Investing in the Future: Upstream Approaches to the Behavioral Health of RI Youth

RISAS Half-Day Conference 2015

Genetics and Epigenetics of Adolescent Risk and Resiliency

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Immediate Past President, RI Society of Addiction Medicine
Member Scientific Advisory Board, Dominion Diagnostics
Former NE Regional Director, American Society of Addiction Medicine
Educational Objectives

• Categorize Risk/Resiliency by ASAM Dimension

• Review genetics and epigenetics of addiction

• Identify high risk individuals by genetic testing

• Develop biologically based clinical protocols for early identification of substance use disorder

• Discuss public health implications of genetics and epigenetics on prevention, early intervention and treatment
Drug Addiction is a Developmental Disease that Starts in Adolescence and Childhood

NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003

Age at cannabis use disorder as per DSM IV

Brain areas where volumes are smaller in adolescents than young adults.

Development is a dance between nurture and nature.

**Experience**
Protective and Personal (versus Insecure and Impersonal)

**Brain Development**
Alterations in Brain Structure and Function

**Epigenetic Changes**
Alterations in the Way the Genetic Program is Read

**Behavior and Development**
Adaptive or Healthy Coping Skills (vs. Maladaptive or Unhealthy Coping Skills)

Source: AAP: Helping Foster And Adoptive Families Cope with Trauma. 2013.
Developmental Stages and Risks

- **Infancy**
  - Influence of quality of home life

- **Elementary School**
  - Close supervision & Transition to non-family peers

- **Middle School**
  - More independent learning, peer involvement and exposure to drugs

- **High School**
  - Peer focus, social activities surrounding alcohol and drugs, educational challenges

- **College & Work**
  - Move away from home, greater exposure and less supervision, independence without monitoring
Control of Emotions Depends on Maturation of Prefrontal Cortex
Risk Factors: ASAM Dimension of Care

Dimension 1 – Substance Use

- Early childhood exposure to substances
  - Marijuana teas, cannabis candy, sipping alcohol
  - Fetal exposure of alcohol, cannabis, opioids, cocaine
- Age of onset of use and developmental timing
- Atypical responses to medications
  - Stimulation by opioids, and sedatives
  - Sedation by stimulants
- Increased concentration of THC in marijuana
- Ability to extract THC from marijuana
Risk Factors: ASAM Dimension of Care

Dimension 2 – Medical Problems

- Family history of alcohol and drug problems
- Atypical responses to medications
- ADD/ADHD
- Anxiety and depression
- Eating disorder and body image
- Inherited drug metabolism
- Physical and sexual abuse
Risk Factors: ASAM Dimension of Care

Dimension 3 – Behavioral Disorders

- Novelty seeking
- Poor impulse control
- Low harm avoidance
- Early aggressive behavior
- Conduct disorder
- Parent – child attachment and nurturing
- Childhood abuse and neglect
- Domestic violence, PTSD
- Peer abuse – bullying, internet
Risk Factors: ASAM Dimension of Care

Dimension 4 – Attitude and Stage of Change

- Perception of risk
- Youth perception of parental approval of substances
- Availability within home and friends
- Belief that drug use = experimentation
  - Snapshot vs. movie
- Increased knowledge/training from internet
- Advertising by alcohol + cigarette legal dealers
- Perception of invulnerability and peer norms
Risk Factors: ASAM Dimension of Care

Dimension 5 – Continued use and relapse potential

- Perception of parental monitoring
- Inconsistent consequences for behavioral deviations of roles and responsibilities
- High sensation seeking
- Novelty seeking
- Poor prediction of long term risks/consequences
- Changes to decision making when using
- Withdrawal avoidance anti-reward
  - Anxiety as symptom of marijuana withdrawal
  - Opioid use to prevent sickness – maintenance use
Risk Factors: ASAM Dimension of Care

Dimension 6 – Recovery and living environment

- Use of substances at home and peers
- Poor parental supervision, monitoring, discipline
- Disrupted families and parental conflict
- Poverty and gang participation
- Academic difficulties and dislike of school
- Social norms – advertising and availability
- Lack of sober models and supports for recovery
- Active drug using peer groups
- Decrease in non-drug related activities
The Reward Pathway and Addiction
All Addictive Substance Involve Dopamine Activity
Addiction is a “tug of war” between the older Meso Cortex Survival Brain and the modern thinking Neo Cortex Brain.

Earth 4.5 Billion Years, Life from 4 Billion Years

- Fish 500 mya
- Cambrian Explosion
- Reptiles 300 mya
- Amphibians 315 mya
- Mammals 220 mya
- Primates 65 mya
- Hominids 5 mya
Addiction is a disorder of ...

