A multi-modal MRI approach to studying air pollution exposure and adolescent neurodevelopment

Presented By:
Megan M. Herting, PhD
Assistant Professor
Department of Preventive Medicine

HEI Brain Health and Air Pollution Symposium
Date: May 13, 2020
Neurotoxicant effects on child behavior

- Developmental delays
- Risk for Autism
- Lower IQ
- Greater behavioral problems

Remaining questions:
- Source(s) and exposure(s) characteristics
- Confounders/covariates
- Heterogeneity of effects (sex, socio-economic, etc.)
- Brain Mechanism(s)
- Which periods of exposure are most important?
- Are the effects long-lasting?
Timing: Prenatal vs. Postnatal?

Prenatal particulate air pollution exposure and body composition in urban preschool children: Examining sensitive windows and sex-specific associations

Yueh-Hsiu Mathilda Chiu a, b, Hsiao-Hsien Leon Hsu b, Ander Wilson c, Brent A. Coull d, e, Mathew P. Pendo f, Andrea Baccarelli f, Itai Kloog g, Joel Schwartz g, Robert O. Wright h, i, Elsie M. Taveras h, i, Rosalind J. Wright h, i, and Megan Herting g, i

N=267; 5 years

Multilevel Analysis of Air Pollution and Early Childhood Neurobehavioral Development

Ching-Chun Lin a, Shih-Kuan Yang b, Kuan-Chia Lin c, Wen-Chao Ho d, Wu-Shian Hsieh e, Bih-Ching Shu f and Pau-Chung Chen g, i, h

N=533; 18 months

Prenatal and postnatal exposure to air pollution and emotional and aggressive symptoms in children from 8 European birth cohorts

Ainhoa Jorcano a, b, c, Małgorzata J. Lubczyńska a, b, c, Livia Pierotti a, b, c, Hicran Altug d, Ferran Ballester e, f, g, Giulia Cesaroni h, Hanan El Marroun h, i, Ana Fernández-Somoano b, i, Carmen Freire c, m, Wojciech Hanke n, Gerard Hoek o, Jesús Ibarluzea s, h, k, m, Carmen Ilhíquez s, f, Pauline W. Jansen h, j, Johanna Lepeule j, Iana Markevych s, n, m, Kinga Polańska n, Daniela Porta a, … Mónica Guxens a, b, c, h, i, n

N=13,182; 7-11 years
Neurodevelopment: A prolonged sensitive period

Sawyer et al., *Lancet*, 2018

- Young adults
- Youth
- Expanded definition of adolescence
- Current definition of adolescence
- Older adolescents
- Teenagers
- Younger (or early) adolescents
- Children
- School-aged children

Age (years)

4 12 20 28 Birth

- Neurulation
- Neuronal Proliferation
- Neural migration
- Myelination
- Synaptogenesis
- Apoptosis
- Pruning of synapses

Keck Medicine of USC
Child and adolescent development: a period of opportunity & vulnerability

- Growth
- Pubertal maturation
- Hormone changes

Physical

- Physical Activity
- Drugs & alcohol
- Autonomy of mobility

Lifestyle

- Planning/goal setting
- Decision-making
- Executive Functioning

Cognitive

- Importance of peers
- Self-identity
- Intimate relationships

Social

- Physical Activity
- Drugs & alcohol
- Autonomy of mobility

- Planning/goal setting
- Decision-making
- Executive Functioning

- Importance of peers
- Self-identity
- Intimate relationships
Child and adolescent development: a period of opportunity & vulnerability

- Heightened risk taking paired with a mis-match in timing of maturation of emotion, reward, and regulation systems
- 50% of all lifetime mental illness begins by age 14
- 75% of all lifetime mental illness by age 24

Lee et al., *Science*, 2014
Interconnections & efficiency of neural systems occur in a systematic fashion

**Early childhood:** sensory and motor regions involved in speaking, listening, and perceived emotions

**Mid-to-Late childhood:** association brain regions to sensory integration and conceptual frameworks of social, emotion, and cognitive concepts

**Early-to-Mid adolescence:** emotional & reward processes, sensitivity to social identity

**Late adolescence to adulthood:** improved emotional regulation, long-term planning, and abstract thinking

Gogtay et al., PNAS, 2004
Does air pollution exposure impact brain structure and function in humans?

