Insights about Substance use from Development Neuroimaging Studies: an Update on the ABCD and HBCD Studies

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Todays Talk

• The ABCD Study
  • Overview
  • Update
  • A few results

• The HBCD Study
  • Overview
  • Update

• Questions
A large longitudinal study beginning in early adolescence will help us understand the normal variability in brain and cognitive development and tease apart the many factors that influence it.

"Thus, the Adolescent Brain Cognitive Development study was created to answer the most pressing public health questions of our day."
www.ABCDstudy.org

• 10-year longitudinal study of 11,878 children (2,100 twins) enrolled at ages 9-10; 21 data collection sites in the United States
• Administrative and Data cores at UCSD
• Recruitment through schools – epidemiologically informed, once a school was selected, all students who were age 9-10 were invited to participate
• Twins recruited through birth registry at twin-sites
• Goal was to recruit a sample that broadly reflected the US population of 9–10-year-olds (in 2015) based on data from the American Community Survey.
• Baseline 11,878 families recruited in 24 months (575 families in Vermont)

<table>
<thead>
<tr>
<th>Household Size</th>
<th>ABCD</th>
<th>ACS</th>
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<tbody>
<tr>
<td>2-3 Persons</td>
<td>17.2%</td>
<td>18.5%</td>
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<tr>
<td>4 Persons</td>
<td>33.5%</td>
<td>33.5%</td>
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<tr>
<td>5 Persons</td>
<td>25.2%</td>
<td>25.3%</td>
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<tr>
<td>6 Persons</td>
<td>14.0%</td>
<td>12.5%</td>
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<tr>
<td>7 or More Persons</td>
<td>10.2%</td>
<td>10.1%</td>
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![Annual Household Income Chart]

- Male: 48%, Female: 52%
- White: 53% (ACS: 49%)
- Hispanic: 22% (ACS: 23%)
- Black: 12% (ACS: 17%)
- Asian: 2% (ACS: 5%)
- Other: 11% (ACS: 5%)

- > 200K: ABCD 11%, ACS 8%
- 100K - 200K: ABCD 30%, ACS 23%
- 75K - 100K: ABCD 15%, ACS 13%
- 50K - 75K: ABCD 14%, ACS 21%
- 25K - 50K: ABCD 15%
- < 25K: ABCD 14%, ACS 18%
ABCD Initiated by NIH Collaborative Research on Addiction (CRAN)

- NIDA, NIAAA, National Cancer Institute
- Many other federal collaborators are now participating

ABCD Youth Protocol Summary: Baseline

**Physical Health**
- PhenX Anthropometrics (height/weight/waist measurements)
- Stellen Vision Screener
- Edinburgh Handedness Inventory
- Youth Risk Behavior Survey: Exercise
- Pubertal Development Scale
- Menstrual Cycle Survey (pubescent girls)
- Screen Time Survey

**Biospecimens**
- Breathalyzer and Oral Fluids (subset)
- Saliva Samples for DNA, Puberty
- Blood Samples (subset)
- Hair Sample
- Baby Teeth

**Mental Health**
- Kiddie Schedule for Affective Disorders and Schizophrenia
  - Background Items Survey
  - Diagnostic Interview for DSM-5 (S modules)
- PhenX UPPS-P for Children Survey
- PhenX Behavioral Inhibition/Behavioral Approach System (BIS/BAS) Scales
- Prosocial Psychosis Scale
- Youth Resilience Scale

**Neurocognition**
- NIH Toolbox Tasks:
  - Picture Vocabulary
  - Flanker Inhibitory Control & Attention
  - List Sorting Working Memory
  - Dimensional Change Card Sort
  - Pattern Comparison Processing Speed
  - Picture Sequencing Memory
  - Oral Reading Recognition
  - Rey Auditory Verbal Learning Task
  - Cash Choice Task
  - Little Man Task
  - Matrix Reasoning Task
  - RAVLT Delayed Recall

**Culture & Environment**
- Prosocial Tendencies Survey
- PhenX Acculturation Survey
- Parental Monitoring Survey
- Acceptance Subscale from Children's Report of Parental Behavior Inventory (CRPI) - Short
- PhenX Family Environment Scale - Family Conflict
- PhenX Neighborhood Safety/Crime Survey
- PhenX School Risk & Protective Factors Survey

**Substance Use**
- For most participants:
  - Timeline Follow-Back Survey
  - PhenX Peer Group Deviance Survey
  - PATH Intention to Use Tobacco Survey
  - Caffeine Intake Survey
  - Participant Last Use Survey (PLUS) for substance use within the last 24 hrs

