Towards the integration of genetics, epigenetics, and intervention

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I appreciate the research support from the Jacobs Foundation for epigenetic analyses and the National Institute of Mental Health (R01-MH67792) for sample recruitment, Collection, and diagnoses.
Prevention Science

• Overarching Objective: Intervening in the course of development to reduce the emergence of maladaptation or psychopathology.
• An additional benefit of prevention interventions is advancing understanding of normative development.

Understanding the processes that can right the course of development

Increasing understanding of the operation of risk of protective factors in normative development
Developmental Psychopathology and Prevention

• Facilitating the development, delivery and evaluation of theoretically-informed prevention and intervention initiatives
• Understanding how some at-risk individuals maintain positive adaptation
• Understanding contributors to the emergence of maladaptation and mental disorders
Multiple Levels of Analysis

Allows for a dynamic conceptualization that more accurately reflects the dynamic fashion in which multiple influences interact over time.
Randomized prevention trials using a multiple level of analysis perspective provides more insights into:

• Mechanisms of change
• Extent to which neural plasticity might be promoted
• Interrelations between biological and psychological processes in maladaptation, psychopathology, and resilience
Experience-Dependent Neural Plasticity

• If biological systems are routinely incorporated in resilience-facilitating intervention, then preventative intervention researchers will be in a position to ascertain whether the nervous system has been modified by experience.

The efficacy of any preventive intervention depends on the ability of the nervous system, at the cellular, metabolic, or anatomic level, to be modified by experience.
Biological Levels of Analysis

• Biological systems can be impacted by interventions

• Our understanding of genetic moderation of intervention efficacy is continually expanding
Biological Levels of Analysis...

• Biological vulnerabilities can give rise to broad classes of homotypic and heterotypic comorbidity

• Understanding common biological risks can lead to the generation of preventative interventions that address a spectrum of interrelated concerns
Biological Measures and Intervention Efficacy

• Cortisol (NR3C1 gene)
  • Cicchetti et al.; Dozier et al.; Gunnar, Fisher et al.,

• Salivary Alpha Amylase
  • Toth et al.

• Event Related Potentials (ERPs) are changes in the EEG signals in relation to specific events such as internal or external stimuli, events, or movement.
Gene-Environment Interaction
(initially one gene – one outcome)

The following two articles have a combined total of 11,400 citations


EFFECT OF MALTREATMENT IN CHILDHOOD ON LIABILITY TO DEPRESSION MODERATED BY 5-HTT GENE (from Caspi et al., 2003, Science)

- s/s = short allele homozygous
- s/l = long allele homozygous
- l/l = heterozygous

Probability of major depression episode

- No maltreatment
- Probable maltreatment
- Severe maltreatment
Critics


Rejoinders


Move to genetic moderation of intervention research


• Thibodeau, E. L., doctoral dissertation on impulsivity
What is Epigenetics?

- Epigenetic changes confer variations in phenotype by altering DNA without changing DNA sequence (i.e., genes)
- These changes interfere with gene transcription (gene silencing) or enabling gene transcription (gene “turned on”)
- Critical early in development
  - Responsible for cell differentiation
  - Allows adaptation to environment
- Influenced by a range of exposures
Epigenetic Change

• Regular and natural occurrence
• Can also be influenced by:
  • Age
  • Environment/lifestyle
  • Disease state
• At least three systems are currently considered to initiate and sustain epigenetic change:
  • DNA methylation
  • Histone modification
  • Non-coding RNA (ncRNA)-associated gene silencing
Waddington’s concept of an epigenetic landscape

Reprinted from Waddington, 1957
A more current view of the Epigenetic Molecular Landscape

Illustrated by Sue Ann Fung-Ho
DNA is Not a Static Entity

• Epigenetic processes play a dynamic role in regulating gene expression and are responsive to the environment.

• Epigenetic regulation of gene expression occurs independently of DNA sequence and operates primarily through changes in DNA methylation and chromatin structure.

• These processes are reversible, although often long lasting and some can even be transmitted across generations.

