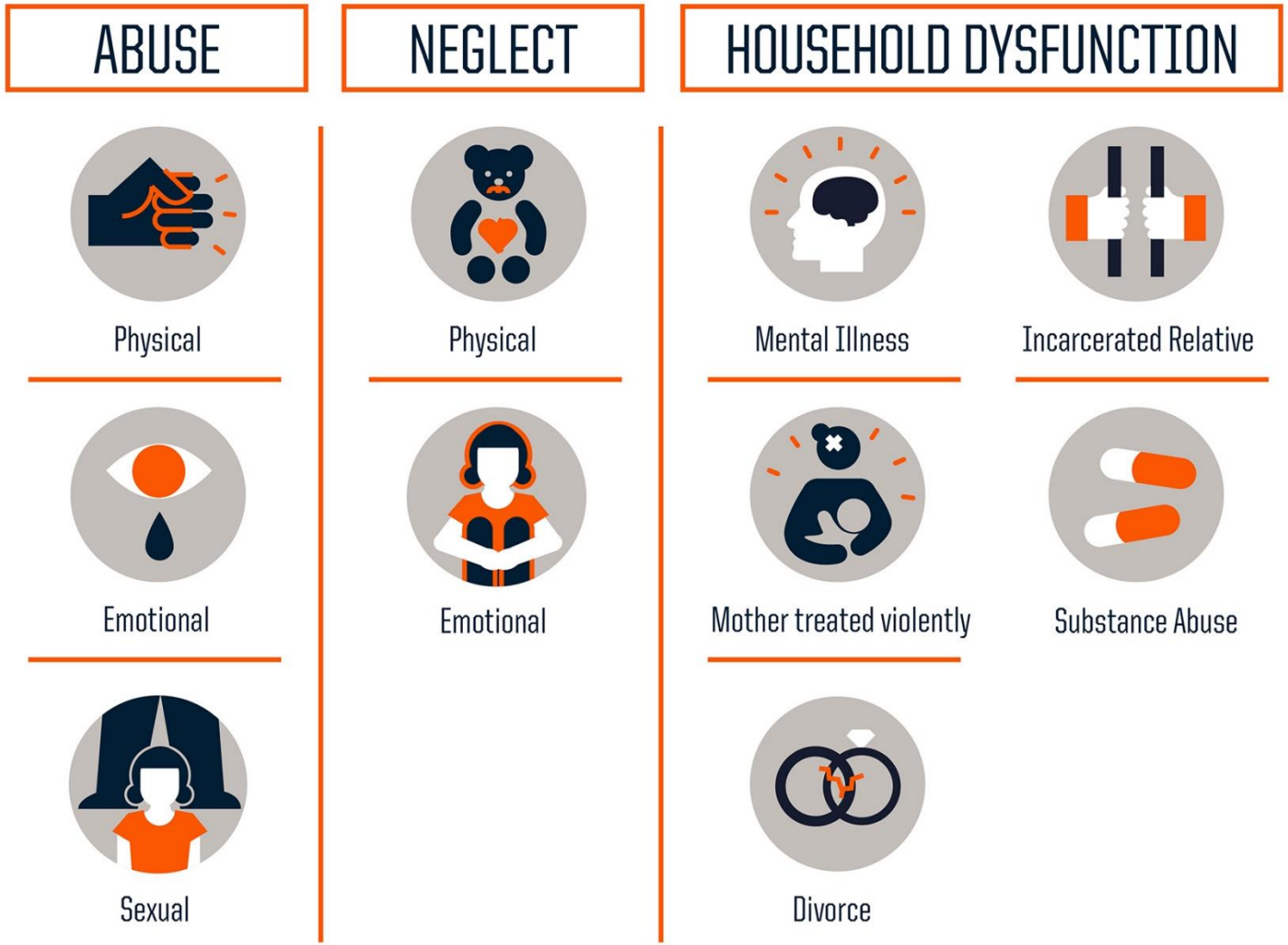
2024 Virtual Conference

Biological Factors of Success in Recovery

Todd Davies, PhD | Division of Addiction Sciences

Adverse Childhood Experience (ACE) Study

SAMHSA, 2018

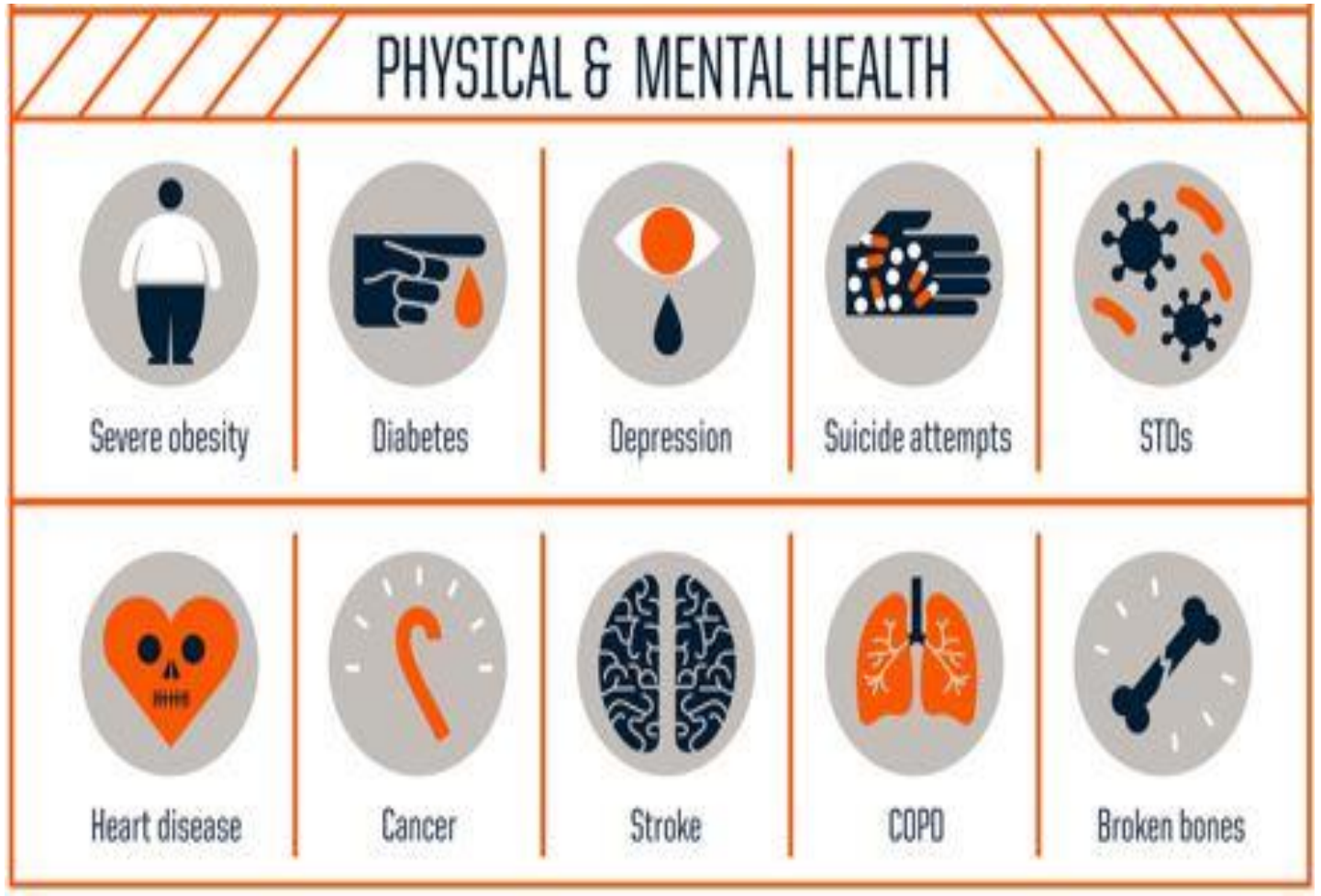


MARSHALL Health

Healthy Connections

