The Neurobiology of Addiction

NOAP 2024 Annual Conference

iday May 17, 2024 – Sanibel Harbor - Ft. Myers, Florida

John C. Tanner, D.O., DABAM, DFASAM, FAOAAM, CCFC, MRO

Disclosure of Relevant Financial Relationships

Name	Commercial Interests	Relevant Financial Relationships: What Was Received	Relevant Financial Relationships: For What Role
John C. Tanner, D.O. **DABAM, DFASAM, FAOAAAM, CCFC, MRO**	Braeburn™ Pharmaceuticals Beginning in the fall of 2023	Honoraria	Speaker Bureau

Involvement as a speaker for Braeburn™.
The product does not directly relate to this lecture.

John C. Tanner, DO, DFASAM, DABAM, FAOAAM, CCFC, MRO

- Medical Director for the Intervention Project for Nurses (IPN) – Florida
- Part-time private Addiction and Behavioral Medicine practice since 1984
- Distinguished Fellow of the American Society of Addiction Medicine (DFASAM)
- Currently serving on the Board of Directors for the Florida Society of Addiction Medicine since 2013
- Inaugural Diplomate of The American Board of Addiction Medicine (DABAM)
- Fellow of the American Osteopathic Academy Of Addiction Medicine (FAOAAM)
- One of the 3 Principal Investigators for the FDA Phase 2 and 3 Clinical Trials for approval of Suboxone® Film
- Clinically Certified Forensic Counselor (CCFC) and Diplomate of The Board of Clinical Forensic Counseling
- Medical Review Officer (MRO)
- Certificate of Added Qualifications in Addiction Medicine by the AOA Bureau of Osteopathic Specialists under the Conjoined Boards
- Assistant Professor, Department of Psychiatry, University of Florida College of Medicine (currently a courtesy appointment)
- Medical Director Tides Edge (functioning more as a consultant and group provider)
- Former Director at Large for the American Society of Addiction Medicine's Board of Directors for two consecutive terms (from 2011 to March 2019)

Continuing Medical Education Activity Objectives

Title of Activity: The Neurobiology of Addiction
Date: ?day, , 2024

OBJECTIVES	OUTLINE	TIME FRAME	PRESENTER	METHODS
Objective 1 Upon completion of this activity the learner will be able to discuss how addiction is linked with the brain's; memory, motivation, reward, and executive function systems and changes functioning of these systems.	A) Understand that reward in the brain is there to reinforce behaviors important for survival. B) Better understand eight brain regions that are affected by the potent reward of psychoactive substances. C) Identify how craving is a linked with the brain's reward system. D) Understand the role that withdrawal plays in perpetuating the addictive process.	10 to 15 minutes	John C. Tanner, D.O., DFASAM, DABAM, CCFC, MRO	Lecture/discussion; PowerPoint; Q&A
Objective 2 Upon completion of this activity the learner will be able to explain some of the basic neuroscience as it relates to substance use disorders.	A) Gain an understanding of the interplay between the frontal cortical areas of the brain and the limbic system. B) Identify some of the neurotransmitters that play a role in addiction. C) Understand that virtually all psychoactive substances have toxic or adverse effects in the gray matter areas of the brain. D) What is recovery, how is it maintained, and what is the role of various regions of the brain in the recovery process?	10 to 15 minutes	John C. Tanner, D.O., DFASAM, DABAM, CCFC, MRO	Lecture/discussion; PowerPoint; Q&A
Objective 3 Upon completion of this activity the learner will be able to list some helpful in therapeutic measures to help someone with a substance use disorder.	A) An accurate diagnosis required to establish appropriate plan. B) Accurate diagnosis may require toxicology testing. C) Deciding what treatments are needed, i.e., psychotherapeutic (psychiatric, psychotherapist, mutual support groups) and some of the medication options.	10 to 15 minutes	John C. Tanner, D.O., DFASAM, DABAM, CCFC, MRO	Lecture/discussion; PowerPoint; Q&A
Objective 4 Upon completion of this activity the learner will be able to understand the evidence that addiction is a chronic relapsing and progressive disease with similarities to other chronic diseases having a genetic and biologic basis.	A) Importance of accepting addiction as a chronic disease as an integral part of providing quality patient care. B) Understanding that addiction is a chronic biologically based disease, affecting very specific brain regions helps to mitigate the stigma, guilt, and shame that impede recovery. C) Unrecognized and untreated substance use disorders lead to significant self-destructive behaviors and premature death.	10 to 15 minutes	John C. Tanner, D.O., DFASAM, DABAM, CCFC, MRO	Lecture/discussion; PowerPoint; Q&A

