Research Society on Alcoholism
Denver, CO
26 June 2017

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

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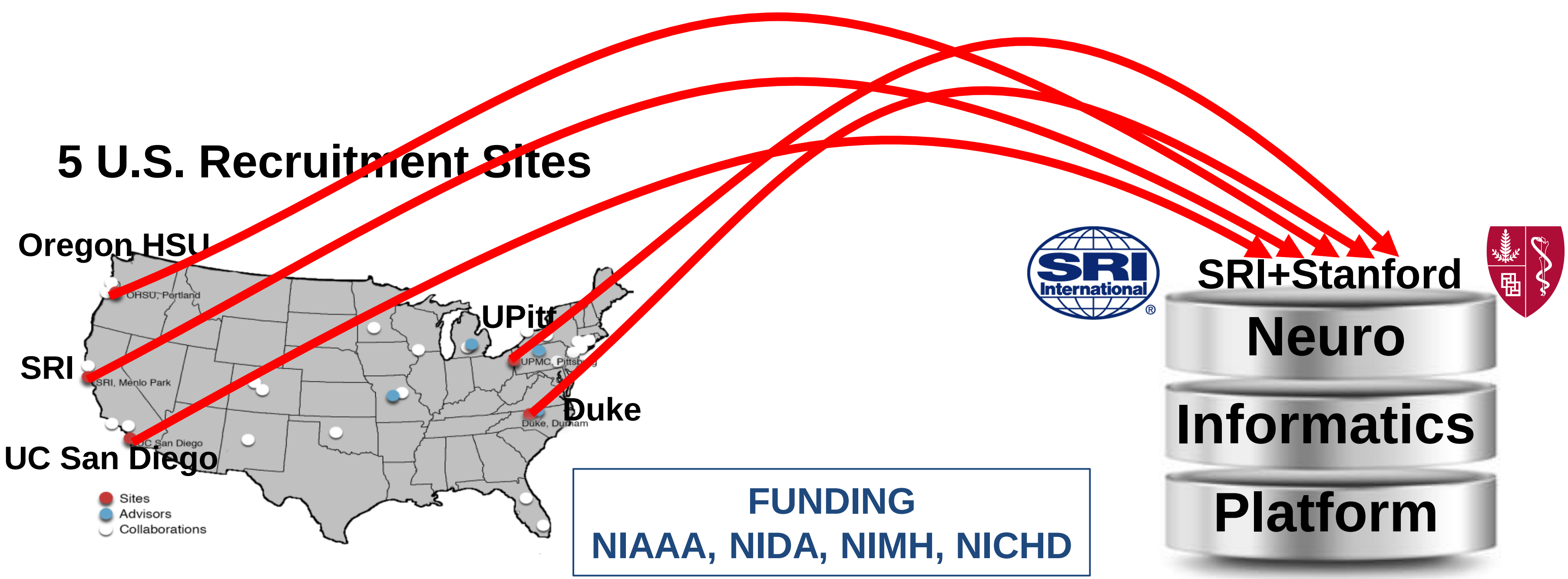
Supported by NIH/NIAAA

Extending Analysis of Imaging Data

Subcortical Brain Iron

Cortical Myelin

Effects of Initiation of Drinking



FUNDING
NIAAA, NIDA, NIMH, NICHD

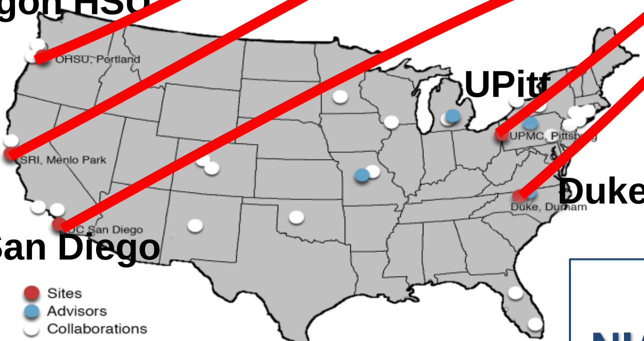
National Consortium on Alcohol and NeuroDevelopment in Adolescence

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



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NIAAA, NIDA, NIMH, NICHD

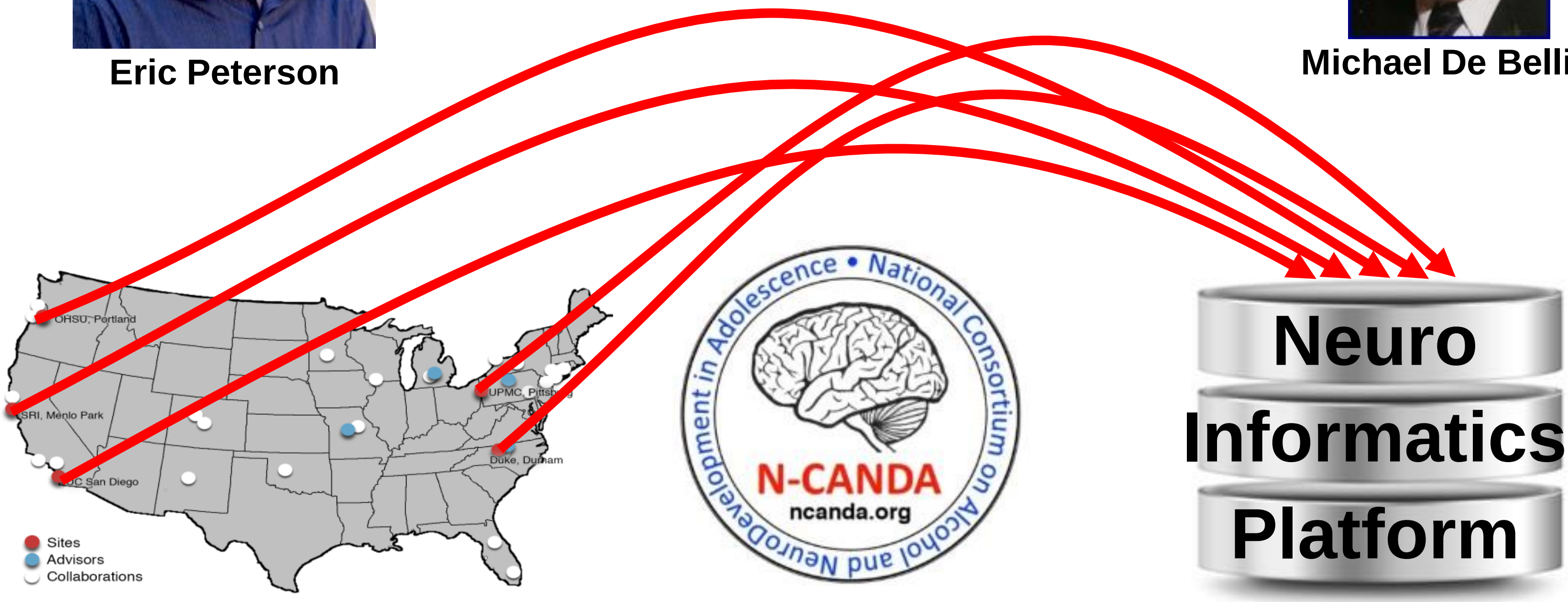
SRI+Stanford

Extending Analysis of Imaging Data

Subcortical Brain Iron

Eric Peterson

Michael De Bellis



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

Iron in the Brain

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

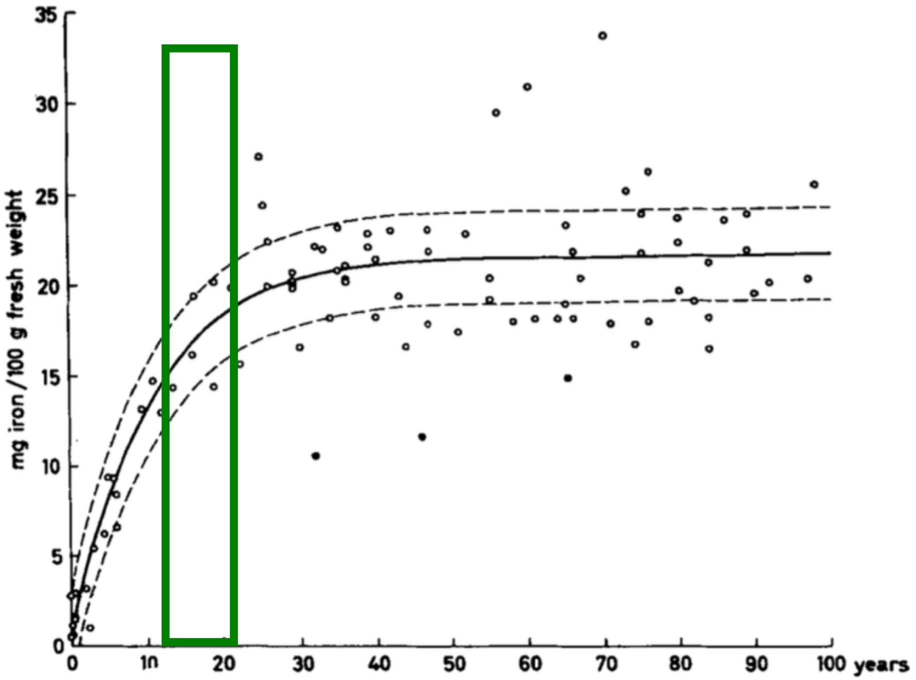
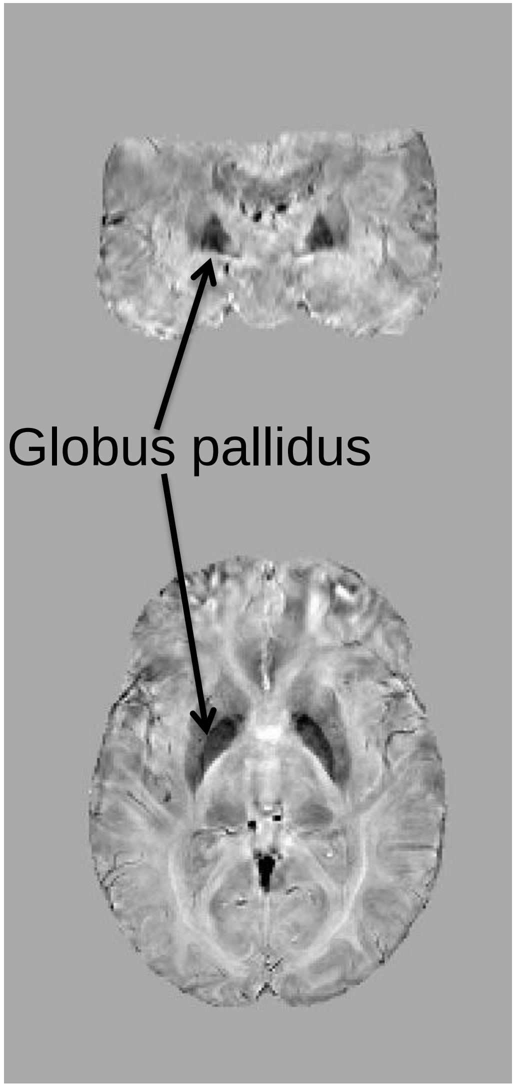


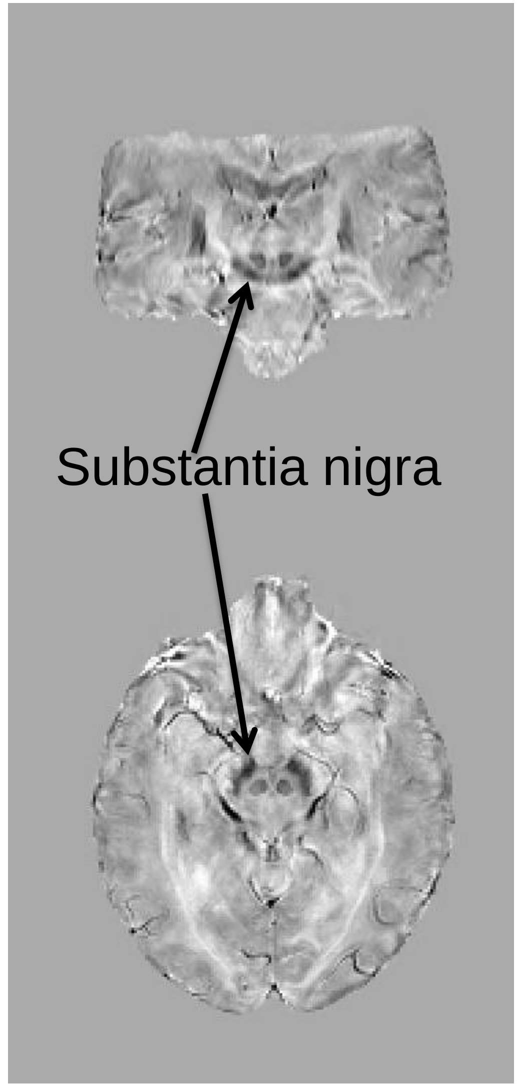
FIG. 2. Non-haemin iron in the globus pallidus at different ages. The filled circles represent cases with large intestinal haemorrhages.
The calculated regression lines have been drawn in Figs. 2–6. The dotted lines denote the the S.E. of estimate; for globus pallidus S.E. = $\pm 3{\cdot}07$.

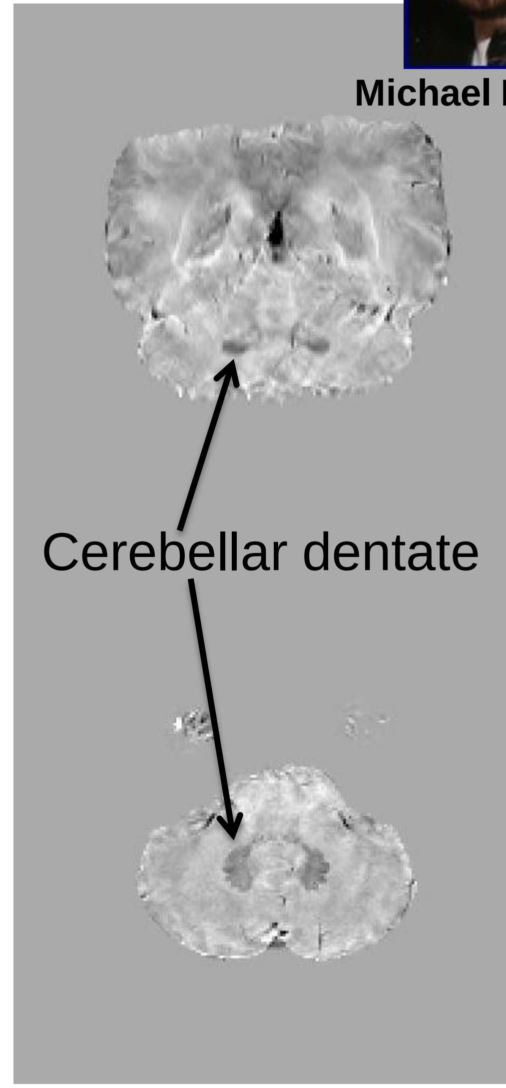
Hallgren and Sourander, Journal of Neurochemistry, 1958

Susceptibility Weighted Imaging (SWI)
(T2* Weighted)

Michael De Bellis

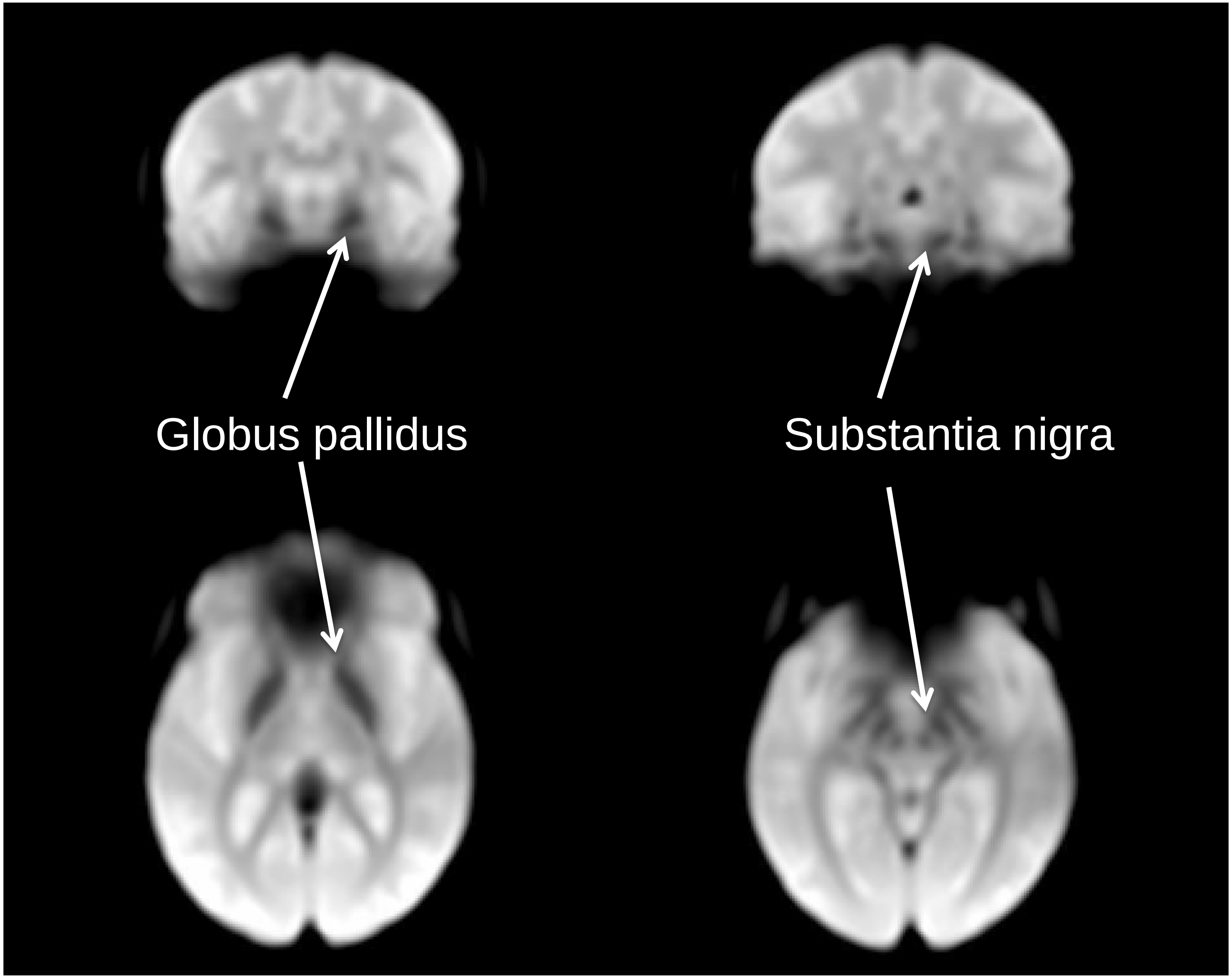






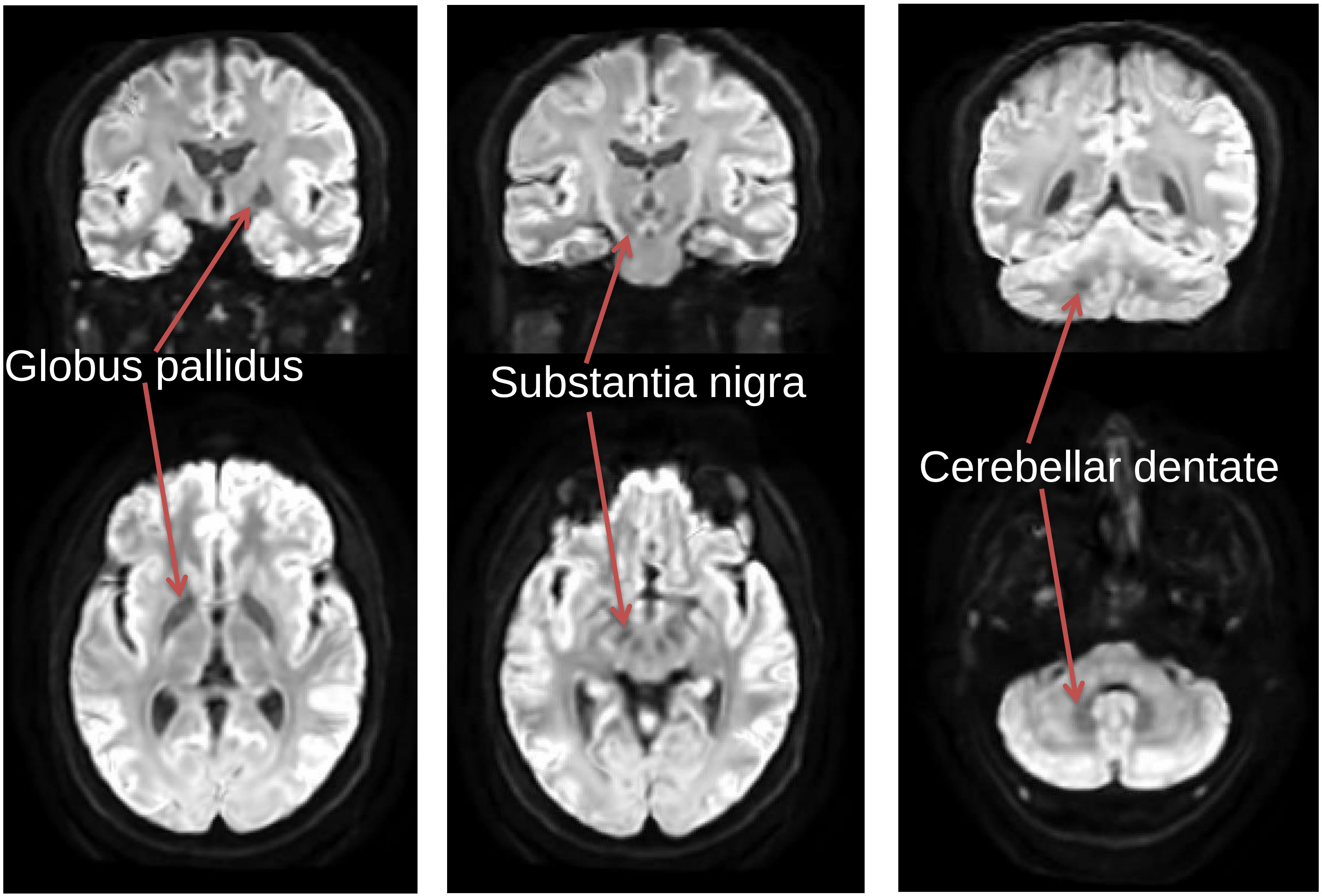
Measurement of protons is "susceptible" to the presence of iron causing signal loss.

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



Measurement of protons is "susceptible" to the presence of iron causing signal loss.

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



Measurement of protons is "susceptible" to the presence of iron causing signal loss.

