resting fMRI, MEG and emotional task

Brain Imaging Studies of COS

Healthy Children

- We first establish the first "norms" for MRI measures of human brain development
- Studied children prospectively throughout childhood and adolescence

Childhood Schizophrenia Patients

- Childhood onset patients lost brain tissue during adolescence
- Their healthy siblings showed some early brain abnormalities that improved with age!

Time Course of Critical Events in the Determination of Human Brain Morphometry

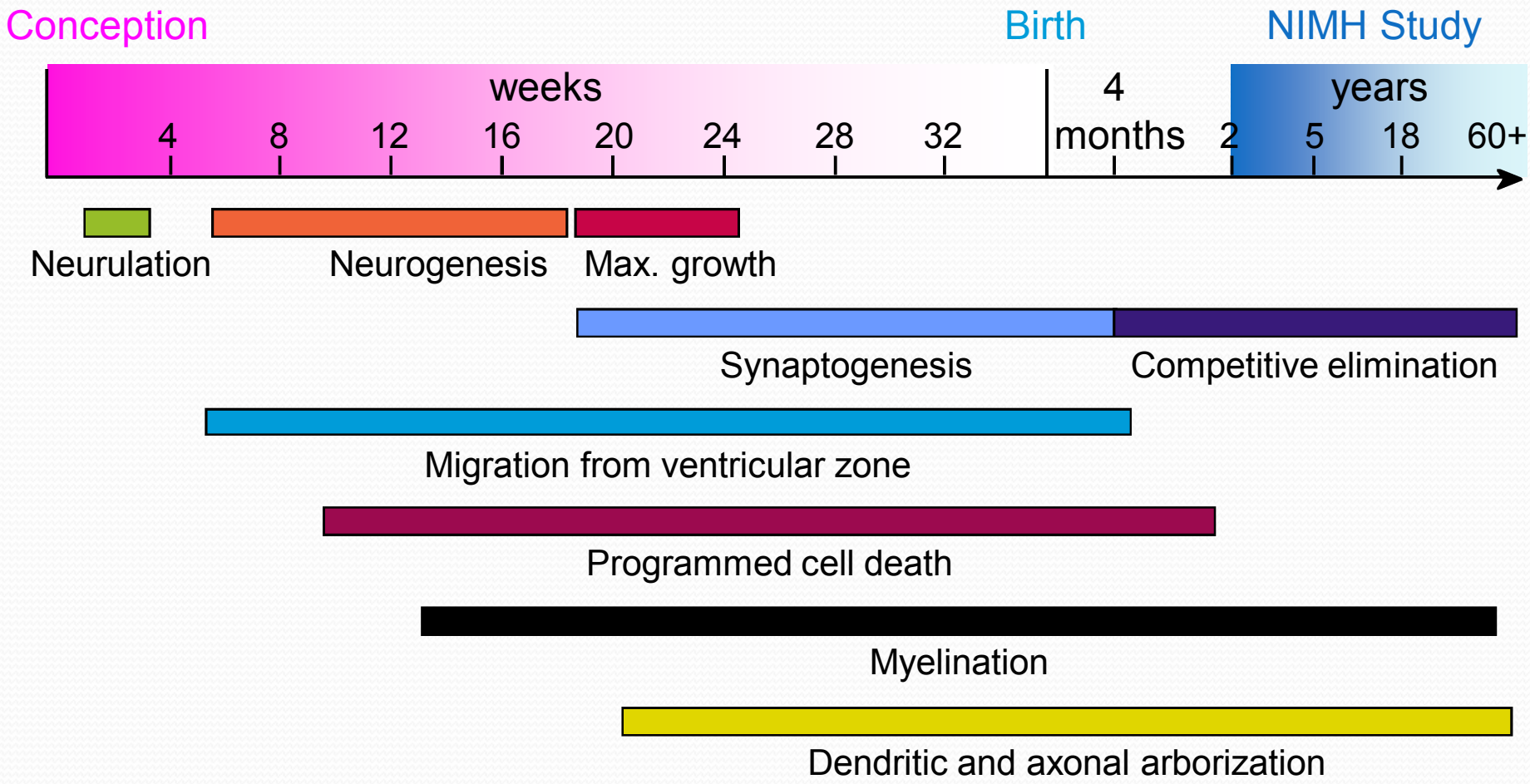
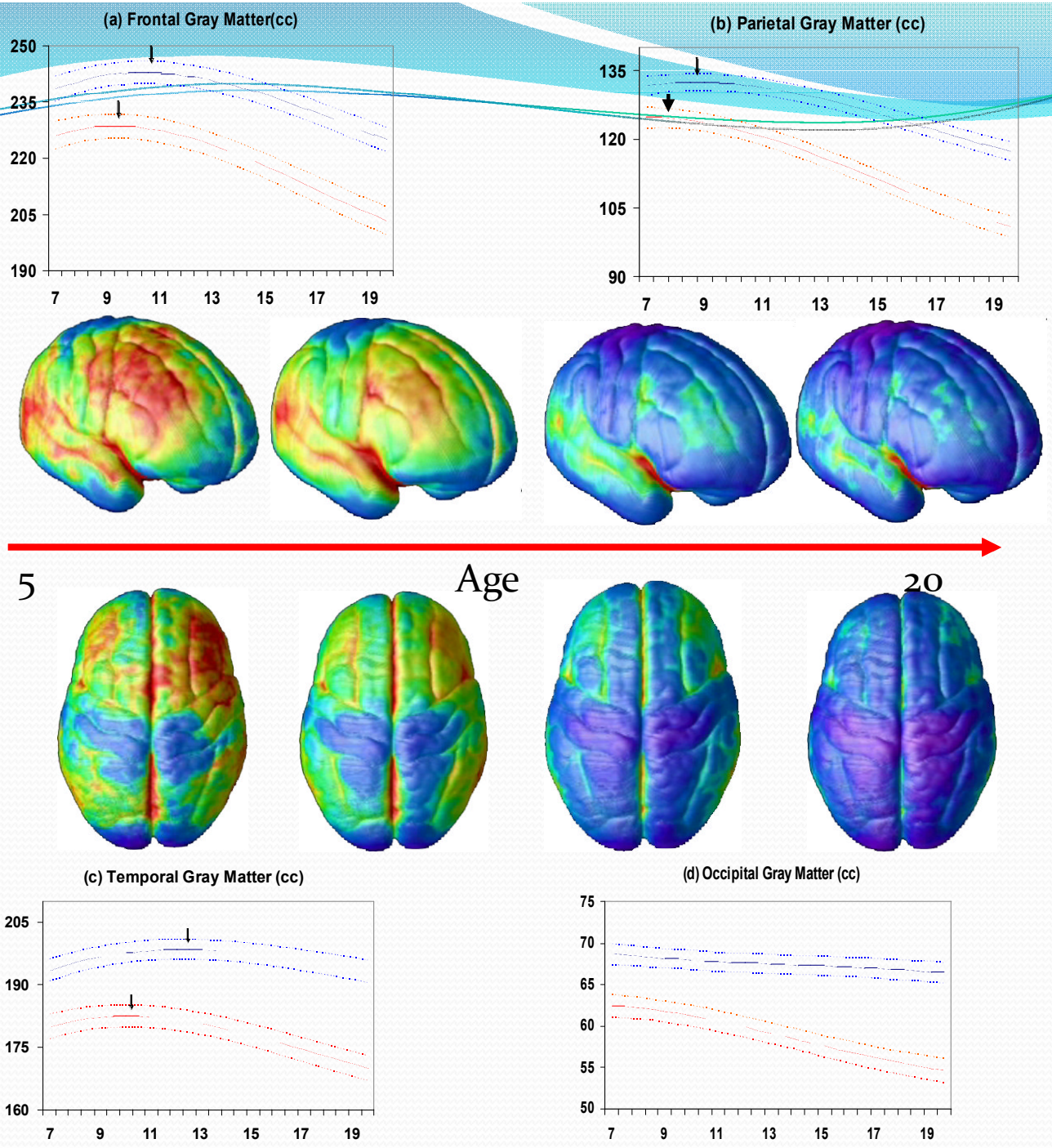
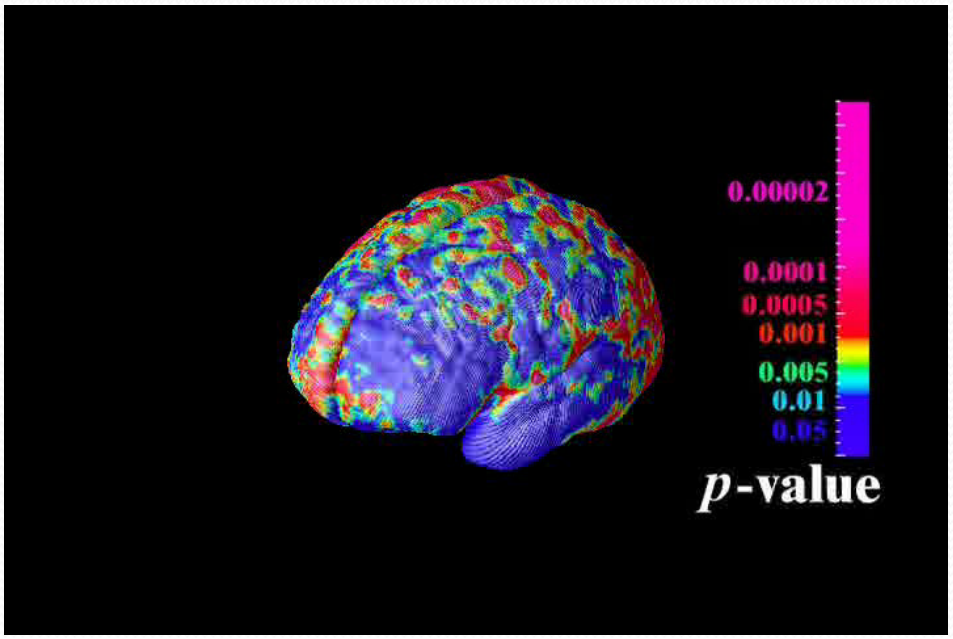


