Can Brain-imaging Predict Consequences of Early-life Childhood Adversity?

Pilot Study in Mirpur District, Dhaka, Bangladesh

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<table>
<thead>
<tr>
<th>Dynamic interactions of genetic, biological, and psychosocial influences and child behavior</th>
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</thead>
<tbody>
<tr>
<td>Exposure to biological and psychosocial risks leads to deficits in brain structure and function, and impaired cognitive and social emotional development</td>
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<tr>
<td>Disparities increase with early, multiple, and cumulative risks</td>
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</tbody>
</table>
Biological risks

Key biological risks identified earlier:
- Chronic undernutrition
- Iron deficiency
- Iodine deficiency

Three additional biological risks:
- Intra-uterine growth restriction
- Severe and/or repeated attacks of malaria
- HIV infection

Lancet Series 2007 & 2011
Psychosocial risks

Major risks for poor development:
- Lack of learning opportunities
- Poor quality of caregiver-child interaction

Additional psychosocial risks:
- Maternal depression
- Exposure to societal violence
- Institutional rearing

Lancet Series 2007 & 2011
Exposure to biological risks leads to exposure to psychosocial risks.

Early childhood adversity

Early environment disrupts normal biology:

- Psychosocial stressors (e.g. child abuse, caregiver insensitivity, domestic violence exposure)
- Depriving environments (e.g. low quality institutional care)
- Malnutrition, undernutrition
  - Toxin exposure
  - Environmental enteropathy, other infectious diseases

Sensitive period effects: Adversity impacts key domains most when concurring with periods of rapid development

Genetic endowment
Genetic variants alter susceptibility to specific adversities ("gene x environment interactions")

Developmental trajectory
- Early setbacks may compound social disadvantage
- Biological change embedded in behavior

Biological change

Epigenetic changes
(e.g. DNA & histone modification causing altered gene expression; telomere shortening)

Altered homeostatic systems
(e.g. derangements in metabolic, immune, and stress regulatory axes)

Neurodevelopmental disruption
(e.g. due to aberrant or absent stimulation; disturbed hormonal or inflammatory environments)

Excess inflammation
(e.g. due to stress response dysregulation after early abuse, or altered gut wall in environmental enteropathy)

Increased risk of:
- Cognitive deficits (e.g. lower IQ, poorer short-term memory)
- Disease

Credit: Anne E. Berens, 2016
Relationship between risk factors in early childhood in Guatemalan children and achievement scores in adolescence (Figure adapted from K. Gorman & E. Pollitt. *Child Dev* 1996;67:314-326.)
Life course impact

Early exposure to risks sets children on a lower developmental path

Long-term effects on schooling and income contribute to continued inequalities in the next generation
Preschool enrolment by region and income – less than 20% for poorer income quintiles

Proportion of young children attending preschool in 58 low-income and middle-income countries by income quintile within country summed across sample countries by region. Data are from UNICEF’s 2005 Multiple Indicator Cluster Survey 3 for children aged 3 and 4 years.
Increasing preschool enrolment benefits attained schooling

Benefit-to-cost ratio from 6.4 to 17.6, depending on what percent of preschool children enrolled in each LAMI country (25% - 50%)

Estimated increase in future earnings was calculated to be US $11 - 34 billion

Inequalities can be reduced with intervention in the early years
Development of inequality

Chart Source: Lancet Series 2011
Protective influences

New evidence identifies protective influences which promote child development

- Responsive caregiver-child interaction
- Opportunities for young children to play and learn
- Breast feeding
- Maternal education

Interventions can effectively reduce developmental delays

Particularly if interventions are

- Early
- Of high quality
- Integrated
Returns to investment in children

Chart source: Heckman & Masterov, 2007
Different domains of development are associated with different critical periods.

Goals of Current Study

- **To recap**: children growing up in profound adversity are at risk for compromised developmental outcomes, mediated, in part, by errors in brain development.

- **Question**: can sophisticated neuroimaging tools be used to detect differences in brain development that vary as a function of early adversity?
Target country: Bangladesh

- **Proximal Goal**: study different cohorts of children in Dhaka, all part of two existing cohorts of children being studied by William Petri, MD, Ph.D. (University of Virginia);

- **Distal Goal**: move the operation to Matlab, Bangladesh, which would represent a rural site and demonstrate feasibility of using such tools in more remote areas of the world.
Dhaka is a city of ~18-20 million people.

