Research Society on Alcoholism
San Antonio, TX
22 June 2015

Differences in Adolescent Cortex Related to Age and Sex: Initial Findings from the National Consortium on Alcohol & NeuroDevelopment in Adolescence

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NCANDA FUNDING: NIAAA, NIDA, NIMH, NICHD

FINANCIAL INTEREST DISCLOSURES

Adolf Pfefferbaum, M.D.

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SRI International

Center for Health Sciences

NIH National Institute on Alcohol Abuse and Alcoholism

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Differences in Adolescent Cortex Related to Age and Sex: Initial Findings from the National Consortium on Alcohol & NeuroDevelopment in Adolescence

Adolf Pfefferbaum, Torsten Rohlfing, Kilian M. Pohl, Barton Lane, Weiwei Chu, Sandra A. Brown, Susan F. Tapert, Kevin Cummins, Wesley K. Thompson, Ty Brumback, M.J. Meloy, Terry L. Jernigan, Anders Dale, Ian M. Colrain, Fiona C. Baker, Devin Prouty, Michael D. De Bellis, James T. Voyvodic, Duncan B. Clark, Beatriz Luna, Tammy Chung, Bonnie Nagel, Edith V. Sullivan

NCANDA FUNDING: NIAAA, NIDA, NIMH, NICHD

Life span and excessive alcohol consumption

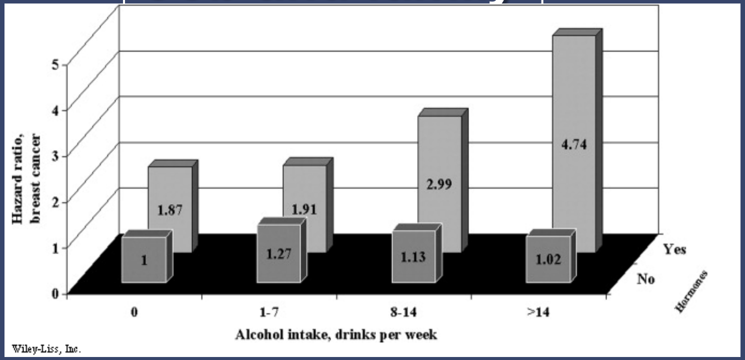
Prenatal
Fetal Alcohol Syndrome

Photo courtesy of
Teresa Kellerman

Teenage and Young Adulthood
Binge drinking
Drunk driving
Unsafe sex

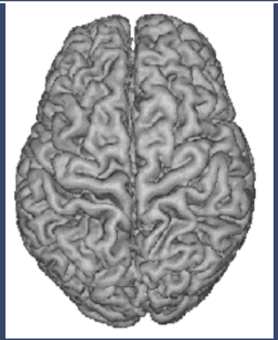
MADD
Activism | Victim Services | Education

Adulthood
Hypertension
Breast cancer
Liver disease
Job and family



Nielsen et al, IntJCancer, 2007.

Maturity
Brain damage
Cognitive impairment



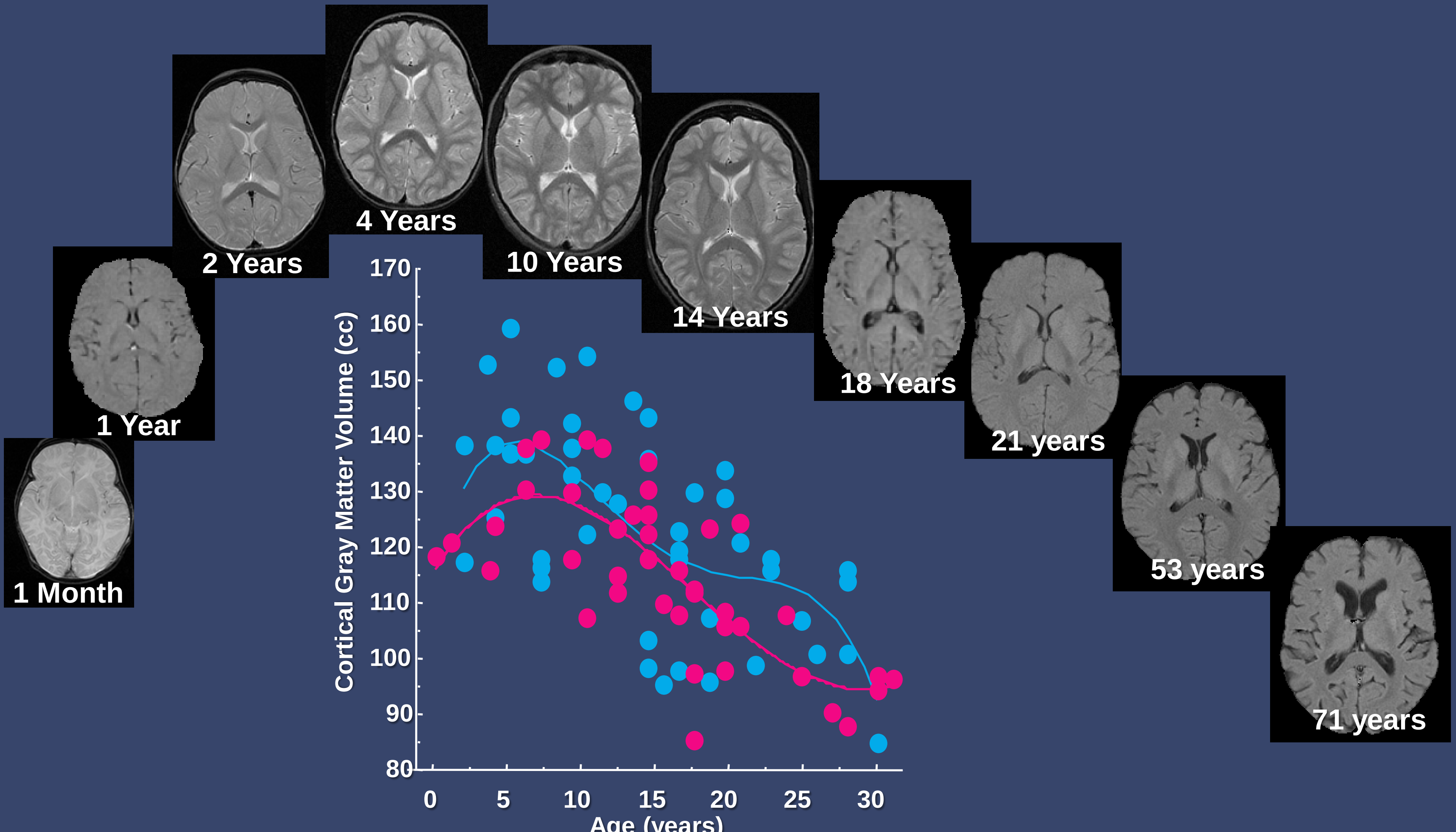
NCANDA MRI

- Age
- Headsize / Supratentorial Volume
- Sex
- Ethnicity
- Prior Alcohol Exposure

Human Brain Growth after Birth

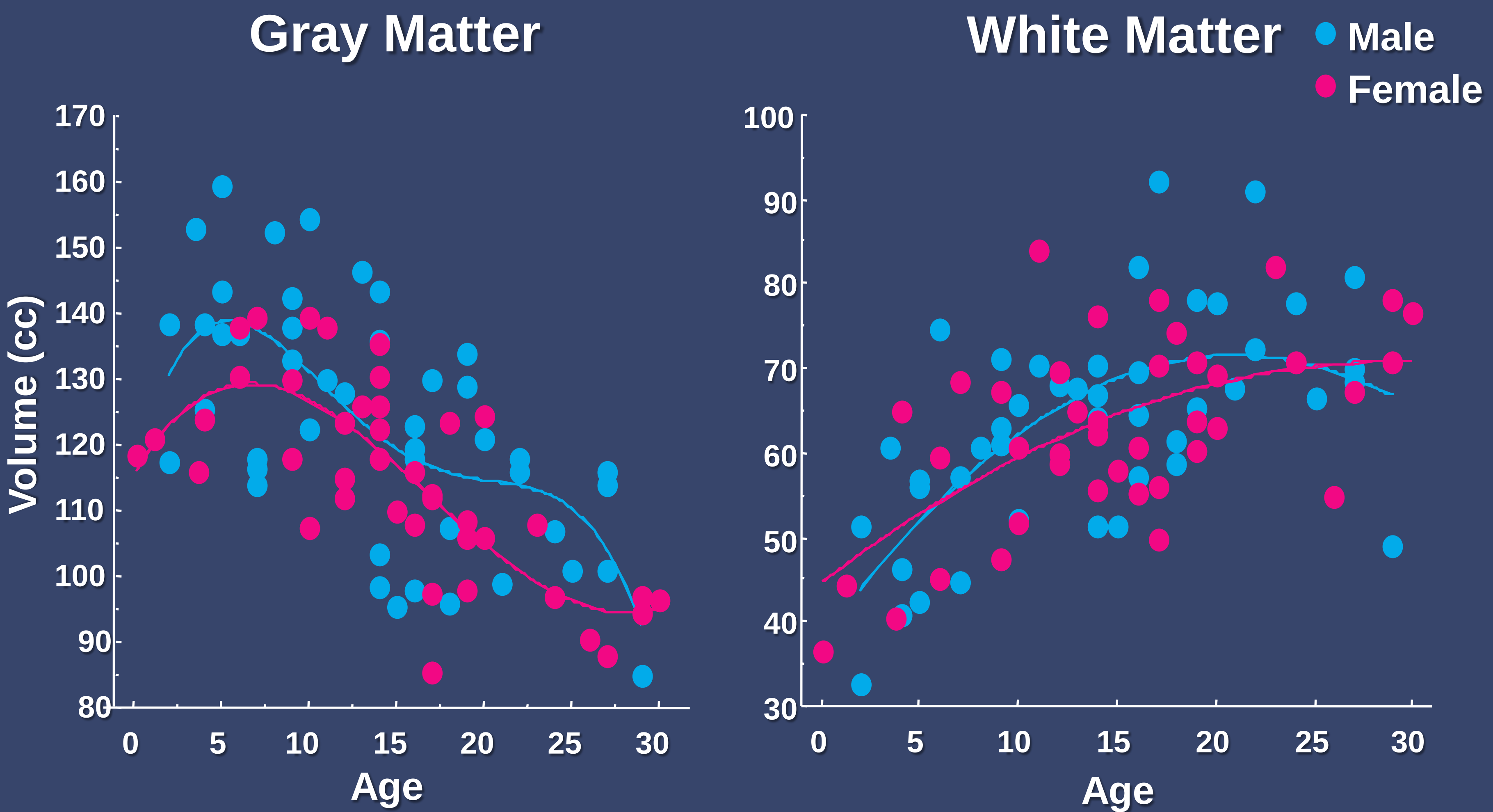
- Brain weight increases fourfold from birth to about 10 years of age
- Gray matter, white matter, and CSF volumes expand but at different rates in different regions of brain

Rise and Fall of Cortical Gray Matter Volume

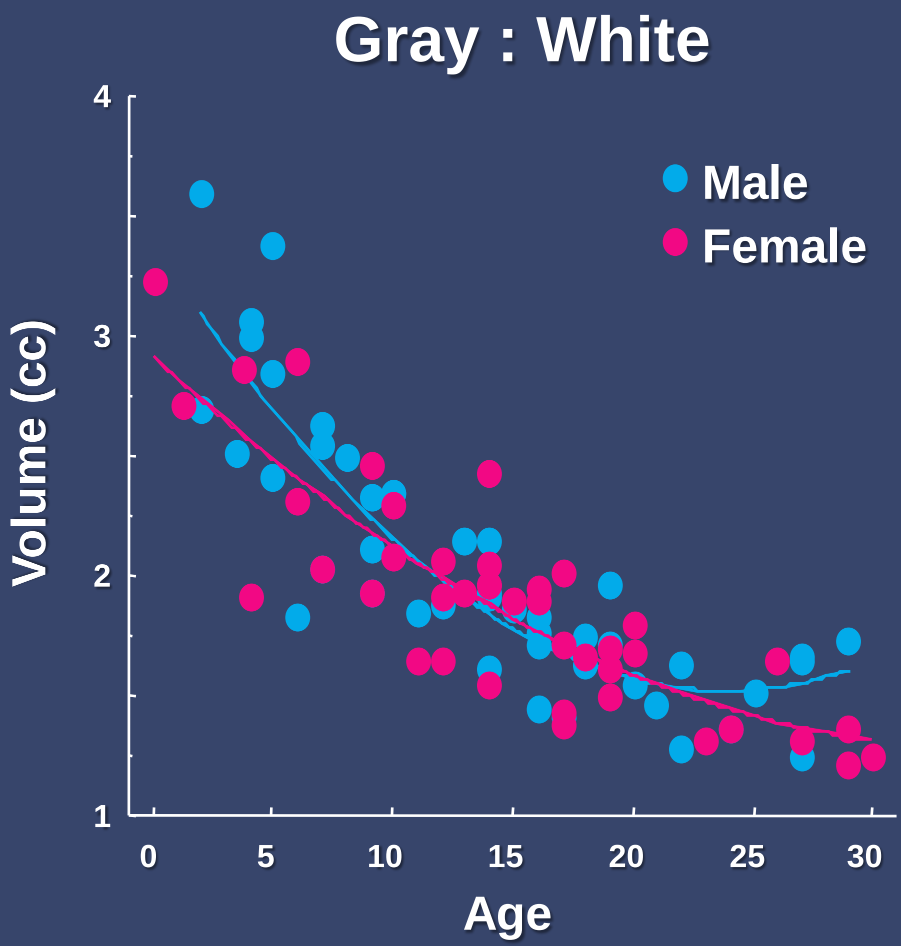


Pfefferbaum et al. *Archives of Neurology* 1994

Cortical Tissue Volumes



Gray to White Matter Ratio



Development of Cortex

Age Differences in PET Local Glucose Metabolism

186 HARRY T. CHUGANI

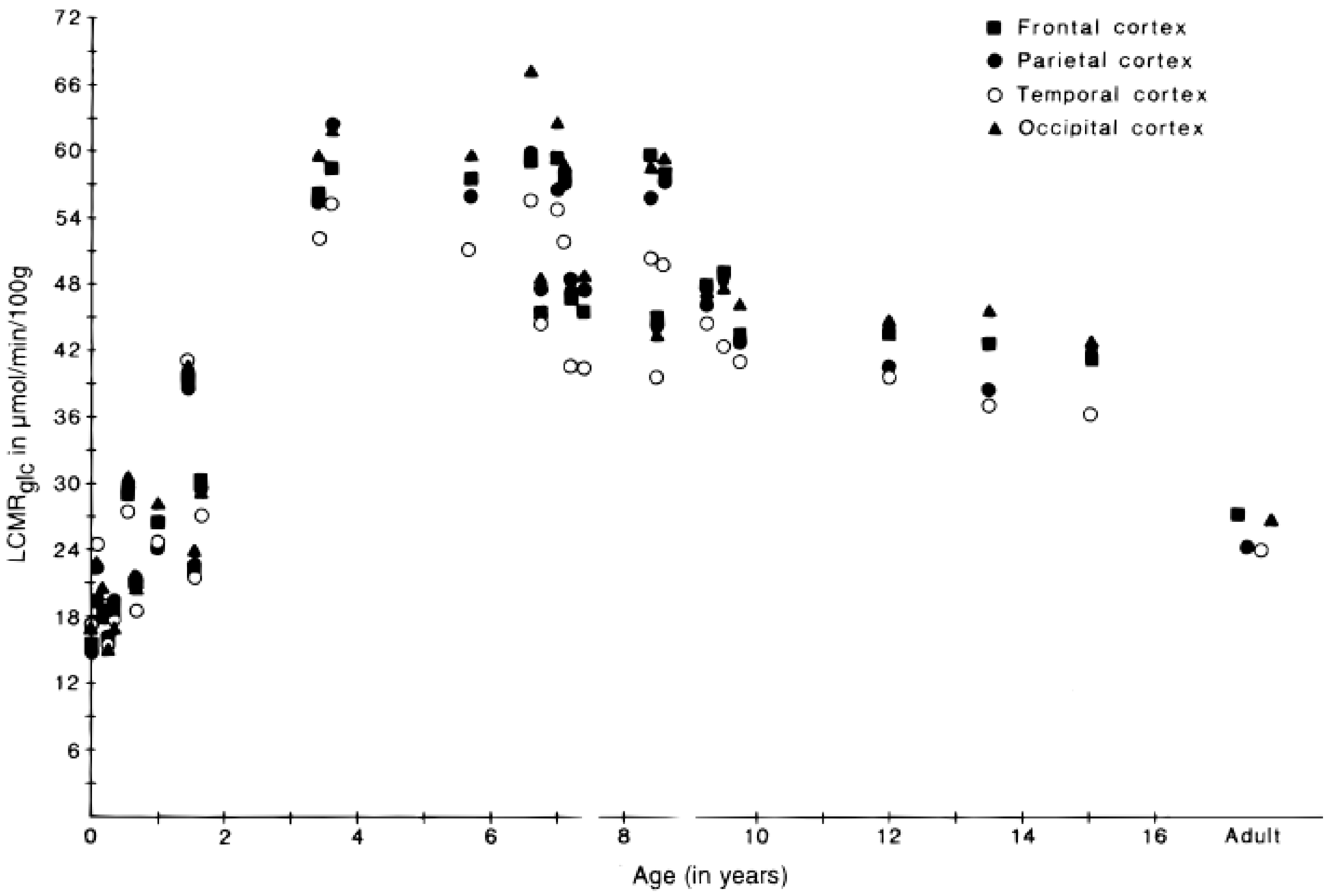
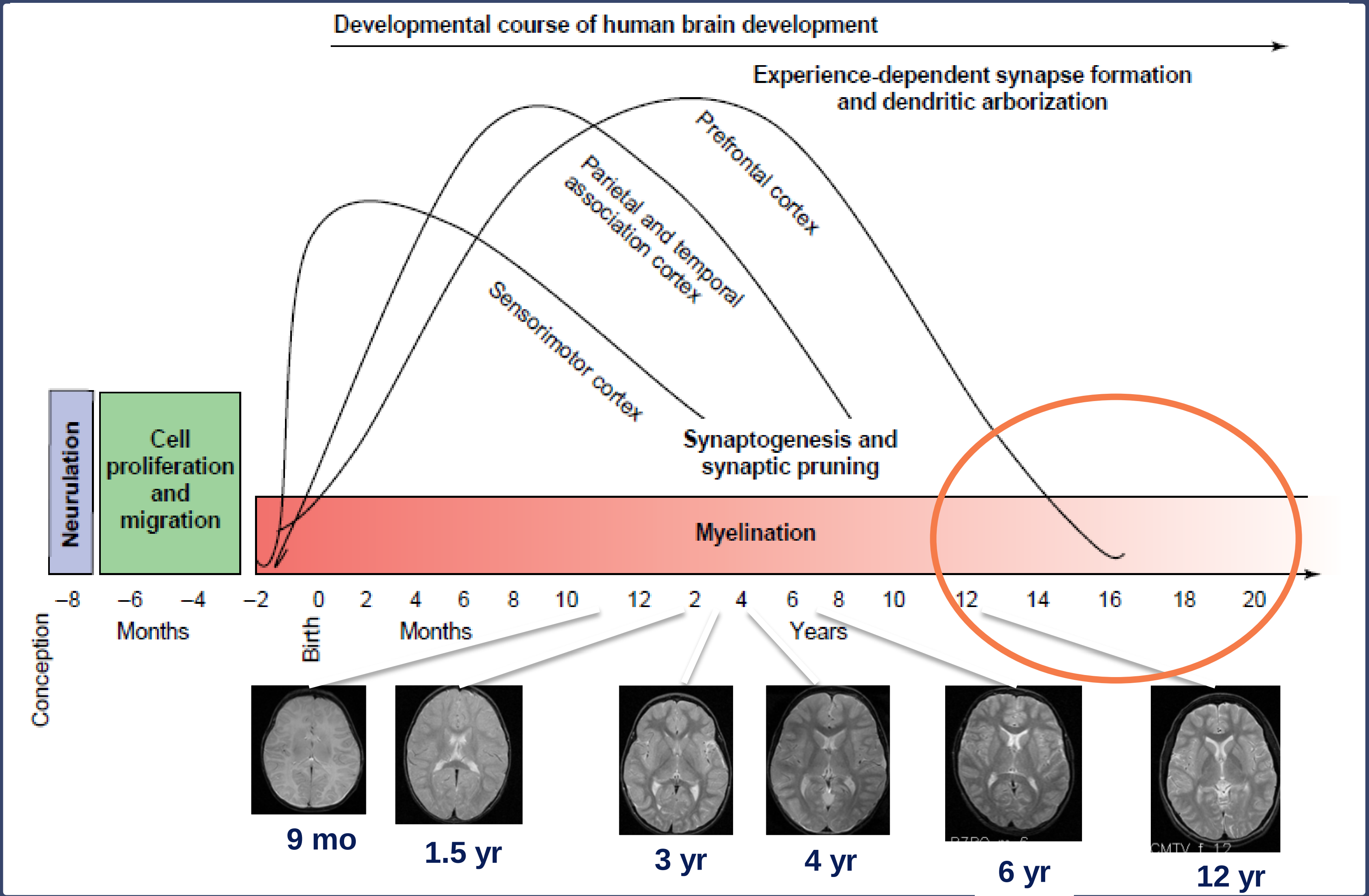


FIG. 4. Absolute values of LCMRglc in cerebral cortex plotted as a function of age in normal infants and children, and corresponding values in seven normal young adults.