Figure 1



Adapted from Gogtay et al. 2004 Giedd et al. 1999

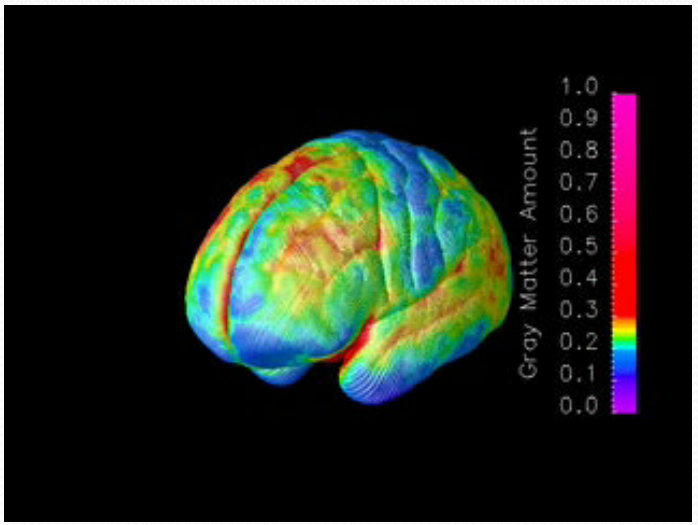
COS Brain Development
Age 12-16



COS n=12 Vs Controls n=12; 3 scans each
Age, sex and scan interval matched.

