American Psychiatric Association
San Diego, CA
24 May 2017

Use of Multimodal Neuroimaging Techniques to Examine Age, Sex, and Alcohol-Related Changes in Brain Structure Through Adolescence and Young Adulthood

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Supported by NIH/NIAAA

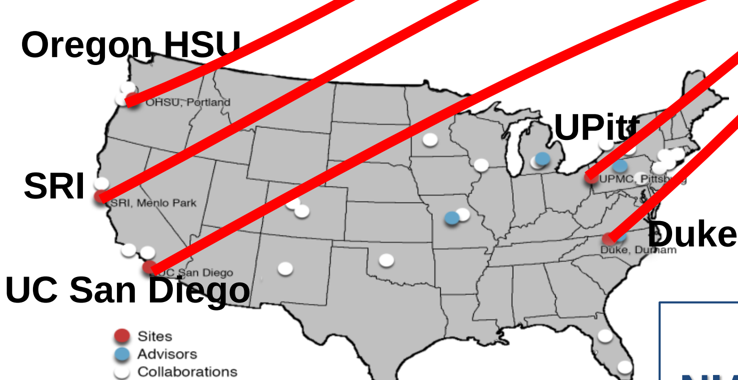
National Consortium on Alcohol and NeuroDevelopment in Adolescence

NCANDA
ncanda.org

Prospective monitoring of brain development in 831 adolescents annually for 5 years to

- **determine the effects of early, heavy alcohol use on brain structure and function before drinking onset**
  - **647 no/low drinking**
  - **134 exceeded criteria**
  - **Cohort sequential design**
    age 12-14, 15-17, 18-21 years

5 U.S. Recruitment Sites



FUNDING
NIAAA, NIDA, NIMH, NICHD

SRI+Stanford

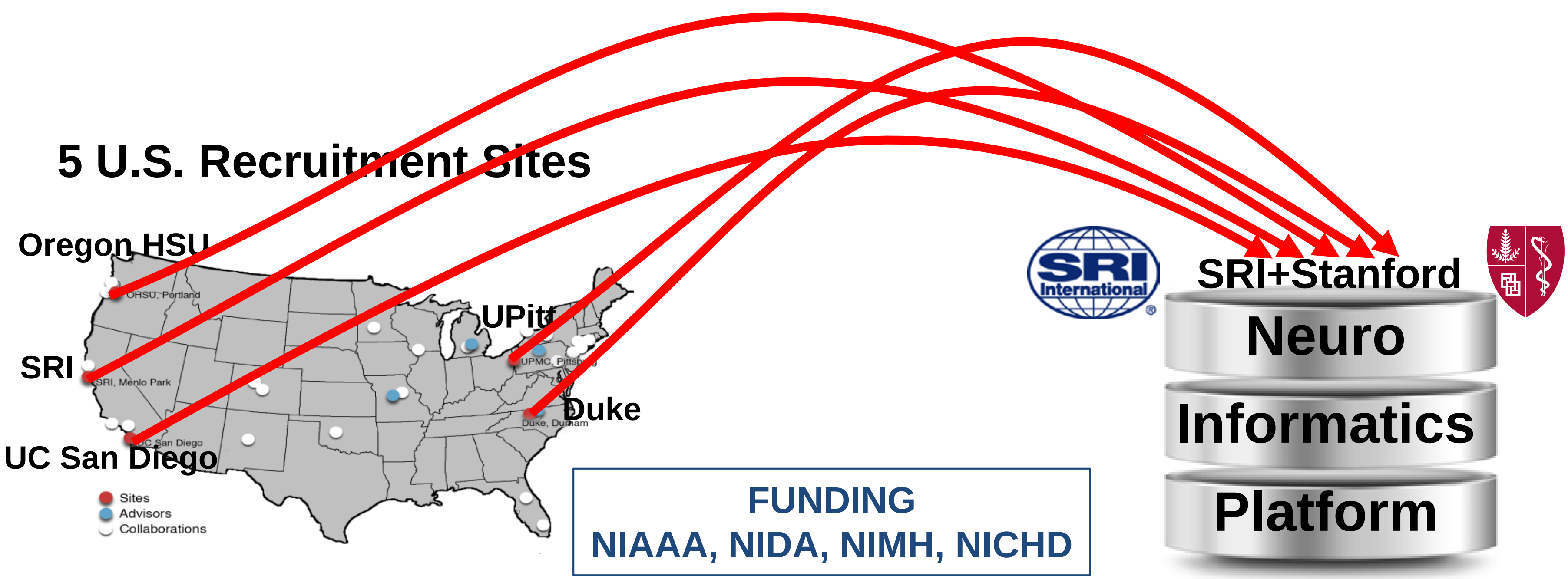
Neuro
Informatics
Platform

Extending Analysis of Imaging Data

Cortical Myelin

Subcortical Brain Iron

Effects of Initiation of Drinking

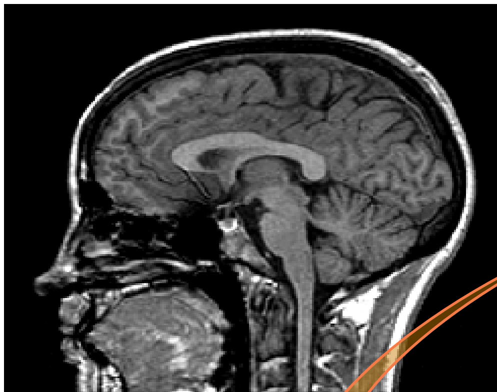


FUNDING
NIAAA, NIDA, NIMH, NICHD

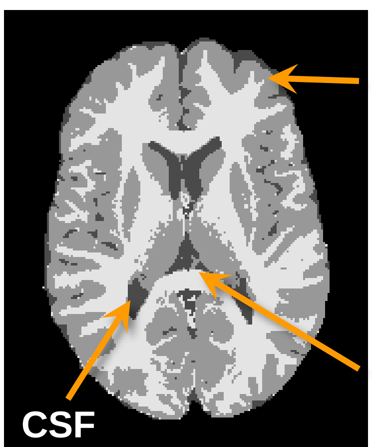
Structural MRI

Quantitative Measures of Regional Brain Tissue

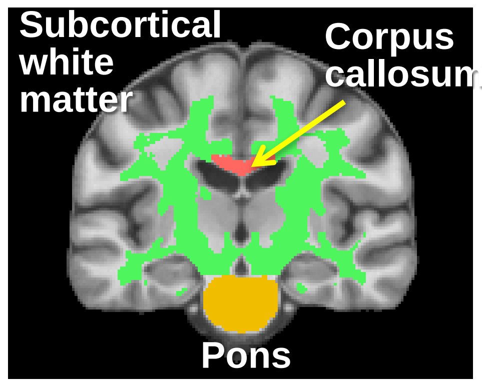
Structural MRI



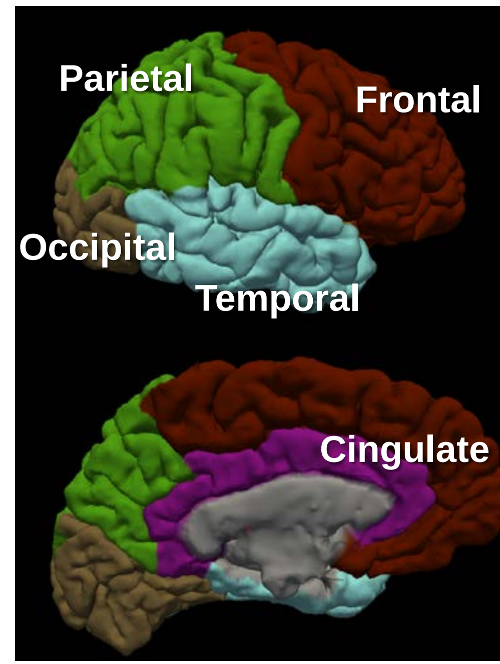
Tissue Segmentation



SRI24 White Matter Regions

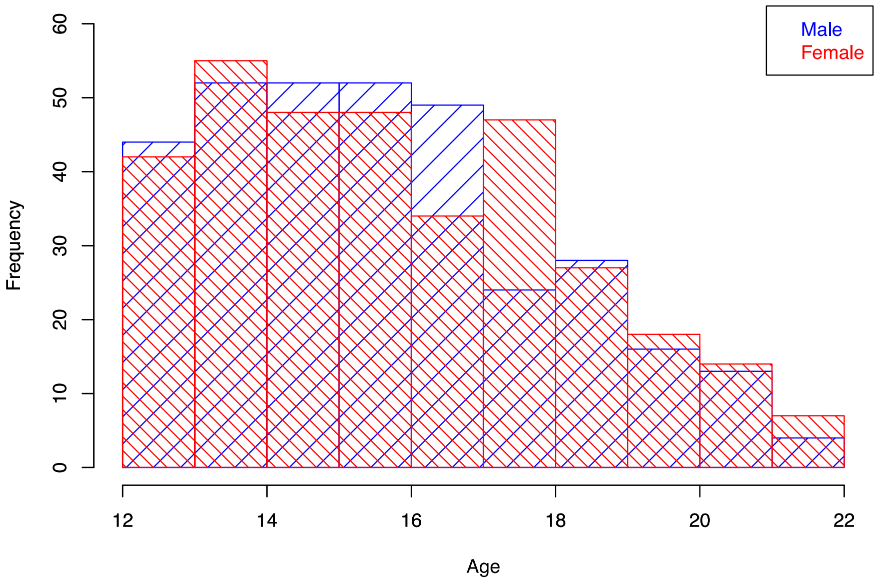


FreeSurfer Gray Matter Regions

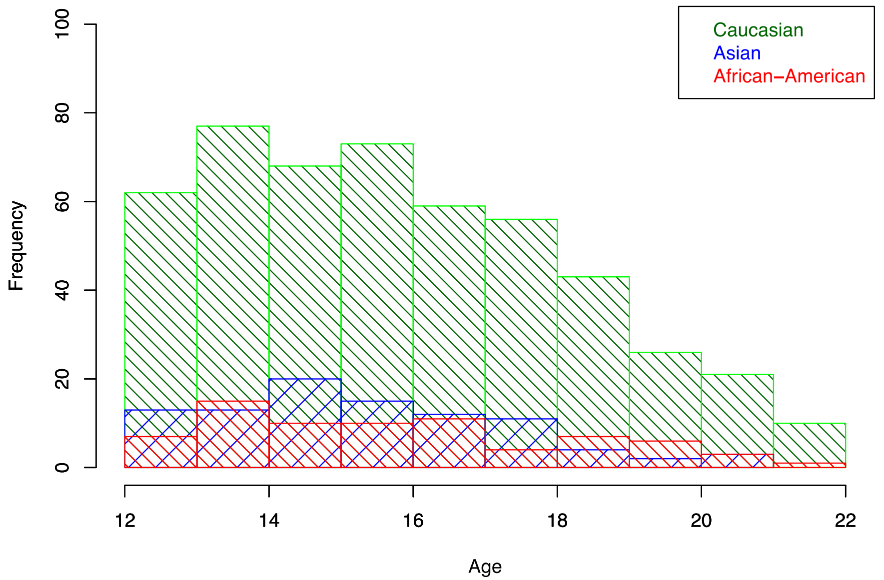


NCANDA 647 No-to-Low Drinking Sample

Sex

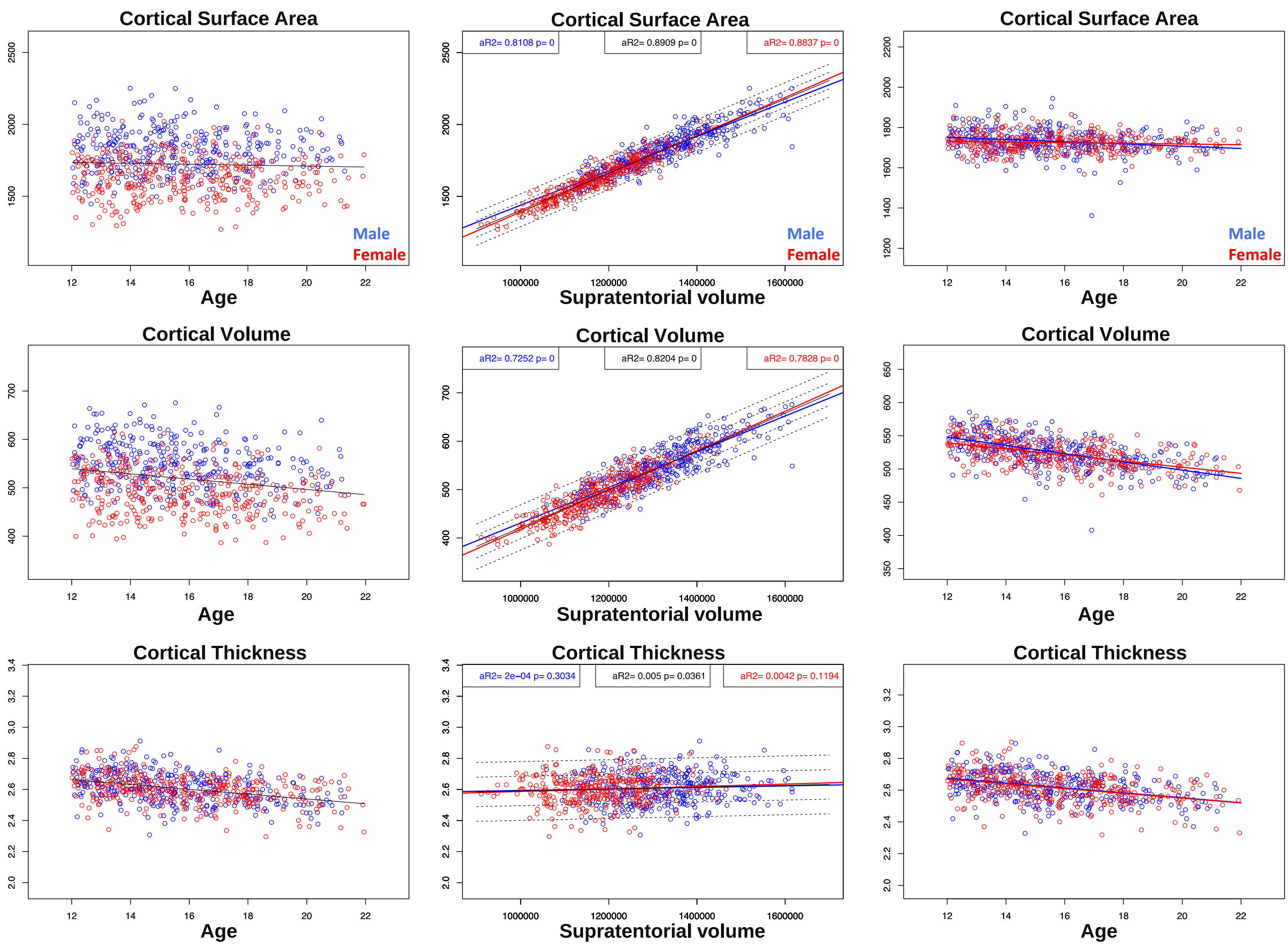


Ethnicity



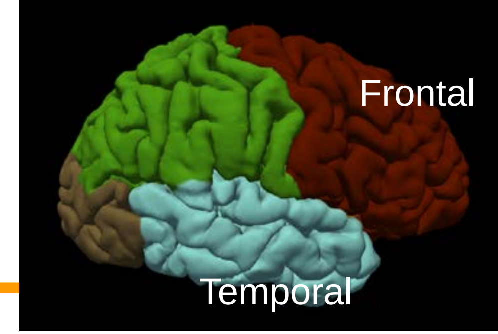
Pfefferbaum et al. *Cerebral Cortex* 2016

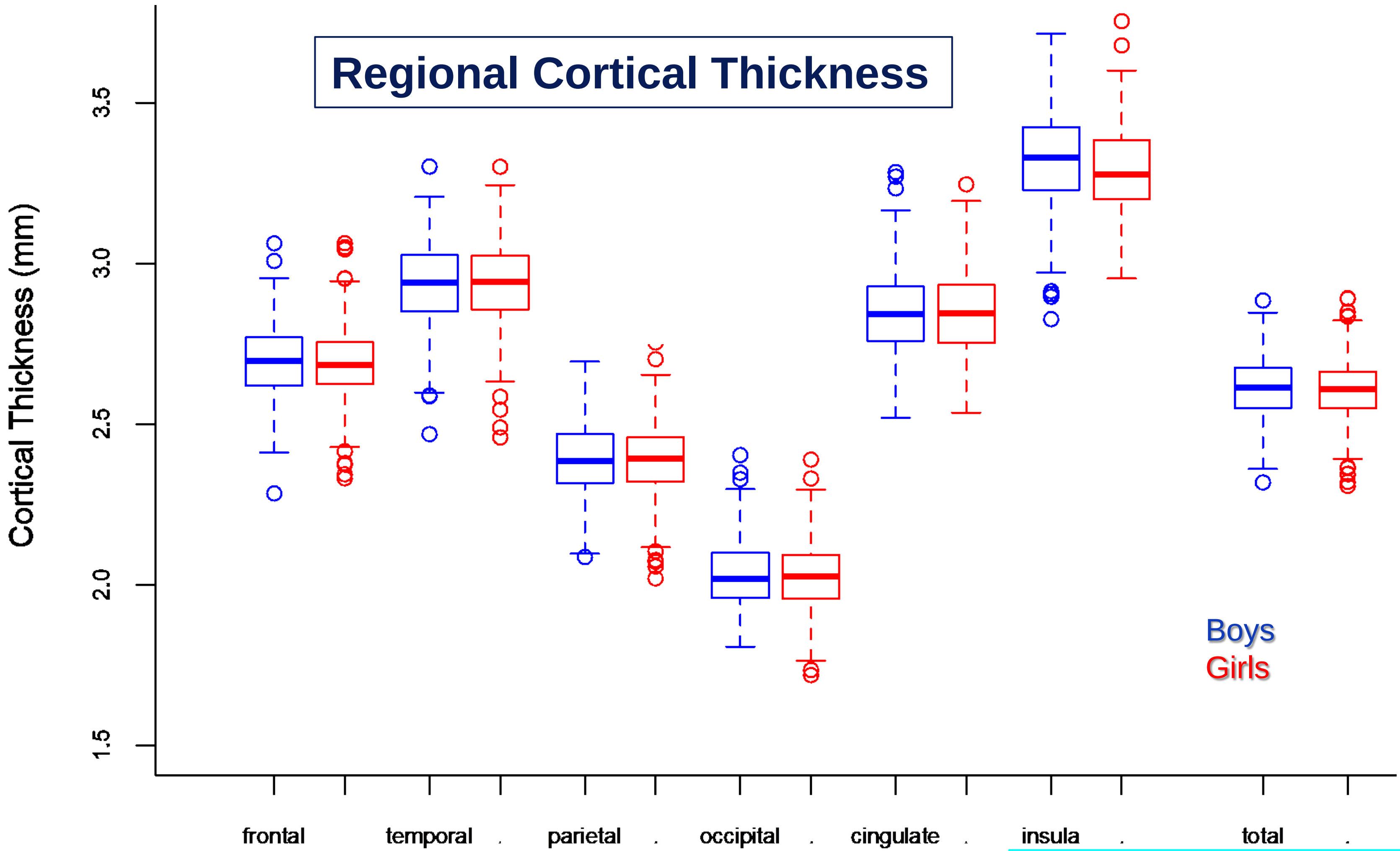
Source of Sex Difference in Cortical Measures



NCANDA Cohort

Baseline MRI by Age and Sex





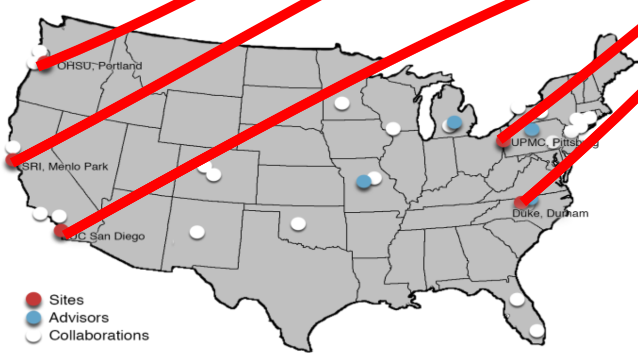
Pfefferbaum et al. *Cerebral Cortex* 2016