Chugani *Preventive Medicine* 1998

Brain Development after Birth

Heterochronicity of Structural Modeling



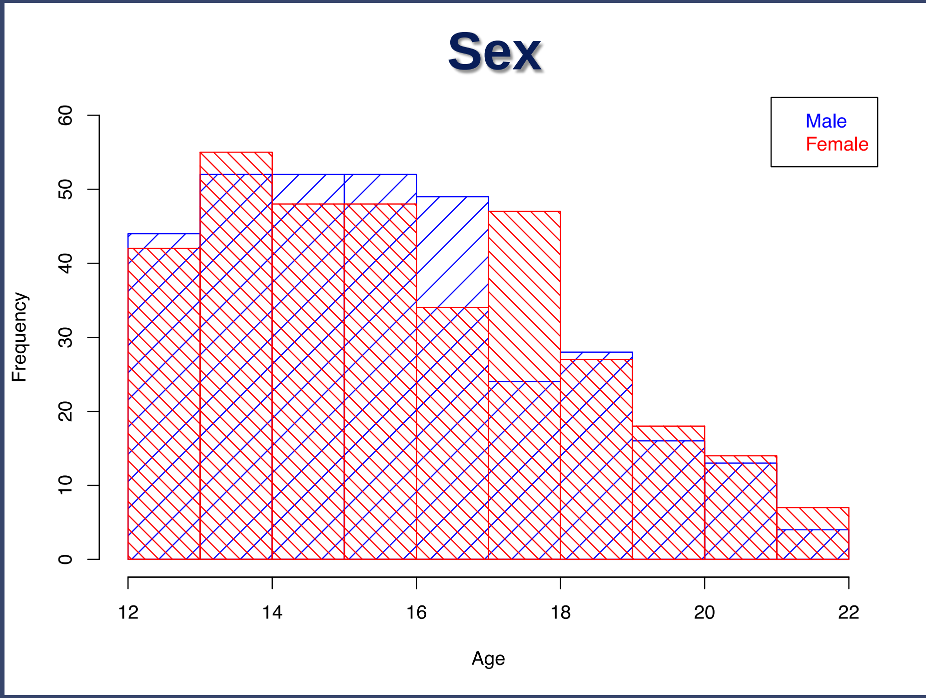
Neuropsychology Review December 2012 cover

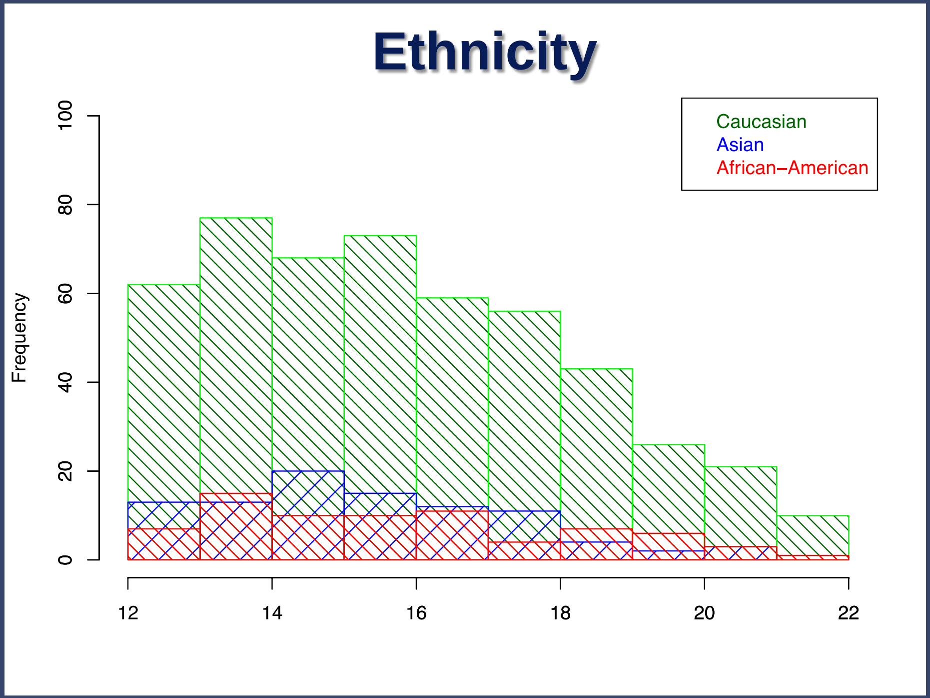
NCANDA

Prospective Study

- National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA)
- 5 U.S. recruitment sites
- 647 no/low drinking
  - 334 male, 340 female
- 134 exceeded criteria
- Age 12-14, 15-17, 18-21 years
- Baseline + annual visits
  - Clinical interview
  - Neuropsychological testing
  - 3T MRI, DTI, resting state-fMRI

NCANDA Sample





Basic NCANDA MRI Protocol

Localizer: 3-Plane Fast Gradient Recalled Echo
(TR=5, TE=1.5, Thick=5.0, Loc=150, FOV=240, xy_matrix=256x128)
T1-weighted structural acquisition: 3D Sagittal IRprep SPGR*
(TR=7, TE=3, TI=640, Thick=1.2, Loc=150, FOV=240, xy_matrix=256x256, Resolution=.9375x.9375x1.2 mm)
T2-weighted structural acquisition: 3D Sagittal Fast Spin-Echo *
(TR=2500, Effective TE=80, ETL=100, Thick=1.2, Loc=150, FOV=240, xy_matrix=256x256, Resolution=.9375x.9375x1.2 mm, Fat Sat=on)
Diffusion Tensor acquisition: 2D Axial Spin Echo Echo-Planar - b=0/1000, 60 directions**
(TR=10,000, TE=85, Thick=2.5, Loc=65, FOV=240, xy_matrix=96x96,
Phase = A/P, Partial k-space (48/64), Acceleration=2, Resolution=2.5x2.5x2.5 mm, Fat Sat=on)
Resting state fMRI: 2D Axial Gradient-Recalled Echo-Planar - 275 TRs=10 min.
(TR=2200ms, TE=30ms, Flip angle=79°, Thick=5 mm, Loc=32, FOV=240, xy_matrix=64x64,
Phase = A/P, Resolution=3.75x3.75x5 mm, Fat Sat=on, Respiration and pulse recorded)
Field Map (for Resting state fMRI B0 inhomogeneity correction): 2D Axial Gradient-Recalled Echo (GRE)
(TR=460 ms, TE=3 and 5 ms, Thick=2.5 mm, Loc=65, FOV=240, xy_matrix=96x96,
Resolution=2.5x2.5x2.5 mm, Save Real, Imaginary and Magnitude data)
* Prospective motion correction with replacement of up 10% of excitations exceeding a variance threshold.
** DTI acquisition will include an additional b=0 image with the echo-planar readout in the opposite direction for B0 inhomogeneity correction without a field map and across-site common 60 gradient direction table.
Sagittal acquisition will extend from ear to ear, top of the scalp and inferior below bottom of cerebellum - locating the superior/inferior midpoint at the top of the corpus callosum usually is adequate.
Axial slice order will be from inferior to superior (I/S). Axial acquisitions must begin at least one slice below the bottom of the cerebellum and extend to or above the top of the scalp.

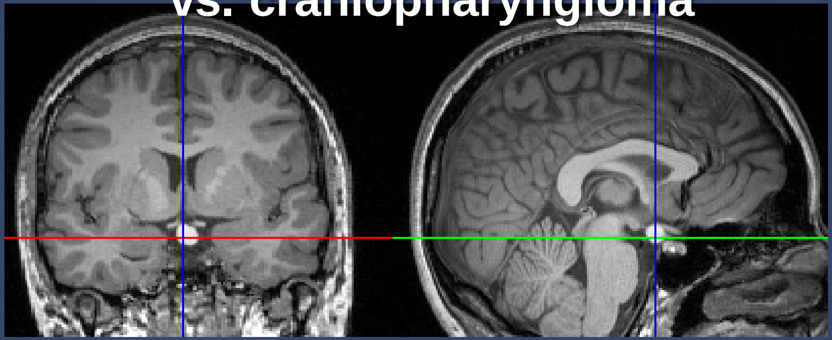
Anomalies Identified on Clinical Readings in 95 Adolescents*

24 mega cysterna magna
15 subarachnoid cysts (primarily temporal and frontal)
12 pineal cysts
11 white matter anomalies (primarily corpus cysts)
6 tonsilar ectopias
5 very prominent perivascular spaces
5 gray matter heterotopias
4 pituitary masses (primarily cysts)
4 abnormally large or asymmetrical lateral ventricles
4 cavum septum pellucidum
3 developmental venous anomalies (DVA)
1 severe cranio-cervical junction stenosis (10/30 mm)
1 *right parietal cortical mass (3 cm)
1 *bilateral tonsillar herniation, medullary distortion (Chiari 1 malformation)
*excluded from NCANDA cohort

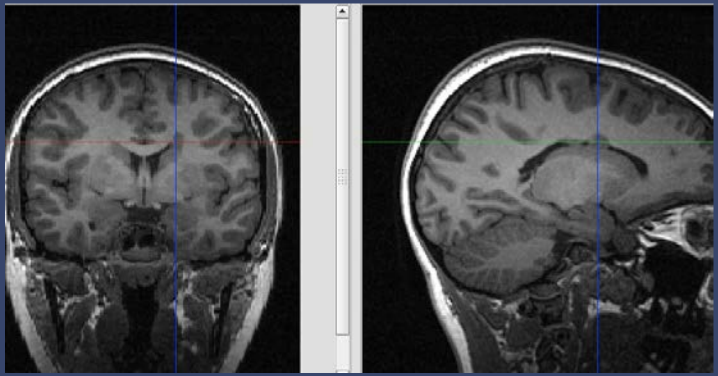
95/833 adolescents = 11.4%
23 excluded from parcellation
*2 excluded from the study

Anomalies Identified on Clinical Readings

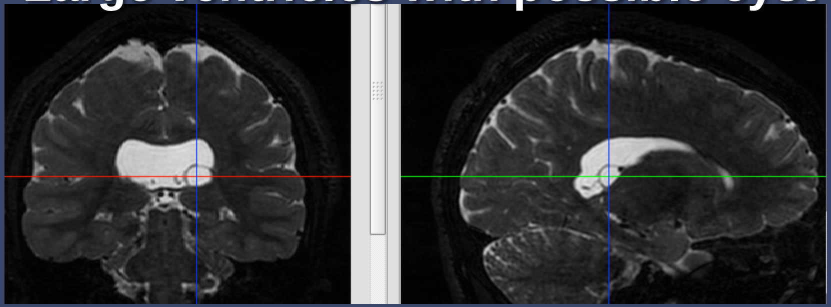
Probable congenital Rathke's cleft cyst vs. craniopharyngioma



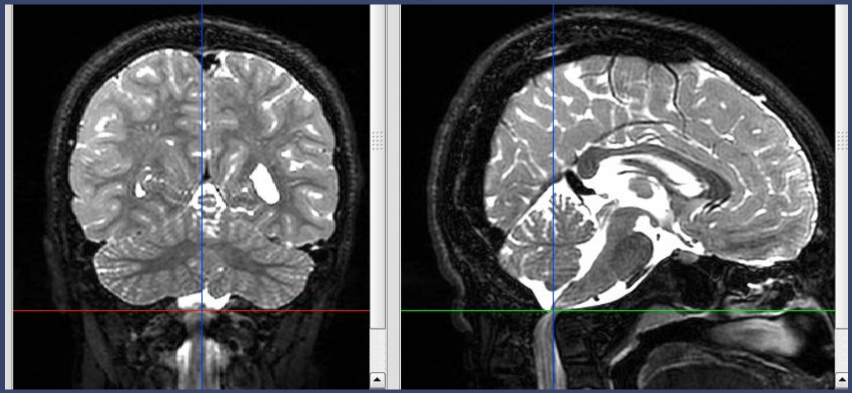
Subependymal heterotopia



Large ventricles with possible cyst



Cranio-cervical junction stenosis



Anomalies Identified on Clinical Readings

Some Precluding Automated Quantification

Subarachnoid cyst in a 17.0 year old girl

Mega cisterna magna in a 15.5 year old boy

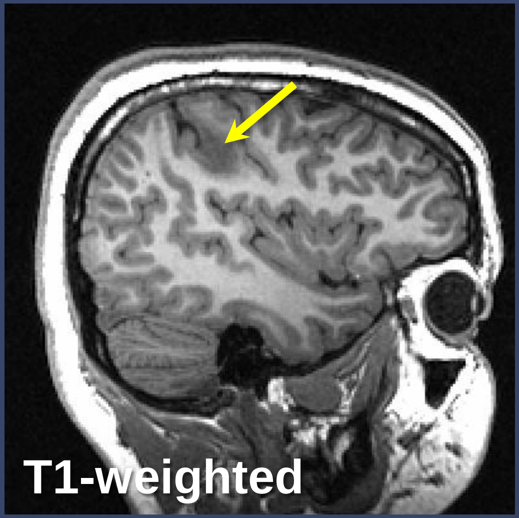
Abnormalities on Clinical Readings

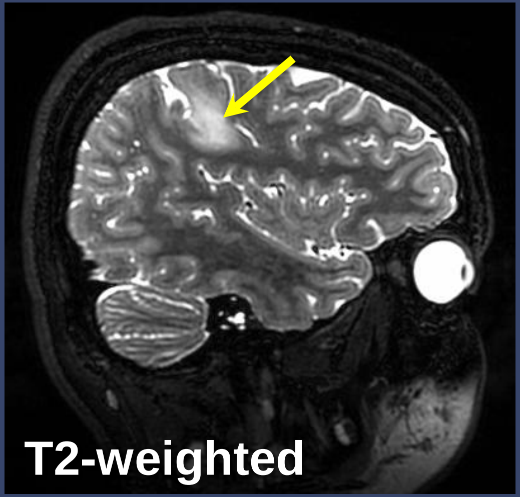
Excluded from Further Study

Chiari 1 malformation

bilateral tonsillar herniation with medullary distortion

right parietal cortical mass





NCANDA Data Analysis Team

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NCANDA Data Analysis Team

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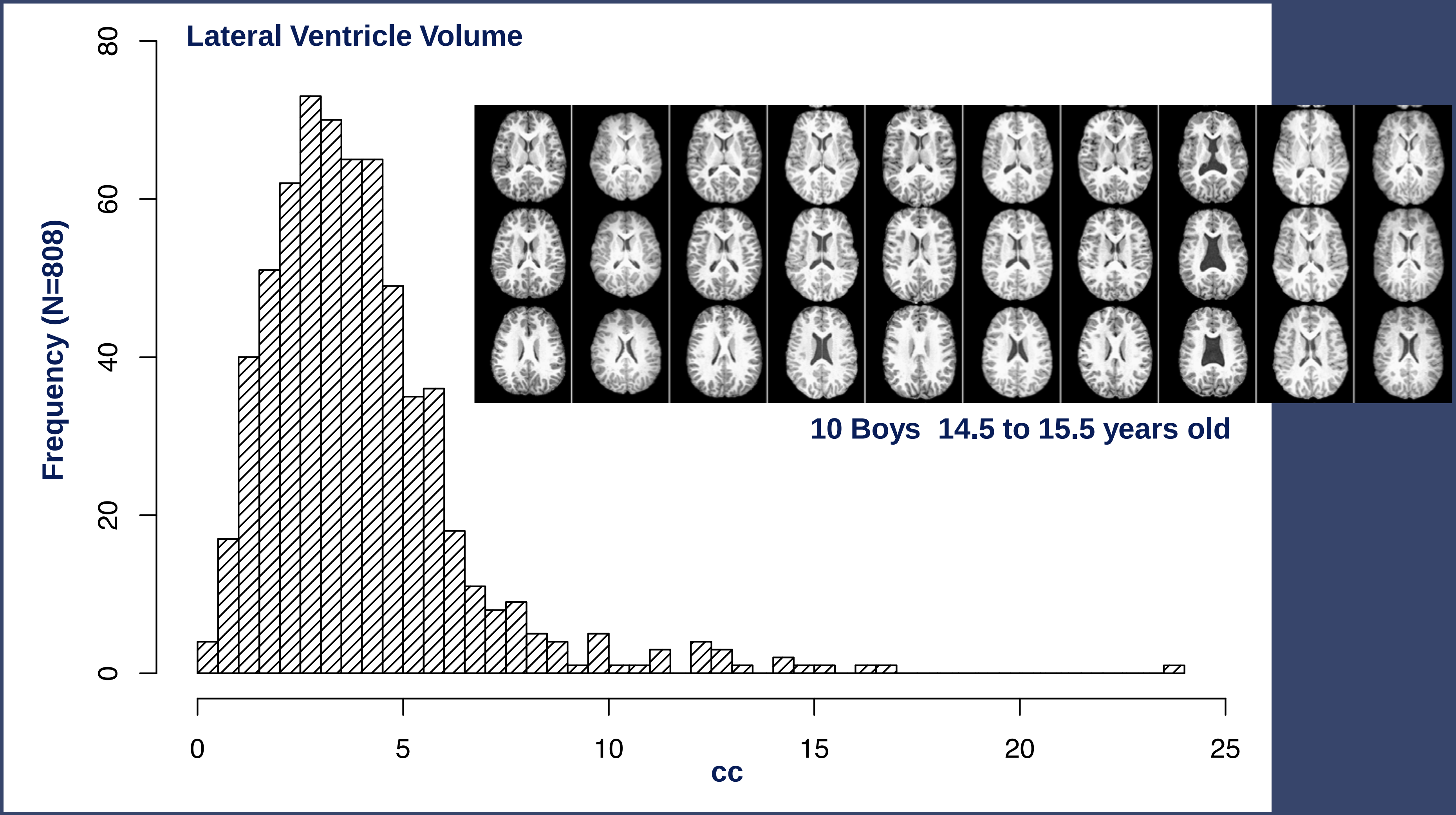
Nolan Nichols, Ph.D.

Dongjin Kwon, Ph.D.

Yong Zheng, Ph.D.

