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

5 U.S. Recruitment Sites

Oregon HSU

SRI

UC San Diego

UPitt

Duke

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

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- Oregon HSU
- SRI
- UC San Diego
- UPitt
- Duke

FUNDING
NIAAA, NIDA, NIMH, NICHD

Funding: NIAAA, NIDA, NIMH, NICHD
NCANDA ncanda.org
Extending Analysis of Imaging Data
Subcortical Brain Iron

\[
\frac{R2}{R2^* \text{ Estimate}} = \frac{\text{Mean Posterior Corpus Callosum Signal Intensity}}{\text{Voxel Signal Intensity}}
\]

Eric Peterson
Michael De Bellis

Neuro Informatics Platform

N-CANDA ncanda.org
Iron in the Brain

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

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**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 s.e. of estimate; for globus pallidus s.e. = ±3.07.

Hallgren and Sourander, Journal of Neurochemistry, 1958
Measurement of protons is "susceptible" to the presence of iron causing signal loss.
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

\[
\frac{R2}{R2^* \text{ Estimate}} = \frac{\text{Mean Posterior Corpus Callosum Signal Intensity}}{\text{Voxel Signal Intensity}}
\]
Substantia nigra

12-14 years old
Estimating Age-related Change in Non-heme Iron Concentration from Standard NCANDA Protocols

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Estimating Non-heme Iron Concentration from Standard NCANDA Protocols
Estimating Non-heme Iron Concentration from Standard NCANDA Protocols

R² estimate from DTI

SWI index (ppm)

Dentate nucleus

Pallidum

Putamen

Red nucleus

Substantia nigra
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

Neuro Informatics Platform

Myelinated Axons

Stiles & Jernigan *Neuropsychology Review* 2010
Measuring Cortical Thickness in No/Low Adolescents at Baseline

Cortical thickness

Average age 12.22
1.78 mm

Average age 21.00
3.63 mm
Computing Cortical Myelin from T1 and T2 MRI
226 adolescents
HCP

Myelin density

(a) Dense myelin
NCANDA

Myelin density

Left Hemisphere Right Hemisphere

(b) Dense slope (c) Dense p-value (d) Parcellated p-value

NCANDA Baseline Siemens, Cortical Myelin density

(a) Dense myelin
Myelin density

HCP

(a) Dense myelin
Age-related Differences in Myelin Content

Average Myelin Density

Motor<br>Sensory<br>Auditory<br>Visual

Difference Across Adolescence

Motor<br>Central Sulcus<br>Posterior Cingulate<br>Posterior Cingulate

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

Myelin density

Difference across age

(a) Dense myelin

(b) Dense slope
HCP 22-38 years

Myelin density

(b) Dense slope

(a) Dense myelin

Dense myelin
Left Hemisphere

Right Hemisphere

Dense p-value

Myelin density Difference across age

HCP S900 Control, Cortical Myelin

HCP 22-38 years
Age-related Differences in Myelin Content in Motor Cortex (area 4)

Human Connectome Project (HCP) (N=686): left
- $r = 0.220$
- $t = 5.899$
- $p = 5.74 \times 10^{-9}$
- slope = 0.001

HCP (N=686): right
- $r = 0.200$
- $t = 5.343$
- $p = 1.24 \times 10^{-7}$
- slope = 0.001
Age-related Differences in Myelin Content in Motor Cortex (area 4)

**Left Motor Cortex**

- NCANDA (N=226): left
  - $r = 0.410$
  - $t = 6.732$
  - $p = 1.38 \times 10^{-10}$
  - slope = 0.003

- HCP (N=686): left
  - $r = 0.220$
  - $t = 5.899$
  - $p = 5.74 \times 10^{-09}$
  - slope = 0.001

**Right Motor Cortex**

- NCANDA (N=226): right
  - $r = 0.375$
  - $t = 6.060$
  - $p = 5.70 \times 10^{-09}$
  - slope = 0.003

- HCP (N=686): right
  - $r = 0.200$
  - $t = 5.343$
  - $p = 1.24 \times 10^{-07}$
  - slope = 0.001
Grooved Pegboard and Myelin Content in the Motor Cortex (area 4)