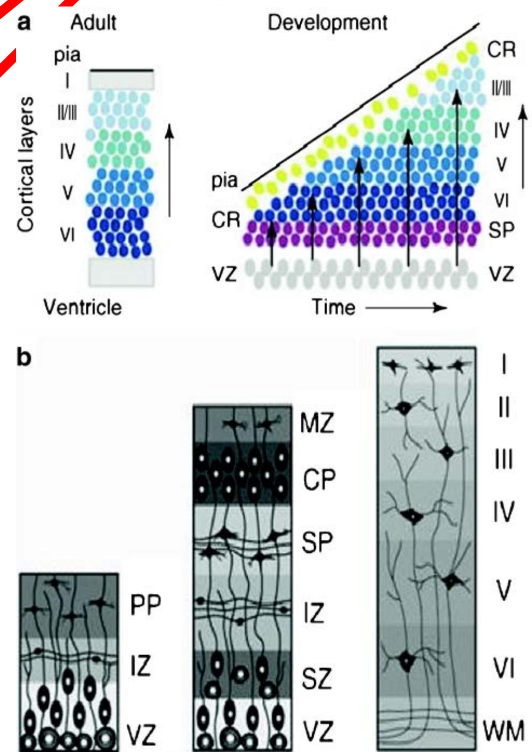
Extending Analysis of Imaging Data

Cortical Myelin

Kilian Pohl

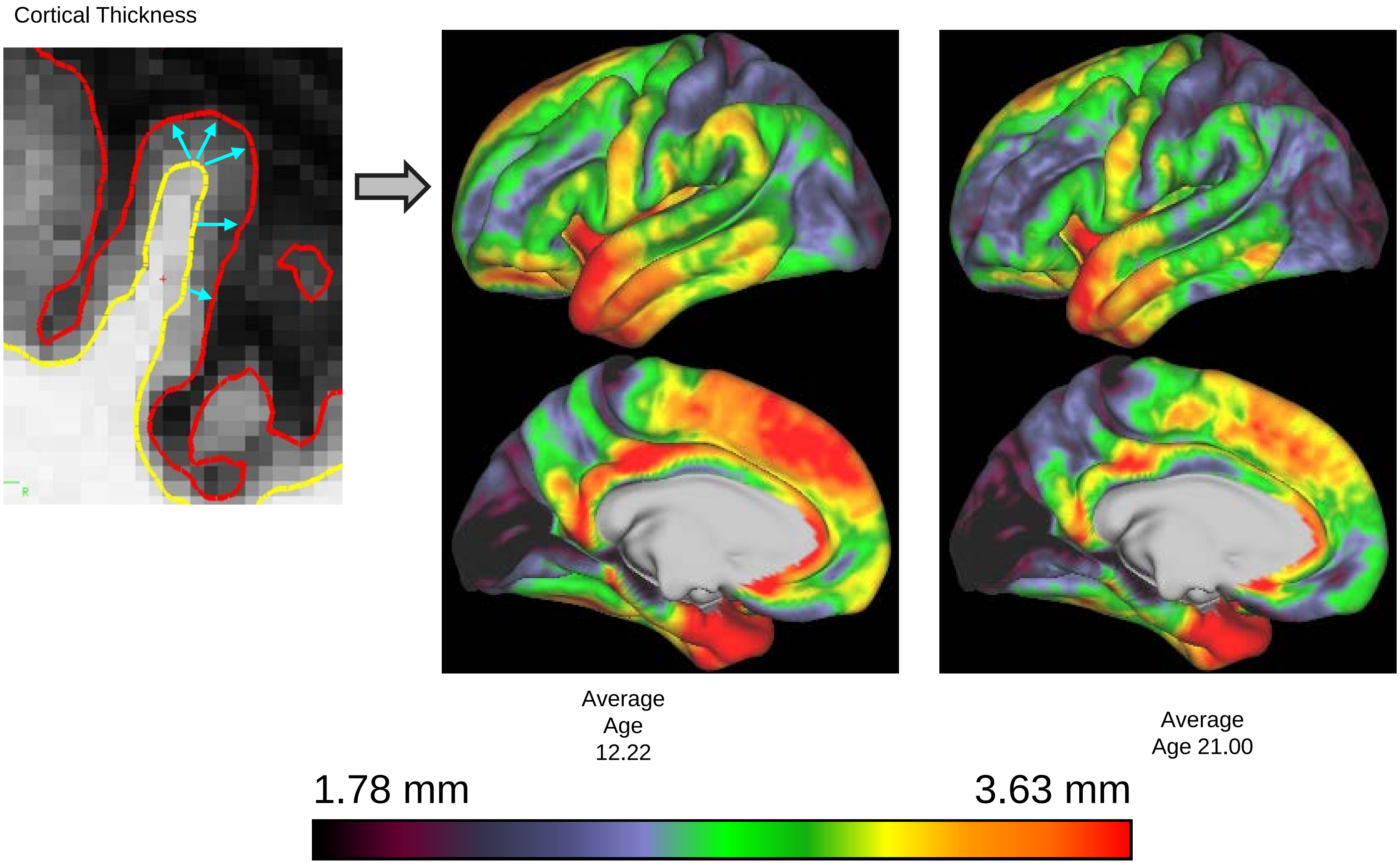
Dongjin Kwon

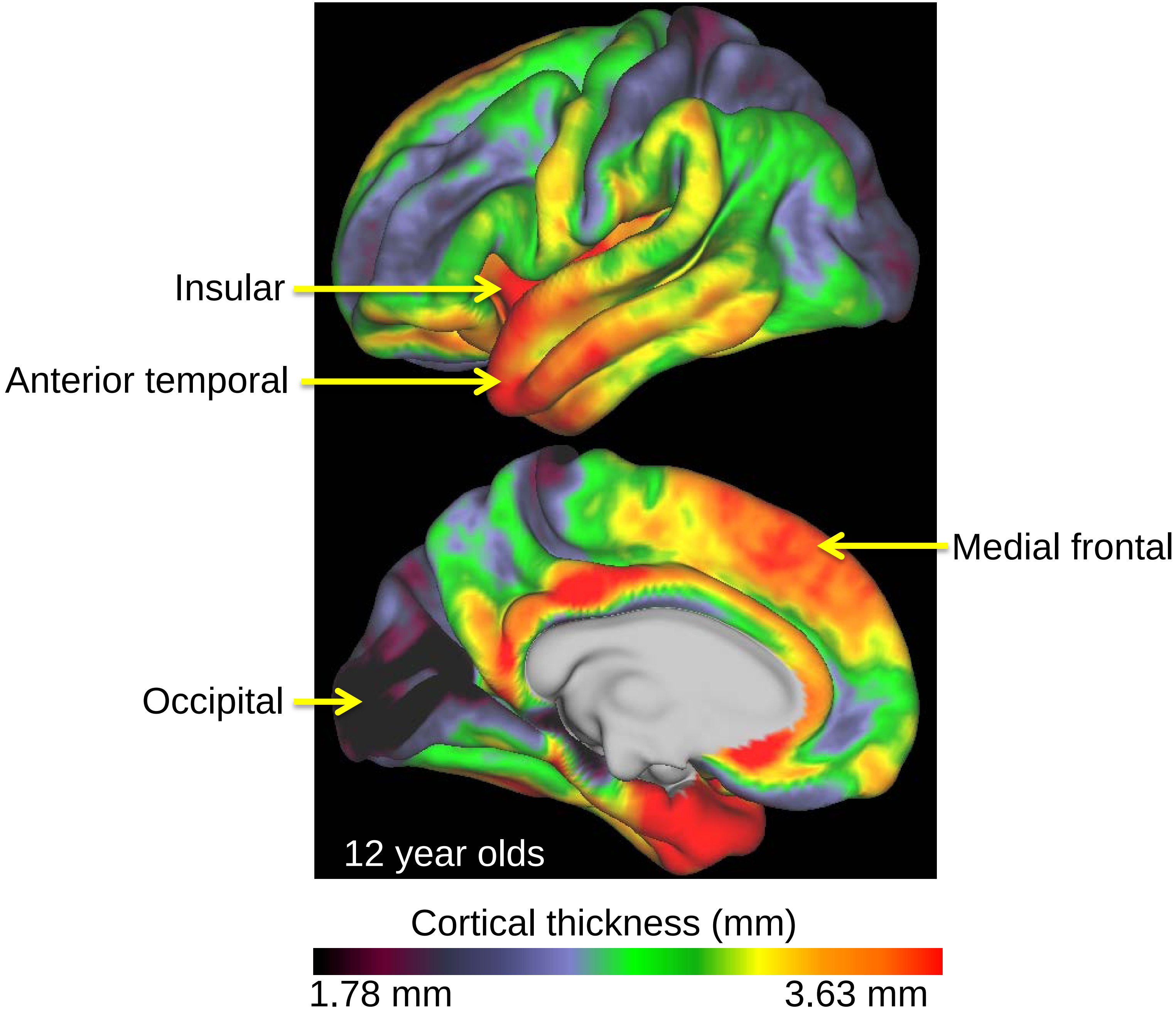


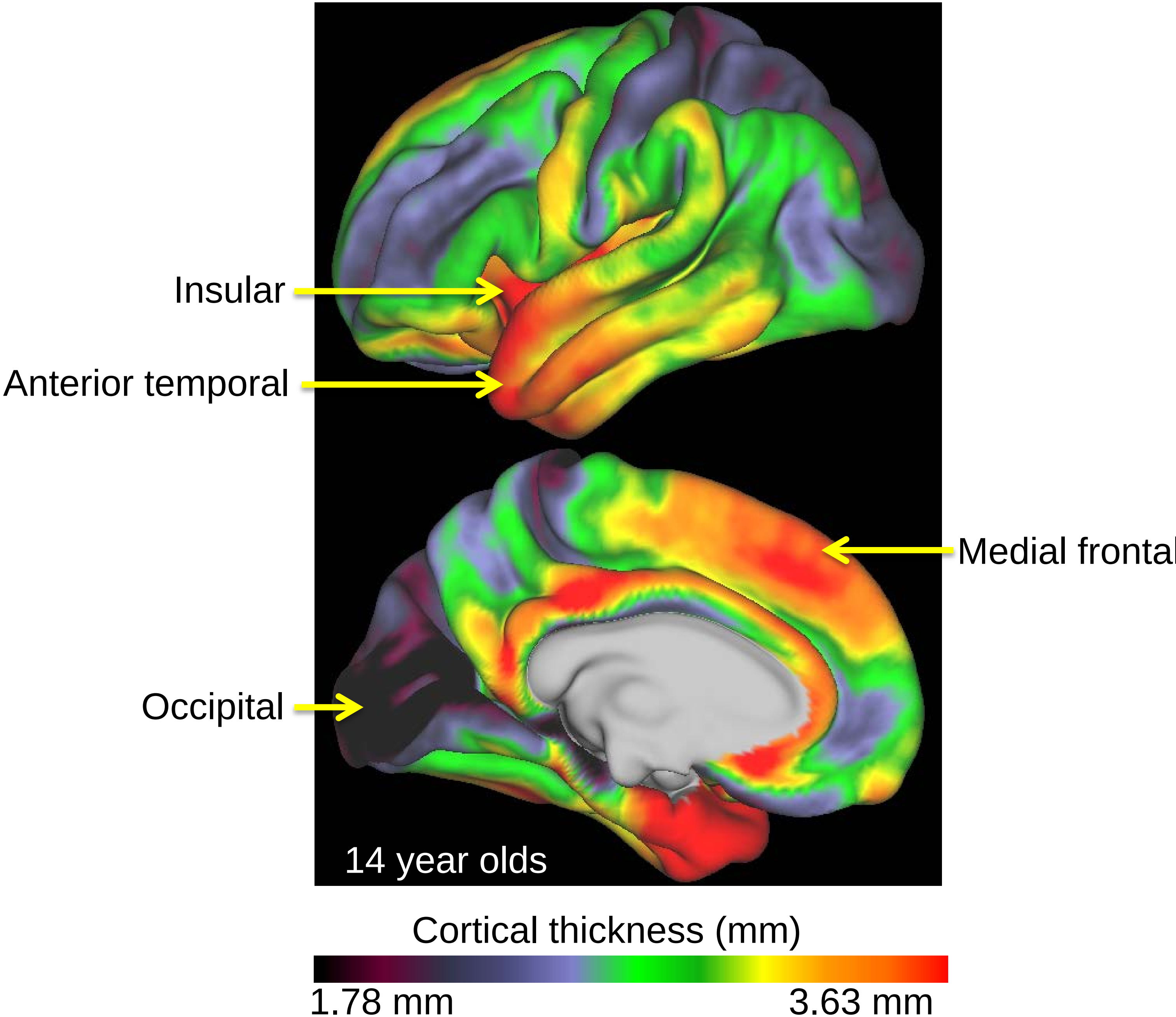


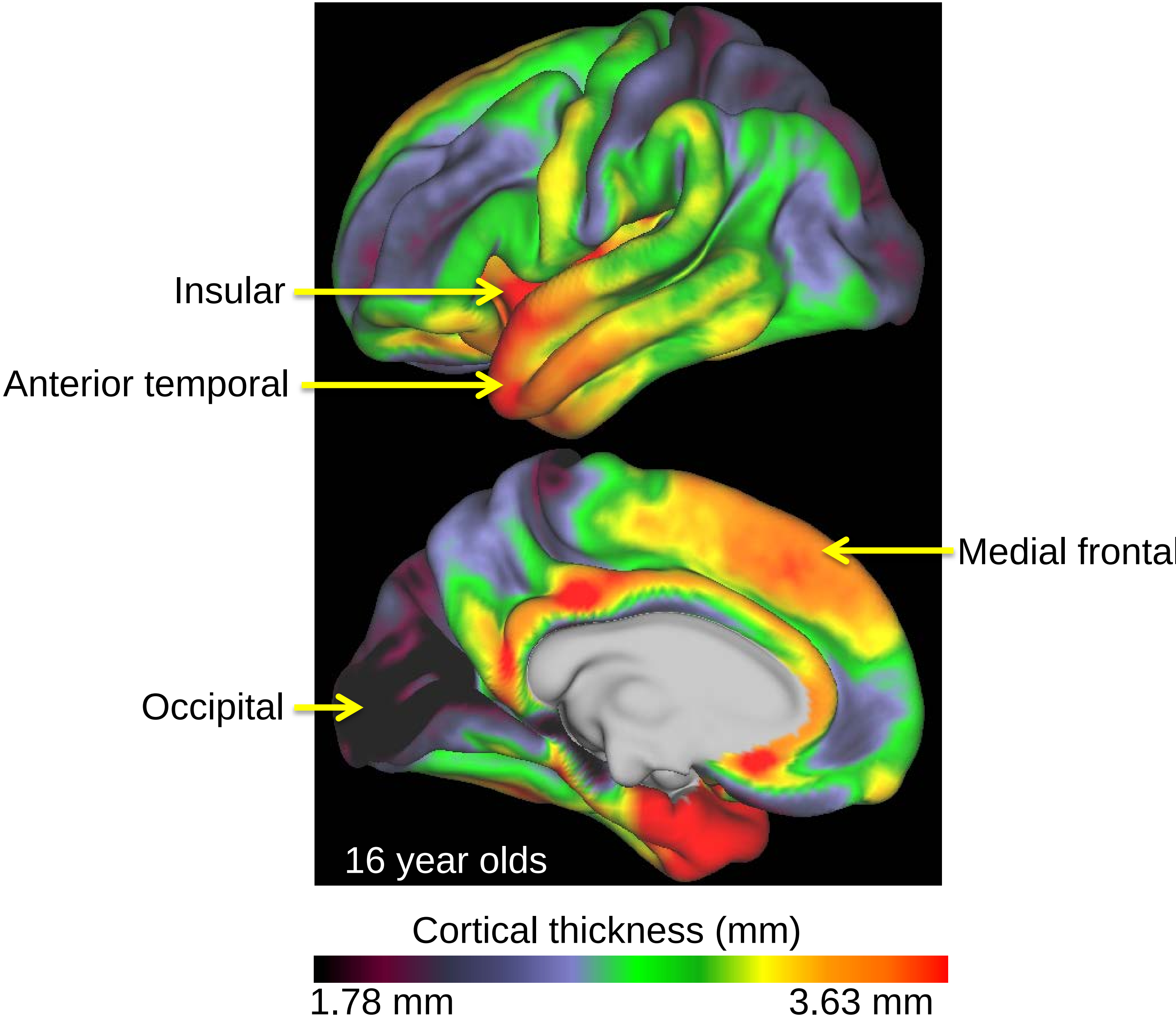
Stiles & Jernigan *Neuropsychology Review* 2010

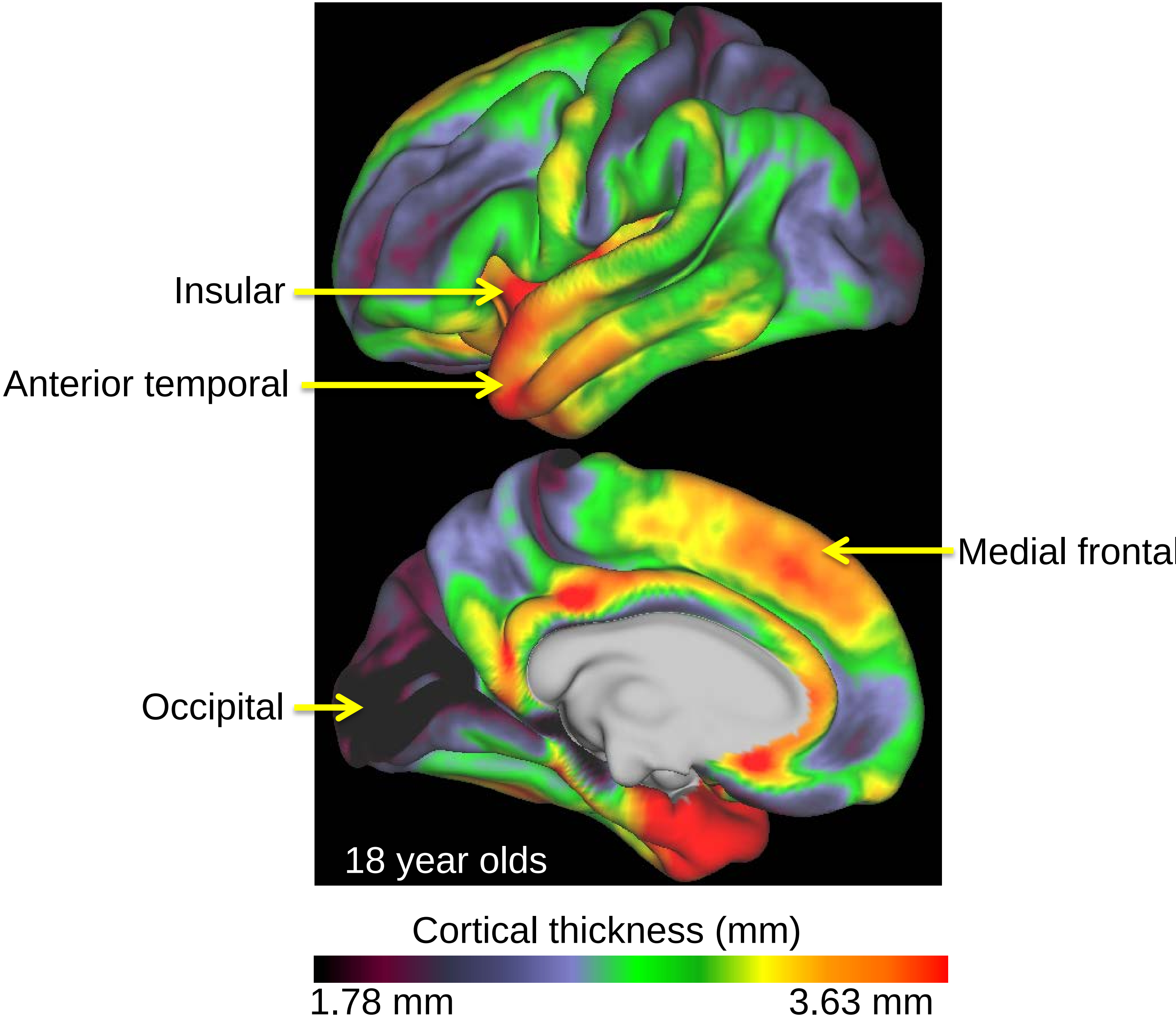
Measuring Cortical Thickness in No/Low Adolescents at Baseline

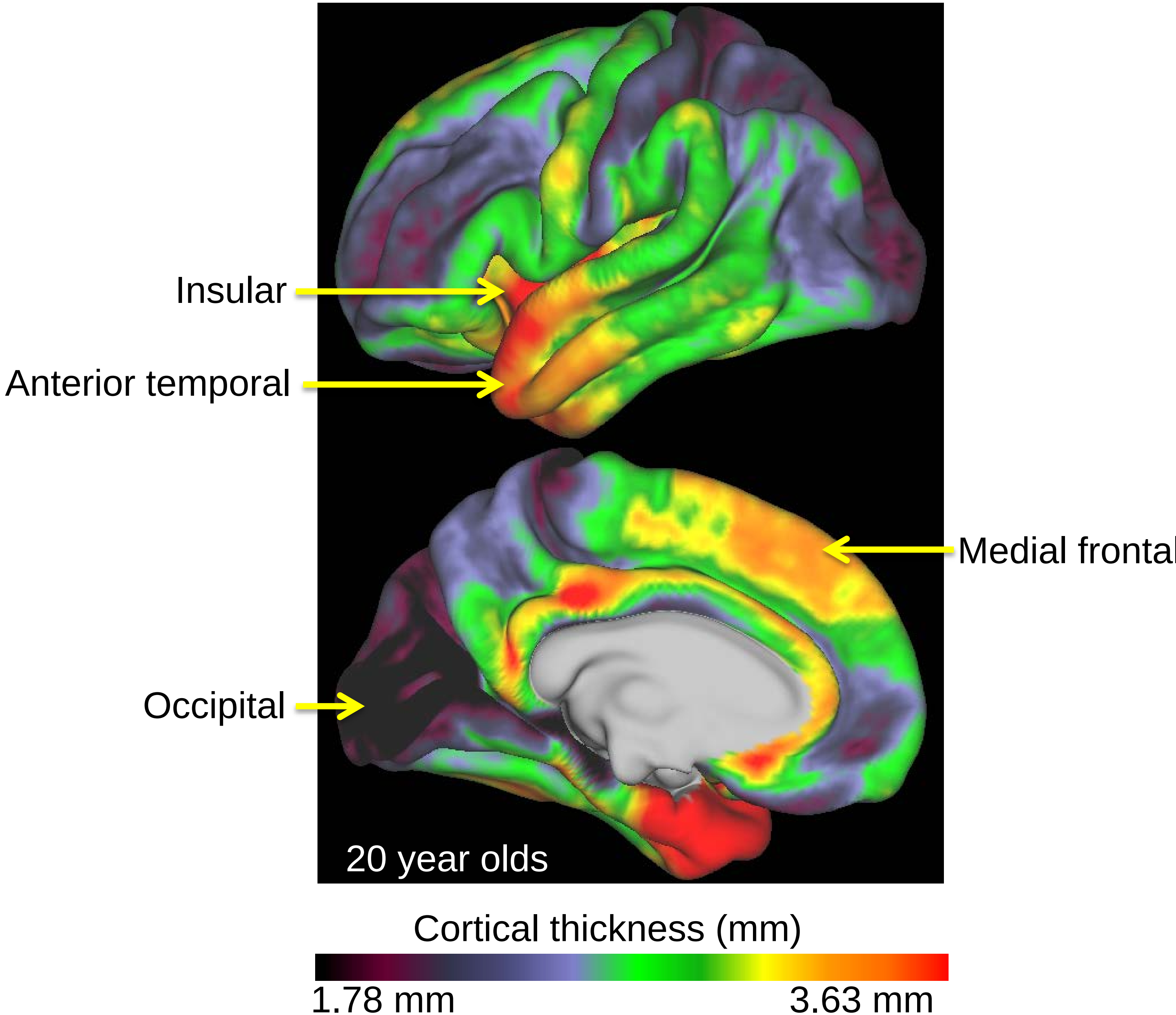



Insular
Anterior temporal
Medial frontal
Occipital
12 year olds
Cortical thickness (mm)
1.78 mm
3.63 mm

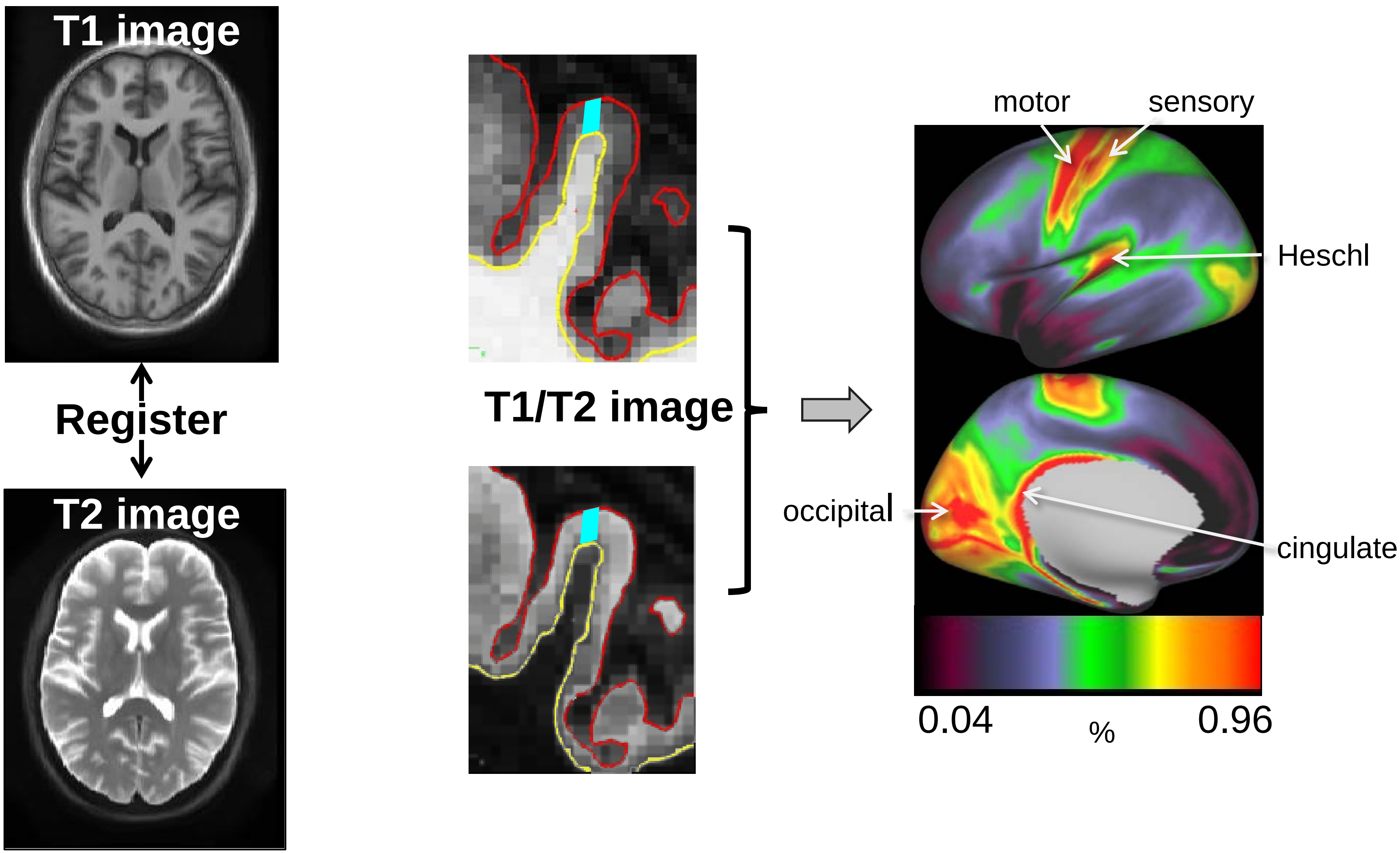

Insular
Anterior temporal
Medial frontal
Occipital
14 year olds
Cortical thickness (mm)
1.78 mm
3.63 mm


