Personalizing and Optimizing Preventive Intervention Models Via a Translational Neuroscience Framework

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Fishbein et al. (2016). The full translational spectrum of prevention science: facilitating the transfer of knowledge to practices and policies that prevent behavioral health problems. Transl. Behav. Med. 6(1), 5-16
Translational Neuroscience: Prevention Research Objectives

Ultimate Question: What works best for whom, why and under what circumstances?

- Apply an etiological understanding of risk behavior to intervention research models

- At present, only small to modest effect sizes. Need to:
  - Elucidate characteristics of favorable responders to standard interventions.
  - Elucidate characteristics of heterogeneous subgroups that are unresponsive.

- Identify underlying malleable mechanisms that explain intervention outcomes: can/do interventions alter these processes?
Factors in the Translational Prevention Model

- **Spatial, Physical, Social, and Economic Environment**
  - Stress/Adversity
  - Family Functioning
  - Neighborhood Conditions
  - Cumulative Burden/Allostatic Load
  - Community Relations
  - Resiliency Conditions
  - Culture/Norms
  - Economy
  - Nutrition
  - Social Supports
  - Health Care Accessibility and Quality
  - Environmental Exposure
  - Teratogenic factors
  - Brain Insult

- **Gene Expression - Epigenetics**

- **Individual Differences**
  - Biological
  - Psychological
  - Social

- **Behavioral Phenotype**
  - Disinhibition
  - Emotional Dysregulation
  - Aggression
  - Impulsivity
  - Mood Disorders
  - ADHD and CD

- **Resiliency Traits**

- **Mediating Mechanisms**
  - Integrity of Brain Function and Connectivity
  - Cognition
  - Emotional Stress Regulation
  - HPA Axis Regulation
  - Developmental Processes

- **Intervention Development, Implementation & Evaluation**
  - School, Community, Outpatient, Inpatient Settings
  - Outcome Assessment
  - Pharmaceuticals
  - Behavioral Health
  - Military Health
  - Medical Care

- **Education, Practice, and Policy**
  - Public Health
  - Health Care
  - Social and Family Services
  - Social Systems
  - Communication
  - Dissemination
  - Program Support and Infrastructure
  - Human Resource Capital
  - Economic Systems

- **Genetic and Congenital Influences**

- **Biomarkers**

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Accumulative Model of Risk for Substance Abuse

Epigenetic modifications

Genetic Risk Variants

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<tr>
<td>DAT</td>
<td>MAOA</td>
<td>SERT</td>
<td>COMT</td>
<td>CNR1</td>
<td>DRD2</td>
<td>?</td>
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</table>

Environmental “Gauges”

Adversity
- Discrimination
- Deprivation
- Witnessing violence
- Childhood maltreatment
- Family dysfunction
- Family history (e.g., drug/alcohol abuse, psychiatric illness)

Resiliency
- Good education
- Adequate housing
- Quality health care
- Positive attachments
- Structured/nurturing family

Intermediate Phenotypes

Brain function

Affect

Cognition

Behavior

Liability/Risk

Abuse threshold

High

Low
Etiological Considerations in Prevention Protocols

- Precursor conditions may interfere with intervention outcomes if not directly addressed: G × P × I

- Targeted intervention can enhance neural growth and development, thereby having an enduring impact on the trajectory of SA.

- Target specific (and novel?) intervention components to well-defined needs of subtypes = precision-based

- Early intervention: Brain is most plastic and susceptible to lasting changes, before complicating factors emerge
Adolescence: The Ultimate Risk Factor!
Addiction is a Developmental Disorder that Starts in Childhood and Adolescence

Age at tobacco, alcohol, and cannabis dependence per DSM IV

Why do most 16-year-olds drive like they’re missing a part of their brain?

Because they are.

