HEALthy Brain and Child Development Study

Kathy Cole, PhD
Chloe Jordan, PhD
Janani Prabhakar, PhD

CRAN Council
May 8, 2024
What is HBCD?

- Ten year longitudinal study
- Enrollment starting in 2\textsuperscript{nd} trimester of pregnancy
- Multi-modal assessments of brain, cognitive and emotional development from birth through childhood
- Characterize neurodevelopmental trajectories from large sample (~7,000)
- Determine how substance exposure and other environmental factors affect developmental trajectories
- Yearly data release beginning in late 2024/early 2025
HBCD Support

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
Translating Research Into Practice
Novel Medications Options
Enhanced Outcomes for Affected Newborns
New Prevention & Treatment Strategies

National Institute on Drug Abuse (NIDA)
National Institute of Mental Health (NIMH)
National Cancer Institute (NCI)

National Institute of Neurological Disorders and Stroke (NINDS)
National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

National Institute of Biomedical Imaging and Bioengineering (NIBIB)
National Institute of Environmental Health Sciences (NIEHS)
National Institute on Minority Health and Health Disparities (NIMHD)

Office of Behavioral and Social Sciences Research (OBSSR)
Office of Research on Women's Health (ORWH)
National Eye Institute (NEI)
HBCD Consortium

Arkansas Children’s Hospital
Boston Children’s Hospital
Cincinnati Children’s Hospital
Children’s Hospital Los Angeles/University of Southern California
Cedars Sinai Medical Center
Children’s Hospital of Philadelphia
Emory University
Johns Hopkins University
New York University
Northwestern University
Oregon Health Sciences University
Oklahoma State University
Pennsylvania State University State College
Pennsylvania State Hershey Medical Center
University of Alabama Birmingham
University of Alabama Tuscaloosa
University of Arkansas Medical School
University of Maryland
University of Minnesota
University of New Mexico
University of North Carolina
University of California San Diego
University of Vermont
University of Wisconsin Madison
Vanderbilt University
Virginia Tech University
Washington University St Louis
HBCD Study Objectives

• What are typical neurodevelopmental trajectories and what is the normal range of variability in brain development from birth through childhood? How do biological and other environmental exposures affect these developmental trajectories?

• How do genetic influences interact with environmental factors to influence neurodevelopment and cognitive, emotional, and social behavior?

• How does early life exposure to opioids, other substances, and/or other adverse environmental circumstances affect developmental trajectories?

• Are there key developmental windows during which the impact of adverse exposures (e.g., stress, COVID 19) influence later neurodevelopmental outcomes?

• Are there key developmental windows during which ameliorating influences (e.g., substance use disorder treatment; social/economic support) are protective against the potential neurodevelopmental insults of early adverse exposures?

• What is the impact of early parent/caretaker interactions with their children on later health and other outcomes?
Child Cognition and Neurodevelopment

Pre-pregnancy Factors

- Prenatal Health
- Substance-use
- Trauma
- Perceived Stress
- Protective Factors

Social and Environmental Determinants

- Early Life Stress
- Environmental Exposures
- Poverty
- Discrimination
- Access to Resources

Biological Factors

- Physical Health
- Genetics
- Nutrition
- Epigenetics
- Microbiome

Parent/Child Factors

- Child-Caregiver Relationship
- Behavioral Regulation
- Mental Health
- Home Environment

Development
HEALthy Brain and Child Development Study

Timeline of Events

Remote assessments will take place at visits 5 (10-17 months), 7 (16-50 months), and 8 (36-60 months).
Protocols: Visit 1-2

Visit 1: Prenatal

- Maternal Health
  - APA DSM-5 Level 1
  - APA PROMIS Level 2
  - DSM-5 Severity Acute Stress
  - DSM-5 Severity PTSD
  - Edinburgh Postnatal Depression Scale (EPDS)
  - Family History Assessment Module (FHAM)
  - Health History

- Substance Use
  - Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)
  - Timeline Followback (TLFB)

- Culture & Environment
  - BFY Services/Support
  - BFY Economic Stress
  - Demographics
  - Intimate Partner Violence (E-HITS)
  - PROMIS Social Support
  - PROMIS Perceived Stress
  - Protective and Compensatory Experiences (PACES)
  - PhenX Discrimination
  - PhenX Neighborhood Safety
  - Work-related Environmental Exposures

- Biospecimens
  - Maternal Blood
  - Maternal Nails
  - Maternal Saliva
  - Maternal Urine

Visit 2: 0-1 Month

- Adult Health
  - APA DSM-5 Level 1
  - APA PROMIS Level 2
  - DSM-5 Severity Acute Stress
  - DSM-5 Severity PTSD
  - Edinburgh Postnatal Depression Scale (EPDS)
  - Health History

- Culture & Environment
  - PROMIS Social Support
  - PROMIS Perceived Stress

- Child Health
  - Head Circumference
  - Health History
  - Height
  - Weight

- Biospecimens
  - Child Saliva
  - Child Stool
  - Child Urine
  - Maternal Nails
  - Maternal Saliva

- Substance Use
  - Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)
  - Timeline Followback (TLFB)