Mirpur is a slum of ~1 million people concentrated in a very small area, characterized by:
- Profound poverty
- Open sewers/contaminated drinking water (e.g., arsenic, bacteria)
- Chronic enteric disease/malnutrition
- Open (coal or wood-burning) fires
- High levels of air pollution
- High levels of domestic violence
- Low levels of education (avg=~grade 2 education)
- High levels of maternal depression (~20-30%)
- Increasing levels of violence (e.g., ISIS)

Thus, children growing up in Mirpur exposed to very high levels of environmental and psychosocial adversity.
Our current study populations

- PROVIDE cohort
  - 36 mo, 140 kids
  - Mirpur
- NIH birth cohort
  - 6 mo, 100 infants
  - Mirpur
- MRI cohort
  - 2-3 mo, 20 infants
  - Mirpur
- Rural cohort
  - 6 mo, 100 infants

The Collaborators
- William Petri, MD, Ph.D., Chair of the Division of Infectious Disease, University of Virginia
- Charles A. Nelson III, PhD., Professor of Pediatrics and Neuroscience, Harvard Medical School; Professor of Education, Harvard University
- International Center for Diarrheal Disease Research, Bangladesh (icddr,b)
Neighborhood children
Study timeline

Visit 1 (Nov 2014)
- Initial site visit
- Observed clinic location, assessed power/outlet needs, sniffed for electrical noise, had initial staff meetings

Boston visit (Feb 2015)
- 3 week intense training visit at BCH on EEG/NIRS systems, MRI data collection and session observation/pilot testing

Visit 2 (March 2015)
- Installation of all equipment
- Intense on the ground training for all local staff on imaging measures/running sessions/consenting/data management/troubleshooting

Visit 3 (May 2015)
- MRI data collection training (scans with no anesthesia/sedation)
- Continued neuroimaging pilot testing/training
Data Base

- All physical growth and metabolomics-related parameters collected by Dr. Petri
- Biological samples (blood, saliva, urine, fecal)
- Cognitive measures
  - Using Mullen Scale, executive functions, behavioral assessments
- Measures of adversity
  - Questionnaires, etc.
- Neuroimaging tools:
  - EEG, ERP
  - fNIRS
  - sMRI
Session NIRS

- Resting state
- ‘Peekaboo’ paradigm
  - Tests brain connectivity and social cognition

Credit: Prof Charles A. Nelson 2016
fNIRS: Using light to see the brain
Paradigm:
Social vs. Non-social stimulus

vs.
36 month old fNIRS sessions
6 months

All Participants: (n=24)

Maternal Education 6 or more years: (n=12)

Maternal Education 5 or fewer years: (n=12)

Credit: Prof Charles A. Nelson  2016
CRP high: (n=15)

CRP low: (n=18)

All Participants: (n=36)

36 months

Visual Social > Non-social
Visual Non-social > Social

Credit: Prof Charles A. Nelson 2016
Ever stunted: (n=16)

Never Stunted: (n=20)

All Participants: (n=36)

36 months

Credit: Prof Charles A. Nelson 2016
Session : EEG

- Baseline EEG
- Visual evoked potential (VEP)
- Event related potential (ERP)
6 and 36 month old EEG sessions
EYE TRACKING TASK
(visual disengagement)

- Gap/overlap task
EEG Preliminary Findings

- The EEG represent the summated electrical activity of large populations of neurons
- This activity volume conducts to the scalp surface, where it can be picked up by small sensors
Stunted vs. non-stunted (6-months)

Maternal education (6-months)

A brief glimpse of the data

Credit: Prof Charles A. Nelson 2016
Functional Connectivity: 36 months Old

CRP low, n=18

CRP high, n=11

Credit: Prof Charles A. Nelson 2016
Low Maternal Education <5 yr; n=18

“high” Maternal Education >6 yr; n=11

Functional Connectivity: 36 months Old

Credit: Prof Charles A. Nelson 2016
ERP conclusions

- We find similar waveforms and components in Bangladeshi children as we would expect to find in populations in middle-high income nations.
- Preliminary data shows potential effects of maternal indicators, stunting, biomarkers on a number of ERP components.
Magnetic Resonance Imaging
Preliminary Findings
MRI

- Scans conducted at NINS
- No anesthesia/sedation
- Children scanned during natural sleep
Structural MRI

- N= 9 (1 dataset is too noisy), n=8, 4 boys and 4 girls were studied in the present study
- Mean age: 2.5 ± 0.2 months
- Structural MRI data were segmented into different tissue types including gray matter, white matter and cerebrospinal fluid using Statistical Parametric Mapping (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/)
Coronal  Axial  Sagittal

Gray matter  White matter  Cerebrospinal Fluid

Global Brain Volumes

3D Rendering of the cortex

Credit: Prof Charles A. Nelson 2016
Resting state functional MRI (fMRI) data were studied in 7 infants (n=7, 2 boys, 5 girls).

Mean age: 2.4 ± 0.1 months

FMRI data were pre-processed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/)

Group ICA of fMRI Toolbox (GIFT, http://mialab.mrn.org/software/gift/index.htm) was used to generate visual network.
Never stunted growth group: n=4

Stunted growth growth group: n=3

Credit: Prof Charles A. Nelson 2016
Visual Network Strength

- Stunted growth (n=3, mean age: 2.63 months, 1 boy, 2 girls)
- Never stunted (n=4, mean age: 2.39 months, 1 boy, 3 girls)
n=5 infants (2 boys, 3 girls) were studied.

