ADDICTION 101 AND 501

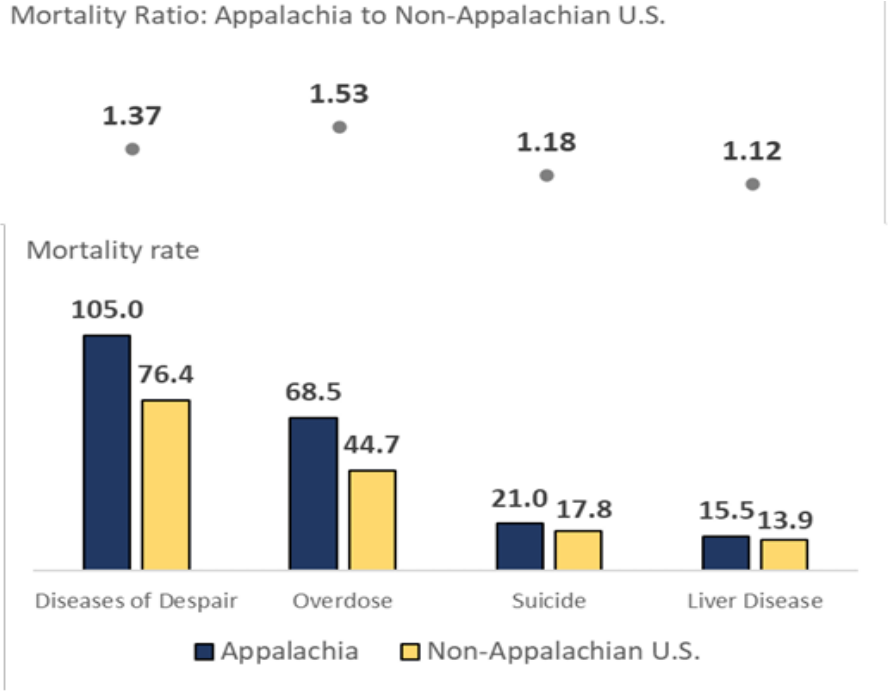
OLLI and WVU Retired Association
James H. Berry, DO
jberry@hsc.wvu.edu

OVERVIEW

- THE EPIDEMIC
- WHAT IS ADDICTION?
- NEUROMODULATION

DEATHS OF DESPAIR

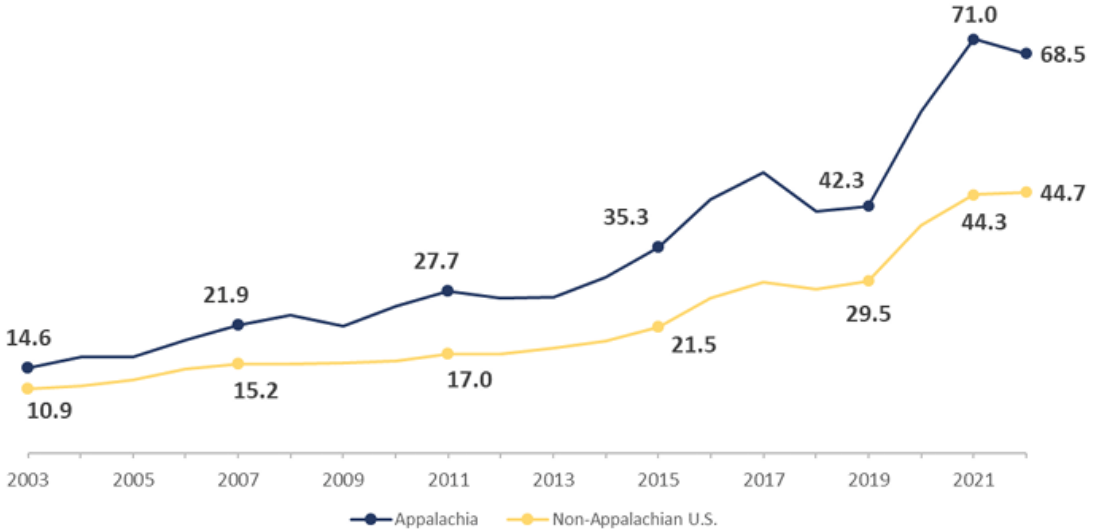
APPALACHIA: DISEASES OF DESPAIR



‡ Rates are presented as deaths per 100,000 population, and are age-adjusted.
* For all diseases, the Appalachian rate is significantly different from the non-Appalachian U.S. rate, $p \leq 0.05$.
Source: Mortality Rates and Standard Errors provided by the Centers for Disease Control and Prevention, National Center for Health Statistics. Accessed at http://wonder.cdc.gov/mcd-icd10.html.

https://www.arc.gov/report/appalachian-diseases-of-despair-2024/

APPALACHIA: OVERDOSE



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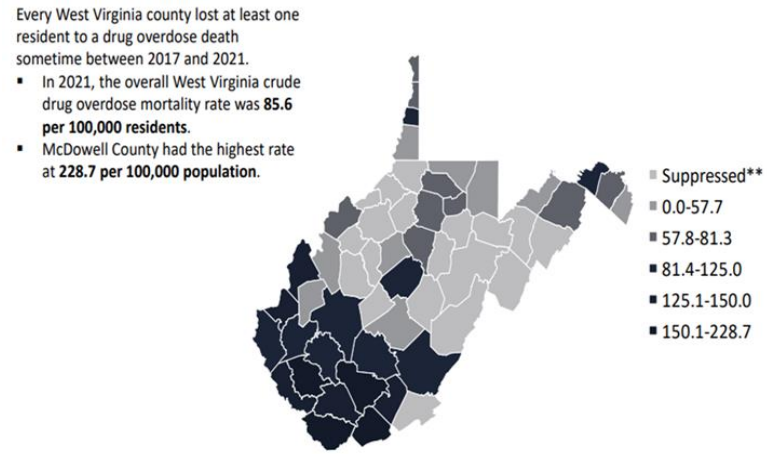
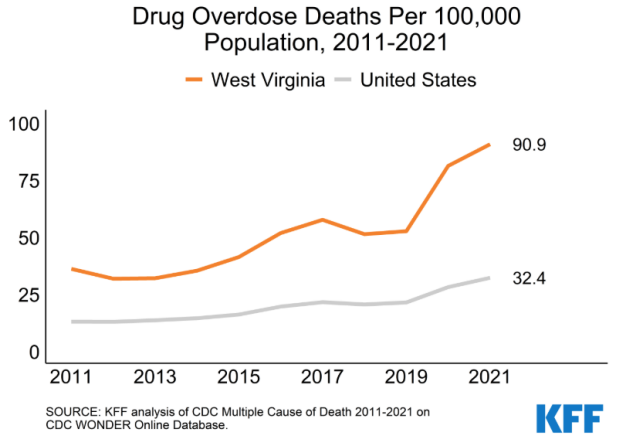
* For all years, the Appalachian rate is significantly different from the non-Appalachian U.S. rate, $p \leq 0.05$.
Source: Mortality Rates and Standard Errors provided by the Centers for Disease Control and Prevention, National Center for Health Statistics. Accessed at http://wonder.cdc.gov/mcd-icd10.html.

https://www.arc.gov/report/appalachian-diseases-of-despair-2024/

WEST VIRGINIA: OVERDOSE

- **Deaths of Despair MR = 158/100k**
- **Record OD death rate in 2021**





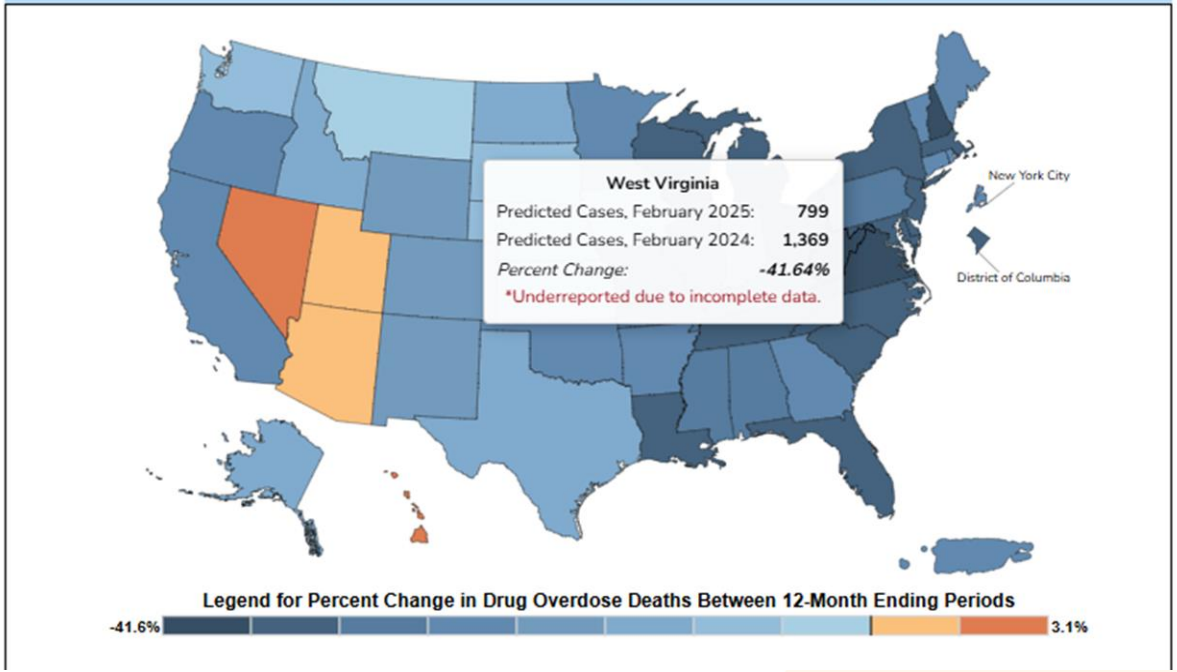
Graphic adapted from WV Medical Examiner Presentation at AAPDAC October 2023

https://www.arc.gov/report/appalachian-diseases-of-despair-2024

https://www.kff.org/statedata/mental-health-and-substance-use-state-fact-sheets/west-virginia/#

WEST VIRGINIA: GOOD NEWS!

Figure 1b. Percent Change in Predicted 12 Month-ending Count of Drug Overdose Deaths, by Jurisdiction: February 2024 to February 2025



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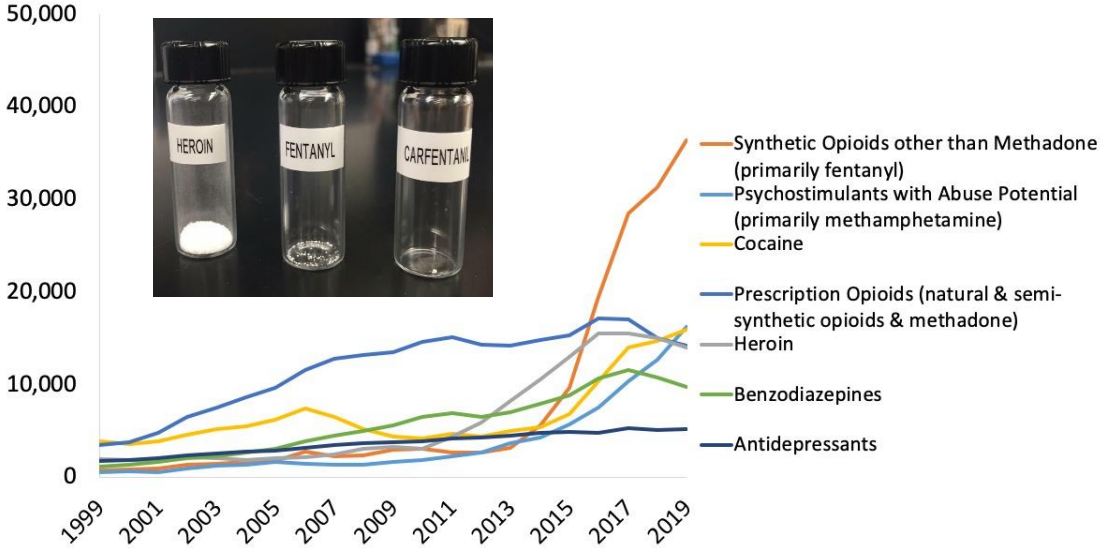
https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

Accessed July 16, 2025

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2019



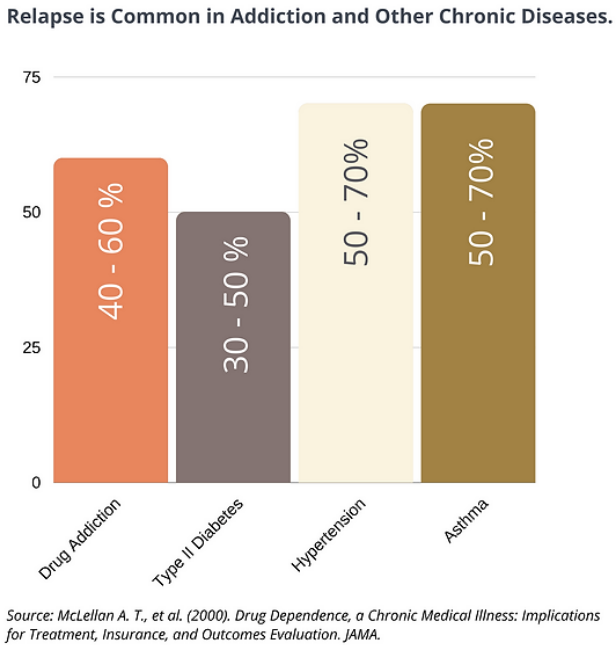
*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released 12/2020.

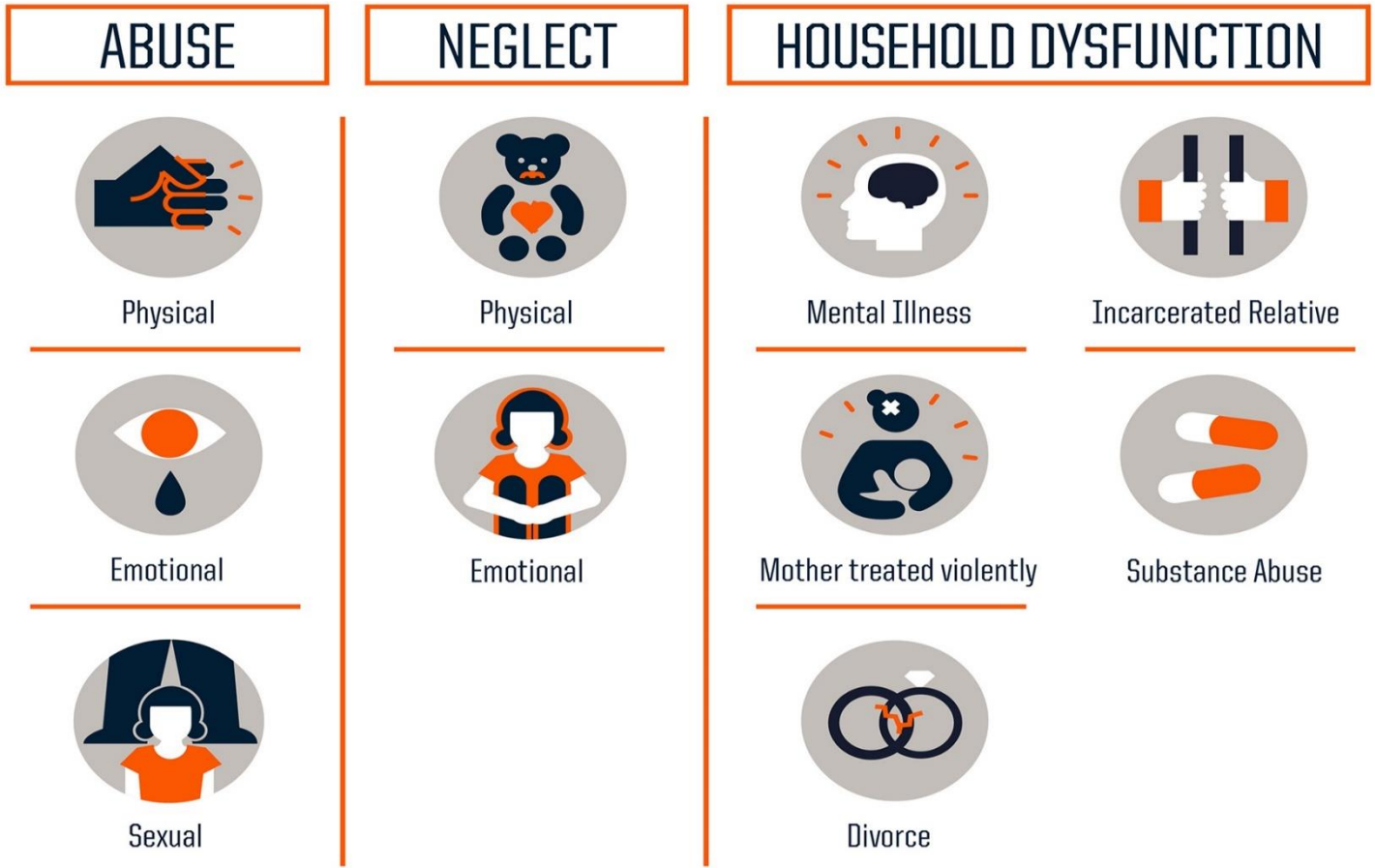
WHAT IS ADDICTION?