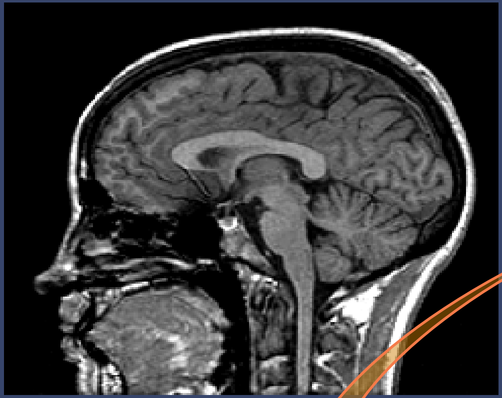
Lateral Ventricle Volume



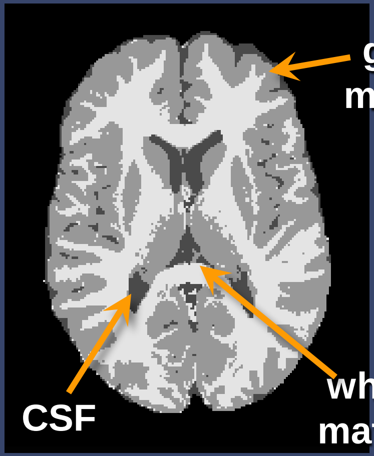
Structural MRI

Quantitative Measures of Regional Brain Tissue

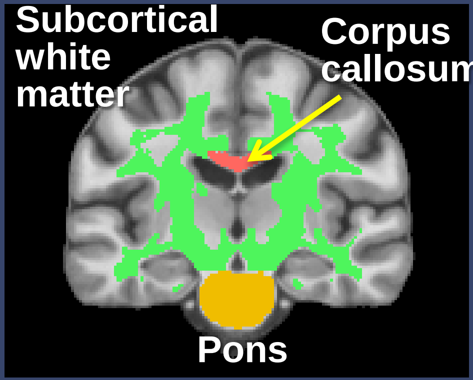
Structural MRI



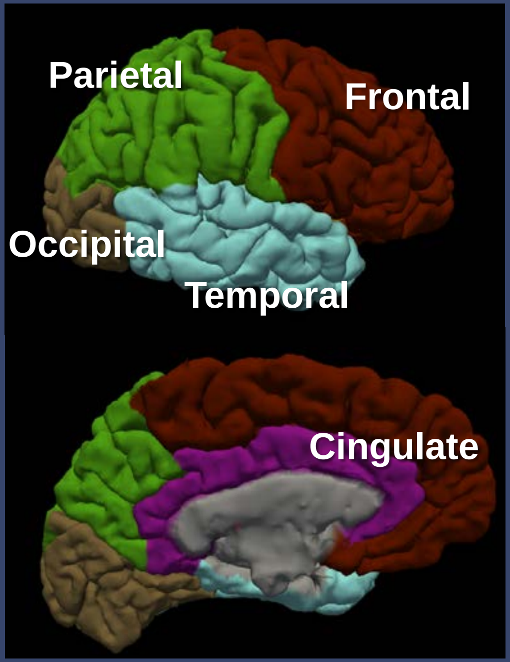
- Tissue Segmentation



SRI24 White Matter Regions



FreeSurfer Gray Matter Regions



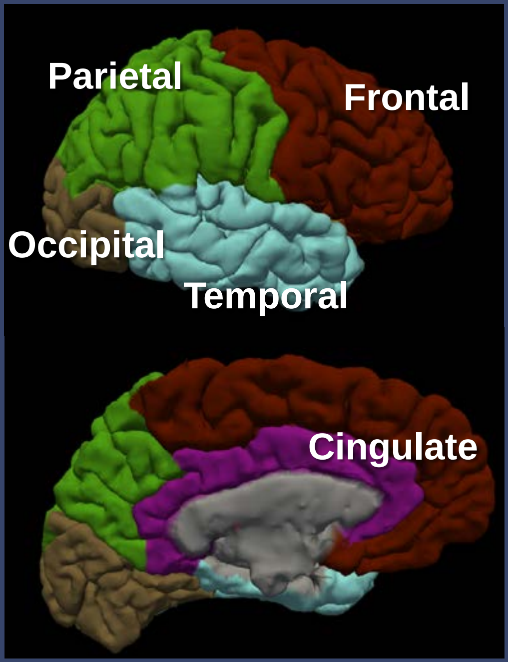
Structural MRI

FreeSurfer Cortical Lobar Volume, Surface & Thickness

Frontal
Superior Frontal
Rostral and Caudal Middle Frontal
Pars Opercularis, Pars Triangularis, and Pars Orbitalis
Lateral and Medial Orbitofrontal
Precentral
Paracentral
Frontal Pole

Temporal
Superior, Middle, and Inferior Temporal
Banks of the Superior Temporal Sulcus
Fusiform
Transverse Temporal
Entorhinal
Temporal Pole
Parahippocampal

Insula



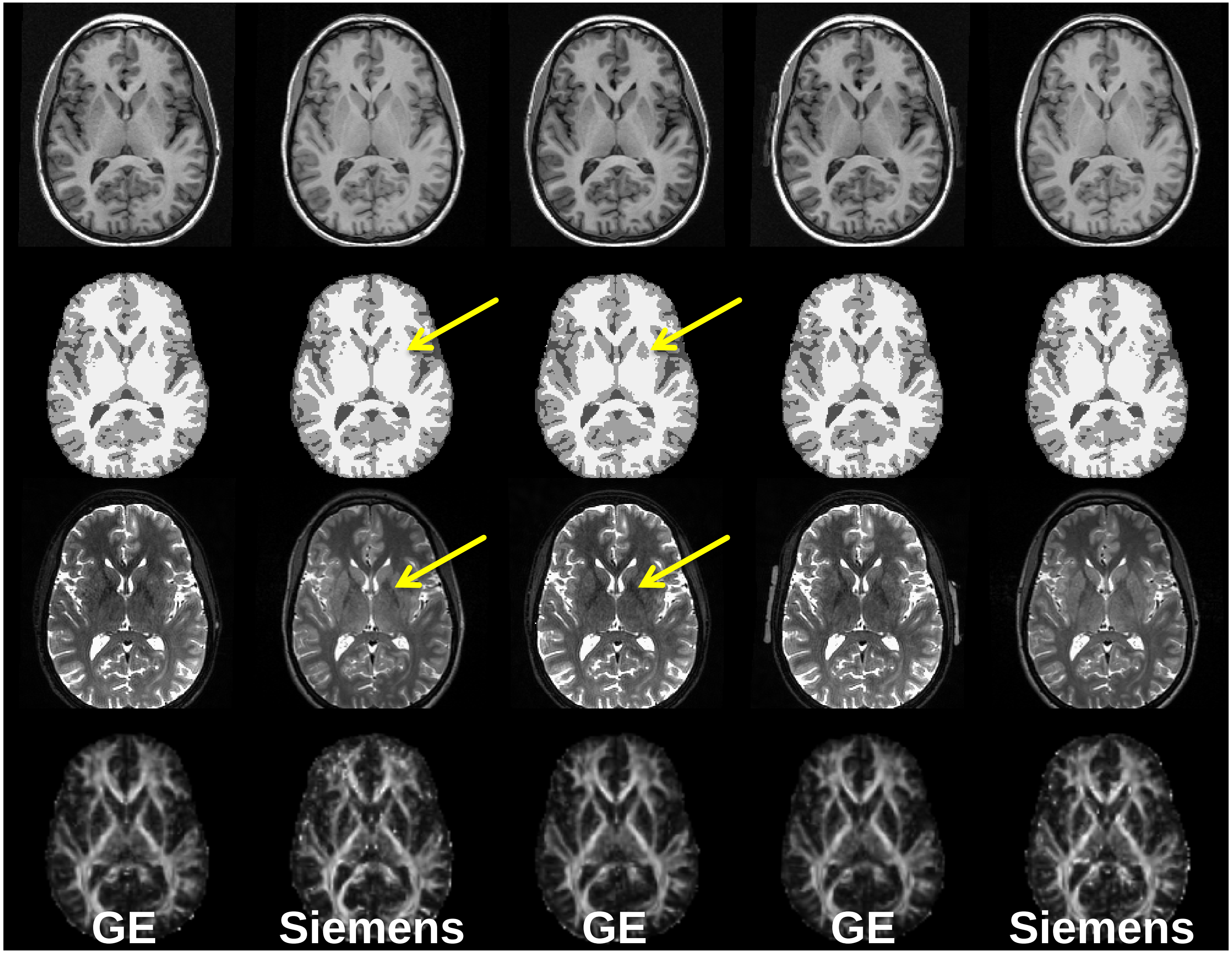
Parietal
Superior Parietal
Inferior Parietal
Supramarginal
Postcentral
Precuneus

Occipital
Lateral Occipital
Lingual
Cuneus
Pericalcarine

Cingulate
Rostral Anterior (Frontal)
Caudal Anterior (Frontal)
Posterior (Parietal)
Isthmus (Parietal)

Human Phantom across Site/Scanner

Harmonization Across 3 GE Sites and 2 Siemens Sites



NCANDA MRI

Brain region ~ age + covariates (sex, ethnicity, SES, etc)

General Additive Model (GAM)

Linear:

$$brain_i \sim \text{®}_0 + \text{®}_1 \text{age}_i + \text{®}_2 \text{mfg}_i + \text{®}_3 \text{ses}_i + \text{®}_4 \text{ethnicity}_i + \text{®}_5 \text{sex}_i + \sum_i$$

Non-linear:

$$brain_i \sim S_0(\text{age}_i) + \text{®}_1 \text{mfg}_i + \text{®}_2 \text{ses}_i + \text{®}_3 \text{ethnicity}_i + \text{®}_4 \text{sex}_i + \sum_i$$

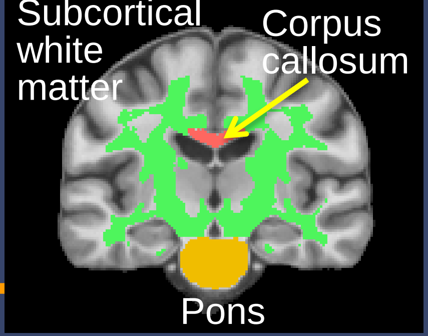
Cross-platform Harmonization done with GAM

NCANDA MRI

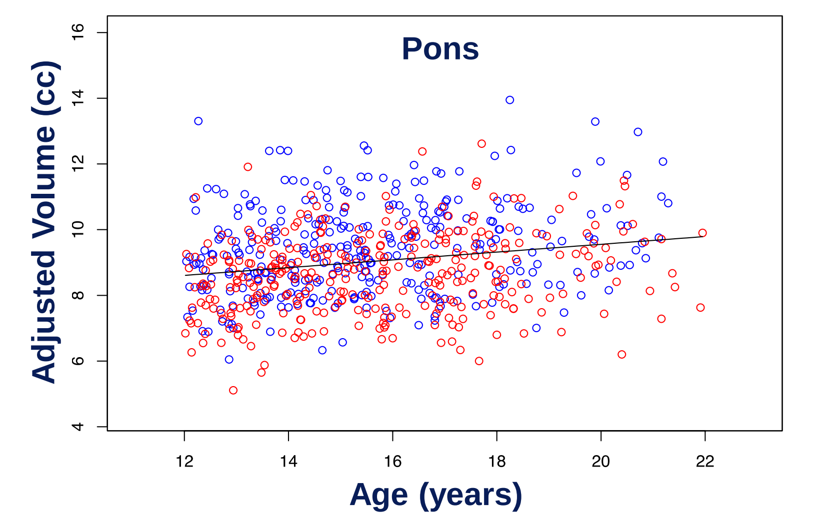
- Age
- Headsize / Supratentorial Volume
- Sex
- Ethnicity
- Prior Alcohol Exposure

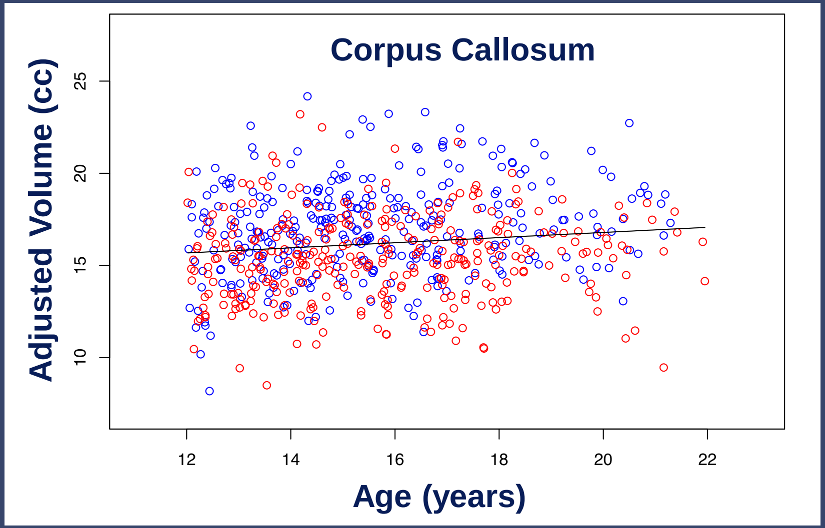
NCANDA Cohort

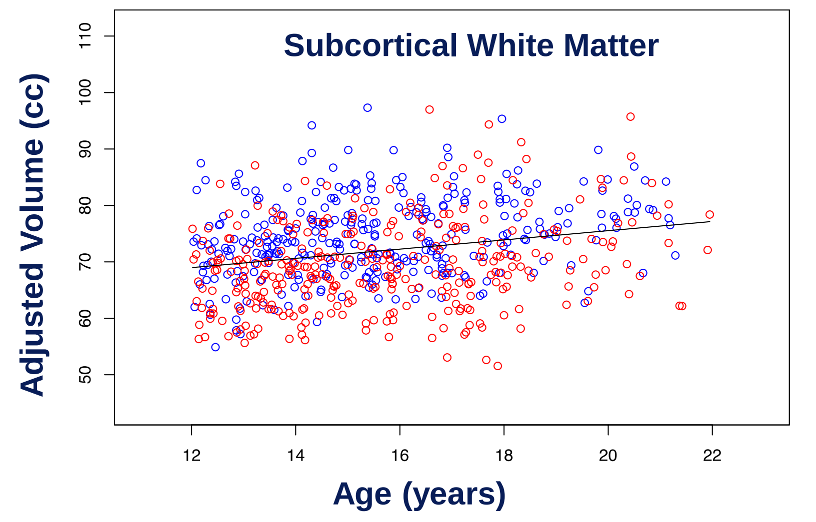
Baseline MRI by Age and Sex



Regional White Matter Volumes

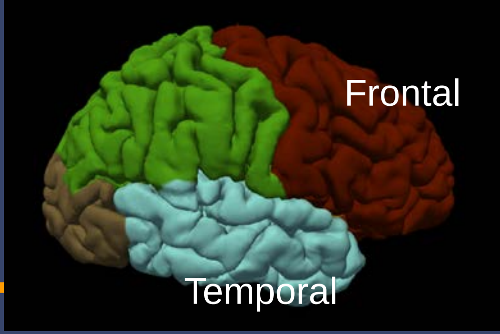


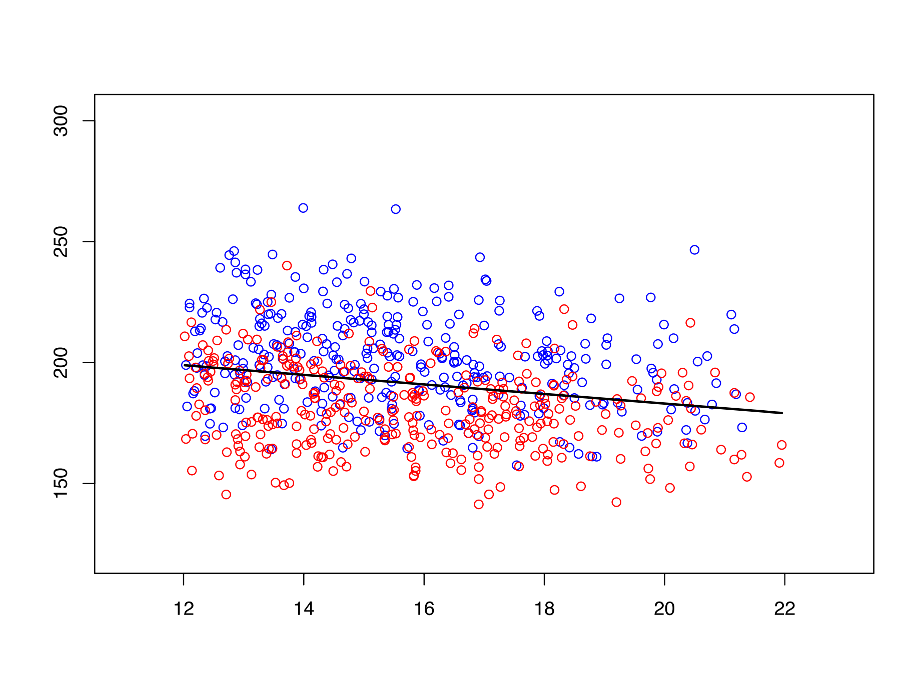


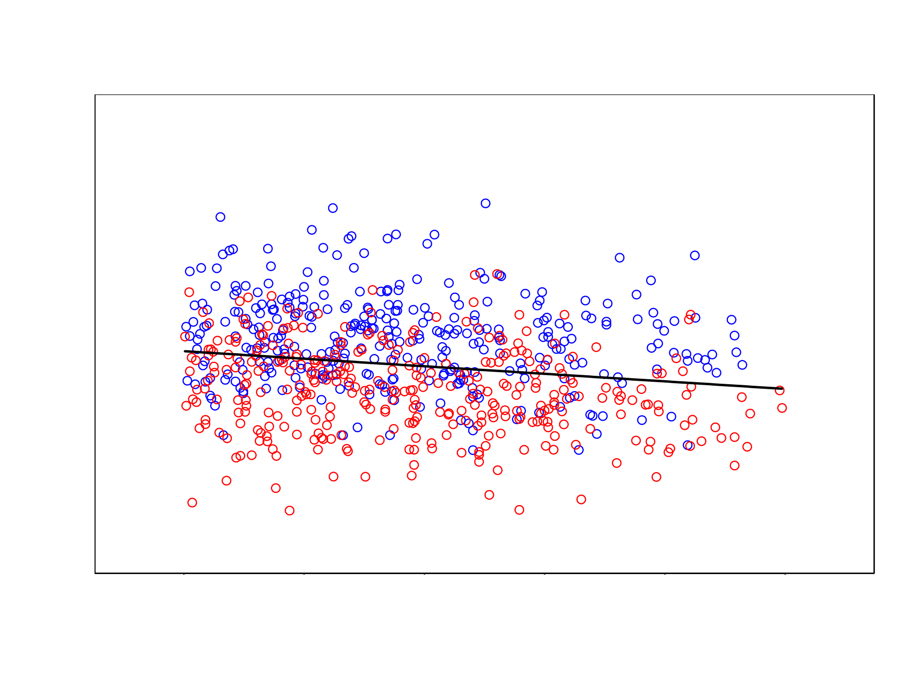


NCANDA Cohort

Baseline MRI by Age and Sex







NCANDA Cohort

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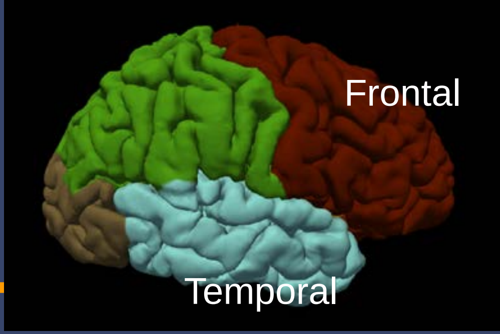
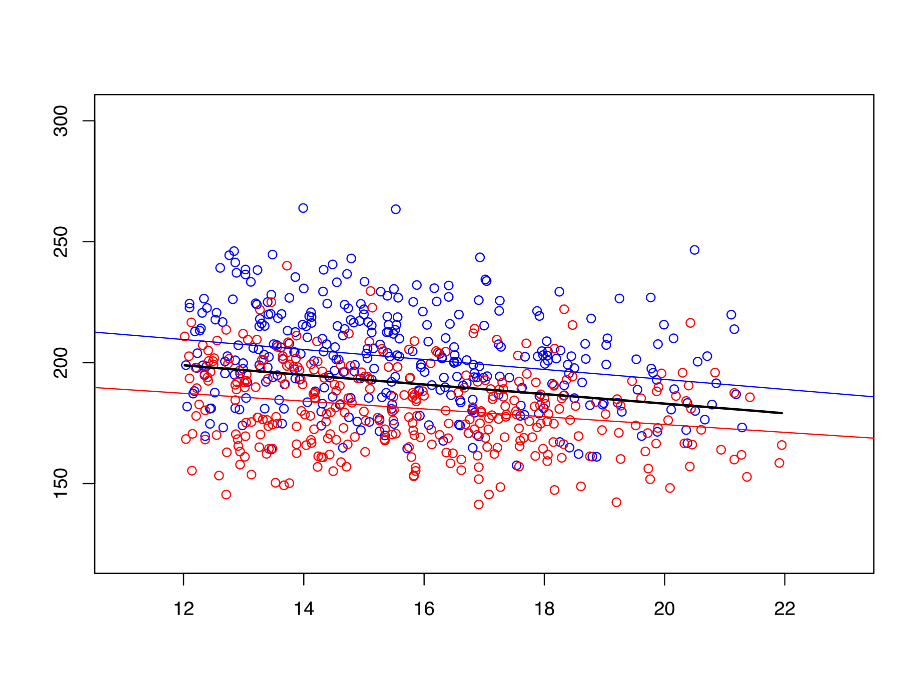
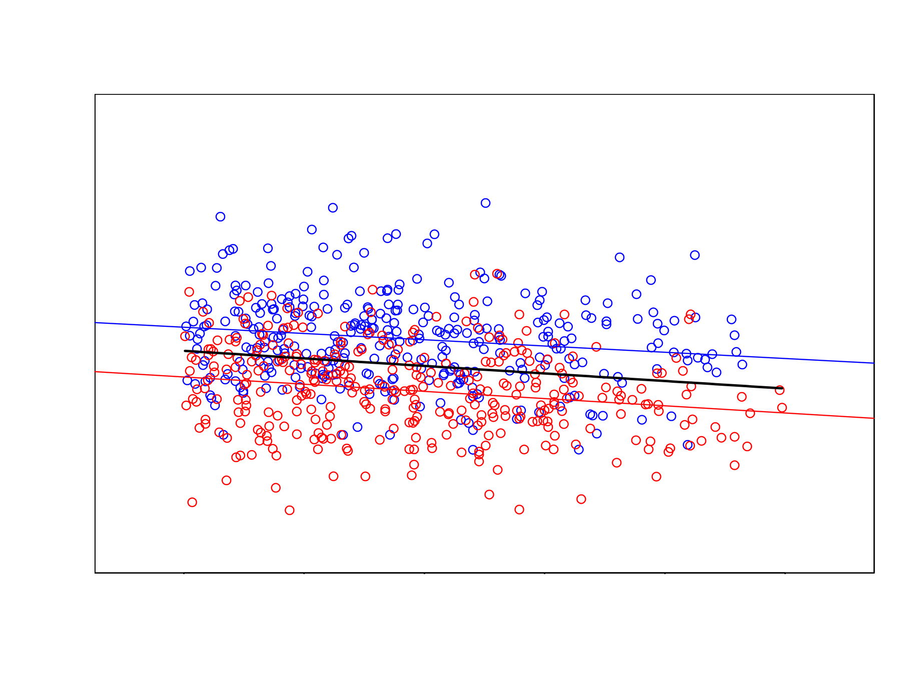
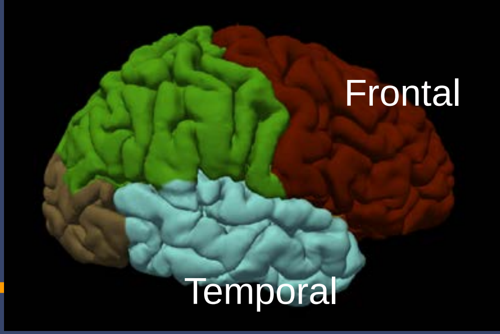