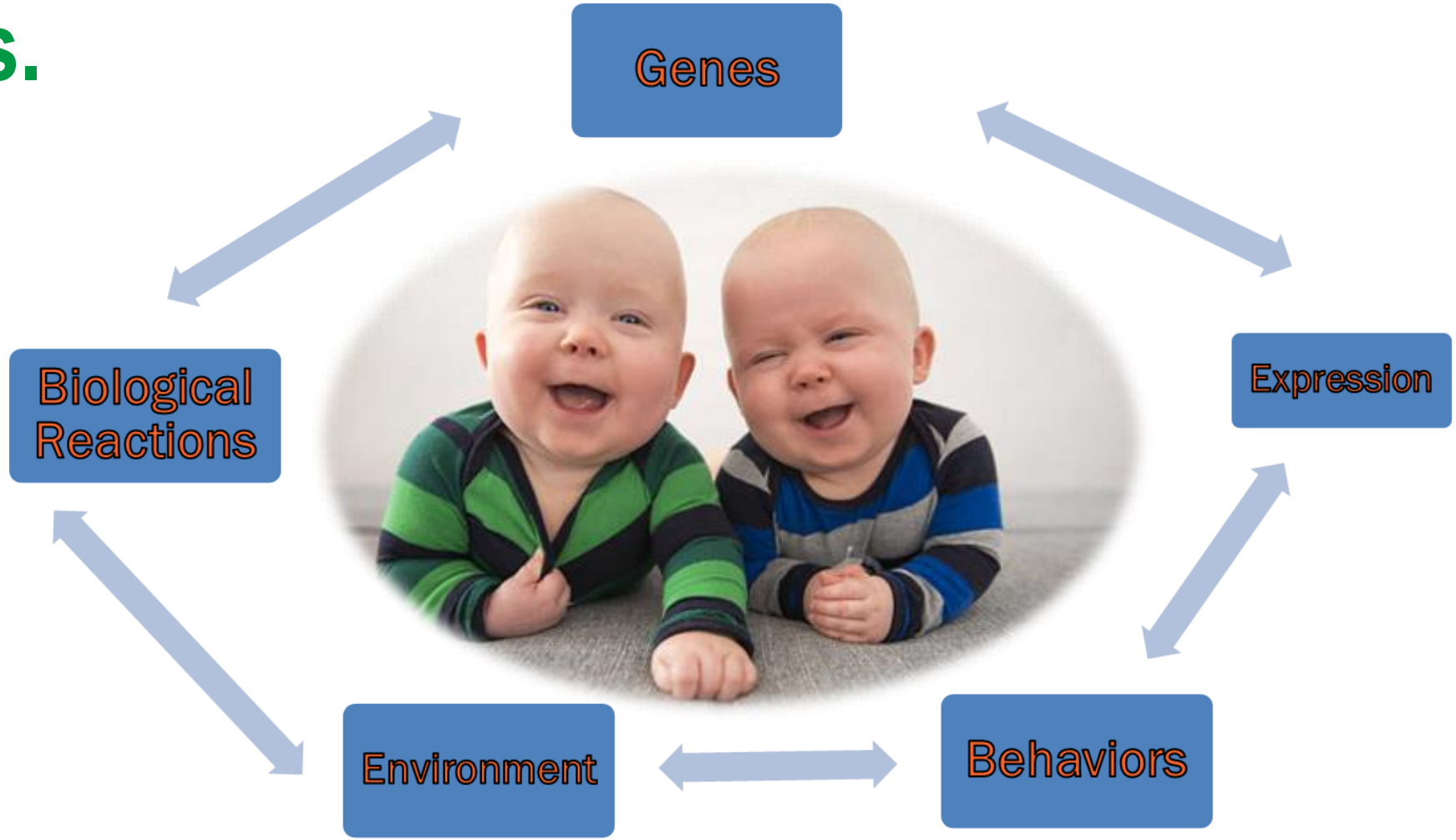
Physical Consequences of ACES

SAMHSA, 2018



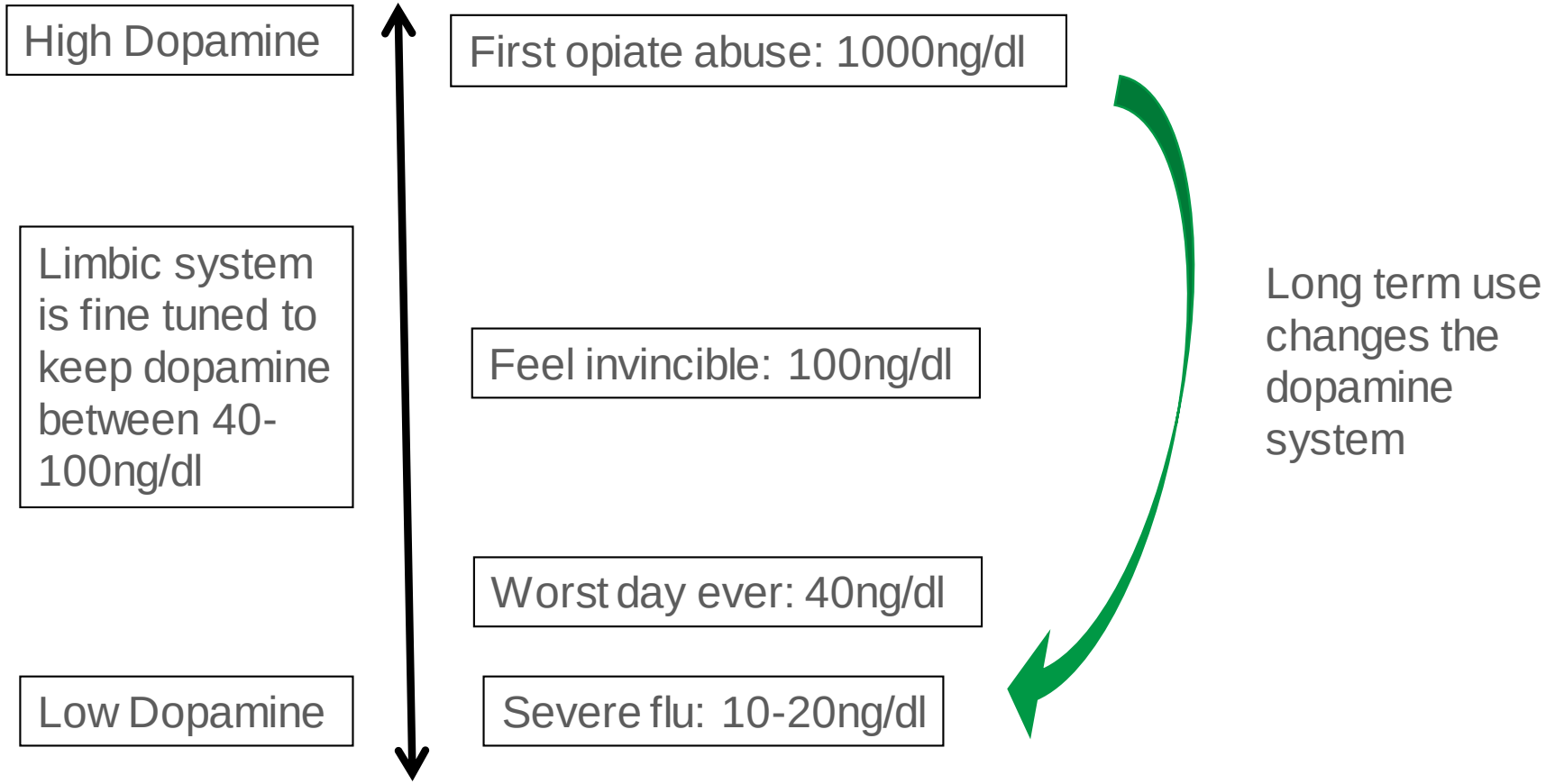
Adverse Childhood Experiences (ACES 1)	Adverse Community Environments (ACES 2)
• Witnessing parental substance misuse or overdose • Witnessing domestic violence • Entering foster care • Experiencing neglect and/or abuse • Long-term separation from parents due to incarceration • Being born with Neonatal Abstinence Syndrome (NAS)	• Food insecurity • Poverty • Disrupted community routines • Limited economic and social opportunities • Stigma and discrimination • Insecure housing • Violence and crime