Thompson et al.
PNAS 2001

Normal Brain Development
Age 4-22

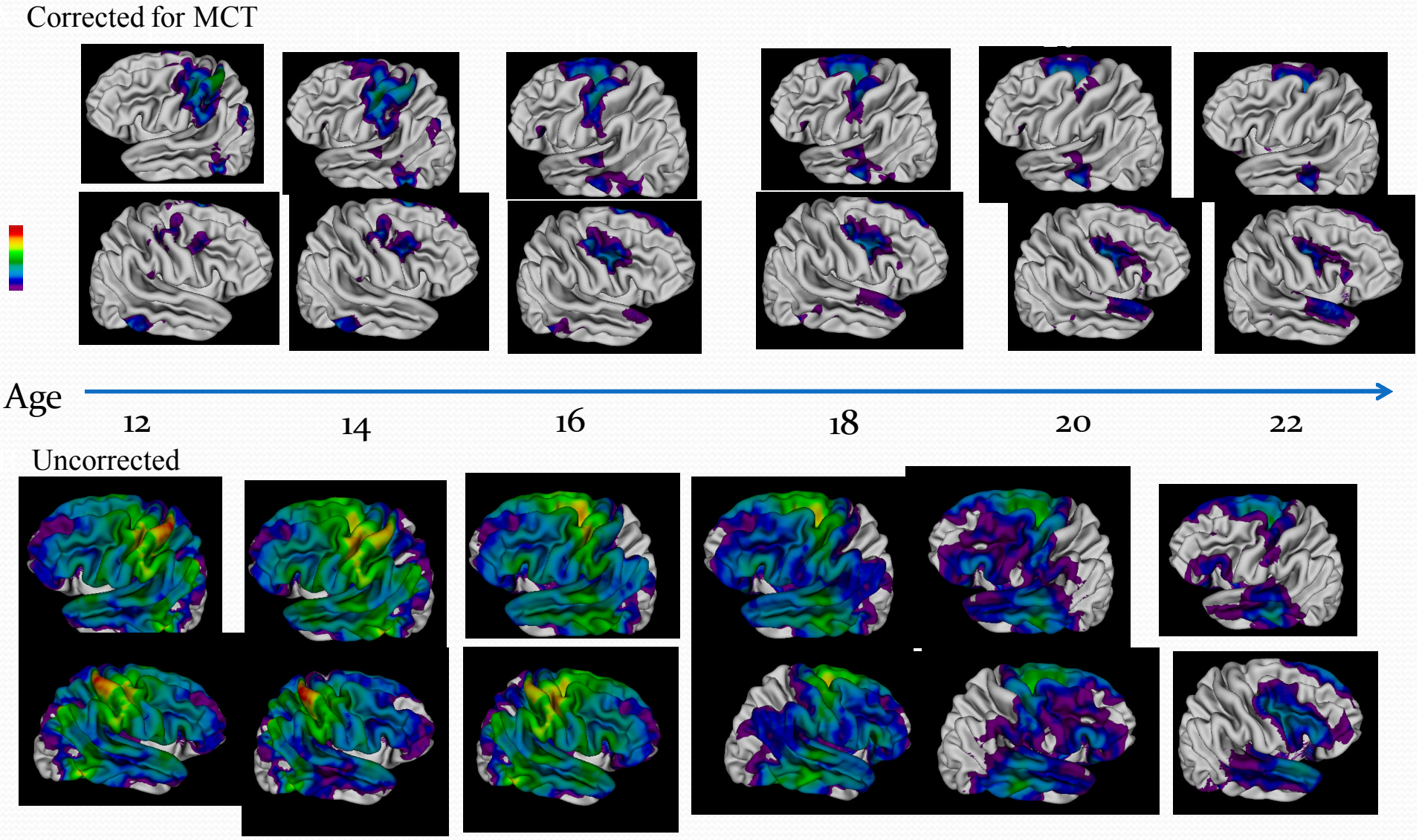


n=13; 51 scans

Gogtay et al. PNAS
2004
COS HAS
EXAGGERATION OF
NORMAL PATTERN
PF CORTICAL
DEVELOPMENT

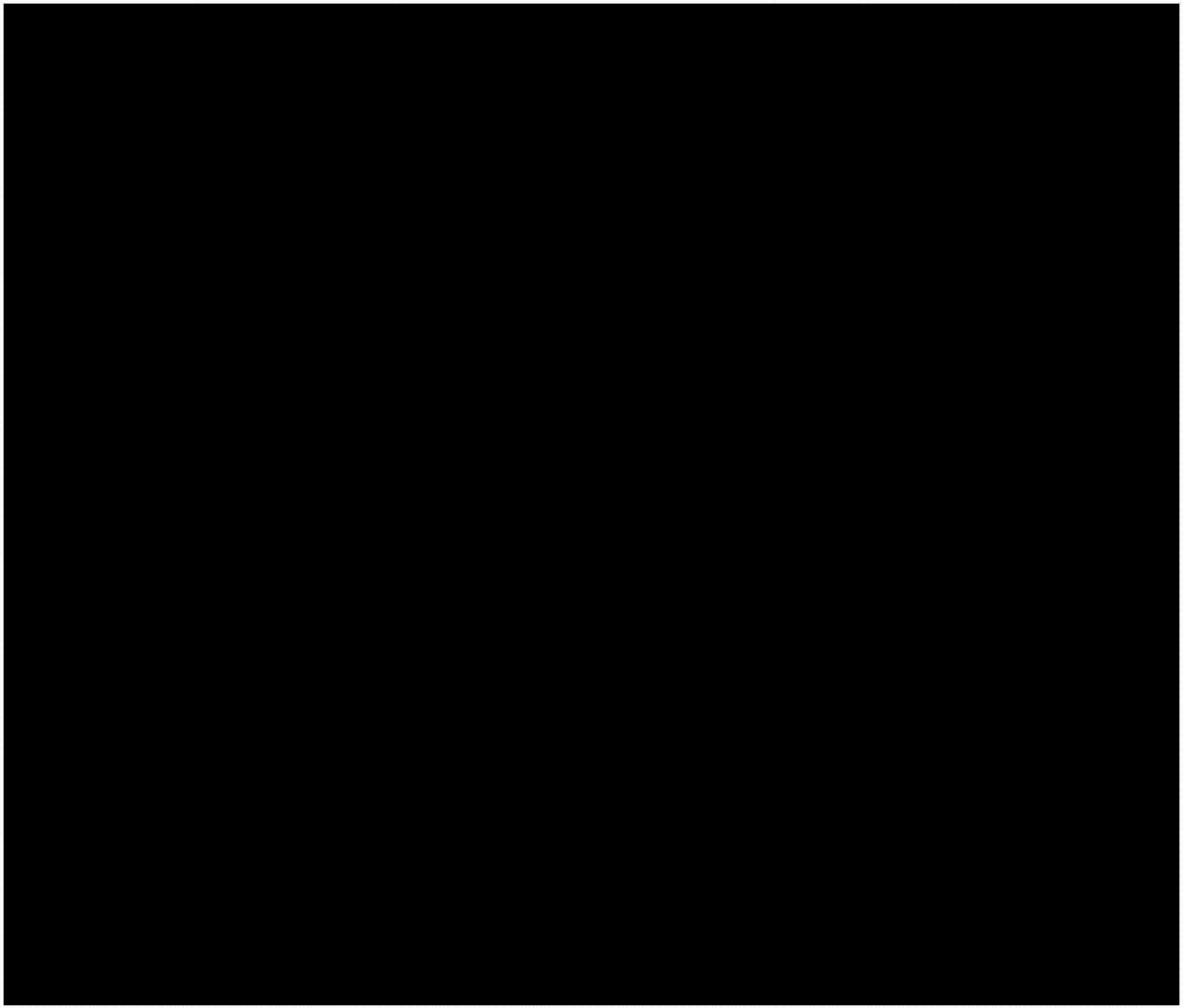
Relative Cortical Thinning Becomes Circumscribed with Age for COS Probands