ASAM's Definition of Addiction

Addiction is a **treatable**, **chronic** medical disease involving complex interactions among **brain** circuits, **genetics**, the **environment**, and an individual's life **experiences**.

People with addiction use substances or engage in behaviors that become **compulsive** and often **continue** despite harmful **consequences**.





Source: Centers for Disease Control and Prevention
Credit: Robert Wood Johnson Foundation

Adverse Childhood Experiences

Traumatic events that can have negative, lasting effects on health and wellbeing

People with 6+ ACEs can die

20 yrs

earlier than those who have none

1/8 of the population have more than 4 ACEs

www.70-30.org.uk
@7030Campaign

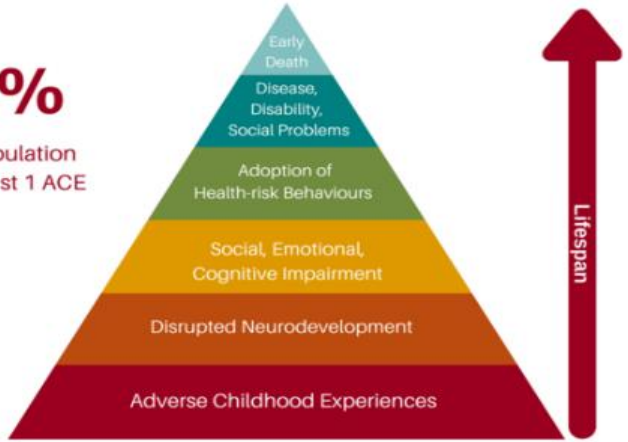
4 or more ACEs

- **3x** the levels of lung disease and adult smoking
- **11x** the level of intravenous drug abuse
- **14x** the number of suicide attempts
- **4x** as likely to have begun intercourse by age 15
- **4.5x** more likely to develop depression
- **2x** the level of liver disease

> **Adverse childhood experiences are the single greatest unaddressed public health threat facing our nation today**
>
> Dr. Robert Block, the former President of the American Academy of Pediatrics

67%

of the population have at least 1 ACE



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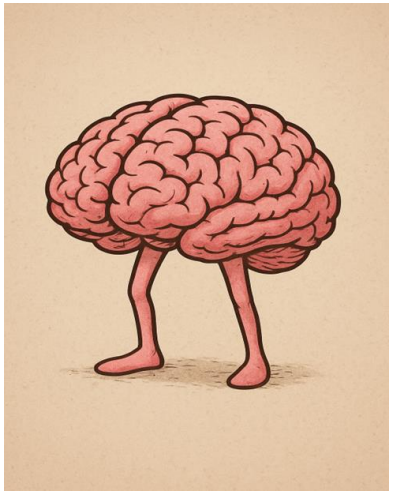
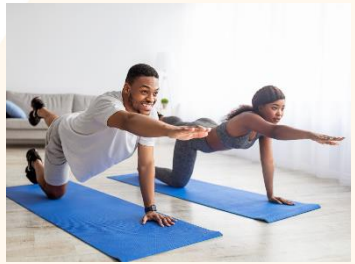
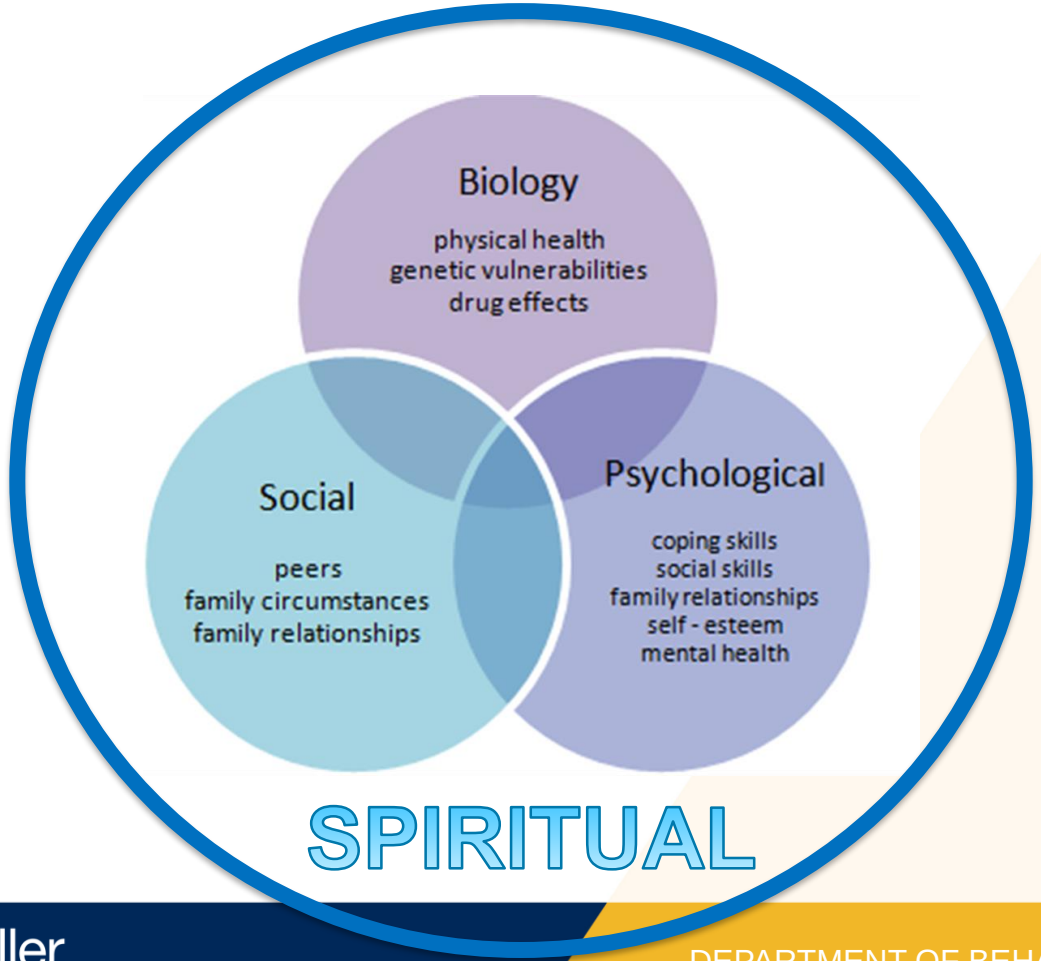
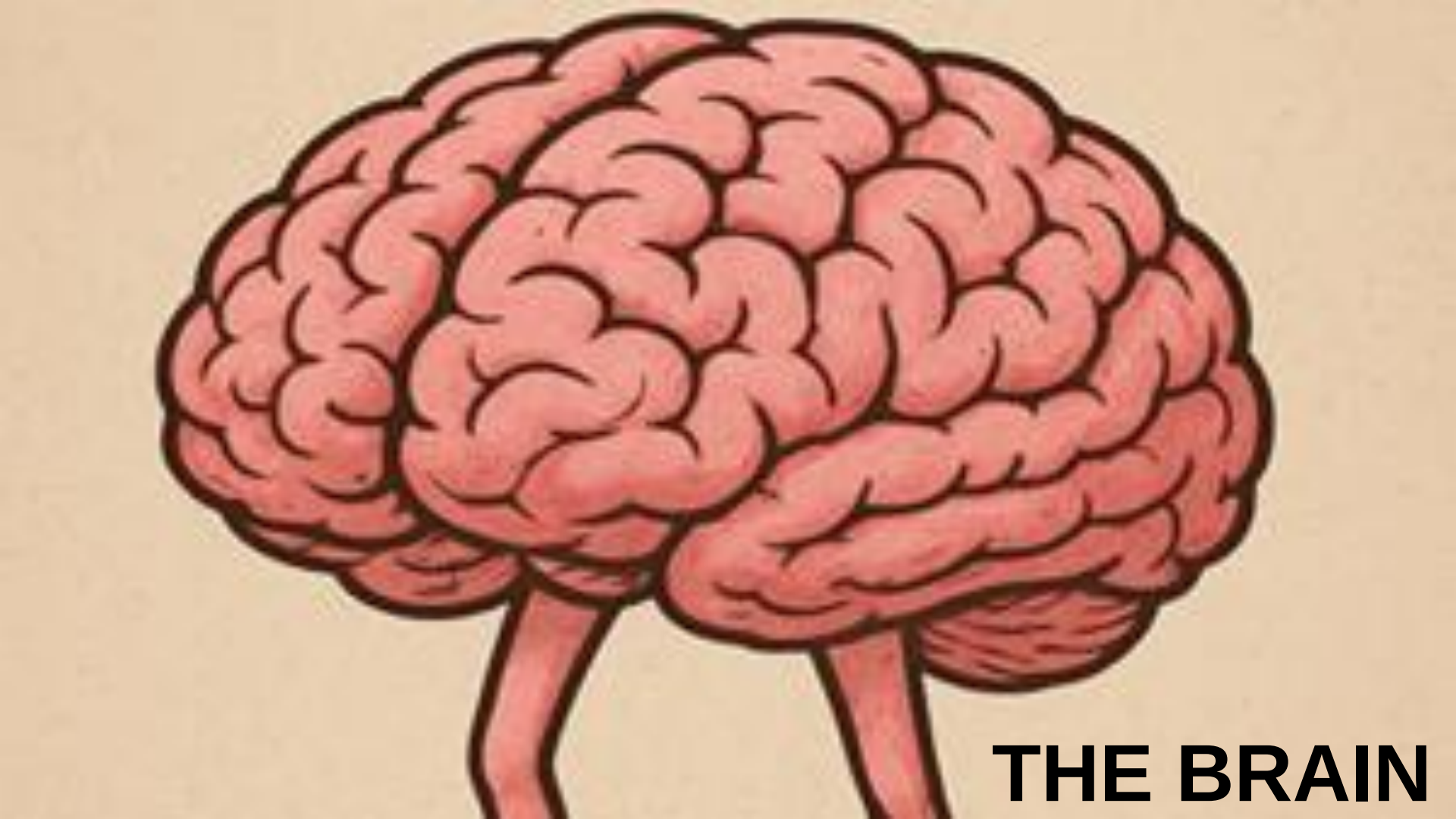
https://www.nationalhealthcorps.org/story/adverse-childhood-experiences

HEALTH = HOLISTIC



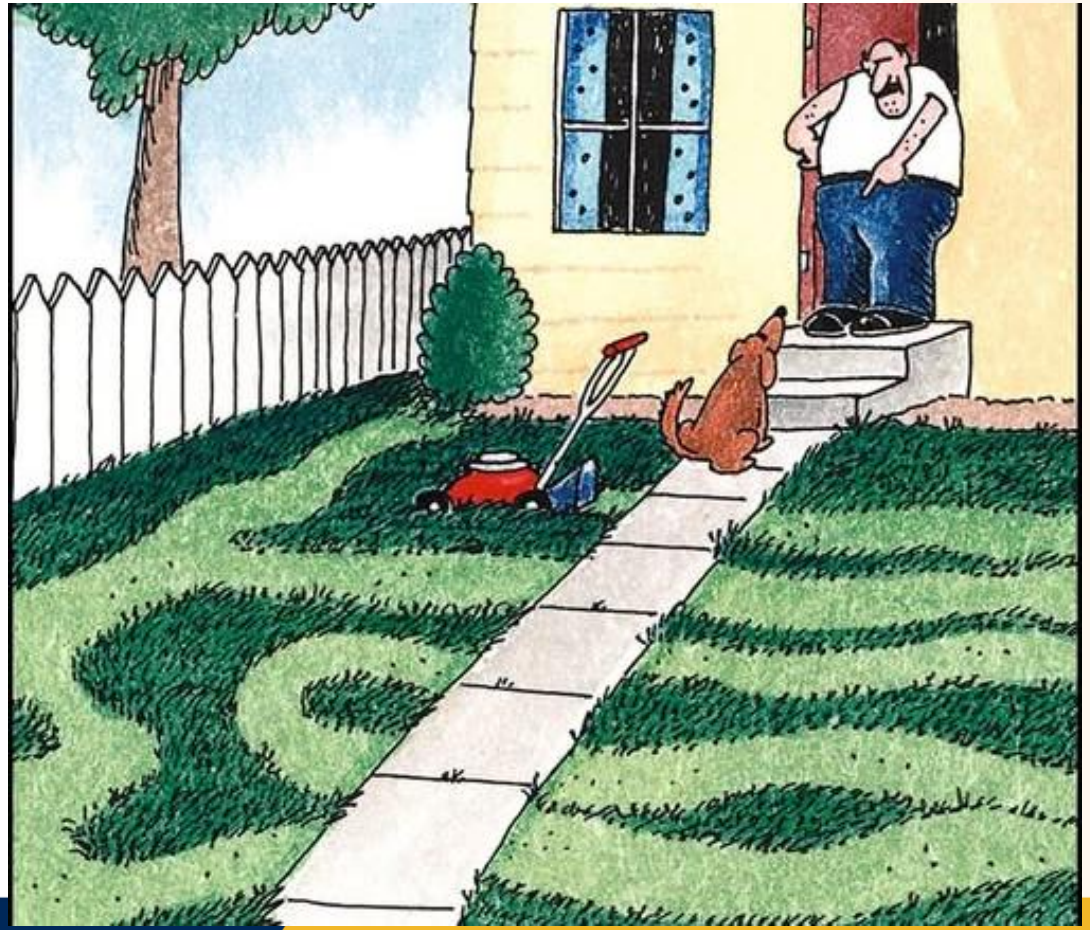



Biology
physical health
genetic vulnerabilities
drug effects
Social
peers
family circumstances
family relationships
Psychological
coping skills
social skills
family relationships
self - esteem
mental health
SPIRITUAL


THE BRAIN

PATHWAYS

“You call that mowin’ the lawn?...Dad dog!...No biscuit!”



The Far Side – Gary Larson


CANADA
UNITED STATES
MEXICO
ROCKY MOUNTAINS
GREAT PLAINS
APPALACHIAN MTNS
PACIFIC OCEAN
ATLANTIC OCEAN
Gulf of Mexico
Idaho Dept. of Transportation
Mule Deer Foundation
Xerces Society
Wyoming Fish and Game
Colorado Dept. of Transportation
Pollinator Partnership
South Platte River
American Bird Conservancy
New Mexico Association of Conservation Districts
Mississippi Alluvial Valley
Aspetuck Land Trust
American Littoral Society
University of South Carolina
MIGRATION PATHS
Monarch
Birds
Migratory Fish
Big game
Migration paths generalized
Not all migration paths shown

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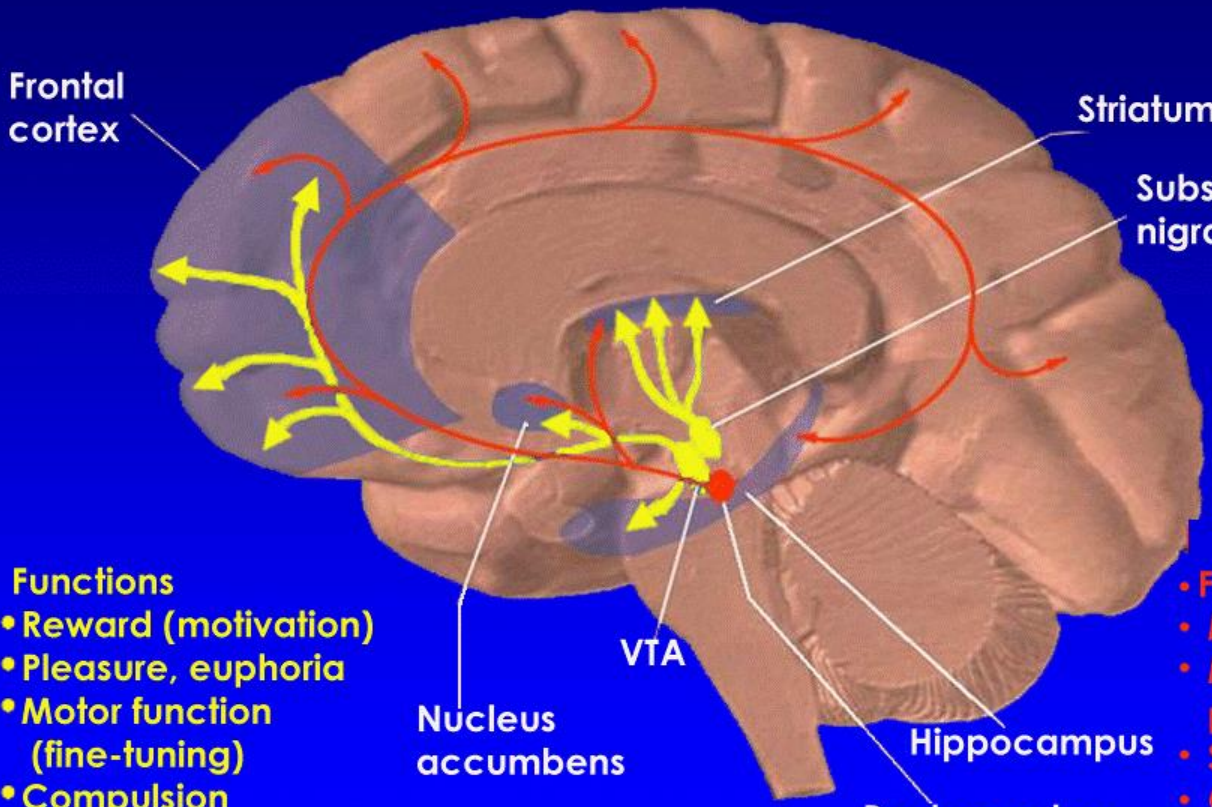
Dopamine Pathways