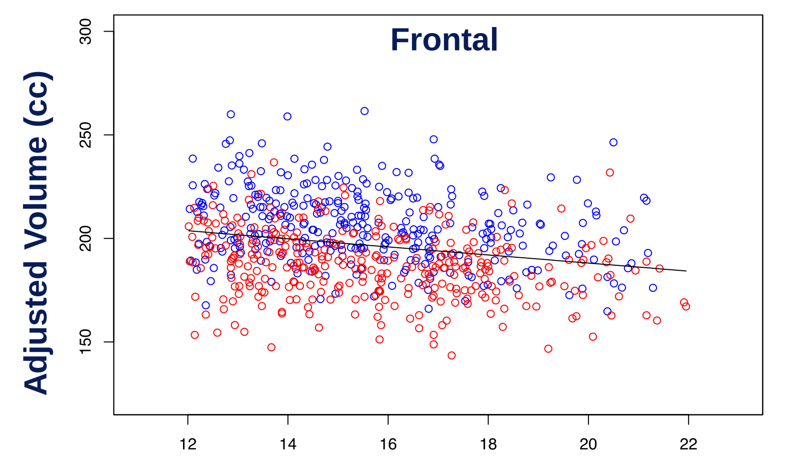


NCANDA Cohort

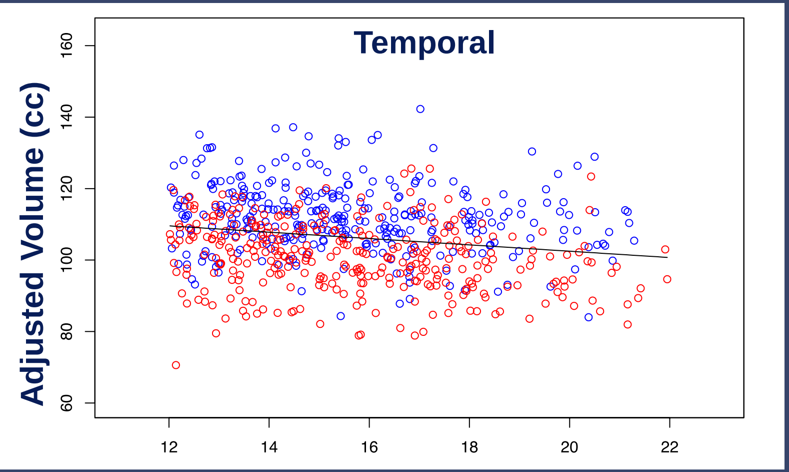
Baseline MRI by Age and Sex



Regional Cortical Volumes



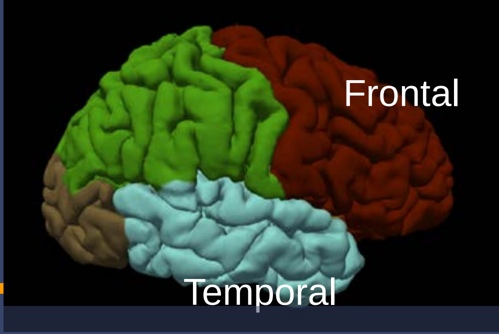
Age (years)



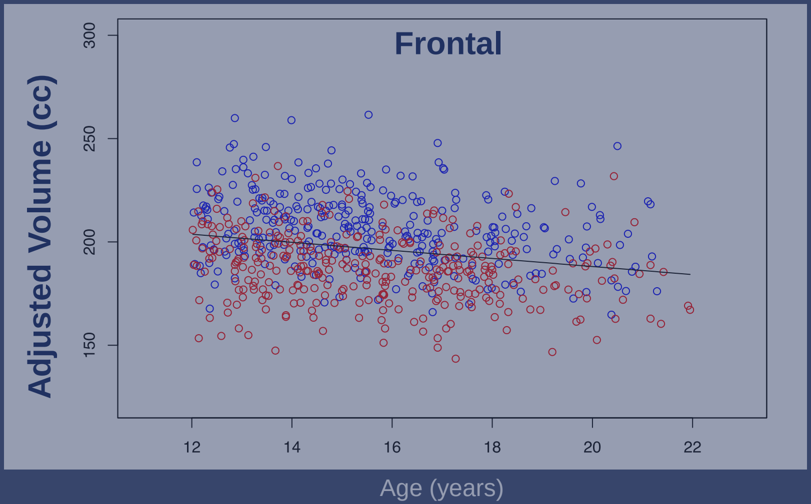
Age (years)

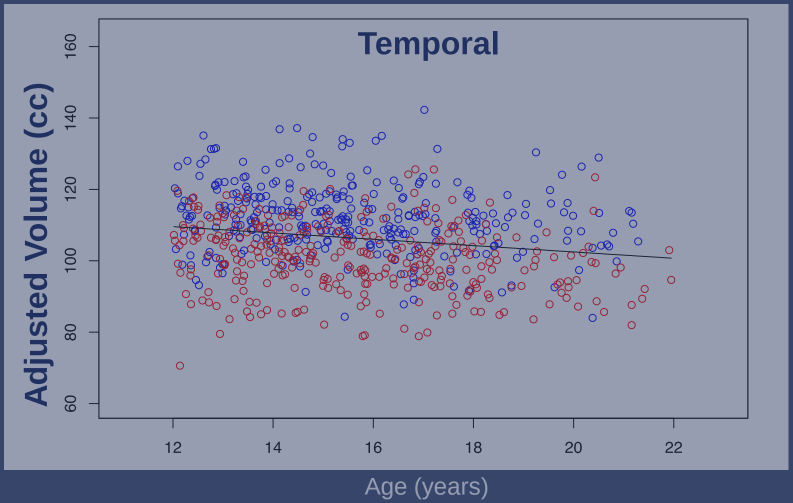
NCANDA Cohort

Baseline MRI by Age and Sex

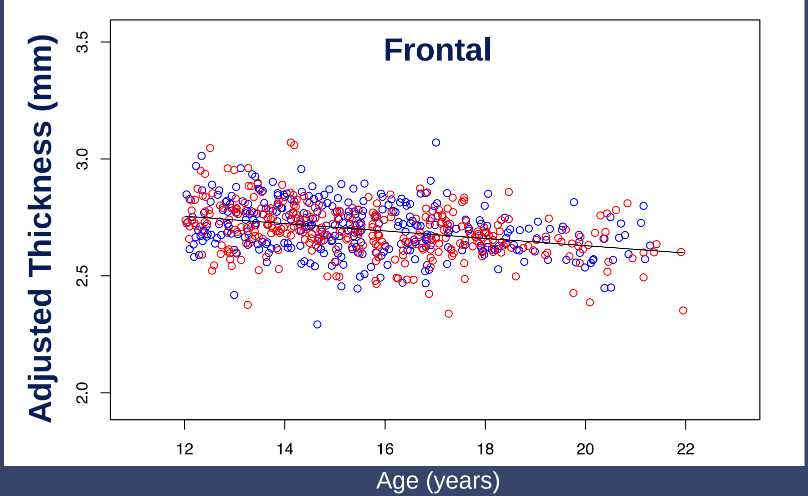


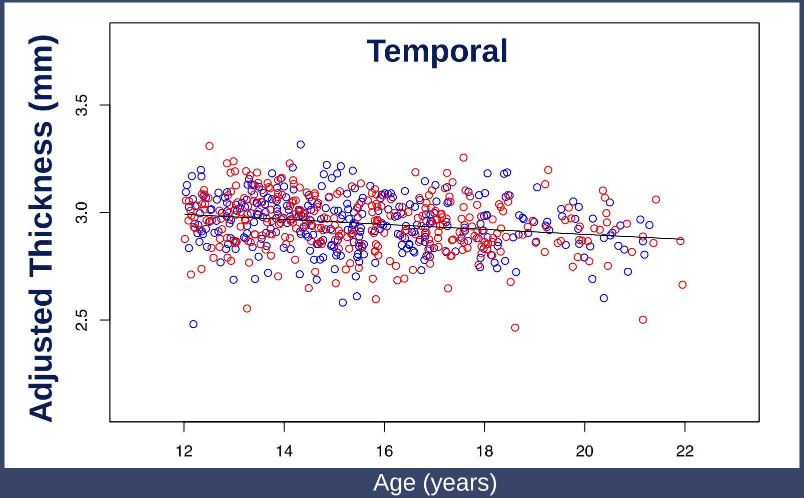
Regional Cortical Volumes





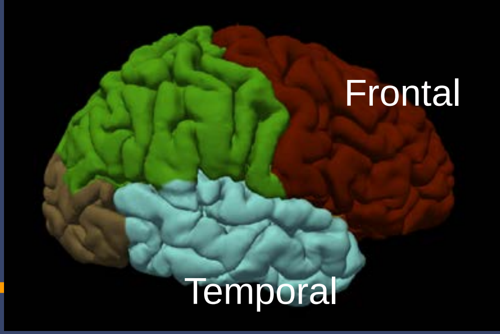
Regional Cortical Thickness

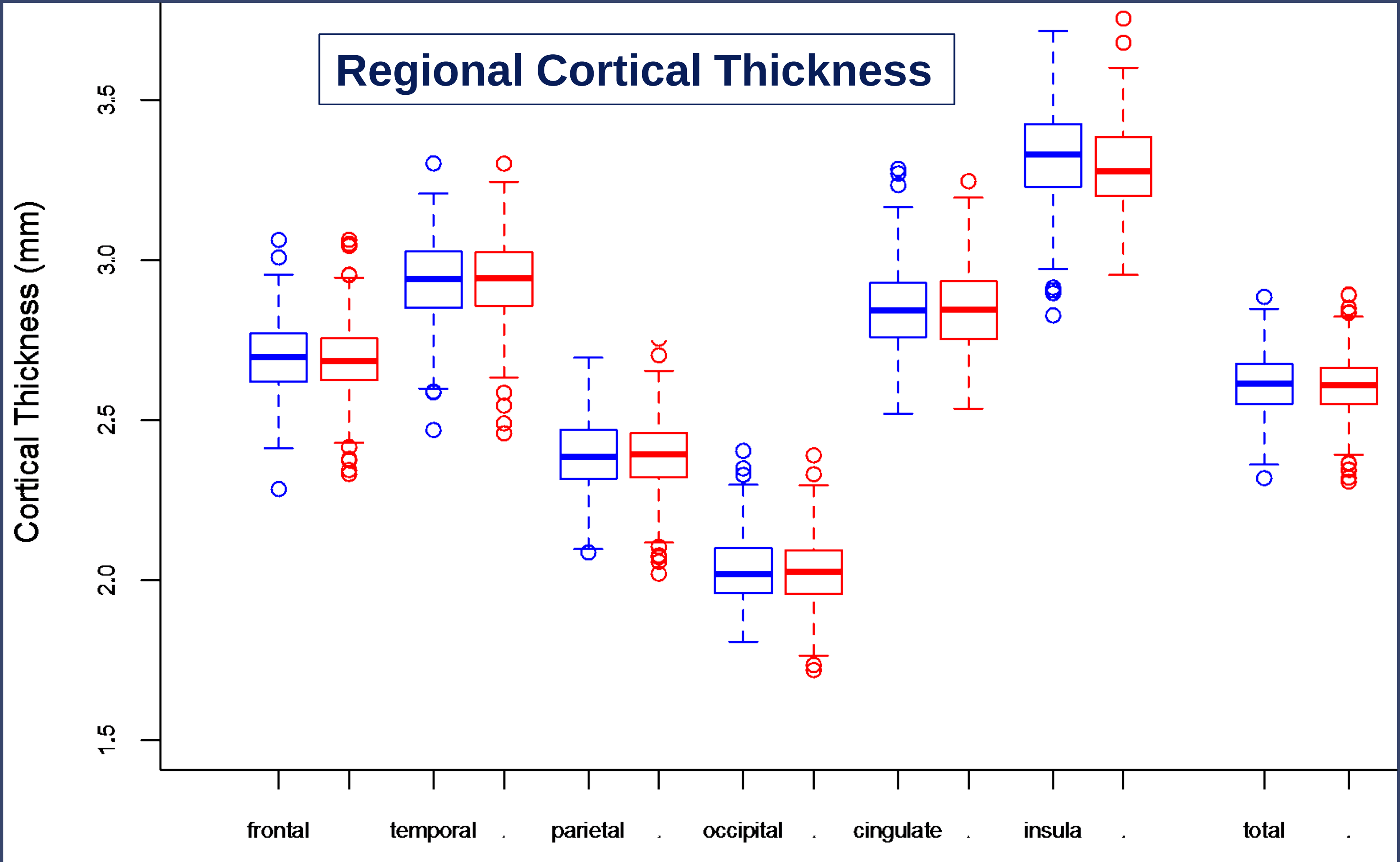




NCANDA Cohort

Baseline MRI by Age and Sex

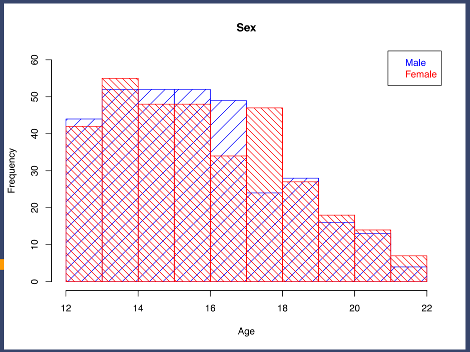


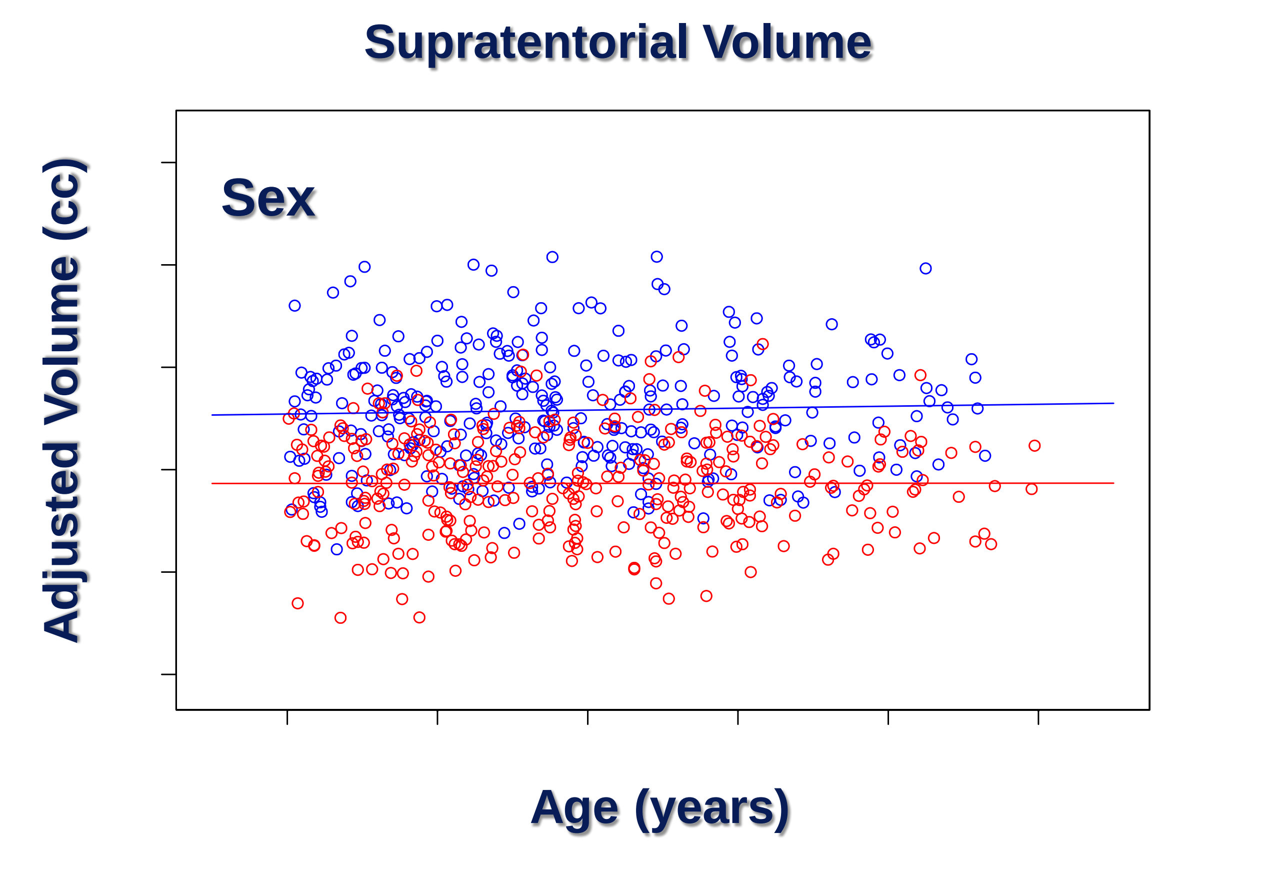


NCANDA MRI

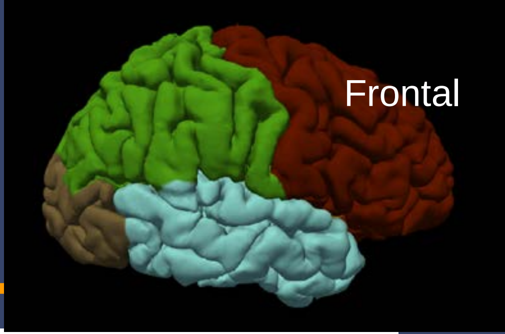
- Age
- **Headsize / Supratentorial Volume**
- Sex
- Ethnicity
- Prior Alcohol Exposure