Previous General Pattern Holds with Extended Sample (COS N= 85, 177scans; NV N= 86,185 scans) and later version of MNI pipeline (CLASP)



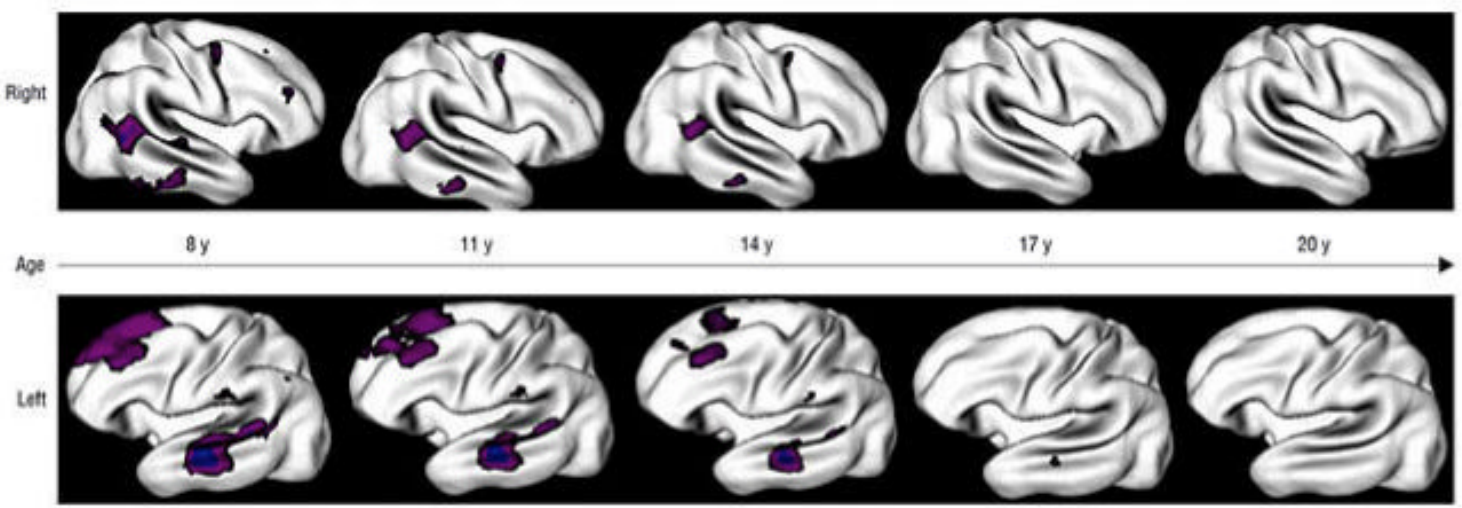
Relative cortical GM thinning in Childhood Onset Schizophrenia (COS) becomes more circumscibed across age 8-24:

COS (n=104, 222 scans) Vs Controls (n=104, 233 scans)]

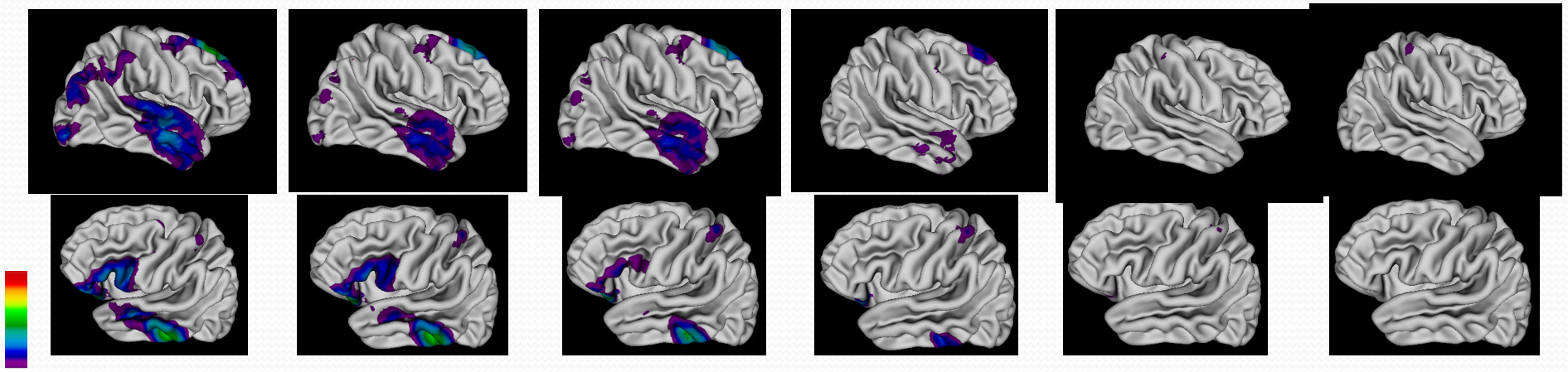


Cortical Brain Development in **Non-Psychotic Full Sibs** of COS Probands

A) Normalizing in healthy sibs (n=52 ; 113scans) v Controls (n= 52; 108 scans) (Gogtay et al Arch Gen Psych 2007)