Insular
Anterior temporal
Medial frontal
Occipital
16 year olds
Cortical thickness (mm)
1.78 mm
3.63 mm


Insular
Anterior temporal
Medial frontal
Occipital
18 year olds
Cortical thickness (mm)
1.78 mm
3.63 mm

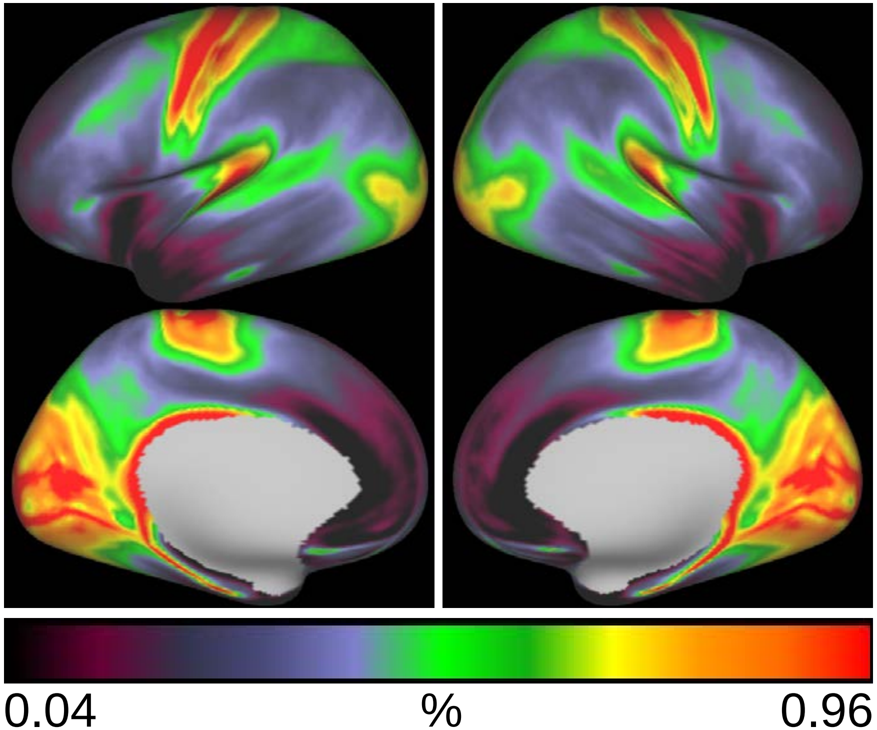

Insular
Anterior temporal
Medial frontal
Occipital
20 year olds
Cortical thickness (mm)
1.78 mm
3.63 mm

Compute Myelin in 226 Adolescents at Baseline



Age-related Difference in Myelin Content

Average

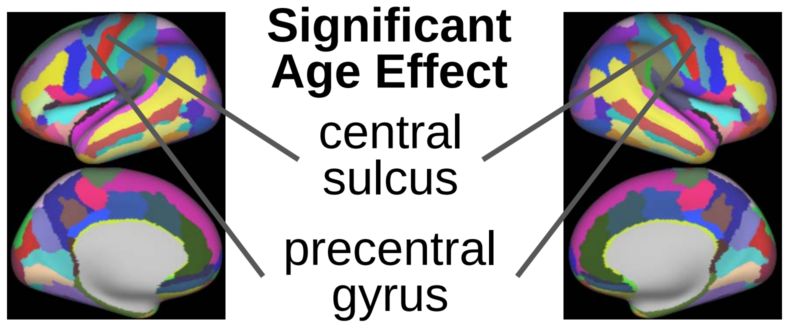


April 4 2017

Age-related Difference in Myelin Content

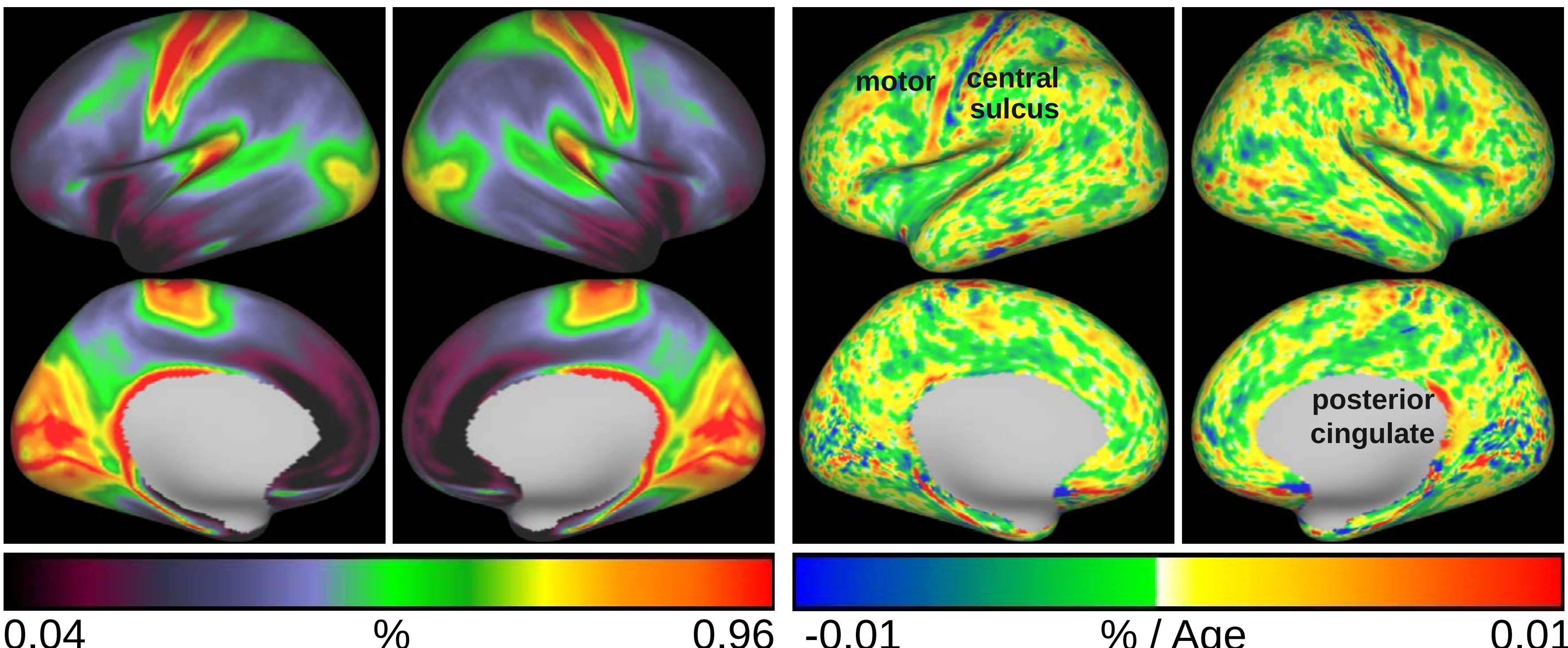
Kilian Pohl

Dongjin Kwon



Average

Developmental Slope



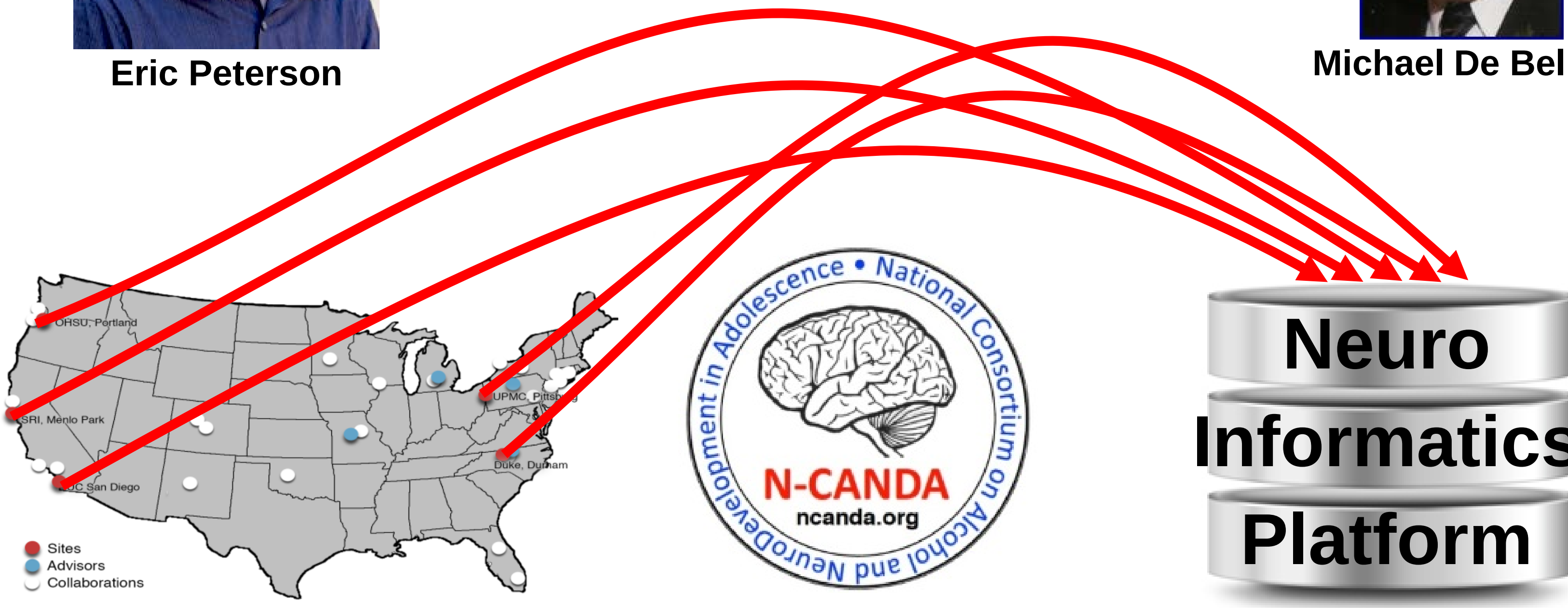
D. Kwon et al. *OHBM* June 27, 2017 Vancouver, Canada

Extending Analysis of Imaging Data

Subcortical Brain Iron

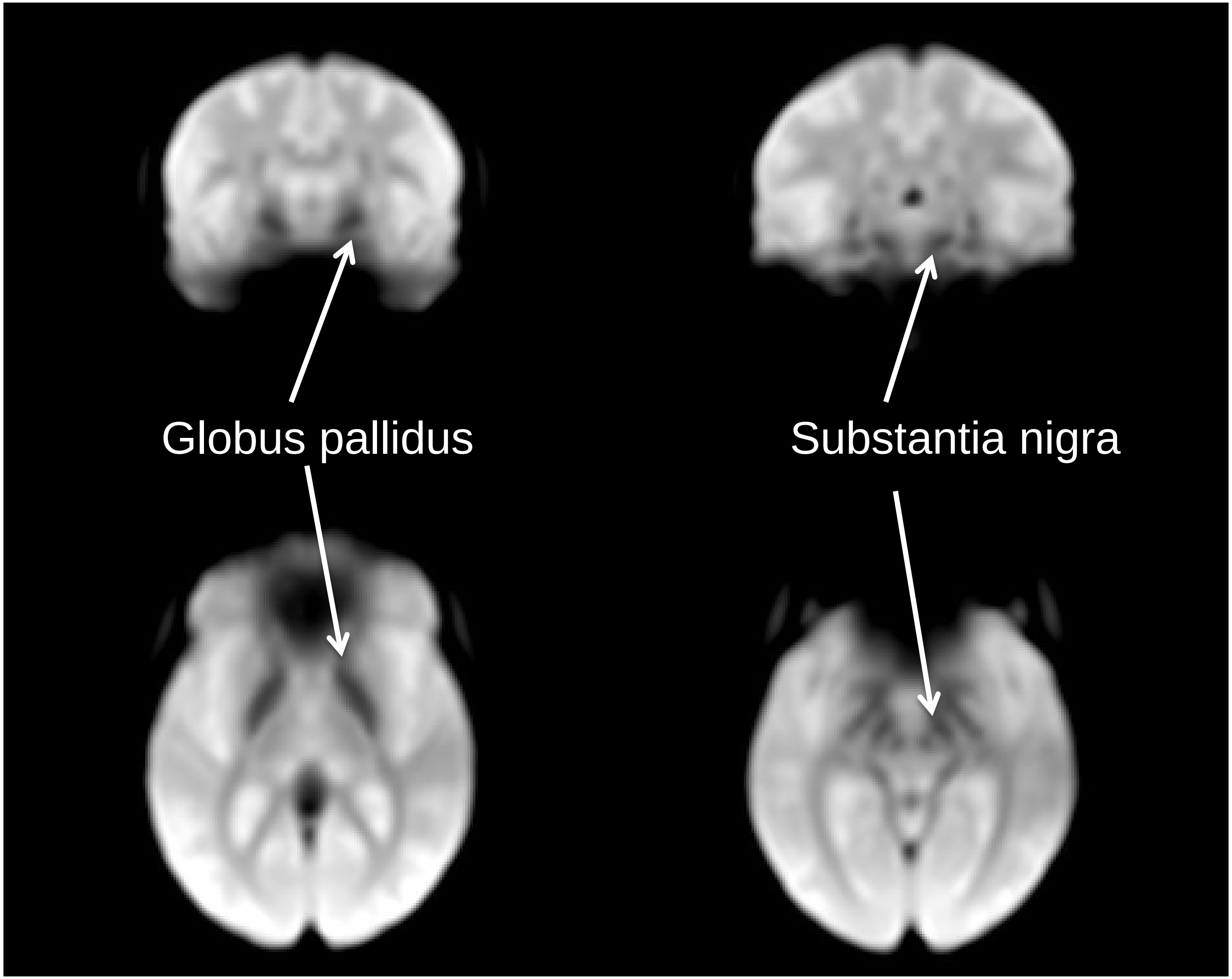
Eric Peterson

Michael De Bellis



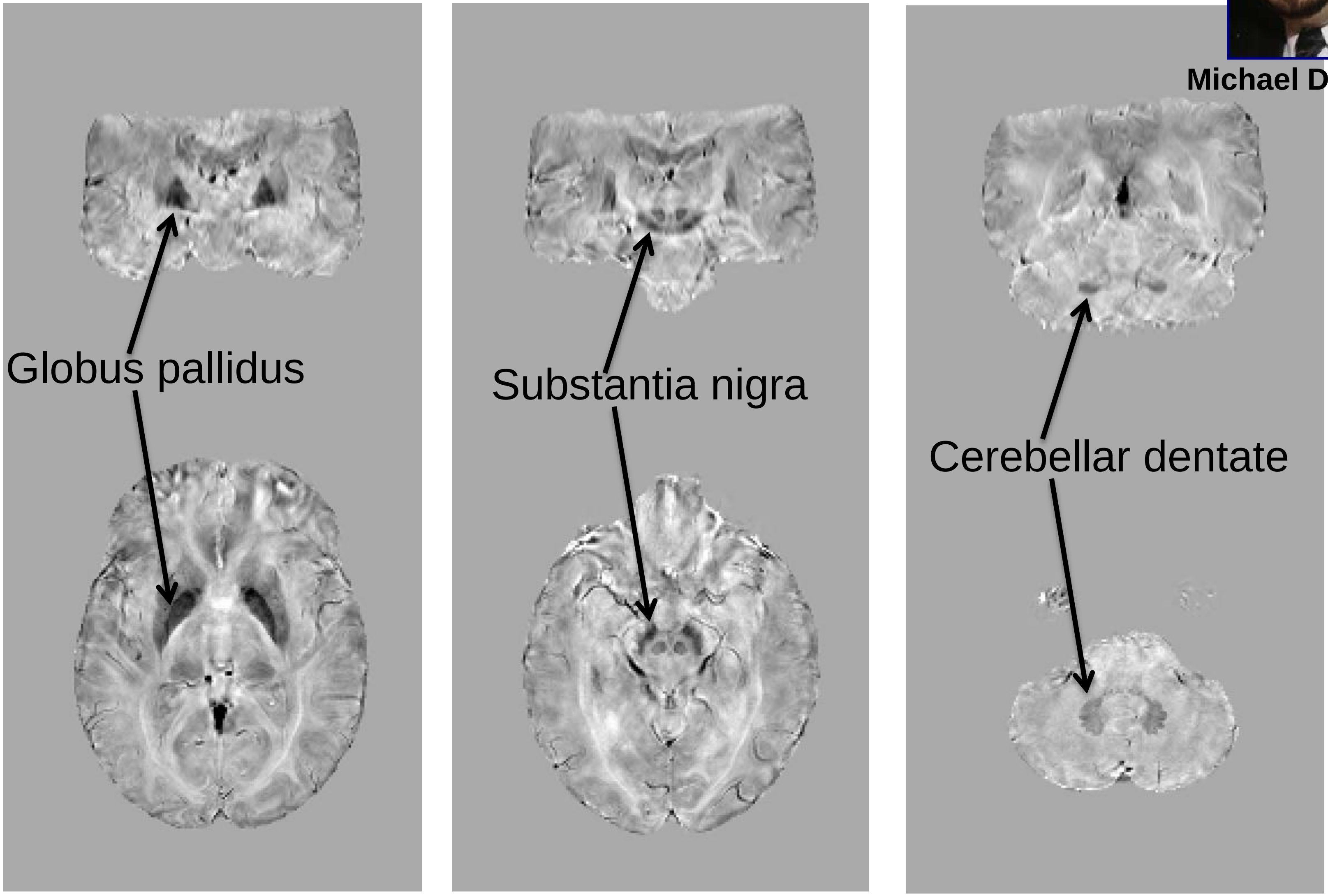
$$R2 / R2^* \ Estimate = \frac{Mean\ Posterior\ Corpus\ Callosum\ Signal\ Intensity}{Voxel\ Signal\ Intensity}$$

Echo-planar Imaging (EPI) fMRI Sequence
(T2* Weighted)

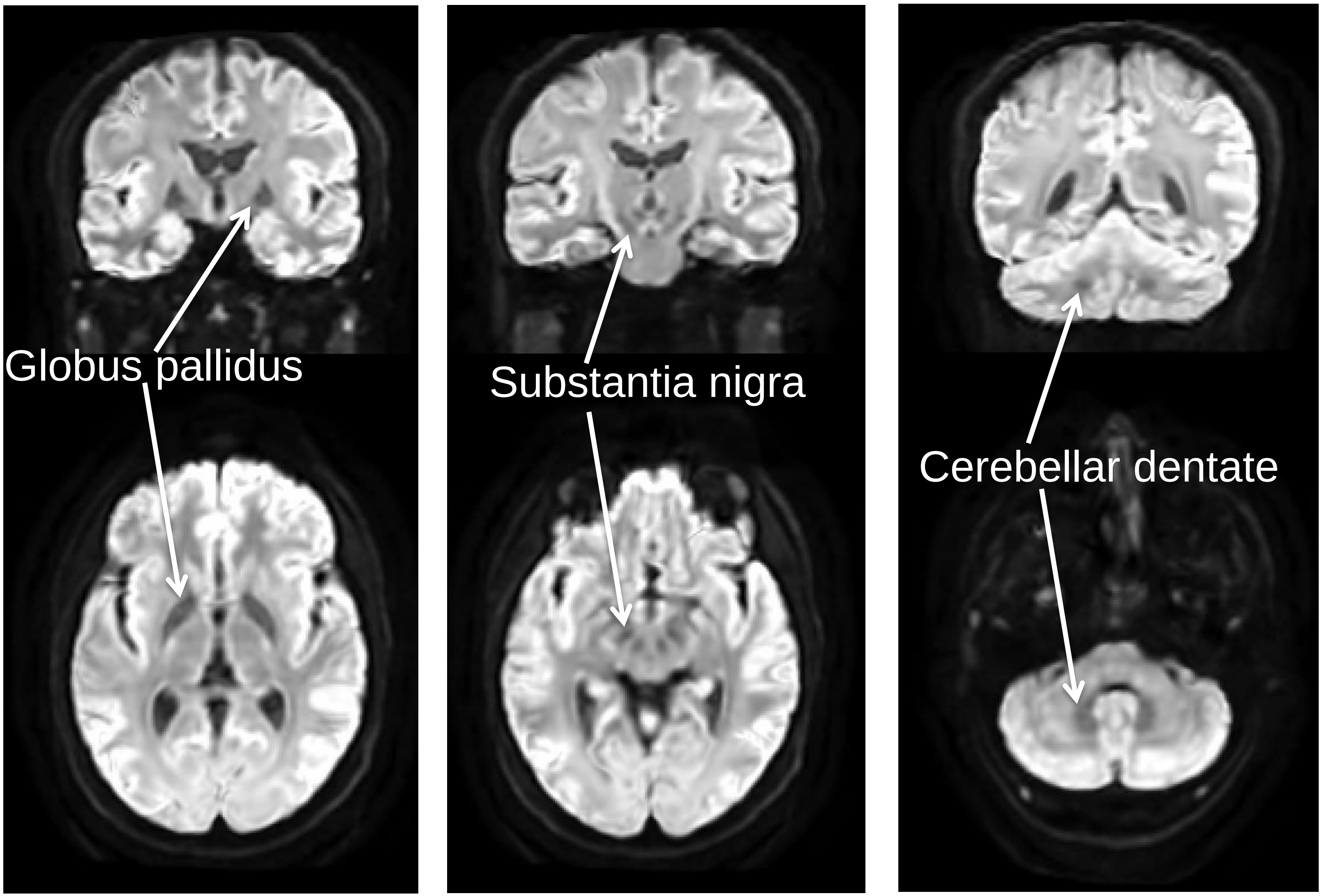


Susceptibility Weighted Imaging (SWI)
(T2* Weighted)


Michael De Bellis



Spin-echo Diffusion Tensor Imaging (DTI)
(T2 Weighted)



Iron in the Brain

- **Non-heme iron in the brain**
  - primary iron deposition not from bleeding
  - necessary for dopamine transmitter function

- **Methods to image iron**
  - Field-Dependent Imaging*
  - Susceptibility Weighted Imaging (SWI)*
  - Quantitative Susceptibility Mapping (QSM)†
  - R2’ mapping‡

*Pfefferbaum et al. NeuroImage, 2009; *Sullivan et al. Brain Imaging Behav. 2010; †Poynton et al. IEEE Trans Med Imaging, 2015; †Bilgic et al. NeuroImage, 2012; ‡Gelman et al. Radiology 1999; ‡Haacke, et al. MRM 2005

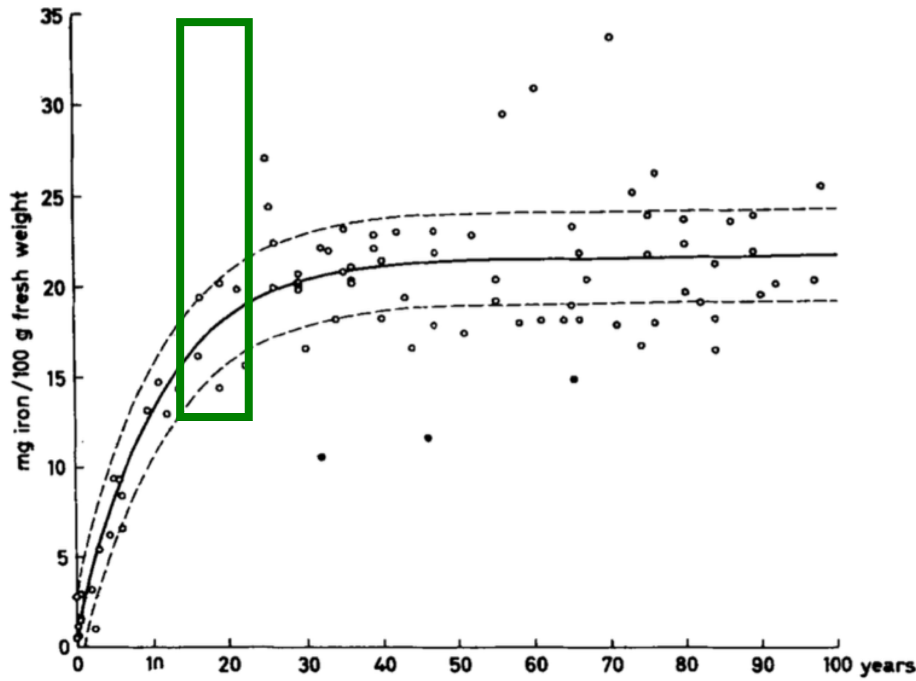


FIG. 2. Non-haemin iron in the globus pallidus at different ages. The filled circles represent cases with large intestinal haemorrhages. The calculated regression lines have been drawn in Figs. 2–6. The dotted lines denote the the S.E. of estimate; for globus pallidus S.E. = ±3·07.