Nondominant hand (seconds)

Myelin density in R_area 4

$r = -0.181$

$p = 0.007$

slope = -78.77
Extending Analysis of Imaging Data
Effects of Initiation of Drinking
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

<table>
<thead>
<tr>
<th>Average drinks per occasion (last 3 months):</th>
<th>1-2</th>
<th>1-2</th>
<th>1-2</th>
<th>3-4</th>
<th>3-4</th>
<th>&gt;4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest # drinks in year:</td>
<td>1-2</td>
<td>3-4</td>
<td>&gt;4</td>
<td>3-4</td>
<td>&gt;4</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Frequency</td>
<td>&lt;1x/year</td>
<td>&lt;1x/month</td>
<td>1-3x/month</td>
<td>4-8x/month</td>
<td>&gt;8x/month</td>
<td>Daily</td>
</tr>
<tr>
<td>Control (N=356)</td>
<td>Moderate Drinker (N=65)</td>
<td>Heavy Drinker (N=62)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Frontal Cortical Gray Matter

No/low drinkers

adapted from Pfefferbaum et al. *Cerebral Cortex* 2016
Frontal Cortical Gray Matter

Baseline

Corrected for intracranial volume

Male
Female

No/low drinkers

adapted from Pfefferbaum et al. *Cerebral Cortex* 2016
Frontal Cortical Gray Matter

No/low drinkers

adapted from Pfefferbaum et al. *Cerebral Cortex* 2016
Frontal Cortical Gray Matter

Longitudinal
1 year

No/low drinkers

Preliminary unpublished data
Frontal Cortical Gray Matter

Longitudinal 2 year

Volume

No/low drinkers 356

Age
Regional Gray Matter Volume Slopes
Decline with Age

Male (N=180)
Female (N=176)

Frontal
Parietal
Temporal
Occipital
Cingulate
Insular

Pfefferbaum et al. in revision
Central White Matter

Baseline

Volume vs Age for No/low drinkers

adapted from Pfefferbaum et al. *Cerebral Cortex* 2016
Central White Matter

Longitudinal
1 year

No/low drinkers

Preliminary unpublished data
Central White Matter

Longitudinal
2 year

No/low drinkers 356

Preliminary unpublished data
Regional White Matter Volume Slopes
Decelerating Growth with Age

Pfefferbaum et al. *in revision*
Frontal Cortical Gray Matter

Longitudinal

No/low drinkers 356

Preliminary unpublished data
Frontal Cortical Gray Matter

No/low drinkers 356
Transitioners 127

Preliminary unpublished data
Frontal Cortical Gray Matter

Longitudinal

No/low drinkers 356
Moderate drinkers 65

Preliminary unpublished data
Frontal Cortical Gray Matter

Longitudinal

Volume

No/low drinkers  356
Heavy drinkers  62

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

No/low
Moderate
Heavy

Frontal
Temporal
Parietal
Occipital
Cingulate
Insular
Total

Pfefferbaum et al. *in revision*
FreeSurfer Parcellated Cortical Regions

34 Regions

- L_banksts
- L_caudalanteriorcingulate
- L_caudalmiddlefrontal
- L_corpuscallosum
- L_cuneus
- L_entorhinal
- L_frontalpole
- L_fusiform
- L_inferiorparietal
- L_inferiortemporal
- Linsula
- L_isthmuscingulate
- L_lateraloccipital
- L_laterorbitofrontal
- L_lingual
- L_medialorbitofrontal
- L_middletemporal
- L_paracentral
- L_parahippocampal
- L_parasplenial
- 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
FreeSurfer Parcellated Cortical Regions

34 Regions

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- L_lateralorbitofrontal
- L_lingual
- L_medialorbitofrontal
- L_middletemporal
- L_paracentral
- L_parahippocampal
- L_parasplenial
- L_parsorbitals
- 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
Steeper Regional Parietal Trajectories
Correlations with Greater Maximum Drinks in Past Year

Moderate drinkers
Heavy drinkers

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
Extending Analysis of Imaging Data

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