And this is normative!
Frontal Cortex is Last to Develop

- Planning, decision-making, impulse control, memory, language, processing social cues
- Continued myelination of cortical regions for faster communication through the teen years and early twenties
- Pruning of excess connections established earlier in development
- New connections established: enhanced integration between brain areas
Focal Point: Executive Functioning

- Weighing Probabilities
- Evaluating Options
- Abstract Reasoning
- Decision Making
- Logic
- Sustained attention
- Estimating Consequences
- Determining Risk
- Impulse Control
Prefrontal Executive Deficits Undermine Regulatory Circuitry

- Inattention
- Impulsivity and novelty seeking
- Inability to accurately interpret social cues

- Permits negative emotions to dominate
- Maladaptive stress responses
- Inattention to punishment
- Heightened sensitivity to rewards; e.g., drugs and risk taking
Dual Process Model of Adolescent Development

**Development**

- **Reward Sensitivity**
  - Inverted U shaped trajectory - largely due to asynchronous PFC/NAcc development
  - Ability of PFC to regulate ventral striatum

- **Inhibitory Control**
  - Linear improvements
  - Largely due to PFC development

**Behavioral Phenotype:**
- Risk taking
- Novelty seeking
- Impulsivity

**Risk:**
- Harm from:
  - Accidents
  - Violence
  - STDs
  - Drugs/Alcohol

Casey et al. 2008; Steinberg 2008; Hardin & Ernst 2009.
Chronic stress primes the brain for novelty seeking and drug use

- Brain initiates orchestrated response to stress
- Chronicity and severity can measurably alter brain development and function
  - Executive functioning
  - Emotion regulation
  - Reward processing
- Disengages coping mechanisms and compromises ability to execute rational choices
- Same brain regions implicated in stress-related psychopathology
- Genetic vulnerabilities affect behavioral outcomes

(Weder & Kaufman, 2010)
Epigenetic Modifications: How environmental events (e.g. rearing, adversity) affect gene expression

- For gene expression, DNA must be unwound
- DNA methylation suppresses gene activity by causing DNA to stay coiled
- These effects are stable – but reversible
  - Via optimal subsequent rearing, enrichment experiences, and pharmacological interventions

Adapted from Taylor, 2006
Potentialities via Epigenetics

Epigenetic modifications are at the very core of G X E interactions

- Not DNA mutations, but via modification of methylation state of DNA
  - turns genes on and off
- For worse (e.g., stress, obesity, depression) or…
- For better: **Huge prevention and public health implications!**

Transgenerational Epigenetic Transmission!

- *Experiences and exposures* in one generation transmit to subsequent generations
  - Even prior to conception
  - Potential to affect at least 2 subsequent generations
Exploiting Brain Plasticity for Preventive Purposes

- Experience changes neural patterns, for better or for worse.
- Creates unique opportunities for emotional-motivational learning
  - Sculpt connections between cognitive control and emotional systems to create lasting changes
- Relevance to prevention, early intervention and policy
  - Scaffolding and social supports
Interventions by Developmental Phase

Prior to Conception  Prenatal  Infancy  Early Childhood  Childhood  Early Adolescence  Adolescence  Young Adulthood

- Pregnancy prevention
- Prenatal care
- Home visiting
- Early childhood interventions
- Parenting skills training
- Social and behavioral skills training
- Classroom-based curriculum to prevent substance abuse, aggressive behavior, or risky sex
- Prevention of depression
- Prevention of schizophrenia
- Prevention focused on specific family adversities (Bereavement, divorce, parental psychopathology, parental substance use, parental incarceration)
- Community interventions
- Policy
Need in Prevention Science to Improve Effect Sizes

Intervention

Mechanisms of Effects

Favorable responders

Experiential and Contextual Influences

Poor responders

Type 1
Type 2
Type 3
Type 4
Type 5
### Moderators and Mechanisms of Behavioral Change in Response to Preventive Intervention