Nature vs. Nurture



Trauma Processing

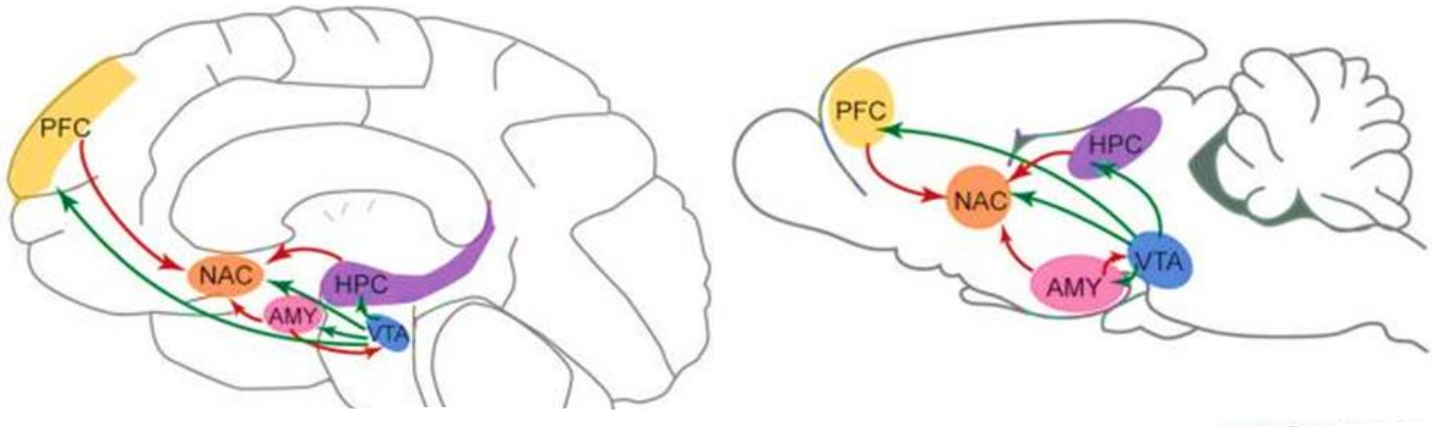
The Dopamine Story



Source: Walker, 2015. California Health Care Foundation

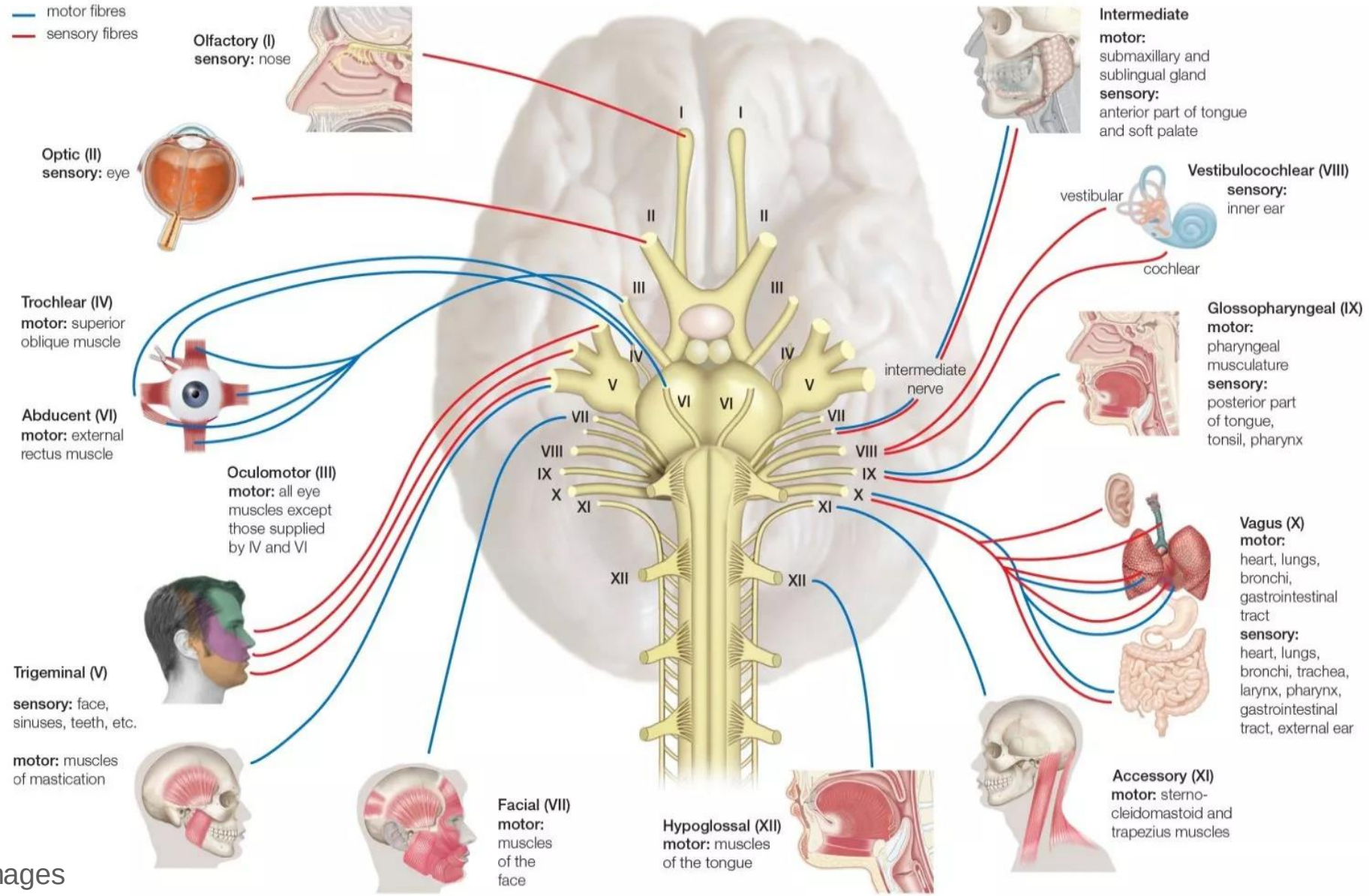
Addiction influences the mesolimbic pathway

- **Prefrontal Cortex (PFC):** Judgment, Self-Control, Decision-Making
- **Nucleus Accumbens (NAC):** Interface between Motivation and Action
- **Amygdala (AMY):** Fear and Threatening Stimuli
- **Hippocampus (HPC):** Learning and Memory
- **Ventral tegmental area (VTA):** Reward, Motivation, Cognition, Aversion