Serotonin Pathways



Functions
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine-tuning)
- Compulsion
- Perseveration

- Functions
- Mood
- Memory processing
- Sleep
- Cognition

NIDA

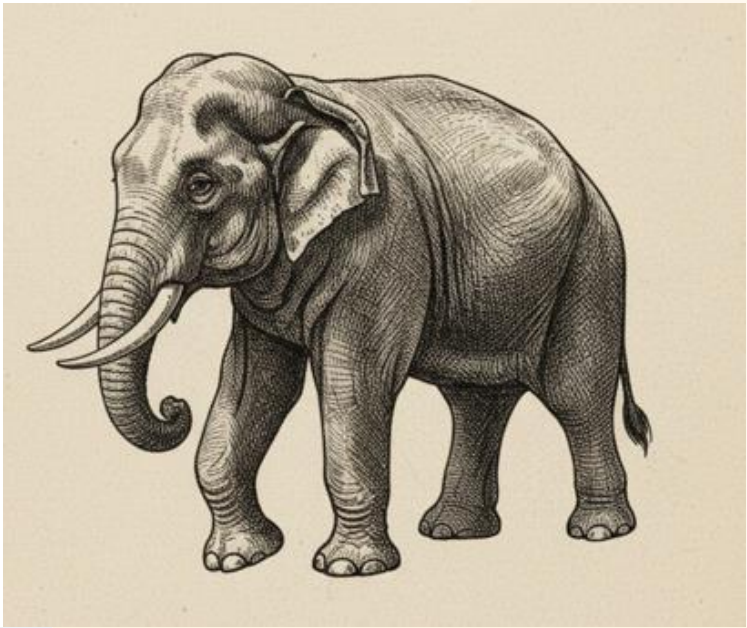
THE RIDER AND THE ELEPHANT

- Jonathan Haidt

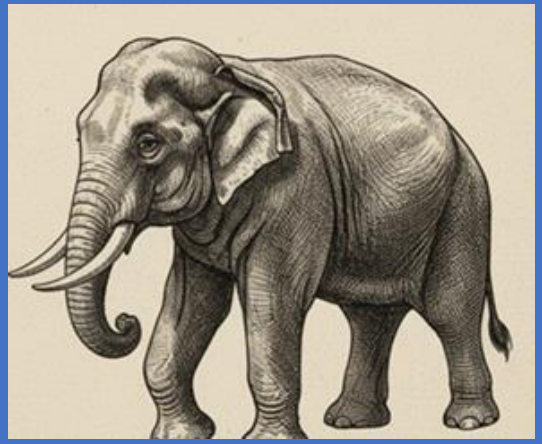
TWO COMPLIMENTARY PARTS

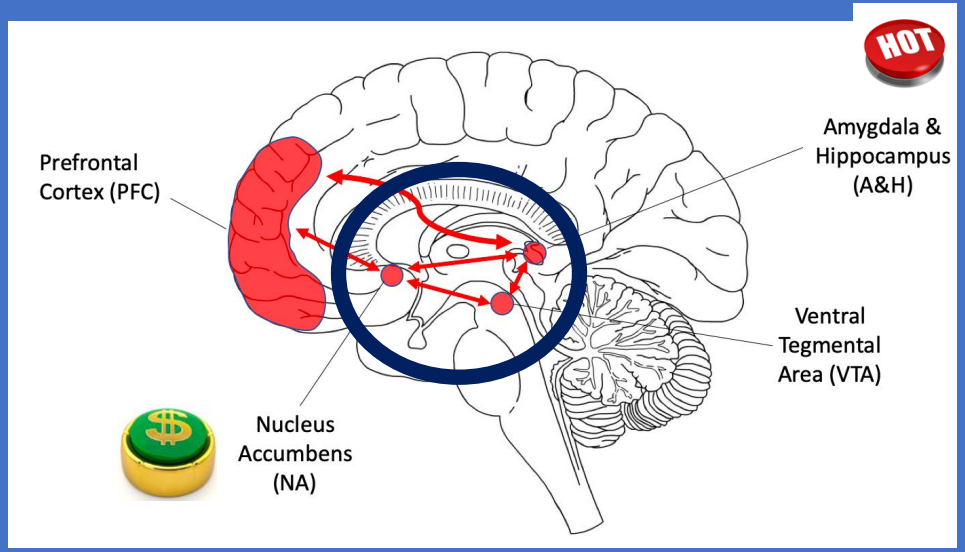
RIDER (REFLECTIVE)

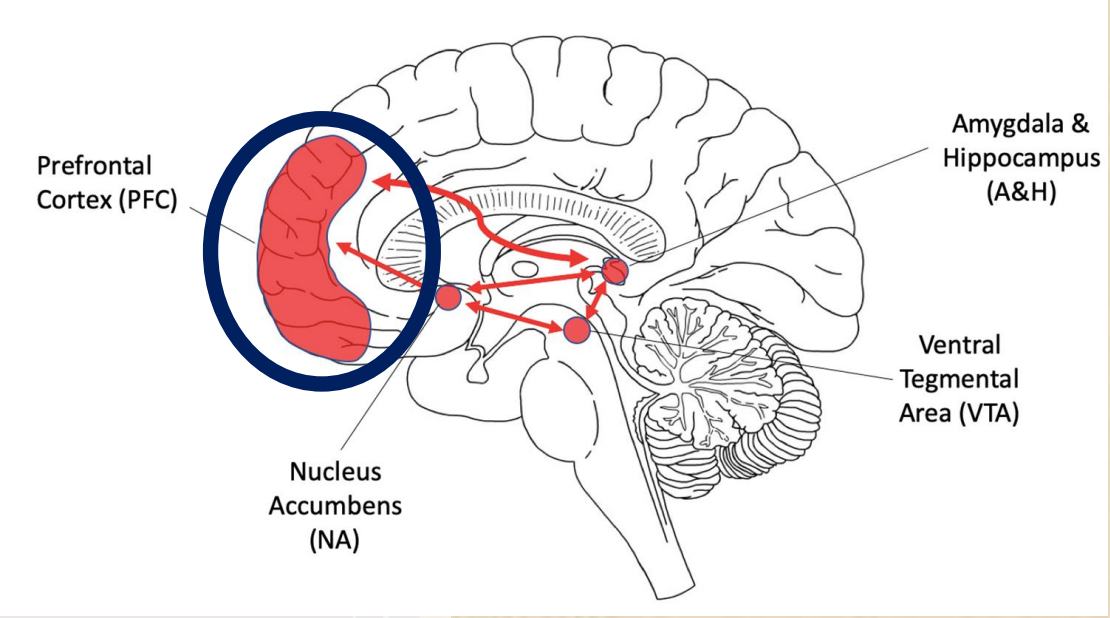
ELEPHANT (REACTIVE)



REACTIVE REWARD SYSTEM

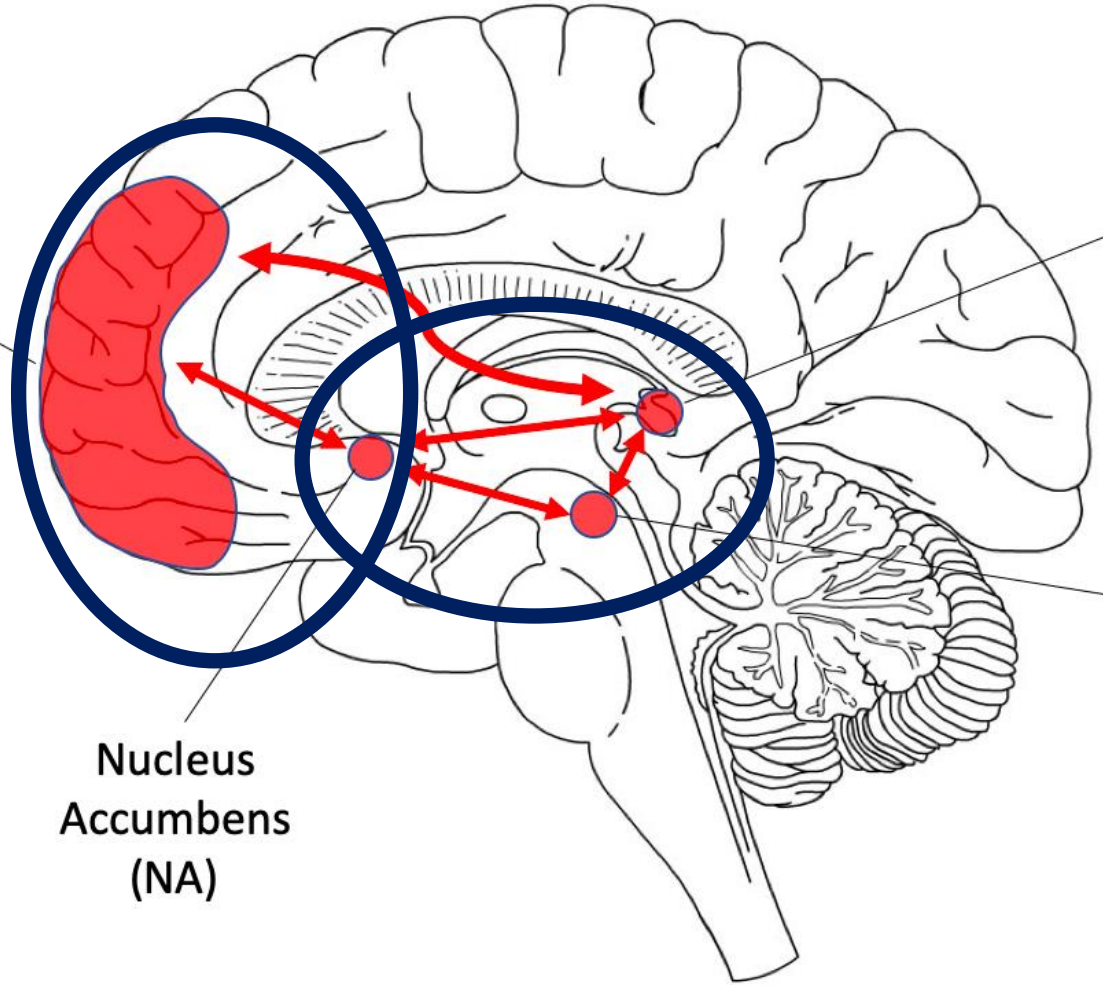






REACTIVE REWARD SYSTEM

ENGAGED

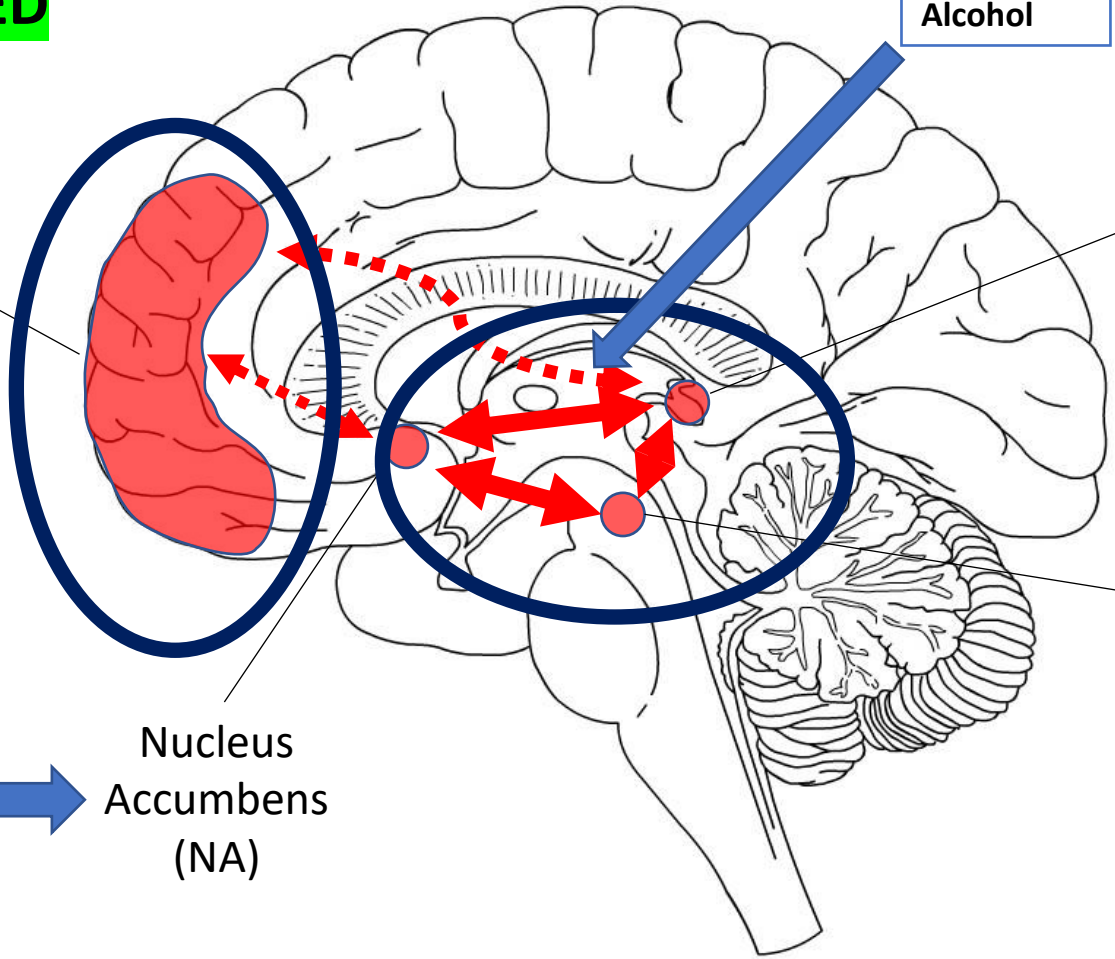

Prefrontal Cortex (PFC)
Amygdala & Hippocampus (A&H)
Ventral Tegmental Area (VTA)
Nucleus Accumbens (NA)

Dear Alcohol,

We had a deal where you would make me funnier, smarter, and a better dancer... I saw the video...

WE NEED TO TALK.