<table>
<thead>
<tr>
<th>Citation</th>
<th>Intervention</th>
<th>Population</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fishbein et al. (in prep)</td>
<td>PATHS</td>
<td>K and 1st graders</td>
<td>Moderation by neurocognitive and stress physiological indicators</td>
</tr>
<tr>
<td>Pihler, et al. (2014)</td>
<td>Early Risers Program</td>
<td>Formerly homeless youth (ages 6 – 12) and families</td>
<td>Program promoted growth in executive function, which reduced conduct problems</td>
</tr>
<tr>
<td>Bierman, et al. (2008)</td>
<td>Head Start REDI</td>
<td>Kindergarten Children</td>
<td>Program promoted gains in executive function, which partially mediated school readiness</td>
</tr>
<tr>
<td>Fisher et al. (2007)</td>
<td>Family-based therapy</td>
<td>3 – 6 year old foster children</td>
<td>Intervention normalized cortisol levels, which improved HPA axis functioning</td>
</tr>
<tr>
<td>Riggs et al. (2006)</td>
<td>PATHS</td>
<td>2nd and 3rd grade children</td>
<td>Inhibitory control and verbal fluency mediated internalizing and externalizing behavior problems</td>
</tr>
<tr>
<td>Carré et al. (2014)</td>
<td>Fast Track Program</td>
<td>Adult males</td>
<td>Reduced testosterone reactivity and aggression to social provocations, and reduced testosterone reactivity mediated aggressive behavior</td>
</tr>
<tr>
<td>Beauchaine et al. (2015)</td>
<td>Incredible Years Intervention</td>
<td>4 – 6 year old children with ADHD</td>
<td>EDA appears to mark resistance to treatment</td>
</tr>
<tr>
<td>Brotman et al. (2007)</td>
<td>Family-based intervention</td>
<td>Preschool age siblings of adjudicated youth</td>
<td>Intervention alters stress response in anticipation of a peer social challenge</td>
</tr>
</tbody>
</table>

**FRAMEWORK REVIEWS**

The Good Behavior Game

- Well-established evidence-based universal school program
- Modest effect sizes
- Who responds well and on what basis?
- Neurobiological predictors/moderators
- Neurodevelopmental mediators
- Guides program refinement
Sub-cortical over-reactivity to reward

Magnitude and extent of limbic system (nucleus accumbens) and frontal cortex activity to reward.

Adolescents (13–17 years) showed greater percent signal change to large rewards than either children (aged 7–11 years) or adults (23–29 years) in subcortical limbic regions.

Neurobiological Model of GBG Effects

- Inhibitory Control
- Emotional Regulation
- Error Monitoring

GBG

Reward Sensitivity

Improvement in Social Relations

Behavioral Outcomes

Reward Sensitivity
Mediation Model (Within Experimental Groups)*

Independent Variable: PATHS

Mediating Variables: Inhibitory Control & Emotion Regulation

Interaction Term: PATHS by Mediators

Outcomes: Externalizing Symptoms; Sociality; School Conduct; Self Control

Mediation Model (Between Experimental and Control Groups)