Estimating Non-heme Iron Concentration from Standard NCANDA Protocols

Non-heme iron →

susceptibility (T2*) signal loss

transverse relaxivity (T2) signal loss

Iron effect

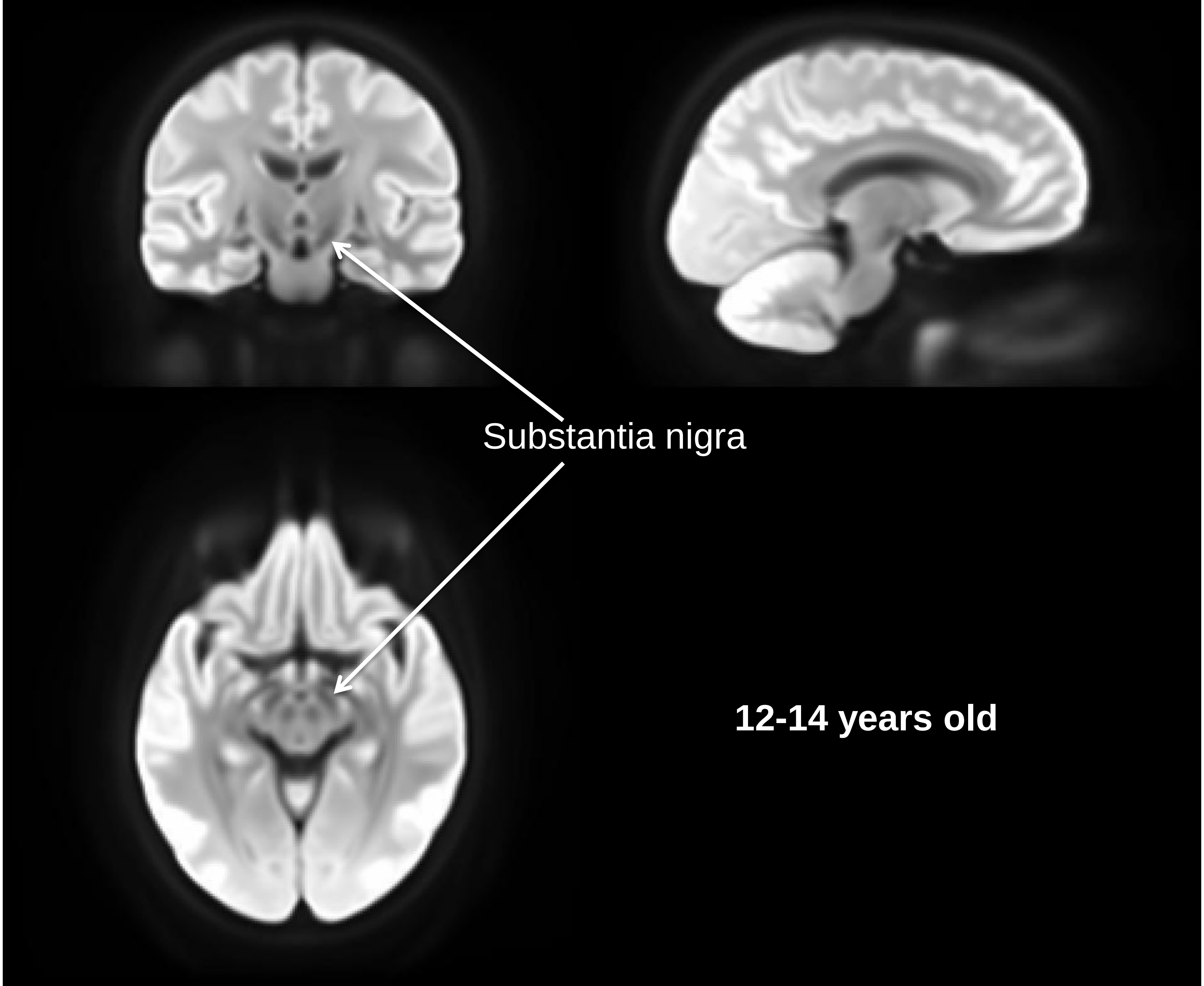
greater T2 and T2* weighting → greater iron effect

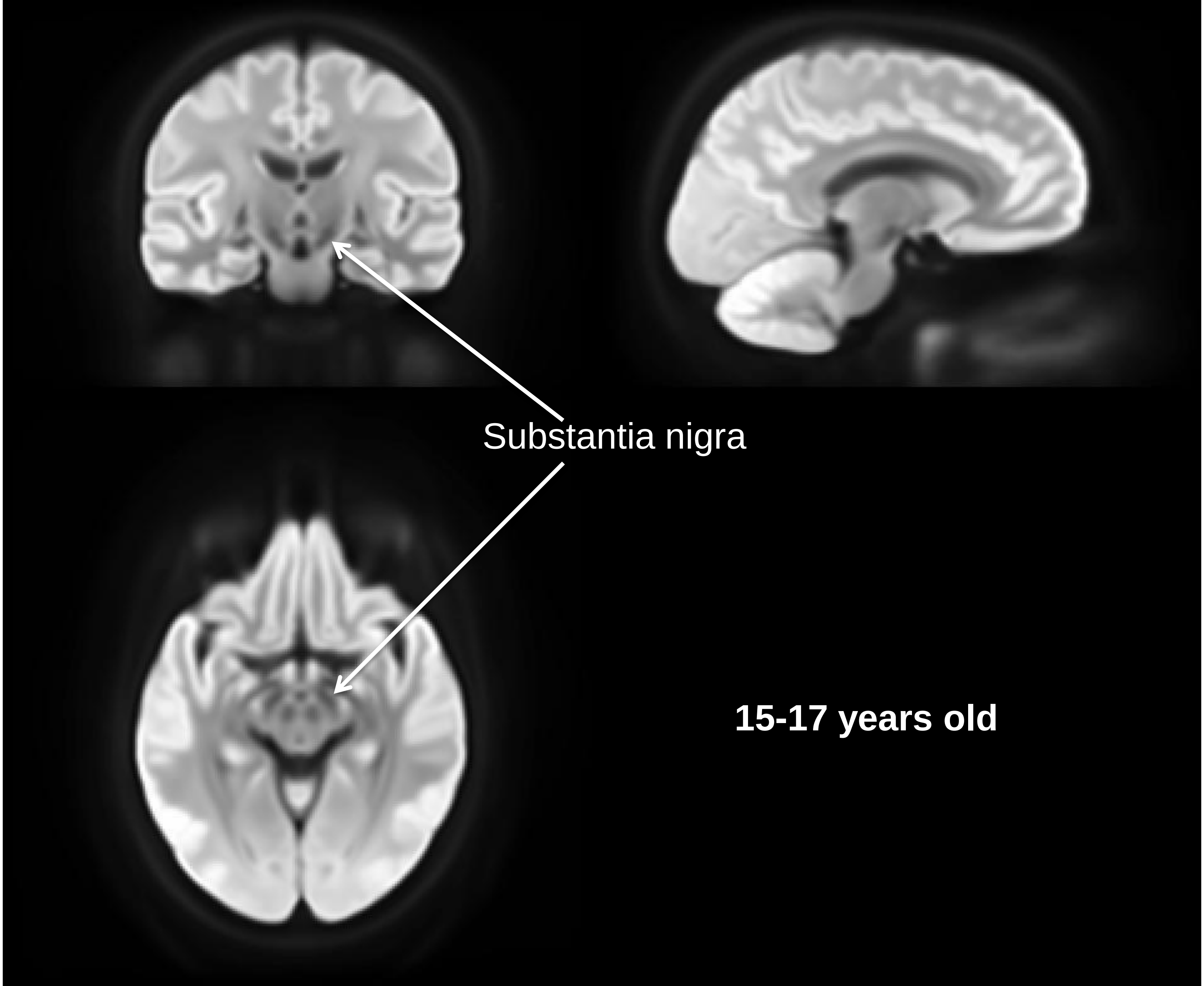
less T1 weighting → greater iron effect

T2* > T2

DTI sequence has higher spatial resolution and less B0 spatial distortion

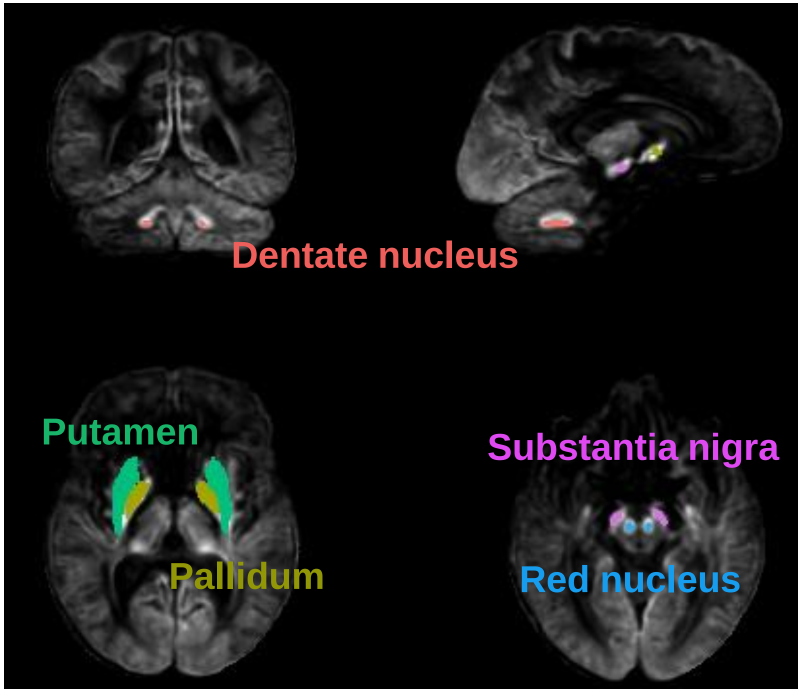
$$R2 / R2^* \ Estimate = \frac{Mean\ Posterior\ Corpus\ Callosum\ Signal\ Intensity}{Voxel\ Signal\ Intensity}$$


Substantia nigra
12-14 years old

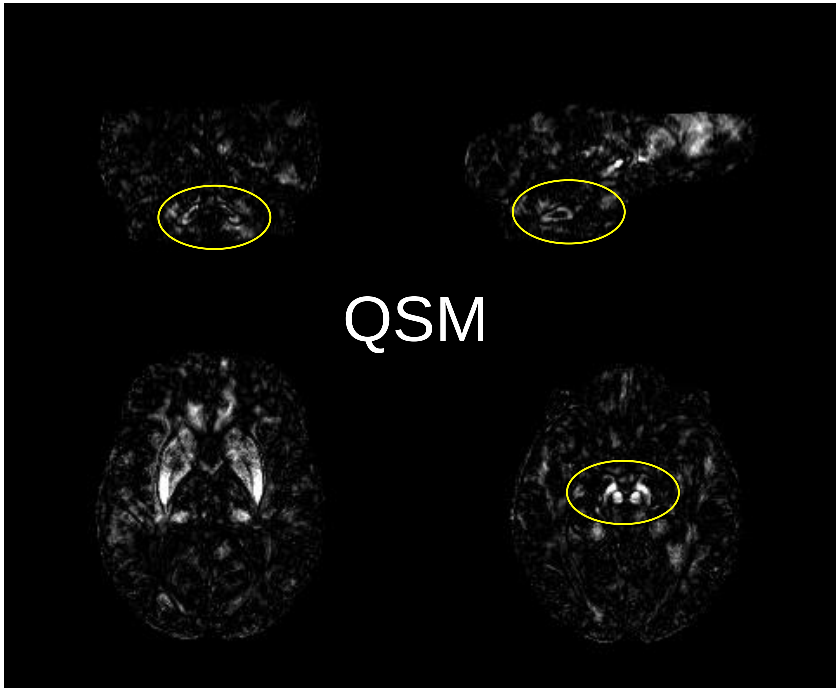

Substantia nigra
15-17 years old


Substantia nigra
18-21 years old

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



R-squared: Signal vs. Age



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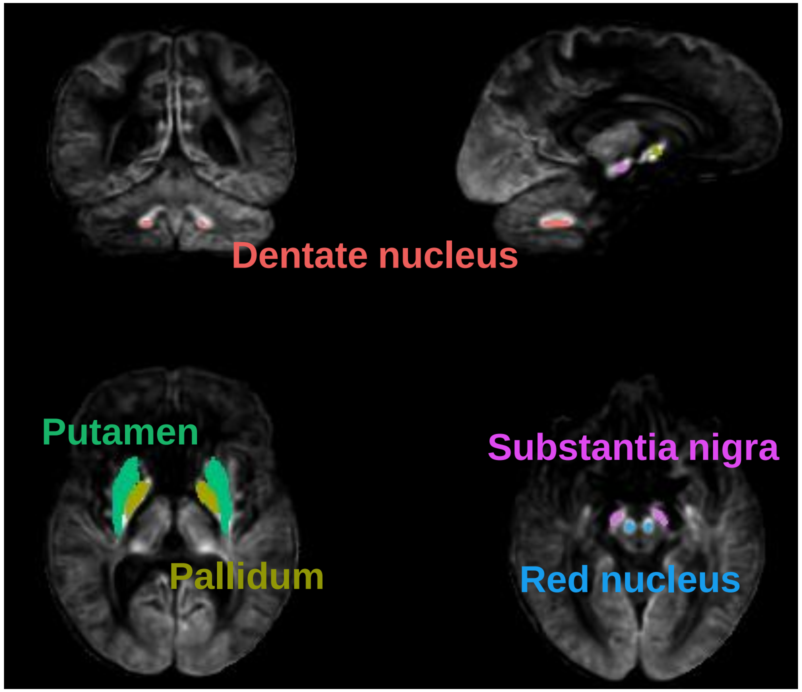

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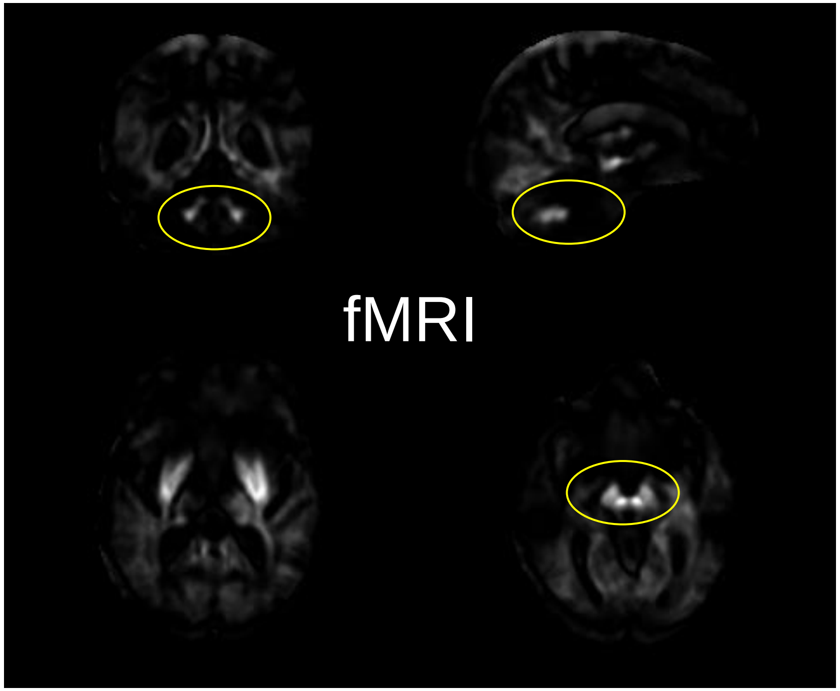

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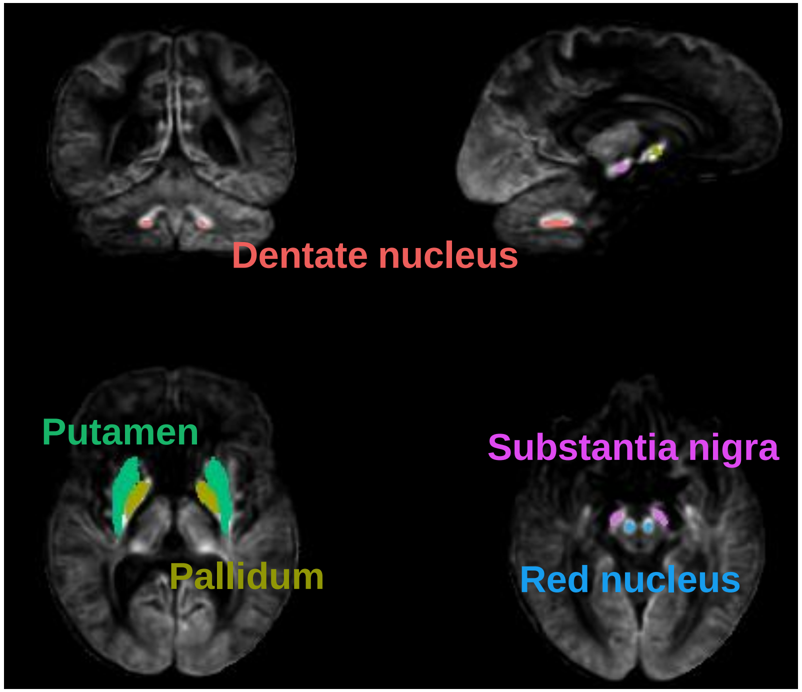

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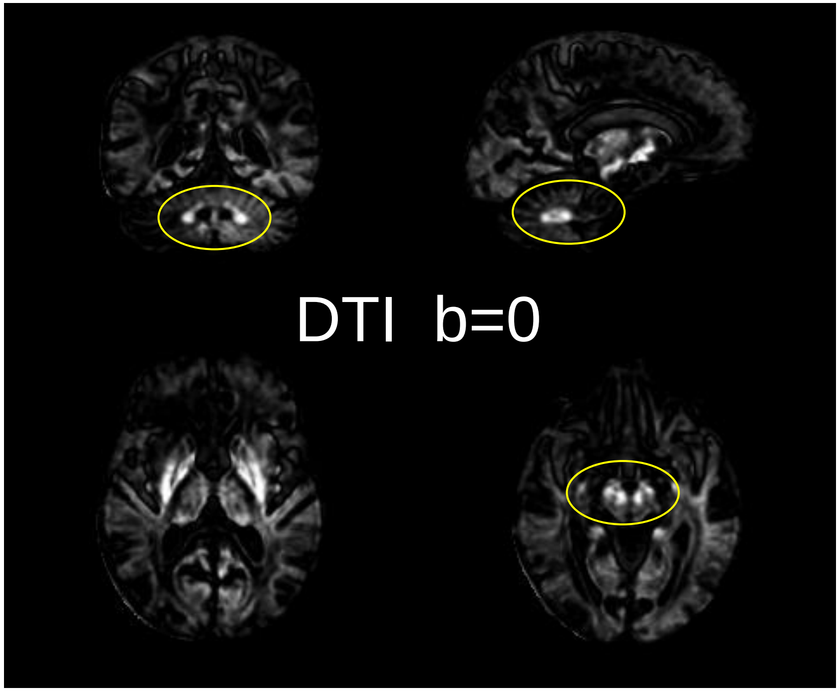

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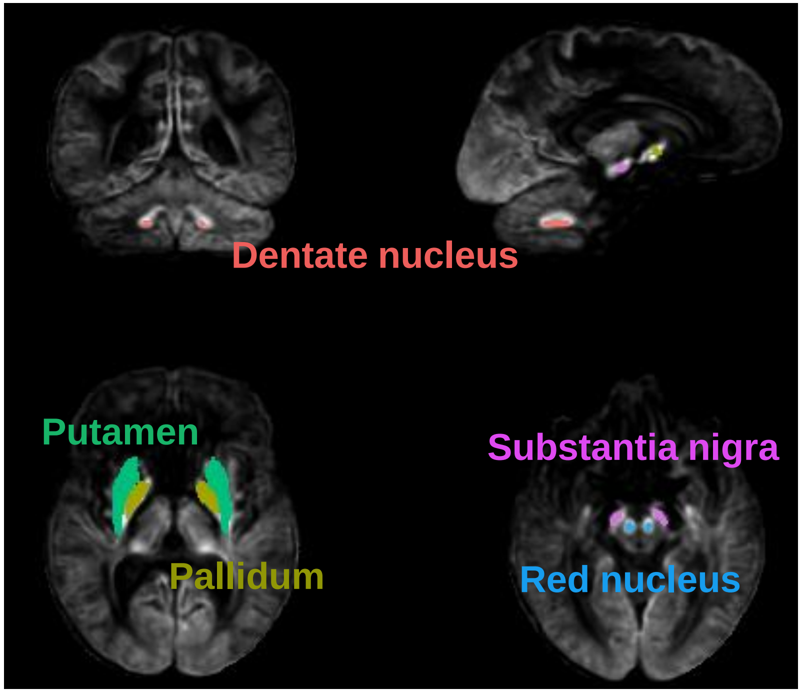

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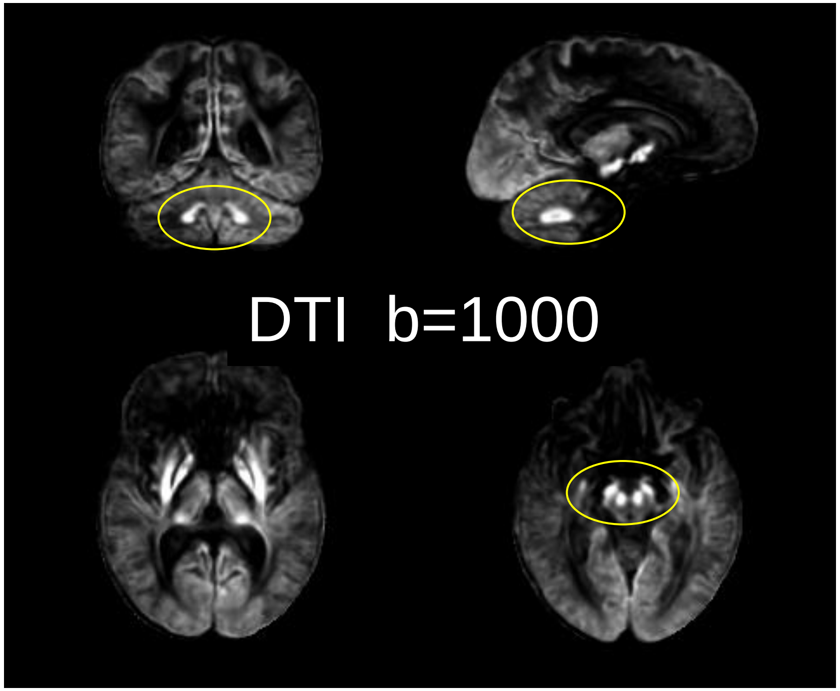

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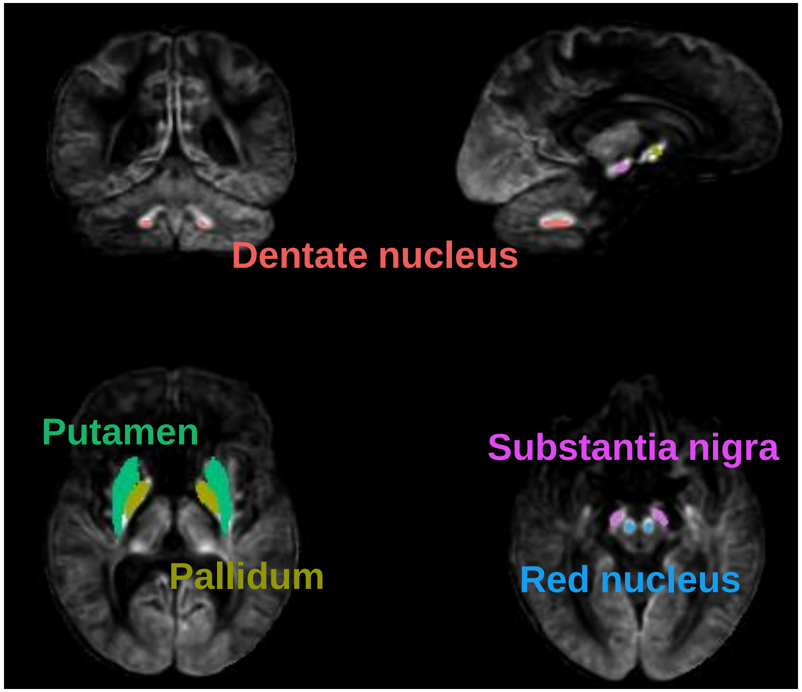

