A Heuristic Domain Framework for Understanding the Prevention, Diagnosis, and Treatment of Alcohol Use Disorders

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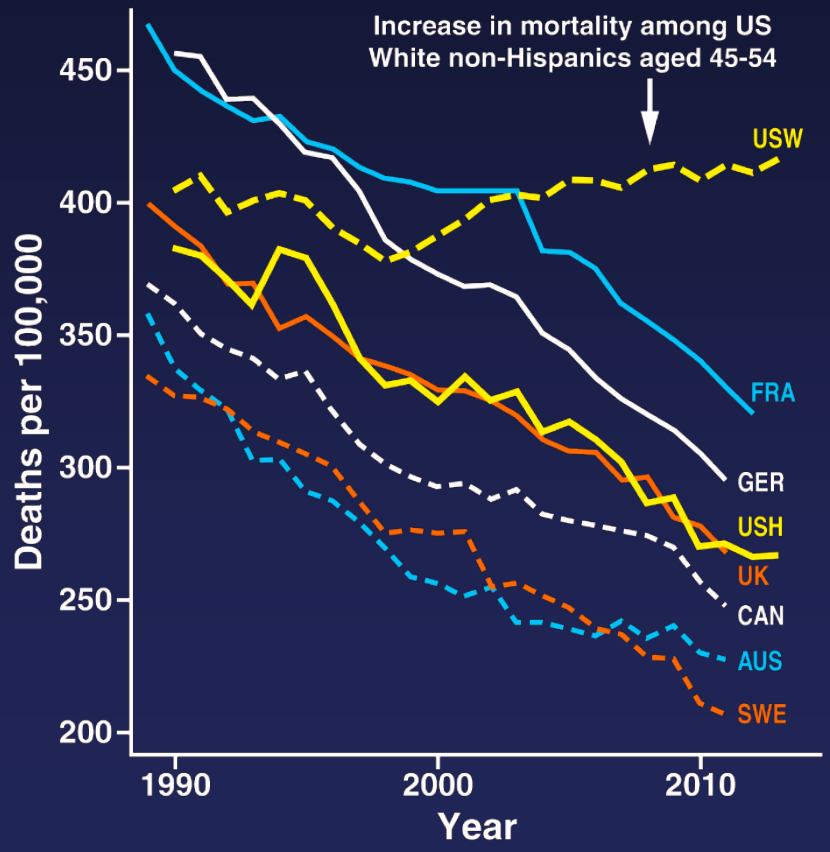
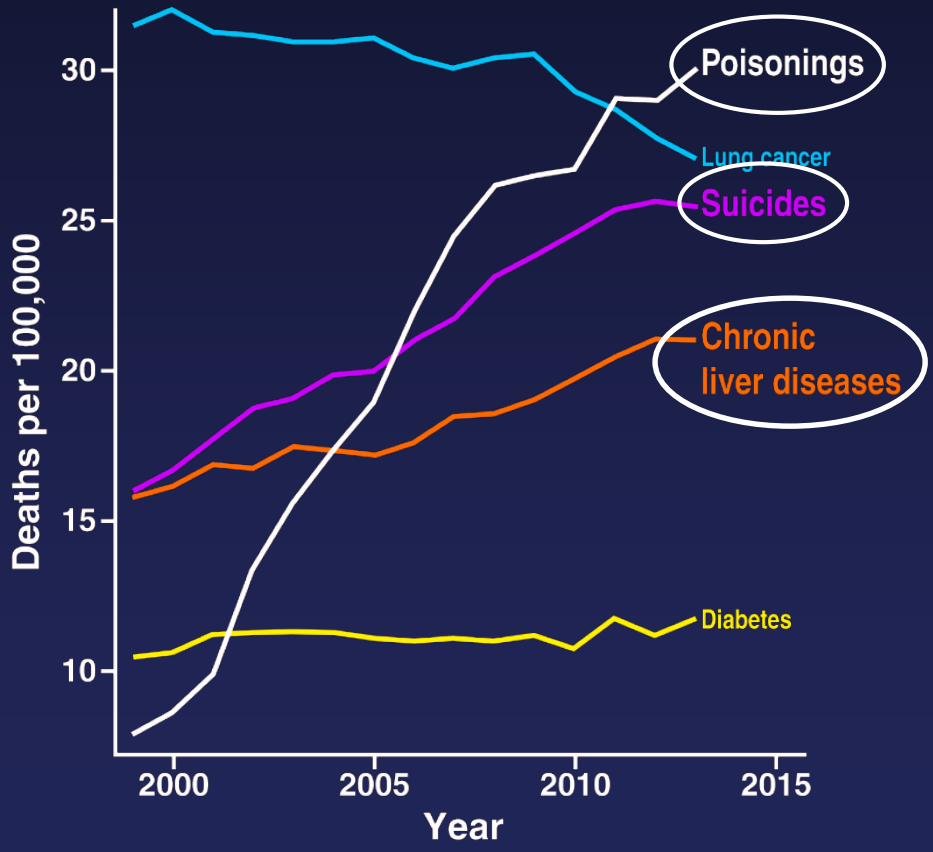
National Institute on Alcohol Abuse and Alcoholism

“Deaths of Despair”

All-cause mortality, ages 45-54 for
US White non-Hispanic (USW), US Hispanics (USH)
and six comparison countries