Order of Mesolimbic Processing of Environmental Stimulus

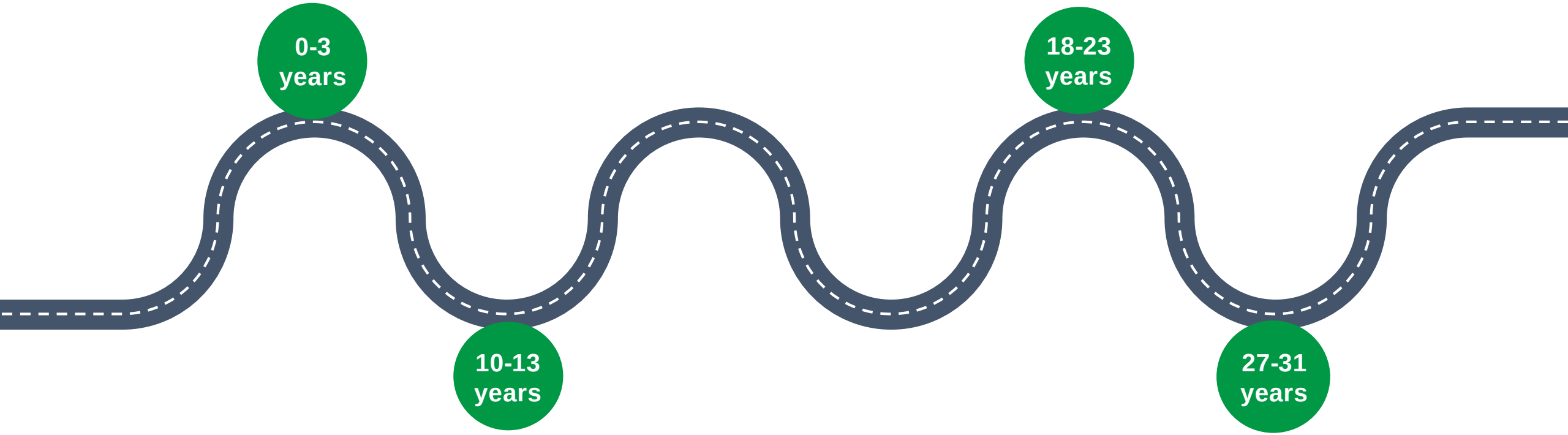
1. Reward - Safe/Unsafe or Pleasure/Pain
2. Emotional Regulation
3. Motor Function
4. Decision Making
5. Judgement



Encyclopedla Britannica / Getty Images

Identification of **Risk Factors** – Major Neurodevelopment

Typical Diagnosis of OUD/SUD – **First Overdose Recorded**



Average Age at First Use – Initial Presentation of Unhealthy Behaviors

Average Age to **Begin Treatment**

DNA

- **Genetics - DNA**
  - DNA modifications found to be associated with addiction are related to receptor binding or drug metabolism

- **Epigenetics – DNA modification**
  - Epigenetic modifications associated with addiction are related to limbic system or HPA Axis
  - Mechanism for long-term biological adaptation of an organism to environmental stimuli
  - Heritable
  - Reversable

Epigenetics - gene expression, not gene change

- A **heritable** and **reversible** modification of gene expression.
  - Methylation of gene promotor
  - Histone acetylation modification
  - Other modification that results in non-coding RNA

- **Often induced by:**
  - Trauma
  - Pre/postnatal stressors
  - Early life rearing

Addiction Influences the Mesolimbic Pathway

Front. Genet., 24 January 2022
Sec. Epigenomics and Epigenetics
Volume 13 - 2022 |
https://doi.org/10.3389/fgene.2022.806685