5. ... CHOICE (motivation)
4. ... STRESS (anti-reward system)
3. ... MEMORY (learning)
2. ... REWARD (hedonic system)
1. ... GENES (vulnerability)
What goes into a “choice?”

- Valuation
- Risk Taking
- Novelty-seeking
- Impulsivity
- Empathy/Narcissism
- Memory/Stress/Trauma
- Social Status
Reward / Reinforcement Pathway

Stop Switch

Prefrontal cortex

Go Switch

Nucleus accumbens
Lateral hypothalamus
Amygdala
Hippocampus
Substantia nigra

Ventral tegmental area
Case Example: Adolescent

- **Clinical characteristics**
  - 17 yo referred because of underage drinking
  - Smoking MJ on weekends only
  - Good student with passing grades
  - Dropped out of school sports
  - Intact and supportive family
  - No major behavioral issues at home
  - No evidence of co-occurring disorders
5 Questions : Risk Assessment

‒ Atypical Response
  • “Perc Up” & Motivation - opioids
  • Slow down & focus - stimulants
‒ Hollow Leg – inherited tolerance
‒ Minimal severity of hangovers
‒ Co-occurring ADD, PTSD, Mood
‒ Family history of alcohol & drugs
Genotype versus Phenotype

- **Genotype**
  - Cause based upon instructional defects
  - Measurement of risk prior to exposure
  - Biologically based prevention strategies

- **Phenotype**
  - Resulting behavior once substance use begins
  - Categories of dysfunctional behaviors are given similar diagnostic “weight”
Cookbook Analogy for Genetics

Genes
- Code for specific products
- Variations in genes SNP
- Transcription DNA-RNA
- Translation RNA-Proteins
- Developmental sequence
- Environmental support
- DNA Damage
- Control instructions

Cookbook
- Instructions for recipe
- Ingredients and amounts
- Preparation and quality food
- Quality of chef and restaurant
- Meal choice and courses
- Skill of preparation
- Improper cooking technique
- Balance of taste, creativity and presentation
The Human Genome

• In the human genome, there are ~3 billion bases (nucleotides)
• In humans, there are estimated to be ~30,000 genes (many but not all identified and annotated)
• Each gene is a sequence of bases or nucleotides

Kreek (Rockefeller University) & Hassin (Columbia P&S), 2004
Single Nucleotide Polymorphisms (SNPs) in Genes: Definitions

- SNP — a single nucleotide polymorphism, that is, one nucleotide or base of any base pair
- Allelic Frequency:
  - <1% low or rare
  - 1–5% intermediate
  - >5% high, frequent

Kreek (Rockefeller University) & Hassin (Columbia P&S), 2004
## Genetic Addiction Risk Score (GARS)

<table>
<thead>
<tr>
<th>GENE/ALLELE</th>
<th>Function and Risk</th>
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<tbody>
<tr>
<td>Caspi MAOA uVNTR</td>
<td>Increased mitochondrial metabolism of dopamine</td>
</tr>
<tr>
<td>DRD4</td>
<td>High risk for novelty seeking</td>
</tr>
<tr>
<td>DAT</td>
<td>Increased reuptake of dopamine – increased ADD risk</td>
</tr>
<tr>
<td>5HTTLLR dialletic</td>
<td>5HTTLLR dialletic</td>
</tr>
<tr>
<td>COMT</td>
<td>Enhanced synaptic catabolism of dopamine</td>
</tr>
<tr>
<td>DRD2</td>
<td>Reduced number of dopamine receptors</td>
</tr>
<tr>
<td>DRD3</td>
<td>Increased risk for cocaine addiction</td>
</tr>
<tr>
<td>OPRM1</td>
<td>Carriers of G Allele hypofunction opioids+dopamine</td>
</tr>
<tr>
<td>GABRA3</td>
<td>Defective hypofunctioning GABA: Increased anxiety</td>
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# Genetic Addiction Risk Score (GARS)

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<th>GENE/ALLELE</th>
<th>GARS results of a total of 70 subjects</th>
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<tr>
<td><strong>Number of Subjects</strong></td>
<td><strong>72</strong></td>
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<tr>
<td><strong>Low Risk</strong></td>
<td><strong>21</strong></td>
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<tr>
<td><strong>Moderate Risk</strong></td>
<td><strong>75</strong></td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td><strong>3</strong></td>
</tr>
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<td><strong>ASI Lifetime Risk Composite</strong></td>
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Individual characteristics that predict high vulnerability to drug-seeking behavior