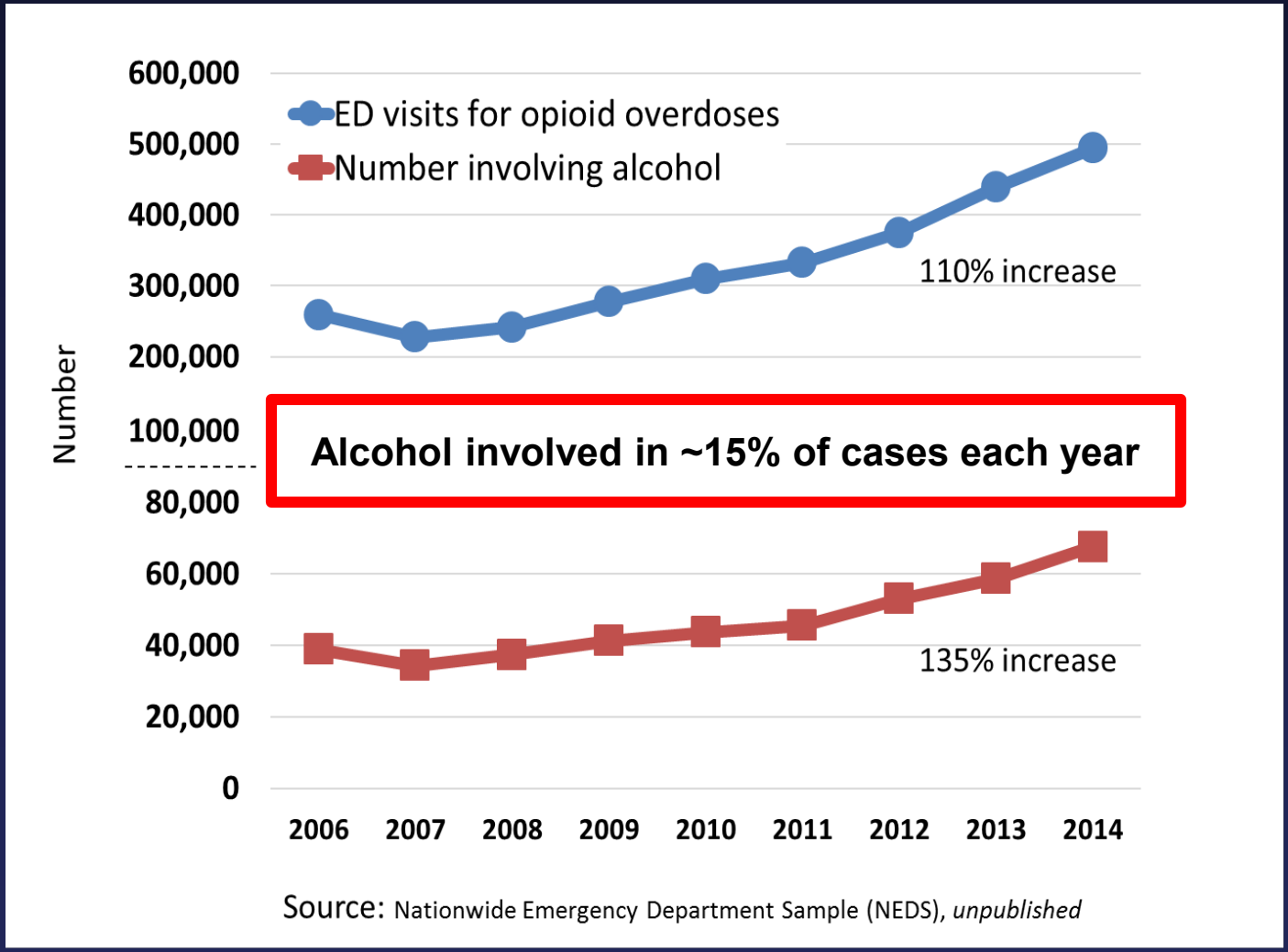
Mortality by cause,
White non-Hispanics ages 45-54



Source: Case, A and Deaton, A (2015) Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. PNAS 112: 15078-15083.