Brain region	DNMT and/or TET evaluations	Global level and/or gene-specific DNA modification measurements	Genome-wide DNA modification profiling
Orbitofrontal Cortex			Kozlenkov et al. (2017)
Prefrontal Cortex	Ponomarev et al. (2012); Tian et al. (2012); Barbier et al. (2015); Wright et al. (2015); Hashimoto et al. (2017); Vrettou et al. (2017); Saad et al. (2019); Fan et al. (2020)	Ponomarev et al. (2012); Tian et al. (2012); Barker et al. (2013); Qiang et al. (2014); Baker-Andresen et al. (2015); Barbier et al. (2015); Wright et al. (2015); Wang F. et al. (2016); Saad et al. (2019); Fan et al. (2020); Salehzadeh et al. (2020); Iamjan et al. (2021); Vrettou et al. (2021); Yang et al. (2021)	Manzardo et al. (2012); Baker-Andresen et al. (2015); Wang F. et al. (2016)
Caudate Putamen	Vrettou et al. (2017); Saad et al. (2019)	Barker et al. (2013); Bendre et al. (2019); Saad et al. (2019); Vaillancourt et al. (2021a); Vaillancourt et al. (2021b); Vaillancourt et al. (2021a); Vaillancourt et al. (2021b); Vrettou et al. (2021)	Vaillancourt et al. (2021b); Zillich et al. (2021)
Nucleus Accumbens	Numachi et al. (2007); Anier et al. (2010); LaPlant et al. (2010); Warnault et al. (2013); Chandra et al. (2015); Feng et al. (2015); Finegersh et al. (2015); Wright et al. (2015); Anier et al. (2018); Cannella et al. (2018); Jayanthi et al. (2018); Urb et al. (2020); Vaher et al. (2020); Jiang et al. (2021)	Anier et al. (2010); Anier et al. (2013); Barbier et al. (2015); Feng et al. (2015); Massart et al. (2015); Wright et al. (2015); Cadet et al. (2017); Cervera-Juanes et al. (2017b), Cervera-Juanes et al. (2017a); Engmann et al. (2017); Anier et al. (2018); Jayanthi et al. (2018); Bendre et al. (2019); Jayanthi et al. (2020); Vaher et al. (2020); Vaher et al. (2020)	Feng et al. (2015); Massart et al. (2015); Cadet et al. (2017); Cervera-Juanes et al. (2017b), Cervera-Juanes et al. (2017a)