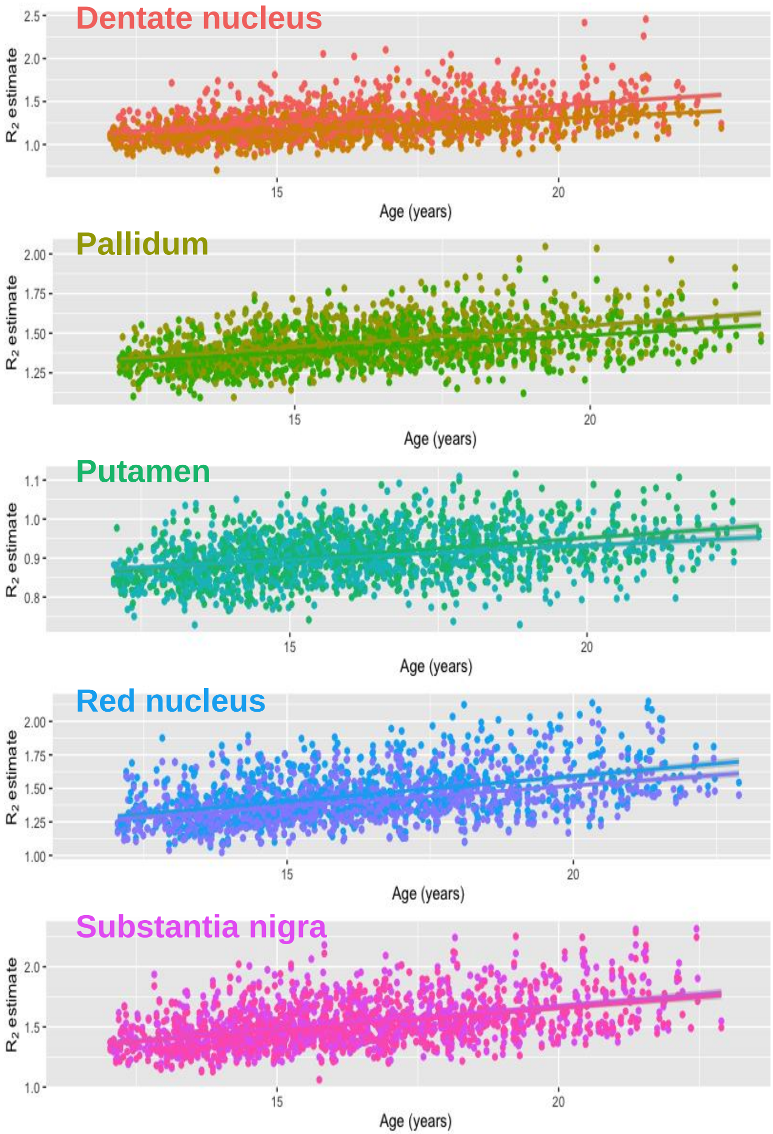

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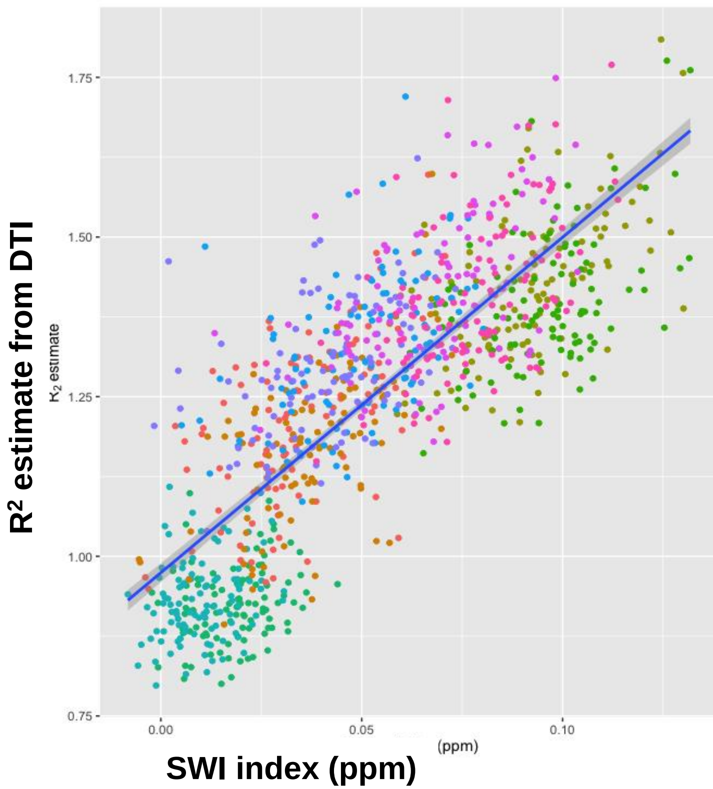
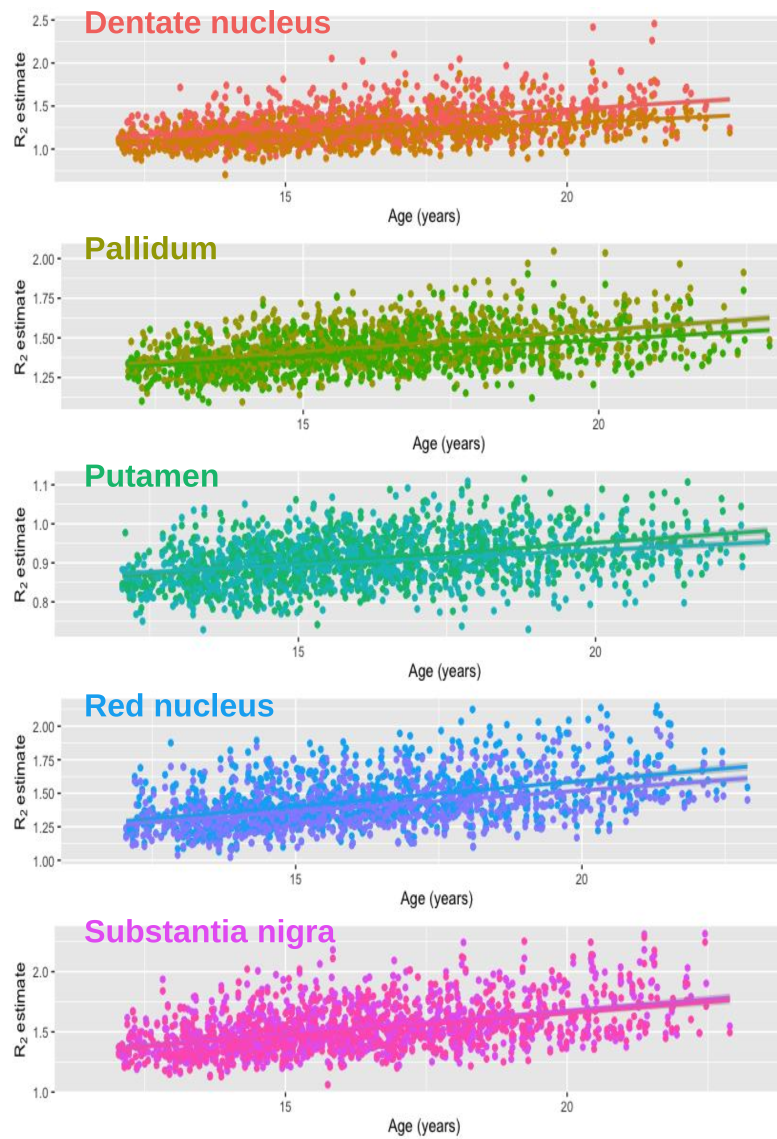




Extending Analysis of Imaging Data

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

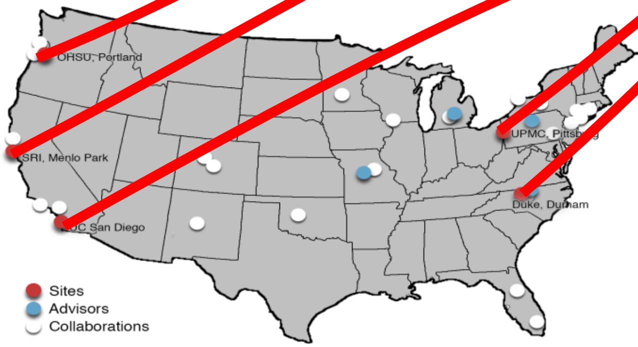
DTI iron estimates correlate well with *in-vivo* QSM susceptibility measures

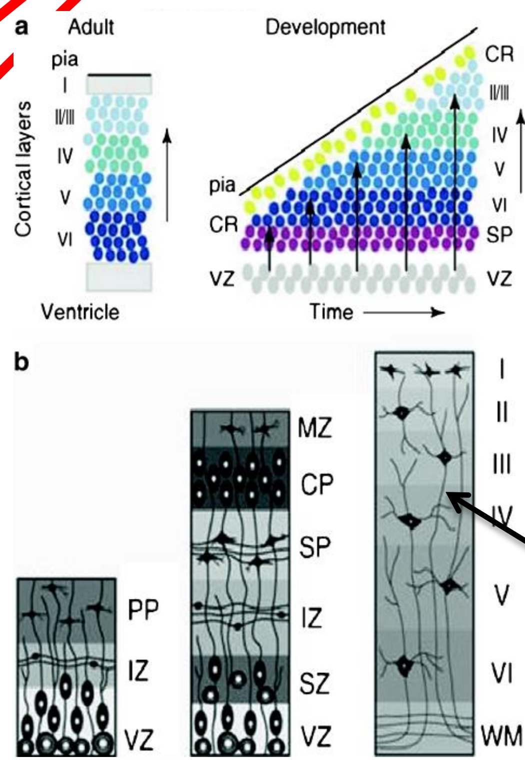
Extending Analysis of Imaging Data

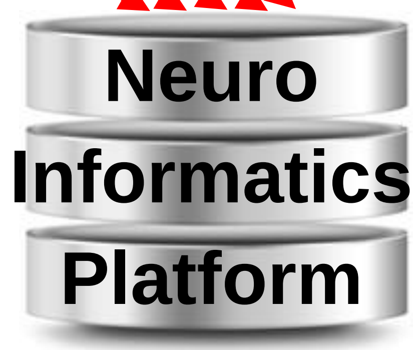
Cortical Myelin

Kilian Pohl

Dongjin Kwon



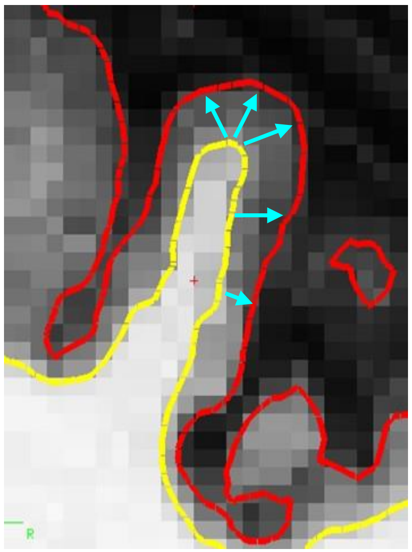


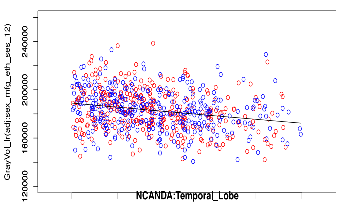


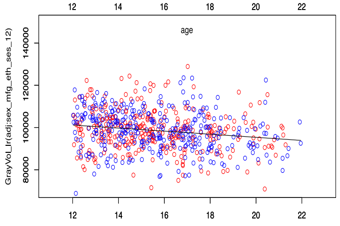
Stiles & Jernigan *Neuropsychology Review* 2010

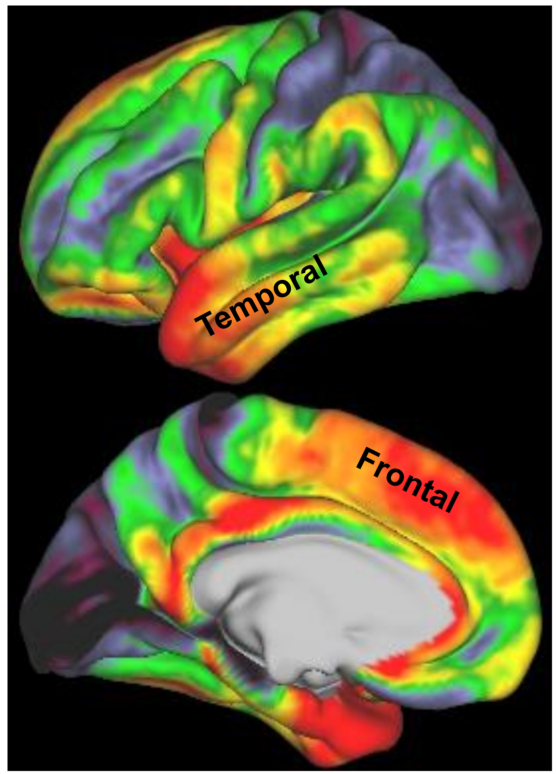
Measuring Cortical Thickness in No/Low Adolescents at Baseline

Cortical thickness

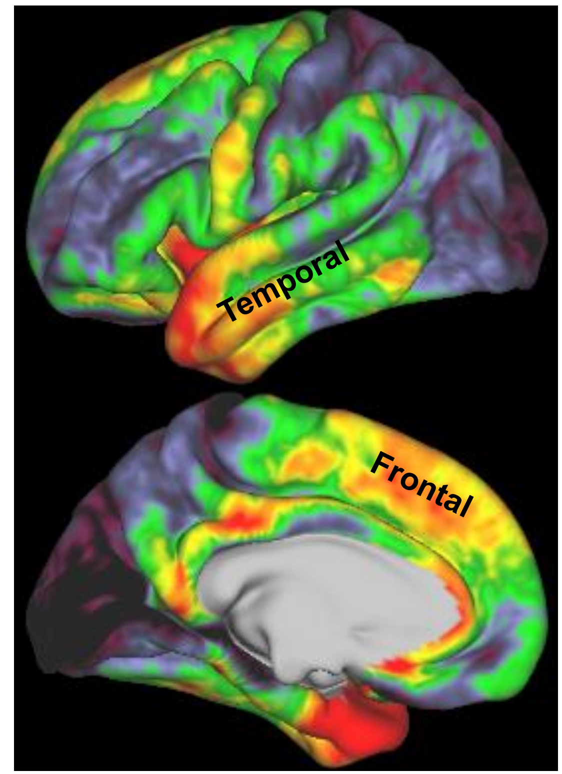






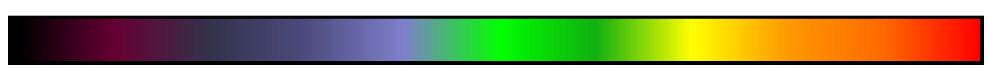


Average age 12.22



Average age 21.00

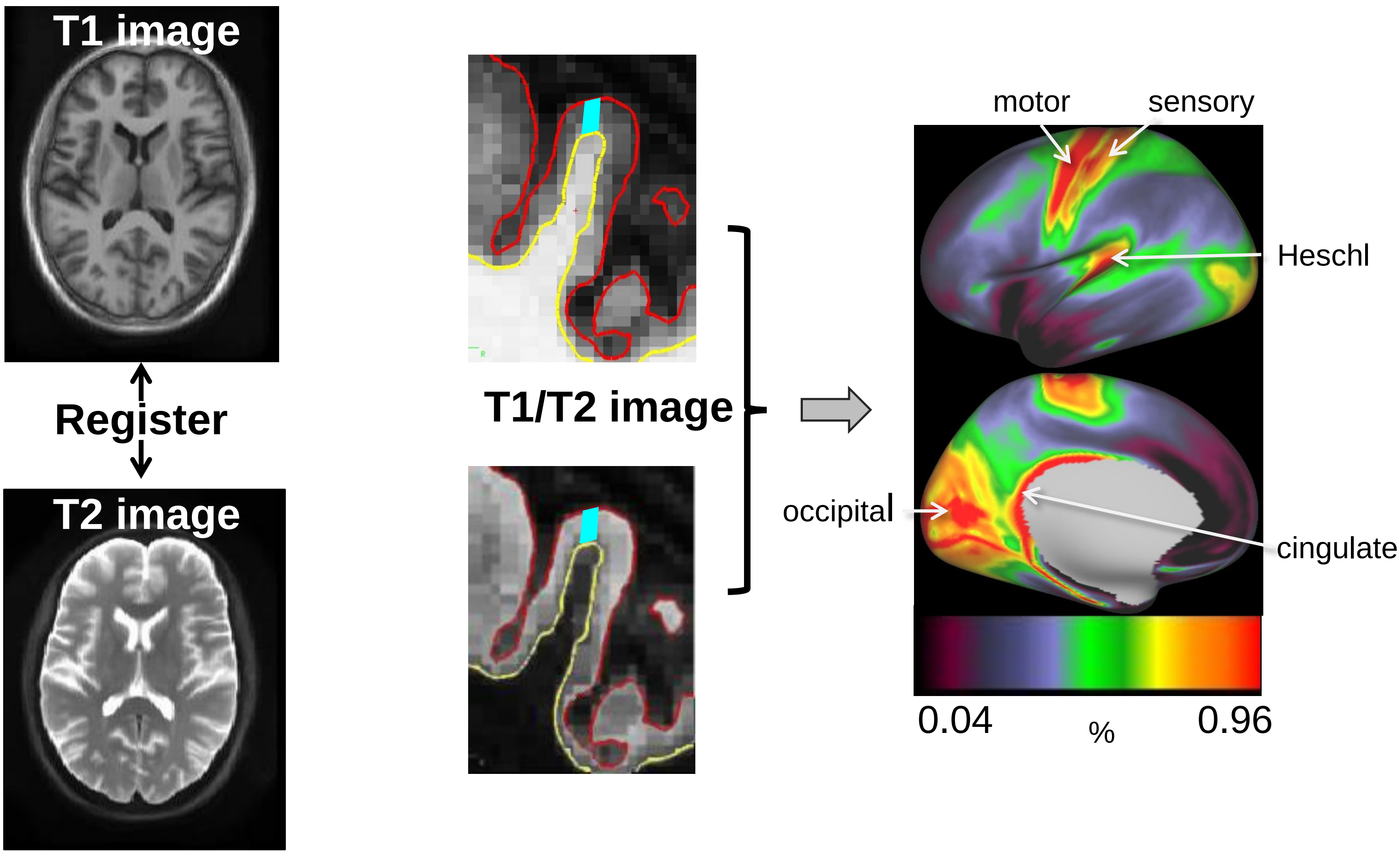
1.78 mm



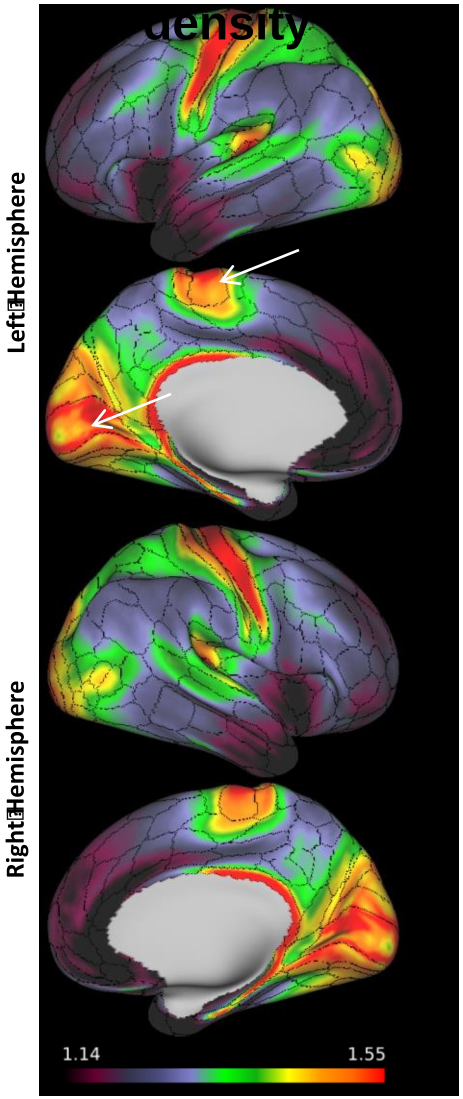
3.63 mm

Computing Cortical Myelin from T1 and T2 MRI

226 adolescents

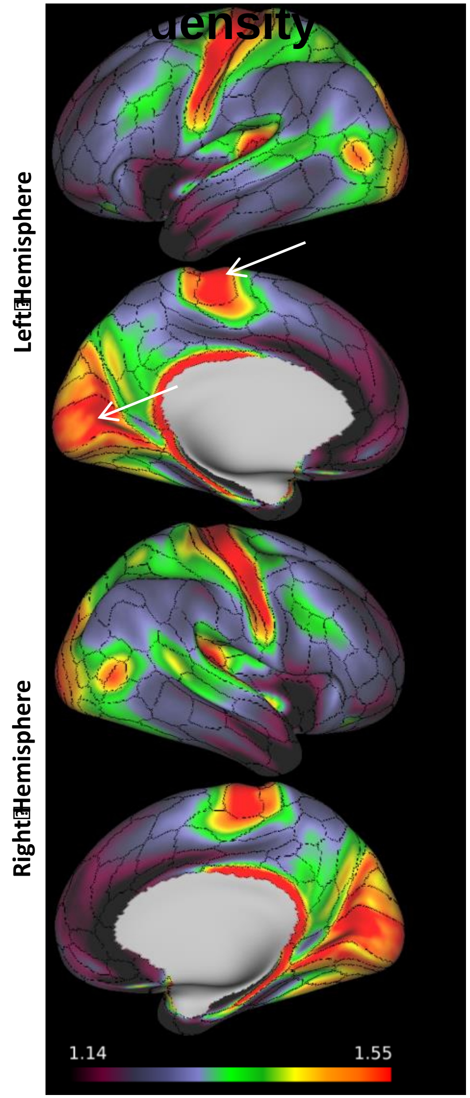


NCANDA Myelin density



(a) Dense myelin

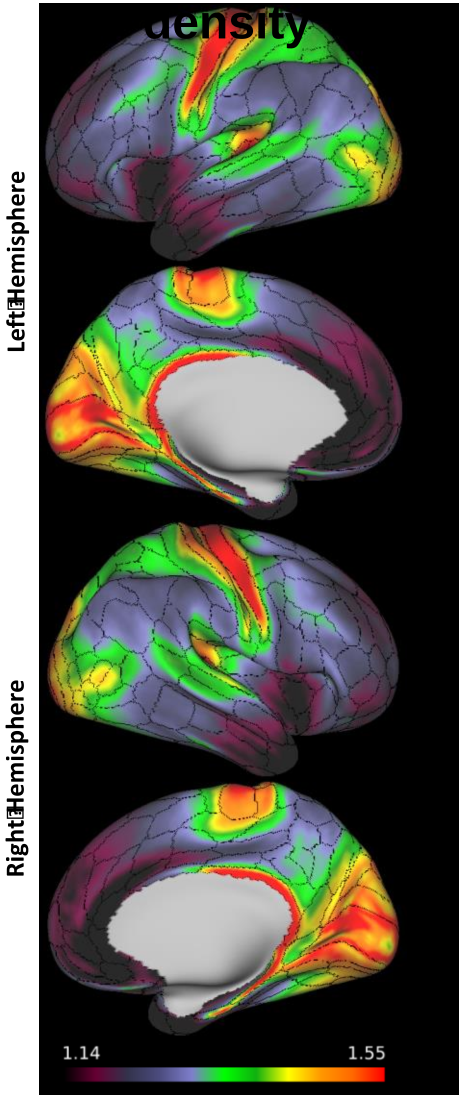
HCP Myelin density



(a) Dense myelin

NCANDA

Myelin density



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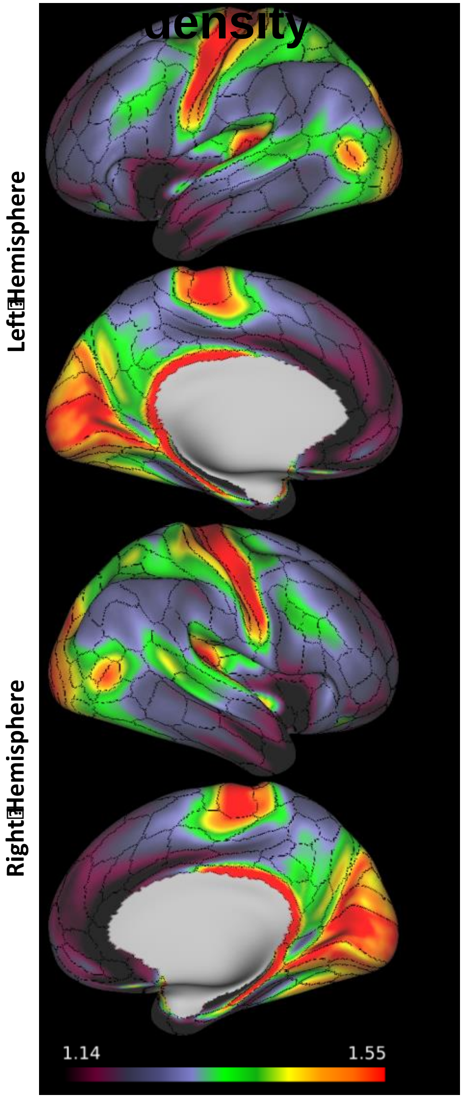