DISENGAGED



Alcohol

Prefrontal Cortex (PFC)

Amygdala & Hippocampus (A&H)

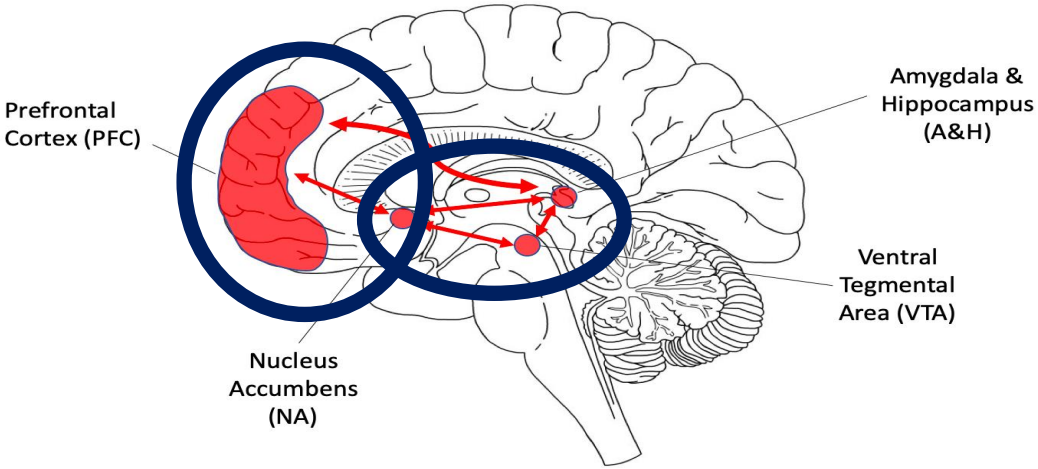
Ventral Tegmental Area (VTA)

Nucleus Accumbens (NA)

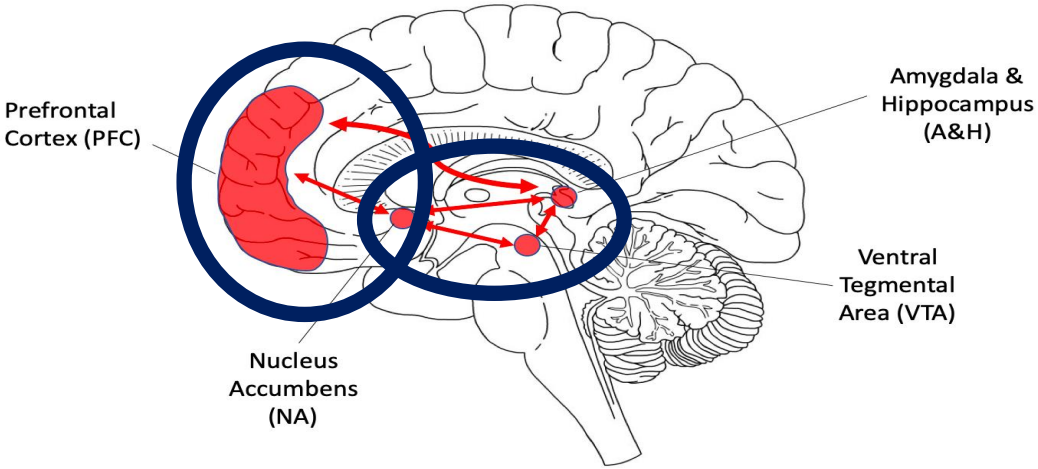
Cocaine
Heroin
Nicotine
Amphetamine
Opioids
THC

Cocaine
Heroin

Understanding Neurobiology and Addiction Treatment



Understanding Neurobiology and Addiction Treatment



BIOLOGICAL

- Diet
- Exercise
- Sleep
- Medications
- Neuromodulation

TWO MAIN GOALS

KEEP THE PERSON ALIVE

INCREASE QUALITY OF LIFE

OPIOID RECOVERY Rx

- Gold standard of treatment for opioid use disorder
- Every professional addiction society recommends using medications
- Three medications FDA approved, all considered first line treatment
  - **Methadone**
  - **Naltrexone**
  - **Buprenorphine**

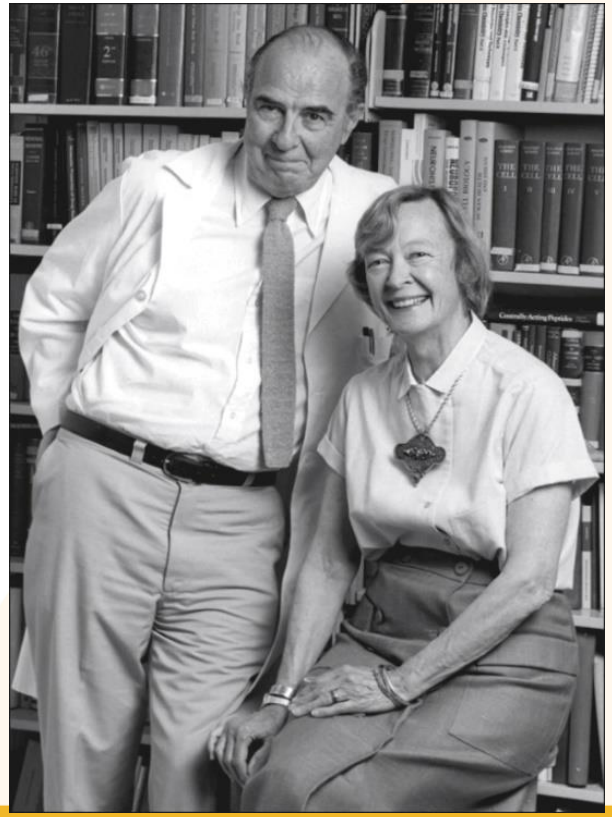
Medication for Opioid Use Disorder

RECEPTORS

- Methadone - full agonist
- Buprenorphine - partial agonist
- Naltrexone - antagonist

MEDICATION FOR OUD

- Dole and Nyswander introduced using methadone in 1960s
  - “Harm Reduction”
- Involves stabilization of endogenous opioid system (Dole 1988)
- Decrease cravings and prevent withdrawal
- Engage in recovery and improve functioning

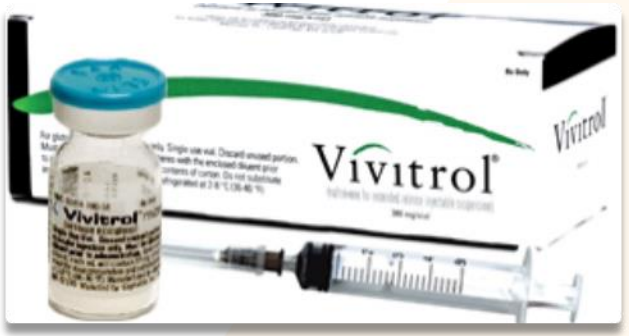


METHADONE

- Full Agonist
- Schedule II
- Use is restricted to non-residential narcotic treatment facilities: Opioid Treatment Programs (OTP) = Methadone Clinics
- Pain is the only legal medical indication in the office setting
- Tricky to start and stop
- Stigma

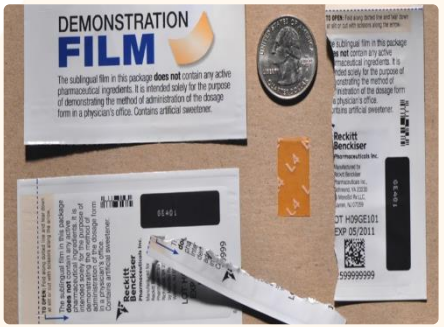
NALTREXONE

- Antagonist (Blocker)
- Tablets
- Long-Acting Injection
- **Must** be through withdrawal!

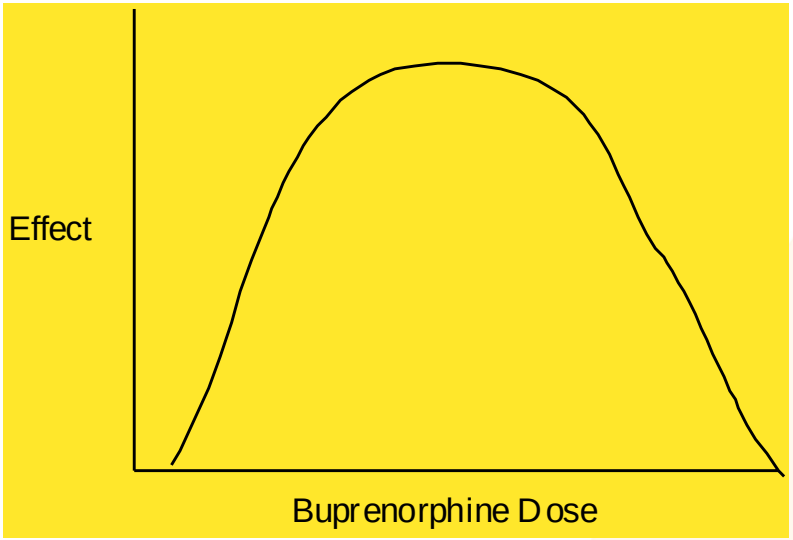


BUPRENORPHINE (Suboxone)

- Partial agonist
- Drug Addiction Treatment Act of 2000 (DATA)
- Tablets, Film
- Injection: 1m or 1wk

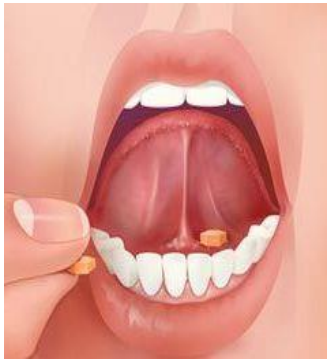


Buprenorphine Pharmacology



Drug and Alcohol Dependence, 2003;70:S61

Buprenorphine/Naloxone



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MOUD SAVES LIVES

Mortality risk during and after MOUD: systemic review and meta-analysis of cohort studies (Sordo 2017)

- n =15,831 treated with buprenorphine 1.1-4.5 years
- MOUD use associated with
  - **3x reduction** in OD mortality
  - **2x reduction** in all cause mortality

Medication after non-fatal overdose and association with mortality: cohort study (Larochelle 2018)

- n=17, 568 OD Survivors followed for 1 year
- Medication use was associated with:
  - **38% reduction** in ODs
  - **37% reduction** in all cause mortality

Comparative effectiveness for different treatment pathways (Wakeman 2020)

- n=40,885 (No tx, inpt detox/res, intensive BH, Bup/Meth, Naltrexone, Non-intensive BH)
- **76%** OD reduction at 3m, 59% at 12m
- **32%** acute care utilization reduction at 3m, 26% at 12m

NEUROMODULATION

WVU Rockefeller Neuroscience Institute

Center for Neuromodulation and Brain Therapeutics

- Advance focused ultrasound innovations for treatment of
  - Alzheimer's, Parkinson's, Lewy Body disease, drug and alcohol addiction, food addiction, PTSD, Hallucinations, tinnitus
- Improve patient care, quality of life, and seek cures
- Establish worldwide training program (clinical, engineering, preclinical, research)
- Facilitate collaborations with other institutions to use this technology
- Develop the next generation technologies and devices

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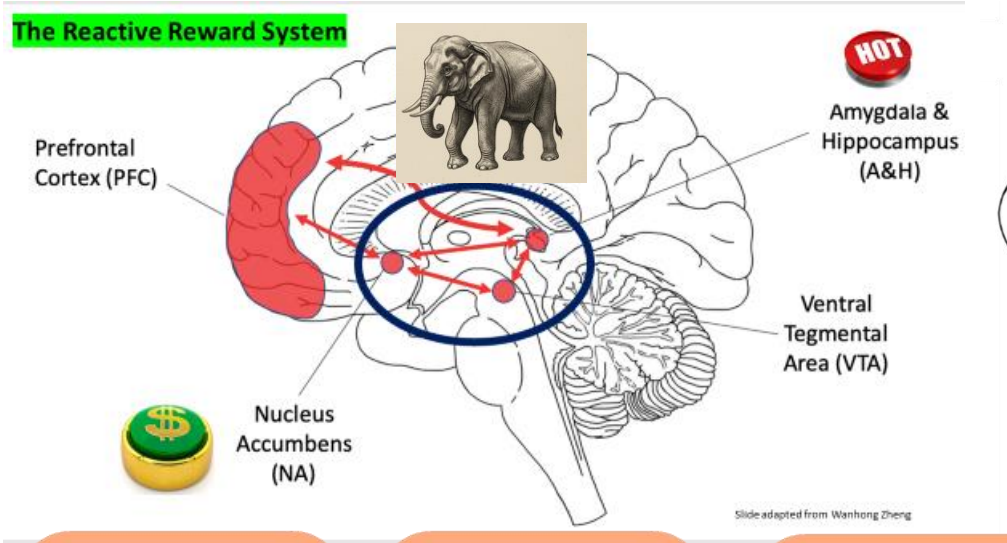
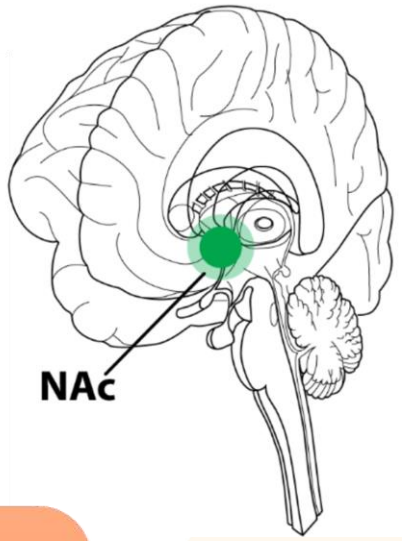
Neuromodulation – Bottom-Up Approach





BOTTOM

UP

Target the Nucleus Accumbens (NAc)

Deep Brain Stimulation (DBS) for SUD

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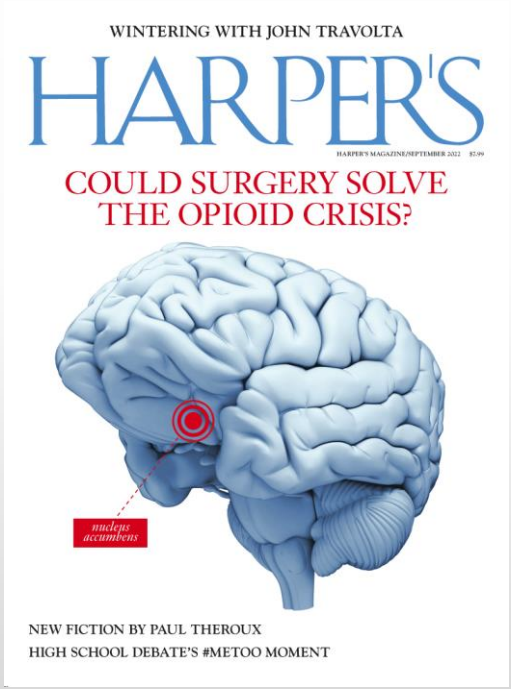
HARPER'S QUESTION: COULD SURGERY SOLVE THE OPIOID CRISIS?

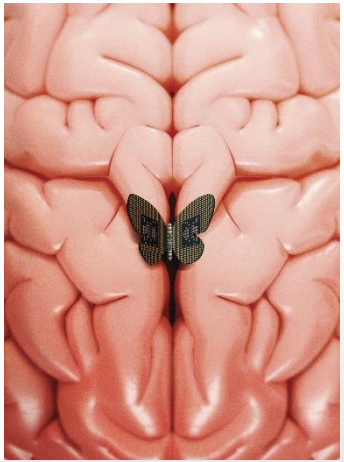


[Report]

A Hole in the Head

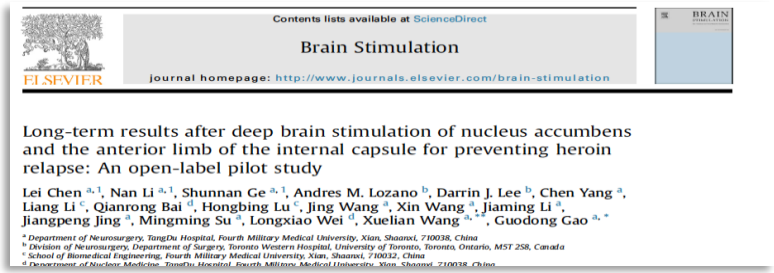
by Zachary Siegel

Can a brain implant treat drug addiction?



Human Studies of Nucleus Accumbens (NAc) DBS for SUD

Several reports of DBS for severe opioid, alcohol, cocaine addiction
Demonstrate safety and reduction in substance craving and use



Contents lists available at ScienceDirect

Brain Stimulation

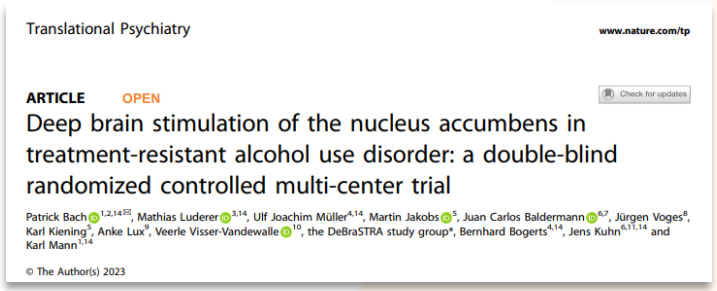
journal homepage: http://www.journals.elsevier.com/brain-stimulation

Long-term results after deep brain stimulation of nucleus accumbens and the anterior limb of the internal capsule for preventing heroin relapse: An open-label pilot study

Lei Chen [a, 1], Nan Li [a, 1], Shunnan Ge [a, 1], Andres M. Lozano [b], Darrin J. Lee [b], Chen Yang [a], Liang Li [c], Qianrong Bai [d], Hongbing Lu [c], Jing Wang [a], Xin Wang [a], Jiaming Li [a], Jiangpeng Jing [a], Mingming Su [a], Longxiao Wei [d], Xuelian Wang [a, **], Guodong Gao [a, *]

[a] Department of Neurosurgery, TangDu Hospital, Fourth Military Medical University, Xian, Shaanxi, 710038, China
[b] Division of Neurosurgery, Department of Surgery, Toronto Western Hospital, University of Toronto, Toronto, Ontario, M5T 2S8, Canada
[c] School of Biomedical Engineering, Fourth Military Medical University, Xian, Shaanxi, 710032, China
[d] Department of Nuclear Medicine, TangDu Hospital, Fourth Military Medical University, Xian, Shaanxi, 710038, China

Brain Stimulation 2019, 12(1):175-183.