Alcohol and Opioids: A Dangerous Combination

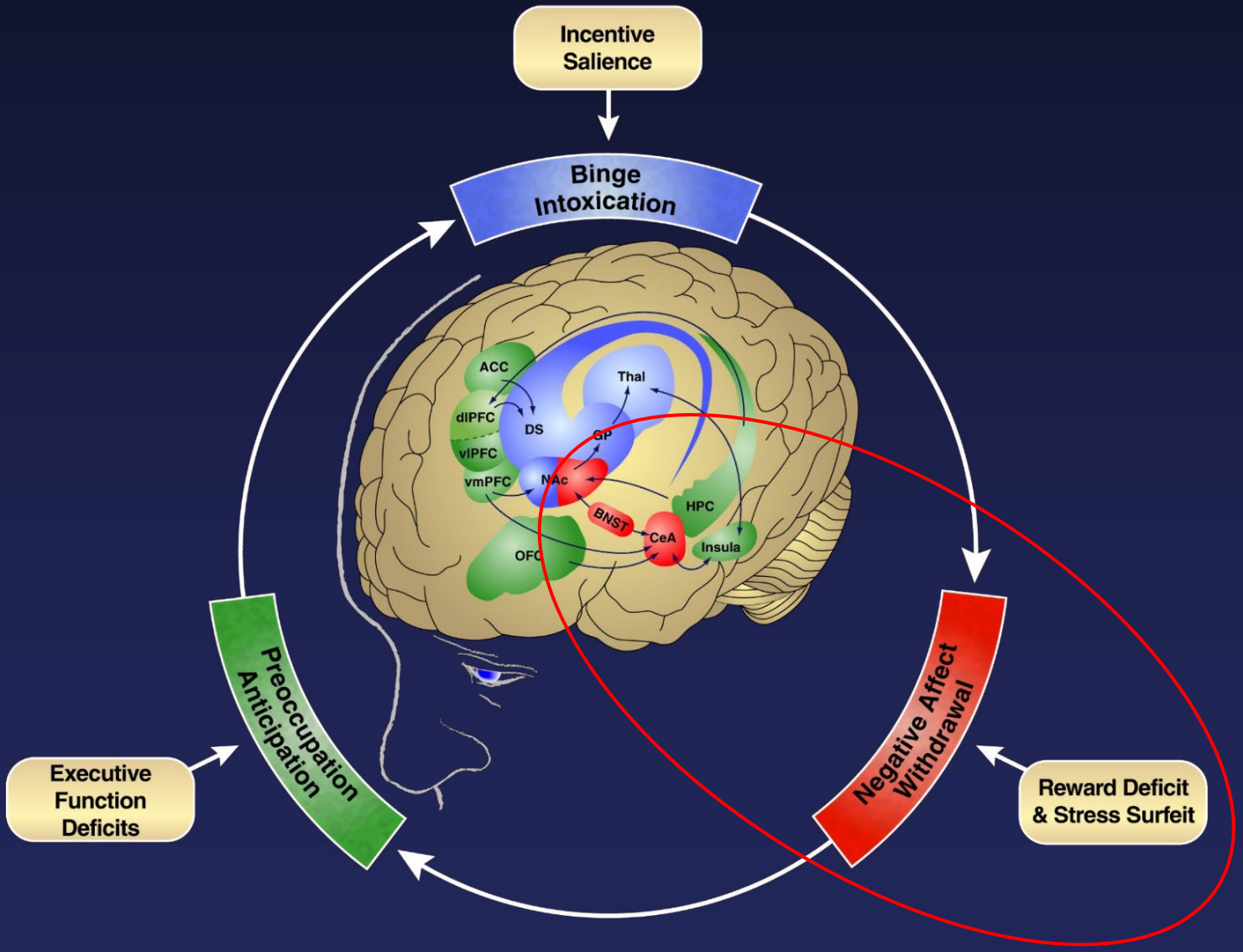
Increase in Emergency Department Visits



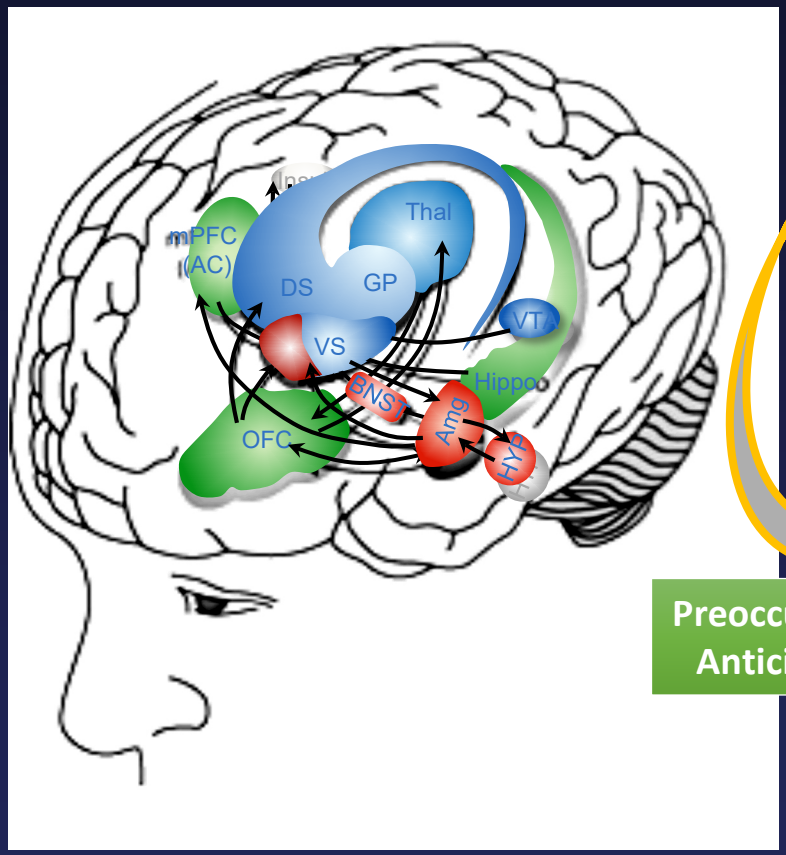
Source: Nationwide Emergency Department Sample (NEDS), *unpublished*

Conceptual Framework

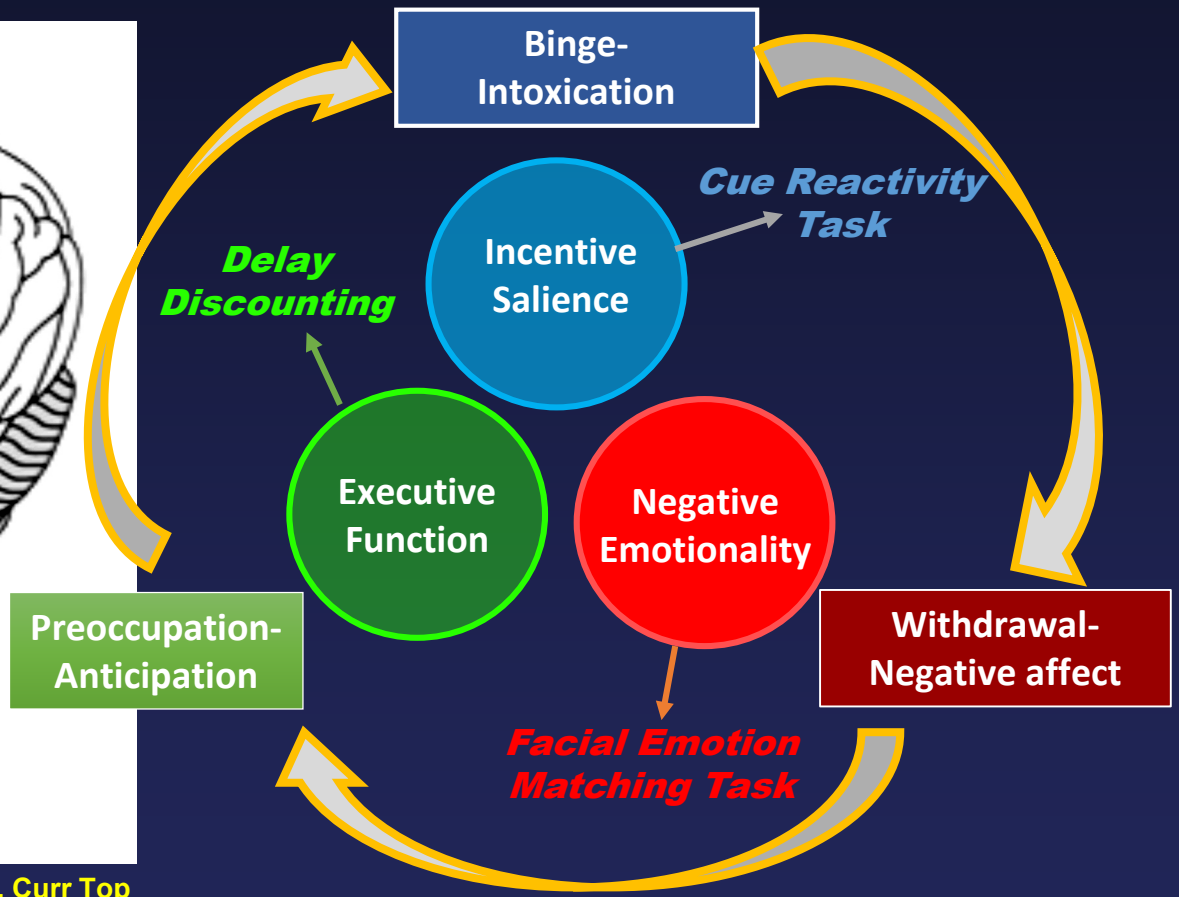
Neurobiological Bases Driving Substance Use Disorders



Addictions Neuroclinical Assessment Associations with Neurocircuits Provides a Framework for improved Diagnosis, Prevention and Treatment



Adapted from George Koob . Curr Top Behav Neurosci. 2011 Jul 10.