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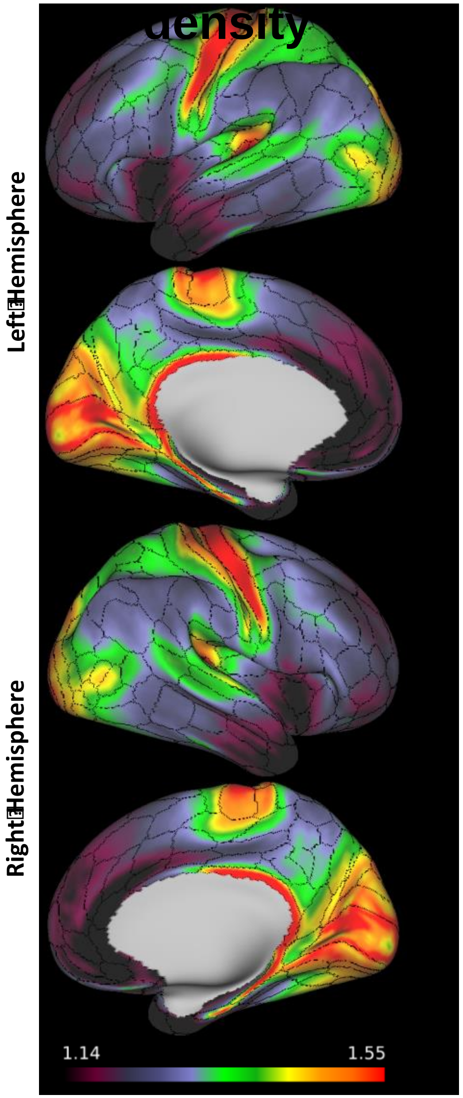
NCANDA Myelin density

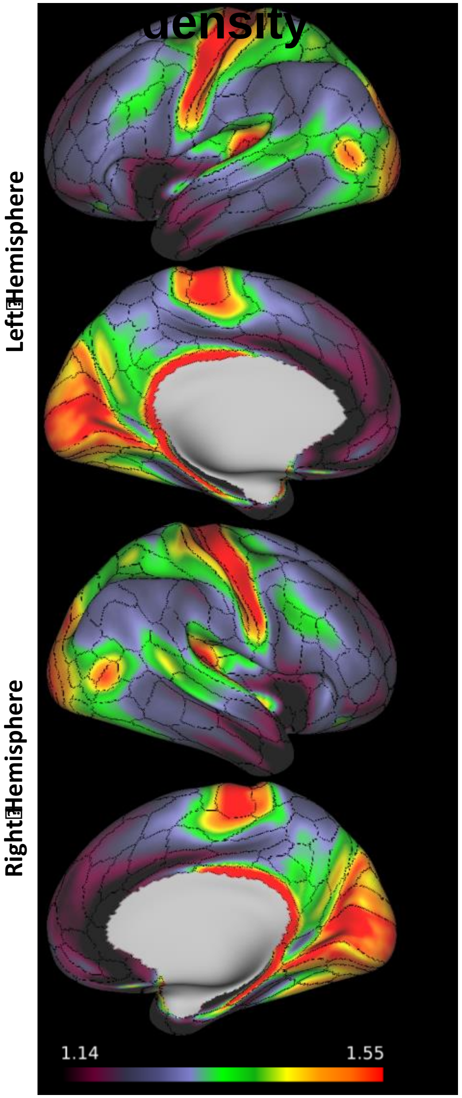


(a) Dense myelin

HCP

Myelin

density



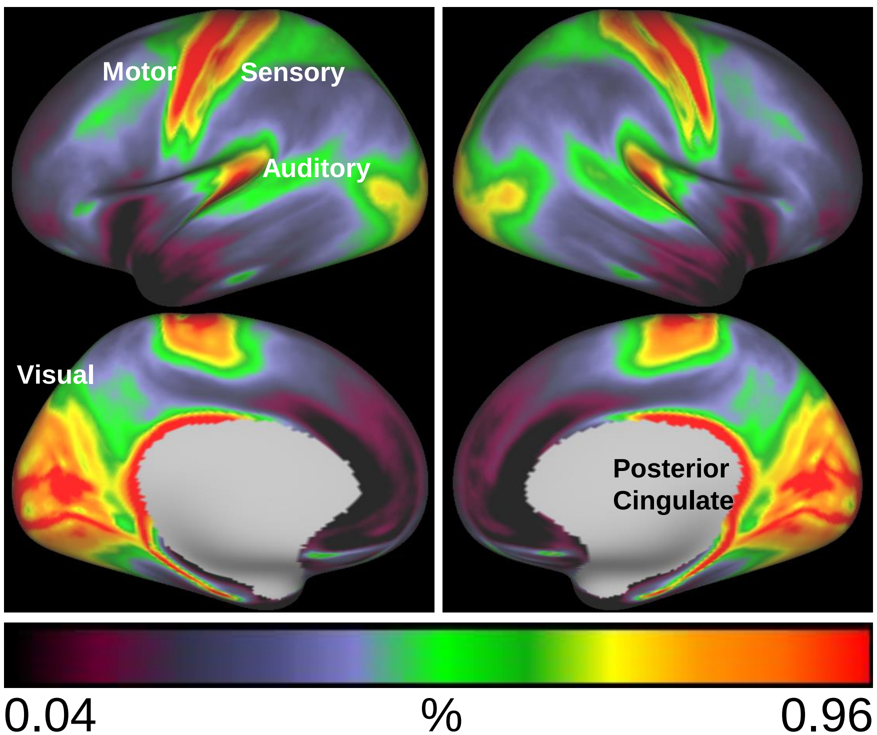
(a) Dense myelin

Age-related Differences in Myelin Content

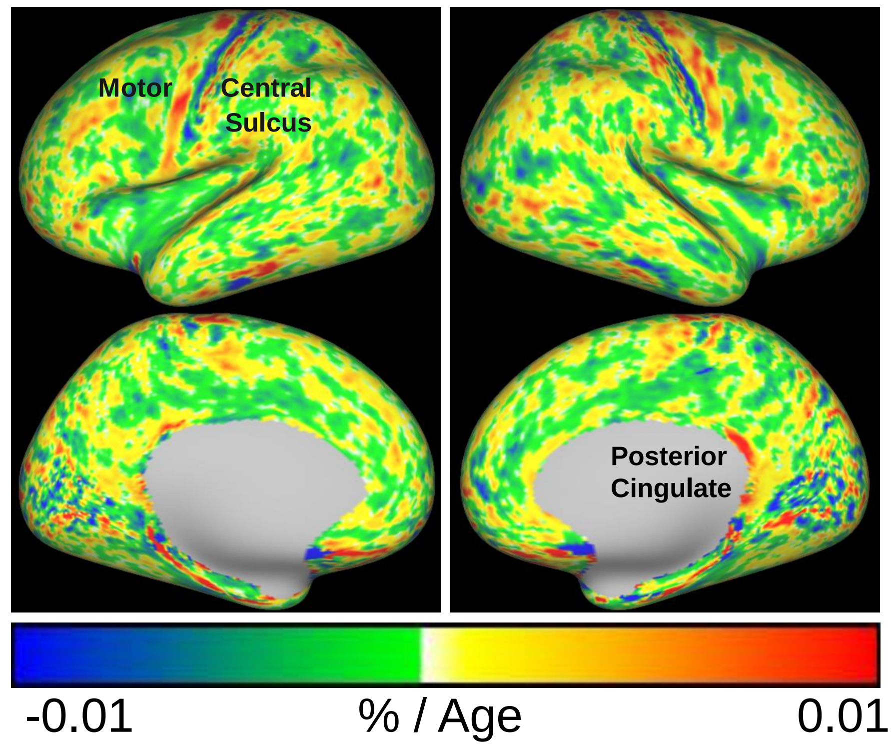
Kilian Pohl

Dongjin Kwon

Average Myelin Density



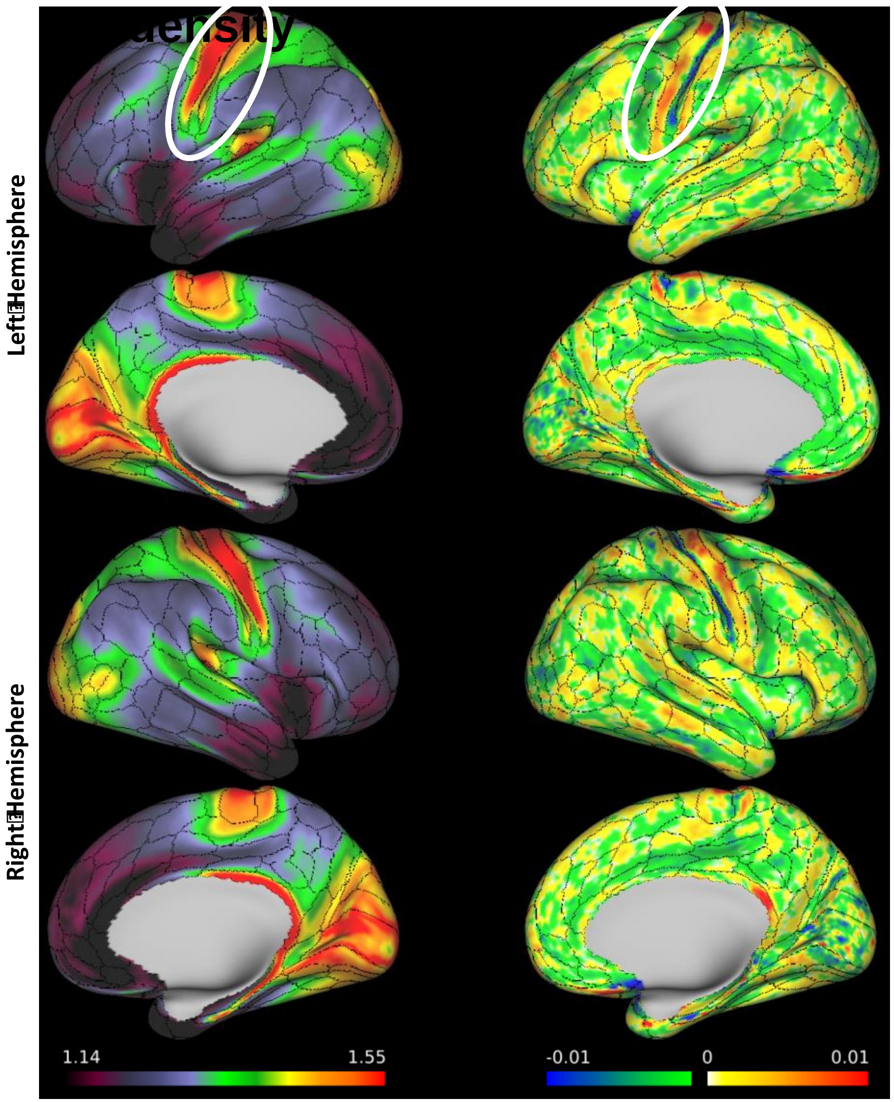
Difference Across Adolescence



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

NCANDA 12-21 years

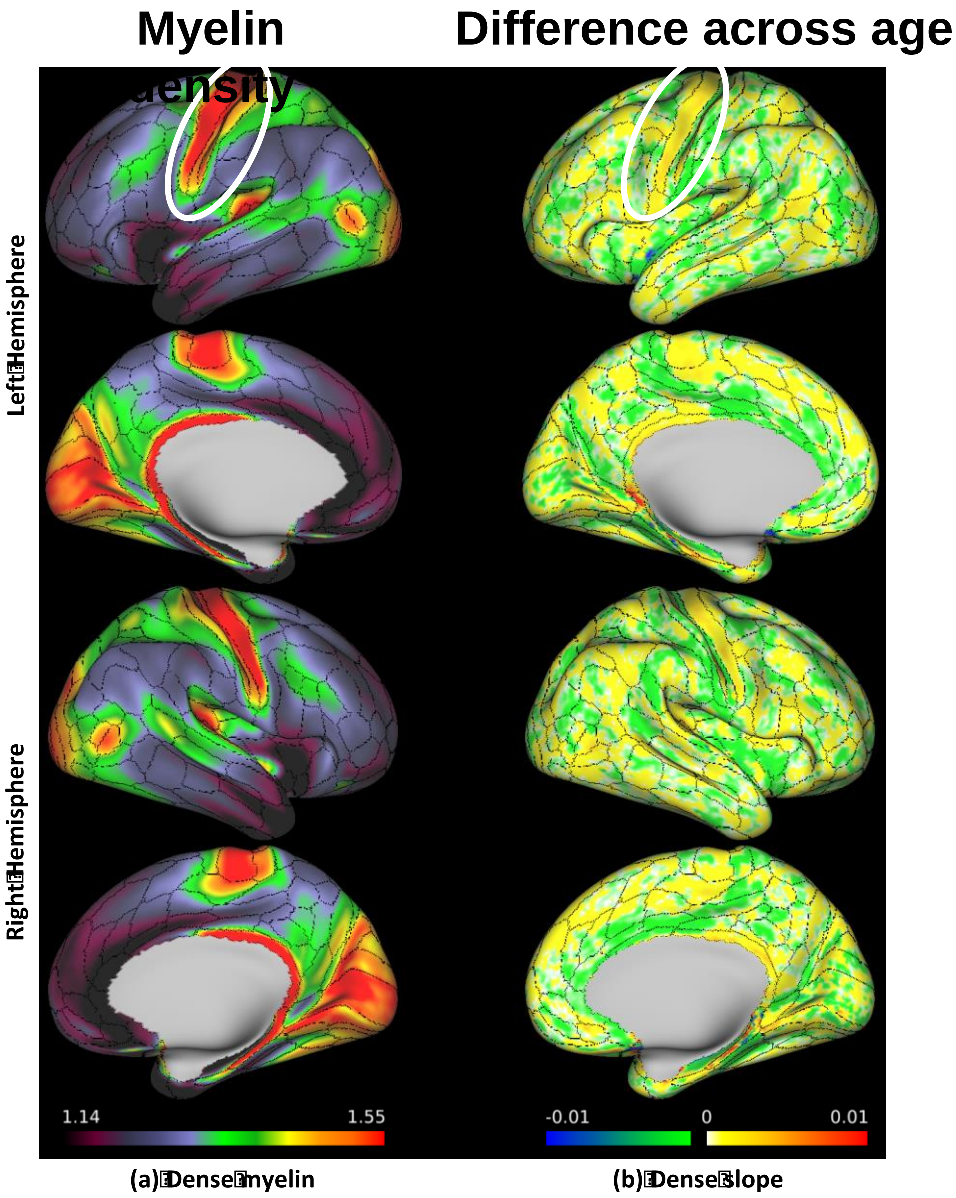
Myelin density | **Difference across age**



(a) Dense myelin

(b) Dense slope

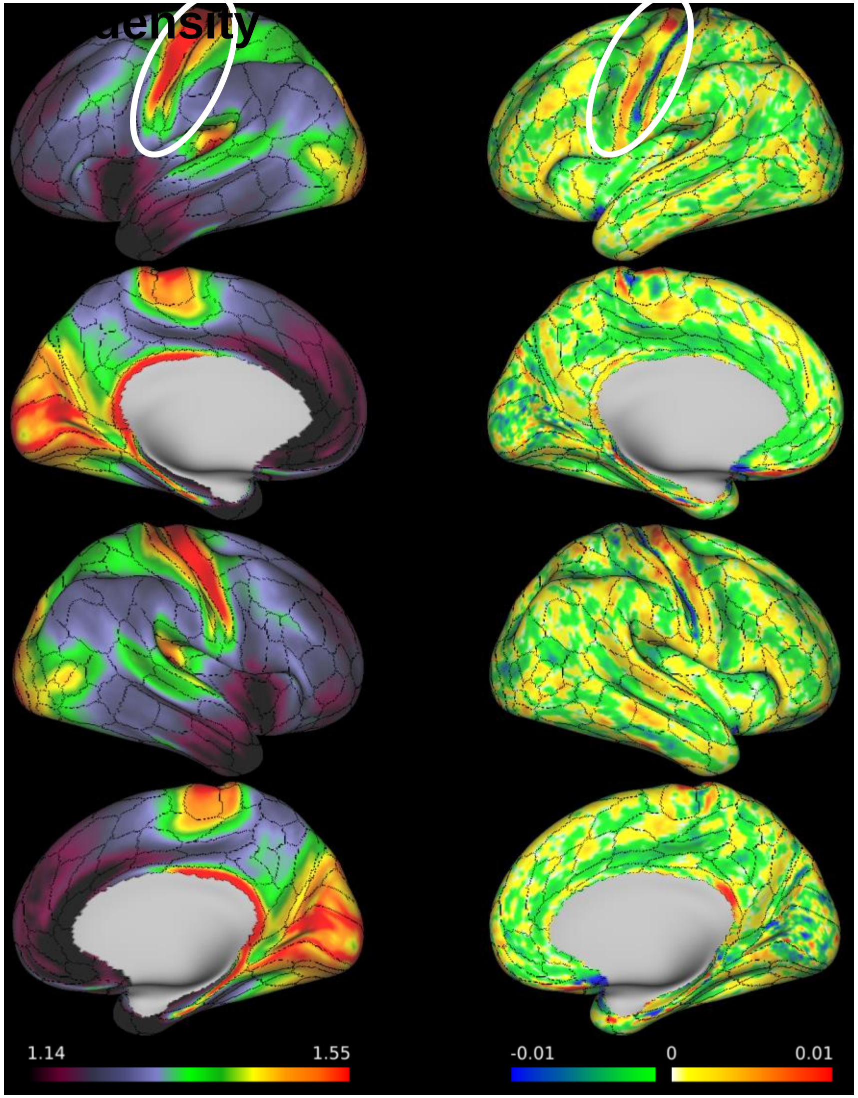
HCP 22-38 years



NCANDA 12-21 years

Myelin density

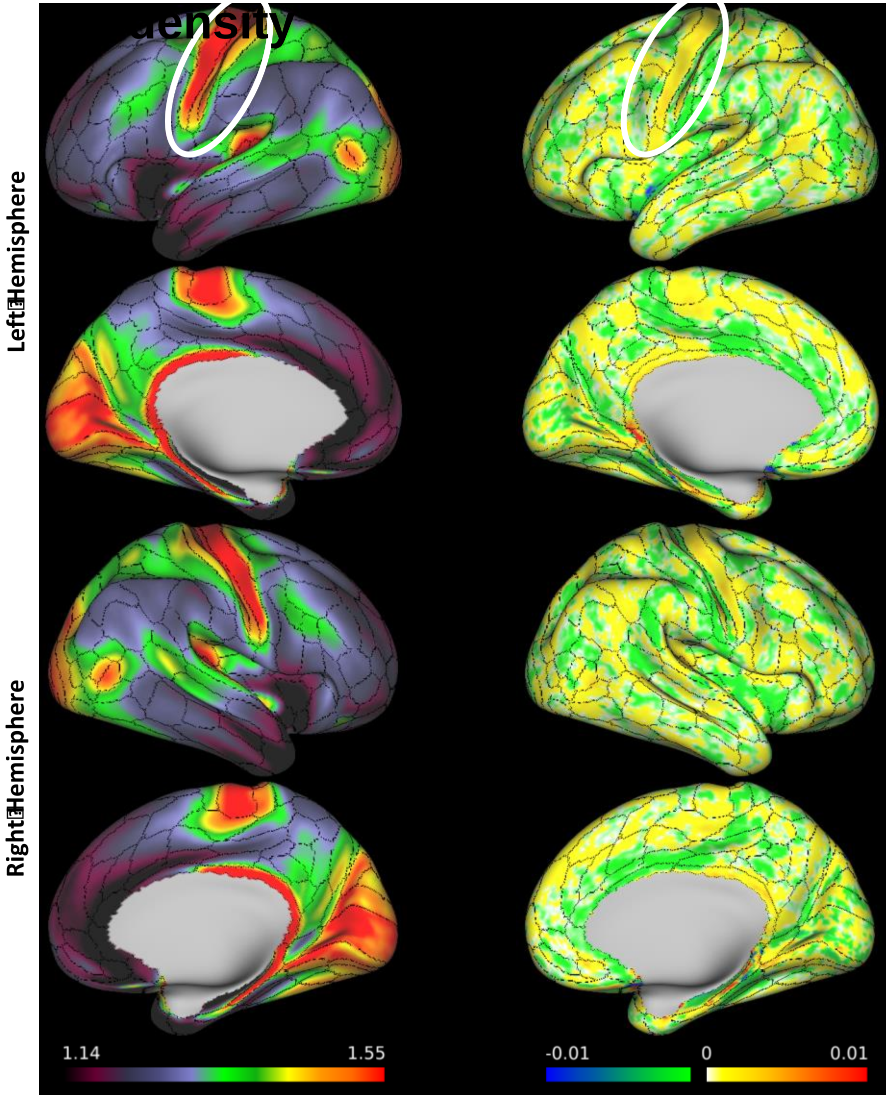
Difference across age



(a) Dense myelin **(b) Dense slope**

HCP 22-38 years

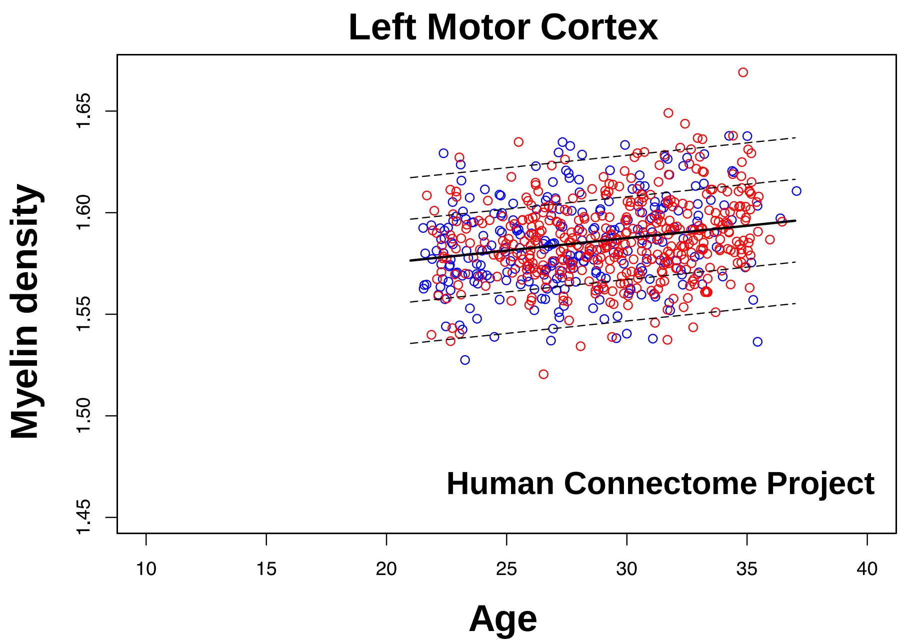
Myelin density | **Difference across age**

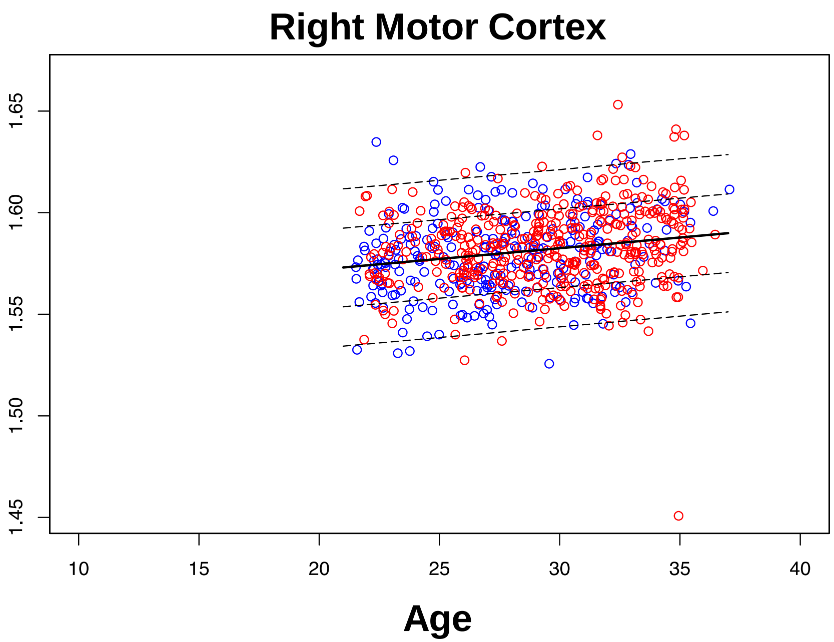


(a) Dense myelin

(b) Dense slope

Age-related Differences in Myelin Content in Motor Cortex (area 4)

