From Scientific Discovery to Program Development and Optimization

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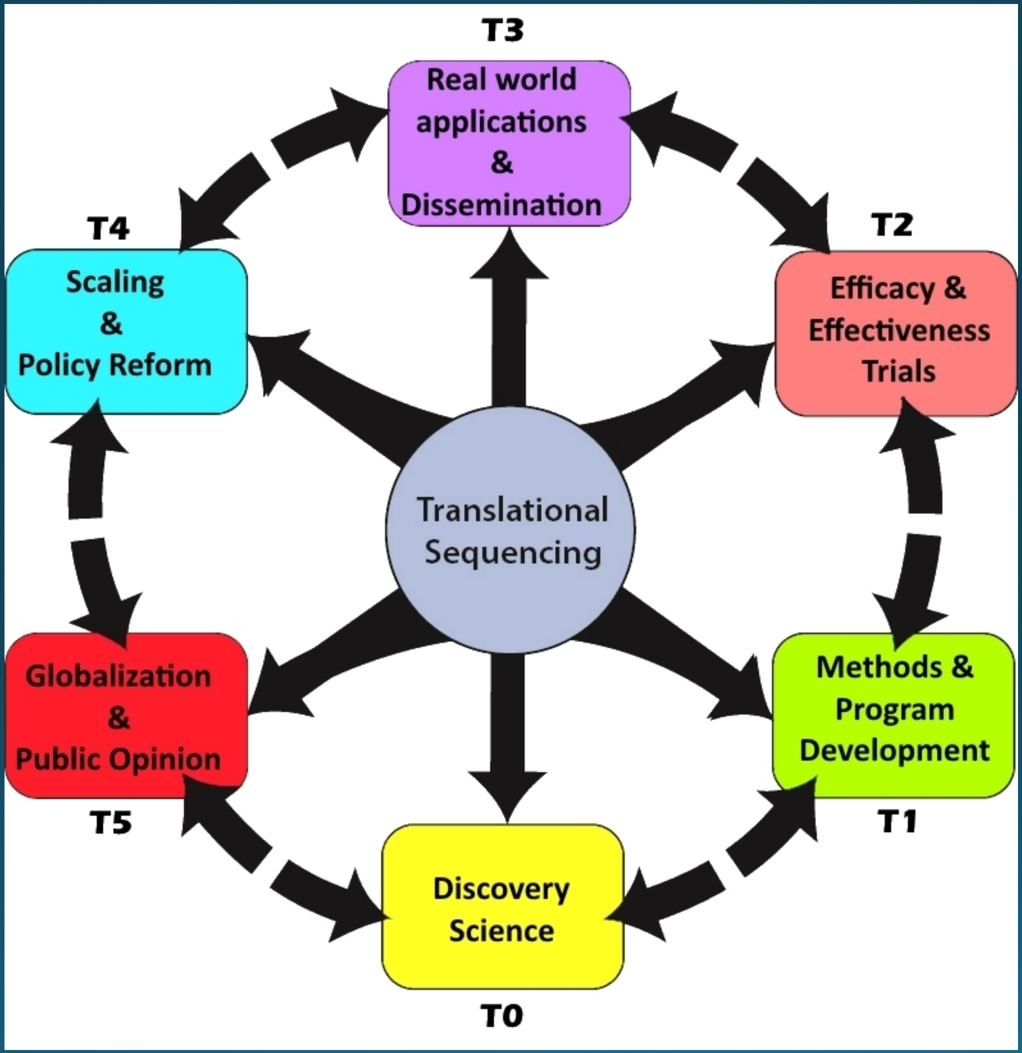
Translational Sequencing



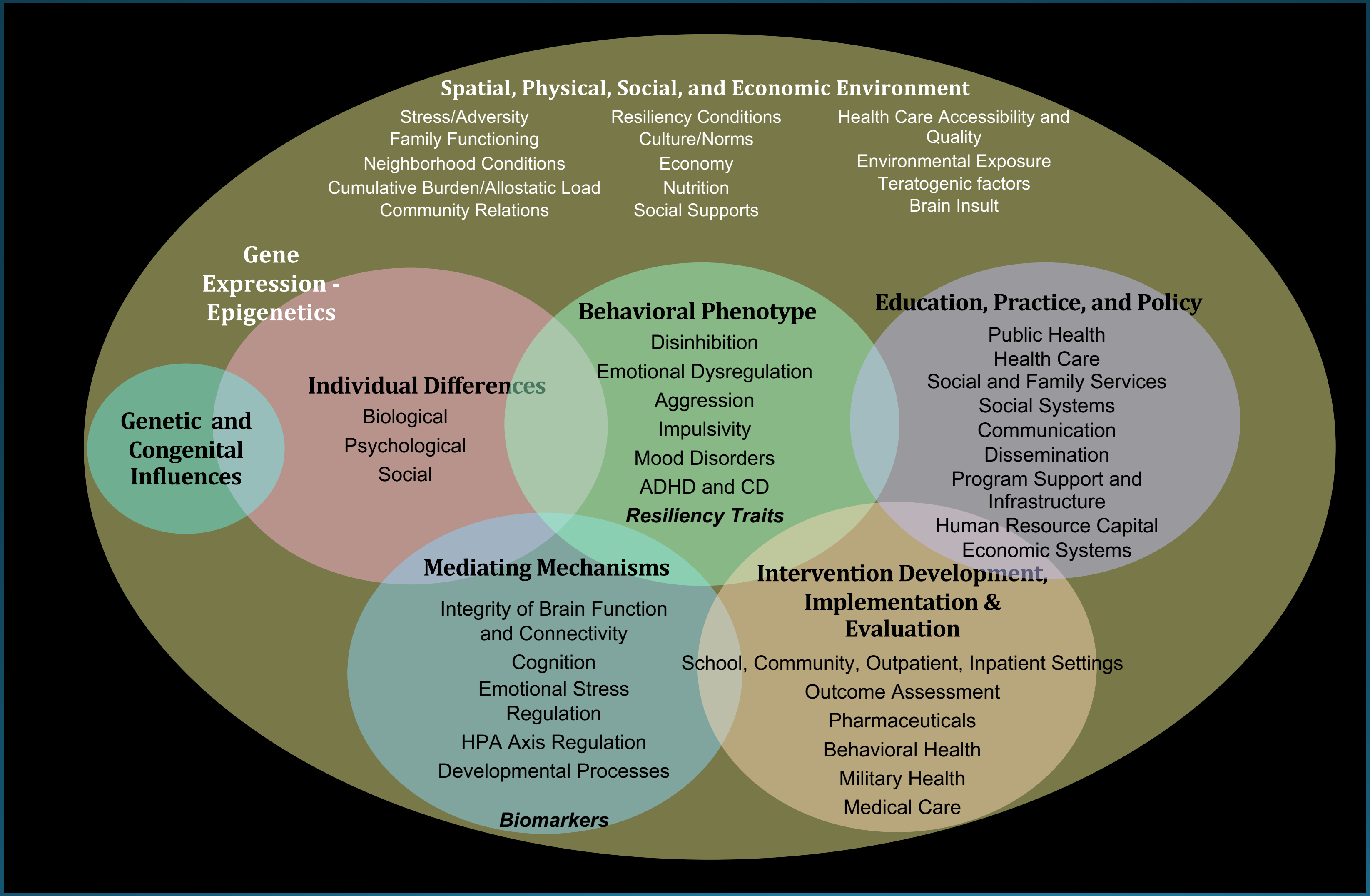
Fishbein et al. (2016). *The full translational spectrum of prevention science: facilitating the transfer of knowledge to practices and policies that prevent behavioral health problems.* *Transl. Behav. Med. 6(1), 5-16*