Megan Hering, PhD
## Outdoor Air Pollution-MRI Studies

<table>
<thead>
<tr>
<th>MRI Technique</th>
<th>Structural MRI (sMRI)</th>
<th>Diffusion MRI (dMRI)</th>
<th>Functional MRI (fMRI)</th>
<th>Arterial Spin Labeling (ASL)</th>
<th>Spectroscopy (MRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tissue composition</td>
<td>water diffusion</td>
<td>blood-oxygen-level-dependent (BOLD) signal</td>
<td>tissue perfusion</td>
<td>proton frequencies</td>
</tr>
<tr>
<td></td>
<td>pial surface</td>
<td>diffusion modeling (e.g. DTI, ball &amp; stick, NODDI)</td>
<td>tractography</td>
<td>stimulus/Event</td>
<td>metabolic frequencies</td>
</tr>
<tr>
<td></td>
<td>white matter surface</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>surface area; cortical thickness; density (VBM)</td>
<td></td>
<td>timecourse correlations</td>
<td>signal change between task conditions</td>
<td>cerebral blood flow</td>
</tr>
</tbody>
</table>

### Measures
- volume
- surface area
- cortical thickness
- density (VBM)
- water restriction/orientation (e.g. FA, ICVF)
- white matter fiber bundles
- timecourse correlations
- signal change between task conditions
- cerebral blood flow
- metabolites

### Functionality
- gray or white matter size & shape
- white matter microstructure
- structural connectivity between regions
- functional connectivity of brain regions
- brain function
- brain blood flow
- brain metabolites

### Biomarkers

- Peterson 2015
- Pujol 2016a
- Pujol 2016b
- Pujol 2016b
- Malgorzata 2020
- Pujol 2016a
- Pujol 2016b
- ?
- Brunst 2019

Herting et al., *Frontiers in Public Health*, 2019
### Outdoor Air Pollution and MRI studies

<table>
<thead>
<tr>
<th>Columbia Center’s Birth Cohort</th>
<th>BREATHE Cohort</th>
<th>Generation R Cohort</th>
<th>CCAAPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• New York Boroughs</td>
<td>• Barcelona, Spain</td>
<td>• Rotterdam, The Netherlands</td>
<td>• Cincinnati, OH</td>
</tr>
<tr>
<td>• 40 children</td>
<td>• 263 children</td>
<td>• 2,900 children</td>
<td>• 135 children</td>
</tr>
<tr>
<td>• PAHs</td>
<td>• School/home, traffic-related, Cu</td>
<td>• NO2, PM$<em>{2.5}$, PM$</em>{10}$, and PM Components</td>
<td>• Elemental carbon attributable to traffic (ECAT)</td>
</tr>
</tbody>
</table>

- Generalizability and reproducibility
- Sources and lifetime of exposure(s)
- Identifying susceptibility risk factors
Covariates, Confounders, Mediators, Moderators

- Community factors
- Genetics
- Parental/family factors

PM2.5

- prenatal/early-life ambient PM$_{2.5}$
- prenatal/early-life residential location
- residential locations during adolescence
- adolescent lifestyle (e.g. physical activity, alcohol/drug use)
- spatial covariates (e.g. noise, greenspace)
- other neurotoxins (e.g. second-hand smoke)
- other determinants of neuromaturation (e.g. gestational age, BMI, asthma)

- parental & individual SES (e.g. income, education)
- socio-demographics (e.g. sex, race/ethnicity)
- neighborhood context during adolescence