**Other Data Sources**
- Geocoding from Residential History
- School Records
- FitBit® (subset)
- Brief Problem Monitor - Teacher Form

*For participants with differing levels of substance use (low, moderate, heavy), follow-up items include: *IQ, Q27 Stopping Items, Tobacco Use Level Use Measure, MJ Use Level Use Measure, PhenX Alcohol Use: Sensitivity to Alcohol, Tobacco, or MJ, Yawney Somatic Scale, Rutgers Alcohol Problem Index (RAPI), Marijuana Dependence (PATH), Drug Problem Index (MAP), MJ Problem Index (MAP)
ABCD Open Science Model –
A Unique Resource for the Entire Scientific Community

Open sharing through the NIMH Data Access Portal (NDA).
• Goal to allow scientists worldwide to conduct “Big Data” analyses, pool resources, and enrich the value of this study.
• Anonymized raw neuroimaging data, within one month of data collection
• Curated derived data, annually, beginning 1 year after start of data collection
ABCD STATUS UPDATE

- Currently collecting Year 6 Follow-up data (ages 15-16)
- **97.9% sample retention in the ABCD Study!**
- Remote data collection during the pandemic.

But note that we have unknown numbers of *de facto* withdrawals and participants at risk for withdrawal.
Funded Grants Leveraging ABCD Data

Funded Grants

<table>
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<tr>
<th></th>
<th>FY2017</th>
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<th>FY2019</th>
<th>FY2020</th>
<th>FY2021</th>
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<td>4</td>
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Research and Training Grants by FY

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<tr>
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<th>FY18</th>
<th>FY19</th>
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<th>FY21</th>
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<td>F30, F31, F32, K01, K02, K08, K23, K99</td>
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<td>8</td>
<td>11</td>
<td>17</td>
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N=73
Funded Grants Leveraging ABCD Data

Grant Mechanisms

- F30
- F31
- F32
- K01
- K02
- K08
- K23
- K99
- T32
- R25
- R13

Funded Grants by IC

- NIAAA
- NHLBI
- NIBIB
- NICHD
- NIDA
- NIDCR
- NIDDK
- NIEHS
- NIGMS
- NIMH
- NIMHD

N=73
Publications – Unexpected Focus Areas

Prevalence of Perceived Racism and Discrimination Among US Children Aged 10 and 11 Years
The Adolescent Brain Cognitive Development (ABCD) Study

Racial Disparities in Elementary School Disciplinary Actions: Findings From the ABCD Study

Association Between Discrimination Stress and Suicidality in Preadolescent Children

Neurobiological antecedents of multisite pain in children
Nucleus accumbens cytoarchitecture predicts weight gain in children

Fine particulate matter exposure during childhood relates to hemispheric-specific differences in brain structure

Polygenic Risk for Insomnia in Adolescents of Diverse Ancestry

Associations between frontal lobe structure, parent-reported obstructive sleep disordered breathing and childhood behavior in the ABCD dataset

Imaging and health metrics in incidental cerebellar tonsillar ectopia: findings from the Adolescent Brain Cognitive Development Study (ABCD)

Early adolescent gender diversity and mental health in the Adolescent Brain Cognitive Development study

Screen time and early adolescent mental health, academic, and social outcomes in 9- and 10-year old children: Utilizing the Adolescent Brain Cognitive Development (ABCD) Study

Deep learning identifies morphological determinants of sex differences in the pre-adolescent brain

Early Adolescent Substance Use Before and During the COVID-19 Pandemic: A Longitudinal Survey in the ABCD Study Cohort
Some key findings from ABCD

- Small effect sizes and the need for large samples (Owens)
- Scientific Training in Addiction Research Techniques (START)
  - Family history of SUD related to brain cortical thickness trajectories (Dibbs-Goncalves)
  - Adolescent positive alcohol expectancies – links to response inhibition and brain function (Adams)
- Effects of prenatal cannabis exposure on adolescent development (Cioffredi)
Reproducible brain-wide association studies require thousands of individuals

Resetting Expectations: Big Data and Small Effects
Owens et al., PLOS One, 2021

195 summary scores from ABCD baseline data yielding 6,669 correlations

- Sleep & total mental health problems (r=.58)
- ASR Parent total psychiatric problem & CBCL child total psychiatric problems (r=.57)
- Fluid intelligence & crystalized intelligence from NIH toolbox (r=.48)
- Age & height (r=.43)
- Parent report of how well child does in school & CBCL Attention problems (r=.43)
- Parent report child has received mental health services & CBCL total problems & (r=.40)
- Parent income and parent reported neighborhood safety (r=.36)
- # of traumatic experiences & CBCL total psychological problems (r=.20)
- Age & pubertal development (r=.17)
- UPPS lack of planning & CBCL attention problems (r=.17)
- Weight & screen time (r=.16)
- CBCL Internalizing symptoms & suicidality (r=.16)
- Parent report Family HX of mental health services & CBCL total problems (r=.15)
- Child report parental acceptance & CBCL total problems (r=.09)
- UPPS lack of planning & detention frequency – parent report (r=.08)
- Sleep problems & total IQ (r=.06)
- Physical activity & weight (r=.03)
Resetting Expectations: Big Data and Small Effects