Translational Neuroscience: Prevention Research Objectives

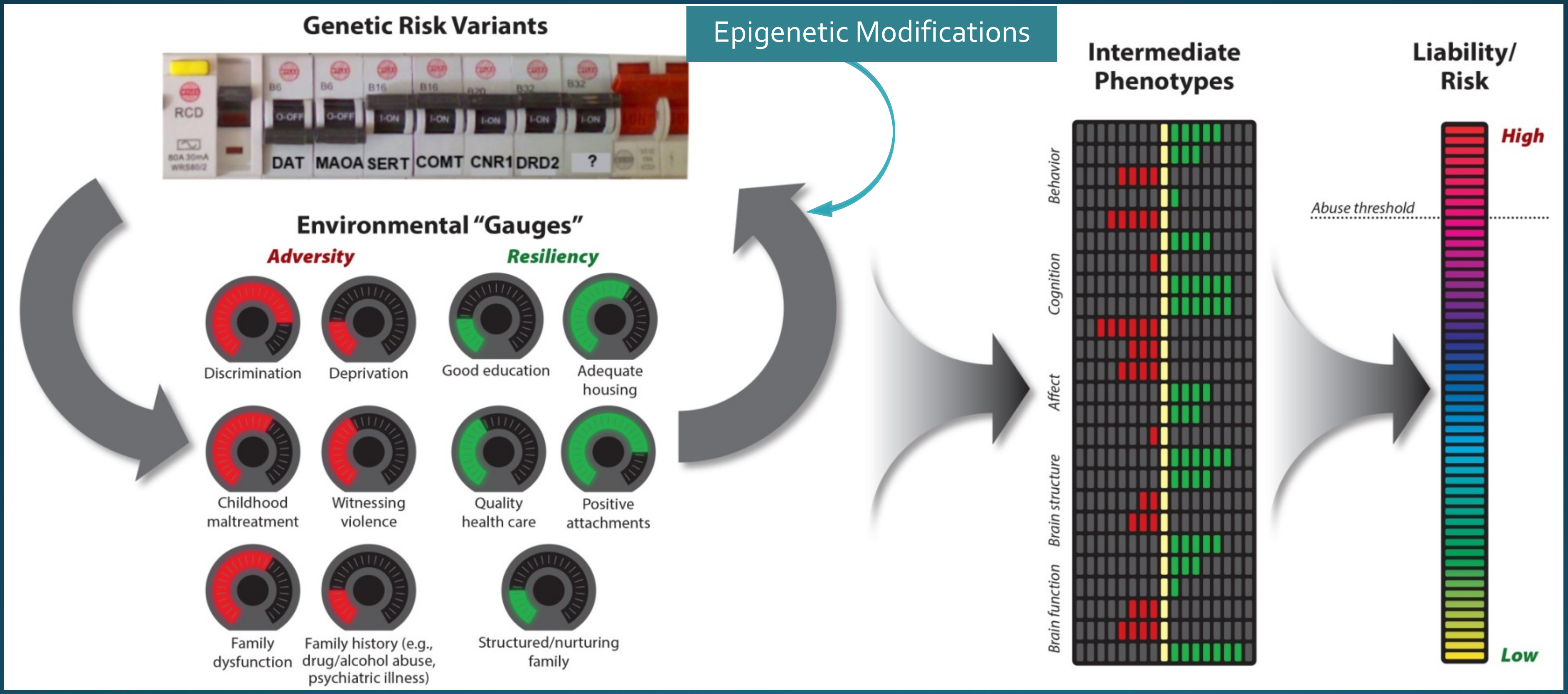
Ultimate Question: What works best for whom, why and under what circumstances?

- Apply an *etiological understanding* of risk behavior to intervention research models.
- 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?
- Target specific (and *novel*?) intervention components to well-defined needs of subtypes = *precision-based*

Factors in the Translational Prevention Model



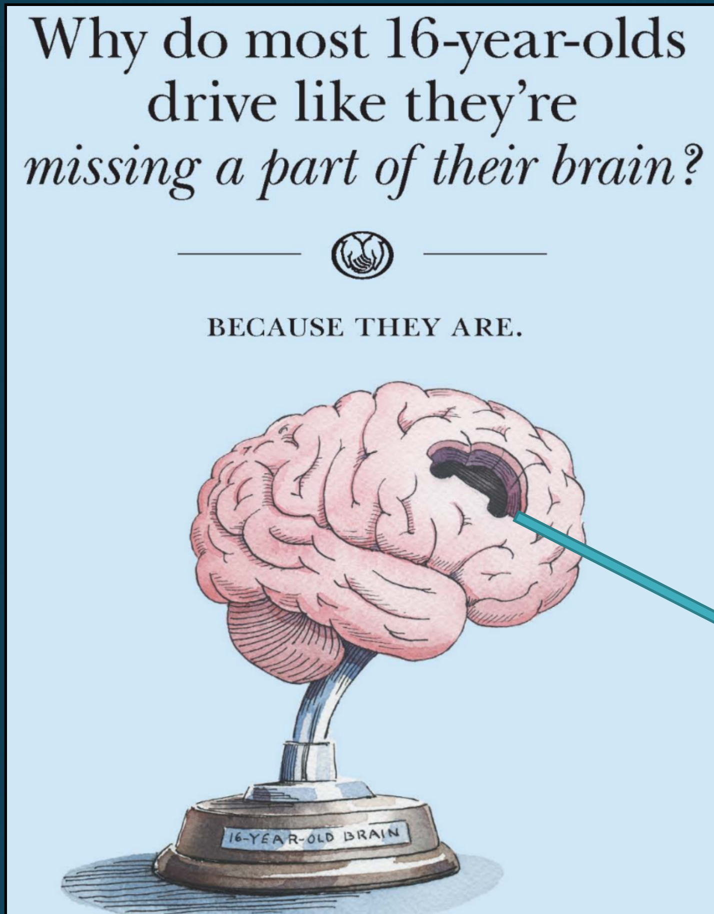
Accumulative Model of Liability for Risk Behaviors



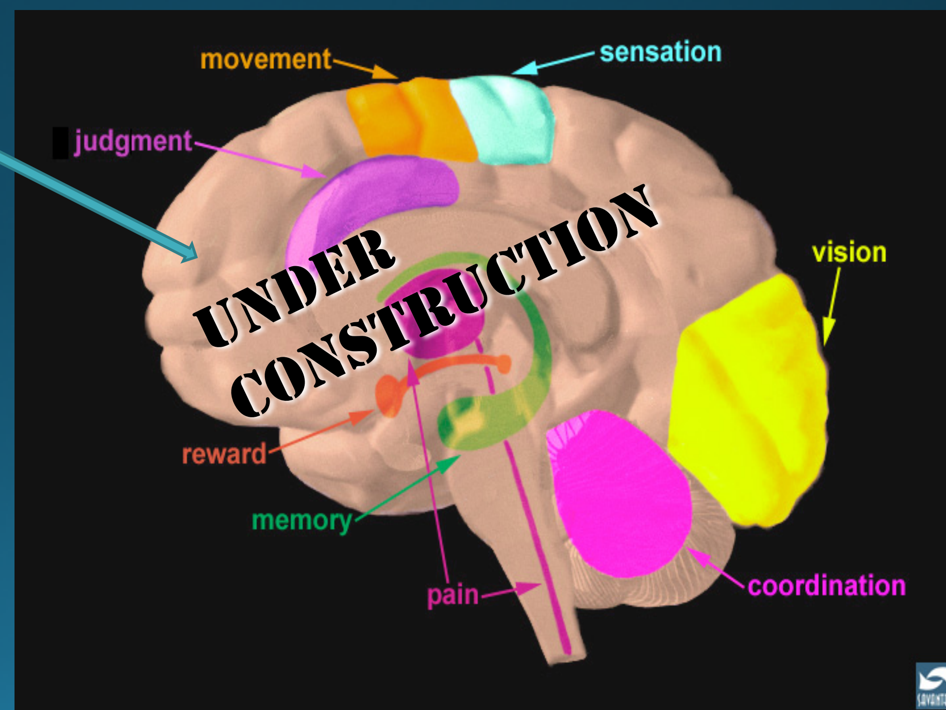
Etiological Considerations in Prevention Protocols