Brain
Timing Effects

Exposure

Brain Scan

Generation R Study

Columbia

CCAAPS

BREATHE

Maturation of neural circuits

<5 yrs  Childhood/Adolescence  Young Adulthood

Sensory systems

Prefrontal and temporal cortices

Synapse refinement & white matter maturation

Neurulation

Neuronal Proliferation

Neural migration

Myelination

Synaptogenesis

Pruning of synapses

Apoptosis

Keck Medicine of USC
Adolescent Brain Cognitive Development Study®

- Largest long-term study of brain development and child health in the U.S.
- 11,873 children ages 9-10 years from 21 research sites across the country
- Annual cognitive and behavioral assessments; brain MRI every 2 years for 10 years

https://abcdstudy.org/
Ambient PM$_{2.5}$ Exposure and Brain Structure at 9-10 years

Cerbik et al., *Under-review*
The Future: Longitudinal MRI Timing Effects

- Child and adolescent windows of vulnerability?
- Neural system and sex-specific effects?
- Long-term effects?
- May help to identify early brain MRI biomarkers of future behavioral problems

Haller et al., DCN, 2018

Keck Medicine of USC
Adolescent Air Pollution Exposure Behavior Studies Suggest Long-term Effects

Wang et al., *PLOS One*, 2017

Roberts et al., *Psychiatry Res.*, 2019

<table>
<thead>
<tr>
<th>Models</th>
<th>PM$_{2.5}$ 1-year prior to baseline</th>
<th>PM$_{2.5}$ 2-years prior to baseline</th>
<th>PM$_{2.5}$ 3-years prior to baseline</th>
<th>PM$_{2.5}$ average over follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base$^b$</td>
<td>β (95% CI)</td>
<td>β (95% CI)</td>
<td>β (95% CI)</td>
<td>β (95% CI)</td>
</tr>
<tr>
<td></td>
<td>0.36* (0.12, 0.60)</td>
<td>0.32* (0.08, 0.56)</td>
<td>0.33* (0.08, 0.58)</td>
<td>0.30* (0.09, 0.52)</td>
</tr>
<tr>
<td>Fully Adjusted$^d$</td>
<td>0.32* (0.06, 0.59)</td>
<td>0.28* (0.02, 0.54)</td>
<td>0.28* (0.01, 0.56)</td>
<td>0.26* (0.02, 0.51)</td>
</tr>
</tbody>
</table>

Harness the power of multi-modal MRI to understand air pollution on neurodevelopment

Mayer et al. Gut, 2019
Potential Moving Forward

**Current**

- Single pollutants
- Prenatal vs. childhood exposure
- Single MRI modalities
- Regional univariate brain analyses

**Future**

- Individual components; sources; multi-pollutant models
- Timing specific and cumulative effects of exposure
- Multivariate analyses to examine large-scaled systems
- Integrated modalities to examine networks
Summary

• Air pollution has been correlated with child and adolescent behavior, as well as multiple neuroimaging biomarkers of brain development

• The processes undergoing neuromaturation when the timing of exposure and the timing of brain assessment are likely important in uncovering how air pollution impacts the brain

• Identify who is at risk and identify lifestyle modifiers (e.g. social stress, physical activity, diet)

• Both new and integrated MRI methods can offer insight into brain health, with the potential to detect alterations prior to clinical onset
Herting Lab
Dora Cserbik, MS
Sandhya Prathap, MS
Claire Campbell, BS
Anisa Azad, MS
Kimberly Felix, BA
Miguel Jaime
Robert Kim, BS

ABCD-E
Rob McConnell, MD
JC Chen, MD
Joel Schwartz, PhD
Wes Thompson, PhD
Elizabeth Sowell, PhD
Daniel Hackman, PhD

Funding
HEI Rosenblith – PI: Herting
NIH P30ES007048-23S1
NIH K01MH108761 – PI: Herting
NIH R03HD090308 – PI: Herting
Rose Hill Foundation – PI: Herting
U01 DA041048 – MPI: Sowell/Herting
UH3 OD023287 – MPI: Gilliland/Breton