Globus Pallidus and Ventral Pallidum		Vetreno et al. (2020)	
Hippocampus	Liu et al. (2018); Fan et al. (2020); Zhang et al. (2020); Chen et al. (2021); Fan et al., 2021; Jiang et al. (2021)	Barker et al. (2013); Barrow et al. (2017); Fan et al. (2019a); Fan et al. (2020); Fan et al. (2021); Iamjan et al. (2021)	Sadakierska-Chudy et al. (2017)
Amygdala	Sakharkar et al. (2014); Augier et al. (2018); Sakharkar et al. (2019)	D'Addario et al. (2013); Sakharkar et al. (2019)	
Hypothalamus		Comasco et al. (2015); Barrow et al. (2017)	
Ventral Tegmental Area	Vrettou et al. (2017); Fan et al. (2019b)	Fan et al. (2019b); Maier et al. (2020); Vrettou et al. (2021)	

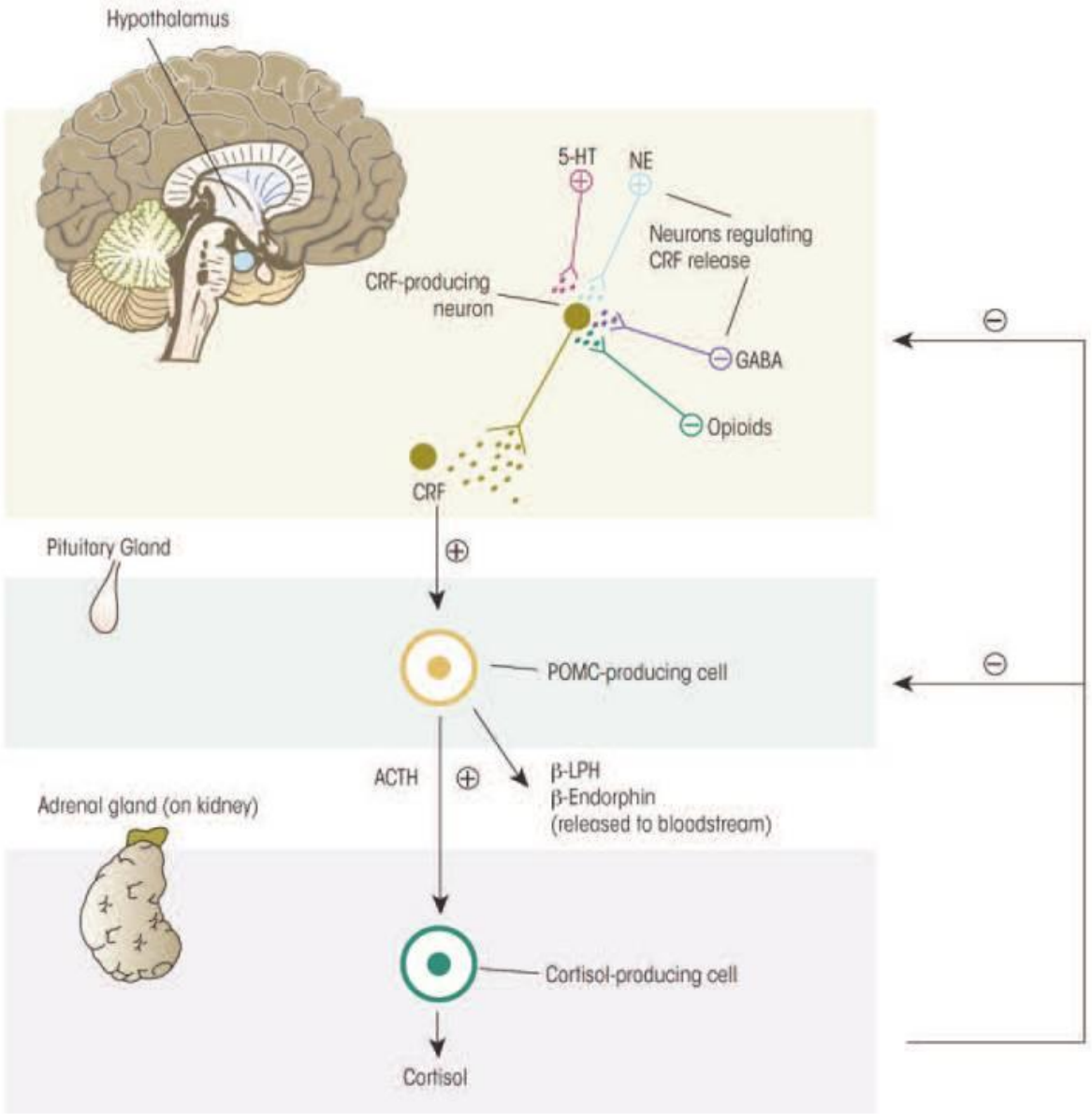
The table summarizes the primary publications that directly assessed DNMT and/or TET expression, global or gene-specific DNA modifications, or profiled genome-wide DNA modification landscapes after drug exposure. All citations are listed in the format of first author and year of publication. "Brain region" denotes the brain area in which results were obtained. "DNMT and/or TET evaluations" includes studies where changes in DNA methyltransferases and/or TET methylcytosine dioxygenases were examined. "Global level and/or gene-specific DNA modification measurements" includes studies where global DNA modification levels and/or gene-specific DNA modifications were assessed. "Genome-wide DNA modification profiling" includes studies in which drug-induced DNA modifications were assessed using a genome-wide or whole-genome approach (i.e., microarray or next-generation sequencing).