Ashes to ashes. Dust to dust.[1] It's what happens between that seems to be a miracle.

- The substances than make up our body come from the earth (thus, we are made from star dust).
- Our brain is the most complex thing in our entire known universe.
- It is believed to have a 86 billion neurons[2,3,4] and 100 trillion connections[5,6].
- At least 1/3 of the approximately 20,000 genes constituting the human genome are expressed primarily in the brain (the highest proportion of genes expressed in any part of the body)[7,8].

1. Genesis 3:19 "… till thou return to the ground; for out of it wast thou taken: for dust thou art, and unto dust shalt thou return."
2. brainfacts.org 3. neuromedia.ca 4. cbmm.mit.edu 5. scientificamerican.com 6. scienceoxygen.com 7. ninds.nih.gov 8. sciencenews.org

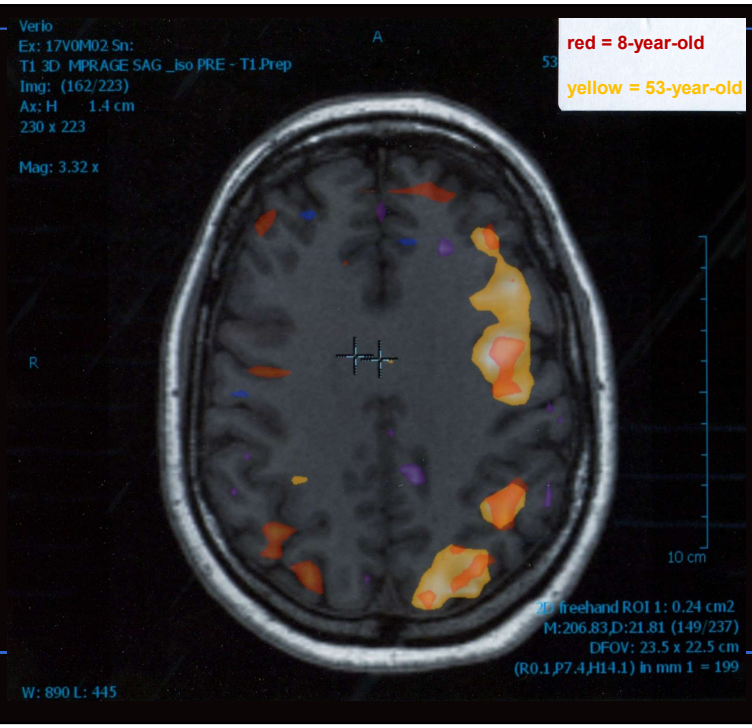
Ashes to ashes. Dust to dust.[1] It's what happens between that seems to be a miracle.

- Despite constituting only 2% of the body mass, it consumes approximately 20–25% of the body's total energy [2,3].
- Most of the brain's energy expenditure, around 80–90%, occurs during its spontaneous activity such as when you're at rest and not performing any specific tasks[3].
- Two-thirds of the brain's energy is dedicated to neuronal communication. Charged ions (sodium, calcium, and potassium) continuously move through cell membranes, allowing neurons to recharge and transmit signals and ATP supplies the energy needed for these ion movements[2].
- The remaining third of the brain's energy expenditure is for cell maintenance.
- On average, the brain consumes approximately 0.3 kilowatt-hours (kWh) per day and for an adult that is more than 100 times what a typical smartphone requires daily[4].