• Even genes that do not carry mutations/increase risk of disease or psychopathology can be harmful if not expressed appropriately in the correct type of cell at the correct time in development.
DNA Methylation

Covalent addition of methyl group to cytosine nucleotide occurring next to a guanine nucleotide (CpG dinucleotide)

- Methylation is the best studied and most stable form of epigenetic alteration, involved in “gene silencing”
- Depending on the gene and location of methylation sites, may allow reversible/dynamic changes
- Glucocorticoid receptor gene (NR3C1) methylation has been the focus of much research.
DNA Methylation Leads to Gene Silencing

Normal State

- Target gene \textit{expressed in normal cell}
- RNA pol
- Promoter
- TF

Epigenetic Modification

- Target gene \textit{inactivated by DNA methylation}
- M
- M
- Promoter
- TF
- Target gene not expressed
Maltreatment vs. Nonmaltreatment Study

Differential methylation analyses of the whole genome

- 548 school-aged, low-income children
  - 47.8% female/52.2% male
  - 67.7% Black
  - $M$ age 9.40 years
  - 54.4% history of maltreatment

Differential methylation analyses revealed pattern of greater methylation at low methylation sites ($n=197$ sites) and medium methylation sites ($n=730$ sites) and less methylation at high methylation sites ($n=907$ sites) among the maltreated children.

- The mean difference in methylation between maltreated and nonmaltreated children was 6.2%
• Known disease biomarkers for mental health, cancer, cardiovascular systems and immune functioning also indicated methylation differences between maltreated and nonmaltreated youth.

• Site-specific analyses for ALDH2, ANKK1, and NR3C1 indicate importance of considering gender and the developmental timing of maltreatment
  • ALDH2: maltreated girls had significantly lower methylation compared to nonmaltreated girls, while maltreated boys had significantly higher methylation than their nonmaltreated counterparts.
  • ANKK1: Early onset-non recent maltreatment was linked to significantly higher methylation compared to nonmaltreated children

• Results were not altered by controlling for genotypic variation of respective genes
Offspring of Depressed Moms vs. Well Moms

• Genome-wide methylation study
  • 114 infants ($M$ age $= 1$ year; $SD = 1.08$) of low-income, urban women
  • 73 with moms diagnosed with Major Depressive Disorder (MDD)
  • 94% of mothers experienced their 1st depression prenatally.
  • 41 with well moms

• Using the $5.0 \times 10^{-7}$ p-value, 2119 loci were found to be significantly different

• Infants of depressed moms had greater methylation at low methylation sites and lower methylation at high methylation sites.

• The mean difference between the two groups was 5.23%
MDD vs well moms cont’d

- Disease by biomarker analyses showed significant cancer-related differences in biomarker networks related to prostatic, ovarian, breast, and colonic neoplasms.

- Significant differences in process networks associated with neuronal development, central nervous system functioning, and cardiac development.
• Understanding the DNA methylation changes that occur in response to experiences like child abuse and neglect could help bring about the design, implementation, and multilevel prevention and intervention strategies that would allow us to change the expression of risky genes through reversal or demethylation and thereby promote mental and physical health development.

• In order to understand the processes through which early adverse experiences impart maladaptation, psychopathology, or resilience, it is critical that genetic variation (functional polymorphisms) and epigenetic modifications be examined.
Genetic Moderation of Intervention (GxE)

Two examples:


Epigenetically Informed Preventive Interventions

• Epigenetic mechanisms may be a realistic target for intervention due to their reversibility.

• Inclusion of methylation assays in measurement batteries to evaluate effects of the interventions on these mechanisms and refine theory.

• Can be conducted genome-wide or at the level of specific regions of candidate genes with known functional properties, (e.g. glucocorticoid receptor gene)

• In DNA, methylation plays a role in responding to experience in fully differentiated tissue, it must be biochemically reversible. That is, DNA should be either methylated or demethylated in response to environmental signals. Reversibility of DNA methylation is also critical for an intervention aimed at resetting epigenetic programming.
Reversibility of DNA Methylation

Although the mechanisms responsible for demethylation are yet unclear, there is evidence that DNA methylation is potentially reversible even in mature fully differentiated neurons.

This knowledge has two important implications:

1. DNA methylation could change in adult tissues and, therefore, even adult tissue should be potentially responsive to environmental cues and readjustment of phenotypes could theoretically occur even in adults.
2. It should be possible to intervene to reverse DNA methylation and alleviate adverse phenotypes.
Are these types of methylation differences limited to the brain?

• Animal studies indicate that impact of early life adversity is system-wide and genome-wide

• Findings consistent with the idea that changes that define the phenotype are not caused solely by inherited genetic polymorphisms

• Still unclear if these findings can be translated to humans and if behavioral interventions could take the place of pharmacological interventions
Critical Questions in Translational Science

1. Could we map DNA methylation changes early in life that predict risk and resilience and provide mechanistic insight as well?