Hallgren and Sourander, Journal of Neurochemistry, 1958

Estimating Non-heme Iron Concentration from Standard NCANDA Protocols

Non-heme iron →

susceptibility (T2*) signal loss
transverse relaxivity (T2) signal loss

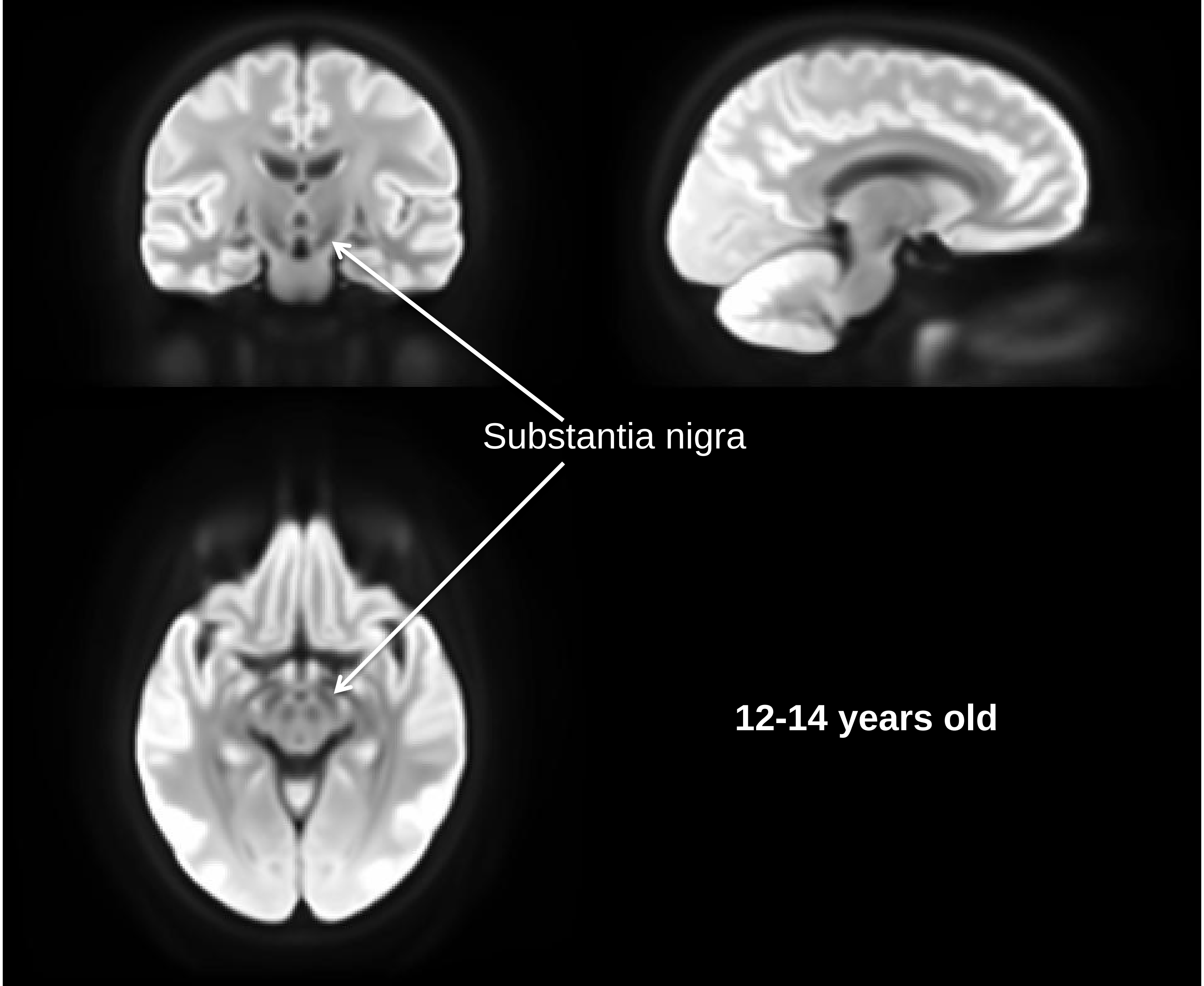
Iron effect

greater T2 and T2* weighting → greater iron effect
less T1 weighting → greater iron effect

T2* > T2

DTI sequence has higher spatial resolution and less B0 spatial distortion

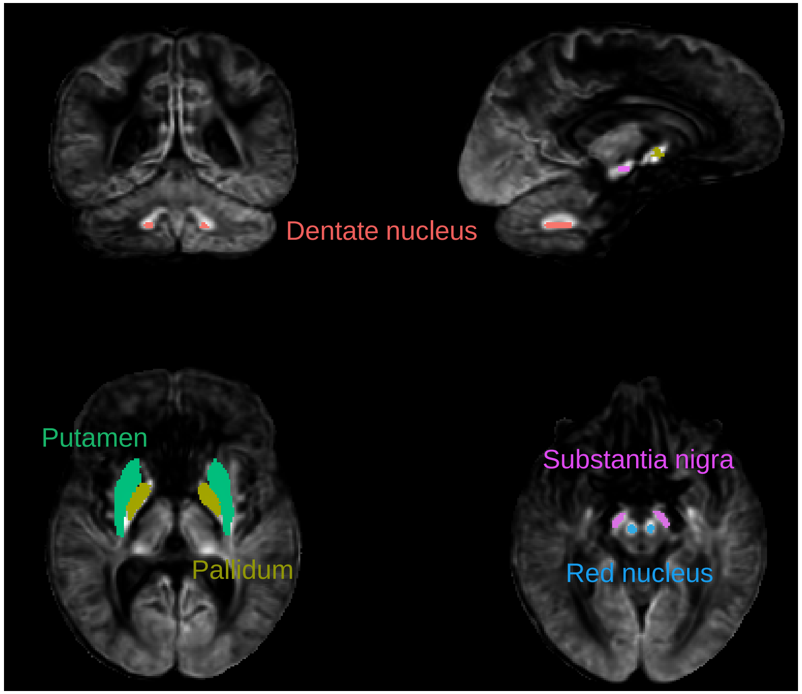
$$R2 / R2^* \ Estimate = \frac{Mean\ Posterior\ Corpus\ Callosum\ Signal\ Intensity}{Voxel\ Signal\ Intensity}$$


Substantia nigra
12-14 years old

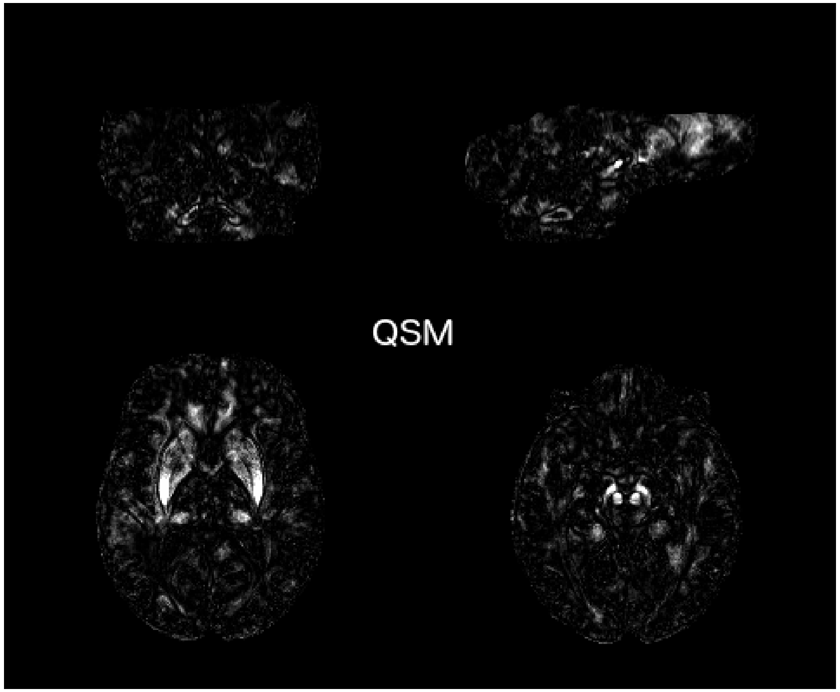

Substantia nigra
15-17 years old


Substantia nigra
18-21 years old

Estimating Age-related Change in Non-heme Iron Concentration from Standard NCANDA Protocols

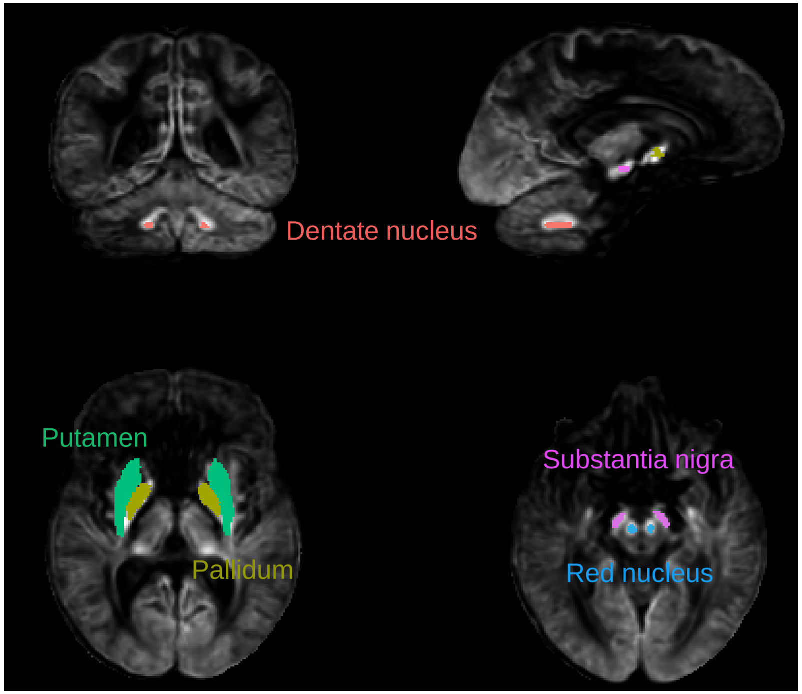


R-squared: Signal vs Age

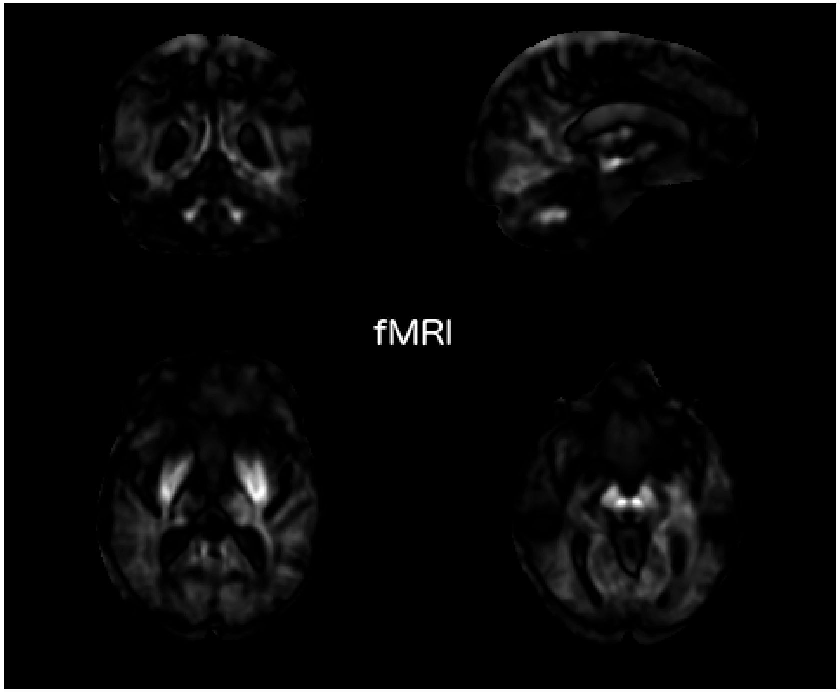


$$R2 / R2^* \ Estimate = \frac{Mean\ Posterior\ Corpus\ Callosum\ Signal\ Intensity}{Voxel\ Signal\ Intensity}$$

Estimating Age-related Change in Non-heme Iron Concentration from Standard NCANDA Protocols

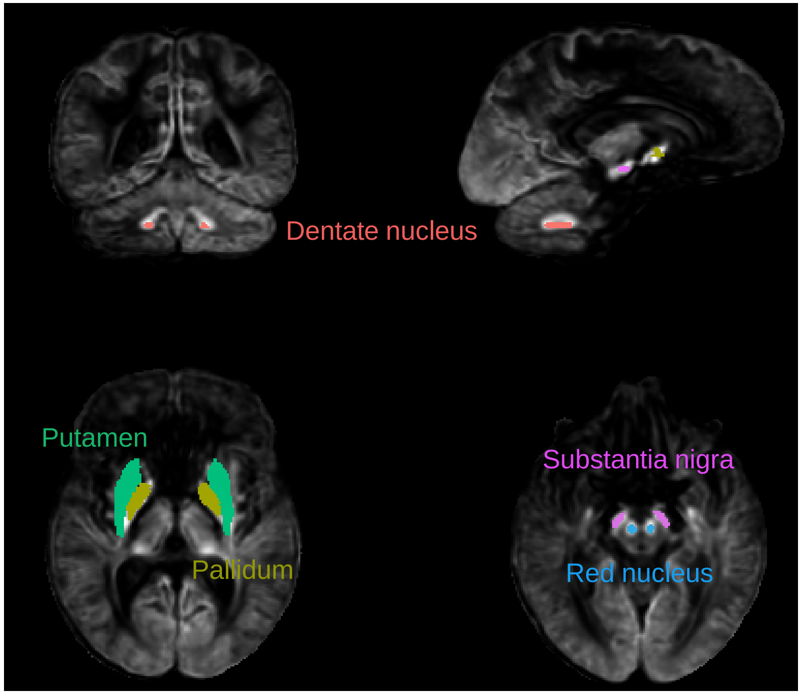


R-squared: Signal vs Age

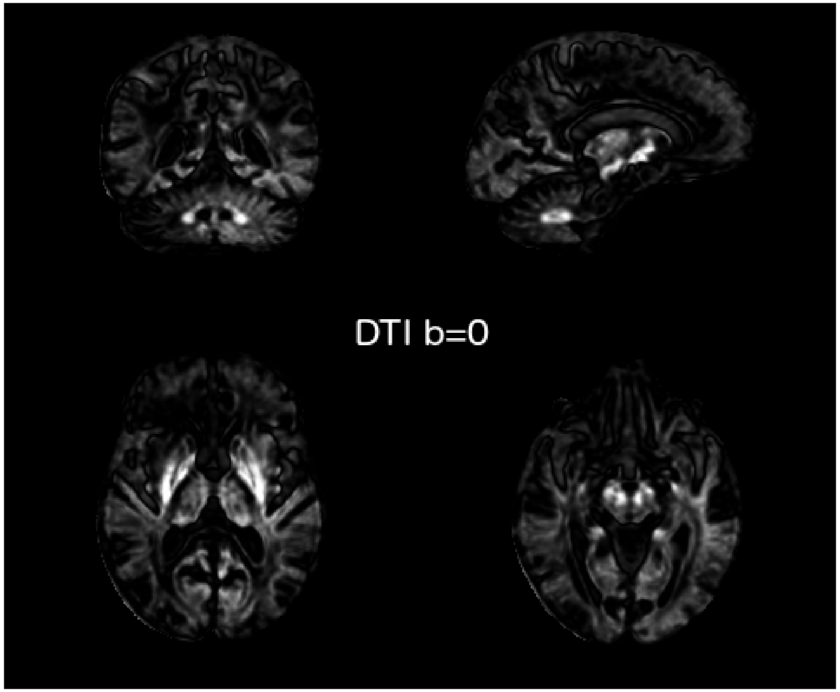


$$R2 / R2^* \ Estimate = \frac{Mean\ Posterior\ Corpus\ Callosum\ Signal\ Intensity}{Voxel\ Signal\ Intensity}$$

Estimating Age-related Change in Non-heme Iron Concentration from Standard NCANDA Protocols



R-squared: Signal vs Age



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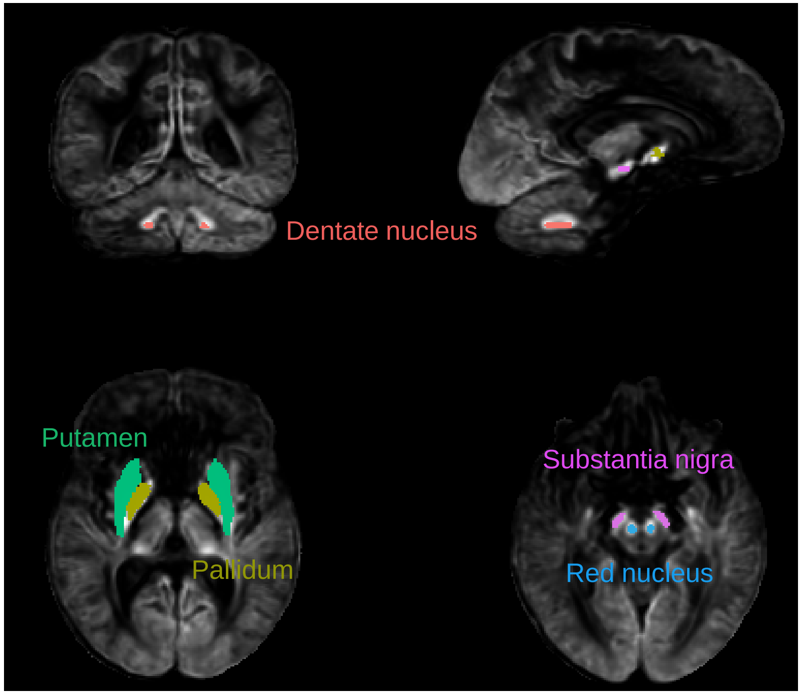
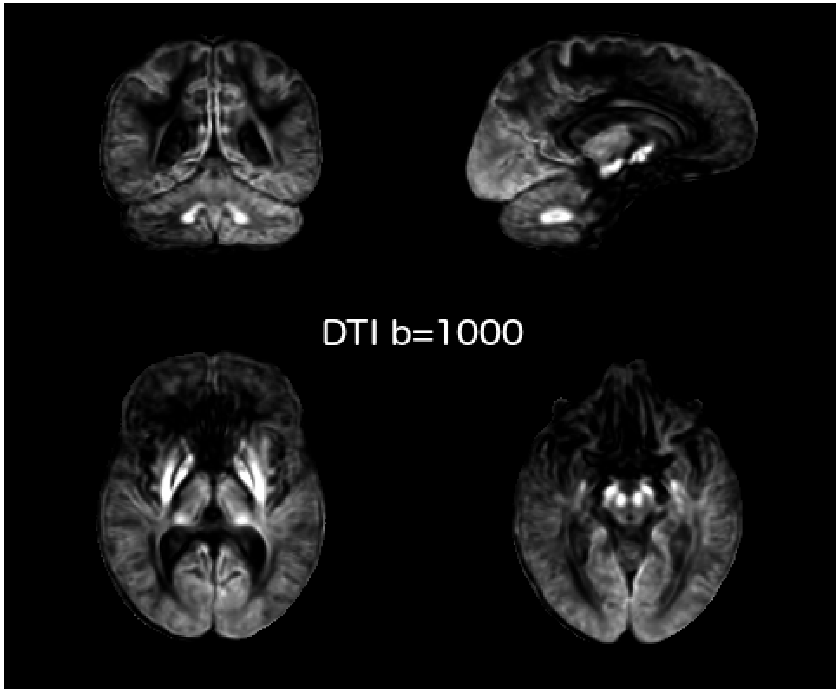
Estimating Age-related Change in Non-heme Iron Concentration from Standard NCANDA Protocols

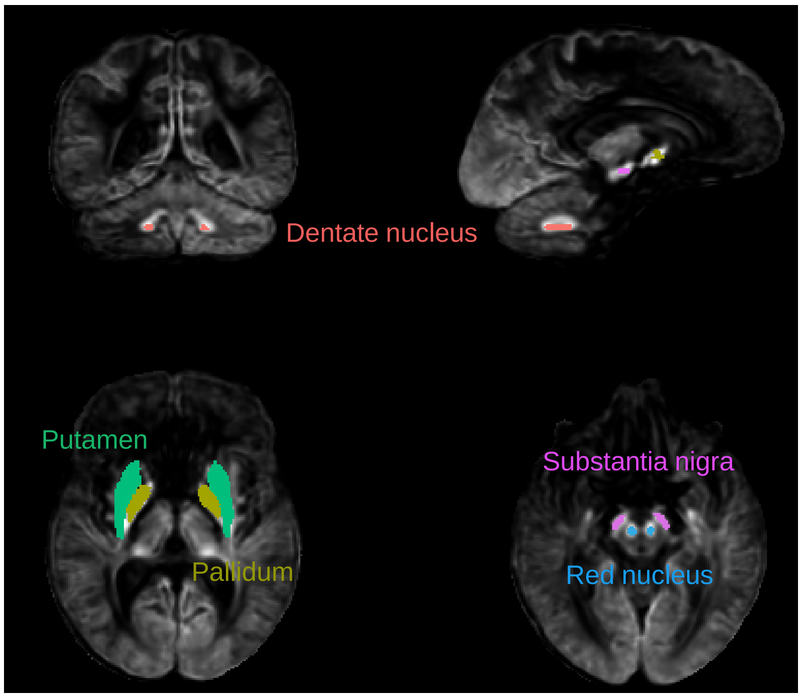


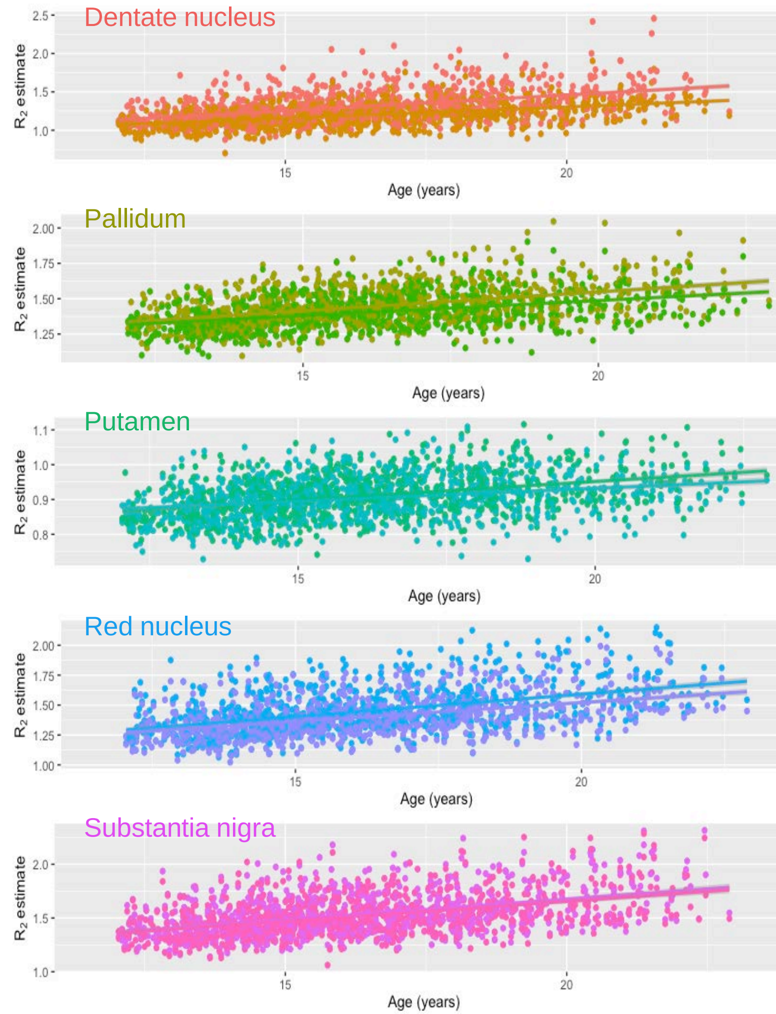
R-squared: Signal vs Age



$$R2\,/\,R2^*\ Estimate = \frac{Mean\ Posterior\ Corpus\ Callosum\ Signal\ Intensity}{Voxel\ Signal\ Intensity}$$

