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

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Life span and excessive alcohol consumption

**Prenatal**
- Fetal Alcohol Syndrome

**Teenage and Young Adulthood**
- Binge drinking
- Drunk driving
- Unsafe sex

**Adulthood**
- Hypertension
- Breast cancer
- Liver disease
- Job and family

**Maturity**
- Brain damage
- Cognitive impairment

**Photo courtesy of Teresa Kellerman**

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 Matter

White Matter

Volume (cc)

Age

Male
Female

Gray Matter

White Matter

Male
Female
Gray to White Matter Ratio

Gray : White

Volume (cc) vs. Age

Male
Female
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.
Brain Development after Birth
Heterochronicity of Structural Modeling

Developmental course of human brain development

Experience-dependent synapse formation and dendritic arborization

Prefrontal cortex
Parietal and temporal association cortex
Sensorimotor cortex

Synaptogenesis and synaptic pruning

Myelination

Conception to 20 months

Neurulation
Cell proliferation and migration

-8 to -2 months
Birth
0 to 20 years

9 mo
1.5 yr
3 yr
4 yr
6 yr
12 yr

9 months
1.5 years
3 years
4 years
6 years
12 years

Neuropsychology Review December 2012 cover
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

Sex

Ethnicity

Caucasian
Asian
African–American
**Basic NCANDA MRI Protocol**

<table>
<thead>
<tr>
<th>Localizer: 3-Plane Fast Gradient Recalled Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(TR=5, TE=1.5, Thick=5.0, Loc=150, FOV=240, xy_matrix=256x128)</td>
</tr>
</tbody>
</table>

**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)

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

*excluded from NCANDA cohort
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

T1-weighted

T2-weighted
Lateral Ventricle Volume

Frequency (N=808)

10 Boys 14.5 to 15.5 years old

cc
Structural MRI
Quantitative Measures of Regional Brain Tissue

Tissue Segmentation

Structural MRI

FreeSurfer Gray Matter Regions

SRI24 White Matter Regions

Subcortical white matter
Corpus callosum

Pons

CSF

gray matter

white matter
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 \sim \text{age} + \text{covariates (sex, ethnicity, SES, etc)}

**General Additive Model (GAM)**

**Linear:**
\[
\text{brain}_i \sim \beta_0 + \beta_1 \text{age}_i + \beta_2 \text{mfg}_i + \beta_3 \text{ses}_i + \beta_4 \text{ethnicity}_i + \beta_5 \text{sex}_i + \sum_i
\]

**Non-linear:**
\[
\text{brain}_i \sim S_0(\text{age}_i) + \beta_2 \text{mfg}_i + \beta_3 \text{ses}_i + \beta_4 \text{ethnicity}_i + \beta_5 \text{sex}_i + \sum_i
\]

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

Pons

Corpus Callosum

Subcortical White Matter
NCANDA Cohort
Baseline MRI by Age and Sex
**NCANDA Cohort**

**Baseline MRI by Age and Sex**

**Regional Cortical Volumes**

**Frontal**

- Adjusted Volume (cc)
- Age (years)

**Temporal**

- Adjusted Volume (cc)
- Age (years)
NCANDA Cohort
Baseline MRI by Age and Sex

Regional Cortical Volumes

Frontal

Temporal

Regional Cortical Thickness

Frontal

Temporal
NCANDA Cohort
Baseline MRI by Age and Sex

Regional Cortical Thickness

Cortical Thickness (mm)

Frontal  Temporal  Parietal  Occipital  Cingulate  Insula  Total
NCANDA MRI

- Age
- Headsize / Supratentorial Volume
- Sex
- Ethnicity
- Prior Alcohol Exposure
Sex Differences in Brain Size

Supratentorial Volume

Adjusted Volume (cc)

Sex

Age (years)
Size Metrics and Supratentorial Volume

- Frontal Gray Matter Volume
- Adjusted Volume (cc)
- Supratentorial Volume (cc)

- Frontal Cortical Surface Area
- Adjusted Area (cm²)
- Supratentorial Volume (cc)

- Frontal Cortical Thickness
- Adjusted Thickness (mm)
- Supratentorial Volume (cc)
NCANDA MRI

- Age
- Headsize / Supratentorial Volume
- Sex
- Ethnicity
- Prior Alcohol Exposure
NCANDA Cohort
Baseline MRI by Age and Sex

Regional Cortical Volumes

Supratentorial Volume - Adjusted Regional Cortical Volumes
NCANDA MRI

- Age
- Headsize / Supratentorial Volume
- Sex
- Ethnicity
- Prior Alcohol Exposure
Frontal Cortex
Baseline MRI by Age, Sex, Ethnicity

Frontal Volume

Adjusted Volume (cc)

Age (years)

Adjusted Thickness (mm)

Asian
A Amer
Cauc
Asian
A Amer
Cauc

Frequency

Caucasian
Asian
African-American
Frontal Cortex
Baseline MRI by Age, Sex, Ethnicity
Adjusted for supratentorial volume

Frontal Volume

Frontal Thickness

Adjusted Thickness (mm)

Adjusted Volume (cc)

Age (years)
% Difference per Year (N=631)
Pubertal Development

- Frontal Gray Matter Volume
- Frontal Cortical Thickness

Graphs showing the relationship between PDS score and age, as well as adjusted volume and thickness for frontal regions.
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
NCANDA and PING
Cortical Volume and Thickness

Volume

Cortical Thickness

Adj. Volume (cc)

Adj. Volume (cc)

Adj. Volume (cc)

Adj. Thick (mm)

Adj. Thick (mm)

Adj. Thick (mm)

Parietal

Occipital

Cingulate

PING
NCANDA
Moderate/high Alcohol
Regional Cortical Volumes and Thickness

Total Cortical Volume

Frontal Cortical Volume

Svol Adjusted Score (cc)

Age (years)

Svol Adjusted Score (mm)

Age (years)
Binge Drinking and Cortical Thickness

Frontal Cortical Thickness

Parietal Cortical Thickness

Binge Episodes in Past Year

Svol Adjusted Score (cc)

Binge Episodes in Past Year

Svol Adjusted Score (cc)
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.
A note of caution ....
NCANDA Clinical MRI Findings
Baseline
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.