- Relevant etiological factors:
  - Psychopathology, adversity/stress, neurogenetic mechanisms, parenting/family, neighborhood, contagion, etc.
- Antecede and potentially confound SA pathways
- Externalizing behaviors in particular exacerbate poor outcomes
- These factors may interfere with intervention outcomes if not directly addressed
- Varying initial level of severity/risk and type may differentially predict intervention outcomes
- Targeted intervention can enhance neural growth and development, thereby having an enduring impact on the trajectory of SA.
- Early intervention:
  - *Brain is most plastic and susceptible to lasting changes, before complicating factors emerge*

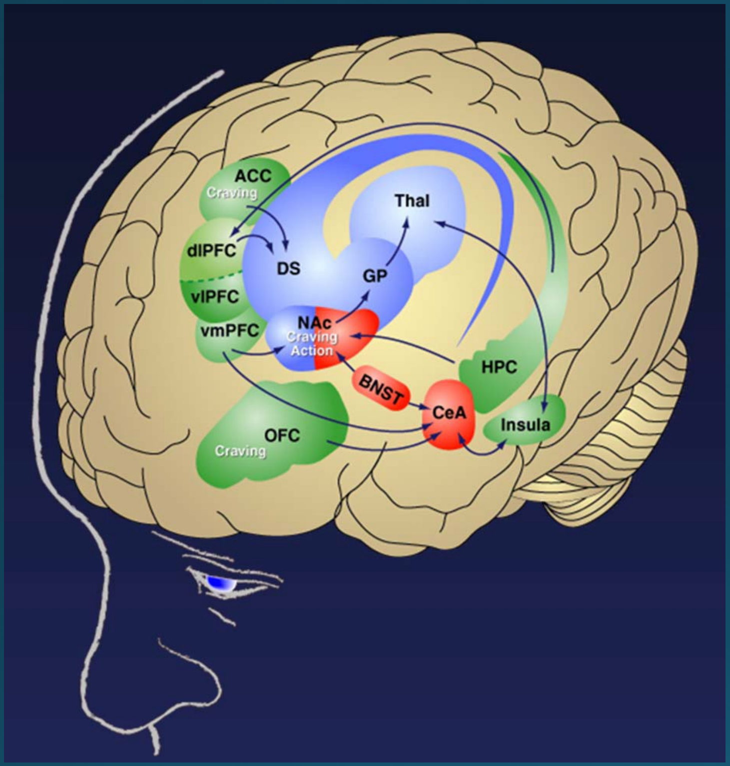
Adolescence: The Ultimate Risk Factor!

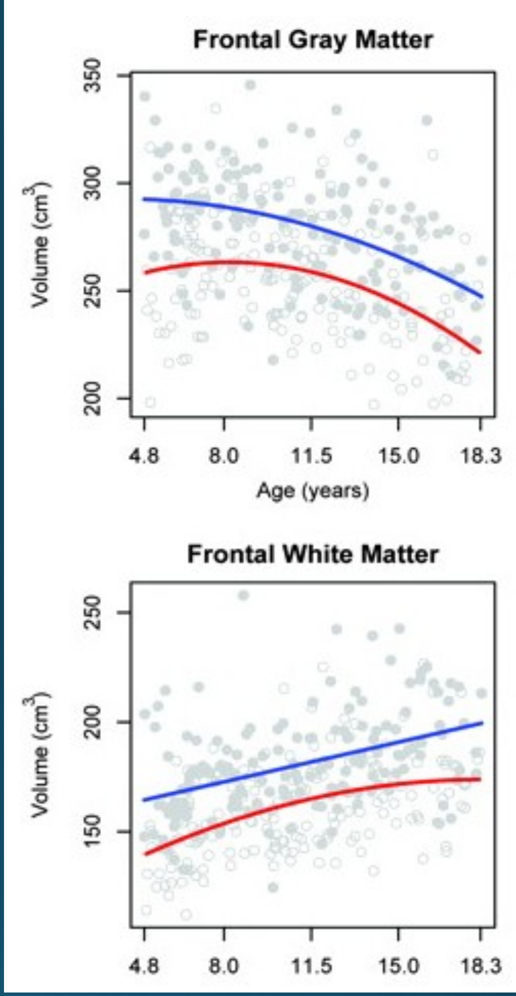


And this is *normative*!



Frontal Lobe Changes During Adolescence

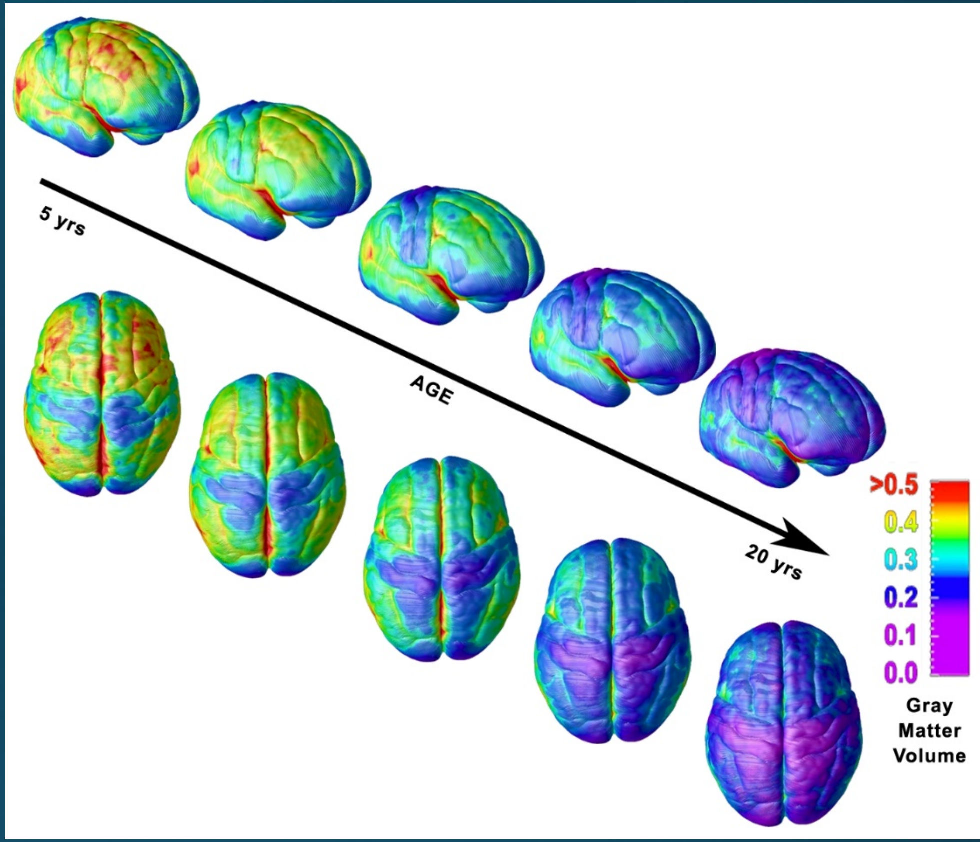




- **Planning, decision-making, impulse control, memory, language, processing social cues**
- **Gray matter goes down, white matter goes up, overall size stays about the same**

From: Ball W et al with the Brain Development Cooperative Group (2012). Total and regional brain volumes in a population-based normative sample from 4 to 18 years: the NIH MRI Study of Normal Brain Development. *Cerebral Cortex*, 22(1):1-12.

