Studying Stress, Neurobiology and Development Genetics and epigenetics

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“..to clarify the concepts of risk, vulnerability and resilience, I have used the analogy of three dolls made of glass, plastic and steal and exposed to the same risk- the blow of a hammer. The first doll breaks down completely, the second shows a dent that it carriers permanently, and the third doll gives out a fine metallic sound. Of course the outcome for the three dolls would be different if their environments were different…..”
Gene x Environment

- Defining the “E”
- Defining the “G”
  - Single genes
  - Single SNPs
  - GWAS, rare variants
  - Cumulative genetic impact
Environment

- Life events
- History of abuse
- History of neglect
- Cumulative exposure
- Additional factors
  - Community
  - School
  - Household stress
  - Caregiving
Levels of evidence for G x E

- Cellular and molecular level studies
  - Does polymorphism result in changes in expression/function consistent with phenotypic associations?
- Animal models- knock outs, genetically engineered
  - Does animal phenotype reflect human associations?
- Observation of associations within specific populations
  - Replication across studies
    - Sample size, power and meta-analysis
- Neuroscience and biological phenotypes
  - Does polymorphism have influence on underlying neural substrates?
Developmental Issues

- Changes in gene expression over development
  - [http://www.brainspan.org/rnaseq/search?type=user_selections](http://www.brainspan.org/rnaseq/search?type=user_selections)

- Changes in environment influence over time
Genes linked to early adversity/care

* 5HTT
* CRHR1
* GR

* BDNF
* MAOA
* GABA

* AVP
* Oxytocin

* DAT
* DRD2
* DRD4
* COMT
Gene $\rightarrow$ Outcome

Gene x Environment $\rightarrow$ Outcome

Gene x Environment $\rightarrow$ Stress reactivity $\rightarrow$ Outcome

Gene x Environment

- Differential Susceptibility
- Biological Sensitivity to Context
- Mismatch Hypothesis
- Adaptive Calibration Model
Diathesis-Stress vs. Differential Susceptibility
Bakermans-Kranenburg & Van IJzendoorn, 2006

Positive

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<tr>
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<td>Positive</td>
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- low susceptibility
- no risk
- high susceptibility
- risk

environment
Plasticity genes

- 5httlpr
- MAOA
- DAT
- DRD4
- DRD2
- BDNF
Parental Depression and Negative Emotionality in 3-Year Olds Moderated by BDNF

Hayden, E. P. et al. (in press). Psychological Science. 2010;0956797610385357
5HTTLPR

- 44 base pair repeat in the promoter region
  - Short allele decreased expression of 5HTT
  - L/L increased uptake of 5HT
- Evolutionary context
  - Only in humans and macaques
  - “weed primates”
BEYOND SINGLE GENES: CUMULATIVE GENETIC PLASTICITY....
THEORETICAL MODEL OF GENETIC-PLASTICITY GRADIENT
Bucharest Early Intervention Project
Intervention Effects on Indiscriminant Social Behavior Among Institutionalized Romanian Children
Moderated by Cumulative Genetic Plasticity: 5-HTTLPR and BDNF
(CAUG: Care as Usual Group; FCG: Foster Care Group)
Figure 1: Externalizing Symptoms by Genetic Plasticity Gradient
One more step...

*Gene x Environment- with stress reactivity
ANS and HPA
finding the tipping point

Asymmetric:
Reactivity in RSA no reactivity in cortisol
Reactivity in cortisol no RSA reactivity

Symmetric:
Reactivity in RSA
Reactivity in cortisol
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<th>B</th>
<th>SE</th>
<th>R² change</th>
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<td>6.40</td>
<td>2.51</td>
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Reactivity and genotype
Genetic plasticity and treatment outcome:
therapy genetics 101
CHILDREN’S RESPONSE TO CBT MODERATED BY 5HTTLPR
(i) Proportion of children free of (a) their primary anxiety disorder and (b) all anxiety disorders at follow-up by 5HTTLPR genotype.
(ii) Symptom severity of primary diagnosis at each time point, as a function of genotype.

PTSD treatment and genetic plasticity

- **Total Symptoms**
  - Group 0: 4
  - Group 1: 5
  - Group 2: 6

- **PTSD Symptoms Change**
  - Group 0: 1
  - Group 1: 4
  - Group 2: 6
Nobel prize in Medicine ‘09

Don’t cut it too short,
I don’t wanna look old

by Viktor S. Poor

Stripped Science
Telomeres

- Catalytic Subunit: TERT (telomerase reverse transcriptase)
- Intrinsic RNA component: TR (telomerase RNA)
- Telomerase-associated proteins

Extension of telomeric DNA by addition of hexanucleotide repeats
Telomere length and percent time

GIRLS: baseline

Boys: 54 months
<table>
<thead>
<tr>
<th>Neighborhood Adversity</th>
<th>Model A</th>
<th></th>
<th>Model B</th>
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<th>Model C</th>
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<td>Concentrated Disadvantage</td>
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<td>Percent Below Poverty</td>
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<tr>
<td>High perceived disorder</td>
<td>3.43 (1.22, 9.62)</td>
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<td>1.02 (1.01, 1.04)</td>
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<tr>
<td>Concentrated disadvantage</td>
<td>----</td>
<td>----</td>
<td>1.10 (0.95, 1.28)</td>
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<tr>
<td>Percent below poverty</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>1.02 (1.01, 1.04)</td>
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*Adjusted Odds Ratio (95% Confidence Interval)*

Table 3. Neighborhood Adversity’s Impact on Lower Telomere Length (N=52 tracts, N= 99 children)
Another layer: the Epigenome

* Evidence that early experience influences epigenome
  * Methylation
  * Histone acetylation
  * Chromatin structure
  * miRNA
  * Static vs labile effects
* **Interactive/additional layer of influence on gene expression**
Genes associated with altered epigenetic marks and psychiatric outcomes

- **AVP
- **ERα
- COMT
- BDNF
- RELN
- **GR
- **GAD1
- GABA-A
- PPIEL
- **POMC
- ** indicates associated with early experience
Challenges to epigenetic studies

- Tissue specificity
- Developmental issues
- Power/Sample size
- Methodological
Use of genetic/epigenetics

- Explain individual differences in outcome
- Explain individual differences in recovery to intervention
- Neurogenetics- using genetics to understand neurobiology
- Epigenetic factors as an additional level of individual variation
- Vulnerability and resilience may be a matter of context
- Combining biophysiology, genetics, neuroscience to advance personalized treatment and development of novel interventions
The “d’s” to think about

- Development
- Different tissues
- Different polymorphisms
- Different environmental/care giving buffers
- Different treatments