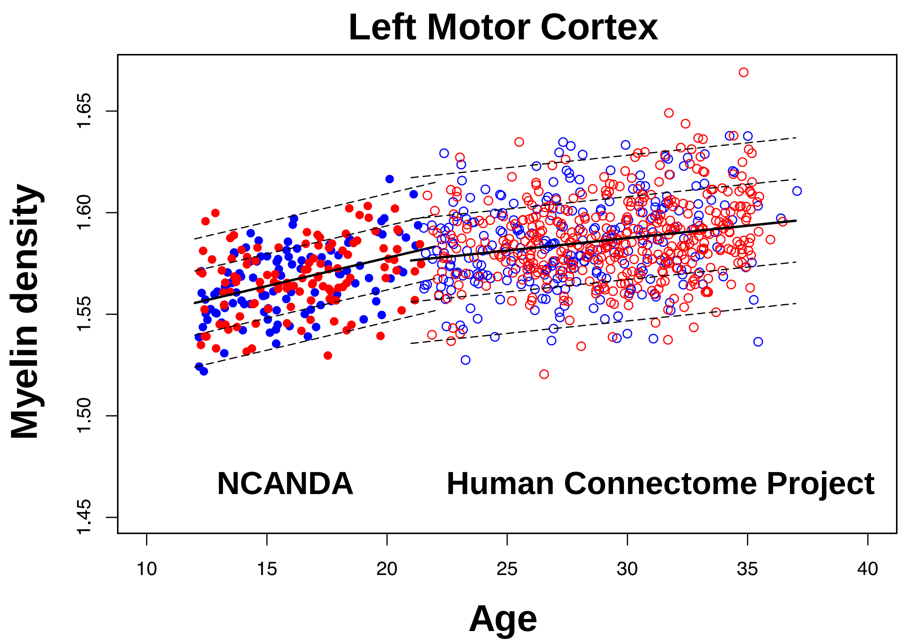


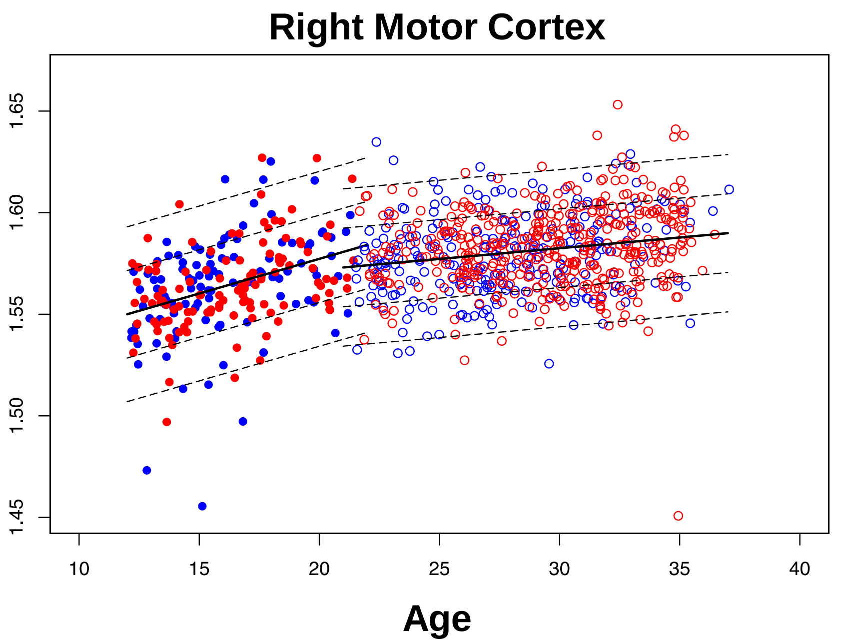


HCP (N=686): left
r = 0.220
t = 5.899
p = 5.74E-09
slope = 0.001

HCP (N=686): right
r = 0.200
t = 5.343
p = 1.24E-07
slope = 0.001

Age-related Differences in Myelin Content in Motor Cortex (area 4)





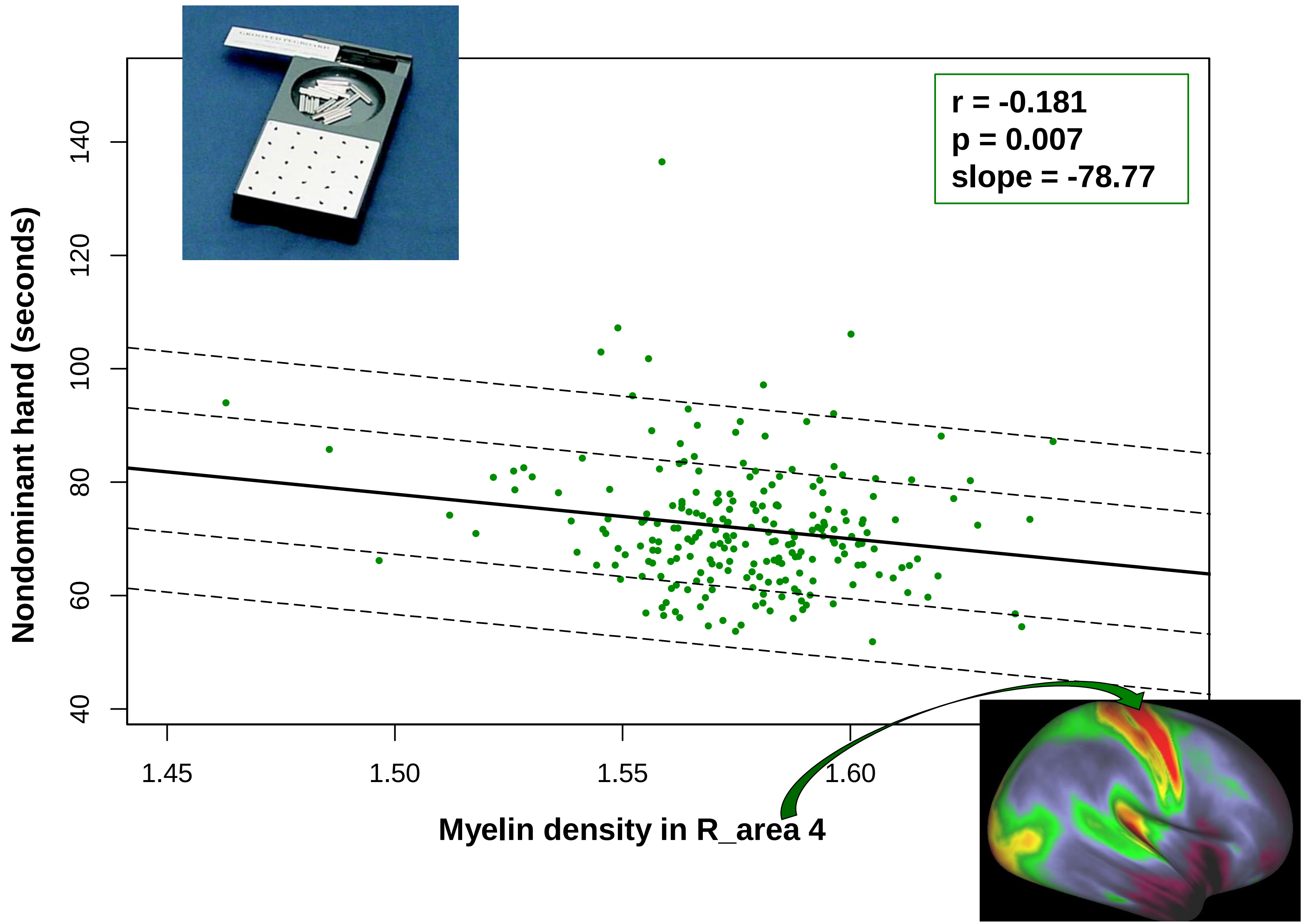
NCANDA (N=226): left
r = 0.410
t = 6.732
p = 1.38E-10
slope = 0.003

HCP (N=686): left
r = 0.220
t = 5.899
p = 5.74E-09
slope = 0.001

NCANDA (N=226): right
r = 0.375
t = 6.060
p = 5.70E-09
slope = 0.003

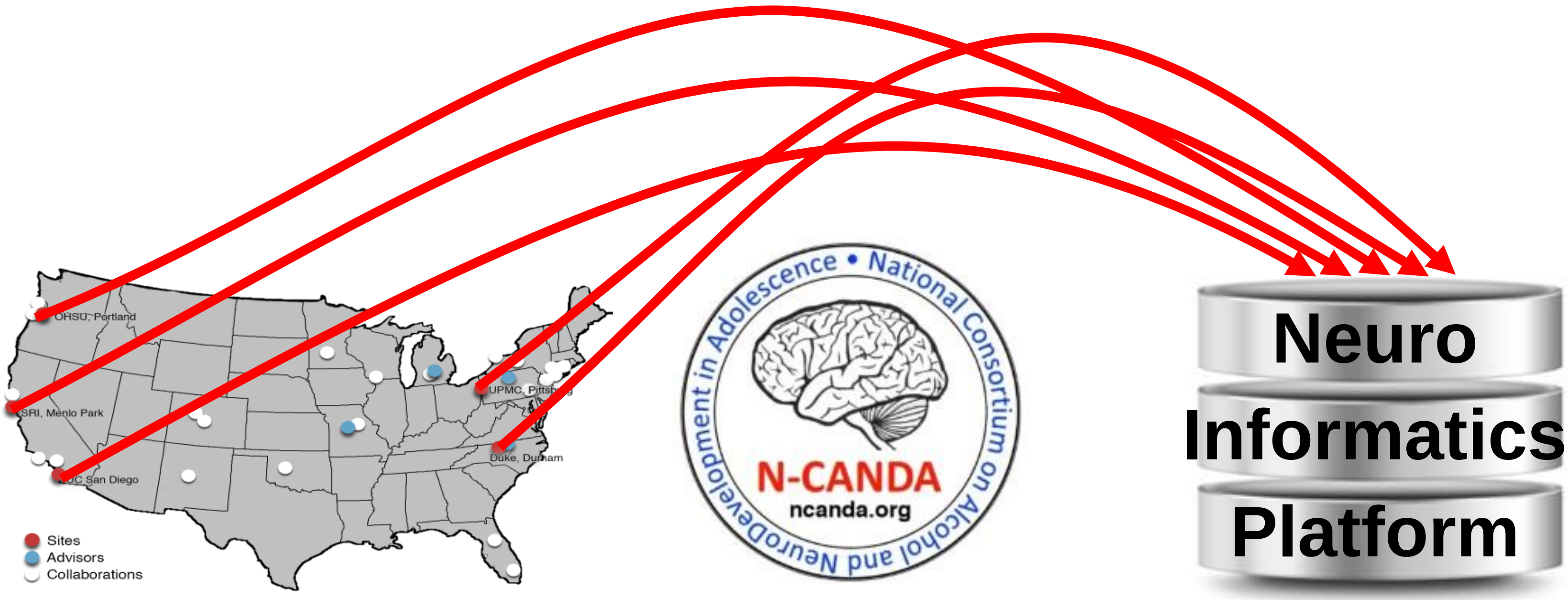
HCP (N=686): right
r = 0.200
t = 5.343
p = 1.24E-07
slope = 0.001

Grooved Pegboard and Myelin Content in the Motor Cortex (area 4)



Extending Analysis of Imaging Data

Effects of Initiation of Drinking



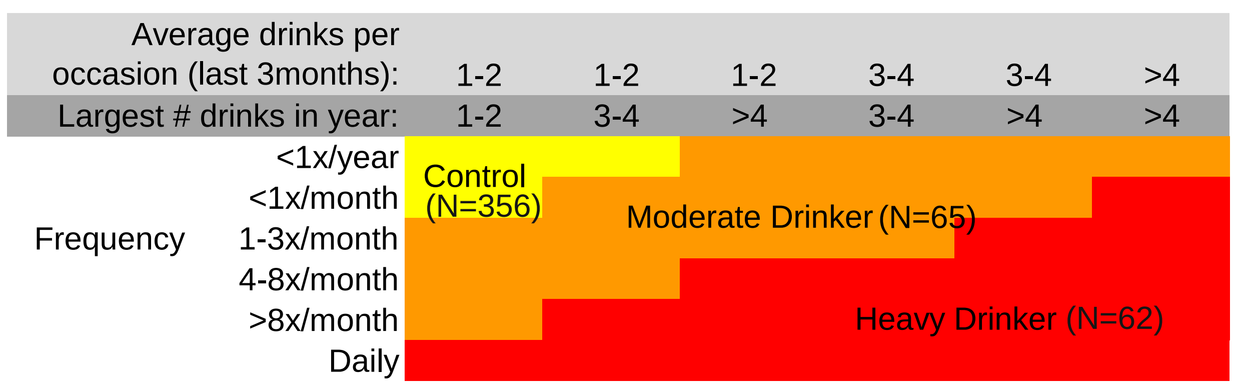

PITTWATER
COUNCIL
ALCOHOL
FREE ZONE
MOTEL
Accommodation
REASONABLE
Rates

NCANDA 2 Year Follow-up

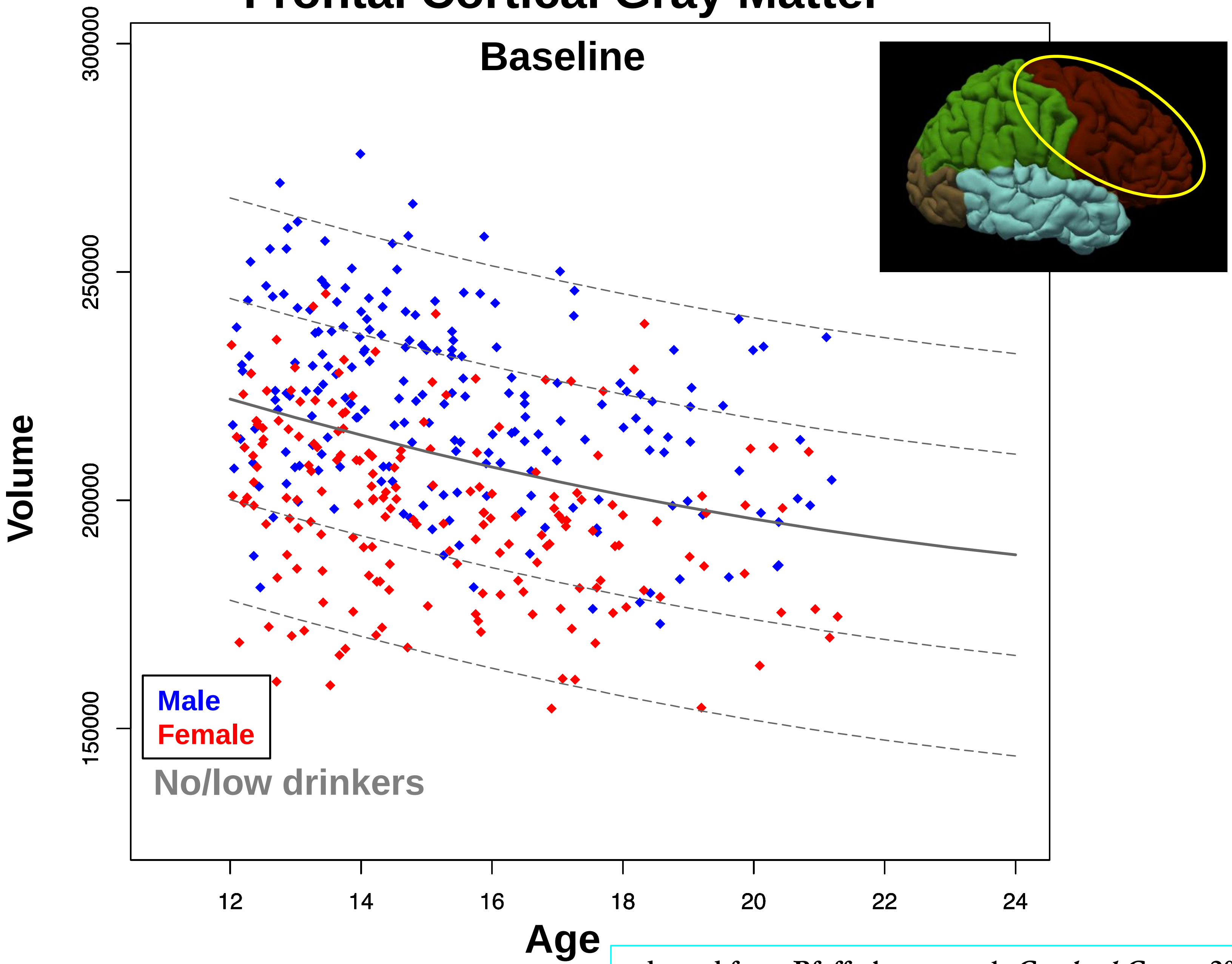
Regional cortical volume trajectories in 483 of 647 no-to-low drinking adolescents meeting imaging and drinking criteria followed longitudinally for 2 years

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

Cahalan et al. Criteria

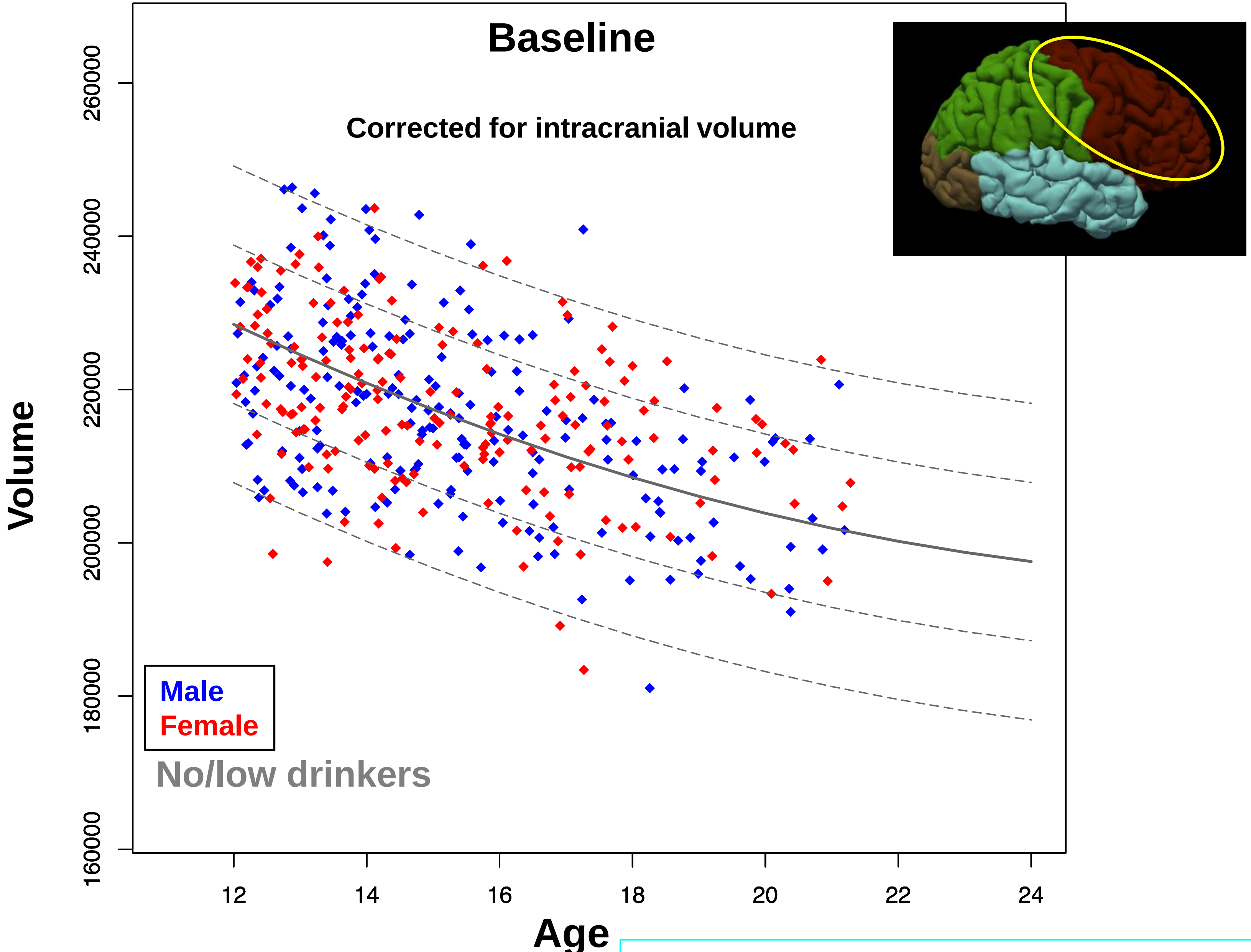


Frontal Cortical Gray Matter



adapted from Pfefferbaum et al. *Cerebral Cortex* 2016

Frontal Cortical Gray Matter



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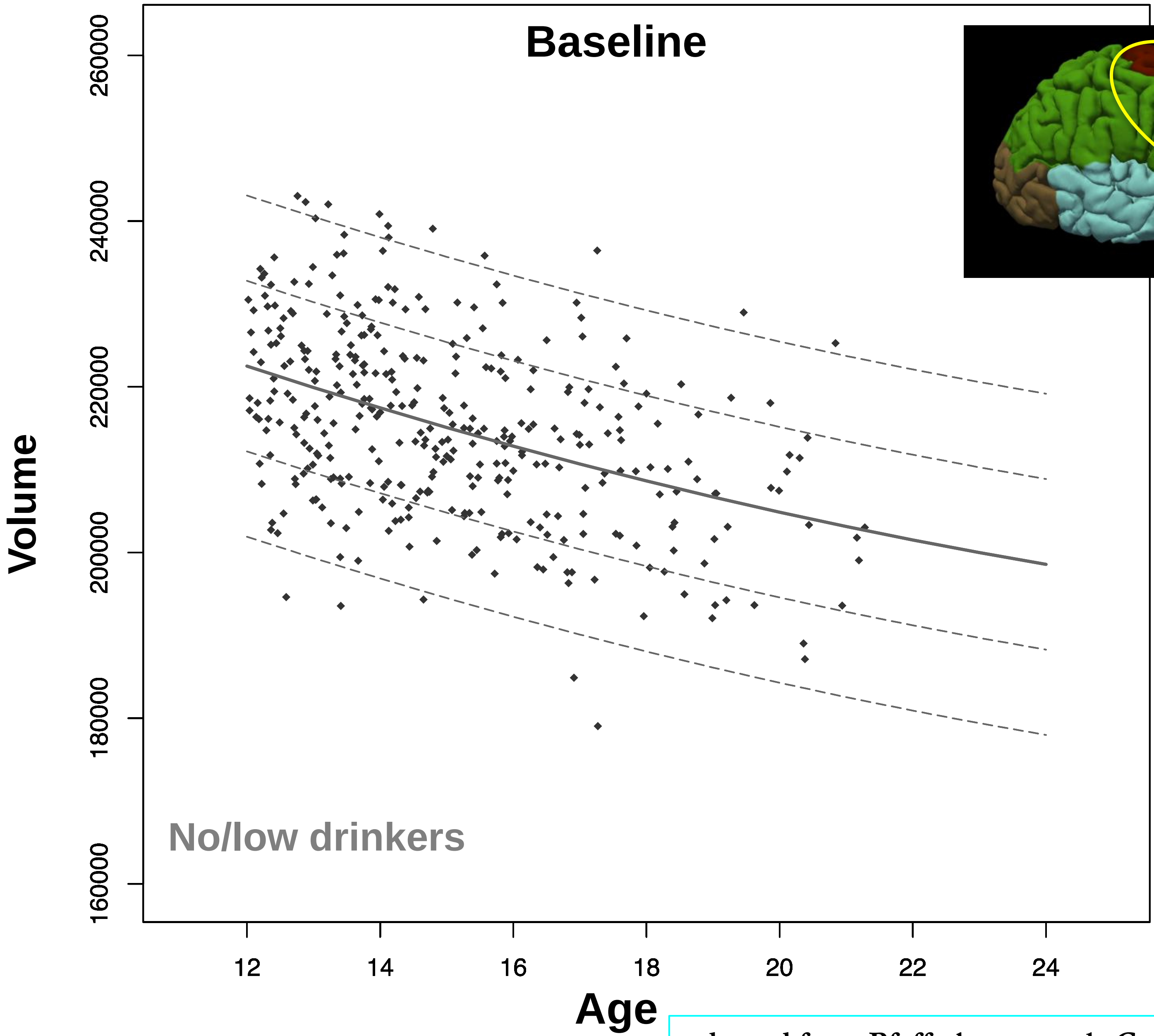