Frontal Cortex is Last to Develop



- Continued myelination of cortical regions

  coating nerve fibers for faster communication through the teen years and early twenties

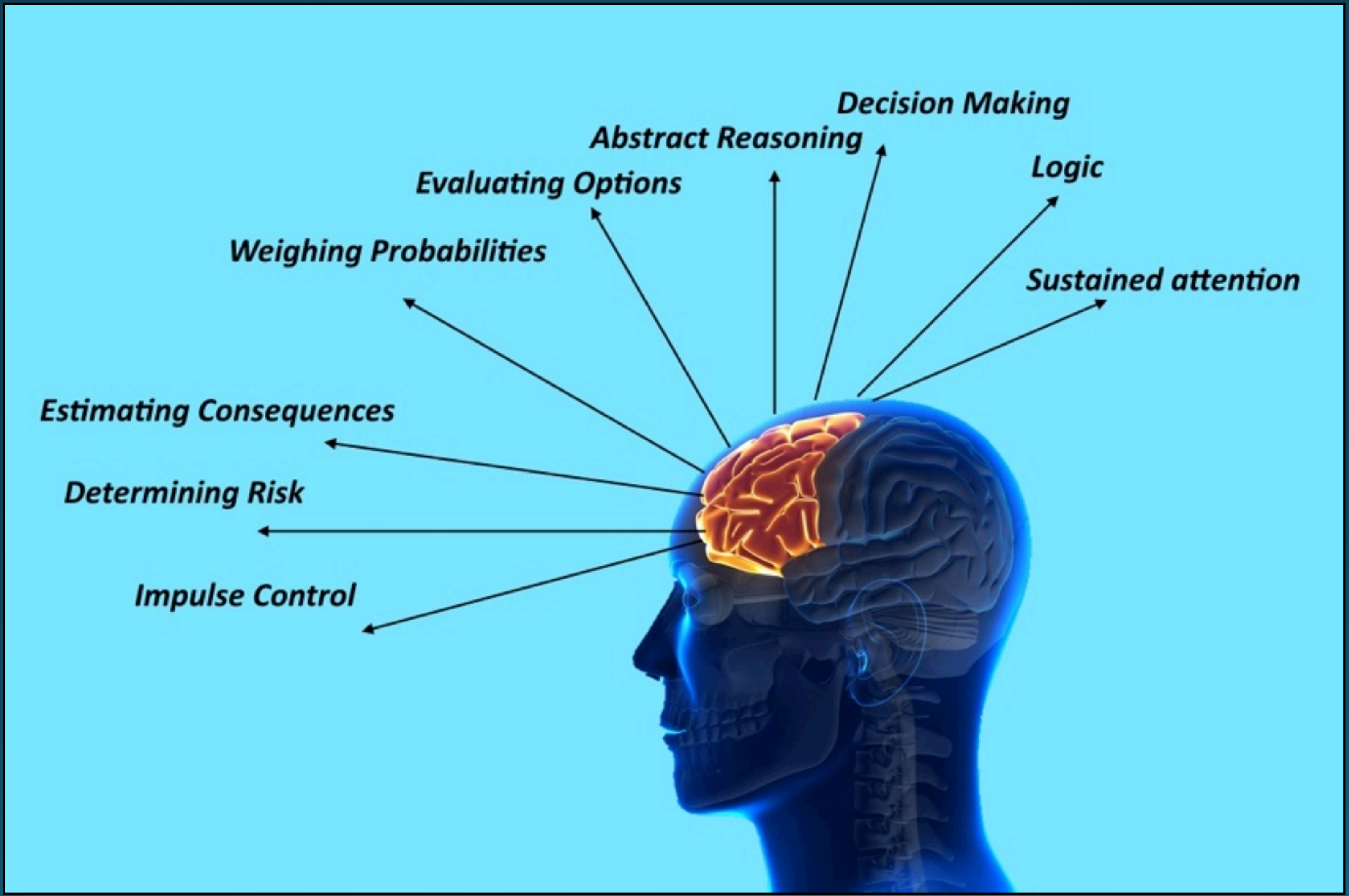
- Pruning of excess connections established earlier in development

  thinning of “grey matter”