Translational Psychiatry

www.nature.com/tp

ARTICLE OPEN

Check for updates

Deep brain stimulation of the nucleus accumbens in treatment-resistant alcohol use disorder: a double-blind randomized controlled multi-center trial

Patrick Bach[1,2,14], Mathias Luderer[3,14], Ulf Joachim Müller[4,14], Martin Jakobs[5], Juan Carlos Baldermann[6,7], Jürgen Voges[8], Karl Kiening[9], Anke Lux[9], Veerle Visser-Vandewalle[10], the DeBraSTRA study group*, Bernhard Bogerts[4,14], Jens Kuhn[6,11,14] and Karl Mann[1,14]

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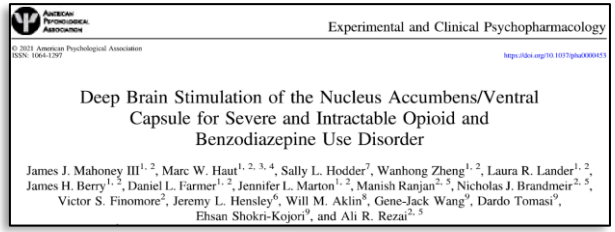

American Psychological Association

Experimental and Clinical Psychopharmacology

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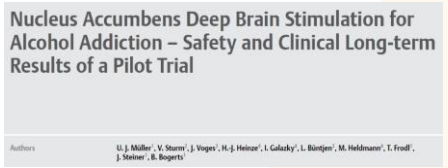
ISSN: 1064-1297

https://doi.org/10.1037/pha0000453

Deep Brain Stimulation of the Nucleus Accumbens/Ventral Capsule for Severe and Intractable Opioid and Benzodiazepine Use Disorder

James J. Mahoney III[1, 2], Marc W. Haut[1, 2, 3, 4], Sally L. Hodder[7], Wanhong Zheng[1, 2], Laura R. Lander[1, 2], James H. Berry[1, 2], Daniel L. Farmer[1, 2], Jennifer L. Marton[1, 2], Manish Ranjan[2, 5], Nicholas J. Brandmeir[2, 5], Victor S. Finomore[2], Jeremy L. Hensley[6], Will M. Aklin[8], Gene-Jack Wang[9], Dardo Tomasi[9], Ehsan Shokri-Kojori[9], and Ali R. Rezai[2, 5]



Nucleus Accumbens Deep Brain Stimulation for Alcohol Addiction – Safety and Clinical Long-term Results of a Pilot Trial

Authors

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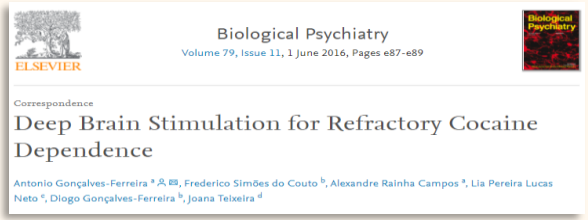
Pharmacopsychiatry 2016; 49: 170–173



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Biological Psychiatry

Volume 79, Issue 11, 1 June 2016, Pages e87-e89

Correspondence

Deep Brain Stimulation for Refractory Cocaine Dependence

Antonio Gonçalves-Ferreira [a, ⁂], Frederico Simões do Couto [b], Alexandre Rainha Campos [a], Lia Pereira Lucas Neto [c], Diogo Gonçalves-Ferreira [b], Joana Teixeira [d]

US Nucleus Accumbens (NAc) DBS for OUD Study

Study Objective

- **Safety and feasibility open label study**

Eligibility

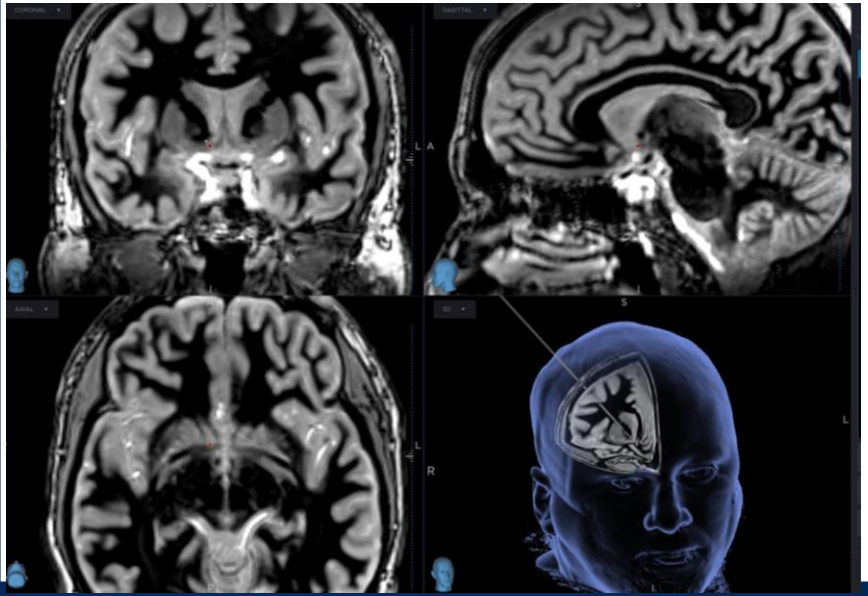
- **Primary Opioid Use Disorder** (can have co-occurring SUDs)
- **Frequent relapses** despite receiving multiple levels of treatment (in-patient, residential, out-patient)
- **Life-threatening complications** (e.g., multiple OD's)
- NIDA sponsored study - UO1-P1UG3DA047714-01
- FDA and IRB approvals
- Monitoring by WVCTSI Clinical Trials Center of Excellence
- DSMB periodic review
- Clinical Trials. Gov, UG3: NCT03950492, FDA IDE: G190011

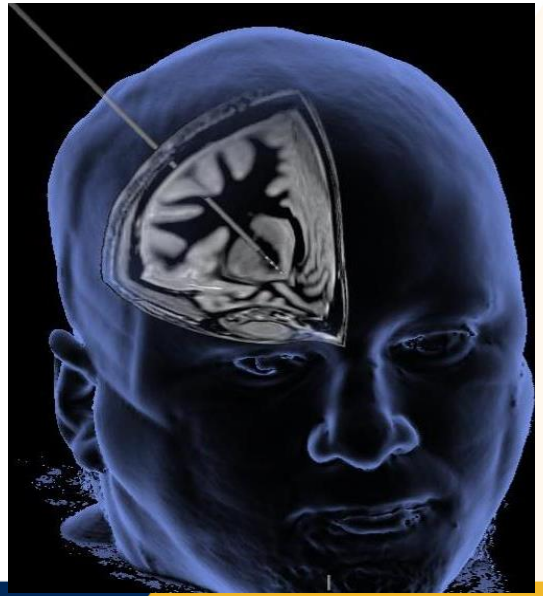
DBS for OUD - Participant Characteristics

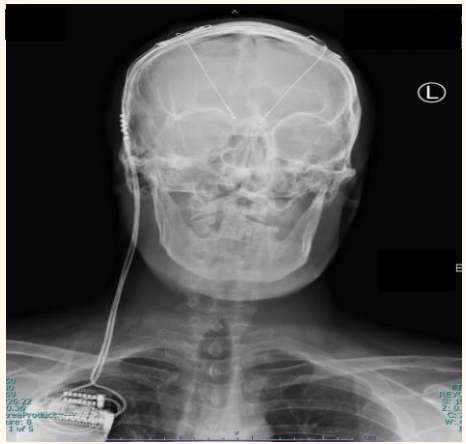
	N = 4
Age (sex)	20 – 44 years (all male)
# of Overdoses	~5 – 11
Opioid Use	
Specific Opioids Used	Heroin, Fentanyl, Hydro/Oxycodone, OxyContin
Age of First Use	13 – 28
Primary Route of Administration	IV (n=3), Nasal (n=1)
Other Substance Regularly Used	alcohol, cannabis, benzos, meth, cocaine
Most Recent Substance Use Prior to Study Involvement	
Time since last use (specific substance)	~1 week (opioids, alcohol, cocaine, benzos)

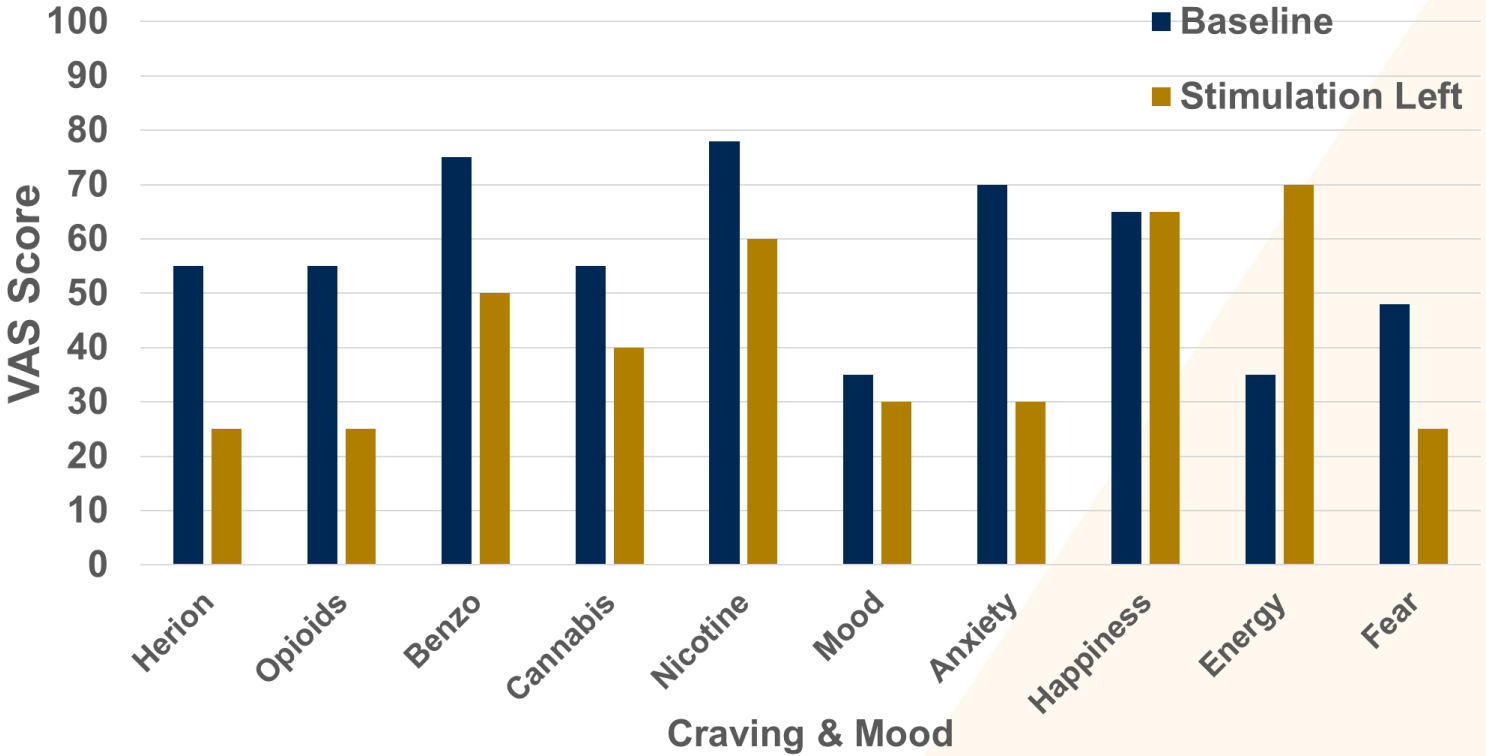
DBS Target: Bilateral Nucleus Accumbens (NAc)

- NAc and ventral anterior internal capsule DBS placement
  - Target localized with high resolution MRI and tractography
  - Medtronic device implant

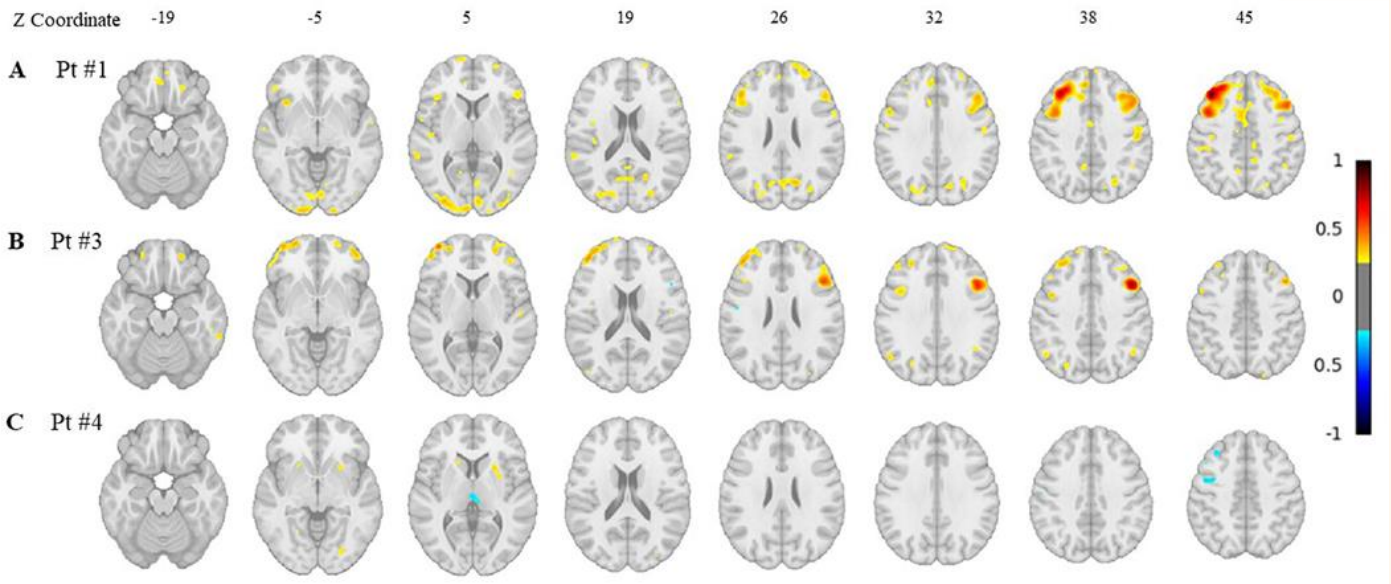







Baseline
Stimulation Left
VAS Score
100
90
80
70
60
50
40
30
20
10
0
Herion
Opioids
Benzo
Cannabis
Nicotine
Mood
Anxiety
Happiness
Energy
Fear
Craving & Mood

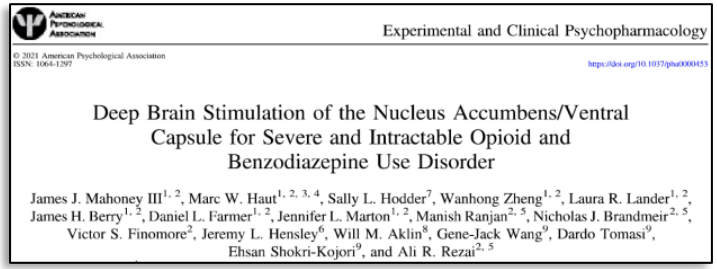
^{18}F-FDG Summary: DBS OUD



^{18}FDG-PET examining changes in glucose metabolism from baseline to outpatient week 12 revealed increased glucose metabolism for participants 1 and 3 with the greatest changes occurring in the dorsolateral prefrontal regions. Participant 4 did not demonstrate notable changes in glucose uptake over time.