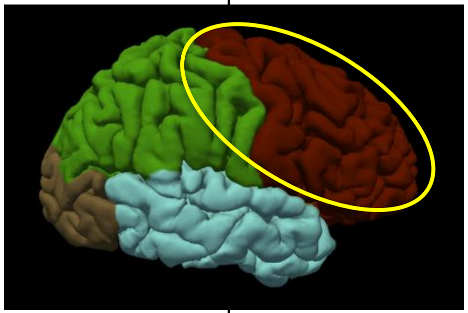

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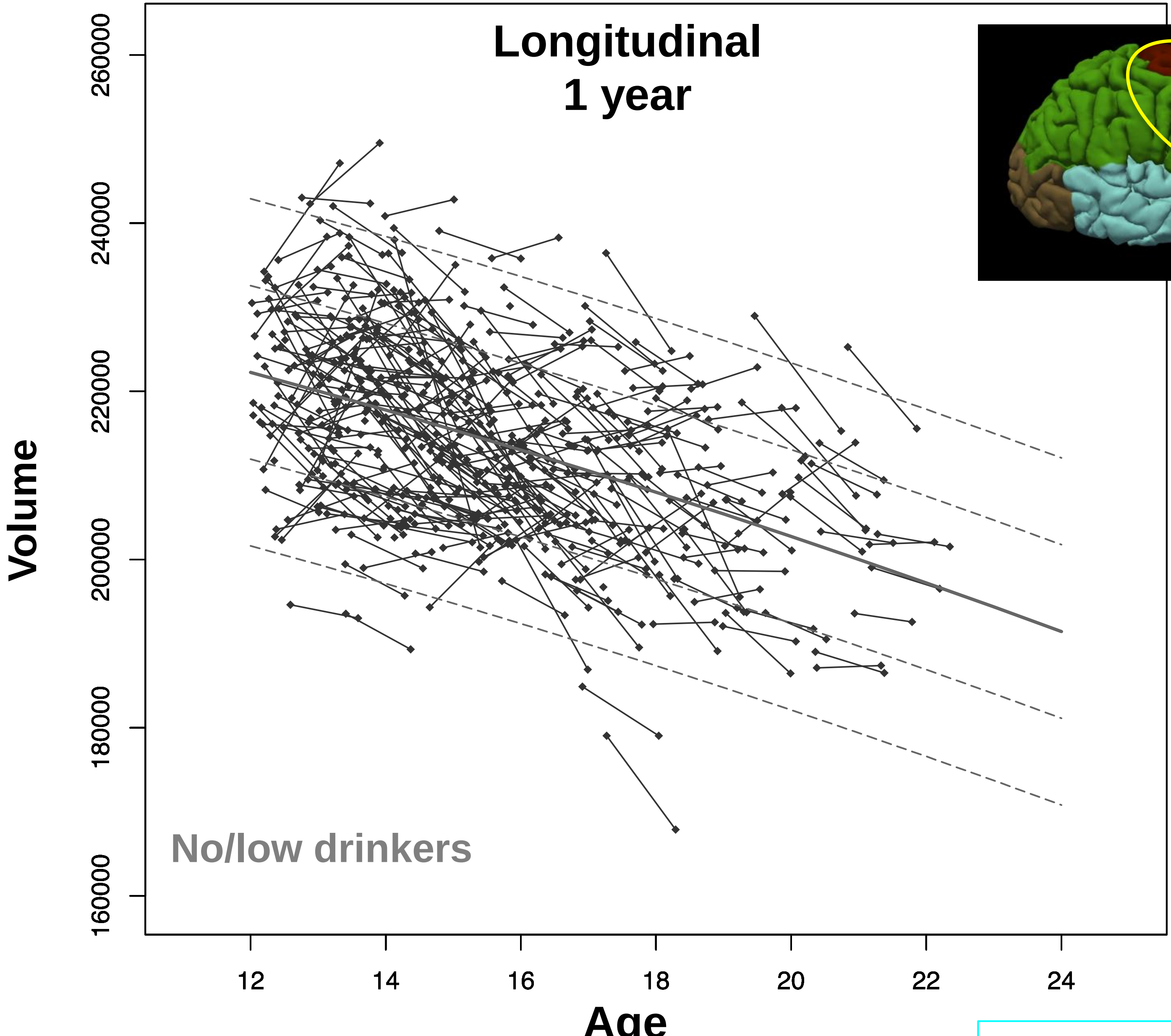
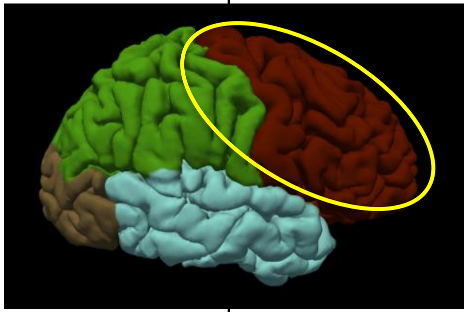
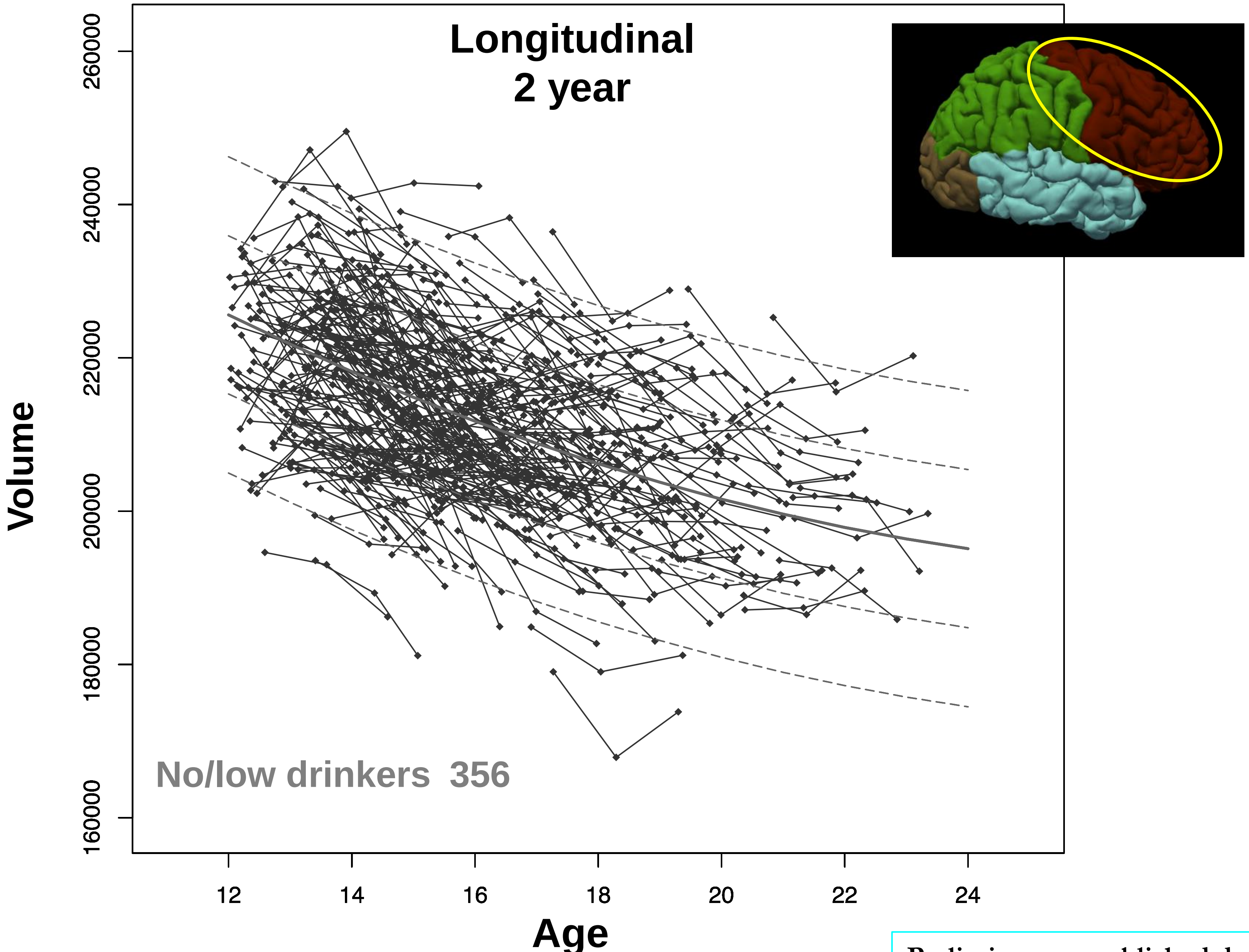
Frontal Cortical Gray Matter