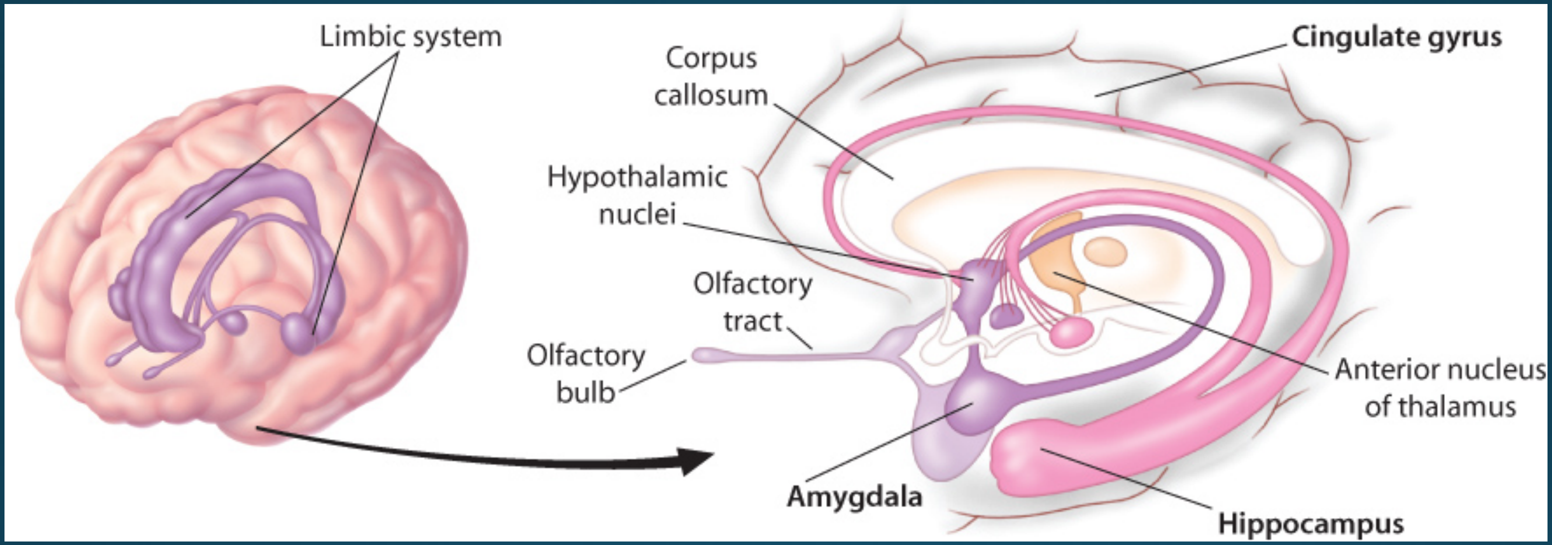
- New connections established

  enhanced integration *between* brain areas

Focal Point: Executive Functioning



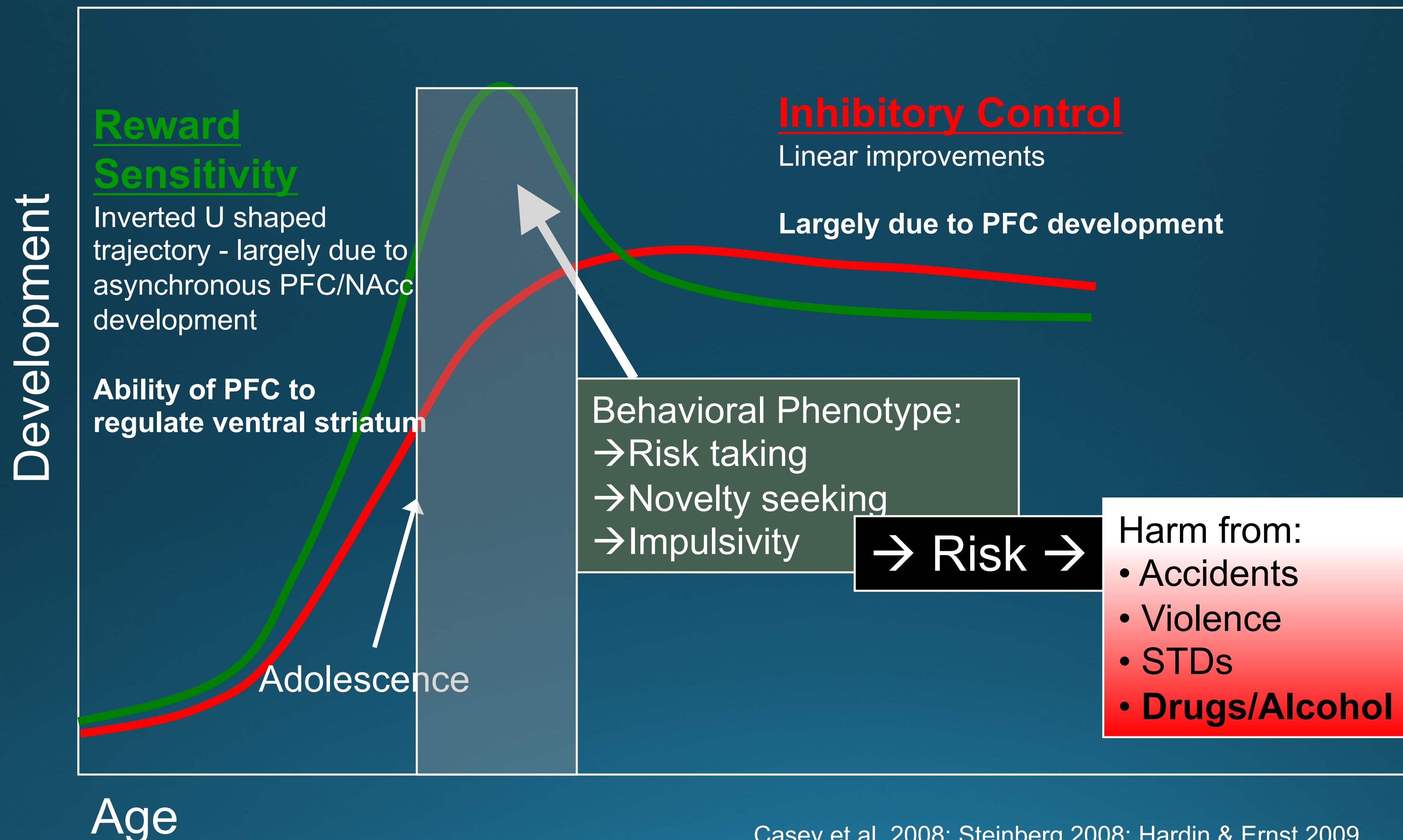
Prefrontal Executive Deficits Undermine Regulatory Circuitry



- 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

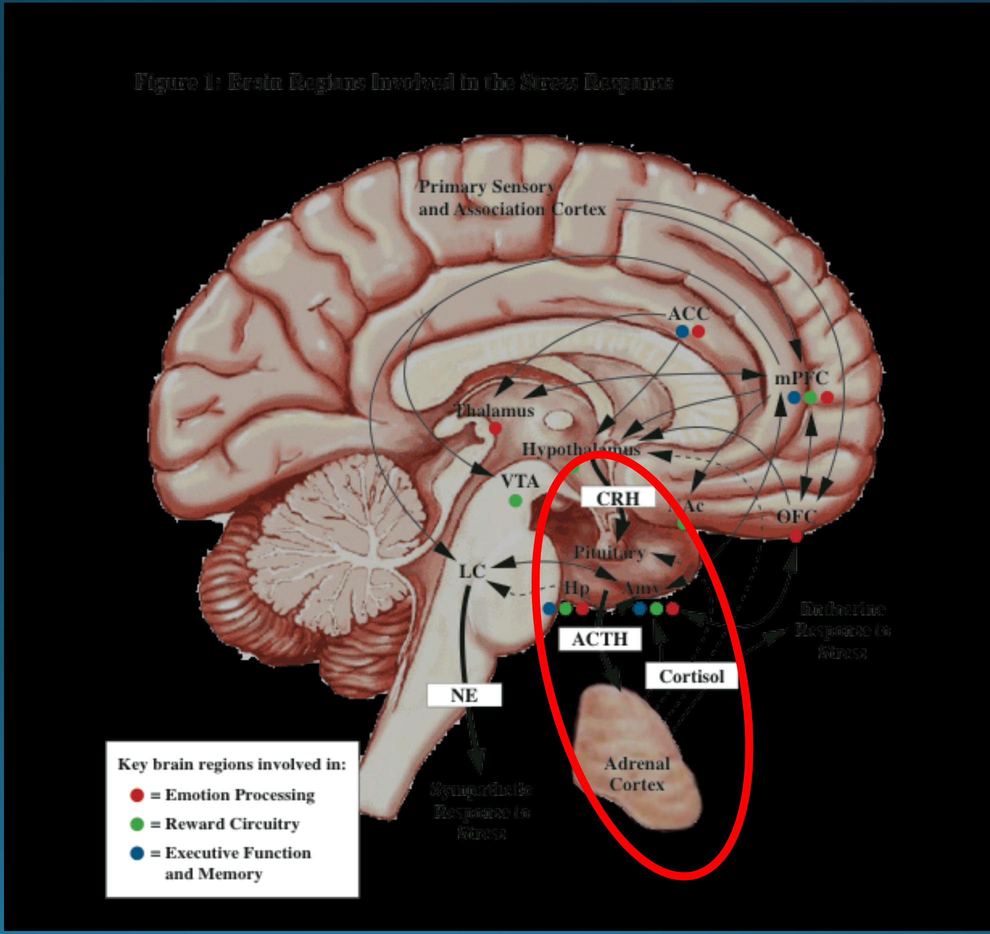
Dual Process Model of Adolescent Development



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)

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**!

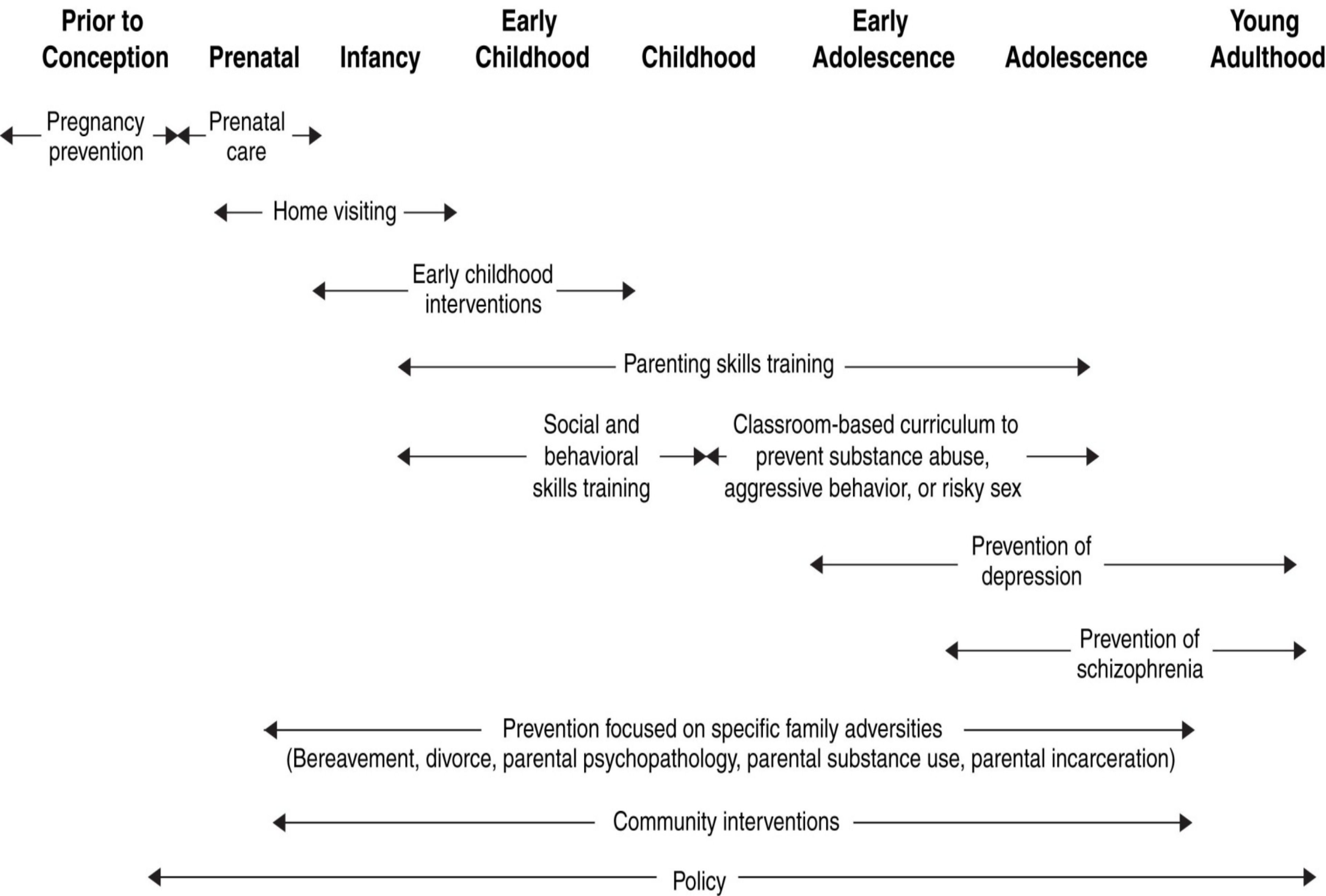
Transgenerational Epigenetic Transmission!