Estimating Non-heme Iron Concentration from Standard NCANDA Protocols





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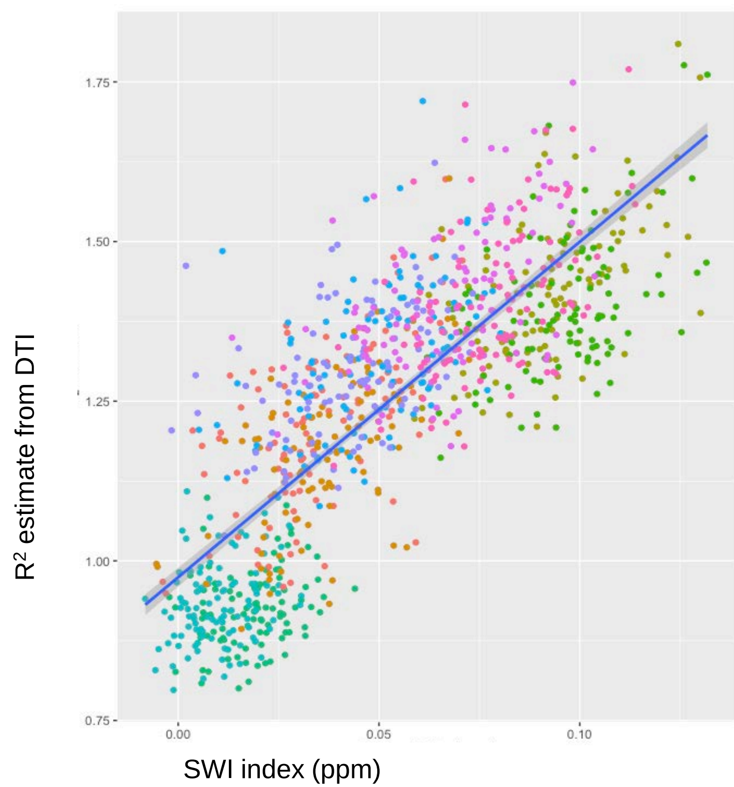
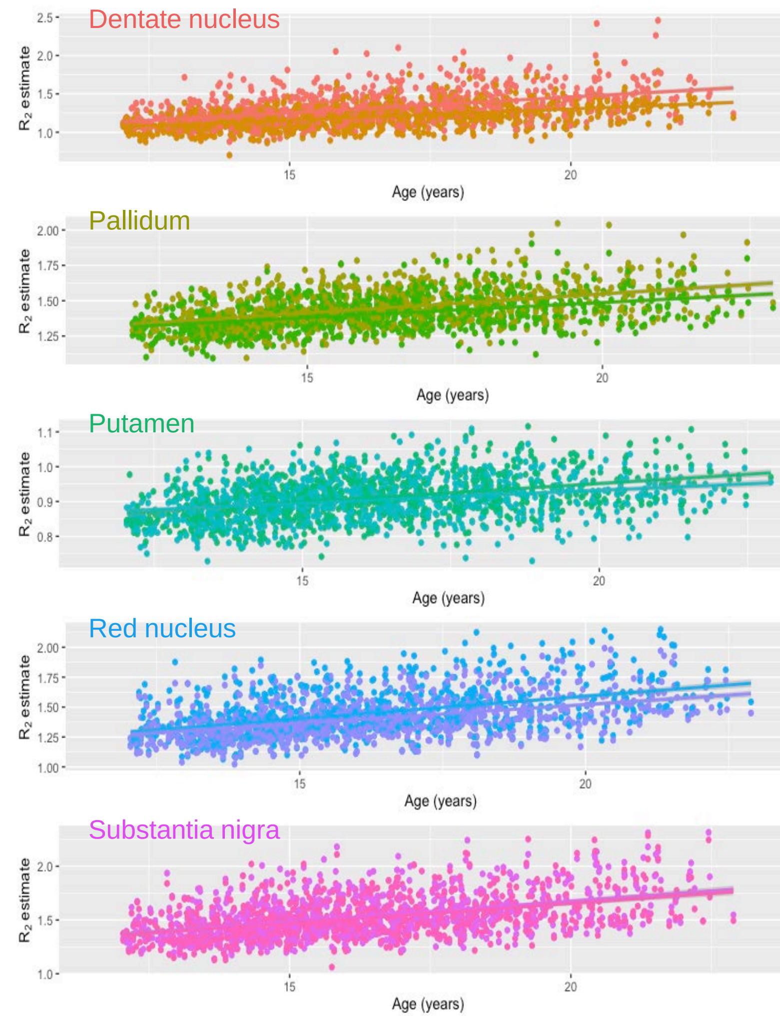
Estimating Non-heme Iron Concentration from Standard NCANDA Protocols





$$R2 / R2^* \ Estimate = \frac{Mean\ Posterior\ Corpus\ Callosum\ Signal\ Intensity}{Voxel\ Signal\ Intensity}$$

Extending Analysis of Imaging Data

Subcortical Brain Iron

Eric Peterson

Michael De Bellis

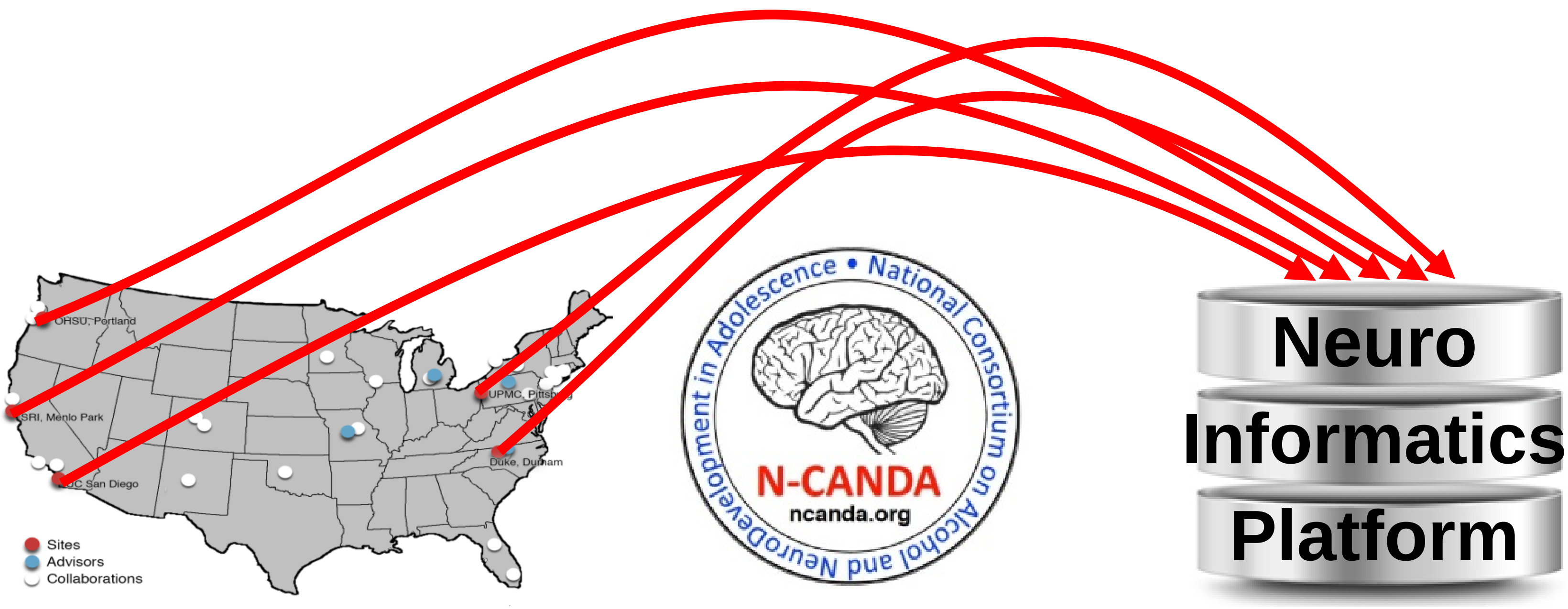
It is possible to estimate iron deposition *using longitudinal and group* DTI or fMRI data

Results are more stable with diffusion-weighted DTI than fMRI

Data can be merged across GE and Siemens scanners

DTI iron estimates correlate well with *in-vivo* QSM susceptibility measures

Extending Analysis of Imaging Data
Effects of Initiation of Drinking



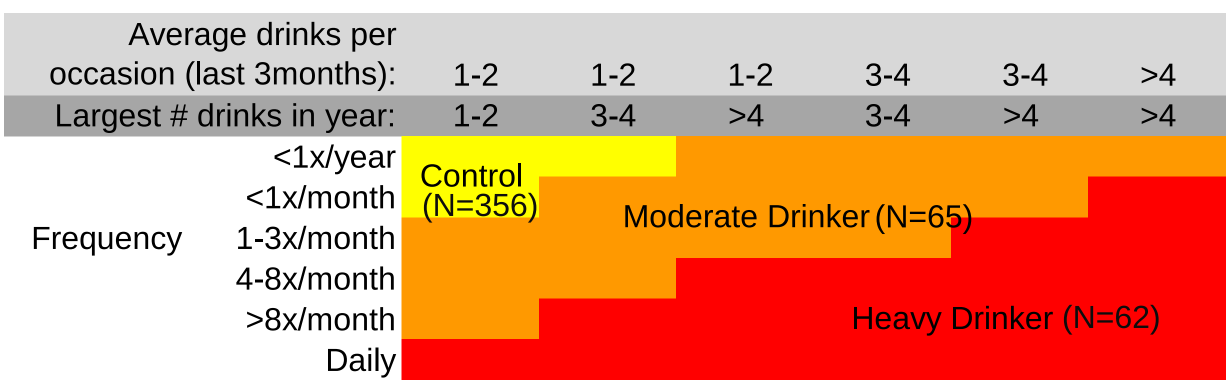

PITTWATER
COUNCIL
ALCOHOL
FREE ZONE
MOTEL
Accommodation
REASONABLE
Rates
HAHN
LIGHT

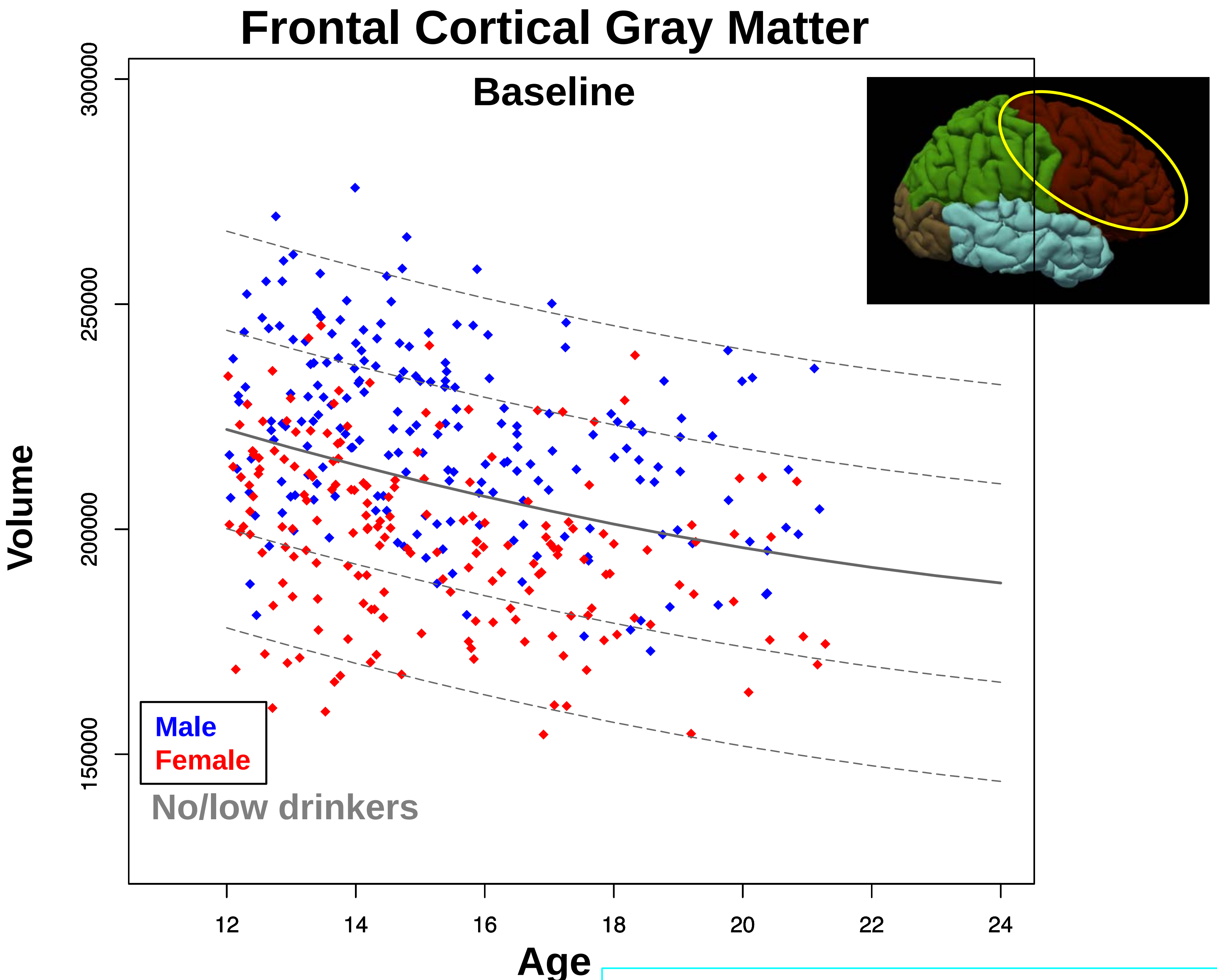
NCANDA 2 Year Follow-up

Regional cortical volume trajectories in 483 of 647 no-to-low drinking adolescents meeting imaging and drinking criteria followed longitudinally for 2 years

- **65 transitioned into moderate drinking**
- **62 transitioned into heavy drinking**
- **356 remained no-to-low drinker**
- **1423 MRI brain scans**

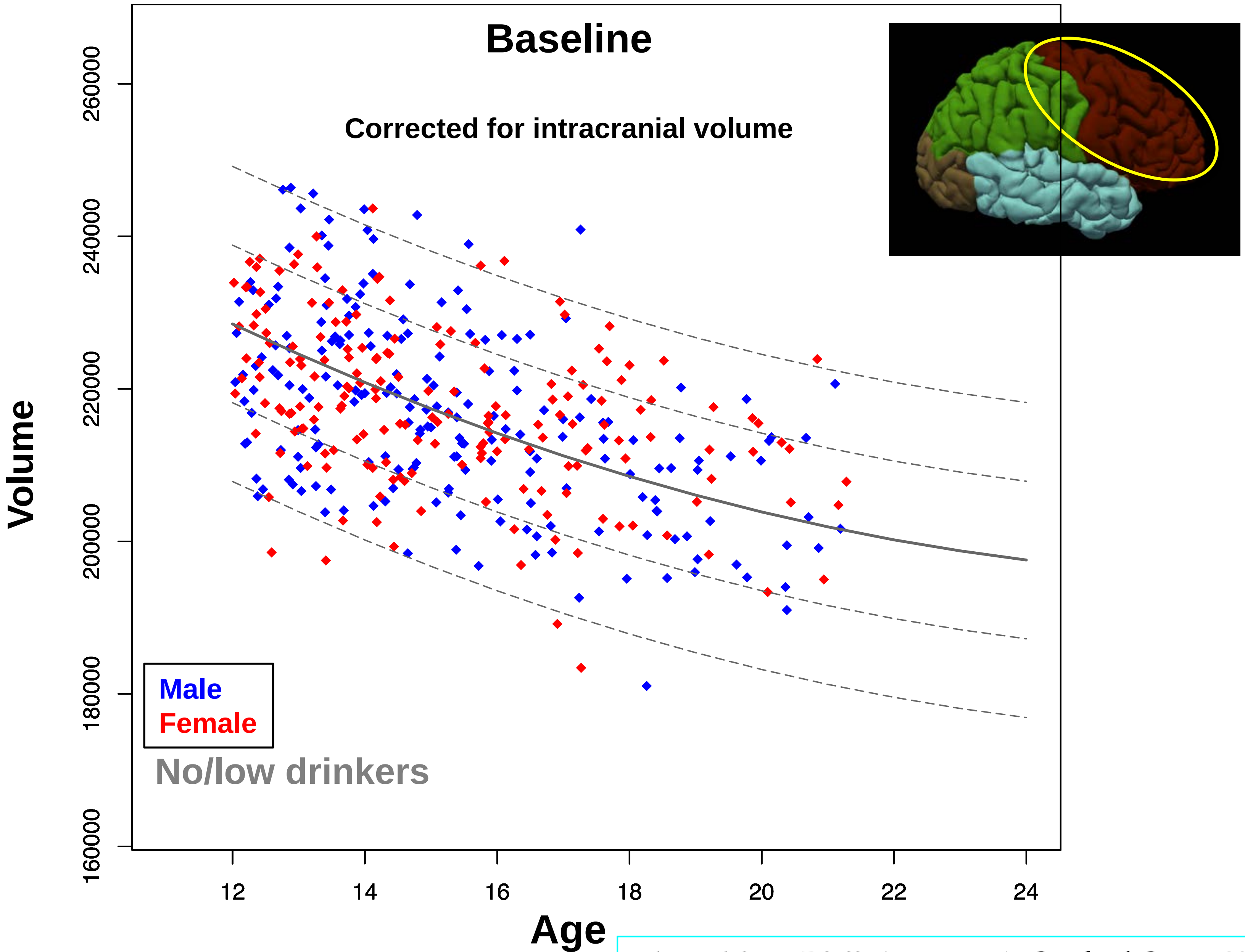
Cahalan et al. Criteria





adapted from Pfefferbaum et al. *Cerebral Cortex* 2016

Frontal Cortical Gray Matter



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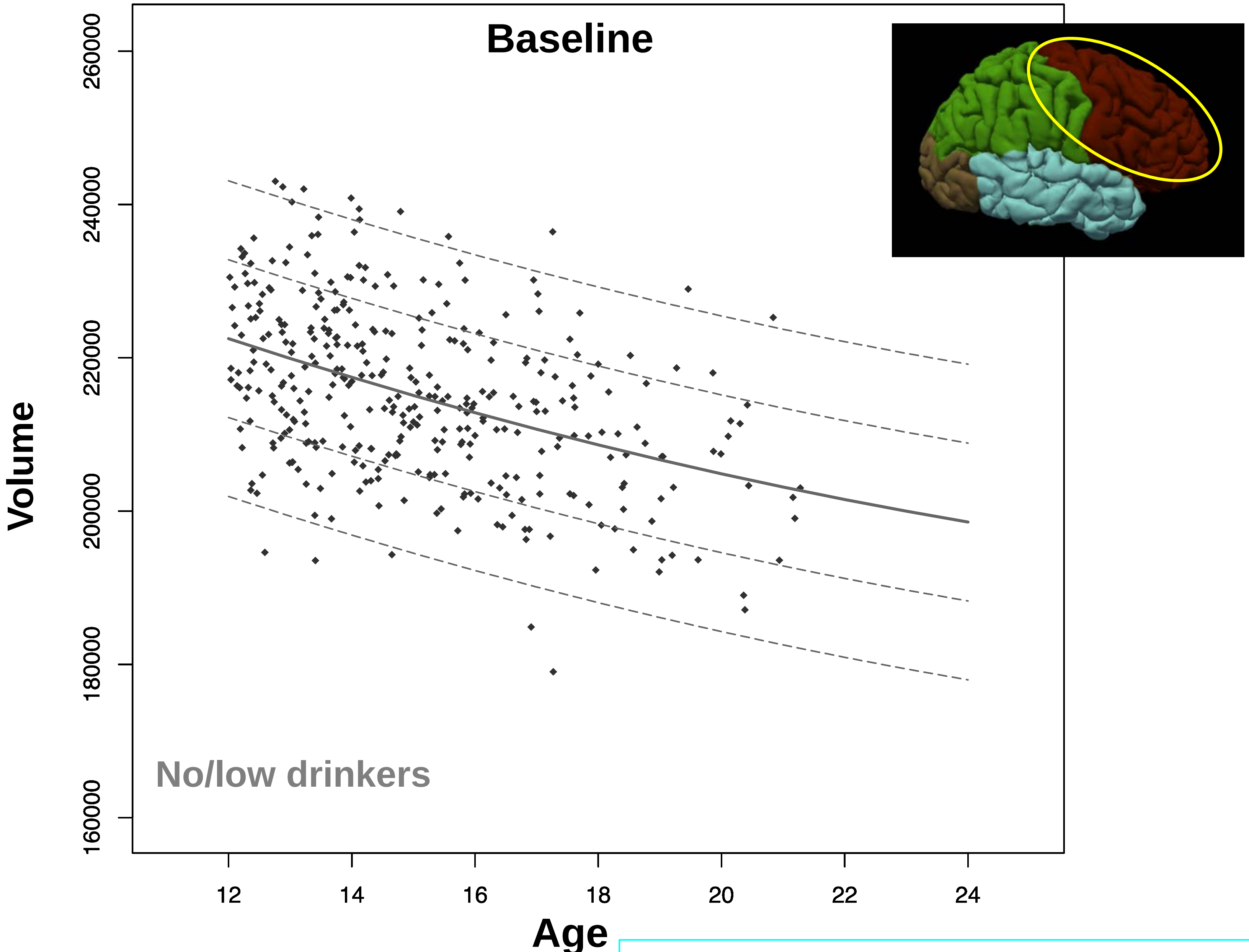
Frontal Cortical Gray Matter