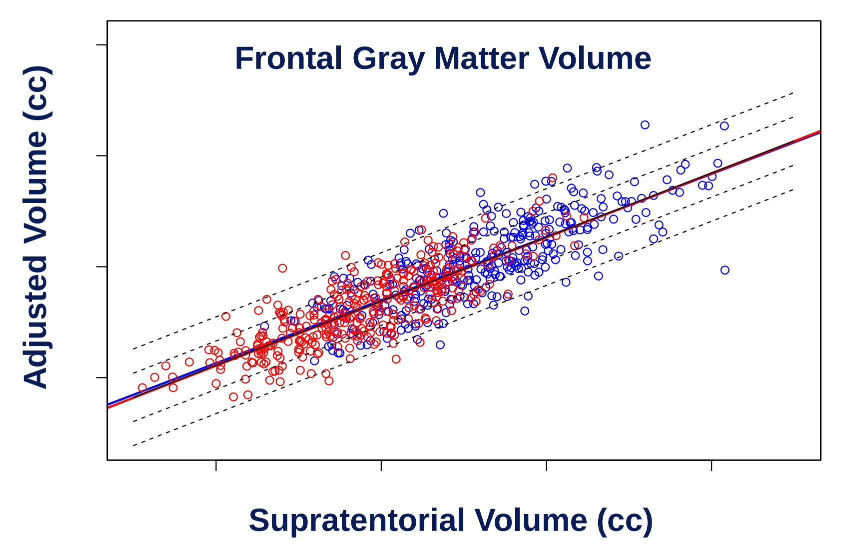
Sex Differences in Brain Size

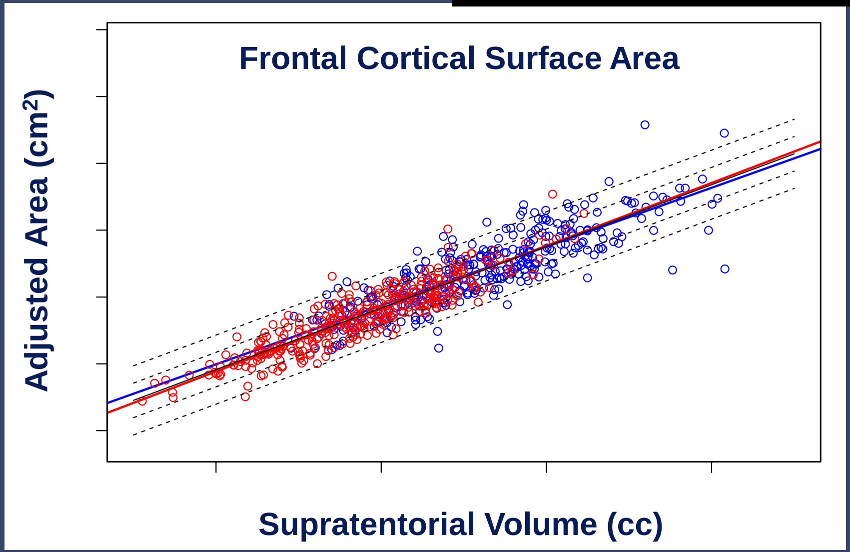


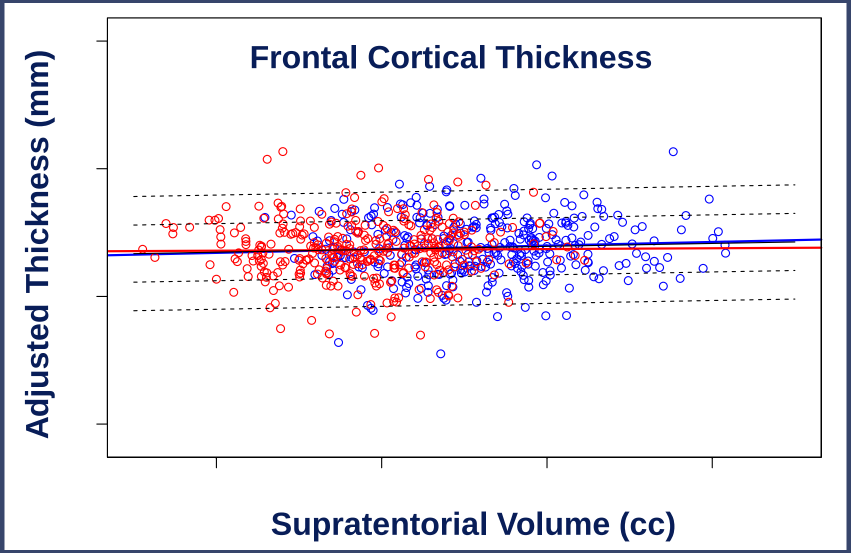


Size Metrics and Supratentorial Volume









NCANDA MRI

- Age
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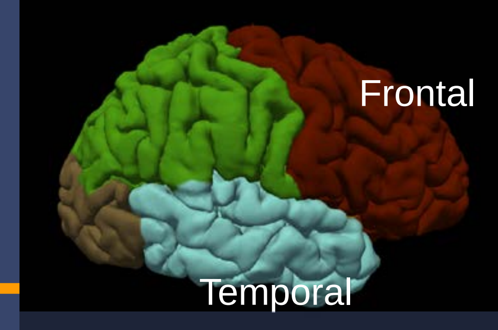
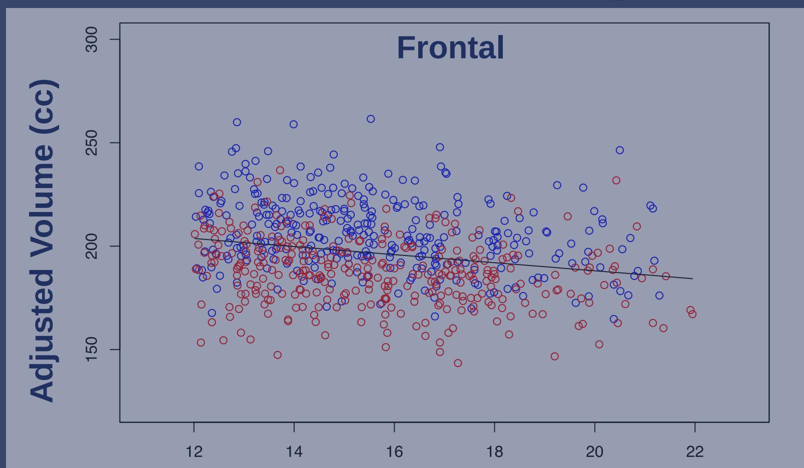
NCANDA Cohort

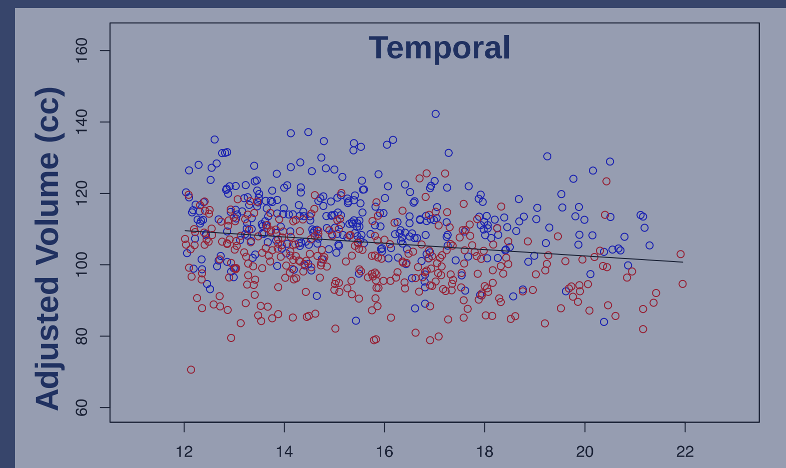
Baseline MRI by Age and Sex



Regional Cortical Volumes

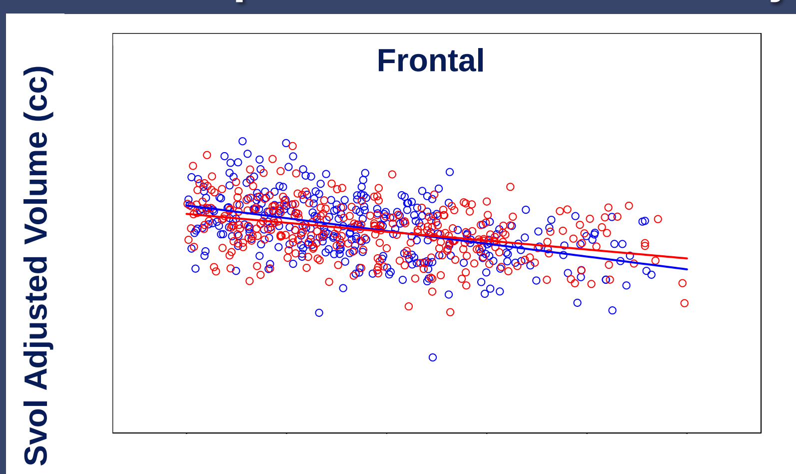


Age (years)

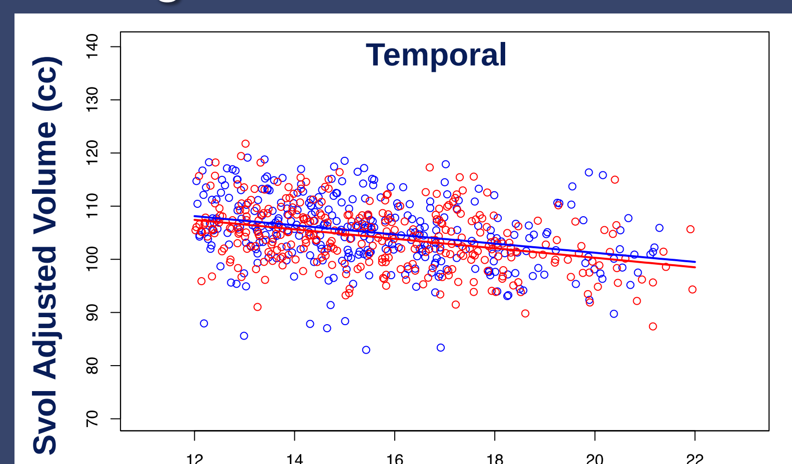


Age (years)

Supratentorial Volume -Adjusted Regional Cortical Volumes



Age (years)



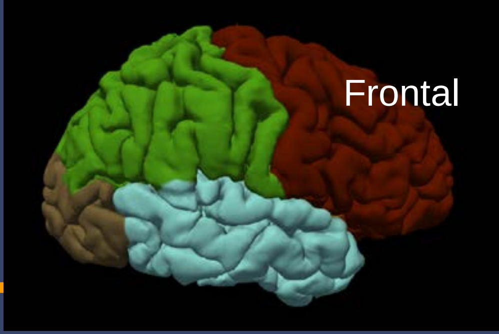
Age (years)

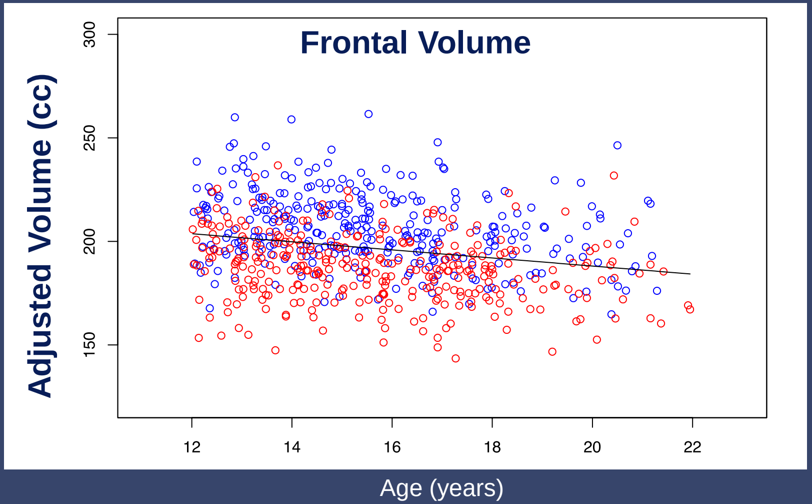
NCANDA MRI

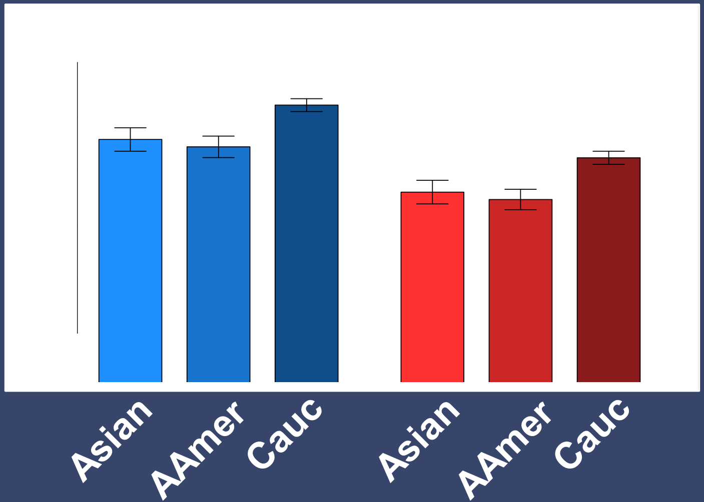
- Age
- Headsize / Supratentorial Volume
- Sex
- Ethnicity
- Prior Alcohol Exposure