- *Experiences* and *exposures* in one generation transmit to subsequent generations
  - Even prior to conception
  - Potential to affect at least 2 subsequent generations

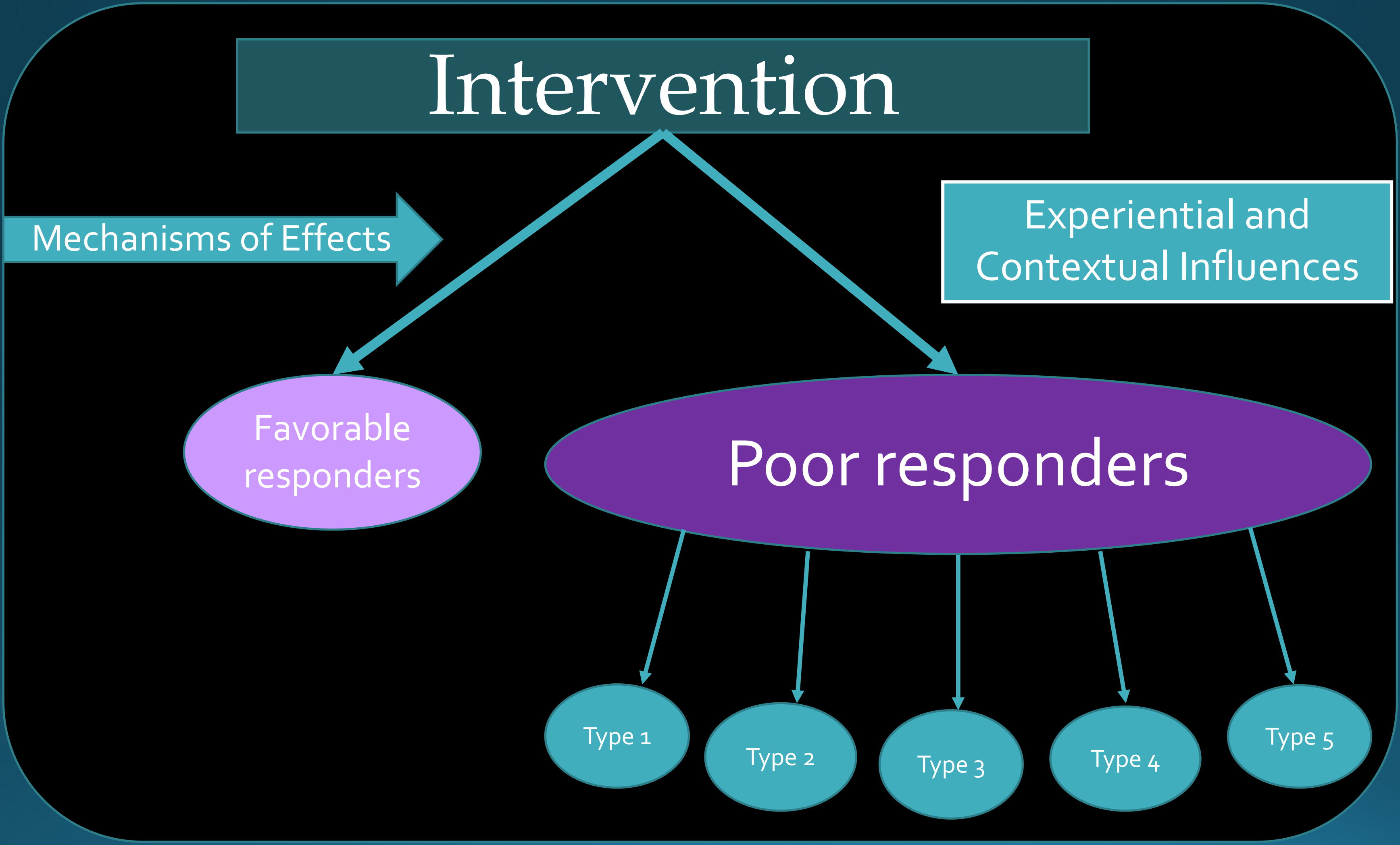
Exploiting Brain Plasticity for Preventive Purposes

- Experience changes neural patterns, for better or for worse.
- Creates unique opportunities for emotional-motivational learning
  - Sculpts 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



Need in Prevention Science to Improve Effect Sizes



Mechanisms of Behavioral Change in Response to Preventive Intervention

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

FRAMEWORK REVIEWS

Berkman, E. T., Graham, A. M., & Fisher, P. A. (2012). Training self-control: a domain-general translational neuroscience approach. Child development perspectives, 6(4), 374-384.

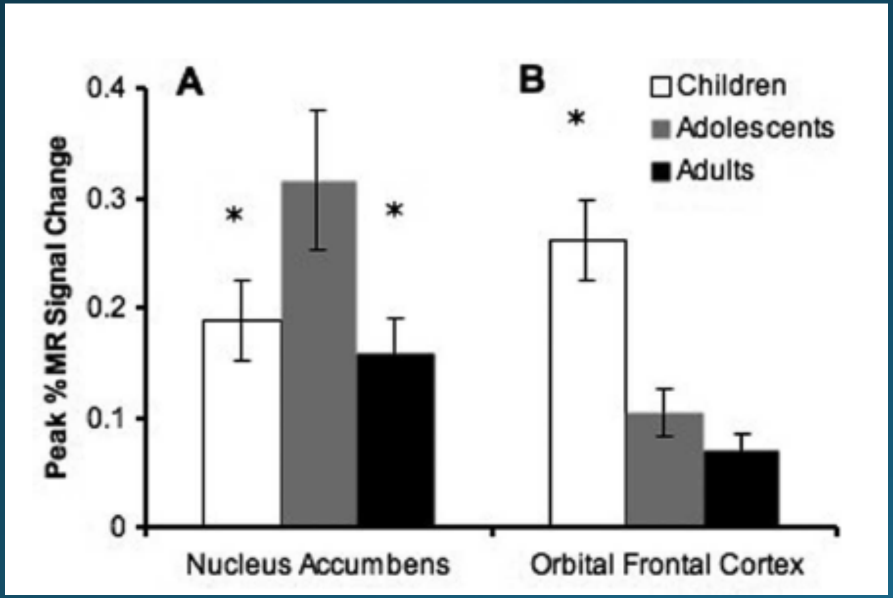
Blair, C., & Diamond, A. (2008). Biological processes in prevention and intervention: The promotion of self-regulation as a means of preventing school failure. Development and psychopathology, 20(03), 899-911.