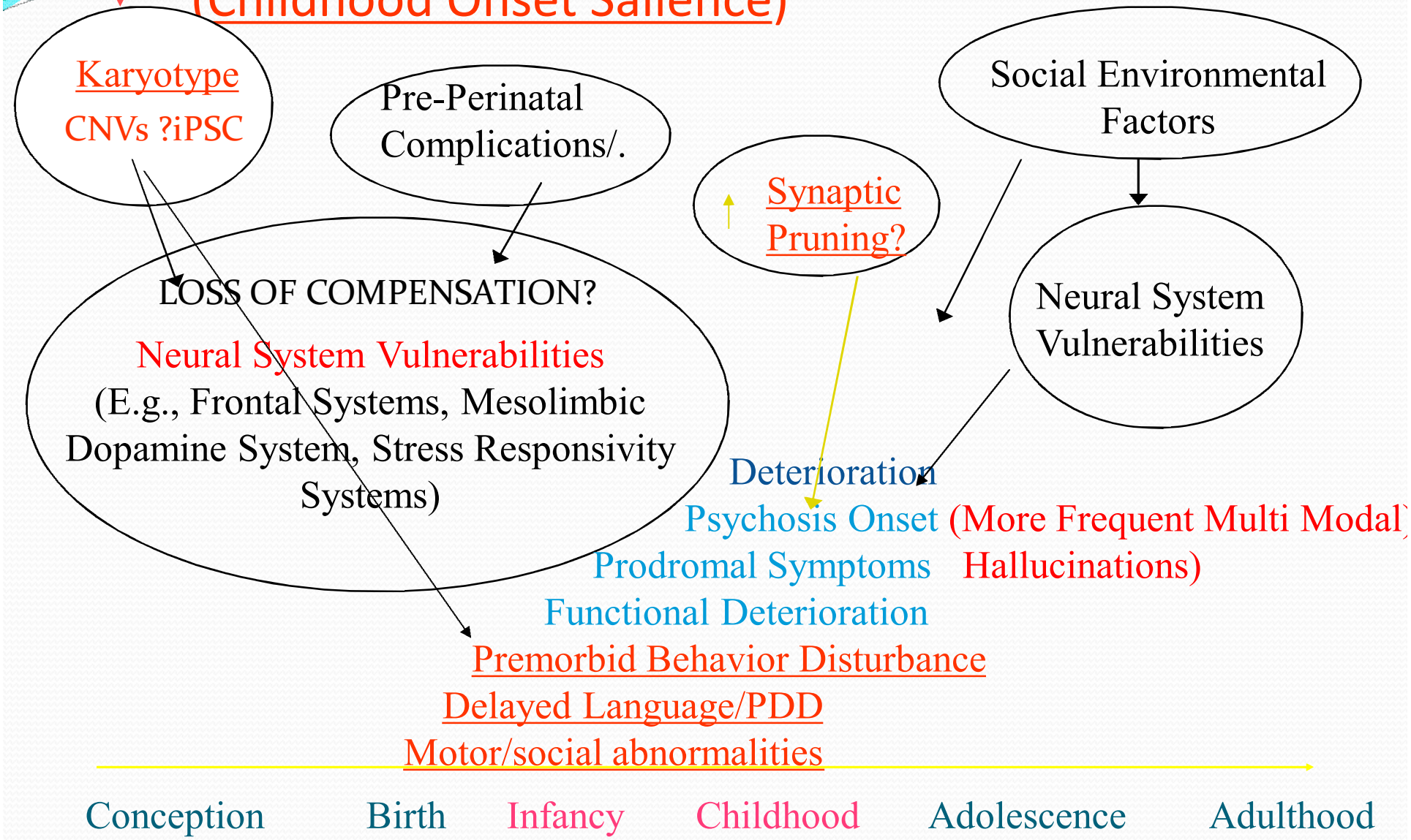
B.BReplication with non-overlapping healthy sibs (sib n= 38; 47 scans) vs. (Controls n=80; 182 scans) Mattai et al 2011) Gogtay, 2009



Relative GM thinning in Healthy COS Siblings (combined sample)

Healthy Siblings (n=91, 185 scans) Vs Controls (n=92, 193 scans)

Schizophrenia:Theoretical Framework (Childhood Onset Salience)

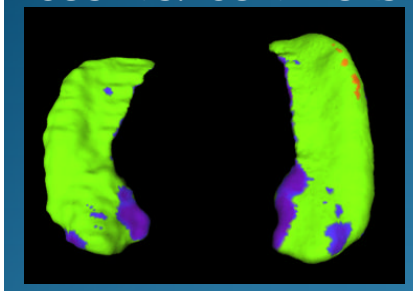


HIPPOCAMPAL VOLUME :FIXED, STATE RELATED:

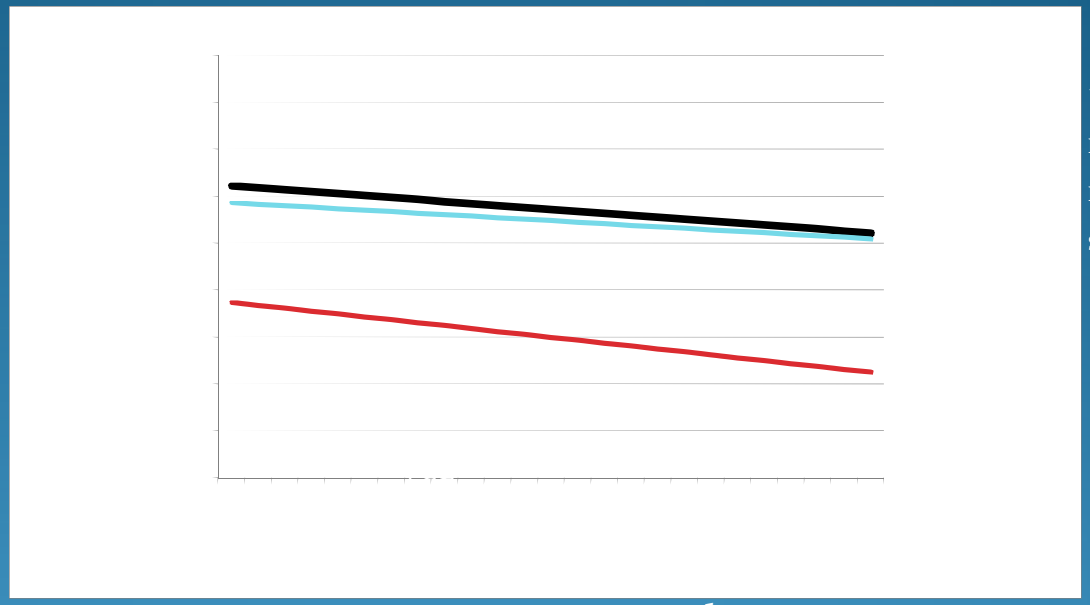
Total Hippocampus

Shape

COS VS. CONTROLS



Johnson et al 2013



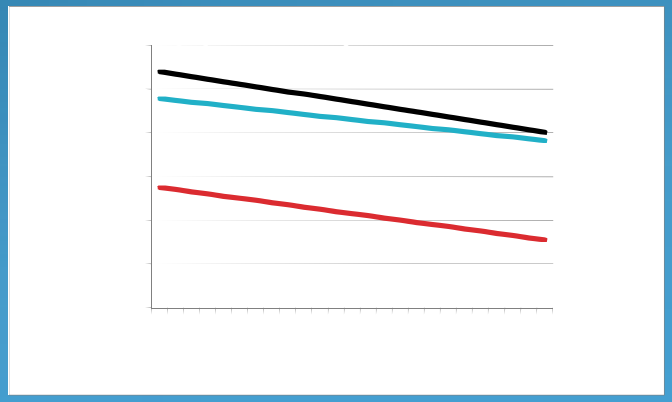
Volume Differences

NV v COS p=0.001

NV v Sib p=0.414

Sib v COS p=0.004

Left



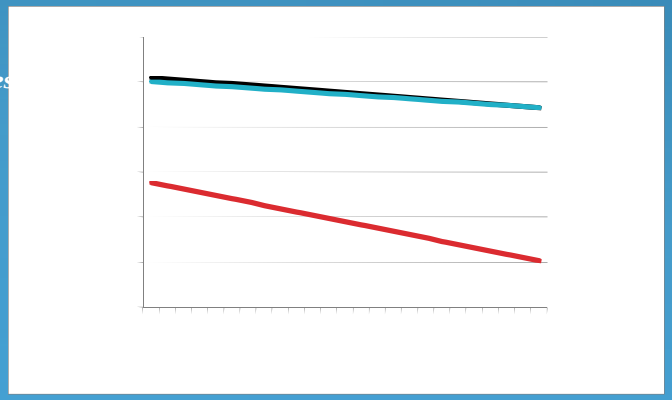
Volume Differences

NV v COS p=0.001

NV v Sib p=0.515

Sib v COS p=0.006

Right



Volume Differenc

NV v COS p=0.001

NV v Sib p=0.818

Sib v COS p=0.001

MATTAI ET AL 2011

No significant shape differences between any trajecto

Childhood onset schizophrenia: Genetic studies

- Copy Number Variants seem to increase risk for many neuro-developmental disorders
- We compared COS with their siblings and with controls
- "Growing Brains in a Dish"
- Skin biopsies(fibroblasts) being used to make embryonic stem cells for each patient
- These stem cells then produce lines of neuronal cells for study

COS: Genetic Studies-Copy Number Variants

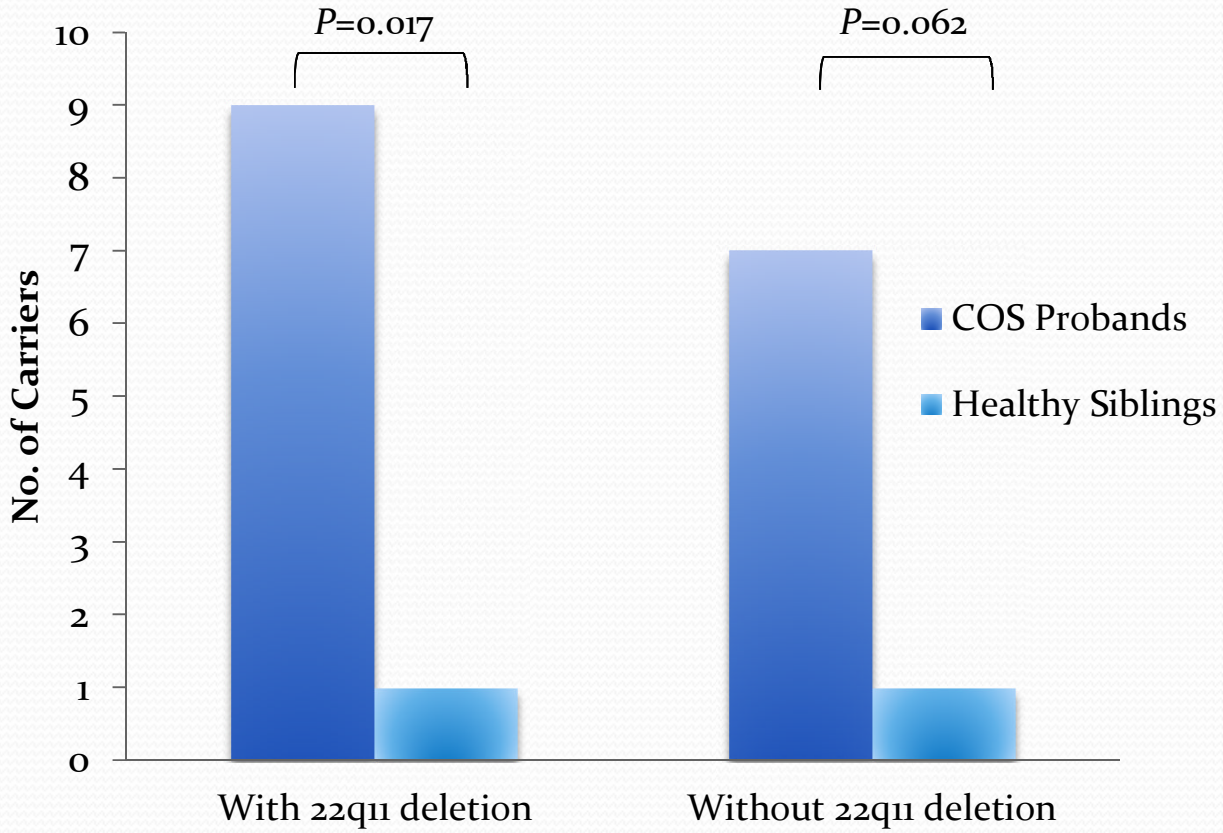
- Large number of CNVs reported for neuro-developmental disorders (schizophrenia, autism, Intellectual Disability, and/or epilepsy)
- Large control populations available for each disorder
- Sufficient COS sample size to also compare rates with healthy full siblings

Neurodevelopmental Risk associated CNVs (autism, ID, epilepsy and/or schizophrenia) in 11.9% of COS probands