1. Genesis 3:19 "… till thou return to the ground; for out of it wast thou taken: for dust thou art, and unto dust shalt thou return."
2. scientificamerican.com 3. frontiersin.org 4. theconversation.com

53 Year Old WF w/DID [1]

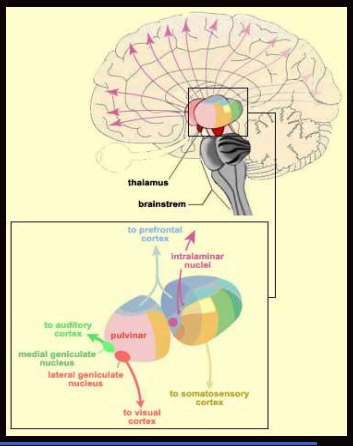
fMRI: showing identical verbal paradigm imaged in red and yellow then superimposed



1 Image from BHF research in Jacksonville

Consciousness – where does it reside?

- [1] Activation of the central lateral thalamus and deep layers of the cerebral cortex drives pathways in the brain that carry information between the parietal and frontal lobe in the brain.
- This circuit is believed to work as the core of our consciousness, enabling conscious thoughts and feelings in primates and likely in humans.
- The scientific team put macaque monkeys under anesthesia, then stimulated different parts of their brains with electrodes at a frequency of 50 Hertz while they were under anesthesia.
- When the central lateral thalamus was stimulated, the monkeys woke up and their brain function resumed, even though they were still under anesthesia.
- Seconds after the scientists switched off the stimulation, the monkeys lost consciousness again.

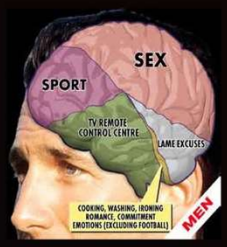


1. Reference:
Neuron, February 12, 2020 DOI: https://doi.org/10.1016/j.neuron.2020.01.005

Brain's Natural Rewards

- Social and nurturing activities
- Food & Water

- Sex

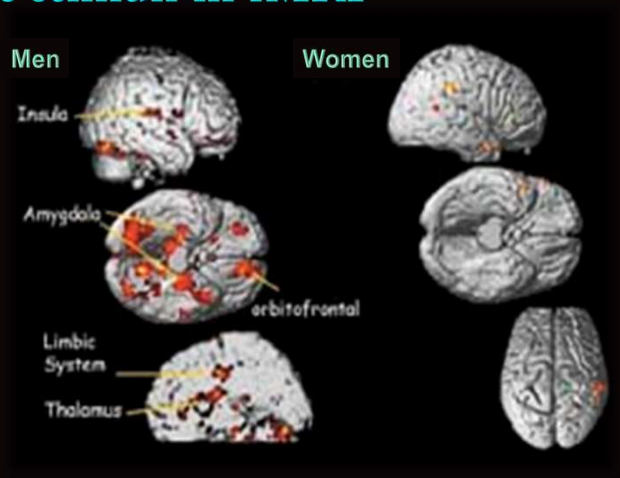


- Etc. (i.e., safety/security, music, exercise, hobbies)

Our brains are very "hard wired" for generating repetition of survival behaviors!!!

Gender differences in cerebral activation when viewing erotic stimuli in fMRI [1]

- For analysis of specific activation, the contrast images of all groups were entered into a two-sample t-test. Interaction-related increase in MR signal is superimposed on three orthogonal sections of 3-D T1 weighted standard brain.
- When viewing erotic film excerpts, statistical parametric maps of areas activated more prominently in men compared with women. Results show activation of left thalamus, left amygdala, anterior cingulate, bilateral orbitofrontal, and insular cortex