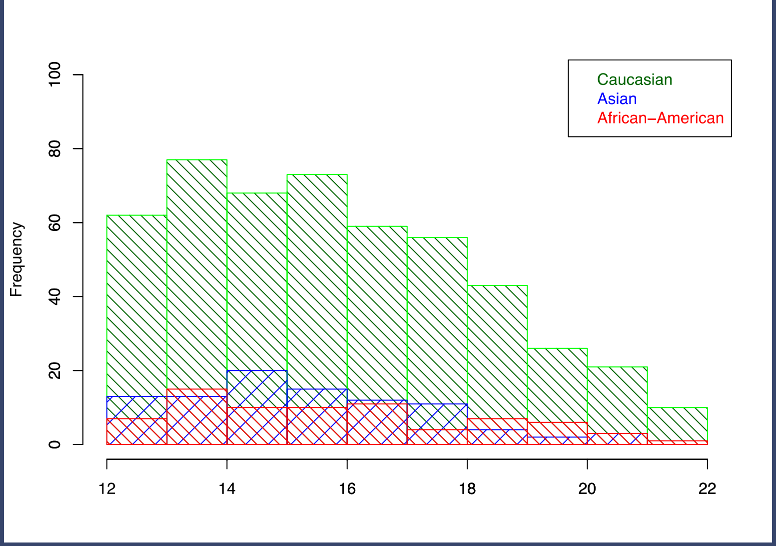
Frontal Cortex

Baseline MRI by Age, Sex, Ethnicity



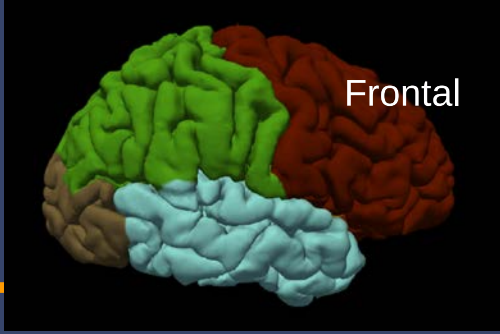




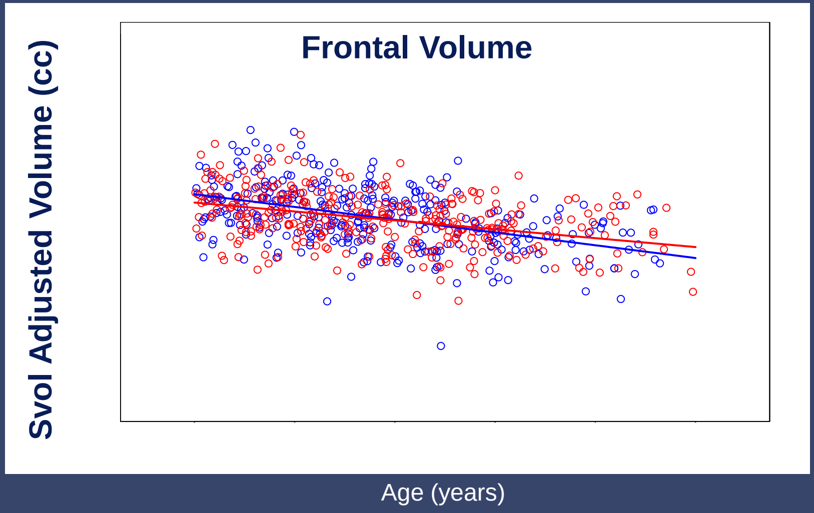


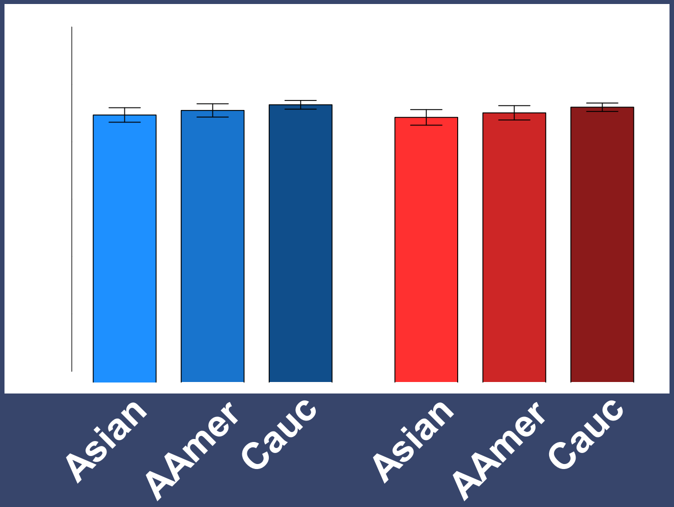
Frontal Cortex

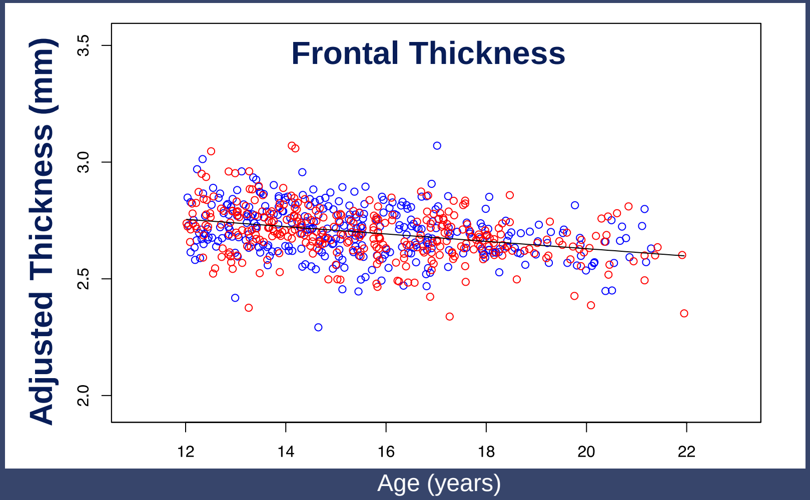
Baseline MRI by Age, Sex, Ethnicity

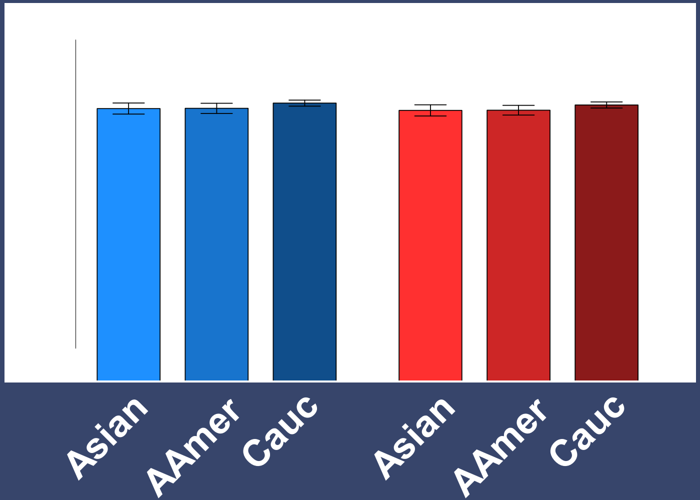


Adjusted for supratentorial volume

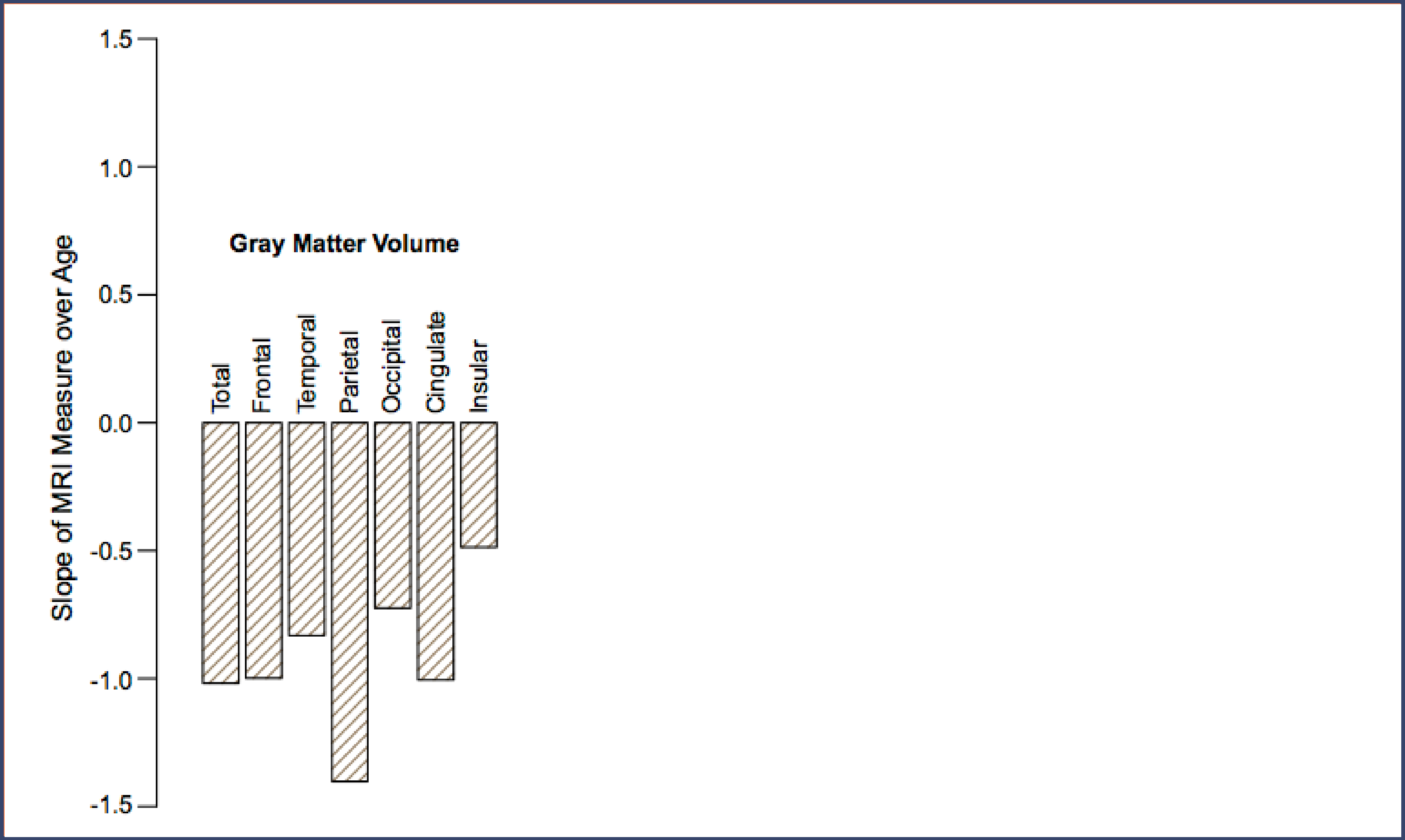




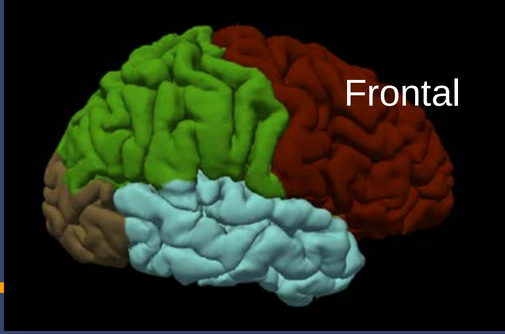


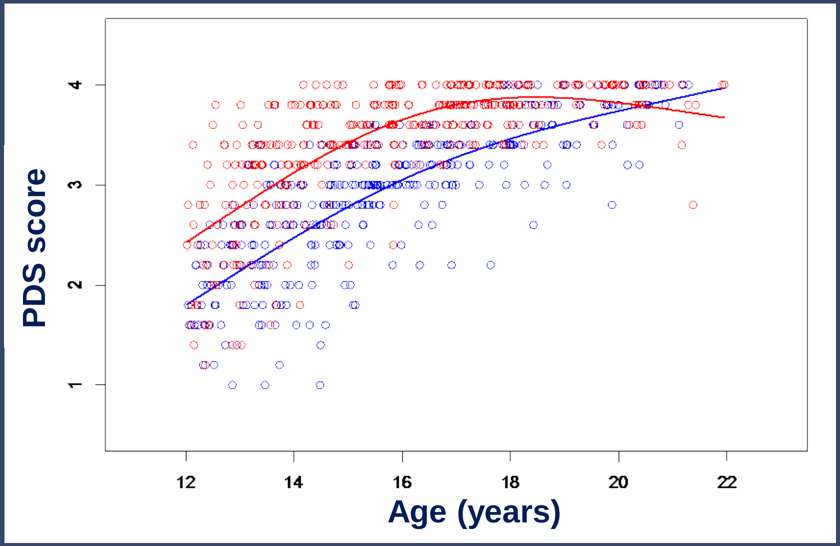


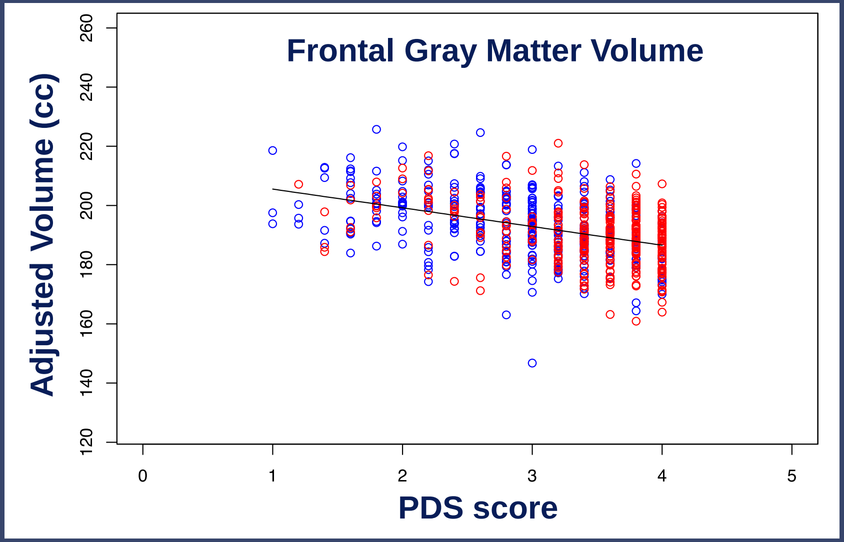
% Difference per Year (N=631)

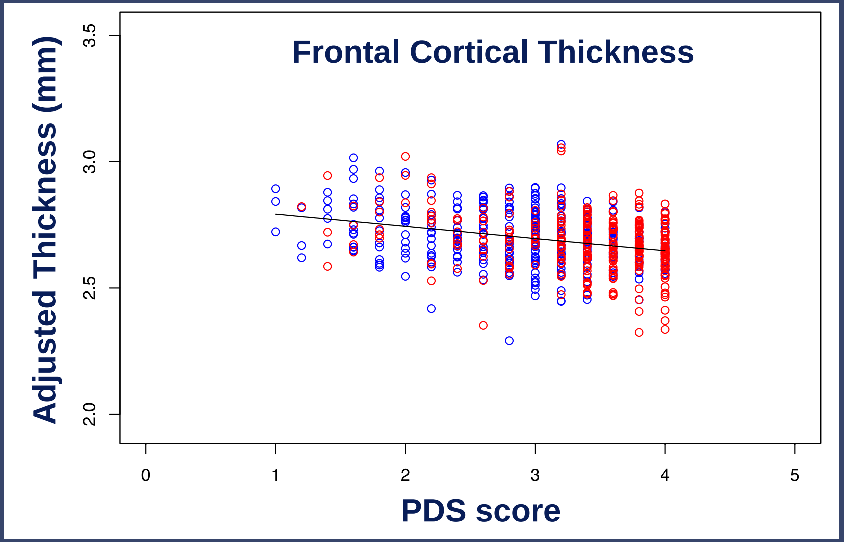


Pubertal Development

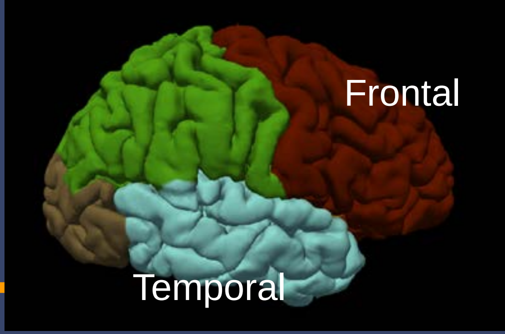






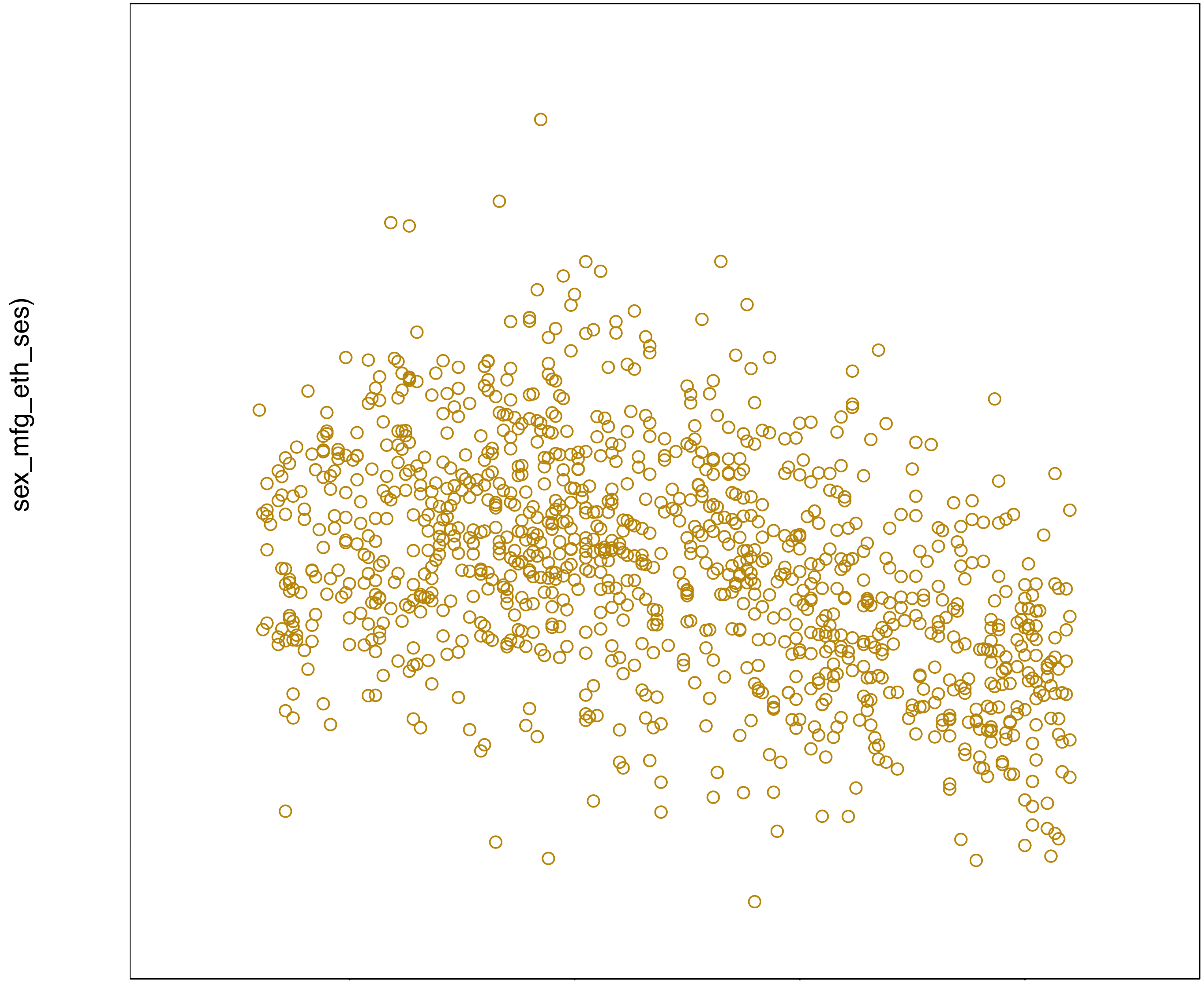


Are the data generalizable?

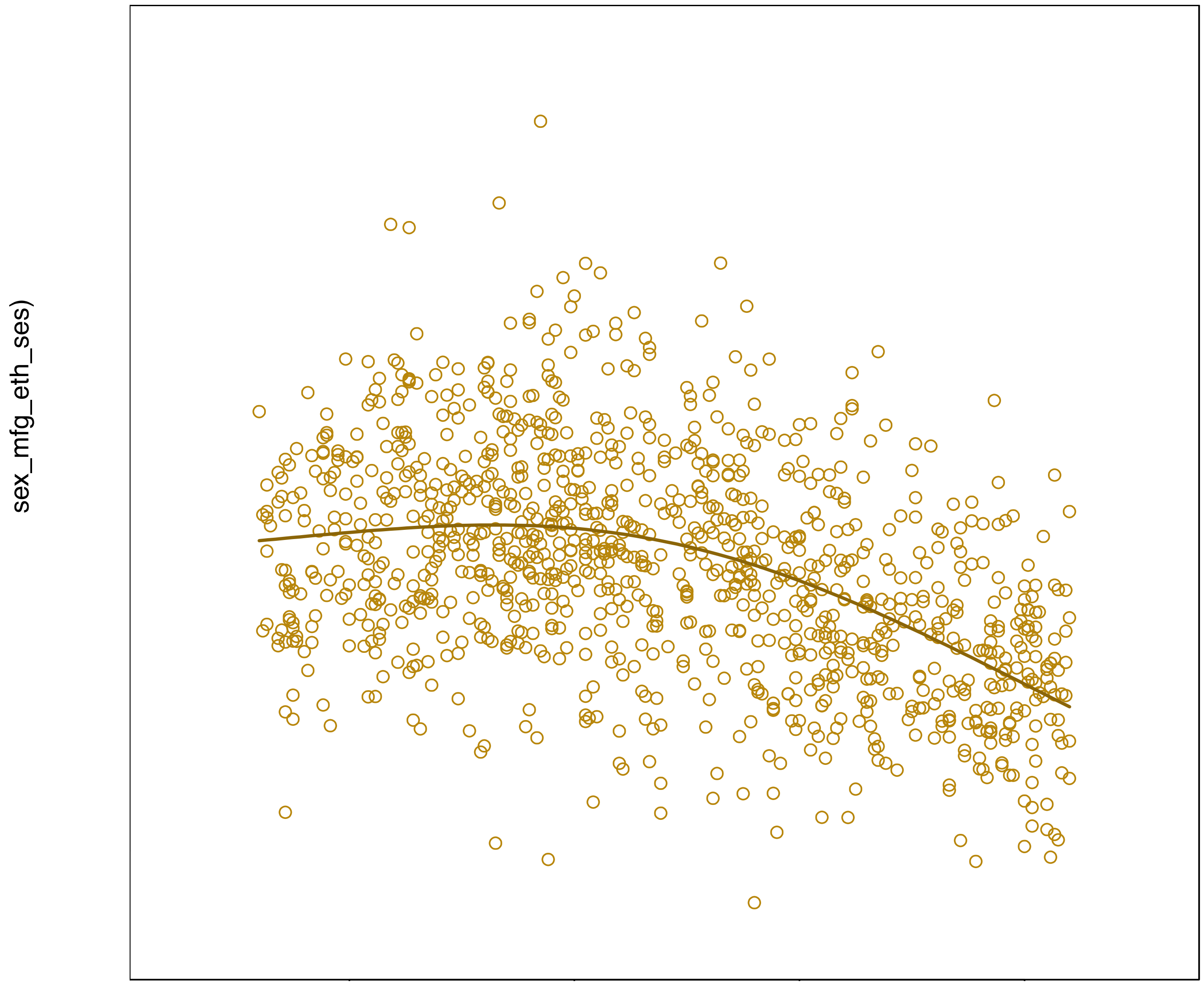


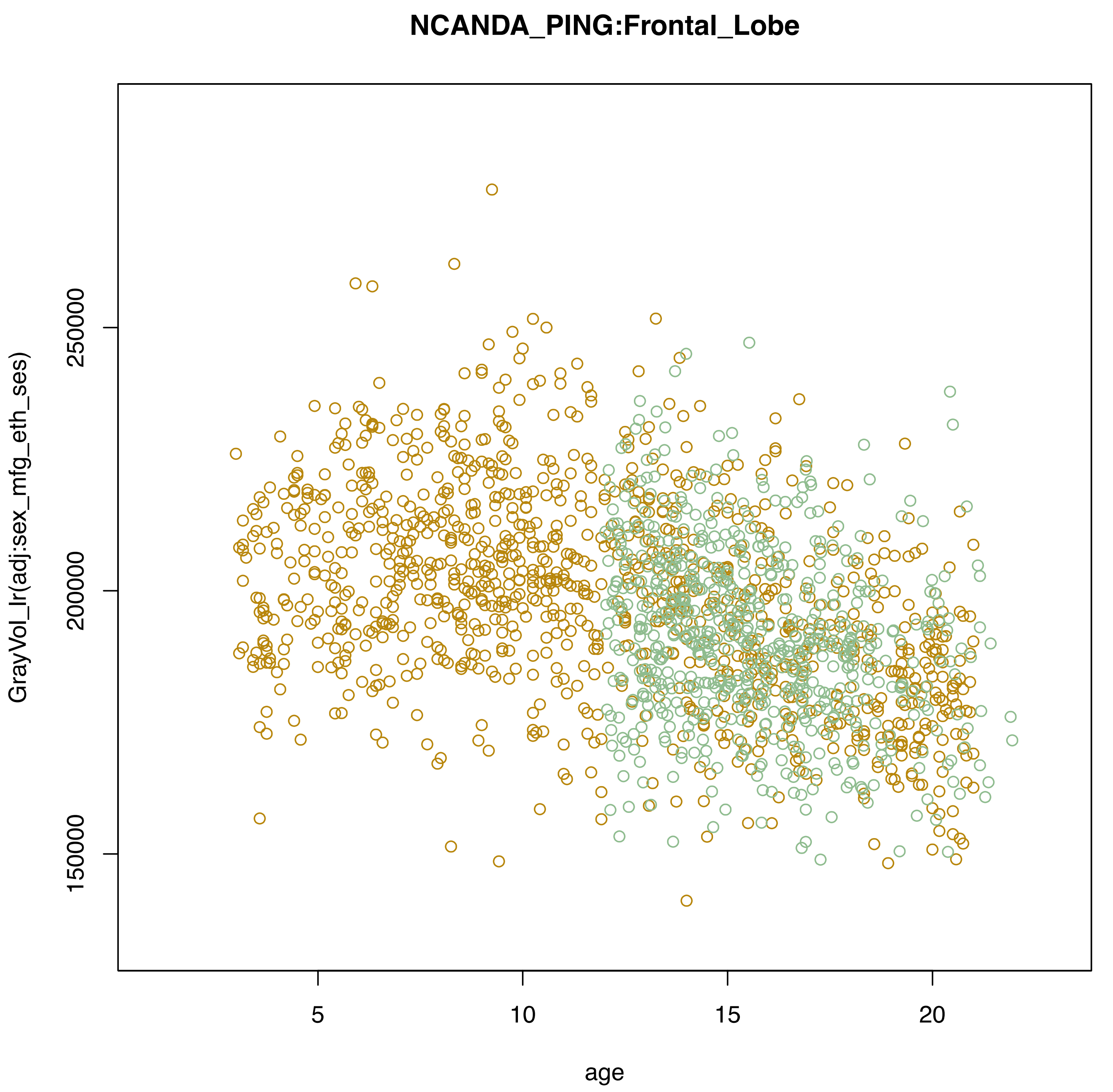
NCANDA and PING
Cortical Volume and Thickness

NCANDA: National Consortium on Alcohol & NeuroDevelopment in Adolescence
PING: Pediatric Imaging, Neurocognition, and Genetics

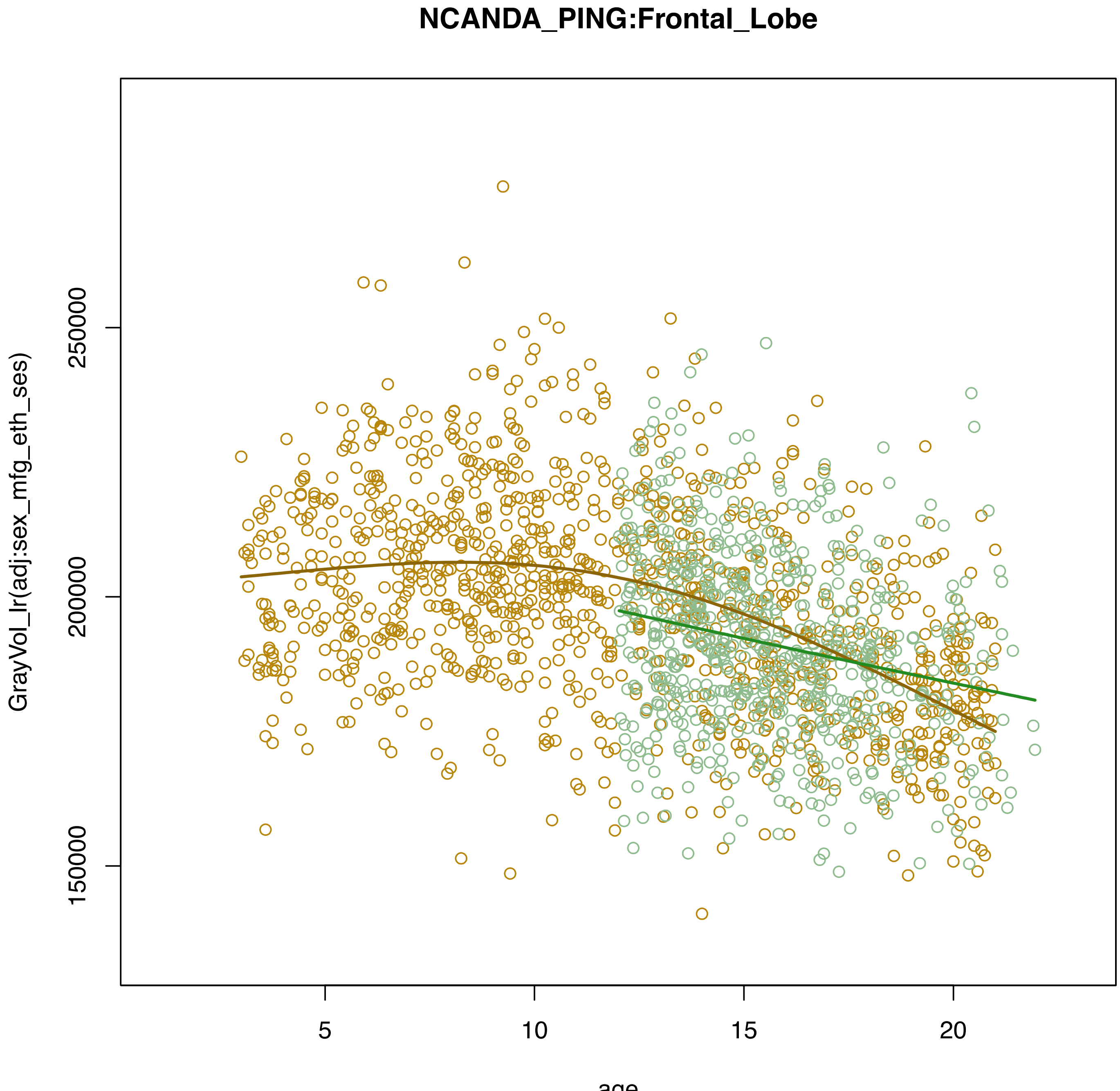


sex_mfg_eth_ses)