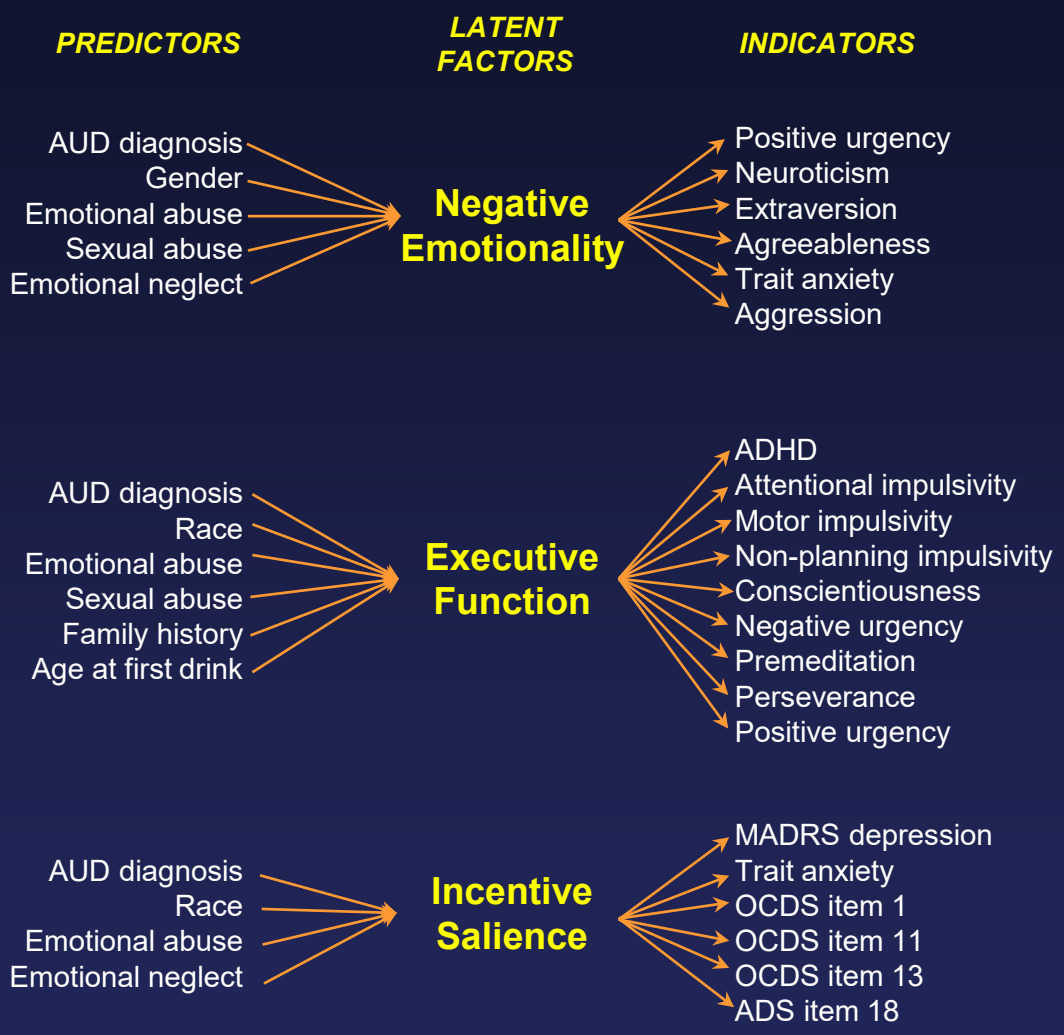


Modified from Kwako LE et al. Biological Psychiatry, 2016

Neurofunctional Domains Derived from Deep Behavioral Phenotyping in Alcohol Use Disorder

This study examined three key neurobiological domains that are critical to the addiction cycle (incentive salience, negative emotionality, and executive function) in a large, diverse clinical sample of individuals representing the spectrum of AUD.

Measures of addiction, personality, cognition, behavior, and exposure to early-life stress were collected. Using a multiple indicators, multiple causes approach, the study confirmed the relevance of the three neurofunctional domains to AUD.



Source: Kwako LE, Schwandt ML, Ramchandani VA, Diazgranados N, Koob GF, Volkow ND, Blanco C, and Goldman D. Am J Psychiatry. Epub 2019 Jan 4.