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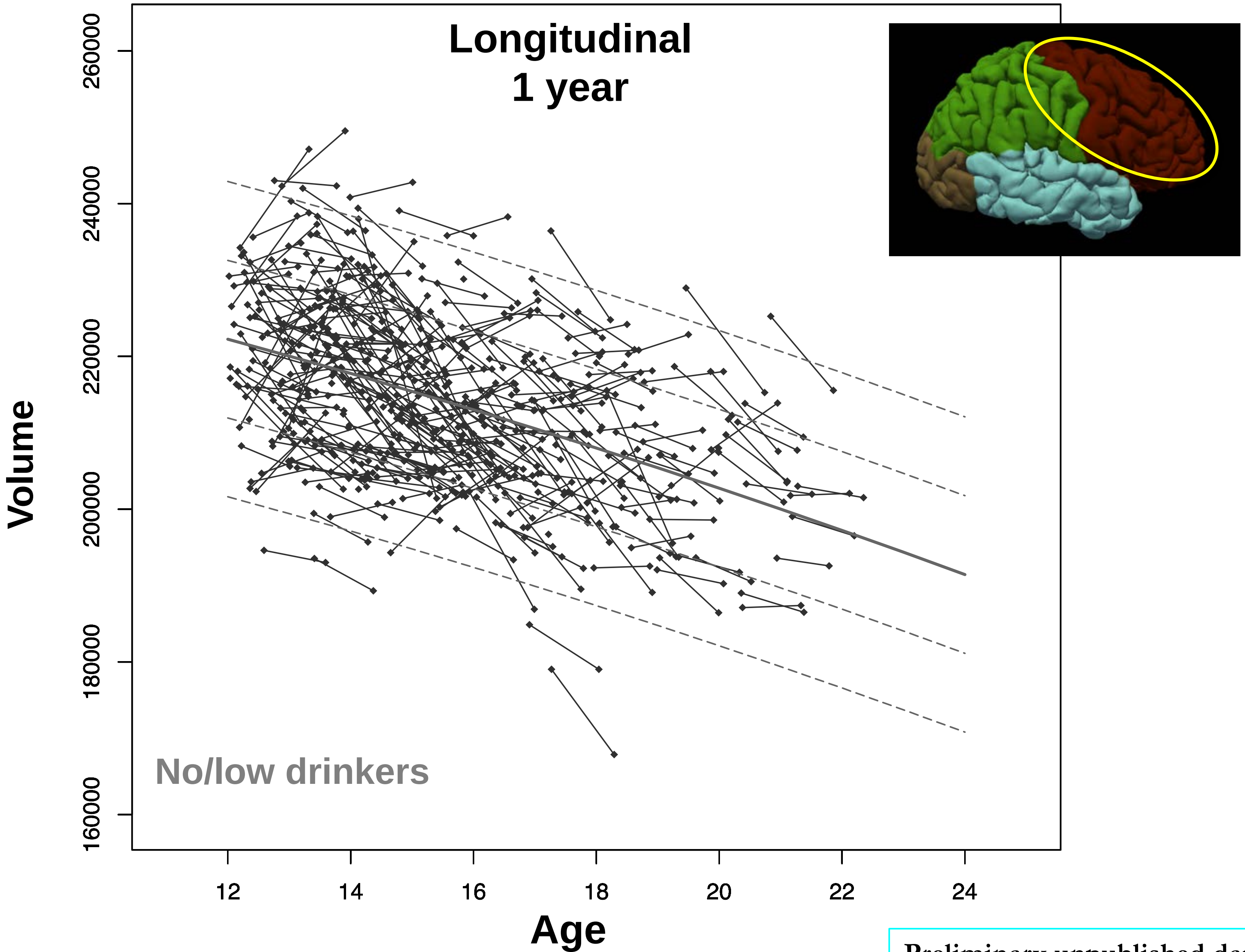
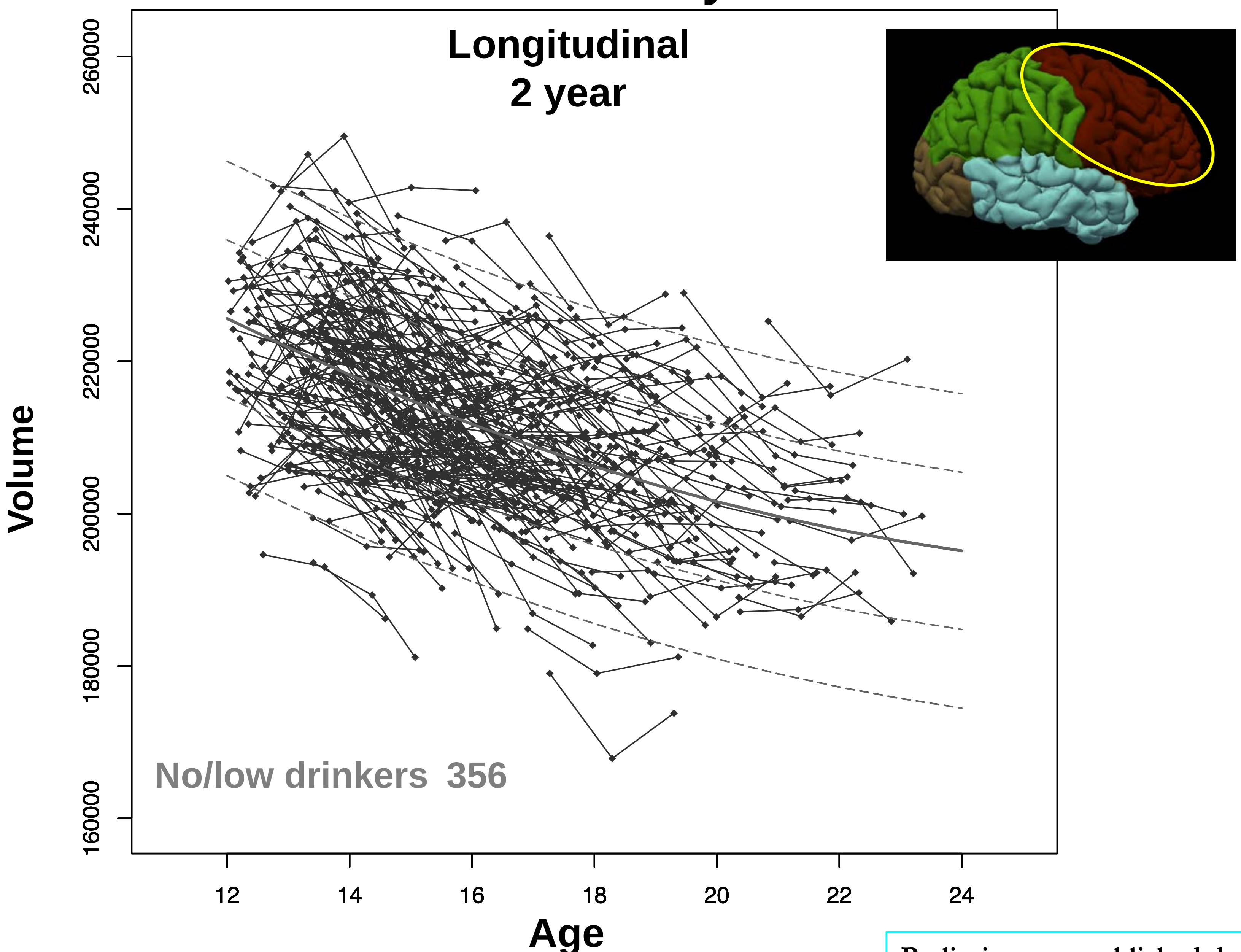
Frontal Cortical Gray Matter