2. Does consistent exposure to positive, supportive environments produce a methylation pattern that places children on a positive developmental trajectory, more resilient to subsequent adversities?

3. Are DNA methylation patterns defined by early life experience altered with childhood, adolescence, and adult experience and how do these changes relate to environmental exposures?

4. When is the best time for intervention?
Critical Questions Cont’d.

• How narrow is the window of opportunity for prevention?

• How do we use epigenetic concepts to design interventions?

Prevention research has shown that early life preventive interventions can have long-lasting effects on the children into adulthood.

• Could epigenetic markers be used to follow up these interventions?

• Are the critical periods absolutely critical or could we successfully intervene later?
Conclusions on Developmental Epigenetics

1. The epigenome is a structural overlay of genome chemical ‘markings’, which target DNA and histone proteins, alter the physical packaging of chromatin, and regulate the expression of genes, without altering the nucleotide sequence itself; epigenetic processes, in embryologic development, are the mechanisms for an enduring differentiation of cells into histologically distinctive cell lines.

2. Experiences and environmental exposures, especially those in early life, can also result in the placement or removal of epigenetic marks, thereby regulating the neurodevelopment that underlies learning, behavior and risks for compromised mental health.
3. These contrasting ontogenetic roles – cell line differentiation and a ‘recording’ of contextual experience – thus result in an ‘epigenetic paradox’, in which the same epigenome becomes the origin of both the longitudinal stability of the body’s cellular structure and its moment-to-moment plasticity in response to environmental events.

4. The GxE interactions increasingly documented within the developmental and mental health literature are likely mediated, in part, through epigenetic events that allow gene effects to be contingent upon experience and experiential influences to be conditional upon allelic variation; the epigenome thus serves as a buffer to the extremes of both genetic and environmental variation.
Conclusions cont’d.

5. Within virtually every contemporary society, the developmental and health effects of early exposure to adversity and stress are socioeconomically partitioned, with children from the lower ranks of social class sustaining greater and more severe threats to normative development; many of these pervasive SES influences on adversity-related, maladaptive outcomes are almost certainly epigenetically mediated.

6. In addition to well-documented main effects of childhood stress on health and development, there are readily observable individual differences in the consequences of such exposures. A relatively small subset of children appear differentially susceptible to the character of their rearing environments, sustain exceptionally poor outcomes in contexts of adversity and threat, but unusually positive outcomes in nurturant, supportive settings; there is evidence that this differential susceptibility to social environmental influence is also epigenetically mediated.
Conclusions cont’d.

7. Environmental influences are modulated by critical periods in development, when neurobiological circuitry is especially responsive to experience and plasticity is most accessible; the opening and closing of critical and sensitive periods are regulated by epigenetic events that guide the maturation of excitatory and inhibitory neural circuitry and the expression of molecular ‘brakes’ that reverse the brain’s inherent plasticity.

8. Epigenetic processes are also the candidate mechanisms for the transmission of risk and disorder from one generation to the next; such transmission appears to occur either through transgenerational replications of behavioral risk and protective factors or through germ line transfers of epigenetic marks.
Cicchetti lab work in progress

• Interpersonal Psychotherapy (IPT) – NIMH Grant
  • Teenage girls with/without depression and with/without trauma, Enhanced Treatment As Usual (ETAU), Normal Control (NC)
  • Randomized Control Trial (RCT)
  • Baseline – Conclusion of Treatment – 1 year follow-up
  • DNA/RNA – DNA/RNA – DNA/RNA

• SOLAR – Chronic Stress of Maltreatment: Drug Use Vulnerability NIDA Grant
  • Longitudinal study of adolescent substance abuse and maltreatment

• MN Parent Child Longitudinal Study (MPCLS)
Work in progress ...

• Building Healthy Children (BHC) – Primiparous moms <21 y.o. & children 1-18 mo.
• ADAPT – with Abi Gewirtz; Parenting in Military Families post deployment
• Borderline Personality Disorder (BPD)—teenagers diagnosed with SCID II
  • RCT; Dialectical Behavior Therapy (DBT)
  • Hillside Children’s Center = referral source
• Child Parent Psychotherapy – Maltreated (CPP Mal)
  • RCT
  • 12 mo. old Baseline – 20 mo. end of CPP – 32 mn. – one year follow up ETAU, NC
Moving Toward Precision Healthcare in Children’s Mental Health: New Perspectives, Methodologies, and Technologies in Therapeutics and Prevention

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