Independent Variable: PATHS

Mediating Variables: Inhibitory Control Emotion Regulation

Outcomes: Externalizing Symptoms; Sociality; School Conduct; Self Control

*Change in mediators will be greater in intervention participants than the control children who experience change due only to maturation.
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<th>Citation</th>
<th>Intervention Type</th>
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<tr>
<td>Davidson et al. (2003).</td>
<td>Mindfulness-Based Stress Reduction</td>
<td>Adult</td>
<td>Positive affect ↗ left-sided anterior activation &amp; group x time interaction with anterior temporal electrode leads. MBSR vs. controls - ↑ antibody titers week 4 vs. week 8</td>
</tr>
<tr>
<td>Tang et al. (2009).</td>
<td>Integrative Body–Mind Training</td>
<td>Undergraduates</td>
<td>↓ HR and SCR, ↑ respiratory amplitude, an &amp; ↓ chest respiratory rate. rCBF right subgenual ACC &amp; adjacent ventral ACC ↑ activity putamen &amp; caudate → ECF and reward systems ↑ theta power in frontal midline electrodes.</td>
</tr>
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<td>Luders et al. (2009).</td>
<td>Meditation (various)</td>
<td>Adults</td>
<td>↑ GM volume: OFF, hippocampus, thalamus &amp; inferior temporal gyrus</td>
</tr>
<tr>
<td>Tang et al. (2012).</td>
<td>IBMT</td>
<td>Undergraduates</td>
<td>↓ radial and axial diffusivity ↑ FA</td>
</tr>
<tr>
<td>Jung et al. (2012).</td>
<td>“Brain Wave Vibration” mind–body training</td>
<td>Adults</td>
<td>Stress level varied according to BDNF (Val/Met &amp;Met/Met vs. Val/Val) Tx by COMT Val158Met interaction for plasma NE concentrations</td>
</tr>
<tr>
<td>Tang et al. (2010).</td>
<td>IBMT vs. RT</td>
<td>Undergraduates</td>
<td>↑ FA : anterior corona radiate, the body and genu of the corpus callosum, superior corona radiata, and superior longitudinal fasciculus.</td>
</tr>
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<td>Kerr et al. (2011).</td>
<td>MBSR</td>
<td>Adults</td>
<td>↑ alpha power modulation in response to cue ↑ in 7–14 Hz alpha modulation in the 600–800ms postcue period 0 vs. 8 weeks ↑ alpha modulation in an alpha sub-band</td>
</tr>
<tr>
<td>Oberle et al. (2011).</td>
<td>Mindfulness and Inhibition Control</td>
<td>4th and 5th grade</td>
<td>↑ self-reported mindfulness → ↑ inhibitory control</td>
</tr>
<tr>
<td>Holzel et al. (2011).</td>
<td>MBSR</td>
<td>Adults</td>
<td>↑ GM volume hippocampus, posterior cingulate cortex, temporoparietal junction and cerebellum</td>
</tr>
<tr>
<td>Kilpatrick et al. (2011).</td>
<td>MBSR</td>
<td>Adults (women)</td>
<td>↑ connectivity w/in auditory &amp; visual networks, and b/t auditory cortex &amp; areas assoc w/ attentional &amp; self-referential processes ↑ anticorrelation b/t auditory and visual cortex, and b/t visual cortex and areas assoc w/ attentional and self-referential processes</td>
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Potential Effects of Mindful Interventions on Regulatory Systems

Yoga

Self Control (yam)
Self-regulation (niyam)
Exercise (asanas)
Controlled breathing (pranayamas)
Controlled senses (pratyahar)
Attention (dharana)
Meditation (dhyana)
Self-Realization (samadhi)

Neurotransmitter and HPA axis homeostasis

Increased vagal flow (physiologic substrate of attention and emotion regulation)

Depression ↓
Anxiety ↓
Negative symptoms ↓
Cognitive functioning ↑
Sleep ↑
Attention ↑
Stress ↑
Reactivity ↓
Coping ↑
## Putative Neurobiological Mechanisms of Action

<table>
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<tr>
<th>Mechanism of Action Involved</th>
<th>Proposed Process</th>
<th>Hypothesized Brain Areas</th>
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<tr>
<td>Increased present-moment awareness</td>
<td><em>Bottom-up</em> processing of salient stimuli with or without <em>top-down</em> modulation of reactivity</td>
<td>Dorsolateral PFC, anterior cingulate cortex, ventral striatum, insula, amygdala</td>
</tr>
<tr>
<td>Improved attentional control</td>
<td><em>Top-down</em> modulation of attention</td>
<td>PFC, anterior cingulate cortex</td>
</tr>
<tr>
<td>Greater self-regulation</td>
<td><em>Top-down</em> improved inhibitory control</td>
<td>Medial PFC, orbitofrontal cortex, anterior cingulate cortex</td>
</tr>
<tr>
<td>Increased self-awareness</td>
<td><em>Bottom-up</em> processing of salient stimuli</td>
<td>Anterior cingulate cortex, insula</td>
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<td>Develop and implement new way to approach discomfort</td>
<td><em>Top-down</em> modulation of responses to discomfort and decision making</td>
<td>Ventromedial PFC, dorsal striatum, amygdala</td>
</tr>
<tr>
<td>Reduced reactivity to stress or substance cues</td>
<td><em>Bottom-up</em> reactivity</td>
<td>Anterior cingulate cortex, ventral striatum</td>
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Adapted from Witkiewitz, Lustyk, and Bowen, 2012
Strengthening Vertical Control

- Top-down (PFC) control over limbic impulses to enhance self-regulation and stress management skills.
  - Poor vertical control linked with impulsivity, sensation-seeking, emotion dysregulation, and externalizing behaviors (e.g., drug abuse)

- Mindful programs capitalize on brain’s plasticity in the neural circuitry of emotions.
  - Influences brain circuits and physiology implicated in disorders such as anxiety, PTSD, depression.