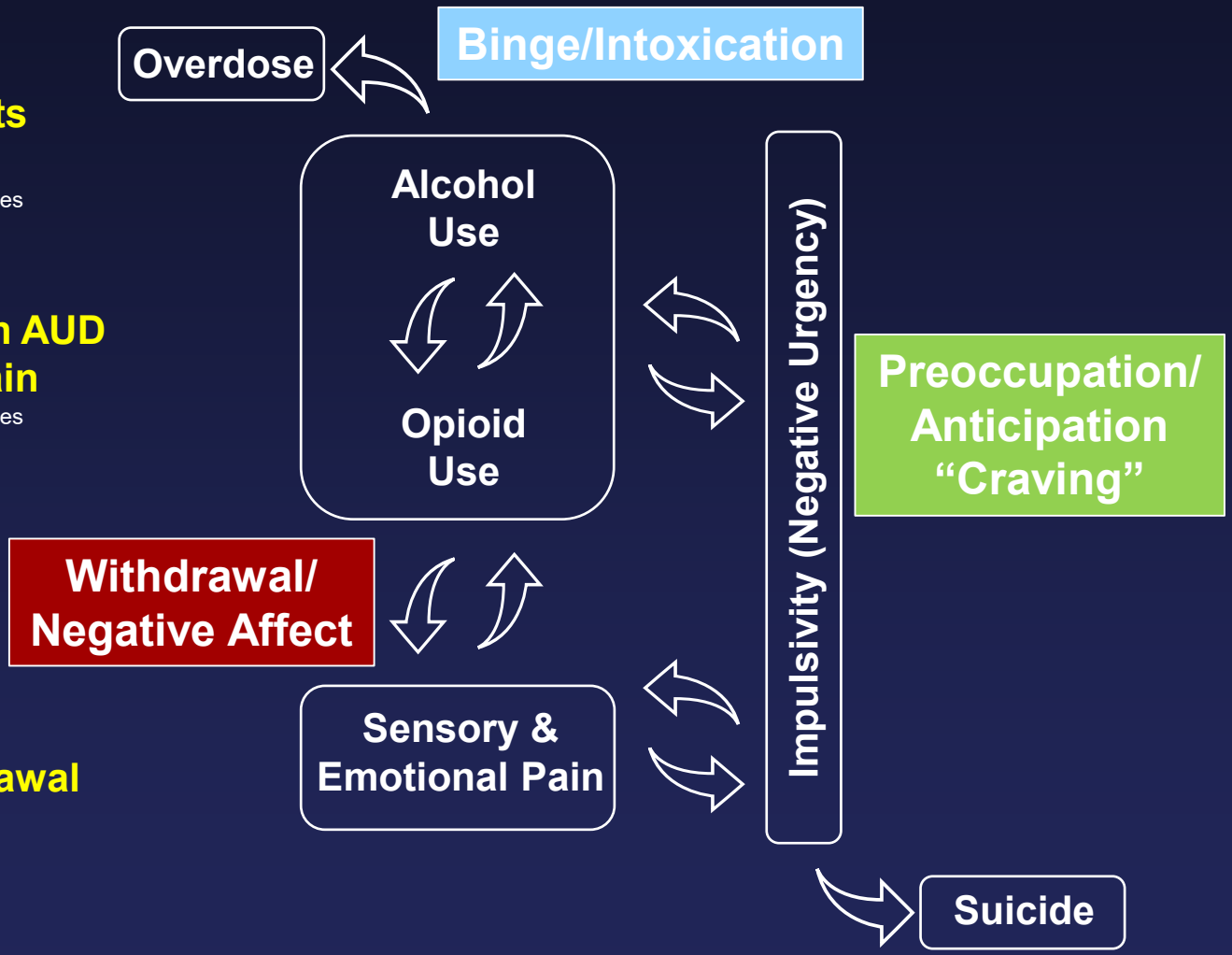
Alcohol, Opioids, and Pain

16-25% chronic pain patients drink heavily or have AUD
K Witkiewitz & KE Vowles (2018) Alcohol Clin Exp Res

43%-73% of individuals with AUD have moderate to severe pain
K Witkiewitz & KE Vowles (2018) Alcohol Clin Exp Res

Acute alcohol (at binge levels) is *analgesic* (relieves pain)
T Thompson et al. (2017) Journal of Pain

Chronic alcohol and withdrawal produce *hyperalgesia* (increased pain sensitivity)
S Edwards et al. (2012) Neuropharmacology



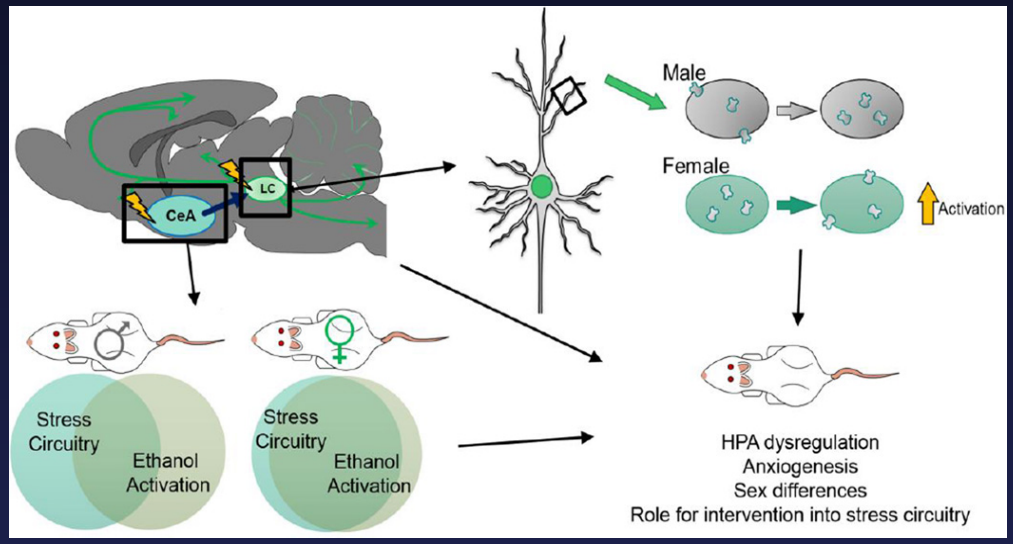
Adapted from Dr. Mark Egli, NIAAA

Preclinical Neurobiological Mechanisms Mediating Increased Stress and Pain in Females

Hypotensive stress causes female locus coeruleus (LC) neurons to fire faster than those of males and is mediated by increased sensitivity to corticotropin releasing factor (CRF) *(Curtis and Valentino, 2006)*

In both central nucleus of the amygdala (CeA) and LC, males show greater habituation to alcohol-induced neuronal activation than females, which may increase female vulnerability to additional stressors *(Retson et al., 2016)*

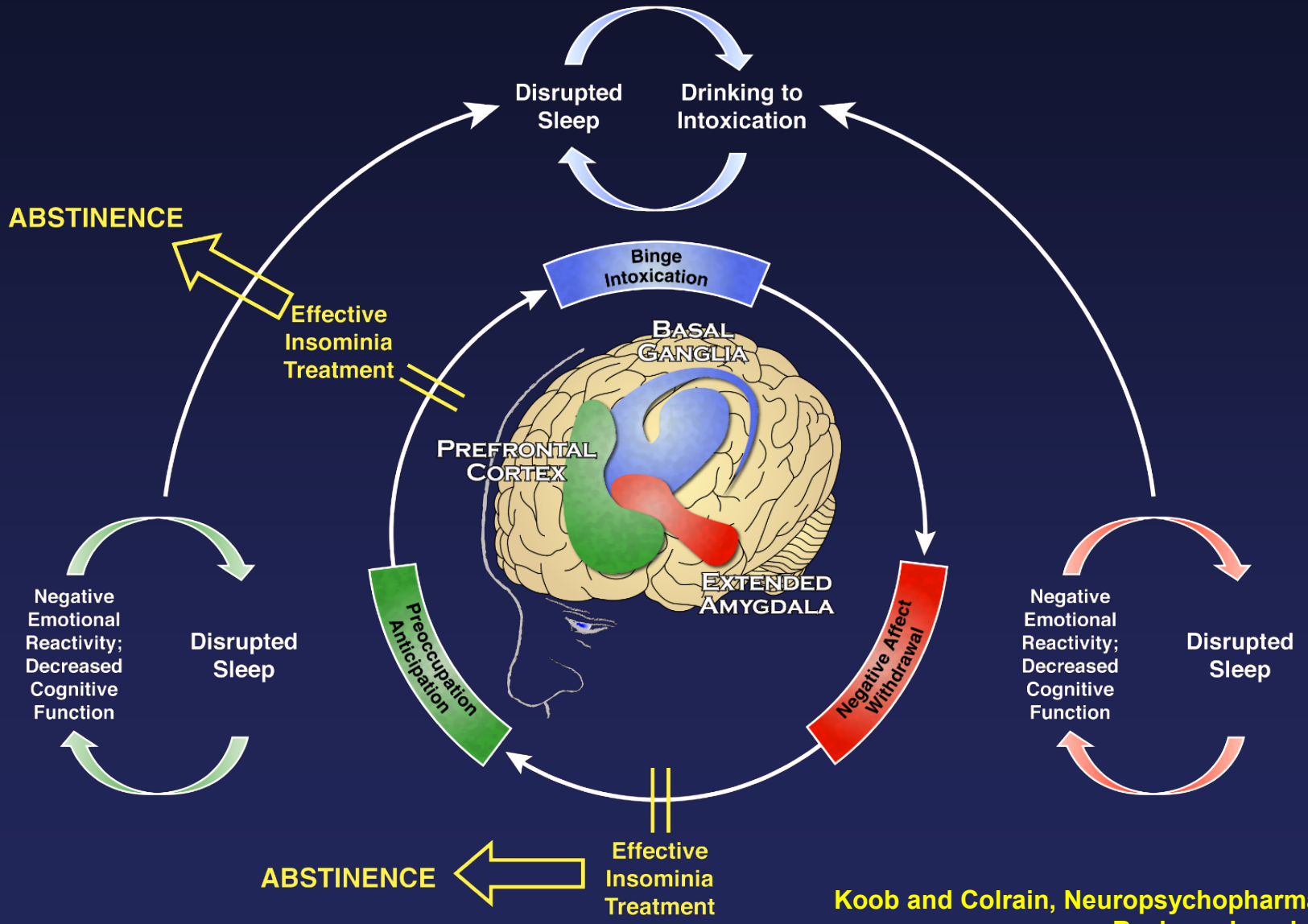
Attenuated morphine analgesic responses are attenuated in females due to increased microglia activation in the periaqueductal gray *(Doyle et al., 2017)*