- High stress reactivity
- High novelty-induced locomotor activity
- High novelty-seeking
- High trait impulsivity
Genetics vs. Epigenetics

**GENETICS**

- Mutations
- Inherited
- Germ line
- Invariable

**EPIGENETICS**

- Alterations
- Stable?
- Soma + germline
- Variability

Figure 3. Genetics Versus Epigenetics
Epigenetics

- Modifications (DNA methylation, Histone acetylation) that effect gene expression
- Tells the cell what genes to express
- Heritable (but reversible) changes in gene expression due to environmental factors
- Allows passage of information from generation to generation that is not encoded in DNA
- Inheritance without DNA sequence change
Rainbow and Copycat

Calico cat coat color cannot be cloned!!!
Not based on genetics
Based on Epigenetics:
Color gene is X-linked
Random X-inactivation of cells in blastula
all daughter cells will inherit that pattern
Differences in the epigenome of monozygotic twins

Fraga et al. PNAS, 2005
**EPIGENETIC MECHANISMS**

are affected by these factors and processes:
- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

**CHROMATIN**

**DNA**

DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

**CHROMOSOME**

**METHYL GROUP**

**HEALTH ENDPOINTS**
- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

**EPIGENETIC FACTOR**

**Histone modification**
The binding of epigenetic factors to histone “tails” alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

Histones are proteins around which DNA can wind for compaction and gene regulation.
Molecular Basis of Epigenetics

- Two primary mechanisms identified.
  - Methylation of cytosine nucleotides in DNA
  - Posttranslational modification to histone proteins.
    - Includes acetylation, methylation and phosphorylation

- A third proposed mechanism involves expression of small interfering RNAs (siRNA).

From David Gardner, PhD. Marian University
Epigenetic effects of drugs

Chromosome
- P arm
- Q arm
- Solenoid loops
- Nucleosome
- DNA
- Base pairs

Solenoid
- Histone

Drugs
- Ion channels
- Reuptake
- NT receptors

Second messengers and protein kinases

Transcription factors:
- CREB, NF-κB, MEF2 and ΔFOSB
- Chromatin and DNA modifiers: HATs, HDACs, HMTs, HDMs and DNMTs

Ribosome
- MicroRNAs

Target gene products:
- Ion channels, receptors, intracellular signalling and cytoskeletal proteins

Long-lasting adaptive changes in neuronal function

Silent gene

Active gene
- pol II
- TF
- RNA

Nucleus
Sensitive Periods in Early Brain Development

Graph developed by **Council for Early Child Development** (ref: Nash, 1997; *Early Years Study*, 1999; Shonkoff, 2000.)
Major Traumatic Event: Impact on the Brain

• 50% of U.S. population experiences at least one major traumatic event in their life, 75% of behavioral health workers and 90% of behavioral health patients

• Trauma changes structure and chemistry of the brain making one more susceptible to addictions and mental health disorders

• Increased vulnerability partly due to Epigenetic Expressions that result from trauma (stress), toxins, diet and even behaviors
Biol Psychiatry

Lasting epigenetic influence of early-life adversity on the BDNF gene.
Roth et al., 2009

brain-derived neurotrophic factor (BDNF) gene

first postnatal week
infant rats exposed
to stressed caretakers
with abusive behaviors

persisting changes in methylation
of BDNF DNA that caused altered BDNF
gene expression in the adult prefrontal cortex

BDNF DNA methylation in offspring of females
that had previously experienced the maltreatment regimen
Adverse Childhood Experiences and Developmental Delay

- Physical, sexual or emotional abuse
- Physical or emotional neglect
- Household mental illness
- Living in a household with substance abuse
- Having a parent/caregiver divorce or separate
- Exposure to domestic violence
- Living in a household where a member was or has been incarcerated
Stress responses:

- **Brain stress circuits**
  - Plasticity max. @ fetal/early childhood periods

- **Hormones and neurochemical systems**
  - Cortisol –
    - Short Term - mobilizes energy stores, enhances certain types of memory, activates immune responses
    - Longer term – suppression of immune function, learning and memory; health issues – metabolic syndrome (pre-diabetes), bone mineral loss, muscle atrophy
Cortisol Studies

• When faced with a scary situation, the child will show fright and seek proximity to his or her parent or other supportive caregiver, but there will be no rise in cortisol.

• Toddlers exposed to clowns, all showed the same frightened behavior, but
  – Children in secure attachment relationships did not register a rise in cortisol,
  – Children in insecure attachment relationships showed elevated cortisol

The difference between the two groups was the children’s expectation of supportiveness from the parents in the room with them.
Hippocampus Volume by Preschool Depression Severity and Maternal Support

Hippocampus region is key to memory and stress regulation.