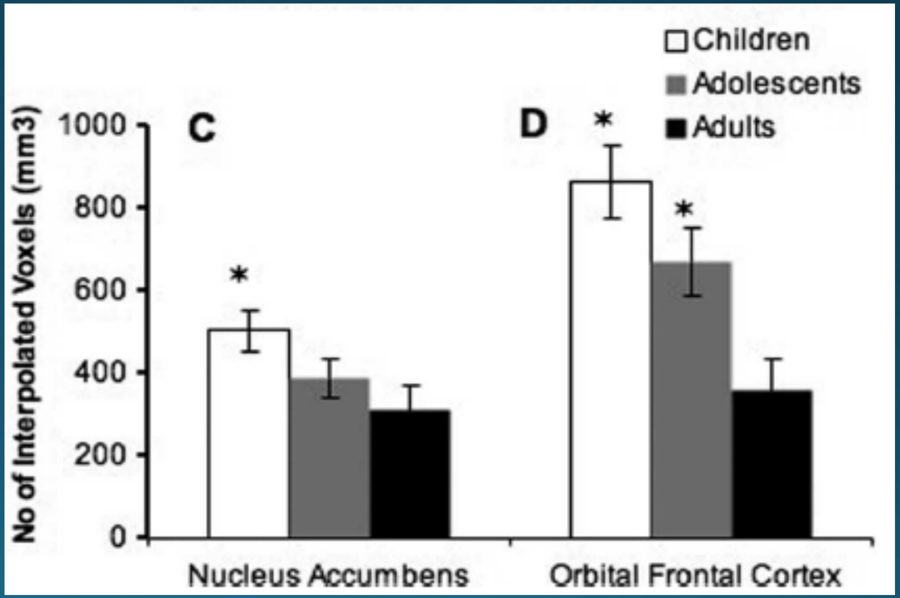
Wetherill, R., & Tapert, S. F. (2013). Adolescent brain development, substance use, and psychotherapeutic change. Psychology of Addictive Behaviors, 27(2), 393.

Sub-cortical over-reactivity to reward

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

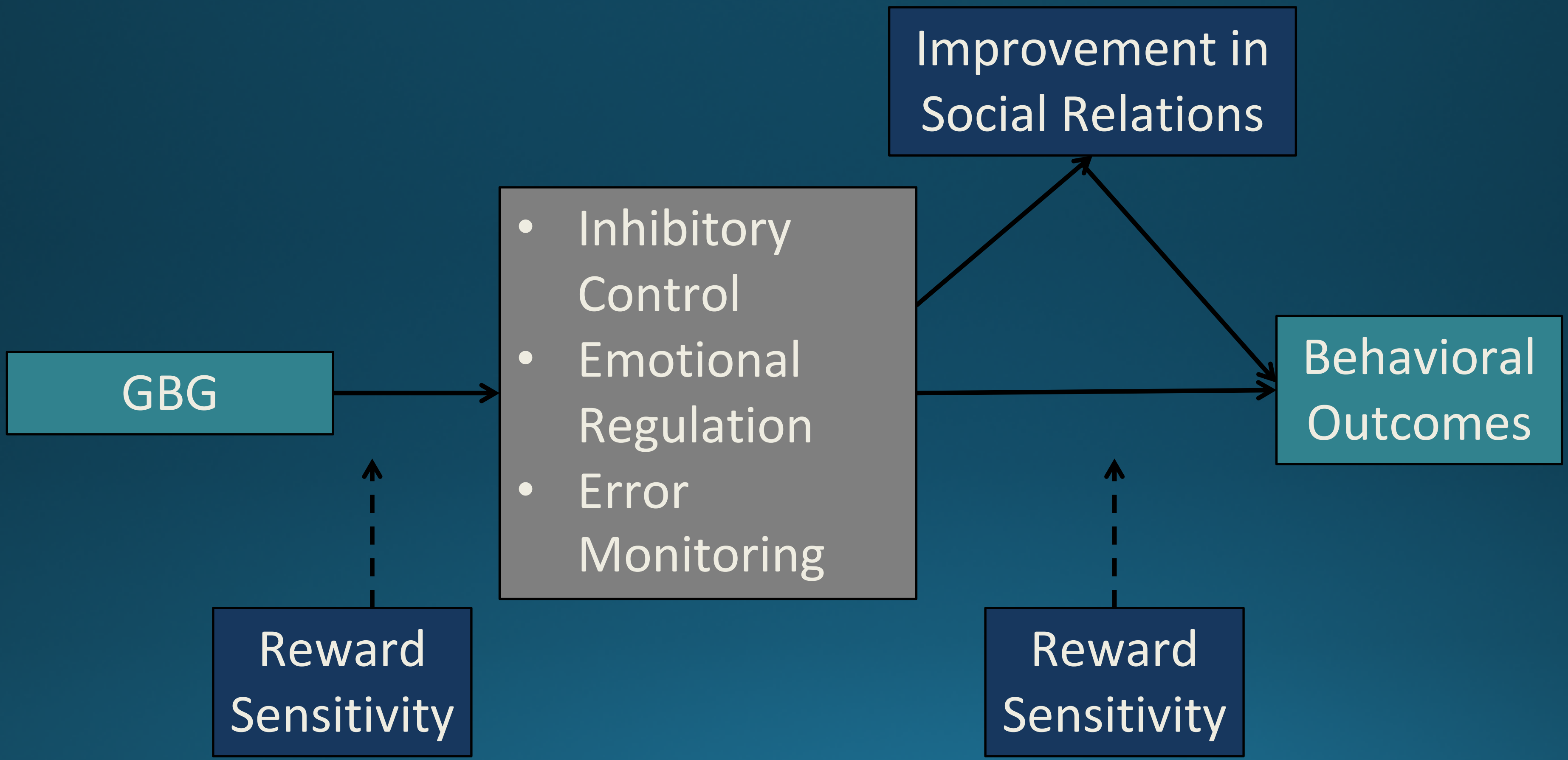
Adolescents (13–17 years) showed greater percent signal change to large rewards than either children (aged 7–11 years) or adults (23–29 years) in subcortical limbic regions.





Galvan, A. et al. (2006). ***Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents.*** *J Neurosci 26 (25), 6885–6892.*