- Effects of mindful-enhanced vertical control through practicing strategies in...
  - Awareness and attention to regulation of cognitions, emotions, and somatic sensations
A previous study found that the HLF Mindful Yoga program improved rumination, intrusive thoughts, and emotional arousal to stressful events in 9-11 year old Baltimore City youth (Mendelson, Greenberg, Dariotis, et al., 2010).
Big Data to Identify Risk Phenotypes
Back Translation: An Essential Component For Precision

• Bidirectional exchange across stages for constant modifications and refinements.
  
  o Negative or unexpected findings inform knowledge about mechanisms identified in prior phases.

• Continuous reevaluation of persistent or emerging findings of individual or group level differences in intervention outcomes.

• Findings from resultant interventions in different populations, cultures, and settings yields greater knowledge of etiological underpinnings
  
  o And as interventions grow more universal, they provide for a more comprehensive and confirmatory assessment of underlying mechanisms of therapeutic outcomes for subgroups or individuals.
The ultimate goal is that, through a transfer of knowledge from etiology to practice and back to etiology, clinical and public health policies will be increasingly responsive, applicable, and precision-based, thereby exerting greater impacts.
Fishbein et al. (2016). *The full translational spectrum of prevention science: facilitating the transfer of knowledge to practices and policies that prevent behavioral health problems.* Transl. Behav. Med. 6(1), 5-16
Barriers to True Translation

• Compartmentalization and silo’ing
  • Vs transdisciplinary communication & collaboration

• Unfamiliarity across disciplines and lack of holistic models (e.g. basic scientists not realizing the relevancy of their work)
  • Vs hand-holding and hand-offs

• System-level barriers, including scientific funding and their reward systems, and institutional disincentives
  • Vs incentivizing precision-based approaches to improve effectiveness and efficiency across all phases of translation

• Lack of end-phase translation
  • Vs knowledge mobilization

• Widespread illiteracy re prevention science in general
  • Vs appreciation for the evidence and potentialities

• Key players lack knowledge and capacity
  • Vs effective targeting, dosing, monitoring and scaling
Policy Goals

- Facilitate transfer of knowledge to inform and reform policy
- Institutionalize EBPs
- Prevention “mentality”
- National resource: clearinghouse
- Training of early career investigators
- Relationship building b/t scientists, practitioners and decision-makers
Comprised of prominent scientists (across disciplines), educators, community stakeholders, practitioners and clinicians, policy makers, advocates, and foundation representatives.

As a collective body, we offer the public and policy-makers with expertise and capabilities in multiple arenas.

Several federal agency administrators (e.g., NIH, SAMHSA, ONDCP, CDC, OJJDP) act as advisors.

Collaborations with like-minded national and community organizations.

www.npscoalandition.org
NPSC Mission

To prevent social ills and promote wellbeing by translating scientific knowledge into effective and sustainable practices, systems and policies.
NPSC Goals

Achieving Socially Significant Outcomes:

- **Translational Science:** To encourage interdisciplinary teams of scientists to apply integrative models to understand
  - conditions that lead to poor mental, behavioral and physical health
  - factors that underlie intervention effects.

- **Implementation and Systems Change:**
  - To advance science-driven practices to reducing risks and disadvantages.
  - To encourage system-wide capacity to effectively implement evidence-based strategies and achieve socially significant outcomes.

- **Advocacy/Policy:** To promote governmental adoption of a "prevention model" to reduce expenditures and benefit society.
Acknowledgements

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National Institute on Drug Abuse
The Science of Drug Abuse & Addiction

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