- Nutrition
  - 2-Item Food Insecurity Screen
  - PhenX Breastfeeding Questionnaire

- Mobile Technology
  - Activity Surveys
  - Heart Rate Sensors
  - Movement Sensors

- Brain Imaging
  - Diffusion MRI
  - Functional MRI
  - MR Spectroscopy
  - Quantitative MRI
  - Structural MRI (T1/T2)
Protocols: Visit 3

Visit 3: 3-9 Months

**Adult Health**
- APA DSM-5 Level 1
- APA PROMIS Level 2
- DSM-5 Severity Acute Stress
- DSM-5 Severity PTSD
- Edinburgh Postnatal Depression Scale (EPDS)

**Culture & Environment**
- PROMIS Social Support
- PROMIS Perceived Stress

**Child Health**
- Head Circumference
- Height
- Weight

**Biospecimens**
- Child Saliva
- Child Stool
- Child Urine
- Maternal Saliva

**Substance Use**
- Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)

**Brain Imaging**
- Diffusion MRI
- Functional MRI
- MR Spectroscopy
- Quantitative MRI
- Structural MRI (T1/T2)

**Brain Activity (EEG)**
- Auditory Oddball Task
- Human Faces Task
- Video Resting State
- Visual Evoked Potential Task

**Nutrition**
- 2-Item Food Insecurity Screen
- PhenX Breastfeeding Questionnaire

**Behavior and Caregiver-Child Interactions**
- Early Regulation in Context Assessment (ERICA)
- oPROMIS - Caregiver-Child Interactions
- Family Culture Matters (FCM)
- Infant Behavior Questionnaire-Revised (IBQ-R)
- Multidimensional Assessment Profile Temper Loss Scale (MAP-DB TL)

**Mobile Technology**
- Activity Surveys
- Heart Rate Sensors
- Movement Sensors

**Neurocognition**
- NIH Baby Toolbox
  - Cognitive & Executive Function
  - Language
  - Memory
- Sensory Processing Measure 2 (SPM-2)
HBCD Enrollment and Timelines

Prenatal Enrollment Across 27 Sites (N=1313)

Race and Ethnicity

Prenatal Substance Use Criteria

Opioids: ≥Weekly for ≥2 weeks
Tobacco/Nicotine: ≥Weekly for ≥4 weeks
Marijuana/Cannabis: ≥Weekly for ≥4 weeks
Alcohol: ≥7 standard drinks/week for ≥2 weeks; or ≥3 standard drinks/occasion on ≥2 occasions

Prenatal Substance Use

(335/1313 = 25.5%)
Neuroimaging Modalities – MRI & EEG

MRI Scans:
- Structural Scans (T1 and T2)
- Diffusion MRI
- Quantitative MRI
- Functional MRI
- Spectroscopy

Default System at Birth
First HBCD Infant (Visit 2)
Neuroimaging Modalities – MRI & EEG

MRI Scans:
- Structural Scans (T1 and T2)
- Diffusion MRI
- Quantitative MRI
- Functional MRI
- Spectroscopy

EEG Domains:
- Resting State/ Baseline
- Response to Faces
- Visual Evoked Potentials
- Auditory Oddball/ MMN

[Images of MRI scans (T1, T2, dMRI) and EEG equipment]
Substance Use Measures

• Substance use is assessed before, during and after pregnancy
• Captured through self-report (Assist and Timeline Follow Back) and analysis of biospecimens
• Thresholds are used for enrollment targets for opioids, alcohol, nicotine and cannabis
# HBCD Biosampling by Visit

<table>
<thead>
<tr>
<th>Sample</th>
<th>Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Prenatal</td>
</tr>
<tr>
<td><strong>Maternal Samples</strong></td>
<td></td>
</tr>
<tr>
<td>Nails (Toenails ~120 mg)</td>
<td>✓</td>
</tr>
<tr>
<td>Blood (Serum, Plasma, Whole Blood)</td>
<td>✓</td>
</tr>
<tr>
<td>Urine (~50 ml)</td>
<td>✓</td>
</tr>
<tr>
<td>Saliva (1 collection)</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Child Samples</strong></td>
<td></td>
</tr>
<tr>
<td>Urine (~5 ml)</td>
<td>✓</td>
</tr>
<tr>
<td>Stool (2 devices)</td>
<td>✓</td>
</tr>
<tr>
<td>Saliva (1 collection)</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Adapted from the HBCD Biospecimens Collection SOP*
**Visit 1 % Positive# Urinalysis (N~753)**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Number of Positive# Specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>8</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>1</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>69</td>
</tr>
<tr>
<td>Nicotine</td>
<td>86</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>10</td>
</tr>
<tr>
<td>Cocaine</td>
<td>3</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>10</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>8</td>
</tr>
<tr>
<td>Methadone</td>
<td>11</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1</td>
</tr>
<tr>
<td>Other Opioids</td>
<td>6</td>
</tr>
</tbody>
</table>

Detection Window: ~2-4 days

- Alcohol: 1.1%
- Benzodiazepines: 0.1%
- Barbiturates: 0.1%
- Cannabinoids: 9.2%
- Nicotine: 11.4%
- Amphetamine: 1.3%
- Cocaine: 0.4%
- Buprenorphine: 1.3%
- Fentanyl: 1.1%
- Methadone: 1.5%
- Oxycodone: 0.1%
- Other Opioids: 0.8%

**Visit 1 Dried Blood Spot Cards (N=982)**

- Detection Window: ~2-4 weeks
- Ethanol Test
- Number of Positive Specimens: 806 (82%)
- PETH NEGATIVE: 176 (18%)

#Positive counts reflect participants with a positive result on initial plus one (or more) confirmatory tests. Select subset of positive specimen tests shown.