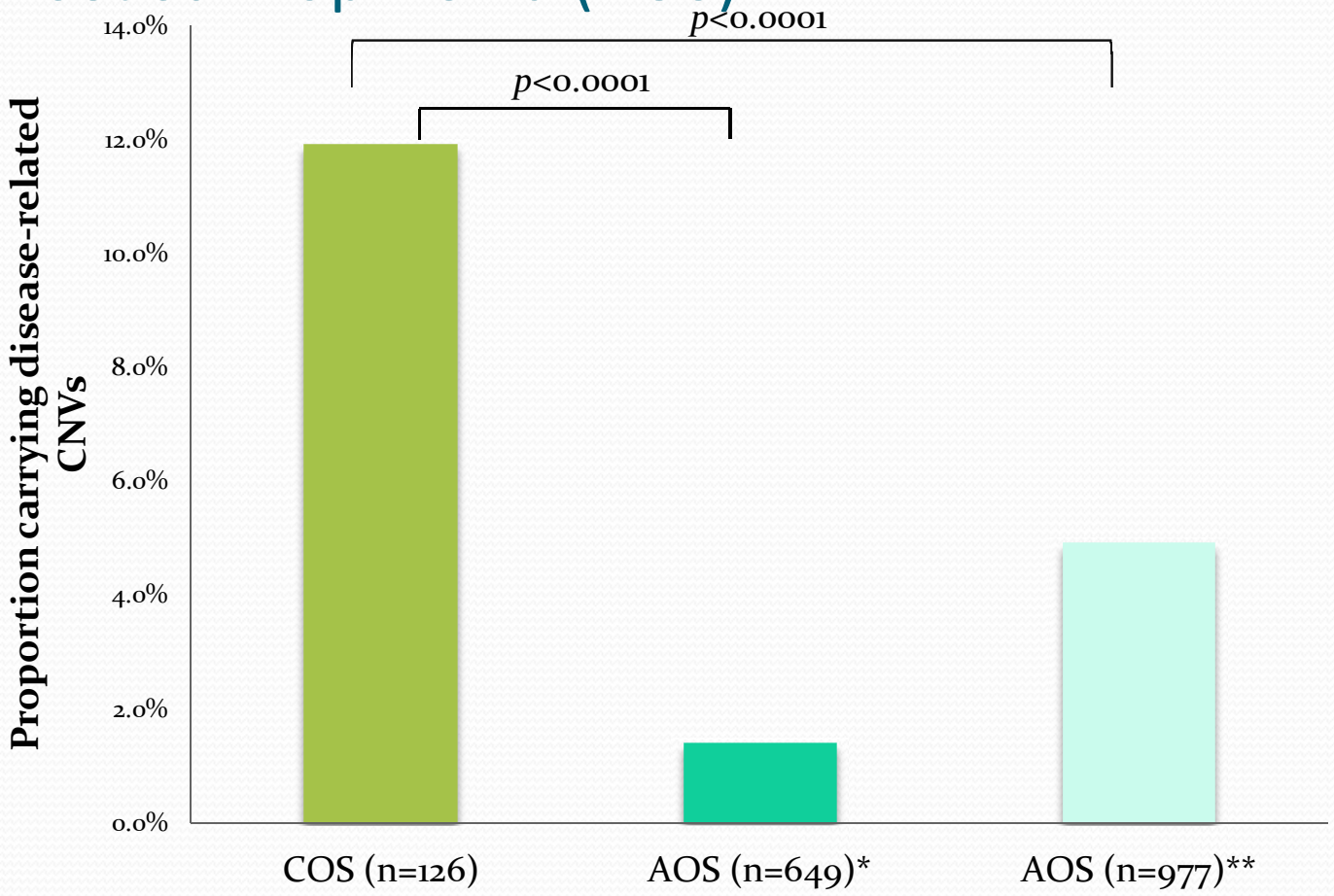
NSBID	Chr. Band	Start (hg18)	Stop (hg18)	Size (kb)	Type	Duplicated or Deleted genes	*Inheritance*	Disease	Reported in 2008
1358^	2p25.3	1,591,064	1,836,375	245	Dup	2	*Mother*	SCZ	Yes
534^	2p25.3	1,720,133	1,827,317	107	Dup	2	*Unknown*	SCZ	Yes
581	2p16.3	50,025,162	50,136,989	112	Del	2	*Unknown*	SCZ, ASD	Yes
534^	8q11.2	53,550,992	54,043,684	493	Dup	3	*Unknown*	ID	No
885	10q22.3	81,415,378	81,588,866	173	Del	5	*de novo*	ID	No
448	15q11.2	18,818,086	20,203,694	1,386	Del	24	*Unknown*	SCZ, Epi	No
1358^	15q11.2	20,203,694	20,778,963	575	Del	13	*Mother*	SCZ, Epi	No
1546^	15q13.3	30,238,780	30,620,951	382	Del	26	*de novo*	SCZ, Epi	No
498	15q13.3	30,238,780	30,713,368	475	Del	30	*Mother*	SCZ, Epi	No
481	16p12.1	21,498,074	21,946,841	449	Del	7	*Father*	ID	No
676^	16p11.2	29,502,984	30,107,306	604	Dup	15	*Father*	SCZ, ASD	Yes
2011	16p11.2	29,782,436	30,227,808	445	Dup	34	*Father*	SCZ, ASD	Yes
1546^	17q21.3	41,321,621	41,706,070	384	Dup	4	*Father*	ID	No
1275	22q11.2	17,092,563	20,077,678	2,985	Del	49	*de novo*	SCZ, ASD, ID	No
1220	22q11.2	17,224,632	19,842,333	2,618	Del	48	*de novo*	SCZ, ASD, ID	No
537	22q11.2	17,257,787	19,855,248	2,597	Del	46	*Unknown*	SCZ, ASD, ID	No
1804	22q11.2	17,257,787	19,963,350	2,706	Del	47	*de novo*	SCZ, ASD, ID	No
3169	22q11.2	17,269,794	20,128,199	2,858	Del	55	*de novo*	SCZ, ASD, ID	No
676^	22q13.3	47,903,228	49,557,485	1,654	Dup	4	*de novo*	ASD	No

Note: ^Individuals with 2 events; CNVs in yellow have not been reported for schizophrenia in large case control studies.

Comparisons of COS proband-Healthy sibling Pairs (n=69)