Preliminary unpublished data

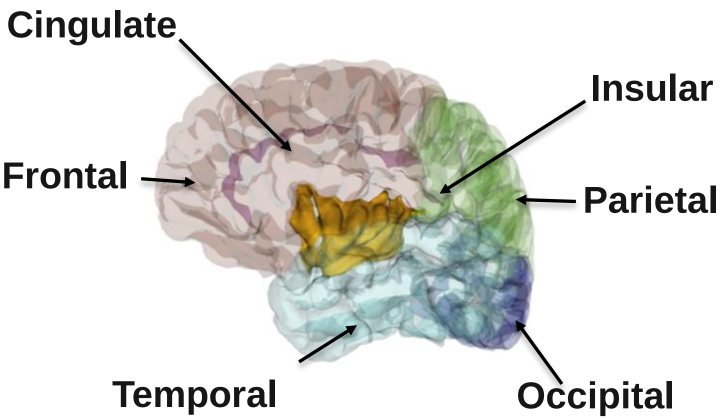
Frontal Cortical Gray Matter

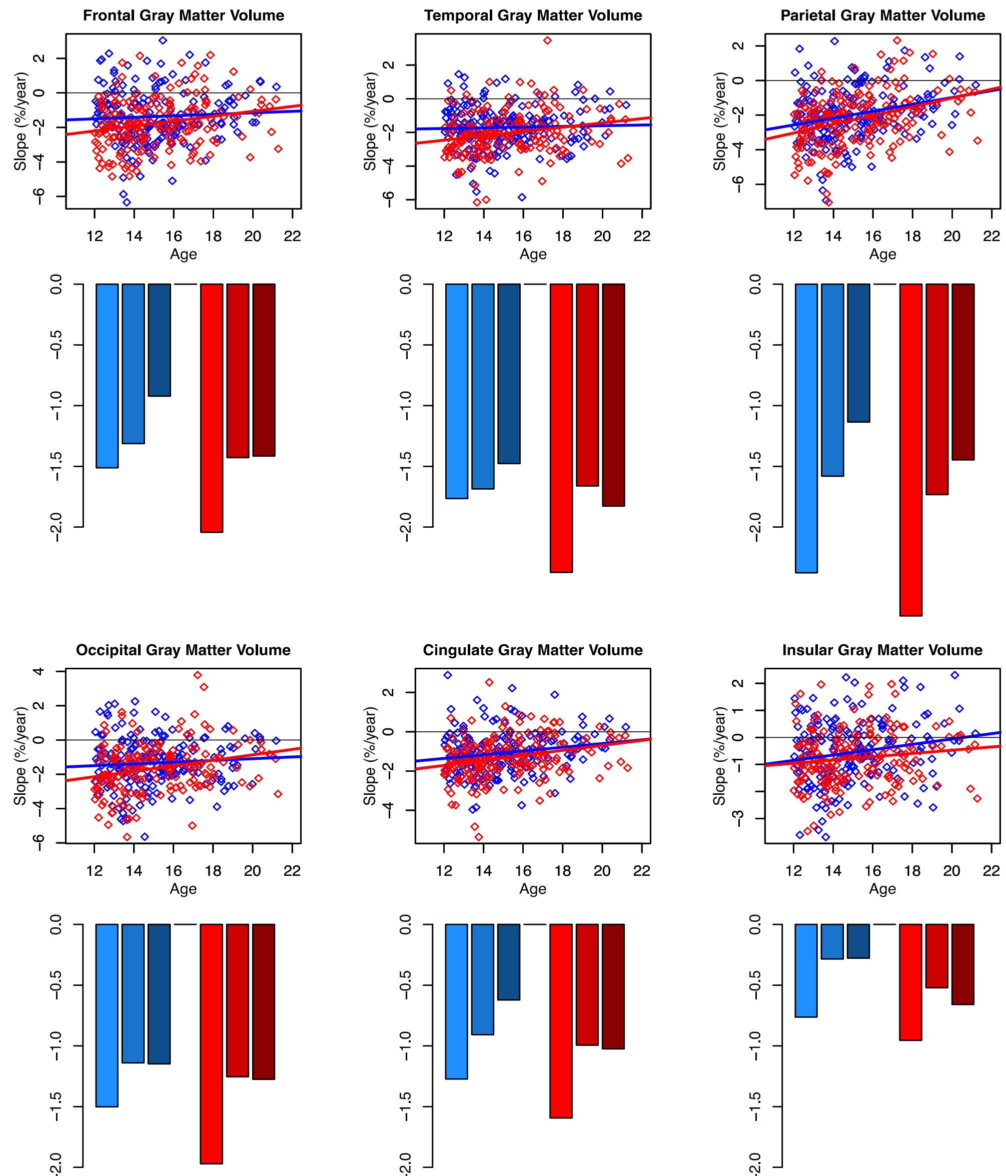


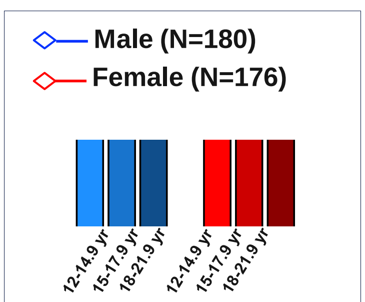
Preliminary unpublished data

Regional Gray Matter Volume Slopes

Decline with Age

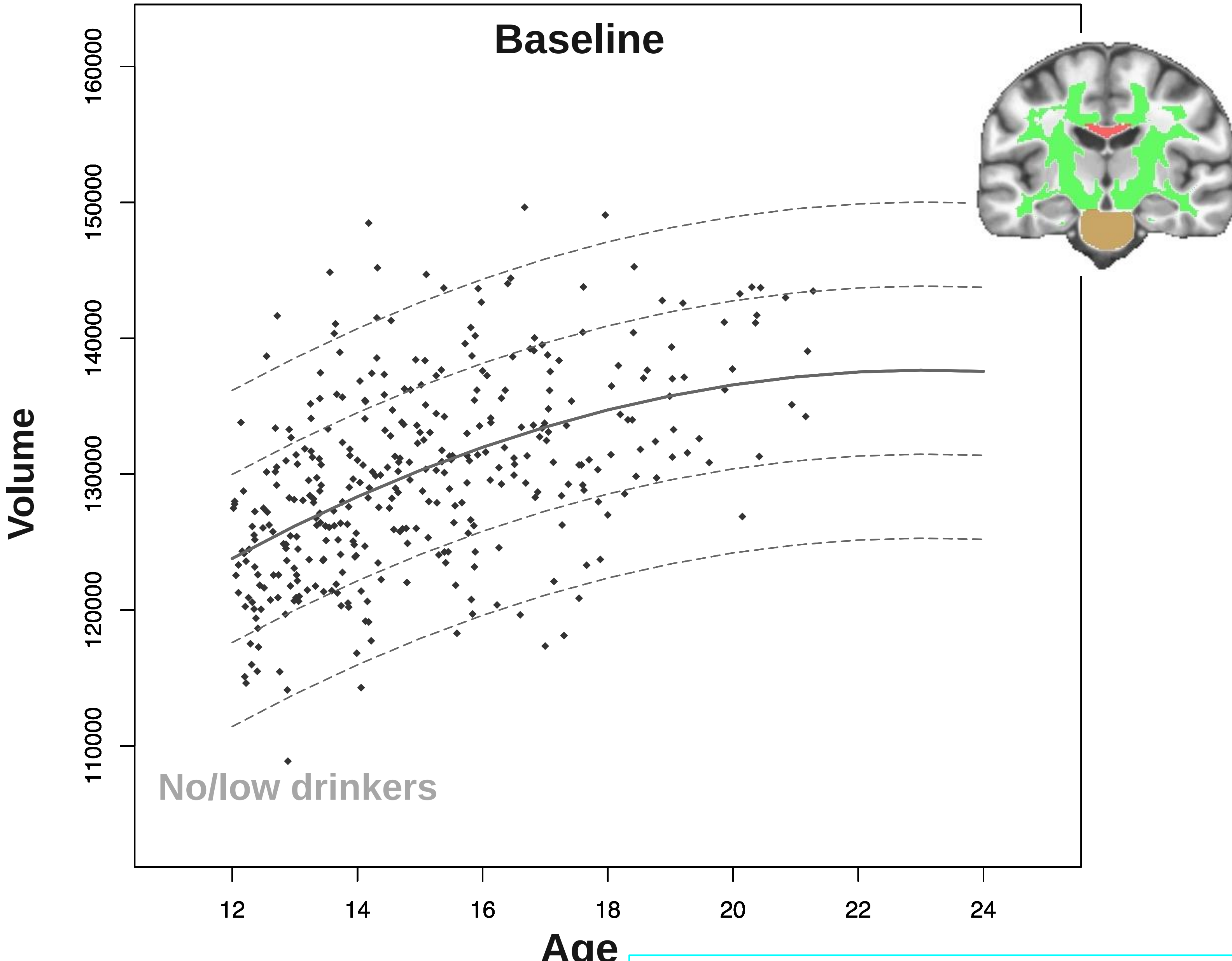






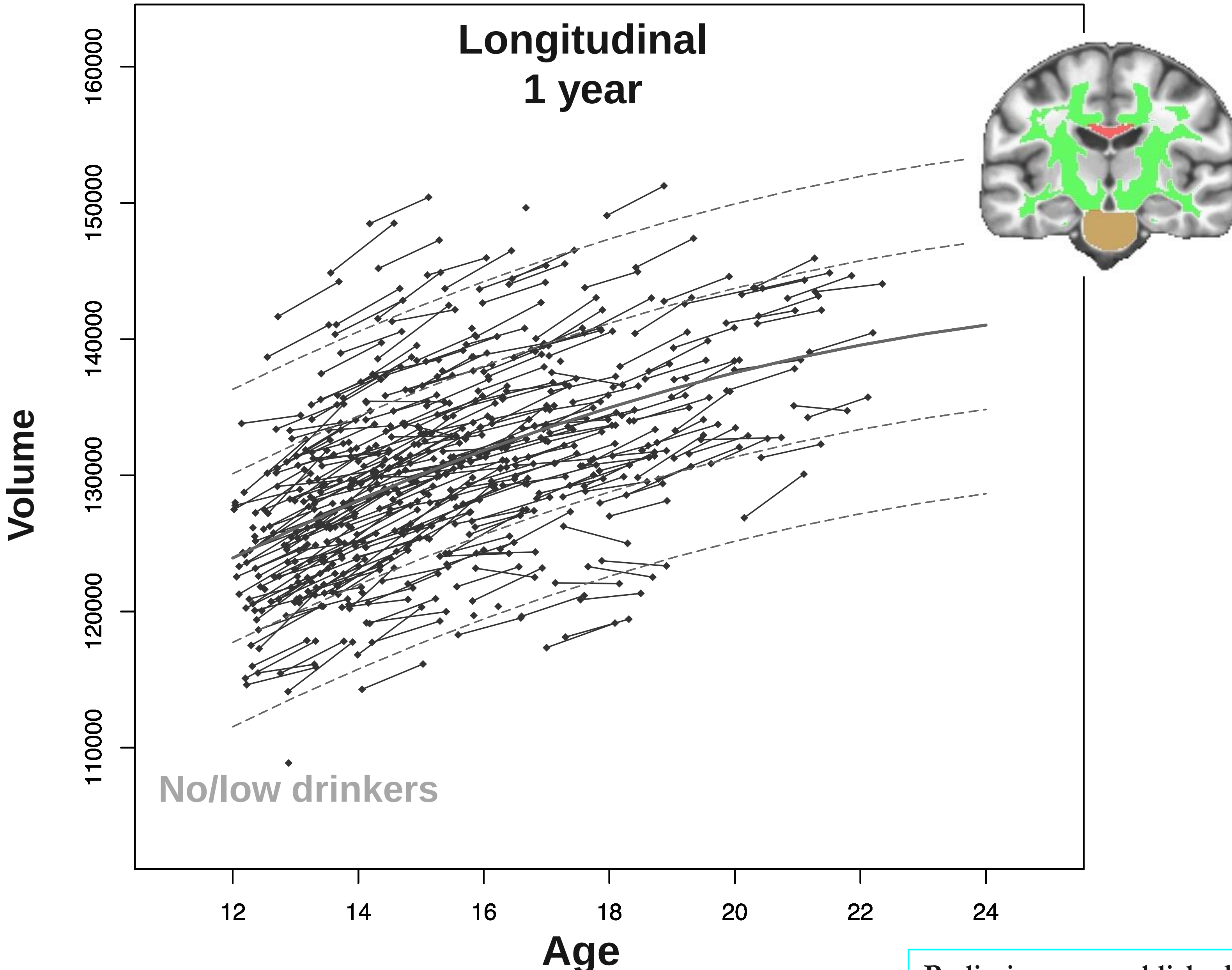
Pfefferbaum et al. *in revision*

Central White Matter

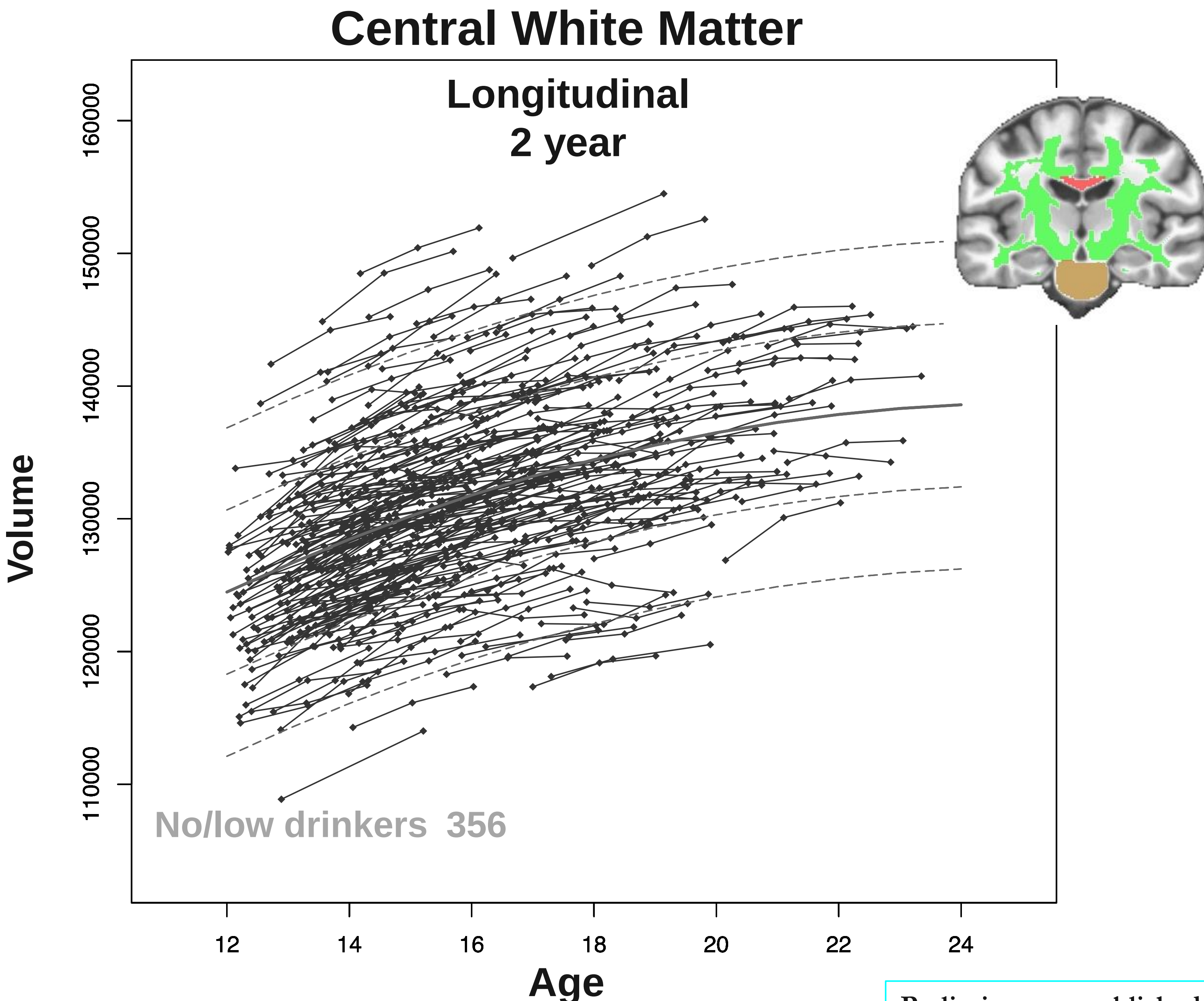


adapted from Pfefferbaum et al. *Cerebral Cortex* 2016

Central White Matter



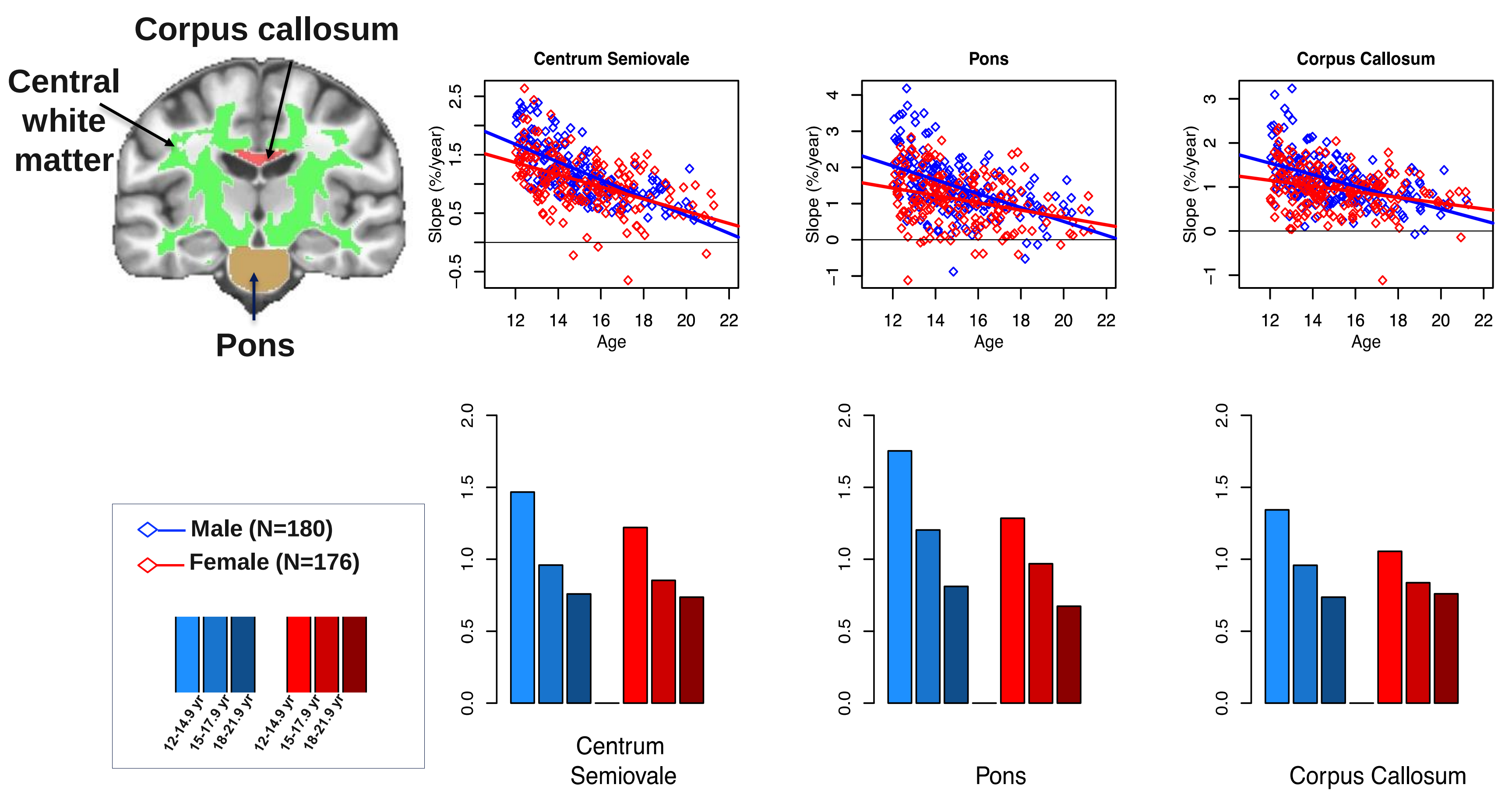
Preliminary unpublished data



Preliminary unpublished data

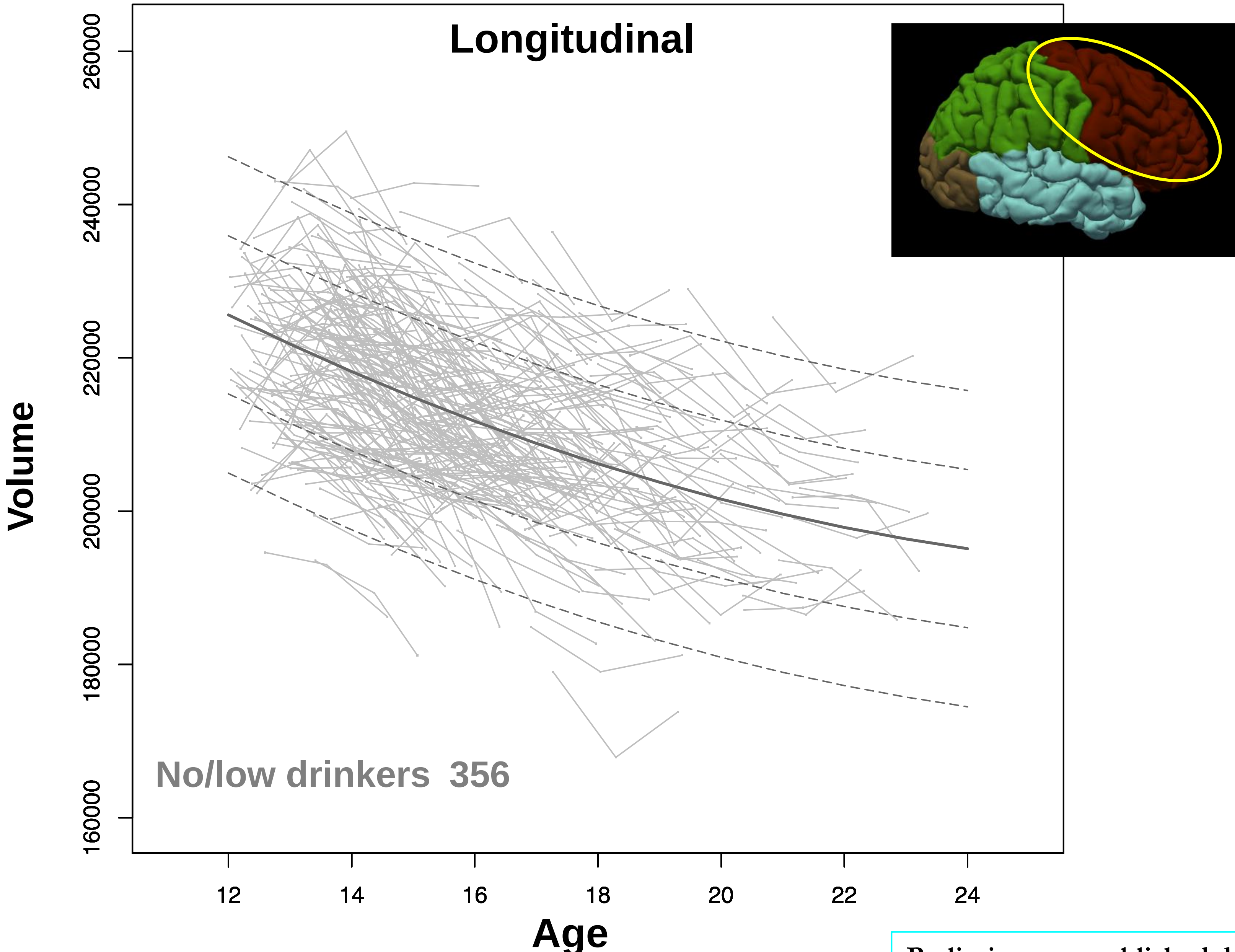
Regional White Matter Volume Slopes

Decelerating Growth with Age



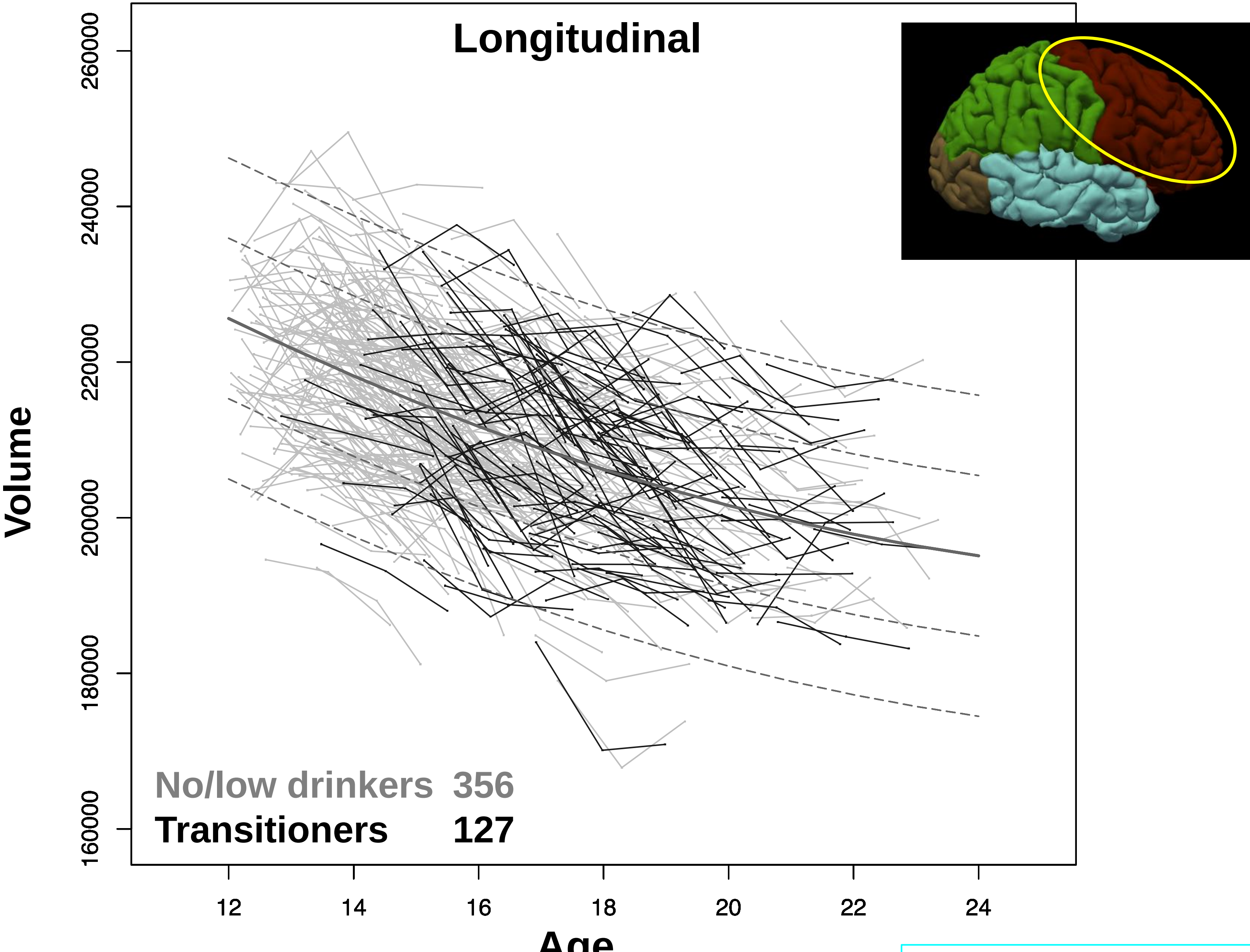
Pfefferbaum et al. *in revision*

Frontal Cortical Gray Matter



Preliminary unpublished data

Frontal Cortical Gray Matter



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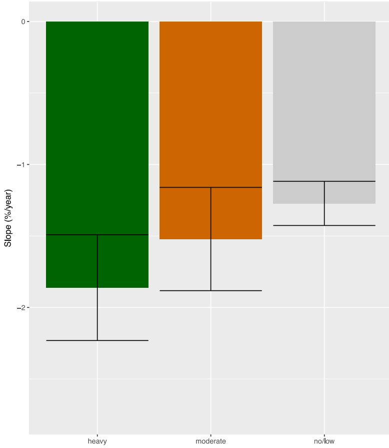
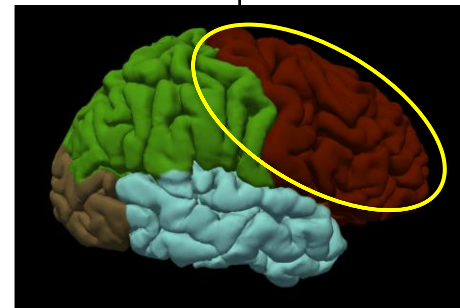
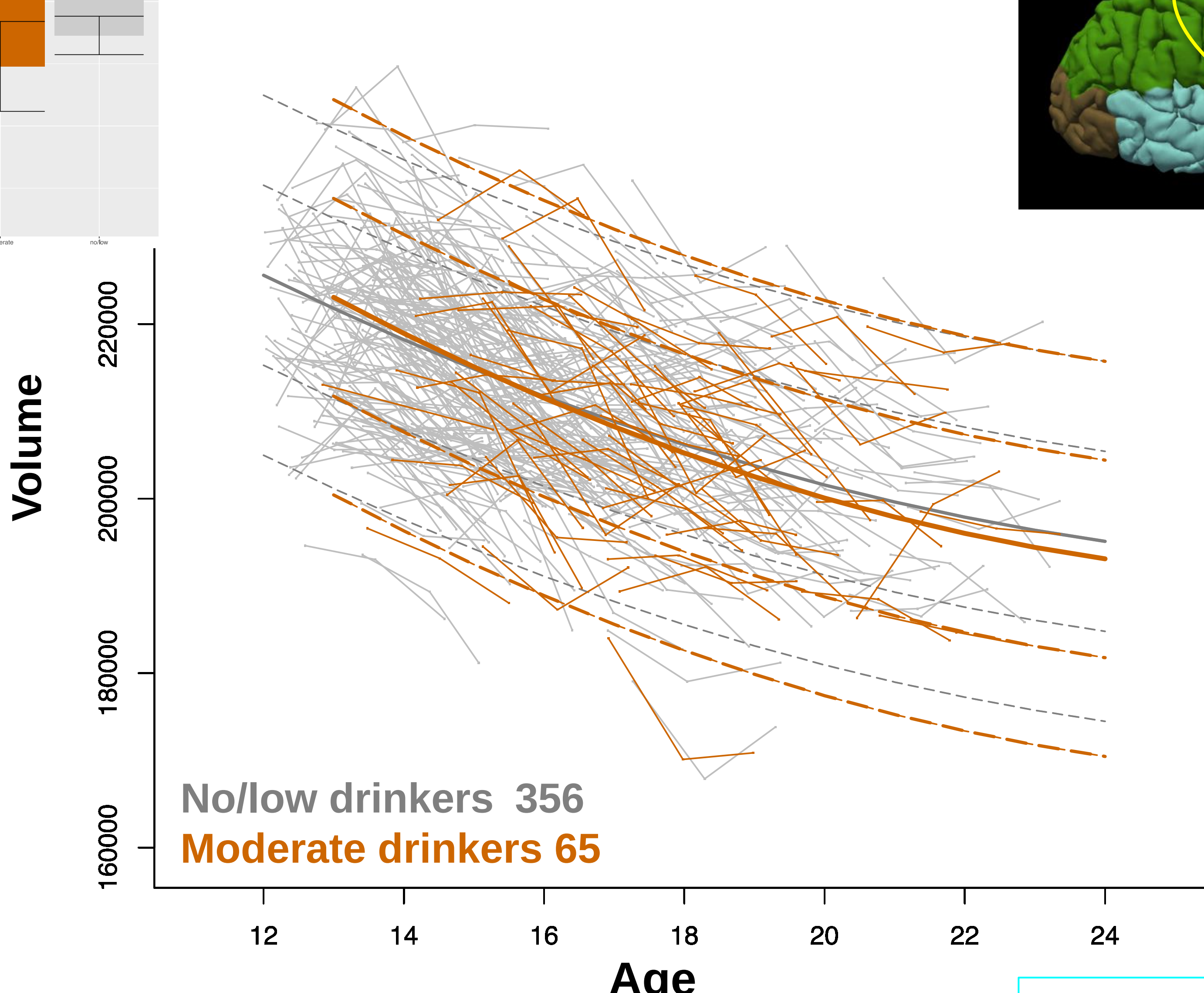