Study Outcomes: NAc DBS for OUD

- DBS well-tolerated – No serious adverse events related to the DBS procedure
- Reduction of craving and anxiety in all participants
- 2 participants
  - Complete substance abstinence (>1,850 and >1,200 days)
  - FDG-PET in the abstinent patients revealed increased glucose metabolism in frontal regions
- 1 participant had drug use recurrences, no overdoses, achieved >4 months of abstinence during primary study
  - Discontinue participation 3 years following DBS implant due to protocol fatigue and non-compliance
- 1 participant was explanted due to early and persistent non-compliance with the study



American Psychological Association

Experimental and Clinical Psychopharmacology

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ISSN: 1064-1297

https://doi.org/10.1037/pha0000453

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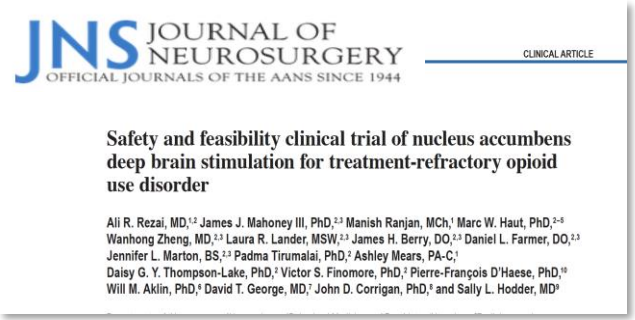

JNS JOURNAL OF NEUROSURGERY

OFFICIAL JOURNALS OF THE AANS SINCE 1944

CLINICAL ARTICLE

Safety and feasibility clinical trial of nucleus accumbens deep brain stimulation for treatment-refractory opioid use disorder

Ali R. Rezai, MD,[1,2] James J. Mahoney III, PhD,[2,3] Manish Ranjan, MCh,[1] Marc W. Haut, PhD,[2–5] Wanhong Zheng, MD,[2,3] Laura R. Lander, MSW,[2,3] James H. Berry, DO,[2,3] Daniel L. Farmer, DO,[2,3] Jennifer L. Marton, BS,[2,3] Padma Tirumalai, PhD,[2] Ashley Mears, PA-C,[1] Daisy G. Y. Thompson-Lake, PhD,[2] Victor S. Finomore, PhD,[2] Pierre-François D'Haese, PhD,[10] Will M. Aklin, PhD,[6] David T. George, MD,[7] John D. Corrigan, PhD,[8] and Sally L. Hodder, MD[9]

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Focused Ultrasound Neuromodulation for OUD Treatment

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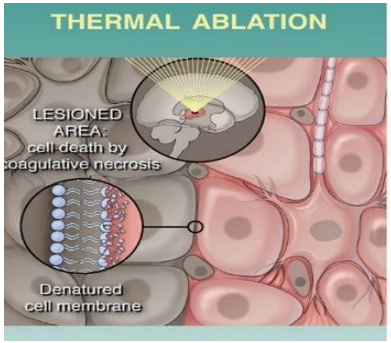
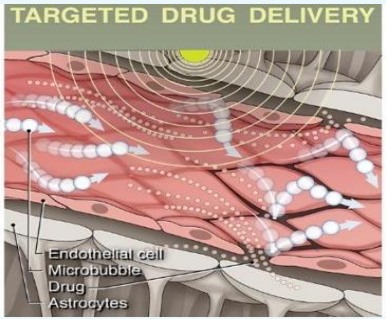
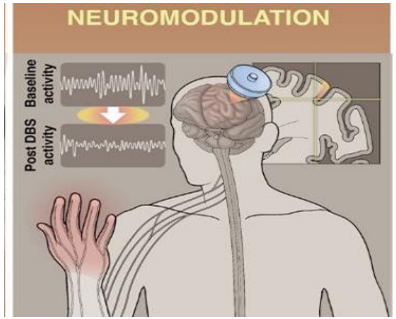
FUS Neuromodulation

FUS

	High Intensity (HIFU)	Low Intensity (LIFU) /Neuromodulation	Low Intensity (LIFU) /BBB opening
Goal	Ablation	Therapeutic effect without tissue damage (no drugs involved)	Drug-device combination therapy (drugs do the work, FUS gets them through BBB)
Potential Indications	Essential Tremor (ET), Parkinson's (PD)	Addiction (substance use disorder, gambling), Obesity (binge eating disorder), Behavioral and Emotional (autism, neurodegenerative), Alzheimer's, Non-motor symptoms PD, PTSD, Tinnitus, ET	Multiple indications depending on drug (Alzheimer's, obesity, etc.)







RNI prefers LIFU-Neuromodulation because it is more scalable and cost-effective

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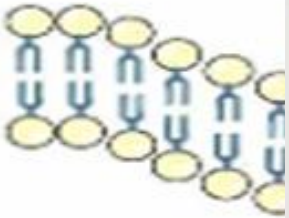

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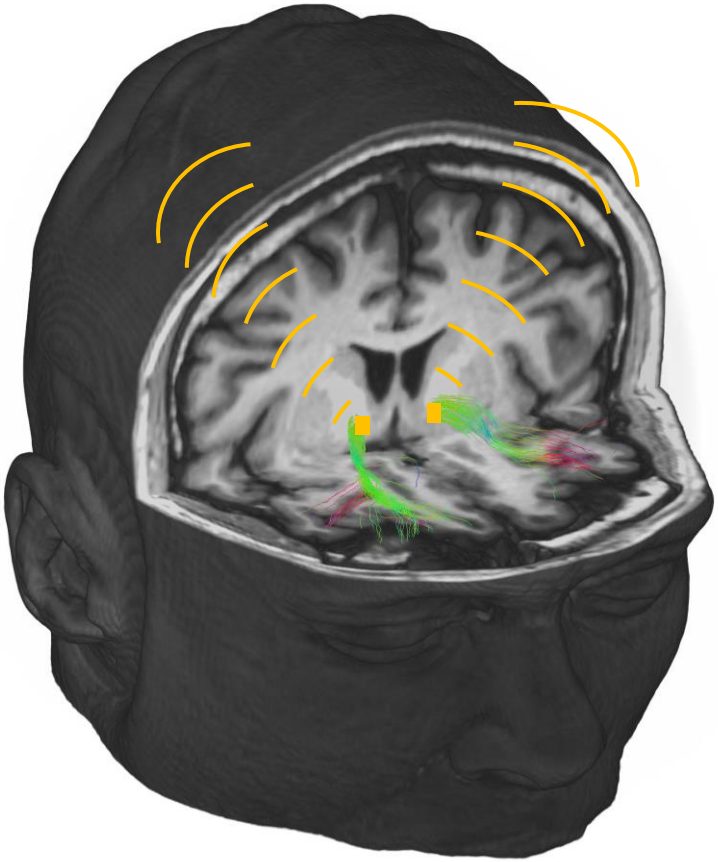
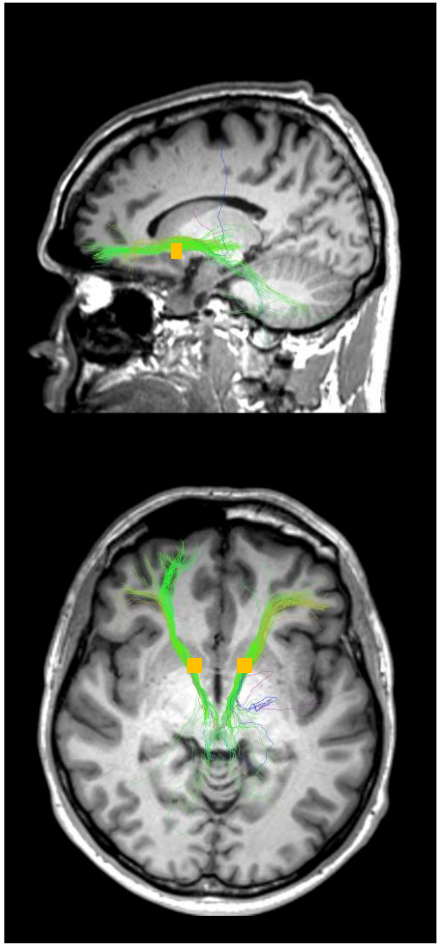
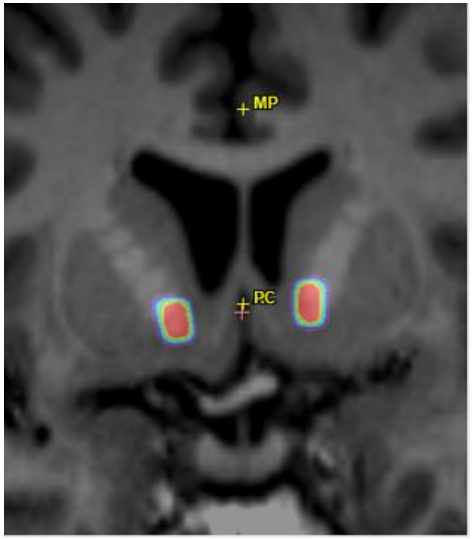
Neuromodulation Addiction Target: Nucleus Accumbens







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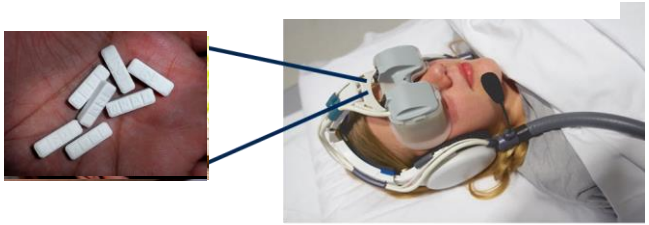
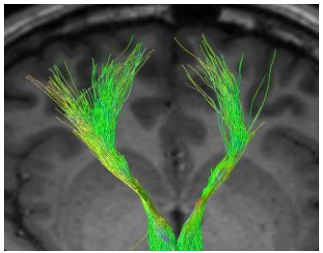
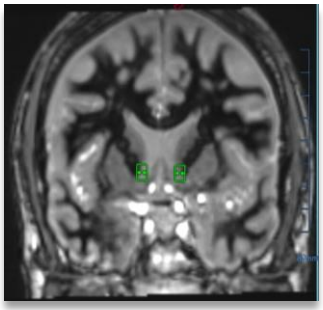
FUS Neuromodulation Procedure

- Non-surgical outpatient MRI suite procedure
- Head frame or frameless dental mold option
- Anatomical target of the NAc and ventral internal capsule refined by tractography
- Personalized visual cue induced craving throughout treatment
- FUS treatment- 20 mins (1h total duration)
- Post FUS behavioral therapy







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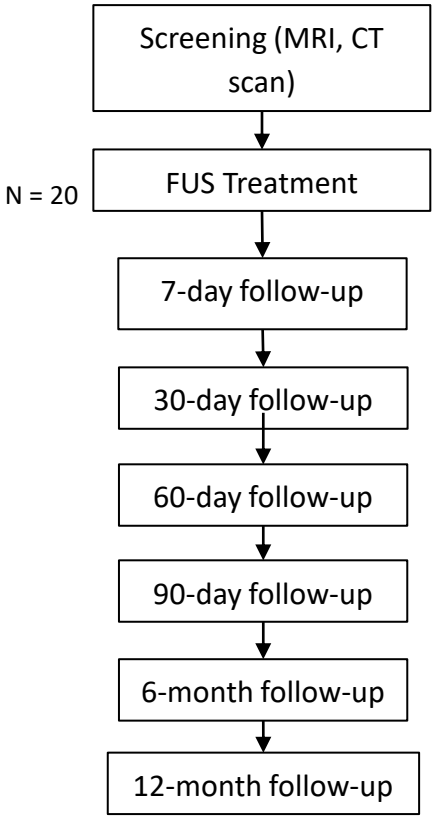
FUS OUD Feasibility Study Design



Single arm, open label clinical study

- Goal: safety and feasibility of FUS
- 29 patients (20 completed), single arm
- Technology:
  - Orchestration system: provides cues to patients, monitors patients and provides input for sonication (closed-loop) – RNI
  - FUS device – Insightec LIFU (non-FDA approved, designed for BBB)
- 20-minute FUS therapy, outpatient
- Eligibility: OUD diagnosis for 2+ years, MRI-eligible, brain lesions
- Endpoints:
  - Safety: AEs within 30 days
  - Efficacy: Urine toxicology, neuropsychological assessments (validated questionnaires)

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FUS for SUD – Open Label Trial

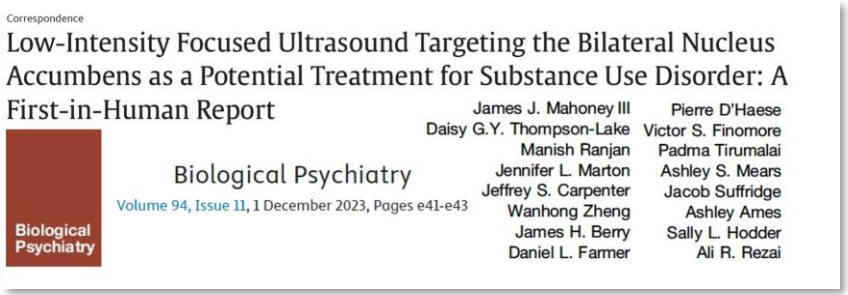
Study 2: 2022 – 2024

- **16** participants recruited from WVU Residential SUD treatment program received Bilateral NAc FUS

Primary Objective – Investigate safety and tolerability of bilateral NAc FUS in SUD through 90 days

Secondary Objectives – Evaluate the effects of FUS on:

- Substance craving
- Substance use
- Functional connectivity assessed via fMRI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Low-Intensity Focused Ultrasound Targeting the Bilateral Nucleus Accumbens as a Potential Treatment for Substance Use Disorder: A First-in-Human Report

James J. Mahoney III, Daisy G.Y. Thompson-Lake, Manish Ranjan, Jennifer L. Marton, Jeffrey S. Carpenter, Wanhong Zheng, James H. Berry, Daniel L. Farmer, Pierre D'Haese, Victor S. Finomore, Padma Tirumalai, Ashley S. Mears, Jacob Suffridge, Ashley Ames, Sally L. Hodder, Ali R. Rezai

Biological Psychiatry

Volume 94, Issue 11, 1 December 2023, Pages e41-e43

Eligibility Criteria

- Patients recruited from a residential 28-day treatment program
- Severe Substance Use Disorder (Primary OUD)
- Compliant with medication for OUD (MOUD) for at least one week prior to enrollment
- FDA and IRB approved, DSMB periodic review

Clinicaltrials.gov ID#: NCT04197921; IDE#: G190092 (Insightec); NIDA: DA047714-04S1

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FUS for SUD Open Label Trial - Participant Characteristics

	N = 16
Age (years)	34.6 [20 – 48]
Sex	13 males/3 female
# of Overdoses	~4 [1 – 5+]
Primary Substance Use Disorder	
Opioid Use Disorder*	n = 14
Meth Use Disorder ONLY	n = 1
Alcohol Use Disorder ONLY	n = 1
*All participants with OUD reported regular use of at least one (usually multiple) other illicit substance(s)	

Opioid and Co-Occurring Substance Use in those with Primary OUD (n = 14)	
Years of Use	
Opioids *(n=14)*	~13.5
Methamphetamine *(n=13)*	~9
Cocaine *(n=12)*	~19
Benzodiazepines *(n=10)*	~19
Alcohol *(n=12)*	~24
Cannabis *(n=12)*	~22
Nicotine *(n=14)*	~21

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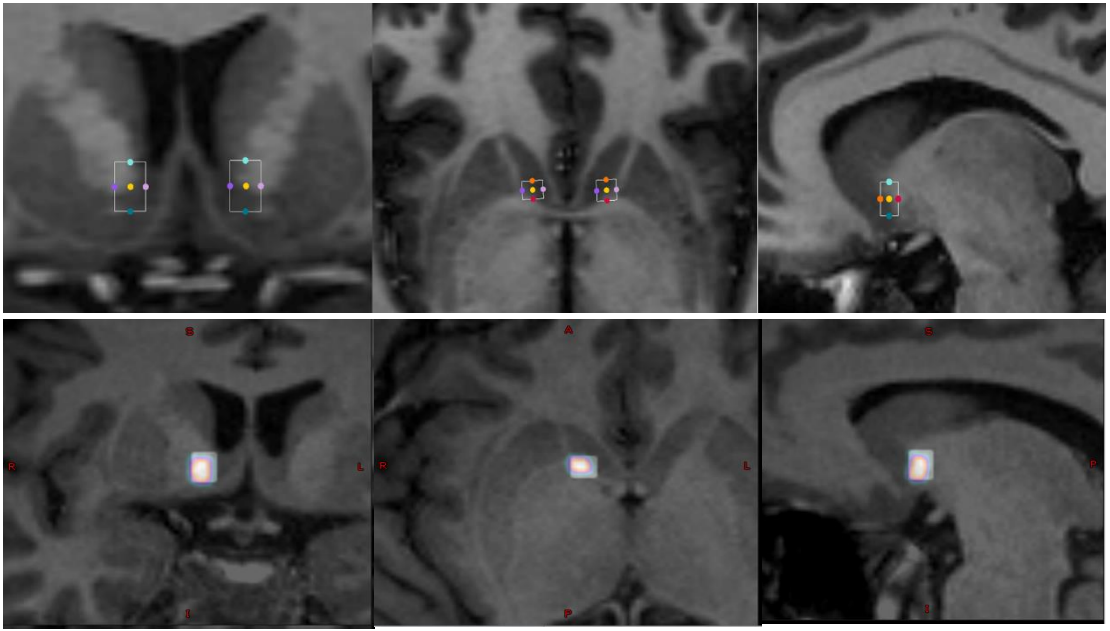
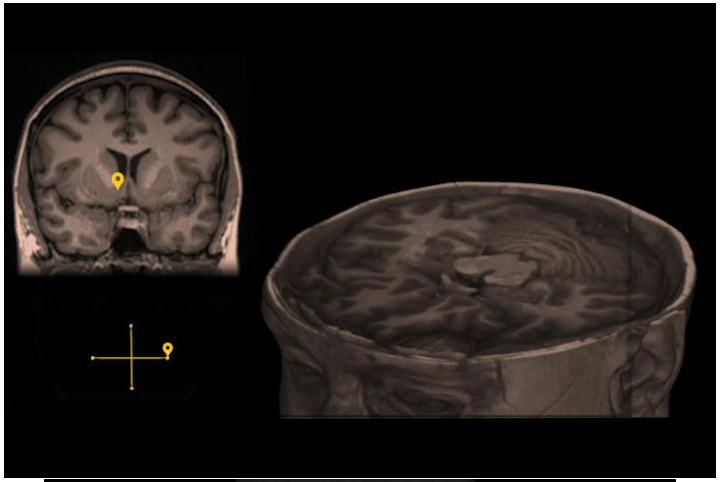
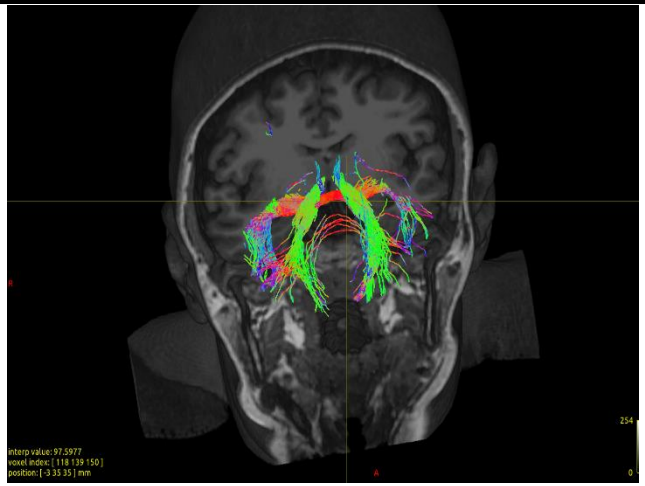
Values represent Median [range]