- Children of nurturing mothers had hippocampal volumes 10% larger than children whose mothers were not so nurturing.

- Note the effect of maternal support even in ‘low severity depression’!!!


92 children in longitudinal study of preschool depression

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MAOA Gene Expression, Childhood Trauma and Antisocial Behavior

MAOA gene related to improved Neural transmission in the brain
Parenting Style & Novelty (thrill) Seeking

• Predict more novelty seeking when there is association between strict maternal parenting style and DRD2 gene
  – When child rearing was punitive, child carrying A1 allele of DRD2 gene had higher scores on novelty seeking than carriers of the A2/A2 genotype.
  – Only females with DRD2 and GABRA6 genotypes showed higher scores for father rejection and parent overprotection.
  – Children with alcoholic fathers who carried the short alleles of DRD4 gene had higher association with high novelty seeking scores.
Parental Rearing and Attachment

• Adolescents and young adults with addiction
  – Experience affect regulation resulting in inability to reach out to others for emotional soothing and comfort

• Social bonding with friends is associated with
  – Child’s oxytocin plasma levels
  – Mother’s oxytocin related genes (rs2254298, rs1042778)
  – Mother’s hormones
  – Child-mother bonding

• Social bonding was not associated with father’s genes, hormones or behavior
Social Networks and Genotype Association

- Birds of a Feather Flock Together
  - Substance Use Disorder and inheritance patterns
    - High incidence of DRD2 A1 allele and DAT 10/10 allele were more common in families with reward deficiency syndrome
  - In one family, 100% of children carrying the A1 allele married someone with the A1 Allele.
  - Breeding is Not random

- Friendship maps of adolescent networks clustered by genotype
  - DRD2A1 hang out with other with DRD2A1 – Drug using friends
  - CYP2A6 negatively correlated with friendship (loner)
Social Bonding & Gene Polymorphisms

- Polymorphisms of oxytocin gene explain differential dopaminergic responses to stress associated with anxiety traits linked to attachment behavior and emotional well-being in females but not in males.

- Parents reporting higher parental care showed
  - Higher plasma oxytocin levels
  - Low risk CD 38 alleles
  - More touch toward their infants

- Infants carrying COMT-Val/Met genotype (hypodopaminergic) showed greater disorganization attachment style than those carrying the slower catabolism COMT genotype.
Environment Impact on Child Behaviors

• Male rat pups who carry SNP variants of the Mu opioid receptor gene (OPRM1) have higher DNA methylation and receive more licking behaviors than female pups (Mama’s Boy???).
  – Increased licking bonding behaviors are protective

• Genetic propensity for risky behaviors is modified by helping relationships (mentoring)
  – DRD2 A1 carriers are associated with school dropout rates compared to A2 carriers in males
  – Youth with A1 allele are less likely to have a mentor compared to A2 carriers
  – Repeated alcohol use during adolescence downregulates DRD2 phosphorylation but not in adults
  – Alcohol use during adolescence alters acetylation of histones H3 and H4 in frontal cortex, nucleus accumbens and striatum. These drug related effects change which genes are expressed and can contribute to vulnerability to addiction.
    • Histone deacetylase (HDAC) and DNA methyltransferase (NNMT) inhibitors are emerging as potential medication for treatment of addiction
Parenting Style & Adolescent Emotional Eating

• Relationship between adverse rearing experiences and emotional eating might be dependent upon genetic makeup

• Adolescents who are DRD2A1 Allele carriers only showed an increase in emotional eating in relation to high parental psychological control compared to DRD2A2.
Pathological Internet Use (PIU)

- Predictors of PIU
  - Suicidal ideation and attempts
  - Depression
  - Anxiety
  - Conduct problems
  - Hyperactivity/inattention (ADD/ADHD)

- Gender differences in PIU
  - Conduct problems, ADHD was associated in females
  - Depression, anxiety and peer relationship problems stronger association in males
Conclusion: Public Health Implications

- 20% of total population are genetically vulnerable

- The “Hidden” young are identified by problematic substance use behavior (phenotype) that was preceded by years of abnormal brain functioning

- Identifying children prior to the onset of substance use by identifying biological and psychosocial risk factors would result in targeted interventions by risk to those who are more likely to respond to them

- Development of gene testing for risk stratification would improve diagnostic accuracy and allow for biologically based interventions

- Separation of vulnerable from resilient could target resources and strategies in a more cost efficient manner and improve public health research and demonstration prevention projects

- Improve addiction and mental health treatment outcome and save lives