Preliminary unpublished data

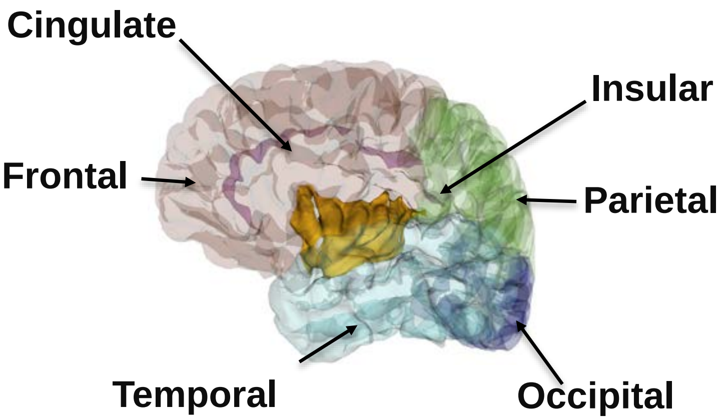
Frontal Cortical Gray Matter

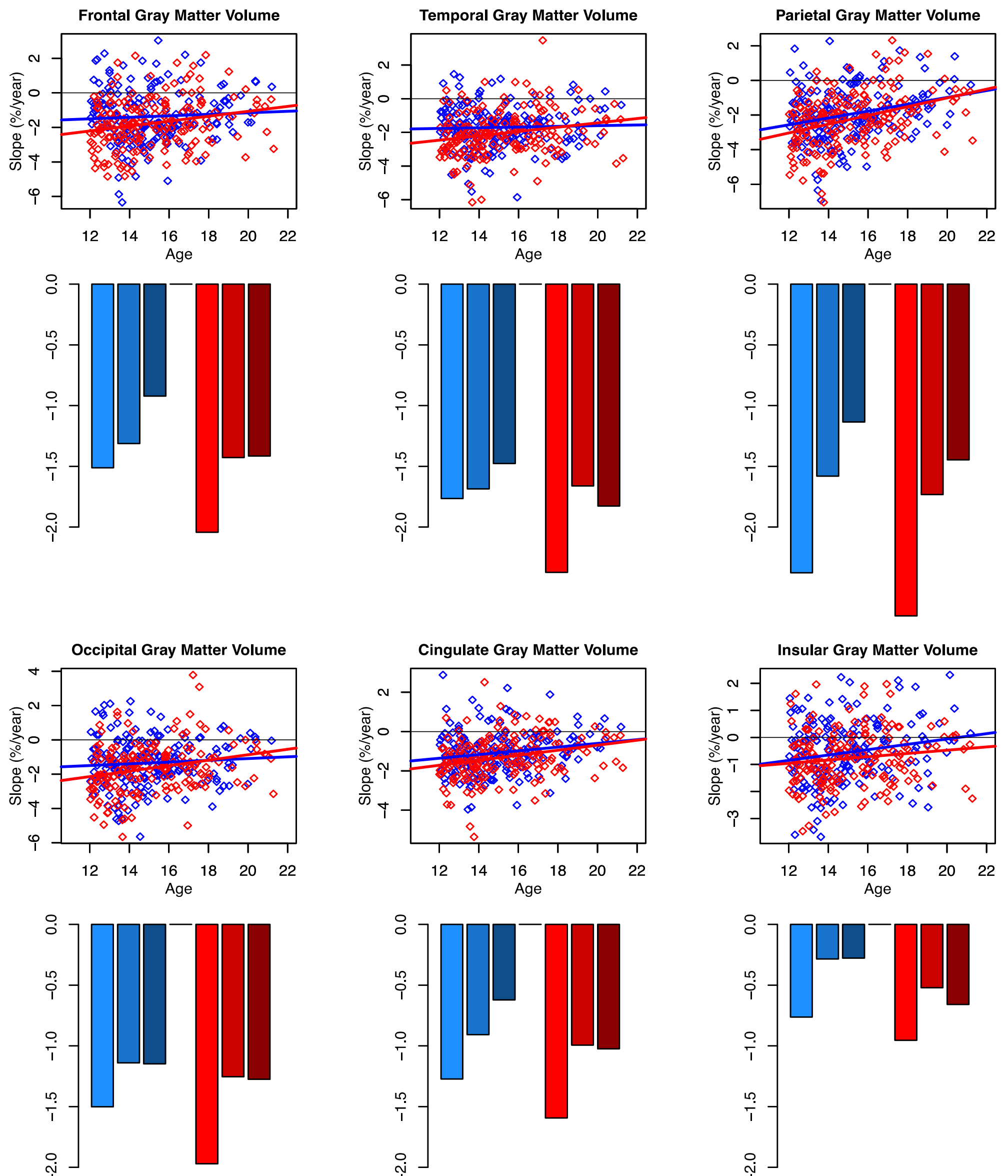


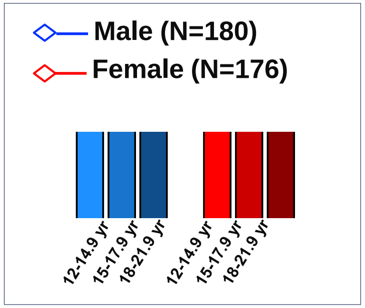
Preliminary unpublished data

Regional Gray Matter Volume Slopes

Decline with Age

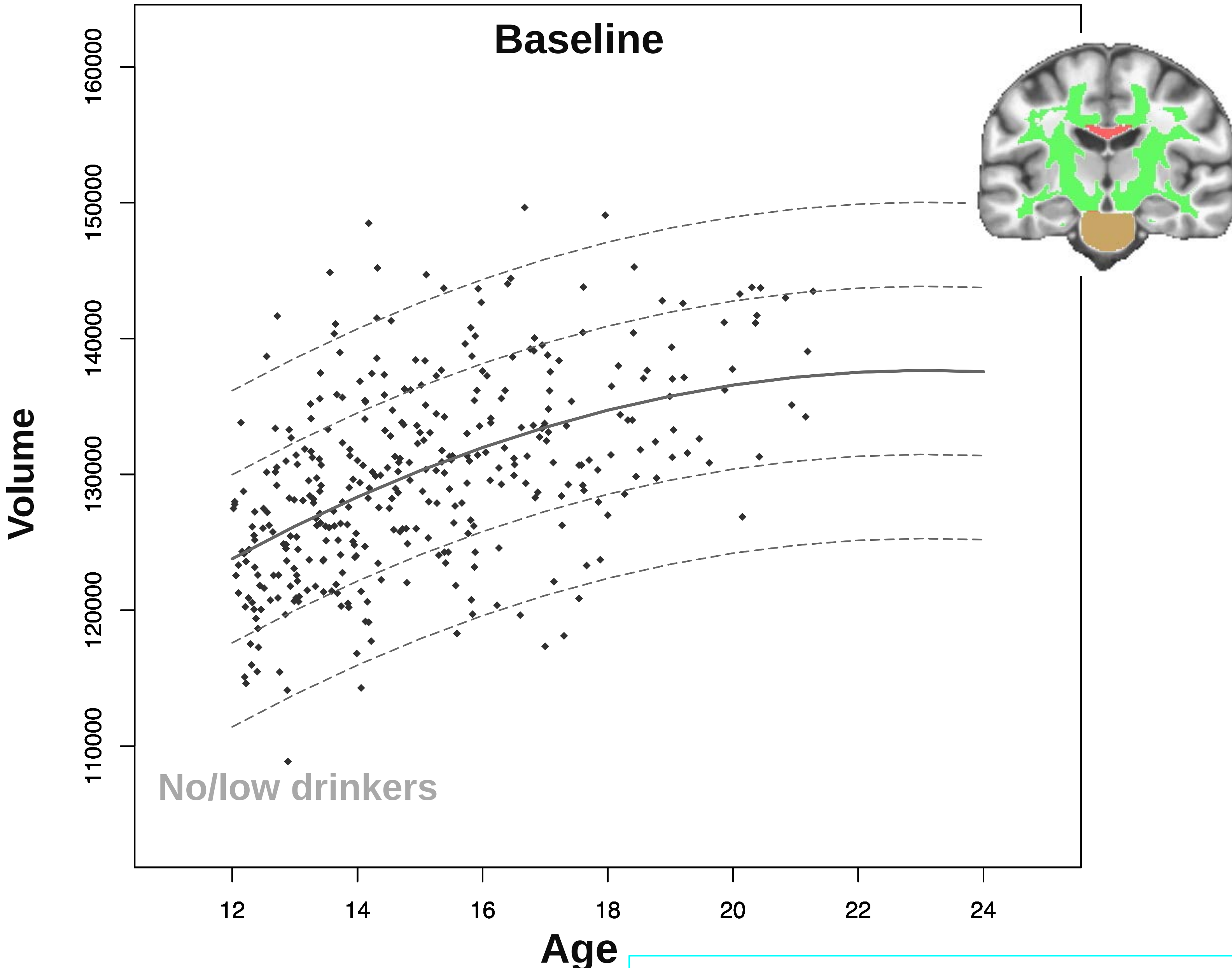






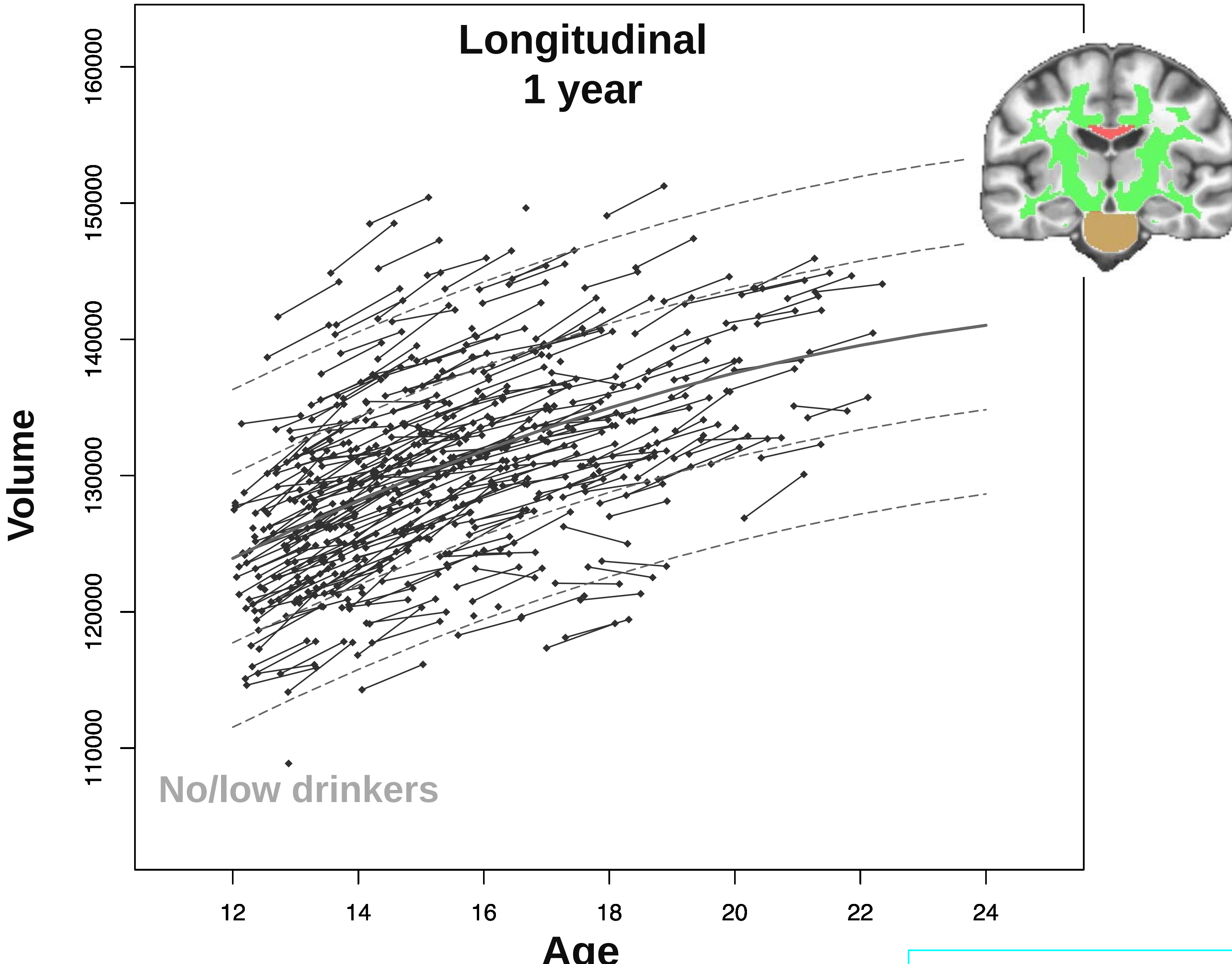
Pfefferbaum et al. *in review*

Central White Matter

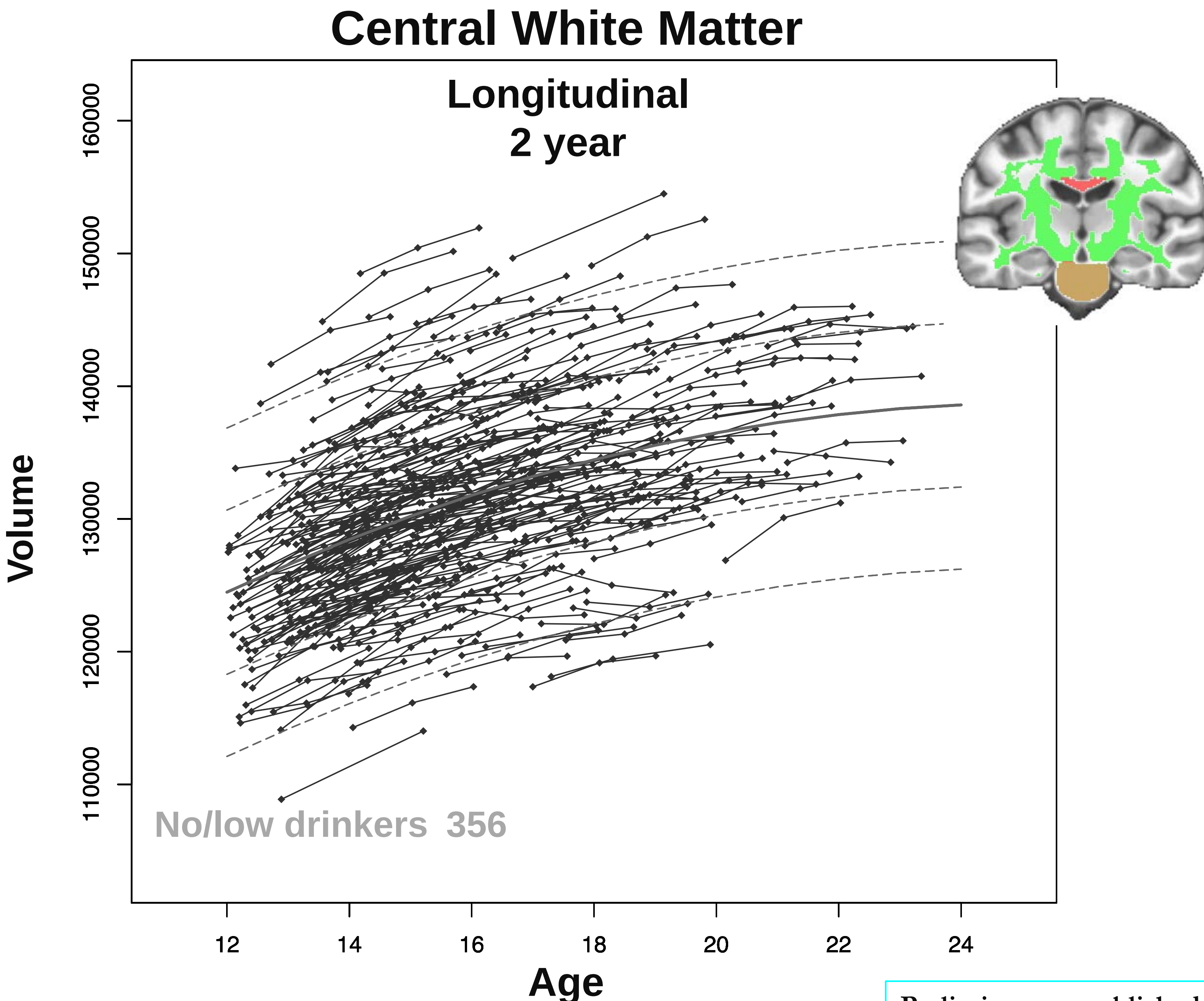


adapted from Pfefferbaum et al. *Cerebral Cortex* 2016

Central White Matter



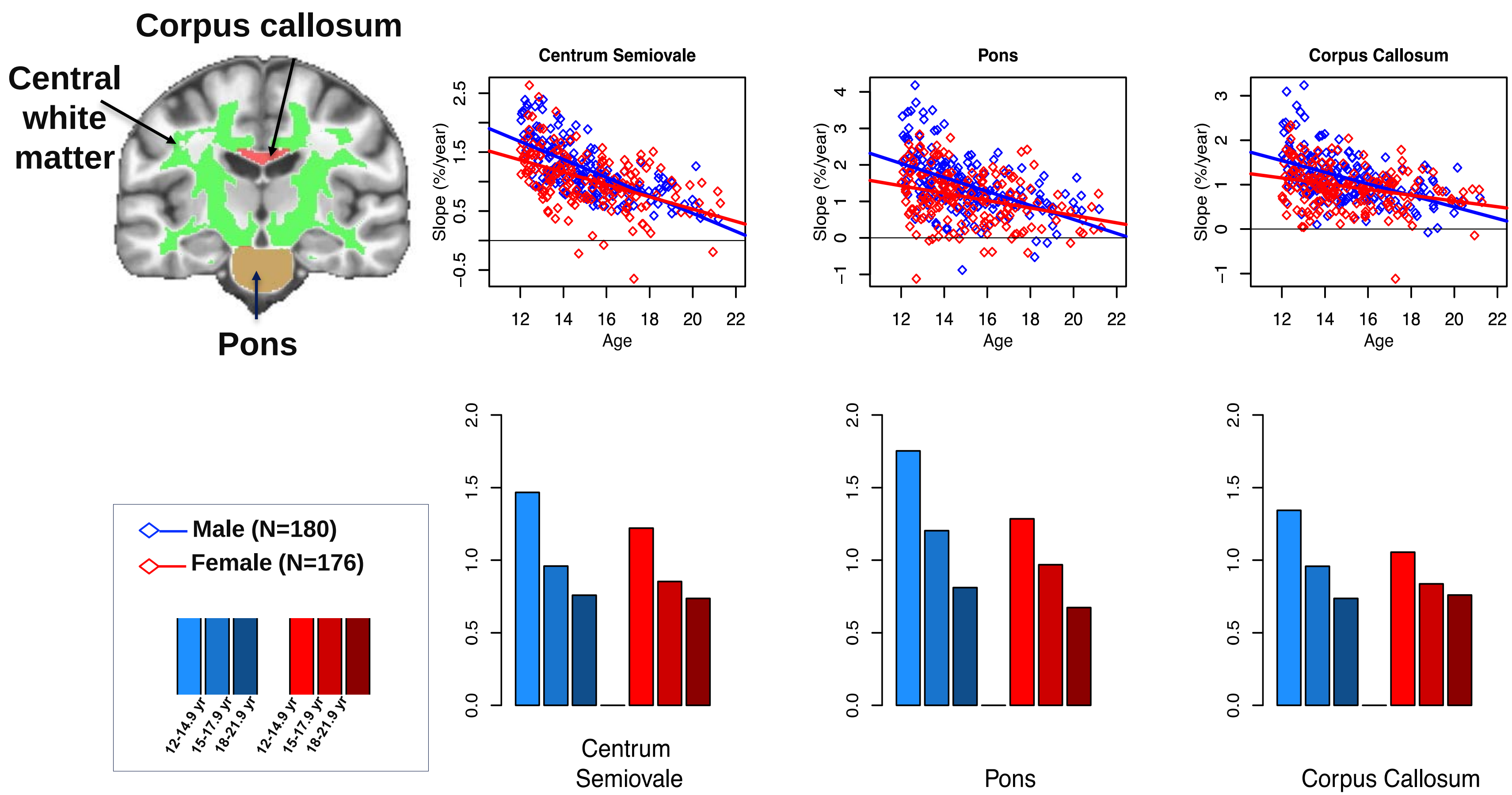
Preliminary unpublished data



Preliminary unpublished data

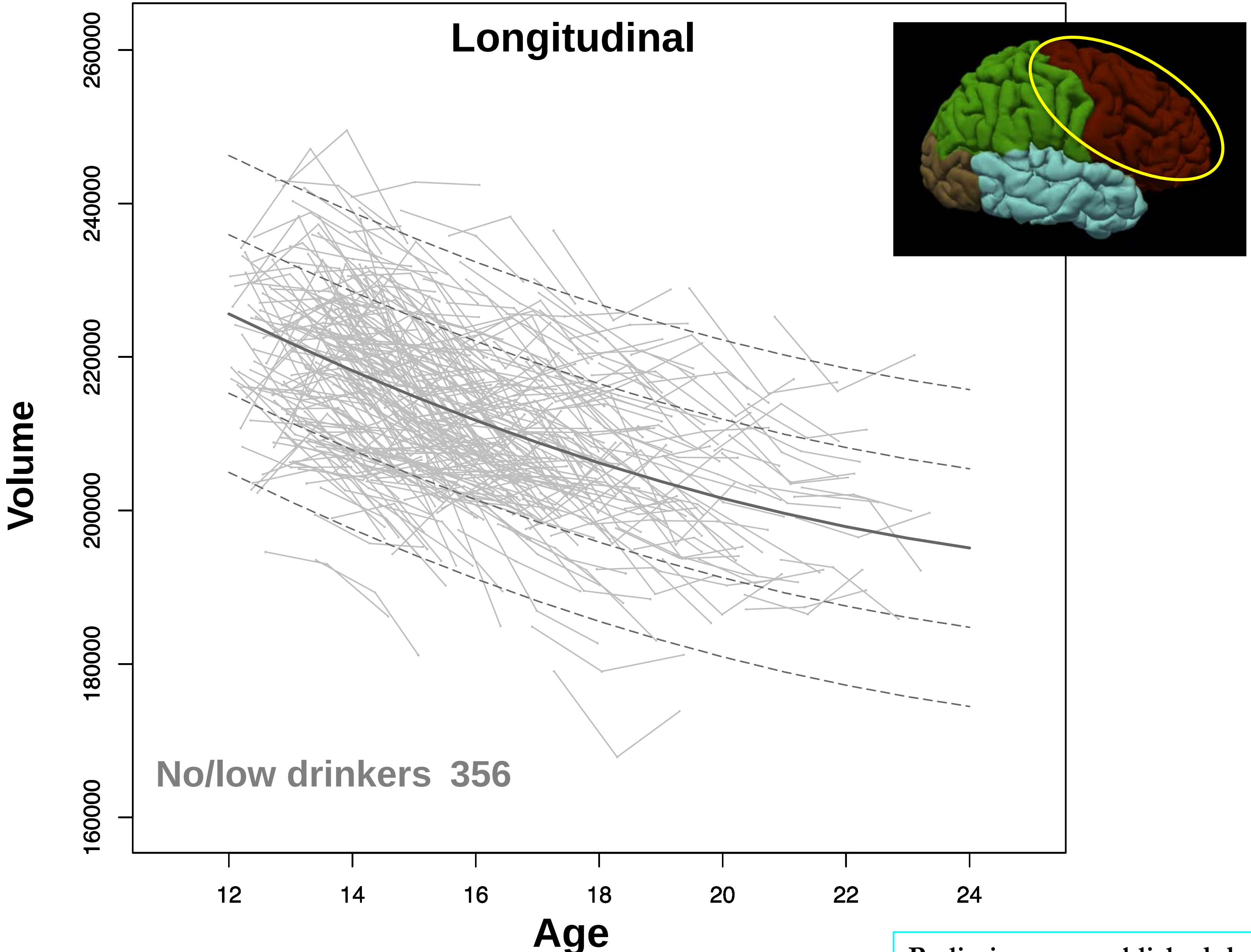
Regional White Matter Volume Slopes

Decelerating Growth with Age



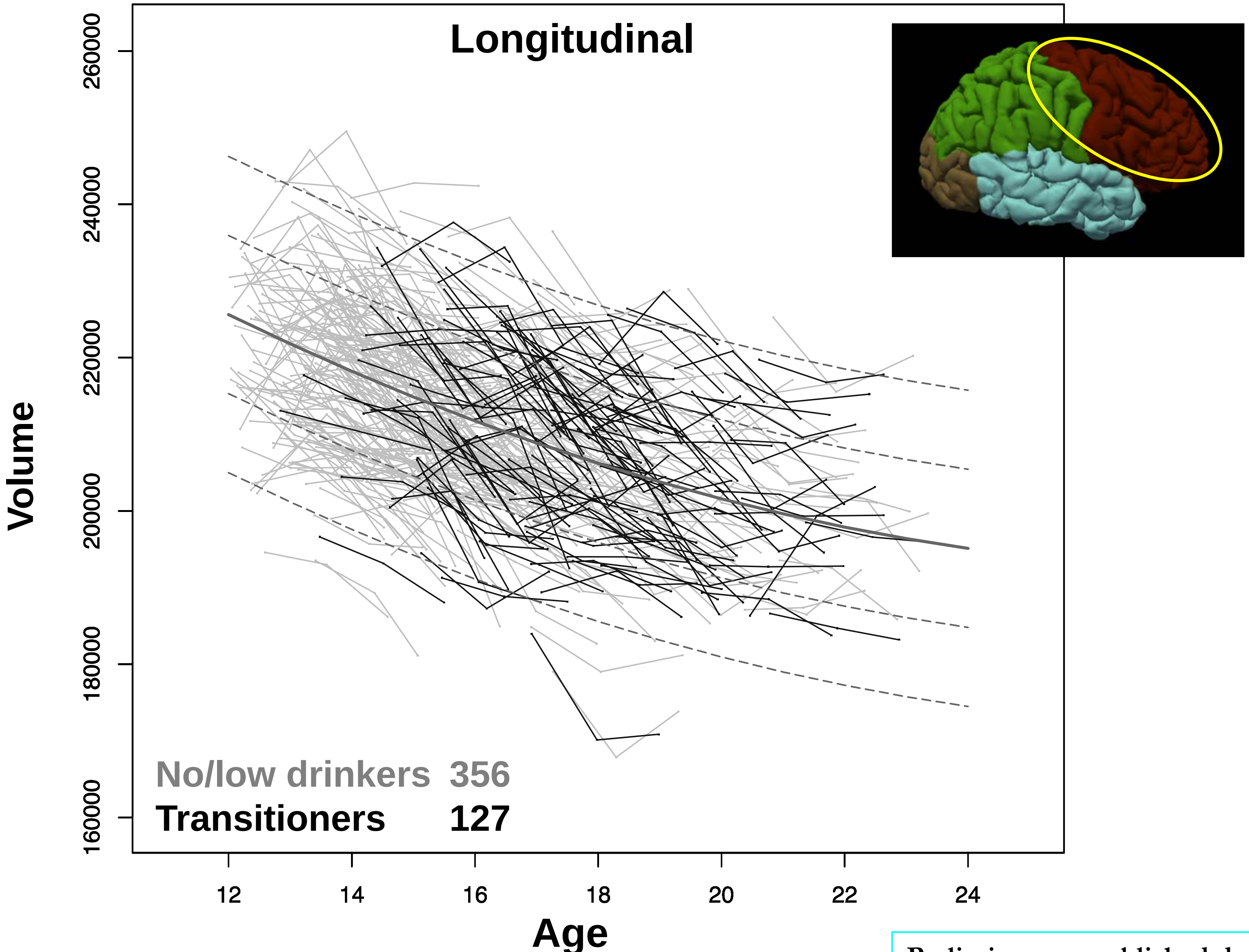
Pfefferbaum et al. ***in review***

Frontal Cortical Gray Matter



Preliminary unpublished data

Frontal Cortical Gray Matter



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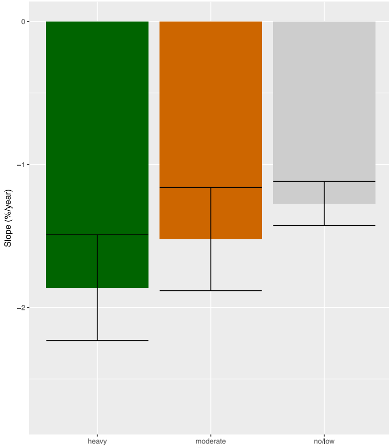

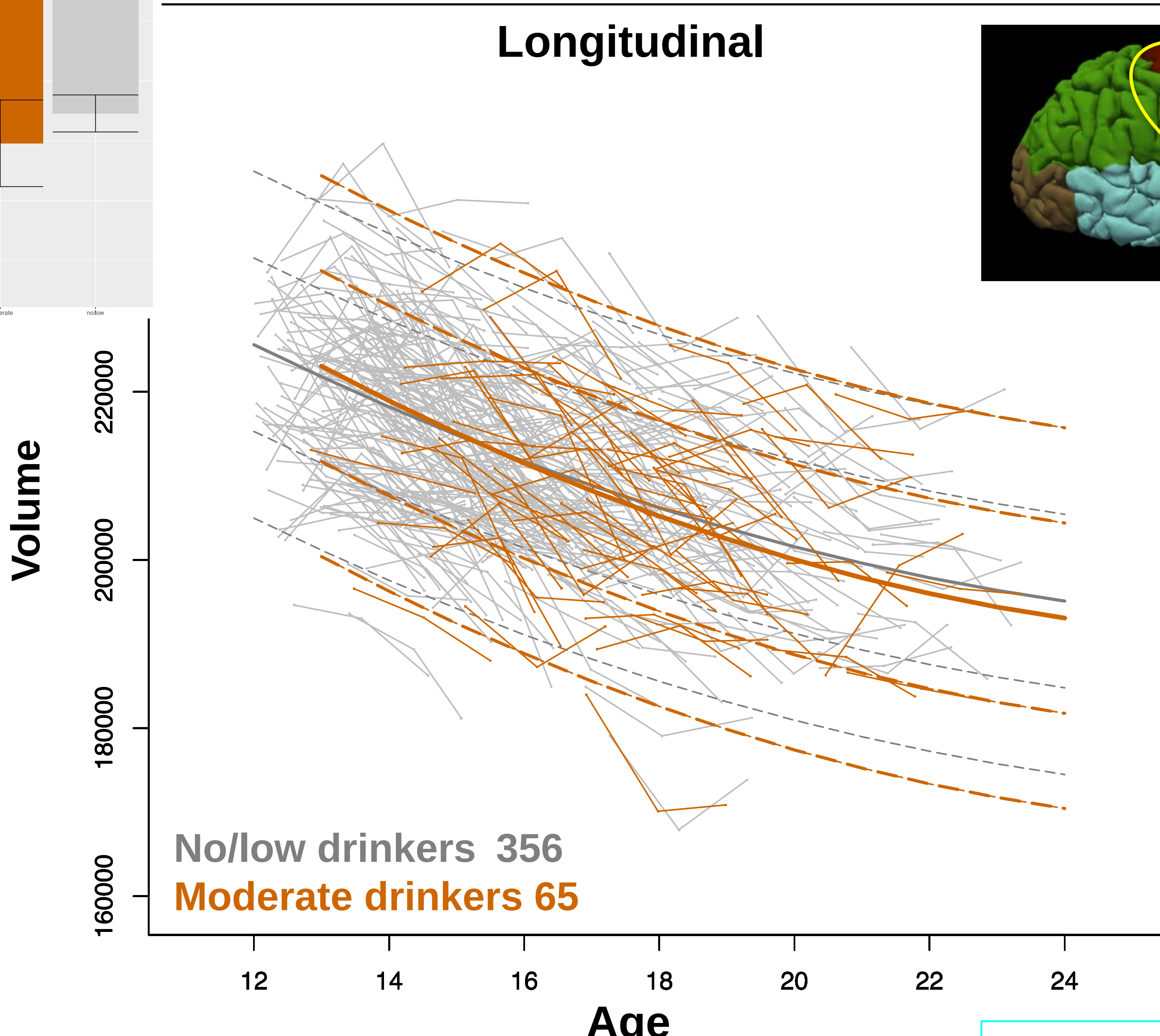

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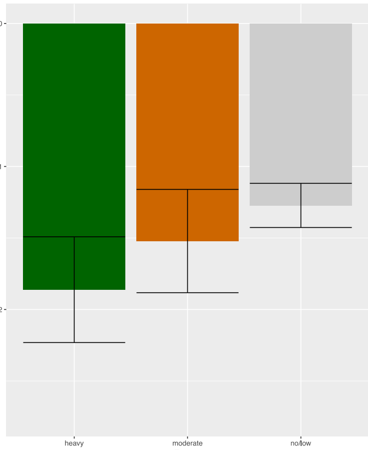
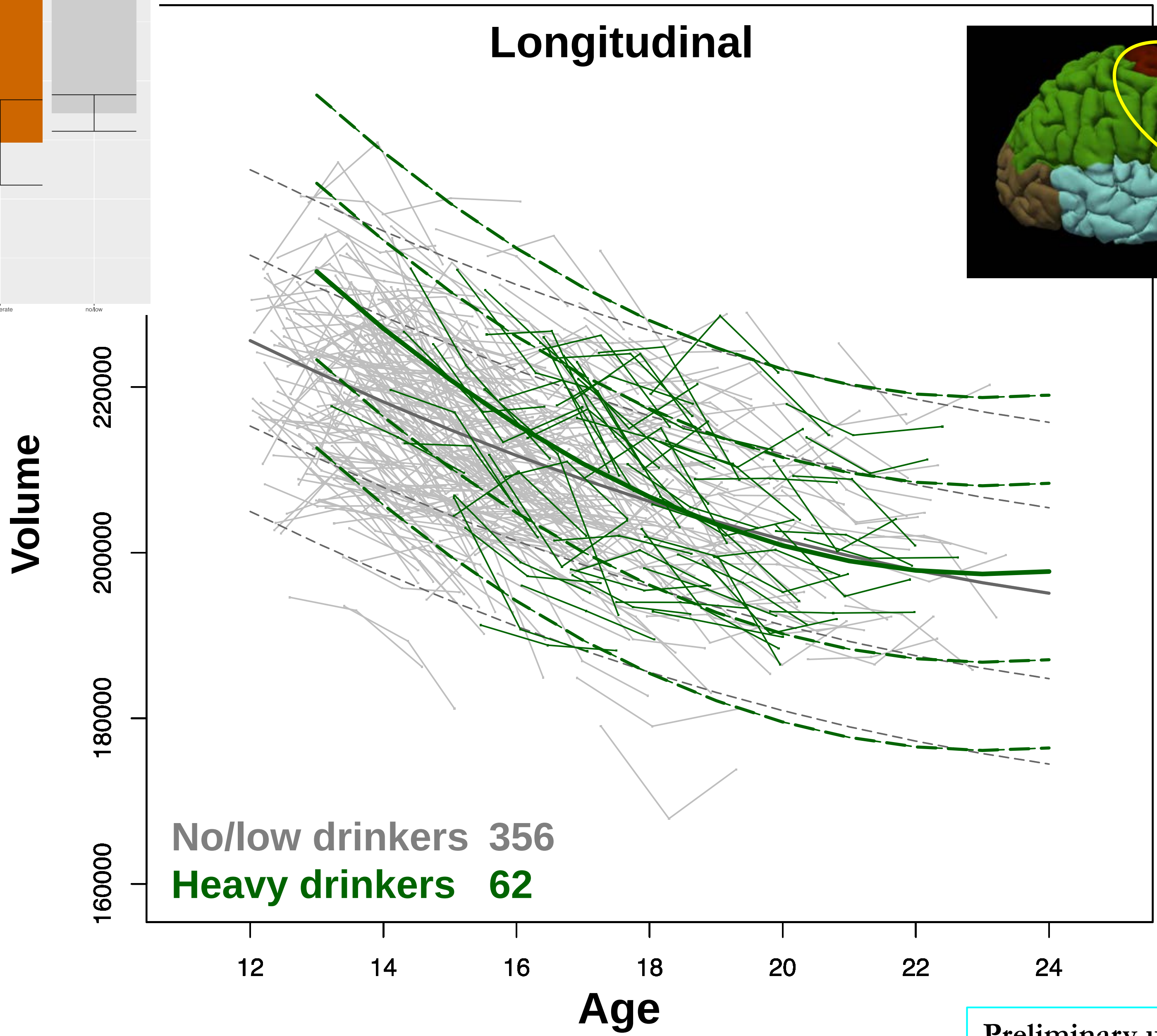
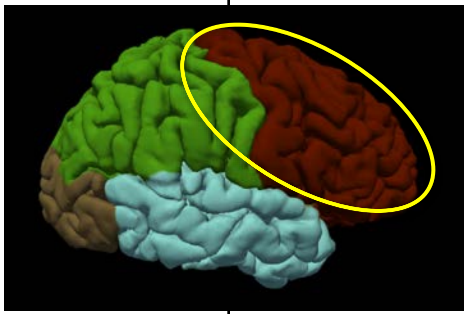
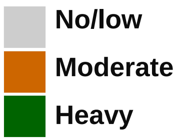