In males, stress and chronic ethanol exposure each activate distinct neuronal populations in the CeA. In females, similar distributions of CeA neurons are activated in response to stress or chronic ethanol exposure.

In the LC, stress alters CRFr function in a sex-specific manner. In females, stress enhances cellular signaling and compromises internalization of CRFrs, which renders females more sensitive to low levels of CRF and less adaptable to high levels of CRF. *(Retson et al., 2016)*

Emerging Issue: Alcohol Use Disorder and Sleep Disturbance – A Feed Forward Allostatic Framework

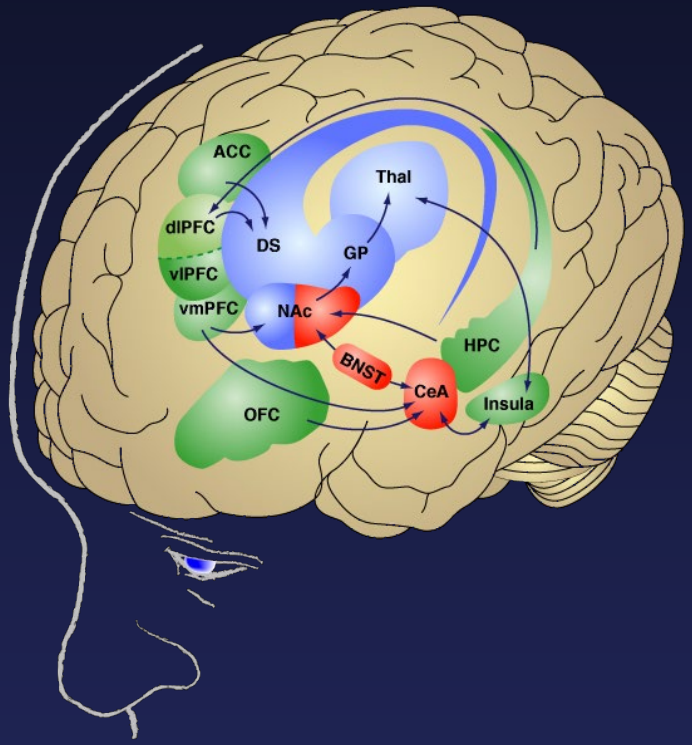


Koob and Colrain, Neuropsychopharmacology Reviews, In submission

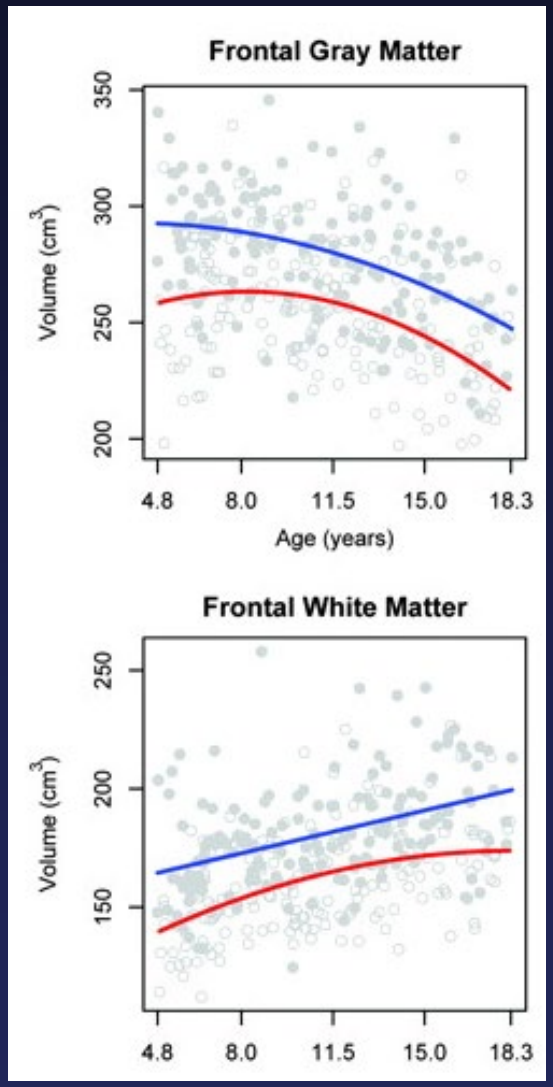
Response to an Emerging Issue: Addressing AUD and Co-Occurring Conditions

- AUD frequently co-occurs with other SUDs and mental health conditions (e.g., depression, bipolar disorder, anxiety disorders, PTSD)
- AUD patients with co-occurring mental health conditions tend to have poorer prognosis
- NIAAA supports research to elucidate the relationship between AUD and co-occurring conditions and develop preventive and treatment interventions
- **Alcohol-PTSD Comorbidity: Preclinical Studies of Models and Mechanisms**
  - RFA Issued in collaboration with Cohen Veterans Bioscience
  - To develop, validate, or apply animal models for **mechanistic studies of comorbid PTSD and AUD**