*Results are preliminary as of 05/01/2024; subject to change.*
Oversight of the HBCD Study: Results-Based Accountability (RBA) Approach

Brenda Jones Harden, Ph.D.
Associate Director for Recruitment & Retention
MPI, U of Maryland site

Terry Jernigan, Ph.D.
Co-Chair, RBA and metrics monitoring
Co-I, HBCD Coordinating Administrative Center

Keri Althoff, Ph.D.
Co-chair, metrics monitoring
Co-I, Johns Hopkins U site

NIH NOA Expectations
HBCD’s Results-Based Accountability (RBA) Approach

NIH NOA Expectations
HBCD Leadership Structure

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

Council of Investigators
Composition: ● ● ● ● ● ● 27 Research Site PIs

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

NIH Institutes
- Project Director
- Program Official
- NIH Science Officials
- Federal Collaborators

External Scientific Board
Makes Recommendations

National Liaison Board
Makes Recommendations

OSMB: Observational Study Monitoring Board

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

27 Recruitment Sites
HCAC
HDCC
Working Groups & Committees
% approximately stable from last month

HBCD Main Study External Validity

- **Highest Education**
  - High school or equivalent graduate or lower
  - Some college or associate's degree
  - Bachelor's degree
  - Graduate or professional degree
  - Unknown

- **Ethnicity**
  - Hispanic or Latino
  - Non-Hispanic or Latino
  - Unknown

- **Income**
  - <10k
  - 10k-75k
  - 75k-100k
  - 100k-200k
  - >200k
  - Unknown

- **Race**
  - White
  - Black/African
  - American Indian and Alaska Native
  - Asian
  - Native Hawaiian and Other Pacific Islander
  - Other
  - Two or more races
  - Unknown

- **Target**
- **Over Target**
- **Under Target**
HBCD Visit Status

- Pending: 53%
- Missed: 5%
- Completed: 41%
- Uncategorized: 7%
HBCD Study Biospecimens in Storage*

Per Participant:

Blood Aliquots
- Buffy coat: 1
- Plasma: 11
- Serum: 10
- Whole Blood: 12

Urine Aliquots
- Birth Parent: 11
- Child: 3

*Specimens in Storage as of 05/01/2024.
Oversight of the HBCD Study: Results-Based Accountability (RBA) Approach

NIH NOA Expectations
Current Study Design

Large Visit Window
- 3 years
- Design constrained by budget cuts
BENEFITS of additional in-person visit

• Refined individual neurodevelopmental trajectories
• Inclusion of instruments validated at 30+ months
• Separation between MRI scans collected while asleep (<30 months) to those collected while awake (+30 months)
• Maintain regular contact and engagement with participants
Neurodevelopmental Trajectories

Ouyang et al., 2019 *NeuroImage*
Trajectory Simulations from Biostats WG

- Simulated data from the current and proposed HBCD visit designs.
- Realistic simulation settings were obtained from the Baby Connectome Project nucleus accumbens volume trajectories.
- Both designs can obtain good estimates of mean trajectories.
- The addition of a visit in the 15–29-month range better captures individual variation in trajectories in this age range.
### Wearable Sensor Data Collection

**During V2 and V3**
- For 72 hours, child wears two movement sensors on legs and an arm band sensor that detects heart rate, O\textsubscript{2} saturation and respiration rate
- Parents fill in daily reports of infant behavior during this 72-hour period.

**Variables we can derive from sensors and their value as indices of health**
- Sleep/wake cycles and sleep state
- Amount and intensity of physical activity
- Patterns of movements across days
- Patterns of Autonomic Nervous System Functioning
Axivity AX6 sensors

- Measure 3 axes of accelerometer data and 3 axes of gyroscope data at 20 samples per second
- Accelerometer = acceleration = rate of change of velocity
  - 0 acceleration = not moving or moving at constant velocity
- Gyroscope = angular velocity = rate of rotation

### Calculated Data

<table>
<thead>
<tr>
<th>Total movements counted</th>
<th>Movement per hour awake (movement/hour)</th>
<th>Estimated sleep time (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of movement (seconds)</td>
<td>Average acceleration per movement (m/s²)</td>
<td>Peak acceleration per movement (m/s²)</td>
</tr>
</tbody>
</table>
Arm Band Sensor Data Analysis

- Arm band data can be used to calculate sleep staging based on pulse rate and respiration rate.

- Measures 3 signals:
  - Pulse Rate
  - Respiratory Rate
  - Blood Oxygen Saturation

Hypnogram of Infant Sleep Showing Typical Sleep Cycles Through The Night