[Owens et al., PLOS One.]

first quartile \( r = .01 \),
median \( r = .03 \),
third quartile \( r = .07 \), and
90\text{th} percentile \( r = .14 \).

Effects are bigger for within vs. between instrument, domain, and reporter … but essentially unchanged.

Also essentially unchanged if you add nuisance covariates or apply statistical thresholds and only look at the significant correlations.

With statistical thresholding

With covariates
Why we need large cohort studies

• Improve reliability of reported associations.
• Intense phenotyping enable research across disciplines – comprehensive look at neurodevelopment.
• Robust analytic methods (i.e., built in replication)
• Disentangle confounded demographics
• Ability to analyze sub-groups matched on particular features to interrogate specific research questions.
Frontal **cortical thickness trajectories** among 9–13-year-old preadolescents with a positive versus negative family history of alcohol/substance use problems.

**Exposure:**
- **FH Positive (FHP)** (24.8%, n=2,696): having $\geq 1$ biological parents and/or $\geq 2$ biological grandparents
- **FH Negative (FHN)** (61.4%, n=6,675), having no parents/grandparents with alcohol/substance use problems
- **Preadolescents with only 1 grandparent** with a history of substance problems (13.9%, n=1,507) were not included in our models.

- Cortical thickness changes in frontal regions (particularly pre- and paracentral regions) were significantly associated with FHP, with overall more rapid thinning.

- The population is largely substance naïve, supporting prior research showing neurological development of youths may be affected by parental history of alcohol/substance use problems.
**Alcohol expectancy:** personal beliefs that a particular behavioral, emotional or cognitive effect will occur when drinking alcohol.

**Positive expectancy is related to earlier alcohol initiation and subsequent use. It may have value as a modifiable factor that could be strategically leveraged for prevention efforts**

**Response inhibition:** ability to stop a pre-potent response – measured with a cognitive task (the stop signal task).

Task performance is related to other forms of impulsivity including ADHD, and SUD. The stop task is one of the fMRI tasks in ABCD

**Positive alcohol expectancy may be related to response inhibition – this may lead to a better understanding of the brain mechanisms by which our beliefs relate to health behaviors.**

**Results:** Positive AE was associated with lower activation in the right anterior insula during response inhibition.
Prenatal cannabis exposure (PCE)

- Cannabis use during pregnancy is increasing in prevalence, frequency, and quantity of use.
- THC readily crosses the placenta and accumulates in fetal tissue.
- The endogenous endocannabinoid system plays a critical role in early brain development.
- Long term effects of exposure remain unclear with the National Academies of Sciences, Engineering, and Medicine concluding in 2017 that only reduced birth weight was robustly linked to exposure.

Volkow et al 2019
NASEM 2017
A case-control study of prenatal cannabis exposure (PCE)

- Prenatal cannabis exposure after knowledge of pregnancy (n=224).
- Tobacco/alcohol exposed group matched on age & sex (n=224).
- Non-exposed group matched on age & sex (n=224).
- Poisson mixed models (family nested within site).
- Covariates:
  - Factors related to childhood ADHD: parental psychopathology, maternal age, duration of breastfeeding.
  - Factors related to neurodevelopment: prematurity, birthweight.
  - Demographics not equivalent after matching: race/ethnicity, household education.
- Outcomes included vertex-wide analysis of the 3 fMRI tasks.
- **PCE associated with increased attention and externalizing problems (both parent and teacher report) and parent reported thought, and social problems.**
- Notably no effects of cognition, or brain activation measures from the 3 fMRI tasks after covariates.