Diffusion weighted imaging (DWI) were analyzed using mrDiffusion toolbox (http://www.vistalab.com)

Fractional anisotropy (FA) as a normalized scalar measure of the degree of diffusion anisotropy, attributed to myelination or axonal properties

Automatic Fiber Quantification (AFQ) technique was used to compute FA profile for different white matter tracts.
Whole Brain Tractography

Stunted growth representative infant

Never stunted growth representative infant

Credit: Prof Charles A. Nelson 2016
Characteristics of Left Arcuate Fasciculus (fractional anisotropy (FA))

- Stunted growth (n=2, mean age: 2.63 months, 1 boy, 1 girl)
- Never stunted (n=2, mean age: 2.37 months, 2 girls)

Frontal lobe Temporal lobe

Credit: Prof Charles A. Nelson 2016
Characteristics of Left Arcuate Fasciculus

Mother’s education level positively correlated with fractional anisotropy value of the temporo-parietal segment of the left arcuate fasciculus.

Scatter Plot

$r = 0.87 \ p = 0.13$

Credit: Prof Charles A. Nelson 2016
Summary

- Observe reductions in gray and white matter volume, resting state connectivity and integrity of white matter tracts as a function of nutrition history (stunted, not stunted).
Session: Mullen/EF

- Mullen Scales of Early Learning - measures development in five subdomains: gross motor, fine motor, expressive language, receptive language, visual reception

- Executive function tasks in 36-month olds
Psychosocial adversity correlates with infant development as measured by Mullen Scales

Mullen scores by childhood adversity exposure level (N=68)

<table>
<thead>
<tr>
<th>Mullen sub-score</th>
<th>Caregiving quality</th>
<th>Maternal education</th>
<th>Maternal depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High adversity (bottom quartile)</td>
<td>Low adversity (top quartile)</td>
<td>High adversity (no formal edu.)</td>
</tr>
<tr>
<td>Gross motor</td>
<td>27.71</td>
<td>29.13</td>
<td>0.060</td>
</tr>
<tr>
<td>Fine motor</td>
<td>30.00</td>
<td>30.38</td>
<td>0.532</td>
</tr>
<tr>
<td>Visual reception</td>
<td>30.71</td>
<td>33.44</td>
<td>0.016</td>
</tr>
<tr>
<td>Receptive language</td>
<td>28.59</td>
<td>30.25</td>
<td>0.033</td>
</tr>
<tr>
<td>Expressive language</td>
<td>27.47</td>
<td>28.31</td>
<td>0.498</td>
</tr>
</tbody>
</table>


Household income was assessed but was not significantly correlated with Mullen scores.
## Existing measures support rudimentary models of aggregate psychosocial adversity

### Mullen scores by aggregate childhood adversity exposure level (N=68)

<table>
<thead>
<tr>
<th>Mullen sub-score</th>
<th>High aggregate adversity</th>
<th>Low aggregate adversity</th>
<th>Effect size (standard deviations)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gross motor</strong></td>
<td>28.16</td>
<td>28.53</td>
<td>0.19</td>
<td>0.606</td>
</tr>
<tr>
<td><strong>Fine motor</strong></td>
<td>30.00</td>
<td>30.63</td>
<td>0.29</td>
<td>0.282</td>
</tr>
<tr>
<td><strong>Visual reception</strong></td>
<td>30.21</td>
<td>33.26</td>
<td>0.90</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td><strong>Receptive language</strong></td>
<td>28.33</td>
<td>30.26</td>
<td>0.89</td>
<td><strong>0.010</strong></td>
</tr>
<tr>
<td><strong>Expressive language</strong></td>
<td>25.11</td>
<td>30.53</td>
<td>1.10</td>
<td><strong>0.006</strong></td>
</tr>
</tbody>
</table>

- **High aggregate adversity** defined here as exposure to 2 or more of the following: (a) maternal depression score above median, (b) caregiving quality score in bottom quartile, (c) no formal maternal education
- **Low aggregate adversity** defined as exposure to 0 of the above.

The Future

- Replicate current 36 month findings with another cohort living in another part of Dhaka (Nestle Foundation)
- Add comparison sample of middle class children living in Mirpur
- Move to a rural field site in southern Bangladesh (Matlab)

...begin to ponder what an intervention would look like
Conclusion

- Study findings indicate promising possibility of neuroimaging in predicting early delays for early intervention, as early as 6 months ages.
- Data comparison with western norms show requirement of minimum cultural adaptations.
- Findings also specify the parts of brain that is more affected due to particular adversity. Which in turn will help in developing specific intervention.
- In this study we will also give us opportunity to compare neuro-imaging with developmental outcomes, assessed by direct behavioral assessments.
THE END
THANK YOU