The Science of Prevention: 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



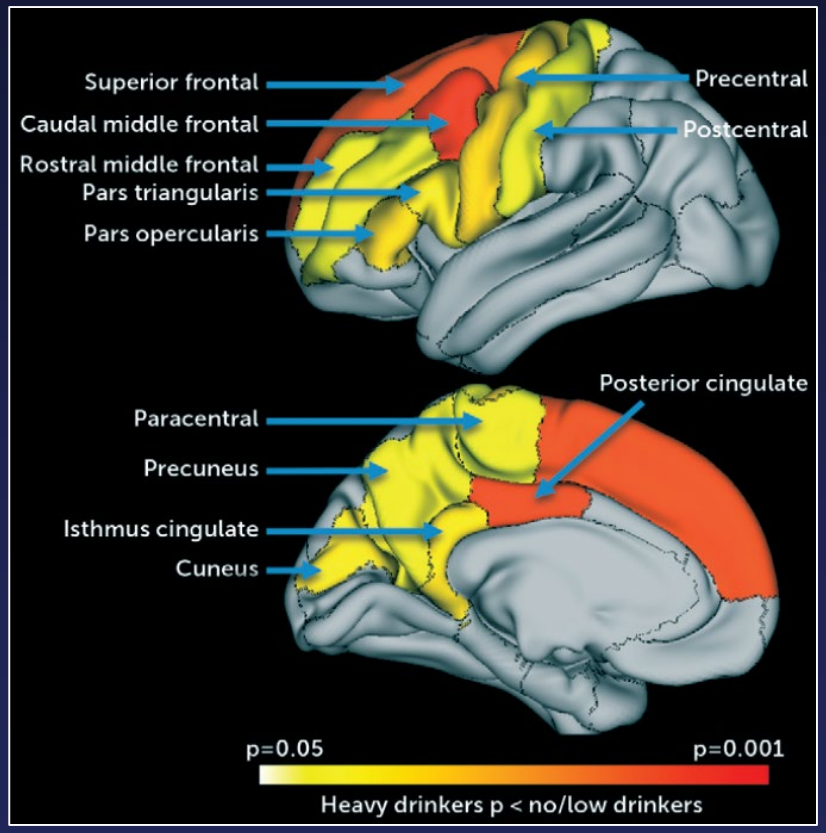
Source: Ball W et al with the Brain Development Cooperative Group (2012). Total and regional brain volumes in a population-based normative sample from 4 to 18 years: the NIH MRI Study of Normal Brain Development. *Cerebral Cortex*, 22(1):1-12.

Neuroprevention: National Consortium on Alcohol and Neurodevelopment in Adolescence (N-CANDA)

- Ongoing multisite longitudinal study of more than **800 youth ages 12-21** using advanced brain images and other tools
- Objectives:
  - To elucidate the **short- and long-term effects of alcohol exposure on the developing brain**
  - To identify **brain structural and functional anomalies** that result from alcohol exposure as well as predict onset of AUD and other psychopathology
- N-CANDA has already generated a number of important research findings including evidence that **youth who drink heavily show structural abnormalities in the frontal cortex of the brain**
- N-CANDA's success demonstrated the much larger Alcohol Brain Cognitive Development (ABCD) Study could be done successfully

Progress:
National Consortium on Alcohol and Neurodevelopment in Adolescence (N-CANDA)

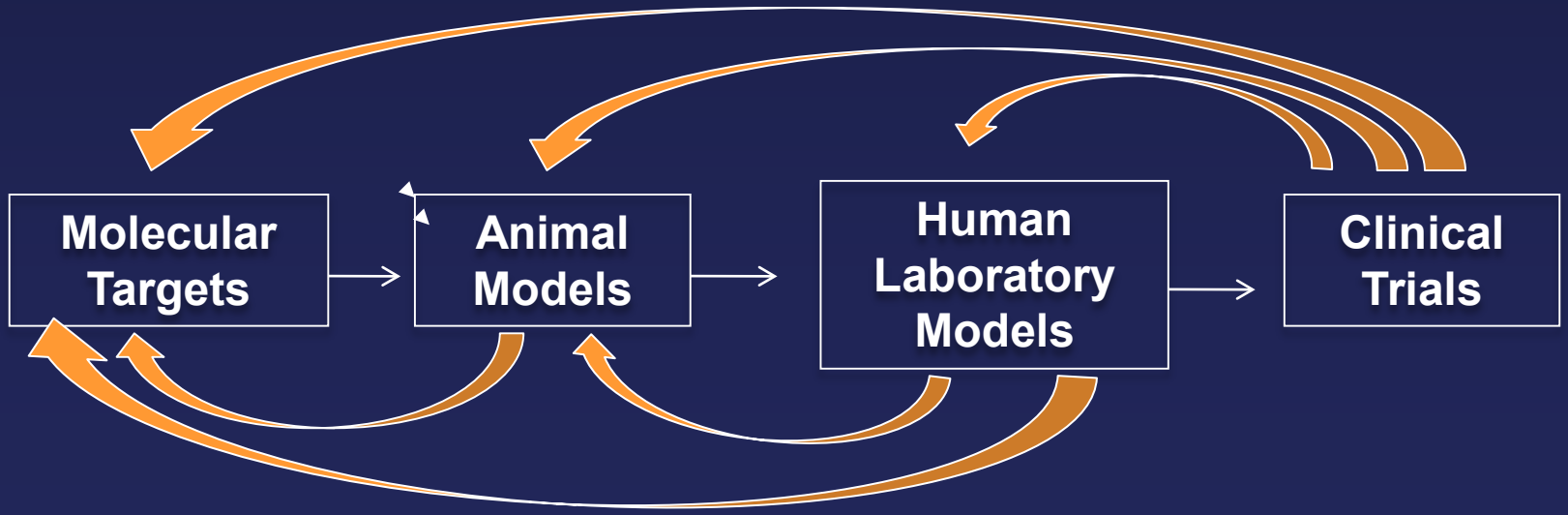
Brain regions where heavy drinking adolescents have steeper reductions in gray matter volume than no/low drinking adolescents



Source: Pfefferbaum A, Kwon D, Brumback T, Thompson WK, Cummins K, Tapert SF, Brown SA, Colrain IM, Baker FC,Prouty D, De Bellis MD, Clark DB, Nagel BJ, Chu W, Park SH, Pohl KM, Sullivan EV. Am J Psychiatry. 2018 Apr 1;175(4):370-380