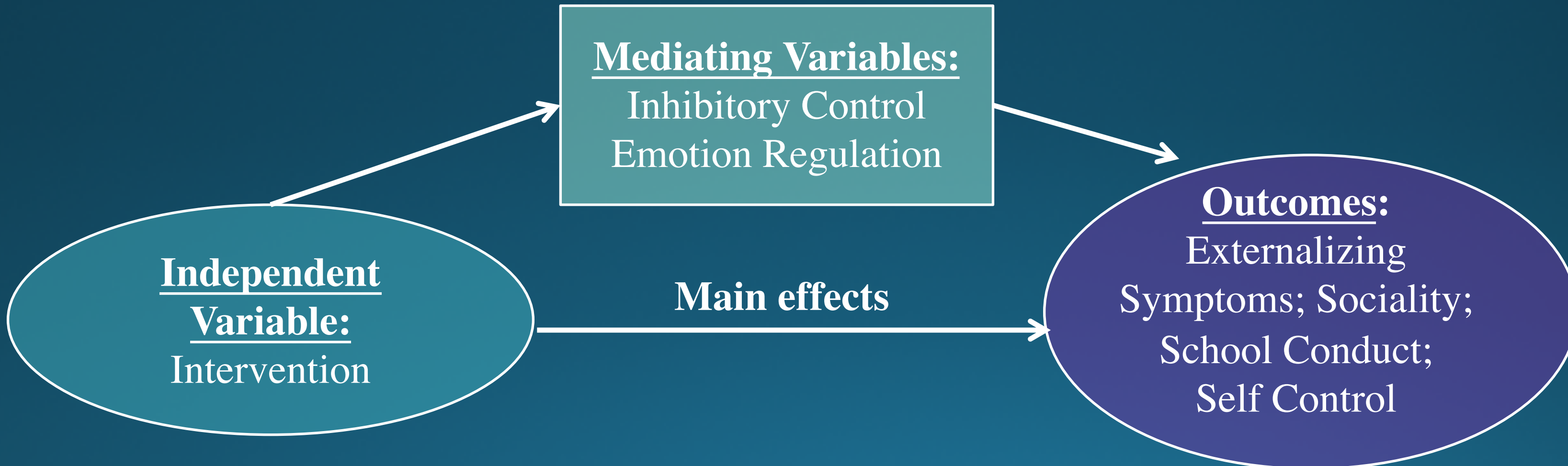
Neurobiological Model of GBG Effects



Neurodevelopmental Moderators and Mediators in Intervention Outcomes

Moderation Model (Between Experimental and Control Groups)

Mediation Model (Within Experimental Groups)*



***Change in mediators will be greater in intervention participants than the control children who experience change due only to maturation.**

Brain-Based Mindfulness Studies

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

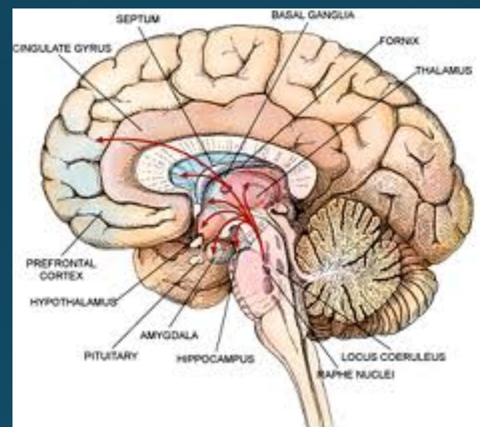
Potential Effects of Mindful Interventions on Regulatory Systems

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



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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

Mechanism of Action Involved	Proposed Process	Hypothesized Brain Areas
Increased present-moment awareness	*Bottom-up* processing of salient stimuli with or without top-down modulation of reactivity	Dorsolateral PFC, anterior cingulate cortex, ventral striatum, insula, amygdala
Improved attentional control	*Top-down* modulation of attention	PFC, anterior cingulate cortex
Greater self-regulation	*Top-down* improved inhibitory control	Medial PFC, orbitofrontal cortex, anterior cingulate cortex
Increased self-awareness	*Bottom-up* processing of salient stimuli	Anterior cingulate cortex, insula
Develop and implement new way to approach discomfort	*Top-down* modulation of responses to discomfort and decision making	Ventromedial PFC, dorsal striatum, amygdala
Reduced reactivity to stress or substance cues	*Bottom-up* reactivity	Anterior cingulate cortex, ventral striatum

Adapted from Witkiewitz, Lustyk, and Bowen, 2012

Optimization

Conceptual Model

Mindful Yoga

Practices and Skills

All Practices
- Physical Poses
- Intention Setting
- Focused Attention

Mindfulness Meditation
- Senses
- Emotion
- Thought

Breath Work

Primary Neurophysiological Mechanisms

Neuroplastic Changes

- Physiologic Patterns of Arousal
- *Executive Control and*
- *Sleep Patterns*

Secondary Psychological Processes

Clinical-Developmental Processes

Emotion Regulation
- Cognitive control over affective responses
- Rumination
- Intrusive Thoughts
- Arousal to Stressful Events

MEASURES

Implementation Data
Analysis of Practices

HRV (Acute Stress & Nocturnal)
Vigilance Task
MAAS-A
Actigraphy
Sleep Diary

Emotion Regulation Questionnaire
DARE
ESM Daily Diaries
Student Surveys
Teacher Surveys

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).

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

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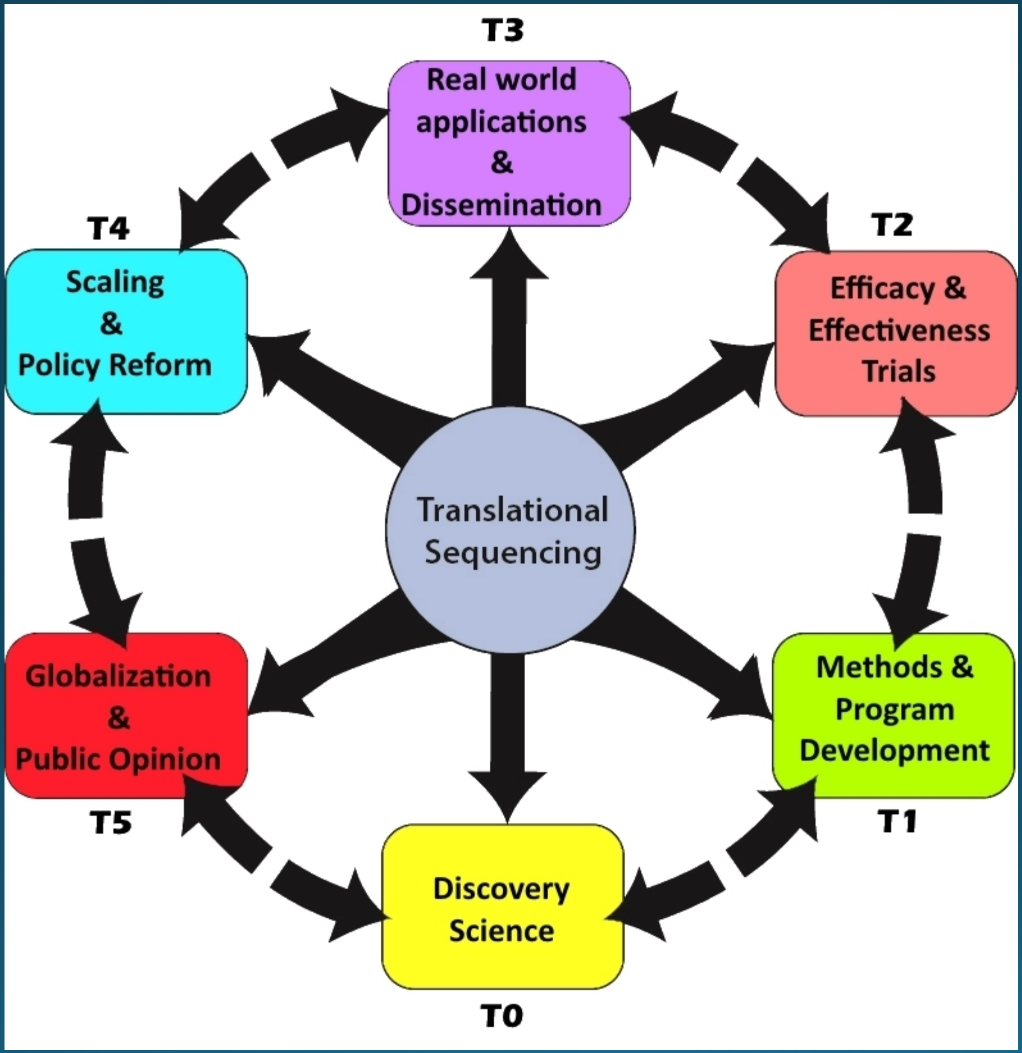

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Policy Goals

- 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

National Prevention Science Coalition to Improve Lives

- 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.npscoalition.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 and
  - 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

NIH National Institute on Alcohol Abuse and Alcoholism

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