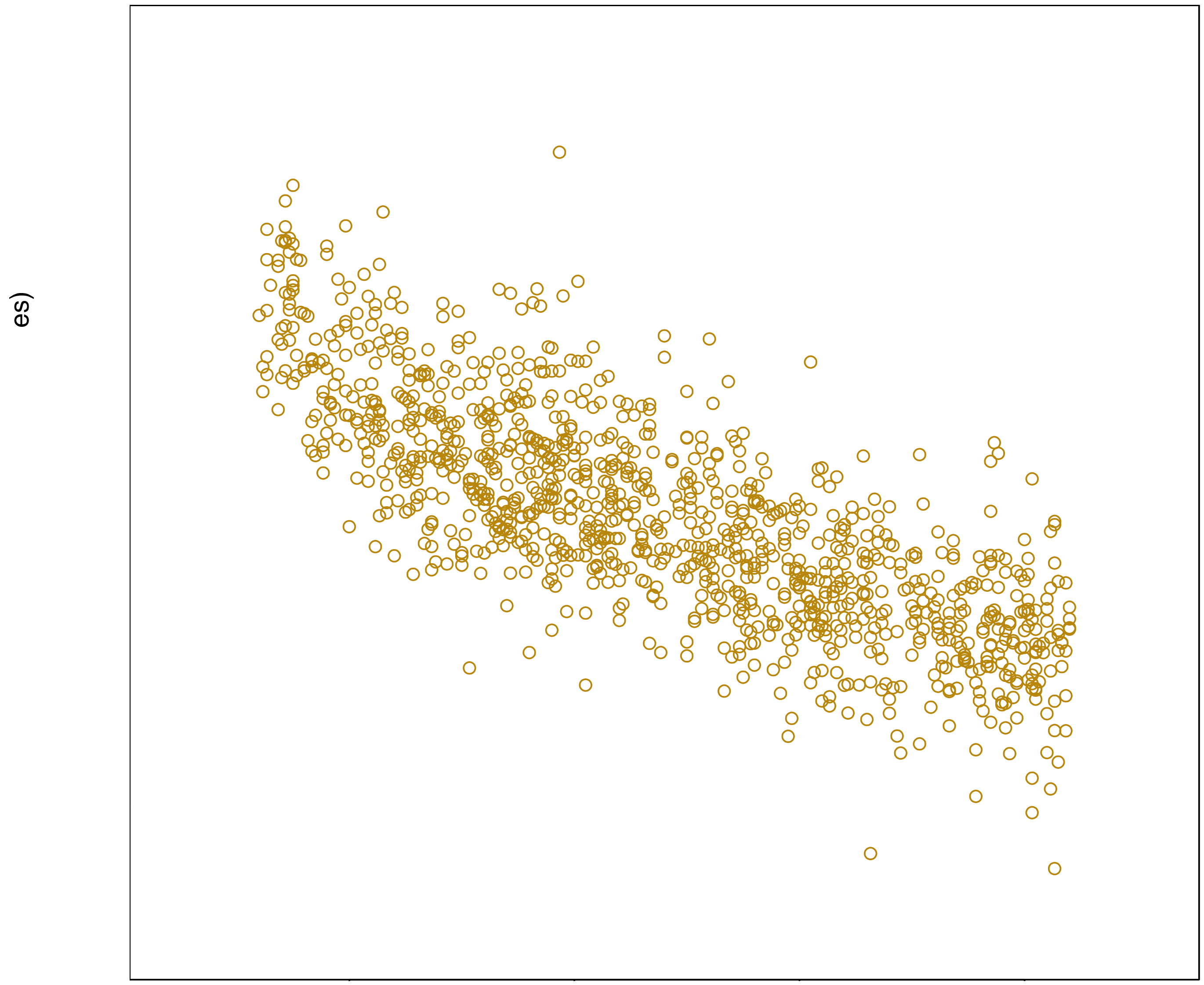

sex_mfg_eth_ses)

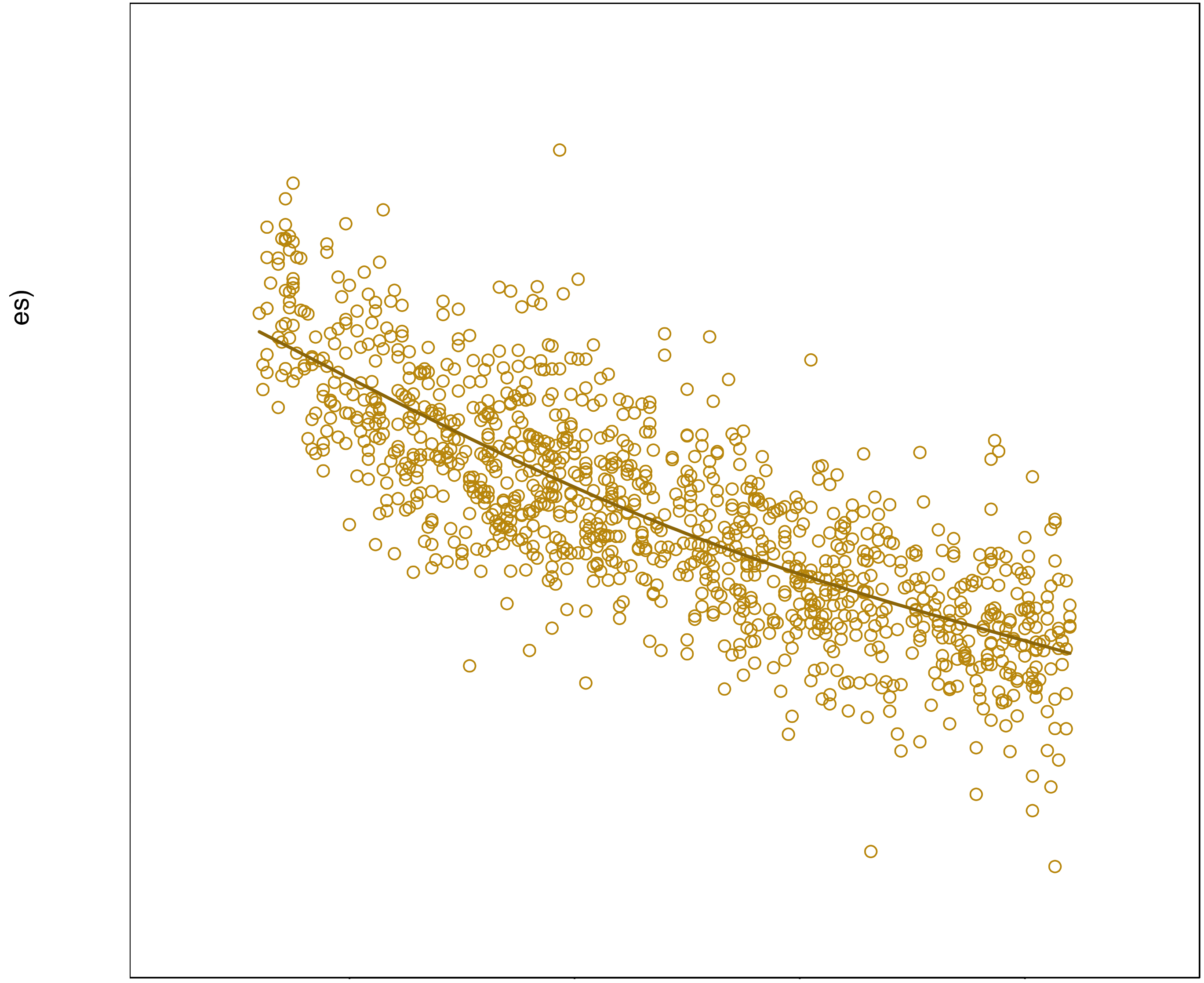


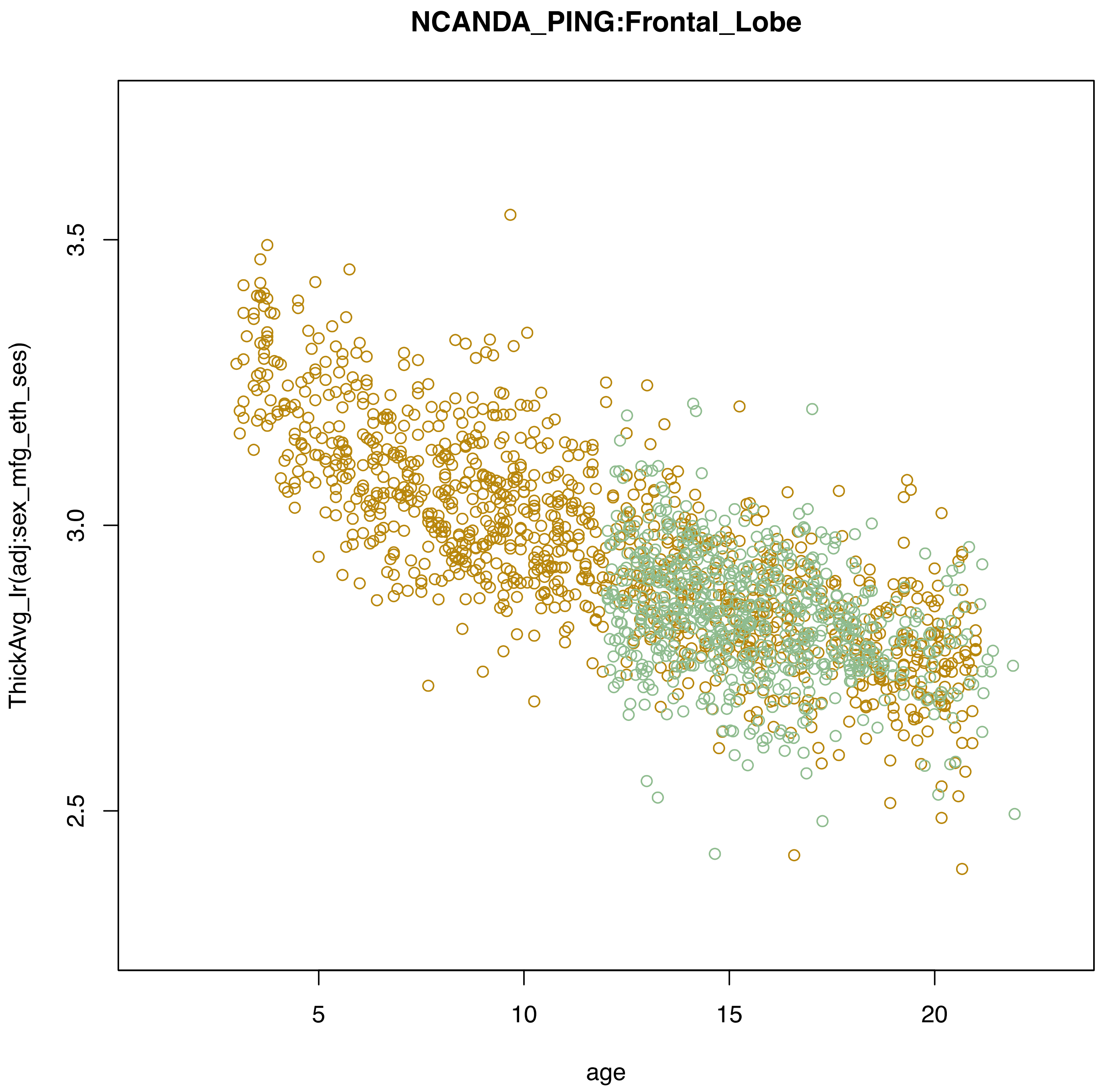
NCANDA_PING:Frontal_Lobe
GrayVol_lr(adj:sex_mfg_eth_ses)
250000
200000
150000
5
10
15
20
age



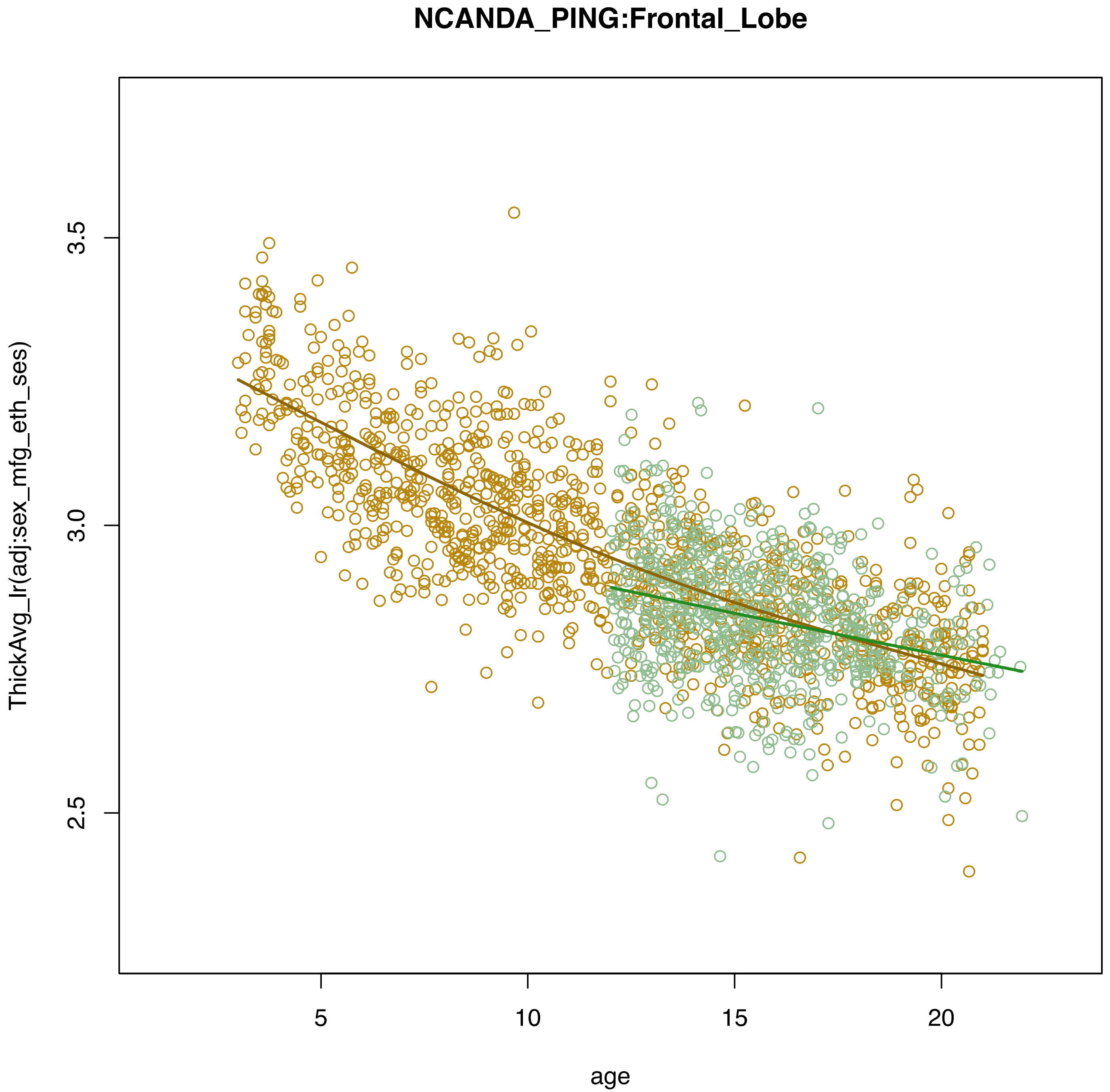
NCANDA_PING:Frontal_Lobe
GrayVol_lr(adj:sex_mfg_eth_ses)
150000
200000
250000
5
10
15
20
age


es)


es)

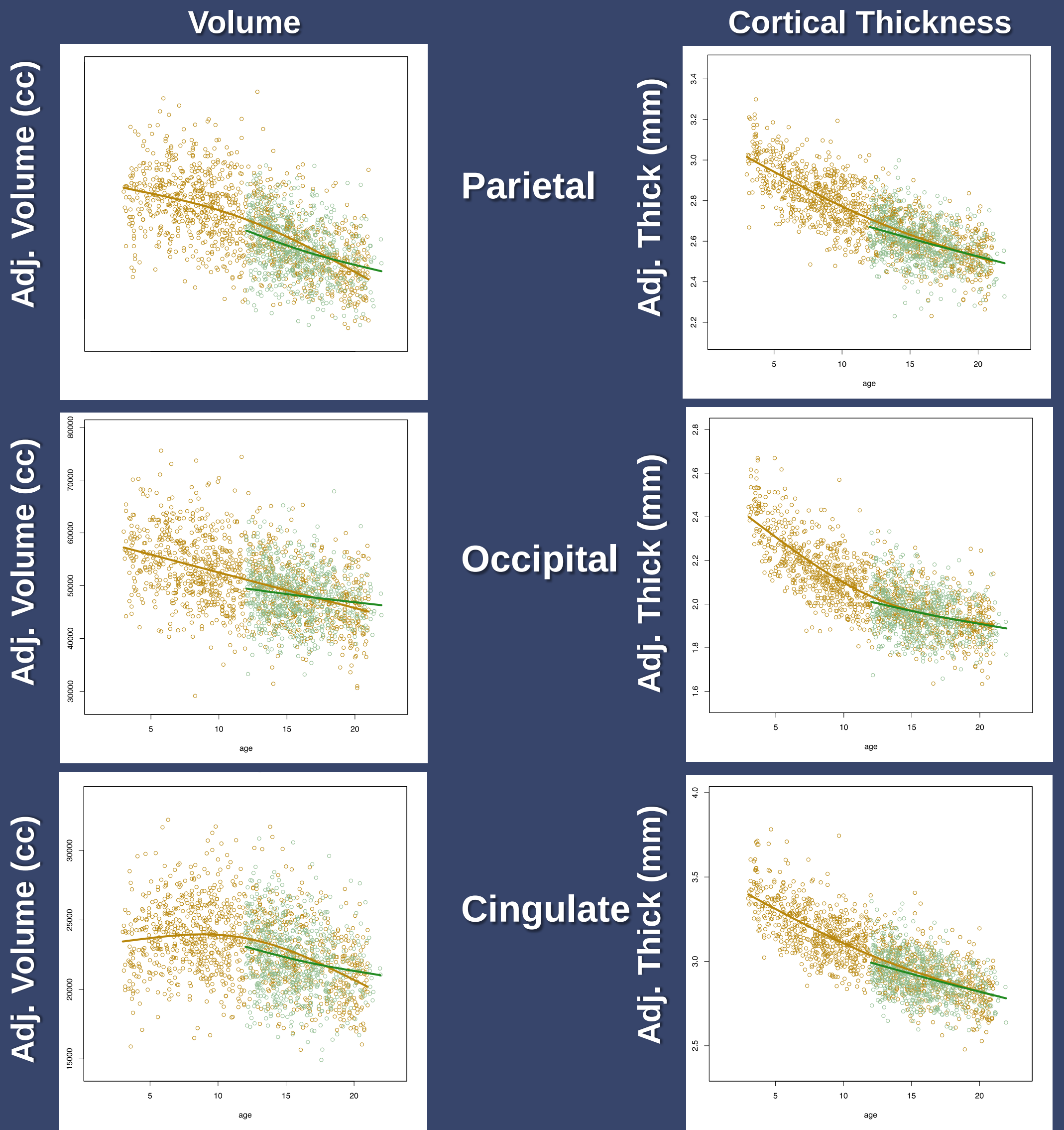


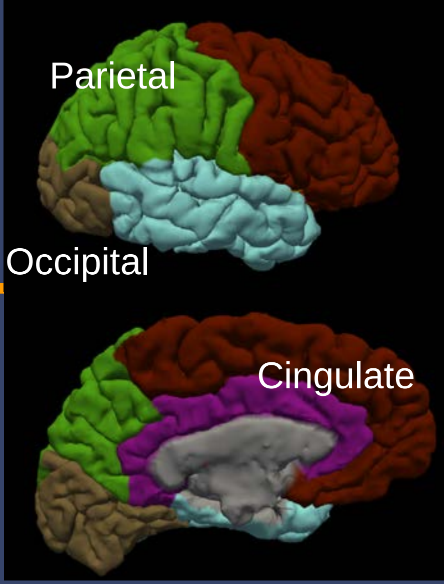
NCANDA_PING:Frontal_Lobe
ThickAvg_lr(adj:sex_mfg_eth_ses)
3.5
3.0
2.5
5
10
15
20
age