Personalized FUS Targets

- Anatomical target of the NAc and anterior limb internal capsule
- Target based on treatment atlas
- Target further refined by tractography







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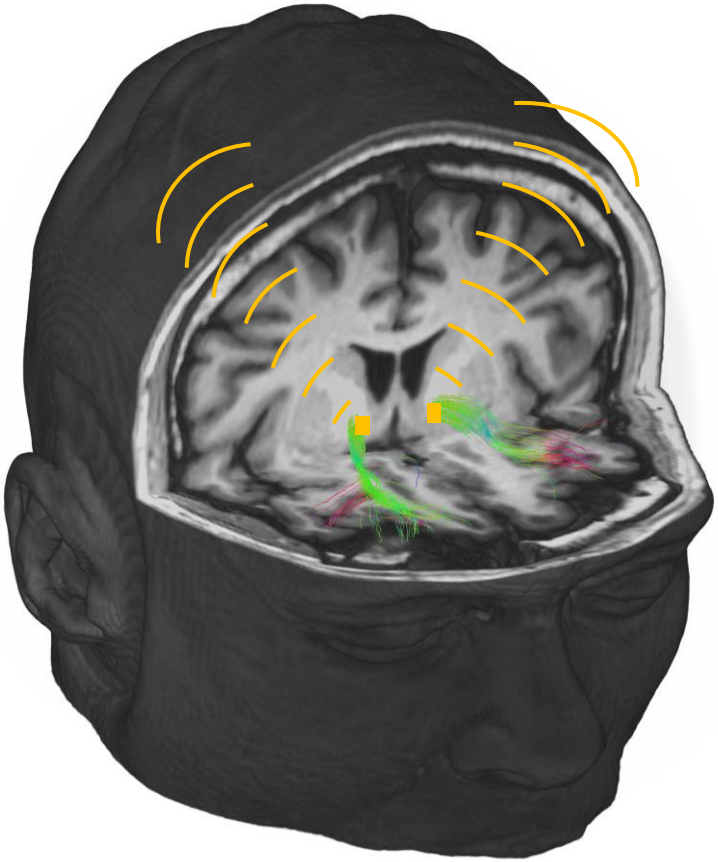
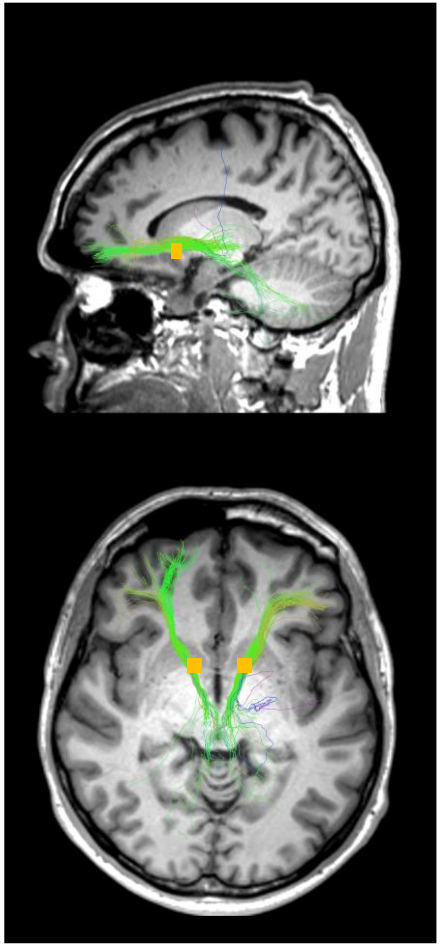
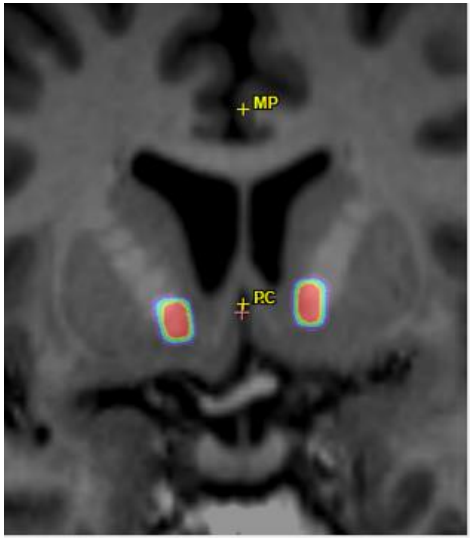
Neuromodulation Addiction Target: Nucleus Accumbens







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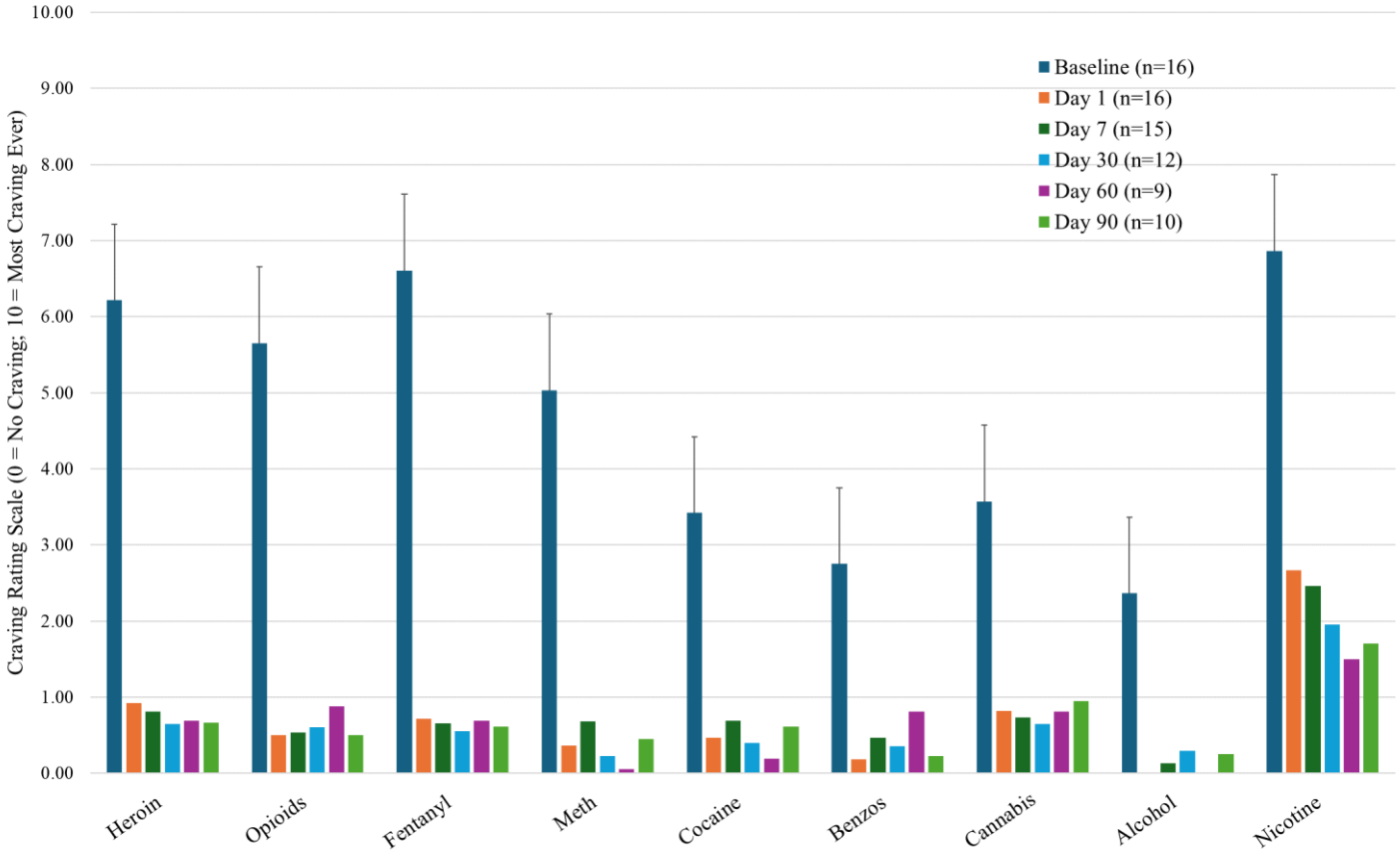
FUS OUD Feasibility Study Long Term Results



90% Decrease in Highest Craved Substance

90% Decrease in all Opioids

91% Decrease in Meth

82% Decrease in Cocaine

92% Decrease in Benzos

73% Decrease in Cannabis

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Urine Toxicology Results at Post-FUS Follow-Up

Pt #	Post-Procedure Follow-Up Visit				
	Day 1	Day 7	Day 30	Day 60	Day 90
5					Fent
6					
7					
8			Fent, Opi, Can		
9				Fent, Can	Can
10					
11					
12				Fent	
13					
14					
15			Alcohol		
16			Meth		
17					
18				Fent, Amp, Coc	
19				Fent	
20					

Overall, 89% Negative

79% Negative
with missed tests

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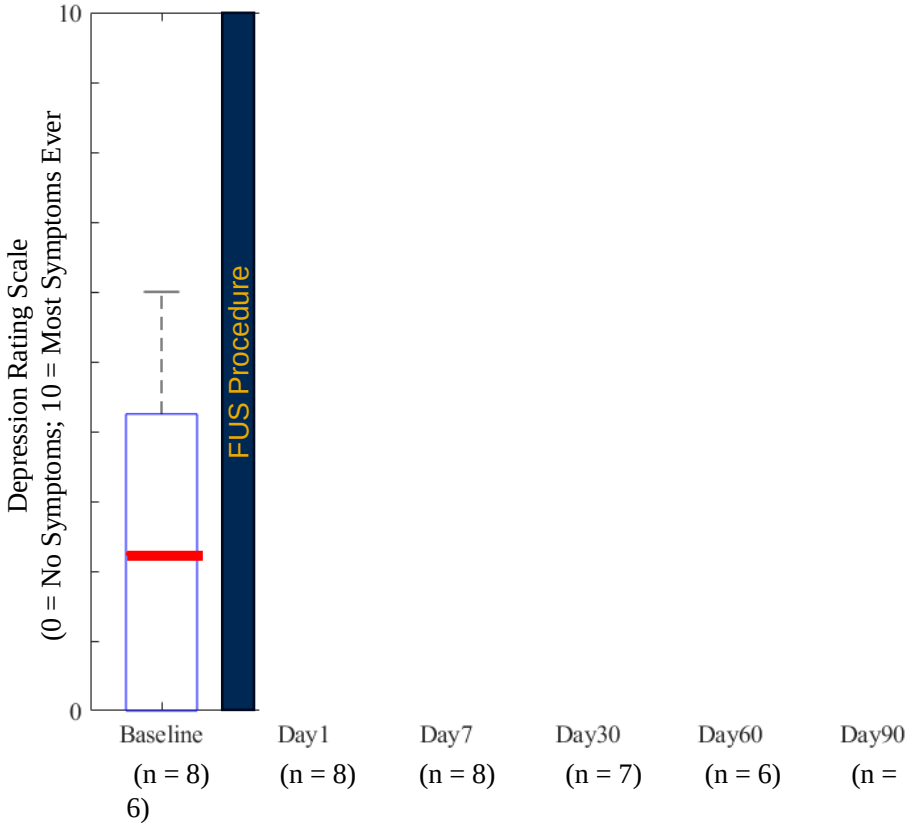
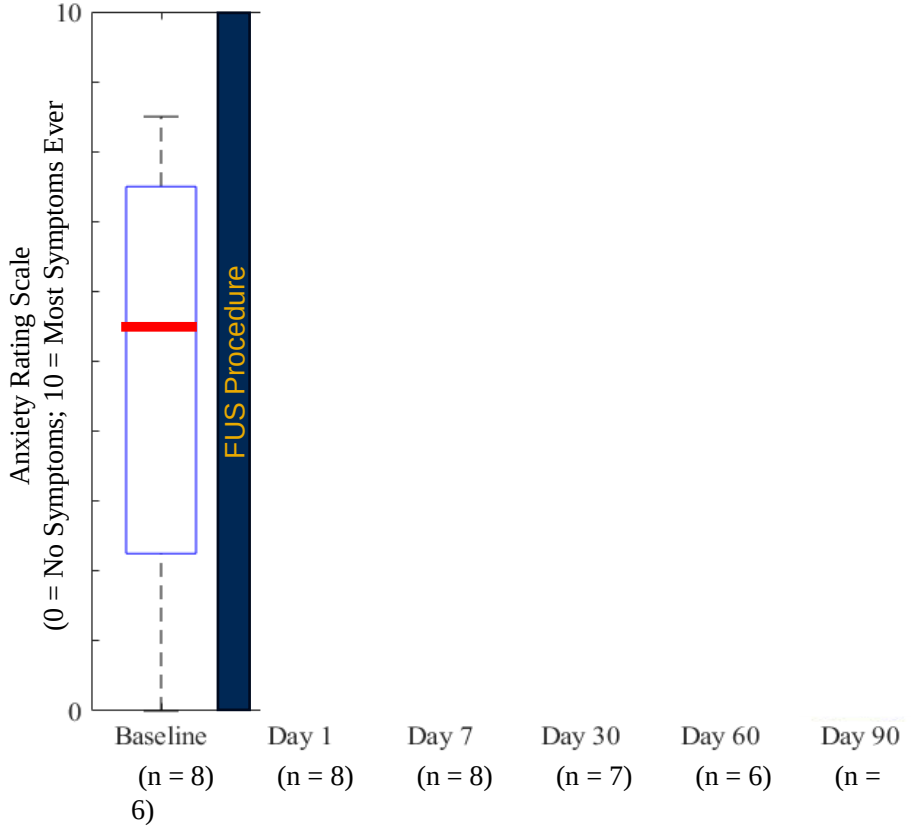
Depression and Anxiety at Baseline Vs. Post FUS Follow-Up





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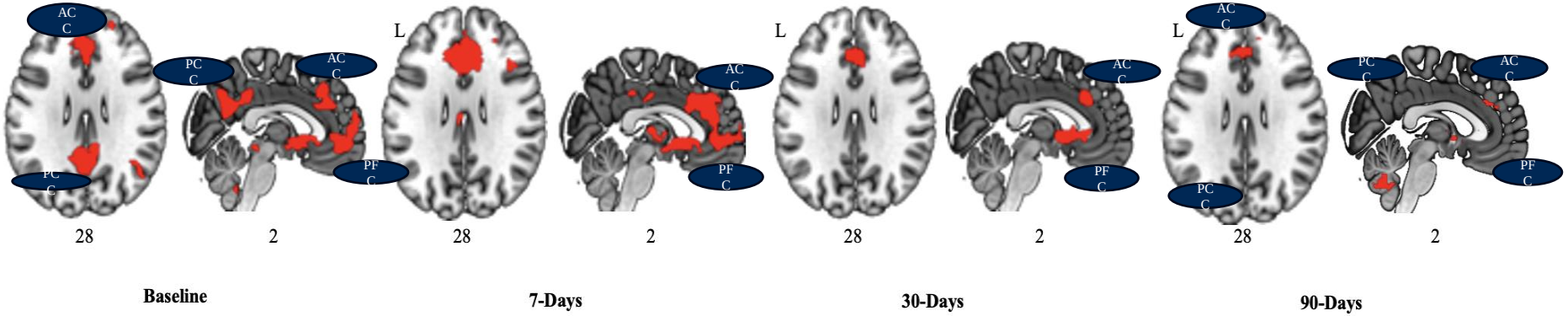
Safety and Tolerability