Epigenetics is a Mechanism by Which Neuroadaptation in Trauma and Substance Use Can Happen

Examples:

Methylation at BDNF-ADS221 [CpG#-448 cg06991510] is positively associated with Household Incarceration (0.71 p=0.038) and negatively associated with negative poor recovery outcomes (length of stay in program: 0.70 p= 0.046).-**Potential Resiliency factor**

Methylation at BDNF-ADS3873 [CpG#4] is negatively associated with Household Incarceration (-0.80 p=0.035) and positively associated with negative poor recovery outcomes (length of stay in program: 1.52 p=0.005). –**Potential Trauma indicator**



Stephens MA, Wand G. Stress and the HPA axis: role of glucocorticoids in alcohol dependence. Alcohol Res. 2012;34(4):468-483.

Catecholamines

Catecholamines: **Dopamine, Adrenaline (Epinephrine), Noradrenaline (Norepinephrine).**

Functions

- **Fight-or-Flight Response:**
  - Increases heart rate and blood pressure.
  - Boosts energy levels.

Neurotransmitter Role:

- Regulates movement, emotions, and memory.

Key Point

- Catecholamines are central in environmental response.

Dopamine the Neurotransmitter

- Movement
- Memory
- Pleasurable reward and motivation
- Behavior and cognition
- Attention
- Sleep and arousal
- Mood
- Learning
- Lactation

Dopamine the Hormone

As a hormone, dopamine is involved in:

- Causes blood vessels to relax (at low doses, it acts as a vasodilator) or constrict (at high doses, it acts as a vasoconstrictor).
- Increases sodium (salt) and urine removal from your body.
- Reduces insulin production in your pancreas.
- Slows gastrointestinal (GI) (gut) content movement and protects your GI lining.
- Reduces lymphocyte activity in your immune system.

Epinephrine and Noerepinephrine as Neurotransmitters and Hormones

As a hormone, epinephrine and noerepinephrine is involved in:

- Epinephrine acts as a hormone and neurotransmitter, increasing heart rate and blood flow during fight-or-flight responses.
- Norepinephrine functions primarily as a neurotransmitter, regulating attention, alertness, and blood pressure.
- Both substances play crucial roles in the body's response to stress but have distinct effects and mechanisms of action

Now for the good stuff!

- Mary Edwards, MS
  - Funding: Pallotine Foundation, St. Joseph Foundation, WV ACEs Coalition
- Taylor Maddox-Rooper, MS
  - Funding: Gilead Foundation grant through UPMC Magee Women and Children's Hospital
- Lacey Andrews, MCT, CCRC, CCRA
  - Funding: NIDA
- Michael Hambuchen, PhD, PharmD
  - Funding: John Marshall University Scholars Program, Marshall University School of Pharmacy Faculty Research Support Program