Ciofreddi et al 2022
Motivation for another large, longitudinal, developmental-neuroimaging study

• Challenges with retrospective report of prenatal environment
• Improved measures are critical for understanding the effects of the prenatal environment.
• Many things happen during early development – hard to untangle prenatal from post-natal effects.
• The HEALthy Brain Child Development (HBCD) Study is designed to address some of these issues.
• Synergies between HBCD and ABCD are built in.
HEALthy Brain Child Development Study

- Prospective longitudinal study of child development from pregnancy through first 10 years of life

- Target sample size 7,500 mother child pairs recruited in mid-pregnancy over a ~3 year period of time

- 25 recruitment sites across the U.S. representing diversity of the population of pregnant persons giving birth.
Over-sampling of substance using pregnant people

- 25% overall target for any SU
  - $\geq 12\%$ opioid
  - $\geq 12\%$ marijuana
  - $\geq 12\%$ alcohol
  - $\geq 12\%$ tobacco

- Based on estimates of pregnancy substance use in NSDUH and polysubstance correlations
- Will require most enhancement for opioid use ($\sim 1\%$ in NSDUH)
- Only modest enhancement for marijuana and alcohol ($8\%$ marijuana, $10\%$ alcohol, in NSDUH)
- Tobacco use is prevalent in the general population of pregnant women ($12\%$ tobacco in NSDUH)
HEALthy Brain Child Development Study

A longitudinal observational study that aims to understand normative neurodevelopment from birth to 10 years with an emphasis on providing information on the impact of *in utero* exposures to potentially harmful substances and environments.

- **EEG** for baseline, auditory evoked potential, visual evoked potentials, and face-object ERP task
- **MRI** for structural, diffusion, resting state connectivity, and MR spectroscopy
- **Biospecimens** for substance use, genomic, epigenomics, nutrition, toxins, and COVID-19
- **Wearable biosensors** for heart rate (HR), HR variability, sleep/wake cycles, and physical activity
- **Behavioral, observational, and neurocognitive assessments**
- **Substance and other risk and protective factor exposures**
Support for HBCD

NIH HEAL INITIATIVE

ENHANCING PAIN MANAGEMENT

IMPROVING TREATMENTS FOR OPIOID MISUSE AND ADDICTION

- Pre-Clinical/Translational Research in Pain Management
- Clinical Research in Pain Management
- Novel Medications Options
- Enhanced Outcomes for Affected Newborns
- New Prevention & Treatment Strategies
- Translating Research Into Practice

National Institute on Drug Abuse
National Institute of Mental Health
National Institute on Alcohol Abuse and Alcoholism
National Institute of Child Health and Human Development
Office of Behavioral and Social Sciences Research
Office of Research on Women’s Health
National Institute of Minority Health and Disparities
National Institute of Environmental Health Sciences
National Institute of Neurological Disorders and Stroke
National Institute of Biomedical Imaging and Bioengineering
HEALthy Brain and Child Development Study

OSMB
Clinical Risk Assessment

Steering Committee
Composition: Decision Making Body
Voting Members (16): HCAC MPIs, HDCC MPIs, Site Representatives and NIH Project Director
Non-voting members: ESB Chair, NIH staff

External Scientific Board
Makes Recommendations

National Liaison Board
Makes Recommendations

Council of Investigators
Composition: 25 Research Site PIs

Operations Group
Composition: Implementation Group
HCAC and HDCC MPIs, Associate Directors
NIH Project Director, and NIH Leaders

NIH Institutes
Federal Collaborators
Project Director, Program Official

NIH Science Officials

25 research sites
HCAC
HDCC

OSMB: Observational Study Monitoring Board
HCAC: Healthy Brain and Child Development Consortium Administrative Core
HDCC: Healthy Brain and Child Development Data Coordinating Center
HEALTHy Brain and Child Development Study

HCAC
2 Directors (MPIs)
4 Associate Directors
- Bioethics & Medical Oversight Group
- Crisis & Communication Team
- Epidemiology/Design
- Equity, Diversity, Inclusion
- Ethics, Legal, Policy Group
- Recruitment & Retention Group
- Rural & Sovereign Communities Group
- Training & Professional Development
- Work Groups for Assessment Domains

HCAC-HDCC-NIH
- Study Enhancement
  HCAC-HDCC-NIH
- Communication Dissemination
  HCAC-HDCC-NIH
- Resource Sharing
  HDCC-HCAC-NIH

HDCC
3 Directors (MPIs)
1 Associate Director
- Image Acquisition Work Group
- EEG Work Group
- External Data EHR, etc
- Image Analysis
- Biostatistics

HCAC: Healthy Brain and Child Development Consortium
Administrative Core
HDCC: Healthy Brain and Child Development Data
Coordinating Center
Conclusions

• The ABCD study is doing well! Retention is high and it is yielding rich longitudinal data.

• The HBCD study has committed to the same open science framework as ABCD providing access to information about early life experiences.

• Together HBCD and ABCD will help to answer questions about neurodevelopment from birth to age 20.

• The ABCD dataset is available to you now, and we strongly encourage you to consider working with it. The first release of HBCD data is anticipated in 2025!
Thank you!

Questions?