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

FUNDING
- NIAAA
- NIDA
- NIMH
- NICHD
Extending Analysis of Imaging Data

Cortical Myelin

Subcortical Brain Iron

Effects of Initiation of Drinking

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FUNDING
NIAAA, NIDA, NIMH, NICHD
Structural MRI
Quantitative Measures of Regional Brain Tissue

- Structural MRI
- Tissue Segmentation
- FreeSurfer Gray Matter Regions
- SRI24 White Matter Regions
  - Subcortical white matter
  - Corpus callosum
  - Pons

CSF

- frontal
- parietal
- occipital
- temporal
- cingulate
NCANDA 647 No-to-Low Drinking Sample

Sex

Ethnicity

Pfefferbaum et al. *Cerebral Cortex* 2016
Source of Sex Difference in Cortical Measures

Cortical Surface Area

Cortical Volume

Cortical Thickness

Supratentorial volume

Male
Female
NCANDA Cohort
Baseline MRI by Age and Sex

Regional Cortical Thickness

Cortical Thickness (mm)

frontal  temporal  parietal  occipital  cingulate  insula  total

Pfefferbaum et al. Cerebral Cortex 2016
Extending Analysis of Imaging Data
Cortical Myelin

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

Cortical Thickness

Average Age 21.00

Average Age 12.22

1.78 mm

3.63 mm
1.78 mm
3.63 mm
Cortical thickness (mm)

14 year olds

Insular
Anterior temporal
Occipital
Medial frontal
Compute Myelin in 226 Adolescents at Baseline
Age-related Difference in Myelin Content

Average

0.04 - 0.96%
Age-related Difference in Myelination Content

Significant Age Effect
- Central sulcus
- Precentral gyrus

Average

Developmental Slope
- Motor central sulcus
- Posterior cingulate

D. Kwon et al. OHBM June 27, 2017 Vancouver, Canada
Extending Analysis of Imaging Data
Subcortical Brain Iron

\[ \frac{R_2}{R_2^* \text{ Estimate}} = \frac{\text{Mean Posterior Corpus Callosum Signal Intensity}}{\text{Voxel Signal Intensity}} \]
Echo-planar Imaging (EPI) fMRI Sequence (T2* Weighted)

Globus pallidus

Substantia nigra
Susceptibility Weighted Imaging (SWI) (T2* Weighted)
Spin-echo Diffusion Tensor Imaging (DTI) (T2 Weighted)

Globus pallidus
Substantia nigra
Cerebellar dentate
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‡

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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. = ±0.07.

Hallgren and Sourander, Journal of Neurochemistry, 1958
Estimating Non-heme Iron Concentration from Standard NCANDA Protocols

Non-heme iron $\rightarrow$
  susceptibility (T2*) signal loss
  transverse relaxivity (T2) signal loss

Iron effect
  greater T2 and T2* weighting $\rightarrow$ greater iron effect
  less T1 weighting $\rightarrow$ greater iron effect

T2* $>$ T2

DTI sequence has higher spatial resolution and less B0 spatial distortion

$$\frac{R2}{R2^* \text{ Estimate}} = \frac{\text{Mean Posterior Corpus Callosum Signal Intensity}}{\text{Voxel Signal Intensity}}$$
12-14 years old

Substantia nigra
15-17 years old

Substantia nigra
Substantia nigra

18-21 years old
Estimating Age-related Change in Non-heme Iron Concentration from Standard NCANDA Protocols

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\]
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
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>
</tbody>
</table>

Frequency

- <1x/year
- <1x/month
- 1-3x/month
- 4-8x/month
- >8x/month
- Daily

Control (N=356)  Moderate Drinker (N=65)  Heavy Drinker (N=62)
Frontal Cortical Gray Matter

Baseline

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

Baseline

Corrected for intracranial volume

Adapted from Pfefferbaum et al. *Cerebral Cortex* 2016

Volume

Age

Male
Female

No/low drinkers
Frontal Cortical Gray Matter

Baseline

No/low drinkers

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

Longitudinal
2 year

Volume

260000
240000
220000
200000
180000
160000

Age

12 14 16 18 20 22 24

No/low drinkers 356

Preliminary unpublished data
Regional Gray Matter Volume Slopes Decline with Age

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

Frontal Parietal Temporal Occipital Cingulate Insular

Pfefferbaum et al. *in review*
Central White Matter

Baseline

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

Longitudinal
1 year

Volume

No/low drinkers

Age

Preliminary unpublished data
Central White Matter

Longitudinal
2 year

No/low drinkers 356
Regional White Matter Volume Slopes
Decelerating Growth with Age

Central white matter

Pons

Corpus callosum

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

Longitudinal

No/low drinkers 356

Preliminary unpublished data
Frontal Cortical Gray Matter

Longitudinal

No/low drinkers 356
Transitioners 127

Preliminary unpublished data
Frontal Cortical Gray Matter

Longitudinal

Preliminary unpublished data

No/low drinkers 356
Moderate drinkers 65
Volume Frontal Cortical Gray Matter

Longitudinal

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

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

34 Regions
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
- L_insula
- L_isthmuscingulate
- L_lateraloccipital
- L_lateralarorbitofrontal
- L_lingual
- L_medialorbitofrontal
- L_middletemporal
- L_paracentral
- L_parahippocampal
- L_parasoccularis
- L_parsorbitalis
- L_parstriangularis
- L_pericalcarine
- L_postcentral
- L_posteriorcingulate
- L_precentral
- L_precuneus
- L_rostralantieriorcingulate
- L_rostralmiddlefrontal
- L_superiorfrontal
- L_superiorparietal
- L_superiortemporal
- L_supramarginal
- L_temporalpole
- L_transversetemporal
FreeSurfer Parcellated Cortical Regions

34 Regions

- pars opercularis
- caudal middle frontal
- rostral middle frontal
- pars triangularis
- pars opercularis
- superior frontal
- postcentral
- precuneus
- isthmus cingulate
- posterior cingulate
- precentral
- paracentral
- cuneus
Steeper Regional Parietal Trajectories
Correlations with Greater Maximum Drinks in Past Year

Superior parietal
\[ r = -0.196, \ p = 0.0271 \]
\[ \text{Rho} = -0.198, \ p = 0.0256 \]

Inferior parietal
\[ r = -0.236, \ p = 0.0076 \]
\[ \text{Rho} = -0.239, \ p = 0.0068 \]

Precuneus
\[ r = -0.203, \ p = 0.0222 \]
\[ \text{Rho} = -0.204, \ p = 0.0217 \]

Total parietal
\[ r = -0.208, \ p = 0.0189 \]
\[ \text{Rho} = -0.204, \ p = 0.0217 \]
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

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