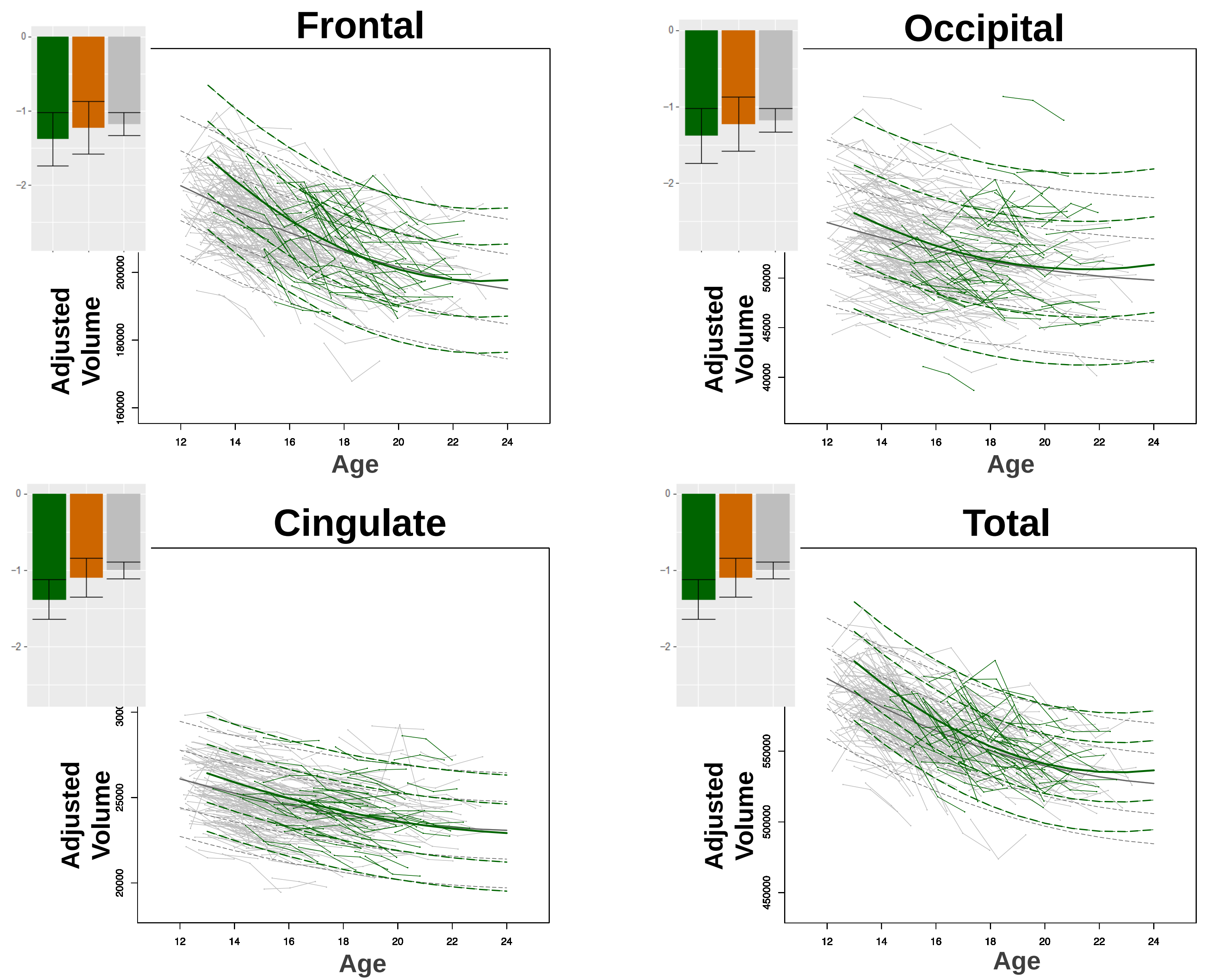




Preliminary unpublished data

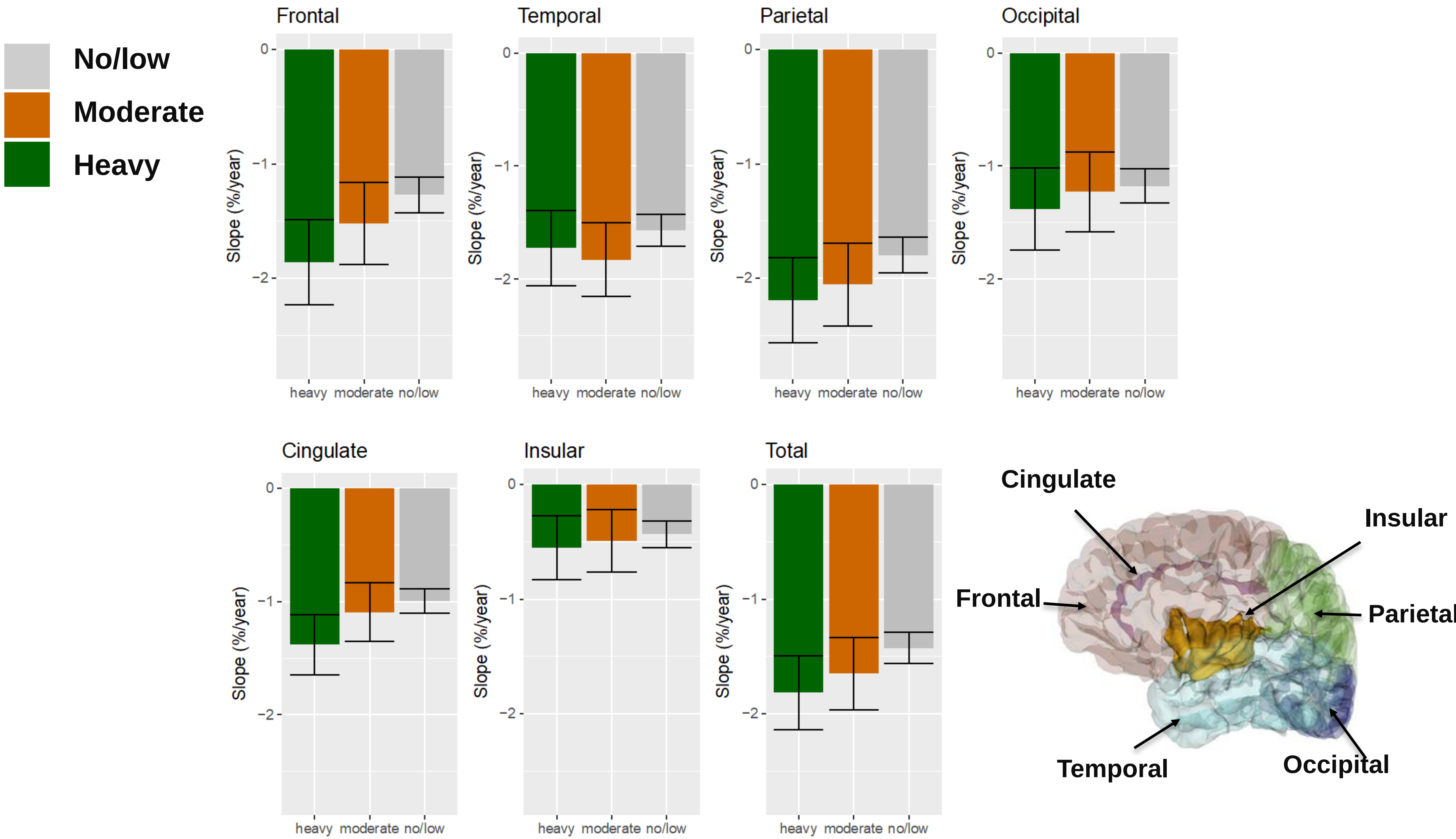
Regions where heavy drinkers have significantly steeper reduction in gray matter volume than no-low drinkers





Regional Gray Matter Volumes

Accelerated Decline with Initiation of Heavy Drinking

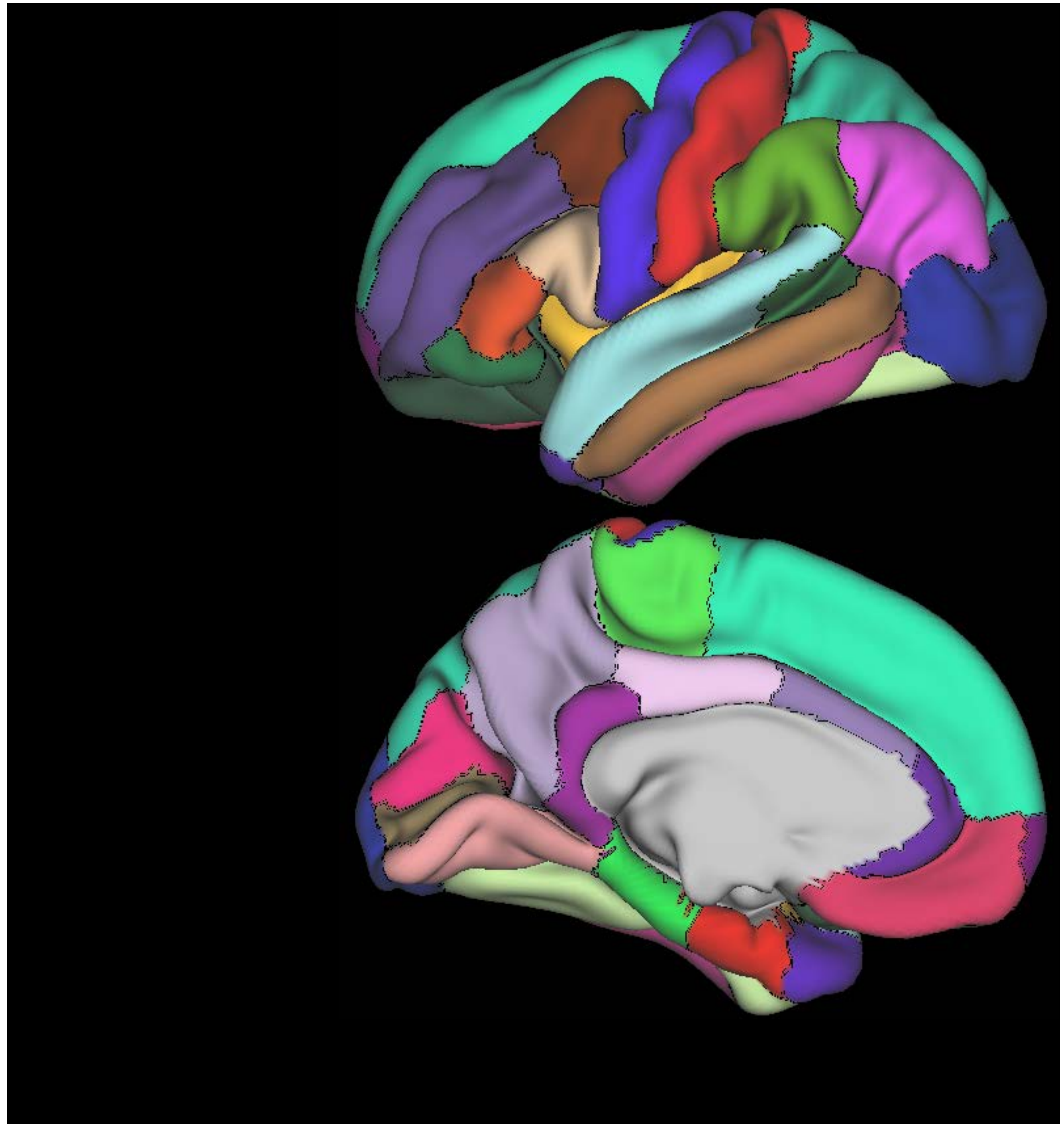


Pfefferbaum et al. ***in review***

FreeSurfer Parcellated Cortical Regions

34 Regions

- L_bankssts
- L_caudalanteriorcingulate
- L_caudalmiddlefrontal
- L_corpuscallosum
- L_cuneus
- L_entorhinal
- L_frontalpole
- L_fusiform
- L_inferiorparietal
- L_inferiortemporal
- L_insula
- L_isthmuscingulate
- L_lateraloccipital
- L_lateralorbitofrontal
- L_lingual
- L_medialorbitofrontal
- L_middletemporal
- L_paracentral
- L_parahippocampal
- L_parsopercularis
- L_parsorbitalis
- L_parstriangularis
- L_pericalcarine
- L_postcentral
- L_posteriorcingulate
- L_precentral
- L_precuneus
- L_rostralanteriorcingulate
- L_rostralmiddlefrontal
- L_superiorfrontal
- L_superiorparietal
- L_superiortemporal
- L_supramarginal
- L_temporalpole
- L_transversetemporal



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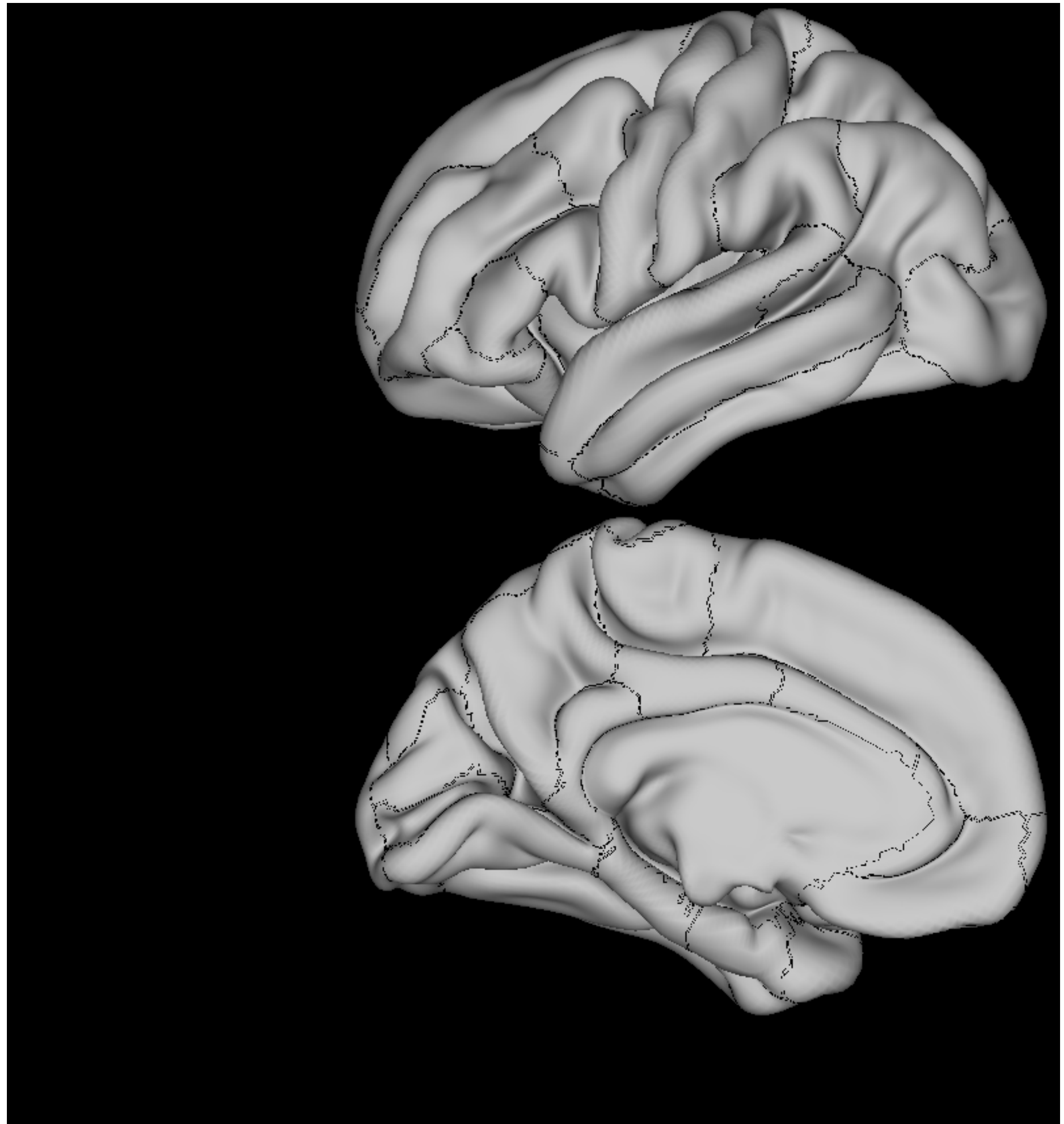

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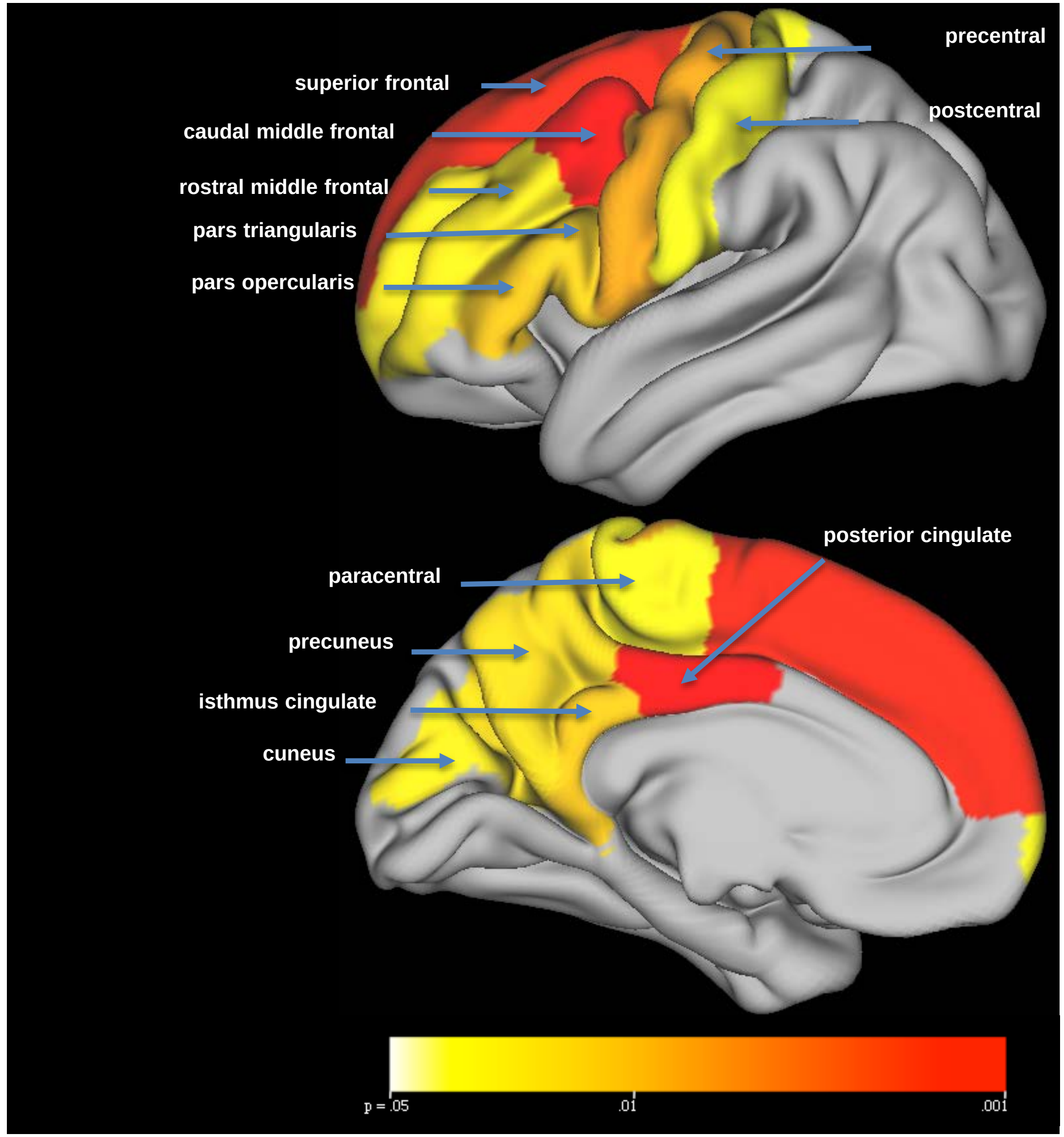
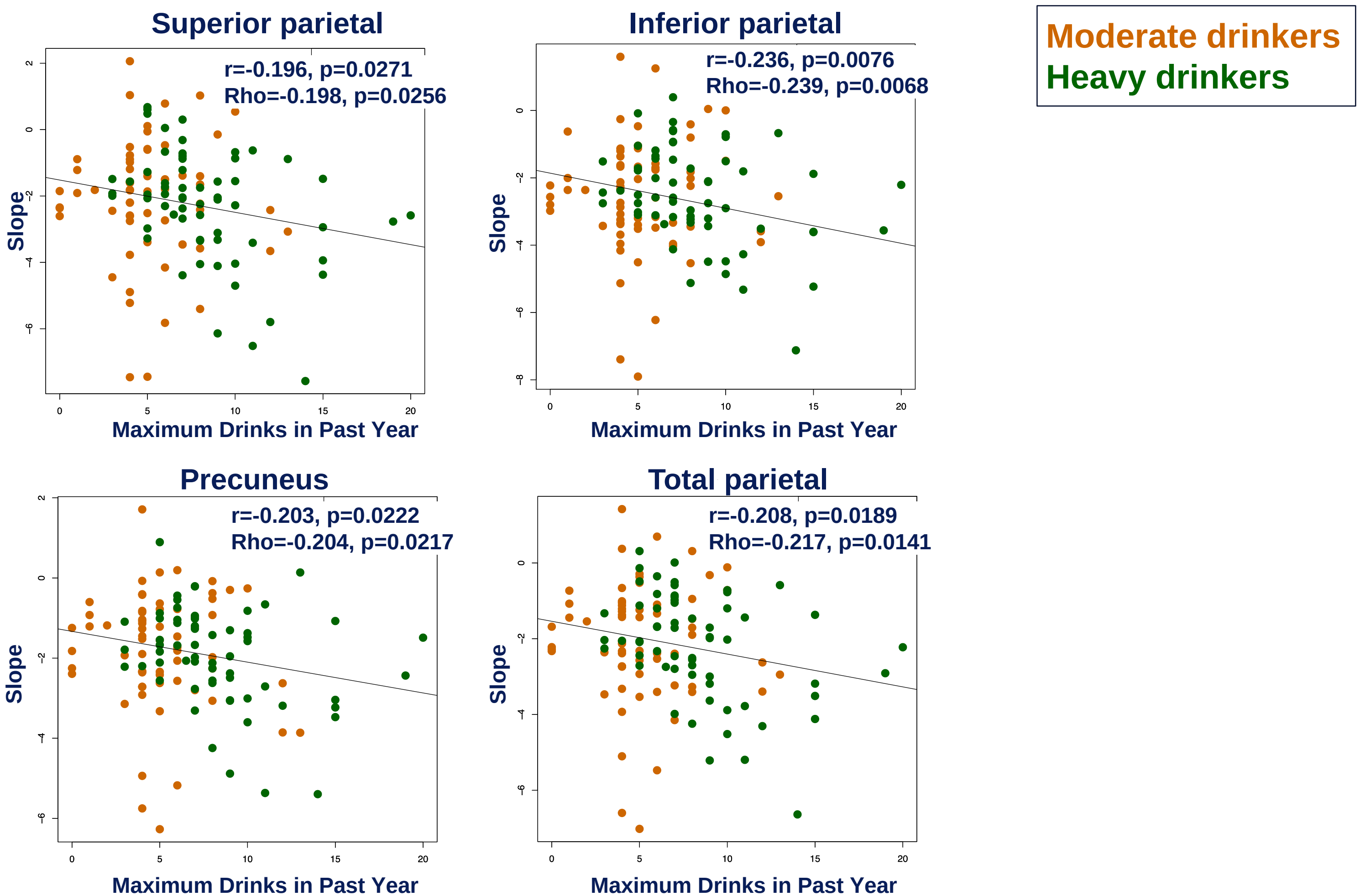


Steeper Regional Parietal Trajectories

Correlations with Greater Maximum Drinks in Past Year



Pfefferbaum et al. ***in review***

Extending Analysis of Imaging Data

Cortical Myelin

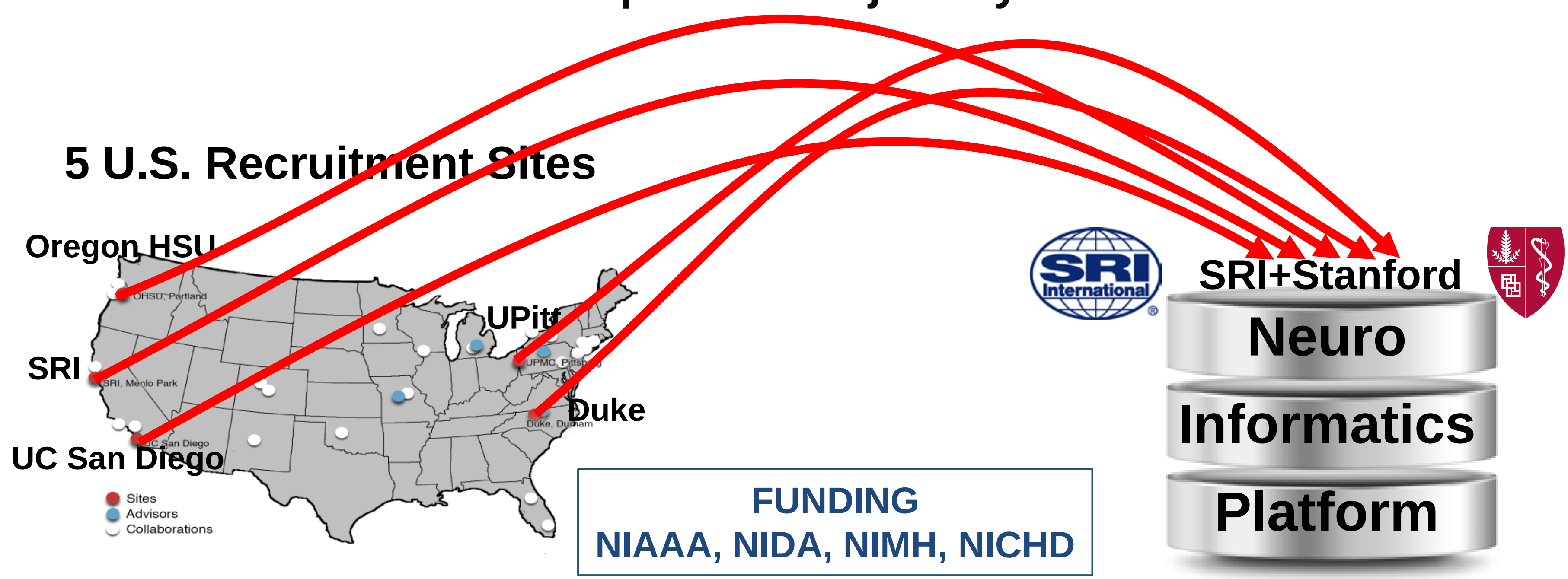
There is a developmental trajectory of cortical myelin increase and decrease

Subcortical Brain Iron

There is a developmental trajectory of subcortical non-heme iron deposition

Effects of Initiation of Drinking

Initiation of heavy drinking alters structural cortical developmental trajectory



FUNDING
NIAAA, NIDA, NIMH, NICHD