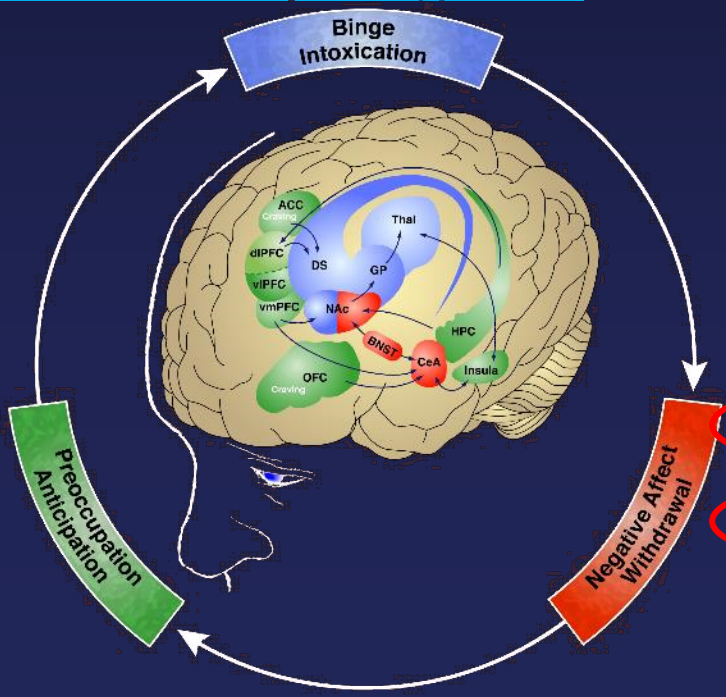
Treatment:
Developing Medications to Treat AUD

- **NIAAA Division of Medications Development:**
  - **SBIR/STTR program** facilitates studies leading to FDA IND application
  - **Human laboratory screening studies** bridge gap between preclinical and clinical trials
  - **NIAAA Clinical Investigations Group (NCIG)** conducts "fast success/fast fail" phase II clinical trials with 18 month turn-around time
- **Intramural program** conducts clinical studies on novel compounds with AUD treatment potential



Treatment:
Novel AUD Targets by Stage of the Addiction Cycle

Dopamine receptors (DRD2)
$GABA_A$ receptors (GABRA2)
Opioid receptors (OPMR1)
Acetylcholine receptors (CNRNA5)
Glycine receptors (GLRA1)
Serotonin receptors (HTR3A)
Serine/Threonine Kinases (MTOR)
Cannabinoid receptors (CNR1)
GIRK channels (KCNJ6)



Phosphodiesterases (PDE10A)
Protein kinases (PRKCE)
Transcription factors (CREB1, FOSB)
NMDA & AMPA receptors (GRIN2B, GRIA1)
Metabotropic glutamate receptors (GRM8)
Actin cytoskeleton (ACTB)
Matrix Metallopeptidase (MMP9)

Norepinephrine receptor (ADRB2)
Hypocretin (Orexin) receptor (HCRTR1)
Neuropeptide Y receptor (NPY1R)
CRF receptor (CRHR1)
Kappa opioid receptor (OPRK1)
Substance P receptor (TACR1)
Nociceptin receptor (OPRL1)
Oxytocin receptor (OXTR)
Vasopressin receptor (AVPR1B)
Glucocorticoid receptor (NR3C1)
Neuroimmune factors (NFKB1)

Treatment:
Enabling of INDs for Medications Development (U44/UT2)

- Small business (SBIR) or Small business and academic partner (STTR) opportunity
- Purpose: Translating research discoveries into new treatments for AUD or alcohol related diseases by supporting efforts to achieve an IND.
- Mechanism: U44/UT2 – cooperative agreement – work closely with NIAAA Medication's Development staff.
- Budget: Up to $1.0M total costs per year for Phase I and up to $1.5M total costs per year for Phase II may be requested.

https://grants.nih.gov/grants/guide/pa-files/PAR-15-153.html

https://grants.nih.gov/grants/guide/pa-files/PAR-15-154.html

Priority: Closing the Treatment Gap

- In the US, fewer than 10% of people with AUD receive any form of treatment
- Routine health care presents a unique opportunity for prevention, early intervention, and treatment of AUD
- However, many health care providers:
  - Do not perform alcohol screening
  - Are not aware of evidence-based
  - Do not know where to refer patients treatment

Goals

Improve physician training in substance abuse prevention and treatment at all levels

and

Integrate prevention, early intervention, and treatment into routine health care

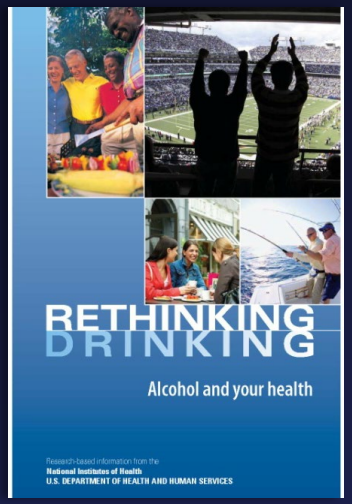
In Development: NIAAA Clinician's Core Resource

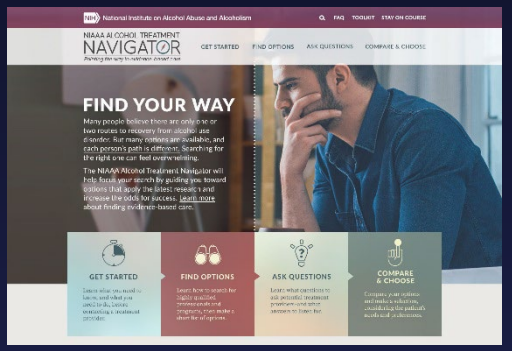
- **What every clinician needs to know about alcohol**
  - Presentation in primary care
  - Role in common co-occurring conditions
  - Neuroscience
  - Alcohol misuse across the lifespan
  - Diagnostic criteria, recommended drinking limits
  - Alcohol withdrawal syndrome
  - Evidence-based therapies/medications
  - Addressing stigma
  - Interactions with commonly used medications
- **Suggestions for practice**
  - How to start the conversation
  - Clinician's Guide, Screening Tools, Rethinking Drinking, etc.

NIAAA

Your source for credible, evidence-based information about prevention, diagnosis and treatment of alcohol use disorder

www.niaaa.nih.gov





Special Thanks:
Rachel Anderson