Frontal Cortical Gray Matter

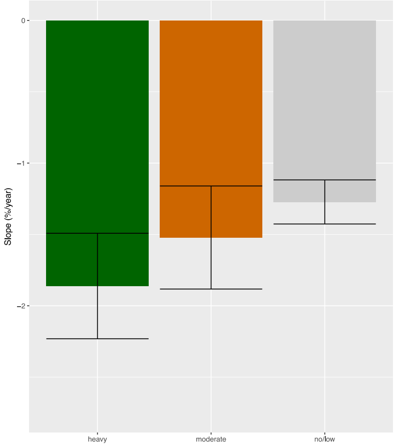
Longitudinal

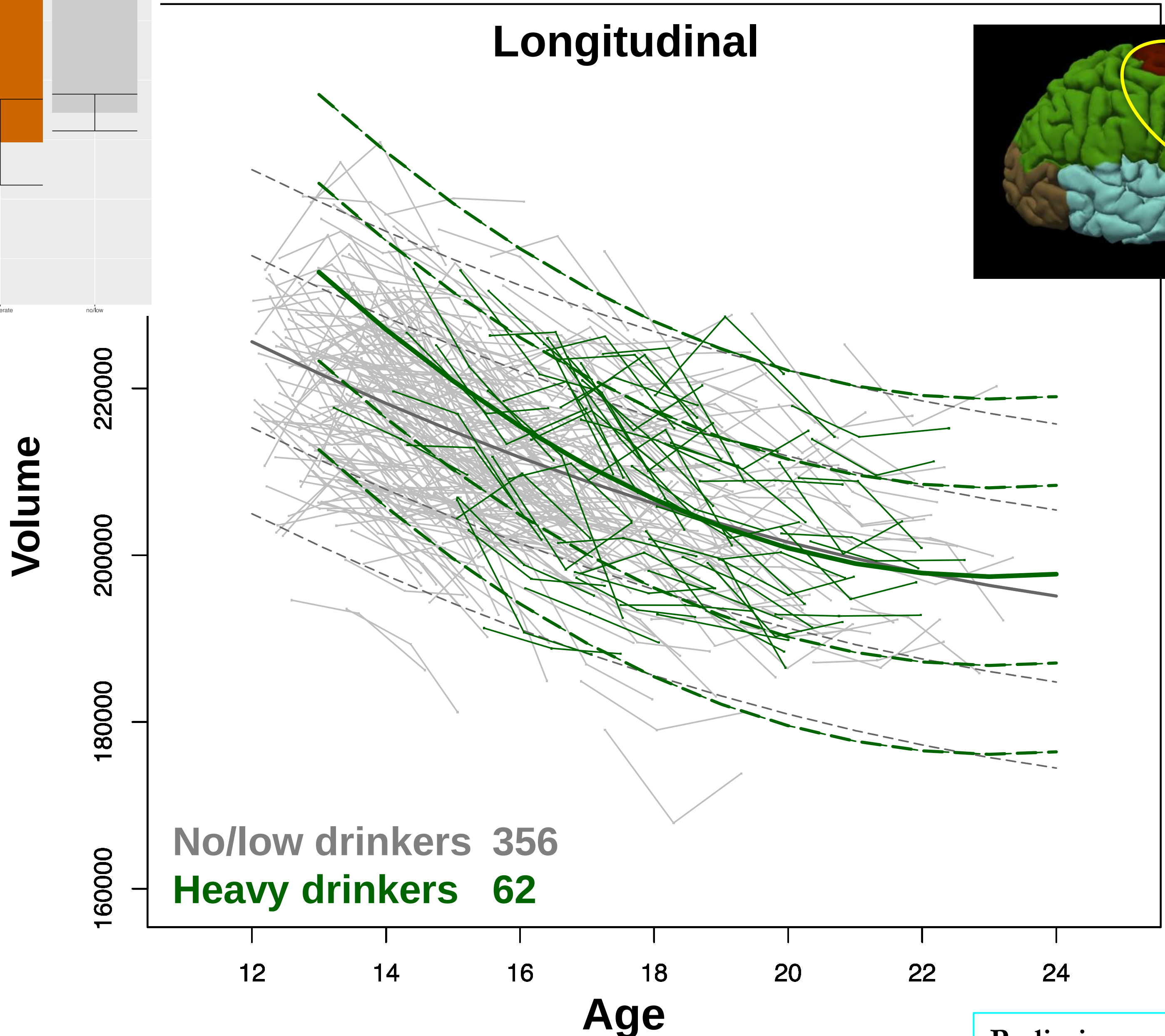


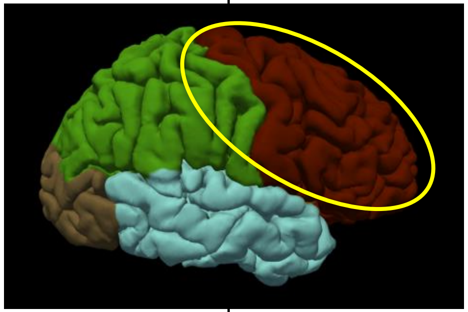


Preliminary unpublished data

Frontal Cortical Gray Matter

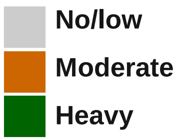


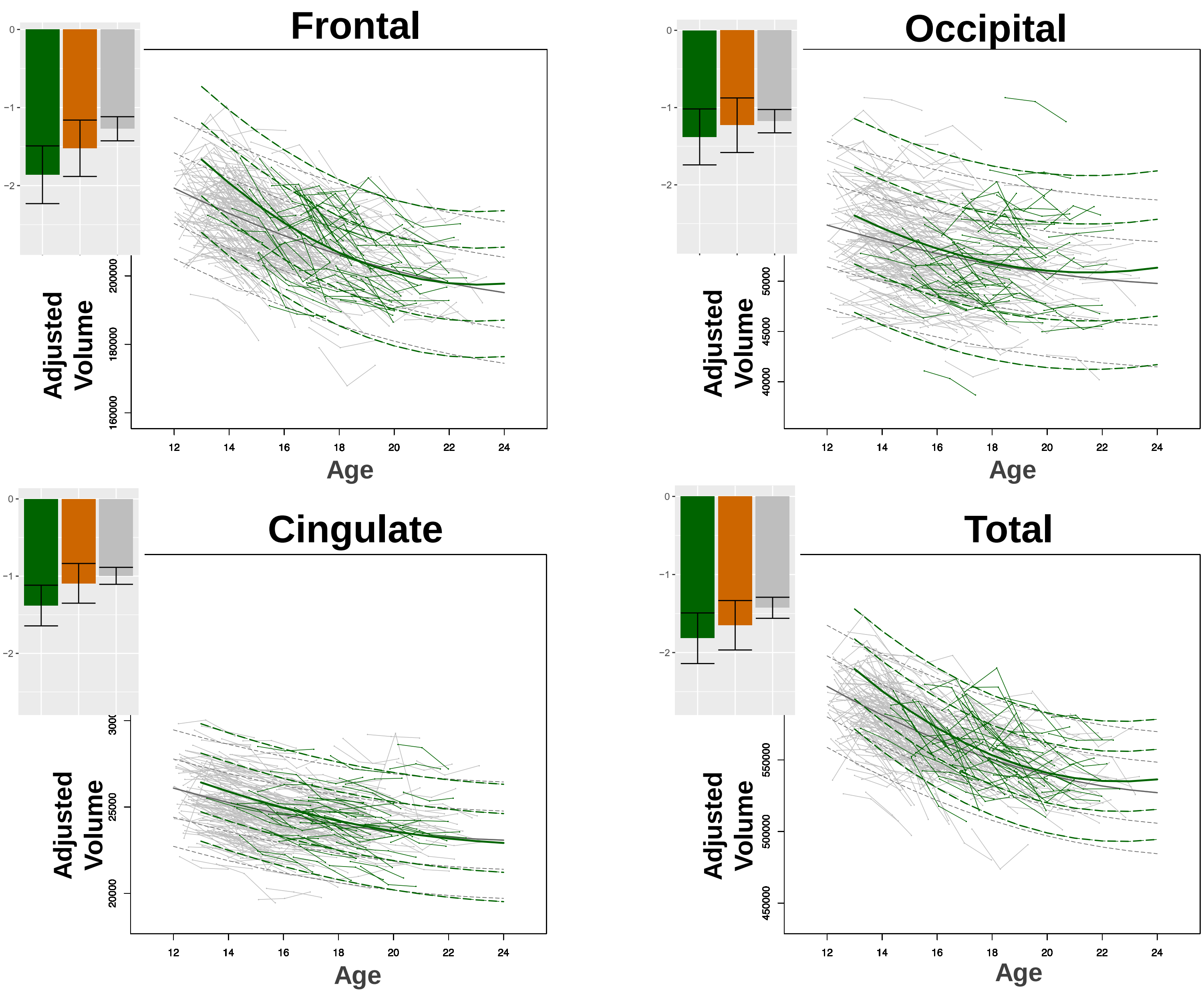




Preliminary unpublished data

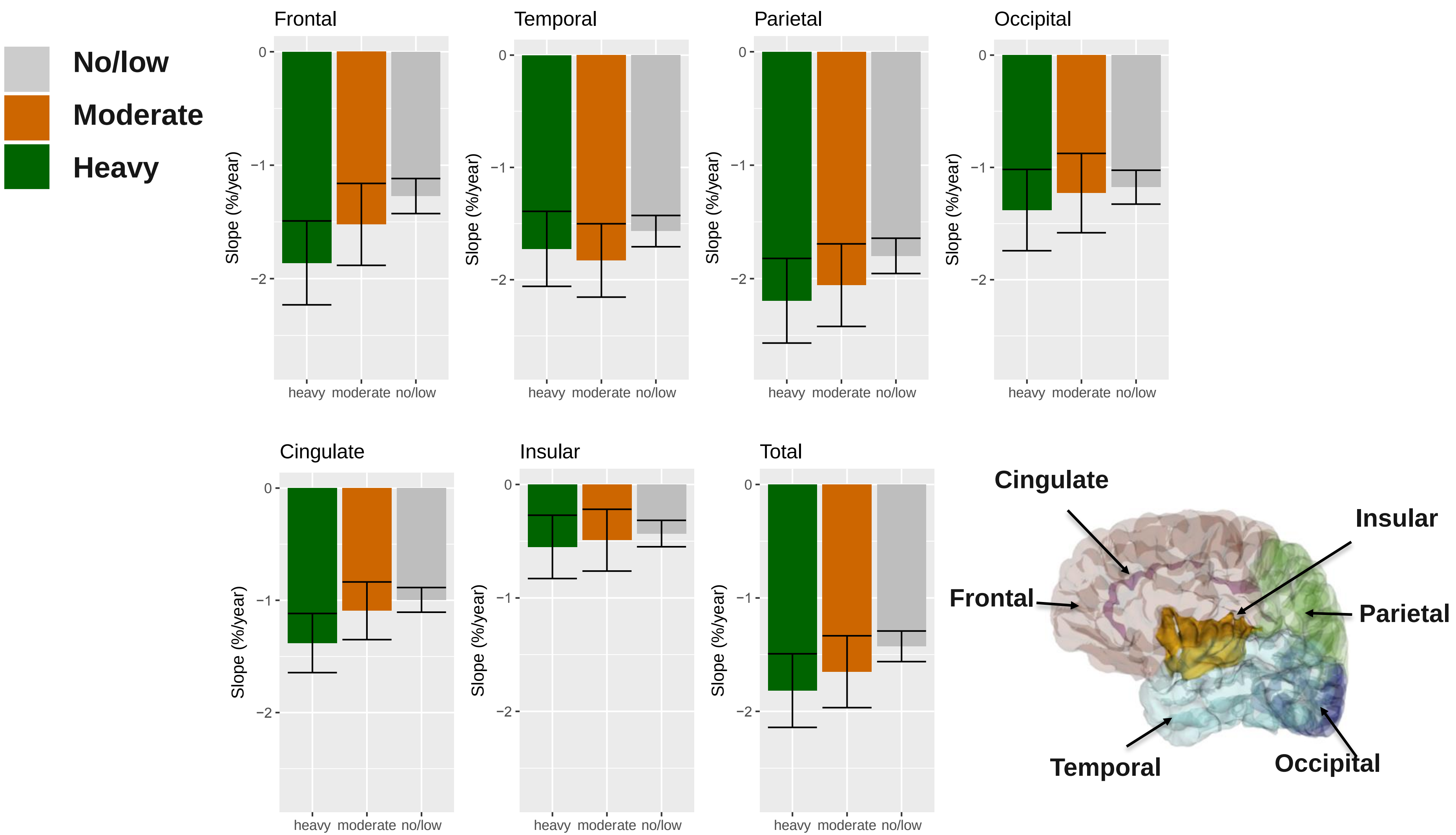
Regions where heavy drinkers have significantly steeper reduction in gray matter volume than no-low drinkers





Regional Gray Matter Volumes

Accelerated Decline with Initiation of Heavy Drinking

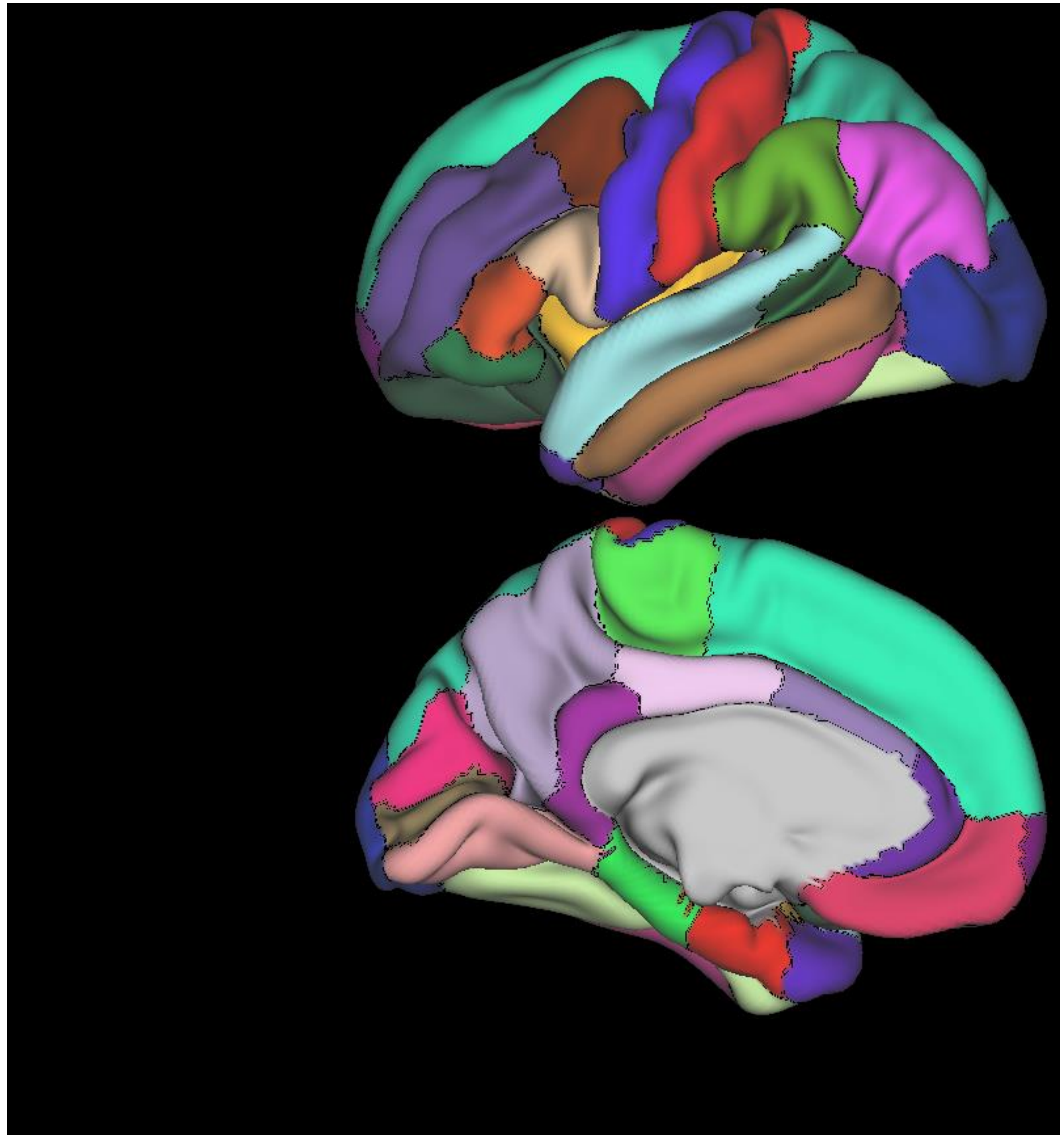


Pfefferbaum et al. *in revision*

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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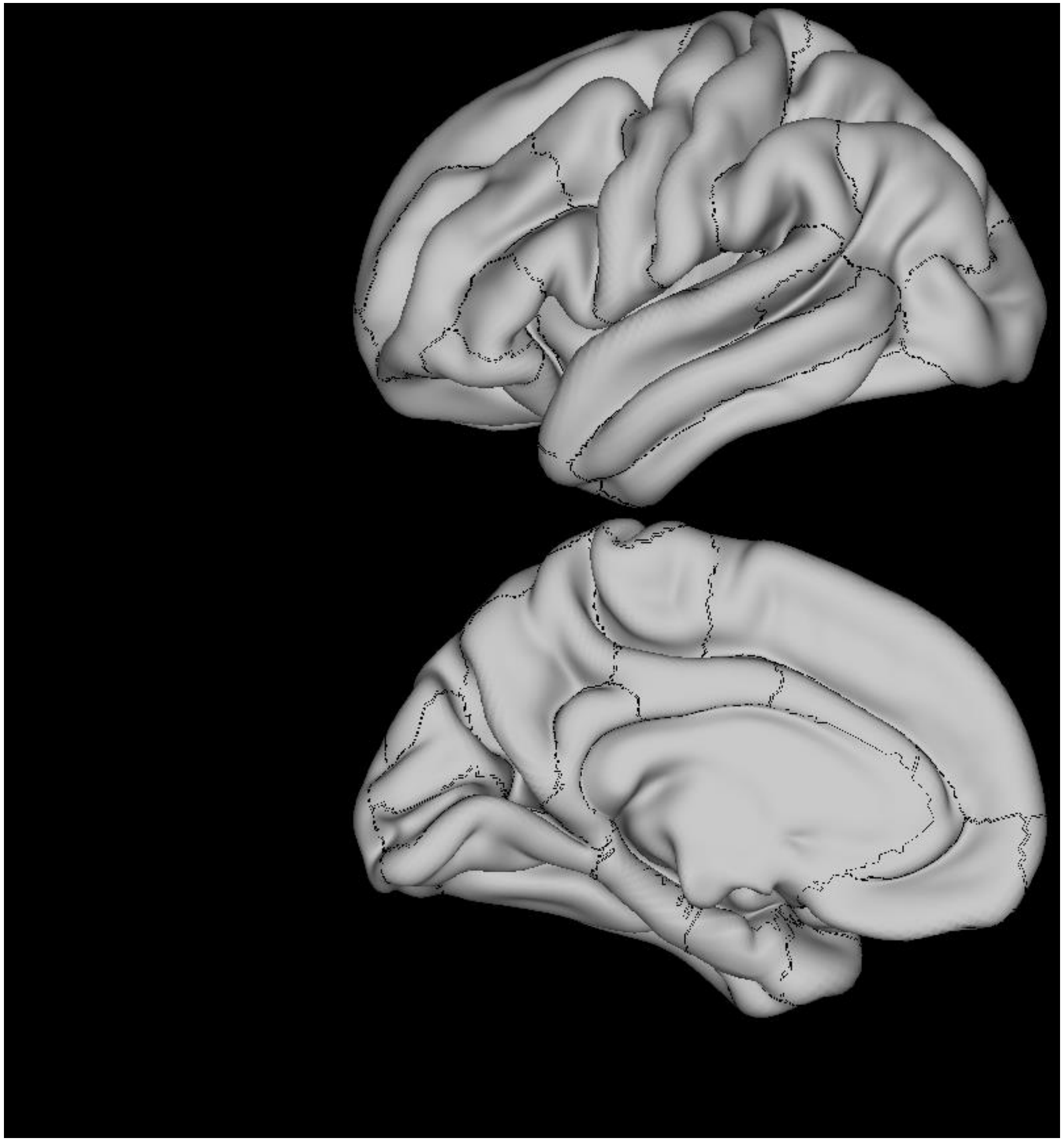

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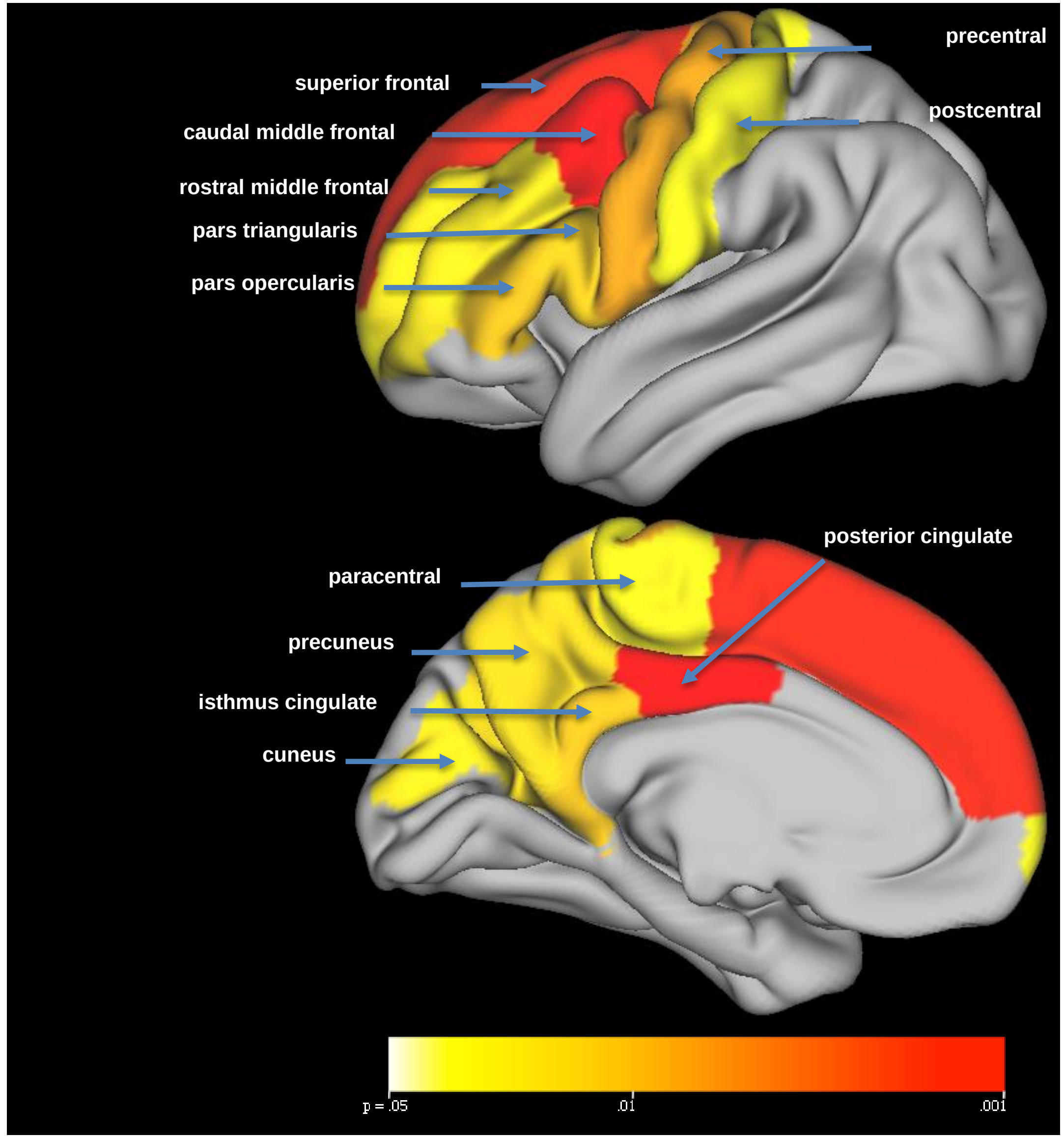
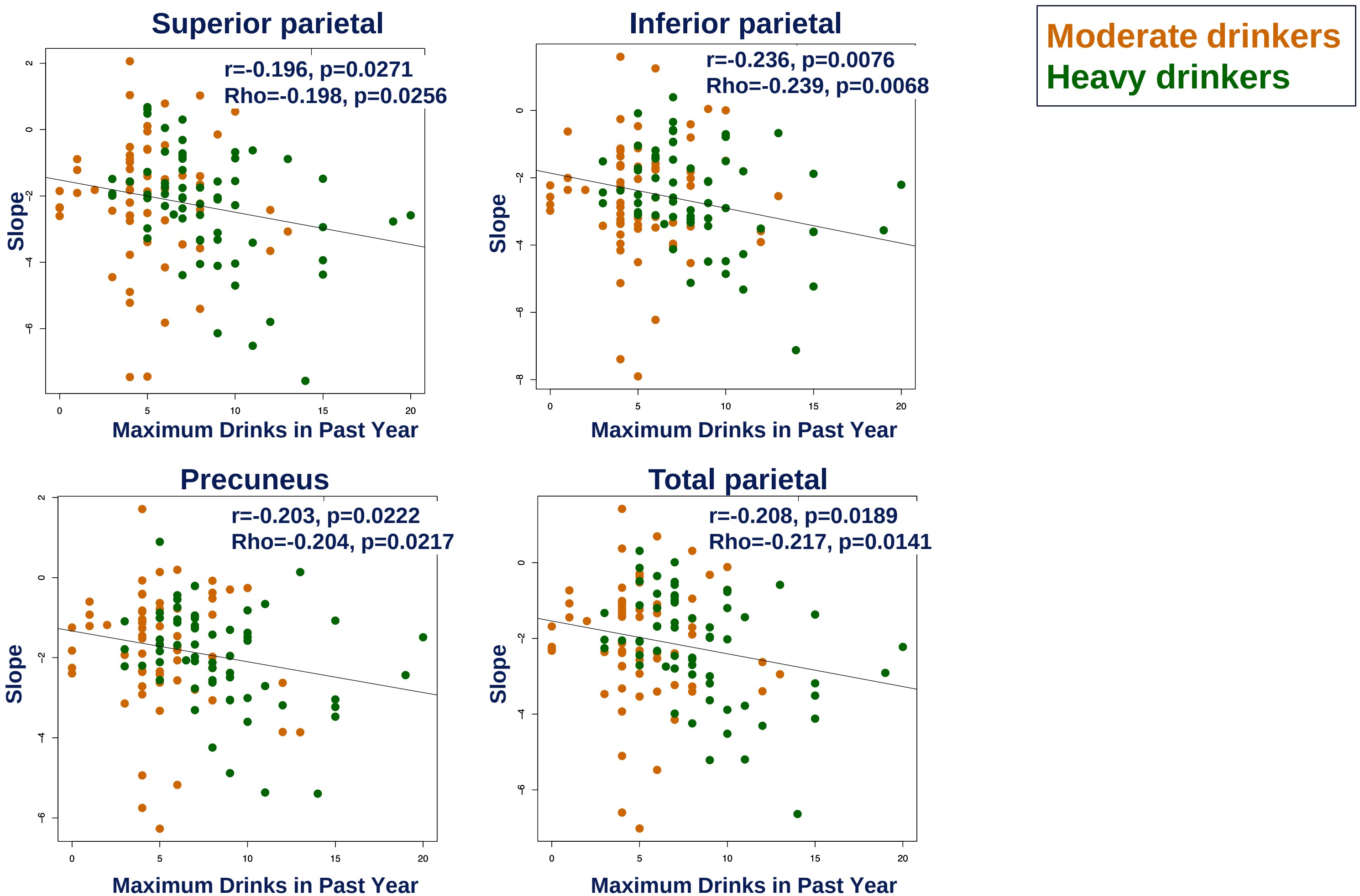


Steeper Regional Parietal Trajectories

Correlations with Greater Maximum Drinks in Past Year



Pfefferbaum et al. *in revision*

Extending Analysis of Imaging Data

Subcortical Brain Iron

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

Cortical Myelin

There is a developmental trajectory of cortical myelin increase

Effects of Initiation of Drinking

Initiation of heavy drinking alters structural cortical developmental trajectory

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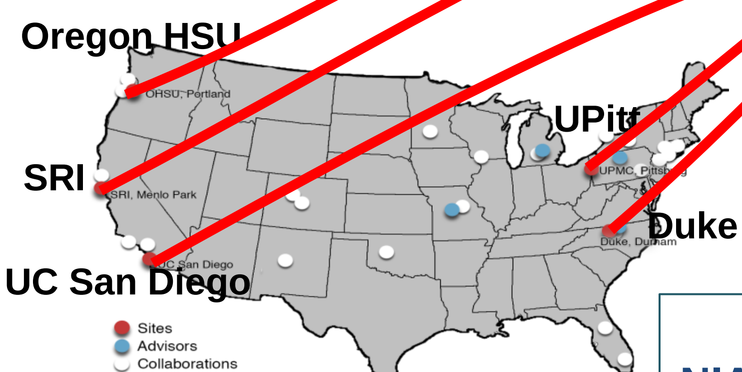
5 U.S. Recruitment Sites



SRI+Stanford

Neuro
Informatics
Platform

FUNDING
NIAAA, NIDA, NIMH, NICHD