NCANDA_PING:Frontal_Lobe
ThickAvg_lr(adj:sex_mfg_eth_ses)
3.5
3.0
2.5
5
10
15
20
age

NCANDA and PING

Cortical Volume and Thickness

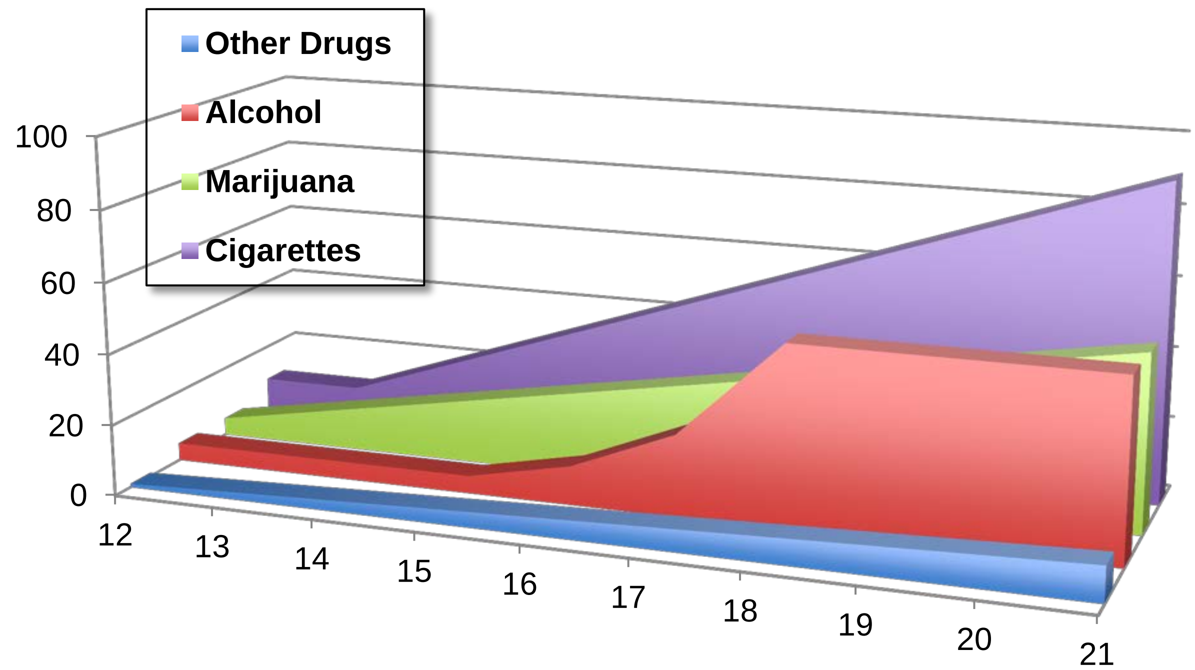


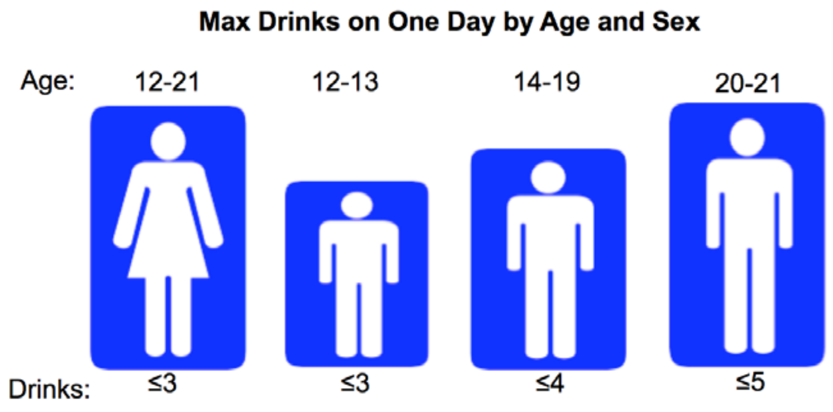


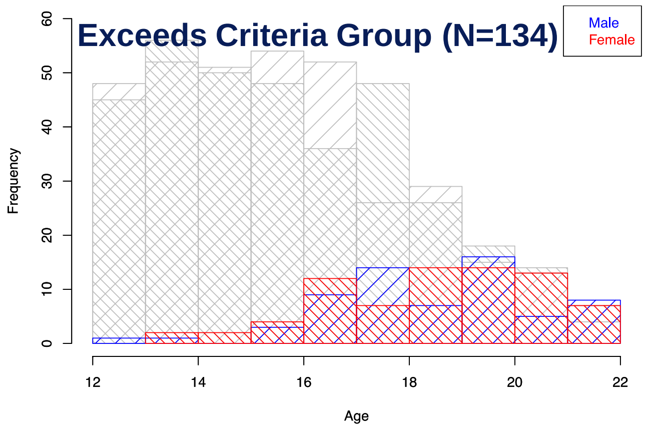
PING
NCANDA

Alcohol and Drug Use Criteria

No/low vs. Exceeds

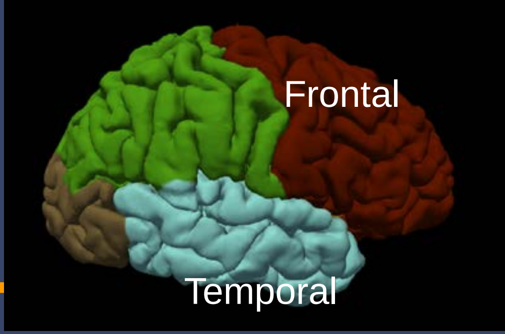


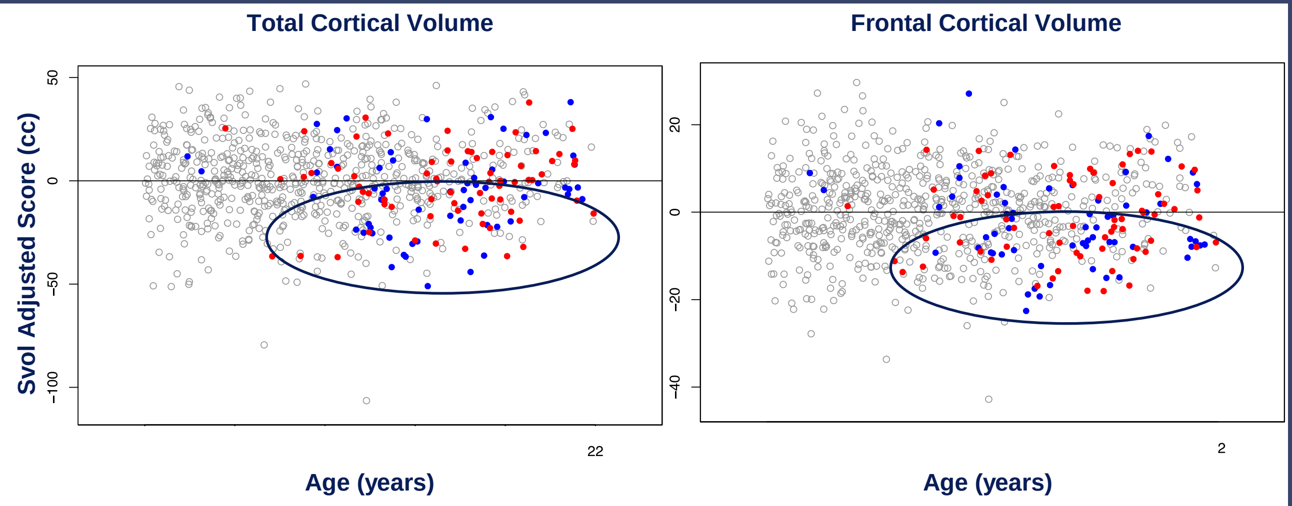




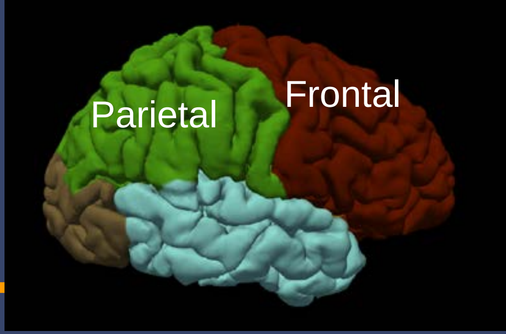
Moderate/high Alcohol

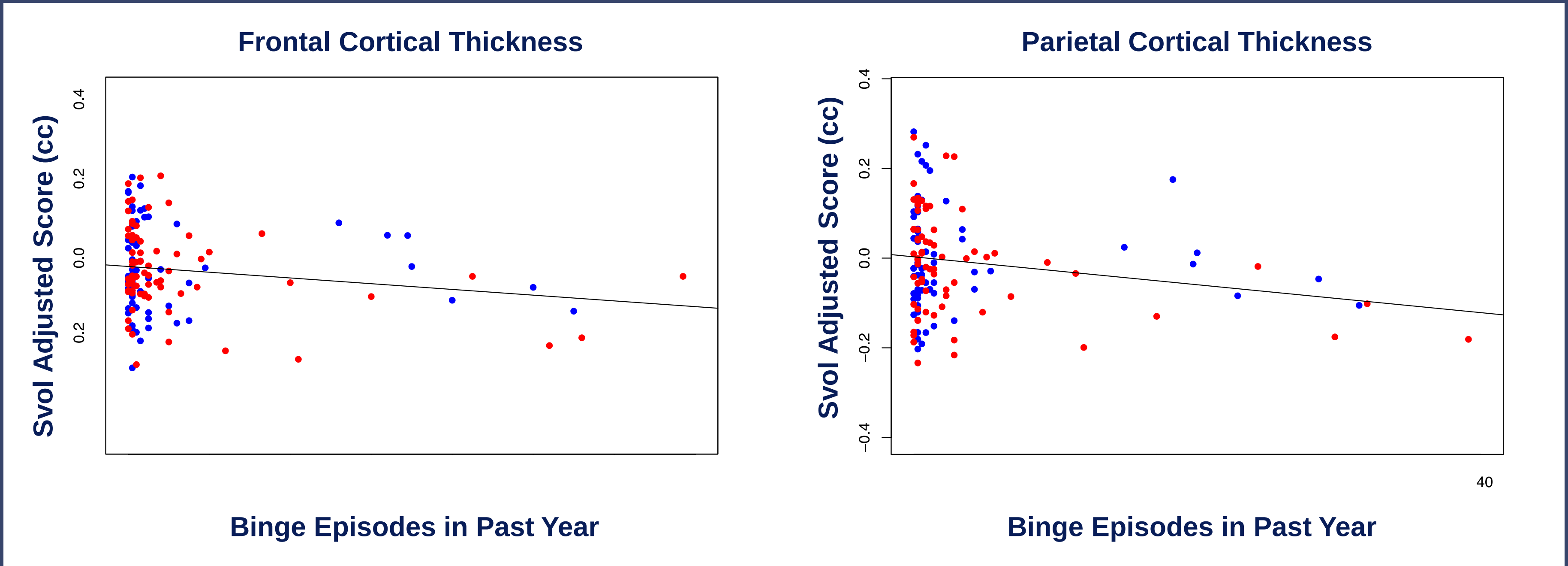
Regional Cortical Volumes and Thickness





Binge Drinking and Cortical Thickness





NCANDA Baseline MRI Findings

- In 833 with MRIs, clinical readings identified structural anomalies in 95 individuals (11.4%), ~3% precluding automated quantification.
- Regional volume and surface, but not thickness, measures showed sex and ethnicity effects that were minimized with adjustment for variation in supratentorial volume.
- NCANDA and PING data showed similar age-related differences in regional cortical volumes and thickness.
- Relative to no/low drinking youth, moderate/high alcohol drinking youth had smaller and thinner cortices in frontal, temporal, and cingulate regions.
- Youth who binged had thinner frontal and parietal cortices than no/low drinking youth.

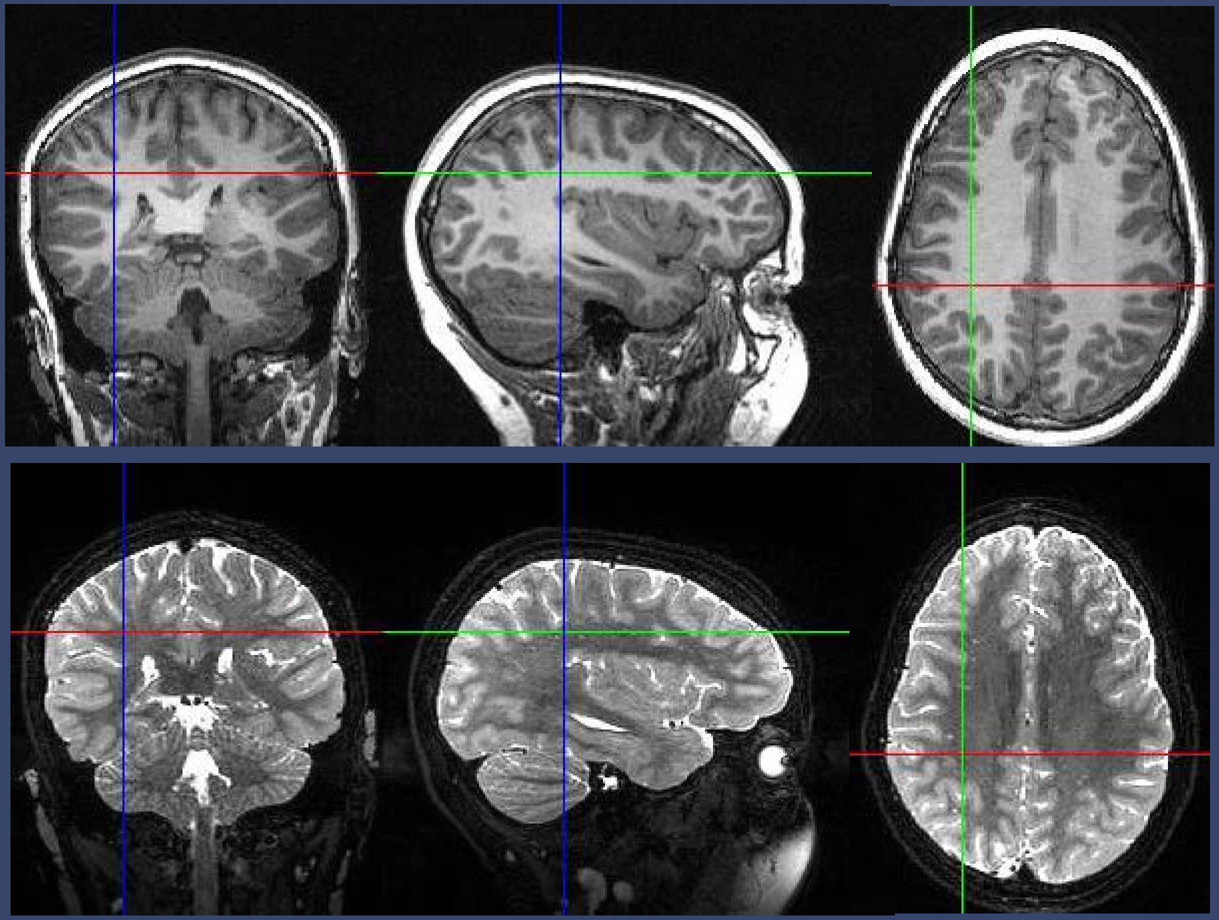
NCANDA Clinical MRI Findings

Baseline

A note of caution ....

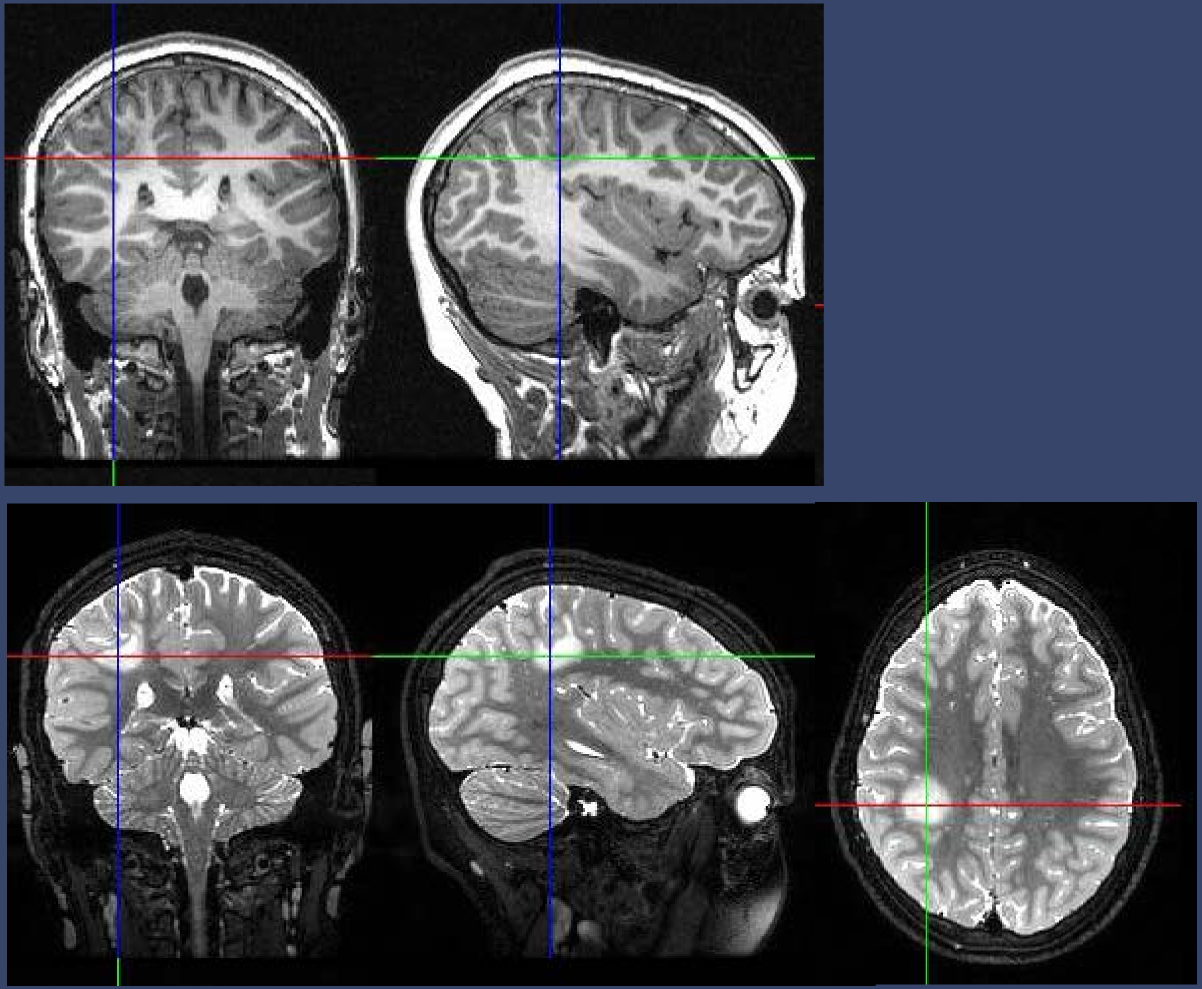
NCANDA Clinical MRI Findings

Baseline



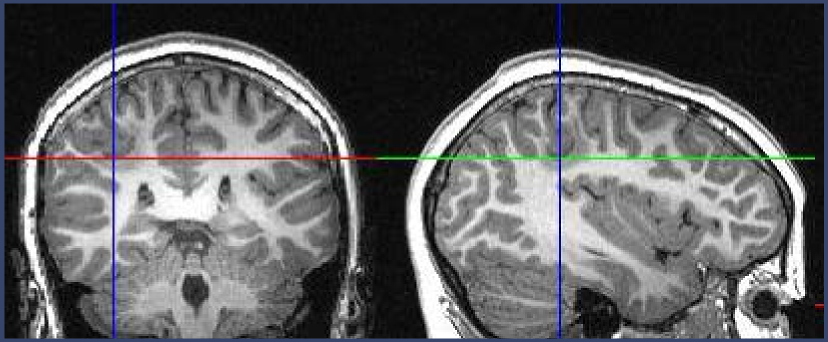
NCANDA Clinical MRI Findings

1-year Followup



NCANDA Clinical MRI Findings

1-year Followup



Even in a group of healthy highly screened participants with normal brain structure at study entry, pathology will emerge in a sample this size.