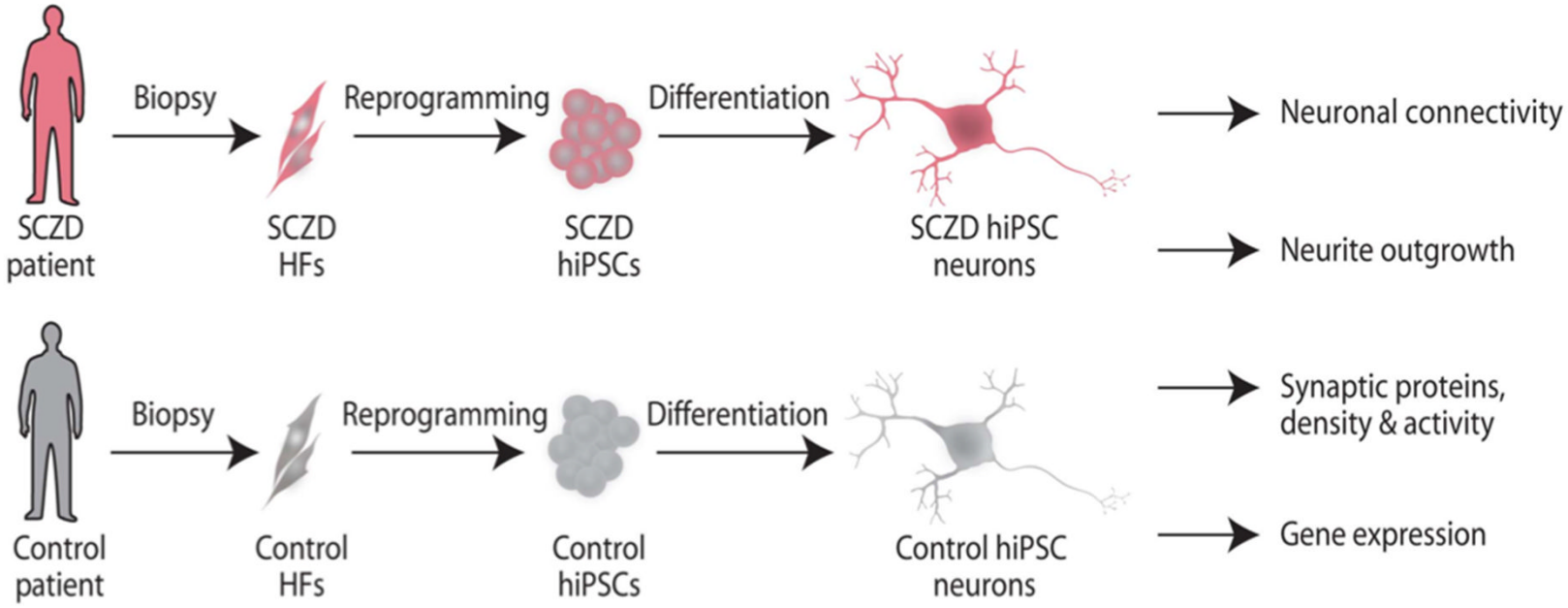
Rates of selected Neurodevelopmental disorder-related CNVs in Childhood onset schizophrenia (COS) vs Adult onset schizophrenia (AOS)



* Samples in Guha *et al.* (in press)

** Samples in Glessner *et al.* (2010)

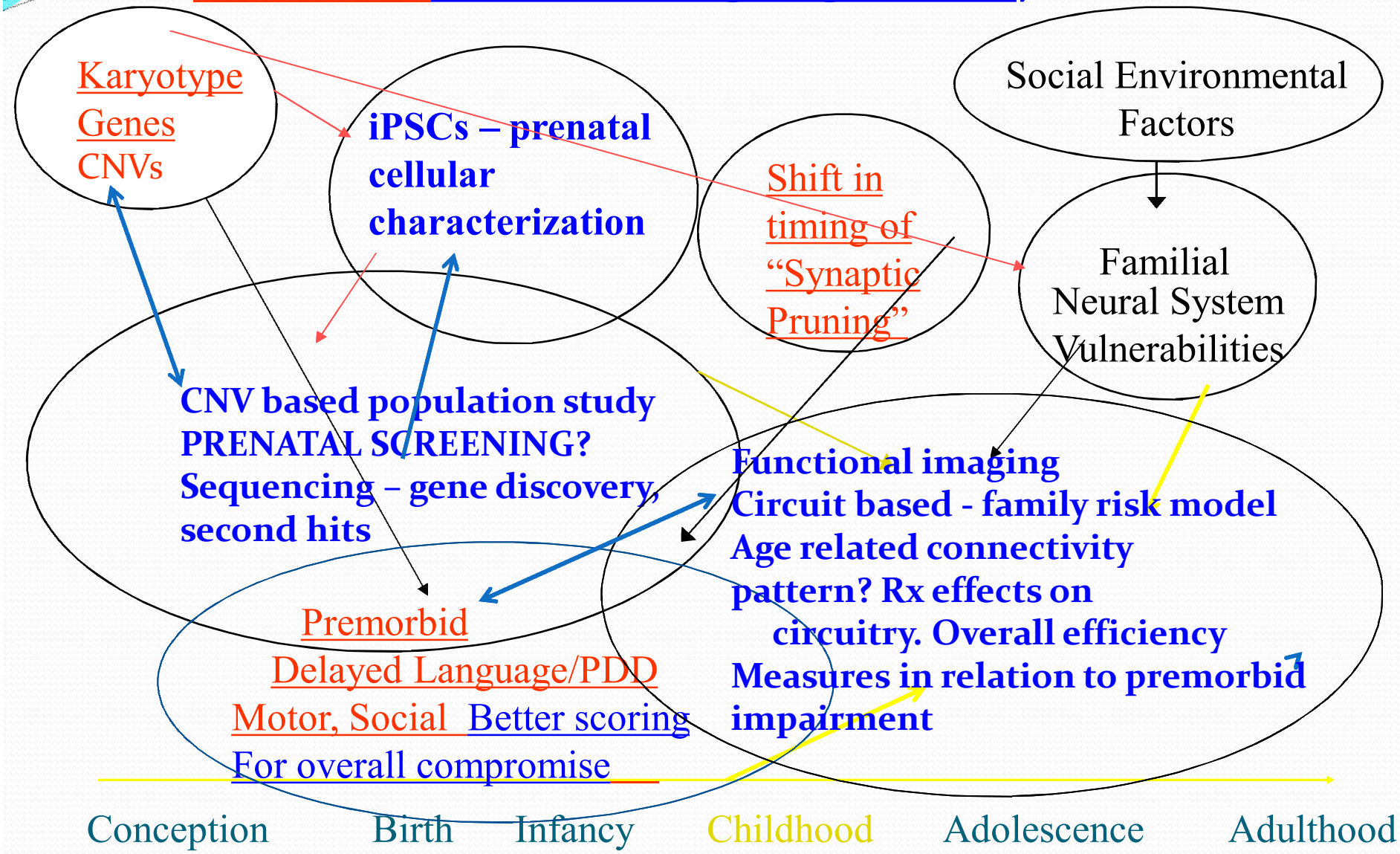
Modeling schizophrenia using human induced pleuripotent stem cells



SI Fig. 1. Experimental schematic of hiPSC modeling of SCZD.

Childhood Onset Schizophrenia:

COS>AOS : Planned/ongoing studies)



Child Psychiatry Branch at NIMH