- **Safety and Tolerability:**
  - Safe and well-tolerated with no unexpected AEs or FUS procedure related SAEs through the 90-day primary endpoint
  - No adverse structural brain changes on multiple MRI sequences noted immediately following the procedure and during post-FUS follow-up MRIs
- **Behavioral and Functional Outcomes:**
  - No worsening depression, anxiety, anhedonia
    - Hamilton Rating Scale for Depression [HRSD] to assess for depressive symptomatology
    - Columbia Suicide Severity Rating Scale [CSSRS] to assess for suicidality
  - No adverse reductions in naturally reinforcing (e.g., eating) and pleasurable behaviors or any other indicators of NAc dysfunction post-FUS
    - Snaith Hamilton Pleasure Scale (SHAPS) and Neuro-Quality of Life Subscales:
      - Satisfaction with Social Roles and Activities, Positive Affect and Well-Being
      - Ability to Participate in Social Roles and Activities

FUS OUD Feasibility Study Results – Objective Functional Data

fMRI Summary: Resting State Connectivity



Nucleus Accumbens (NAc) Seed Analysis corresponds to cravings' reduction

- Observations of clusters with decrease in positive connectivity from the NAc to ventromedial prefrontal cortex, anterior cingulate cortex, and posterior cingulate cortex at different time points
- Decrease in functional connectivity in the brain's reward circuitry and cognitive control systems

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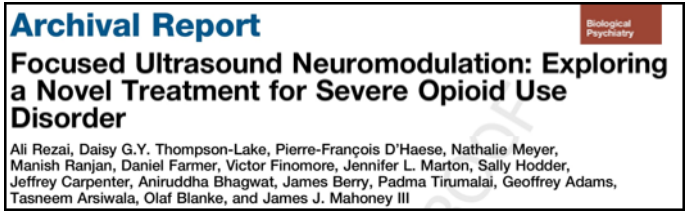
FUS Low Intensity Neuromodulation for Addiction (2021-Present)

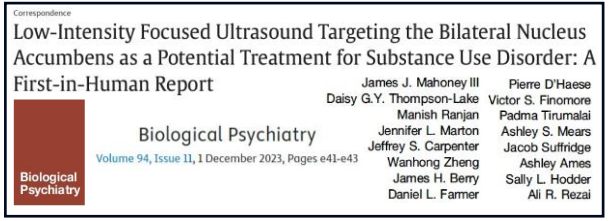
- 38 patients with severe substance use disorder
  - Failed multiple in-patient, residential 28 day, and other treatments
  - Multiple overdoses
- FDA, NIDA, IRB study
- 20-30-minute focused ultrasound treatment
- Safe and Feasible (1 device SAE)
  - 1 Unanticipated Adverse Device Affect (UADE)
- Drug craving and Substance Use reduced
  - Opioid, benzo, cocaine, methamphetamine, alcohol
- Long term sustainability (1year)
- Placebo controlled RCT (In progress-11 Participants)


Archival Report

Biological Psychiatry

Focused Ultrasound Neuromodulation: Exploring a Novel Treatment for Severe Opioid Use Disorder

Ali Rezai, Daisy G.Y. Thompson-Lake, Pierre-François D'Haese, Nathalie Meyer, Manish Ranjan, Daniel Farmer, Victor Finomore, Jennifer L. Marton, Sally Hodder, Jeffrey Carpenter, Aniruddha Bhagwat, James Berry, Padma Tirumalai, Geoffrey Adams, Tasneem Arsiwala, Olaf Blanke, and James J. Mahoney III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Low-Intensity Focused Ultrasound Targeting the Bilateral Nucleus Accumbens as a Potential Treatment for Substance Use Disorder: A First-in-Human Report

James J. Mahoney III, Daisy G.Y. Thompson-Lake, Manish Ranjan, Jennifer L. Marton, Jeffrey S. Carpenter, Wanhong Zheng, James H. Berry, Daniel L. Farmer, Pierre D'Haese, Victor S. Finomore, Padma Tirumalai, Ashley S. Mears, Jacob Suffridge, Ashley Ames, Sally L. Hodder, Ali R. Rezai

Biological Psychiatry

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Volume 94, Issue 11, 1 December 2023, Pages e41-e43


frontiers | Frontiers in Psychiatry

TYPE Original Research
PUBLISHED 15 September 2023
DOI 10.3389/fpsyt.2023.1211566

Low-intensity focused ultrasound targeting the nucleus accumbens as a potential treatment for substance use disorder: safety and feasibility clinical trial

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- **90% reduction in substance cravings post FUS**
- **>70% negative urine toxicology screen at last visit**

Clinical trials.gov ID#: NCT04197921

IDE#: G190092 NIDA: DA047714-04S1

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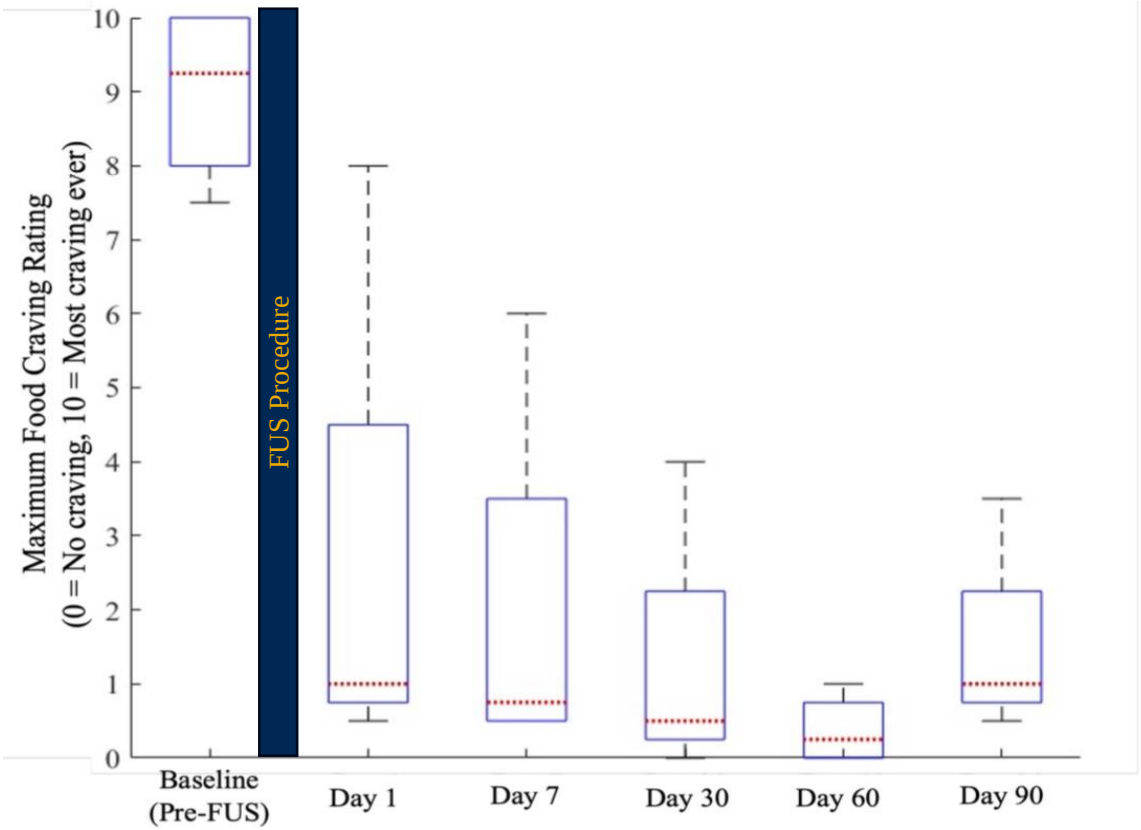
FUS Neuromodulation: Binge Eating Disorder, Food Noise Food Craving at Baseline Vs. Post FUS Follow-Up (n=4)



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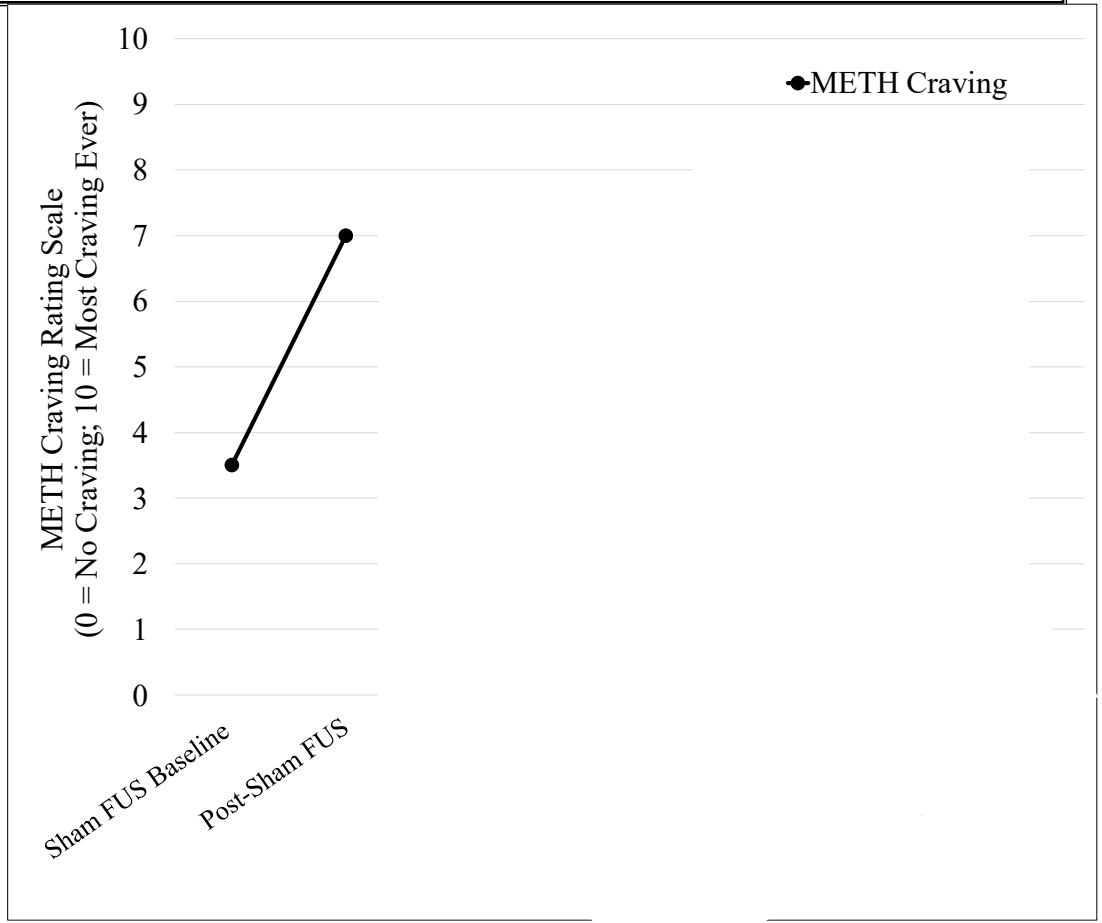
Primary Methamphetamine Use Disorder – NO OUD *(n=1)*

Within-Session Cue Induced Craving (Sham Versus Active FUS)

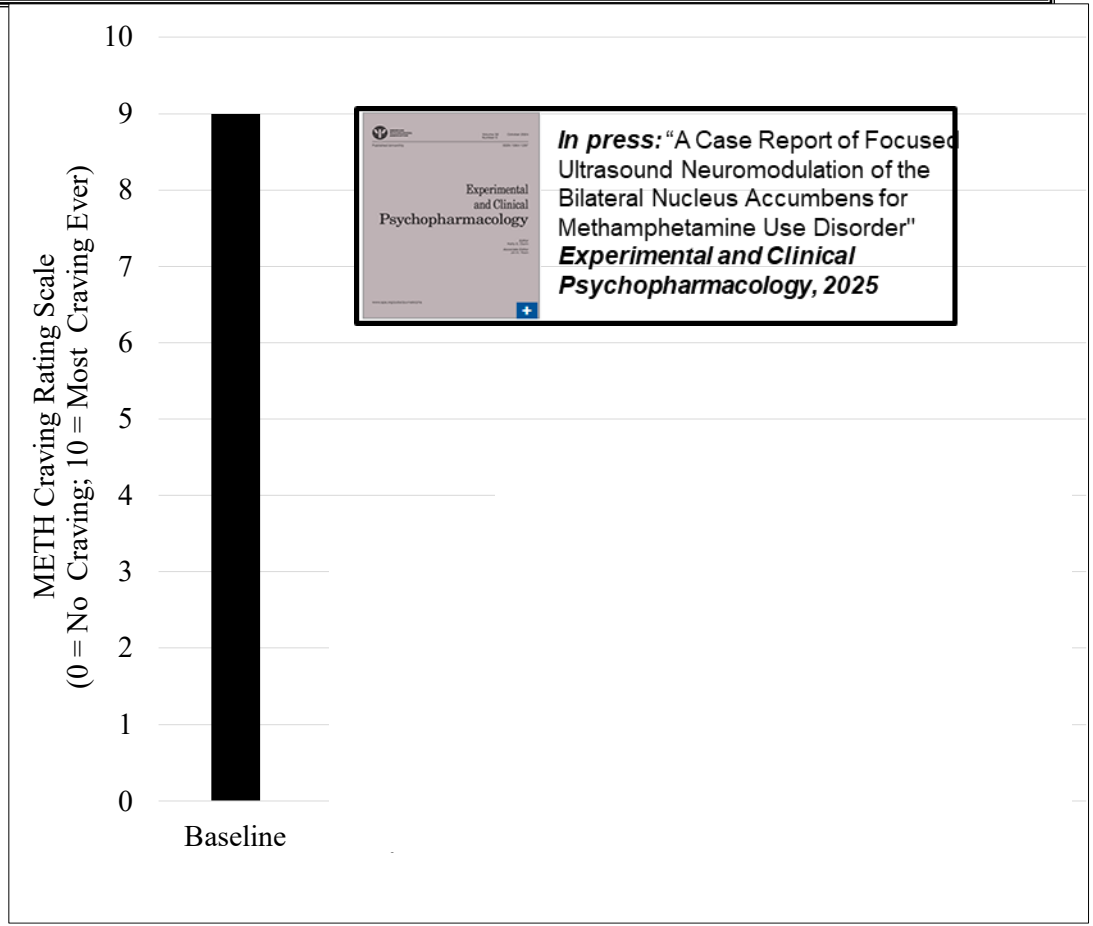
- Increase in Craving following Sham FUS
- Substantial Decrease in Craving following 5 mins of Active FUS (70W)
- Complete Suppression in Craving following additional 5 min blocks of Active FUS (90W and 100W)



Primary Methamphetamine Use Disorder – NO OUD *(n=1)*

Pre-FUS Baseline Versus Post-FUS Follow-Up

- High Baseline Meth Craving during screening prior to receiving FUS
- Cravings entirely suppressed during the 24-hour post-FUS assessment
- Craving entirely suppressed during all follow-up assessments through 90 Days
- Urine toxicology negative for all illicit substances including Meth during 7, 30, 60, 90-day post-FUS follow-ups



FUS SUMMARY FINDINGS

Craving Reduction

- **Significant decrease in cravings** in familiar settings
- **Difficulty "connecting" to the cues** which would normally induce craving and use
- **Reduced thoughts and dreams related to drugs or alcohol**

Emotional Improvement

- **Reduced anxiety and depression**
- **Reduced anhedonia**
- **Reduced shame and self guilt**

Enhanced Social / Life

- **More involved in community, social aspects and treatment**
- **Stable Desires**: No change in pleasure (e.g., food)
- **Enhanced Mood:** Improved anxiety, frustration tolerance, and reduced irritability.
- **Sharper Focus**: Boosted motivation, clearer thinking, and more goal-driven.
- **Life Engagement:** More involved in family, work, and education.

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THANK YOU!!!

Behavioral Medicine
- James Mahoney
- Daisy Thompson-Lake
- James Berry
- Daniel Farmer

Neurosurgery
- Ali Rezai
- Manish Ranjan

Neuroradiology
- Jeffery Carpenter
- Pierre-François D'Haese
- Peng Weng

Research Scientists
- Victor Finomore
- Tasneem Arsiwala
- Geoffrey Adams
- Jacob Suffridge

Clinical & Translational Medicine
- Sally Hodder

Clinical Trial Management
- Padma Tirumalai
- Jennifer Marton

Thank you for the Support and Guidance from NIDA team
- Drs Volkow, Walton, Aklin, Wang, Wong
- UO1-P1UG3DA047714-01

Thank you to research collaborators
- Medtronic, Insightec, & Dr. Blanke's Lab at EPFL

Thank you for financial support form
- The Harry T. Mangurian Foundation

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ALCOHOLICS ANONYMOUS: Why does it work?

THE PROTECTIVE WALL OF HUMAN COMMUNITY

QUESTIONS?