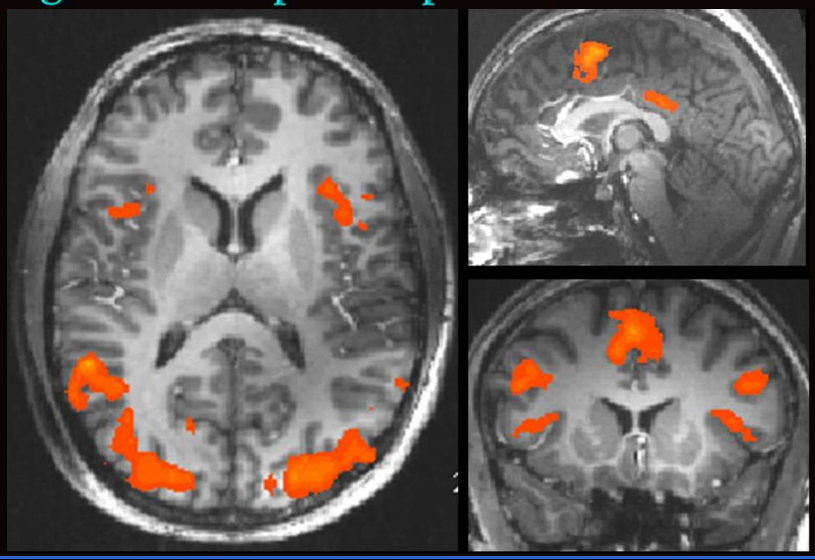
1. Reference: University Clinic Essen 03/01/2006; Elke Gizewski, MD, Elke Gizewski

Activation during sex anticipation period

[1]

Cortical activation during anticipation period.

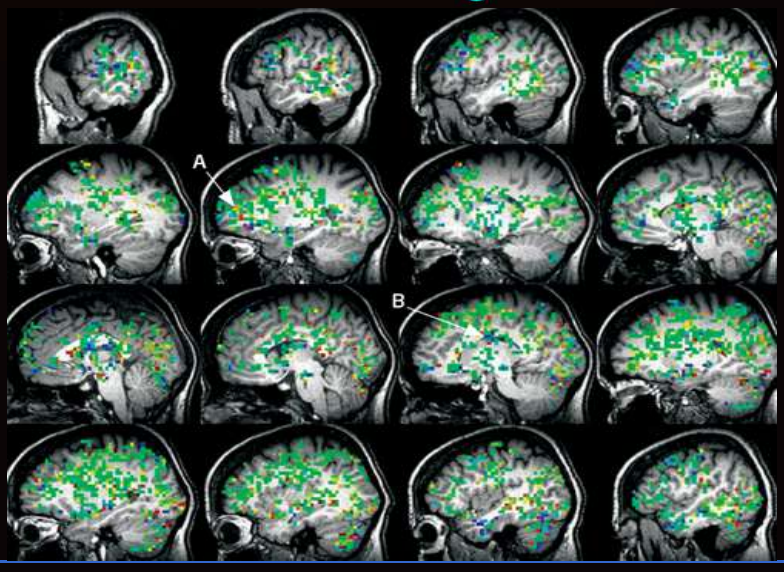
Regions with significant signal increases during anticipation period [erotic anticipation × emotional anticipation] (conj. $p < 0.05$ uncorrected, x: −1, y: 1, z: −10).



1. Reference: Front. Neuroanat., 01 November 2010 | doi: 10.3389/fnana.2010.00138

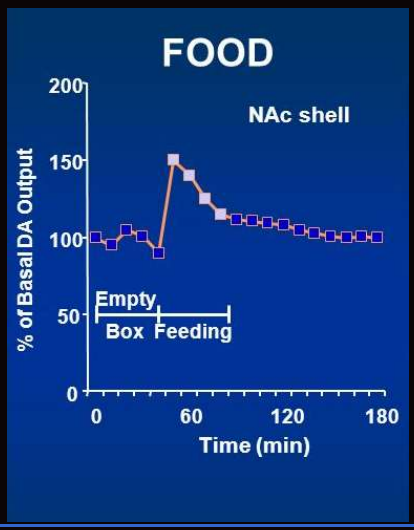
fMRI images of a woman's brain throughout an orgasm[1]

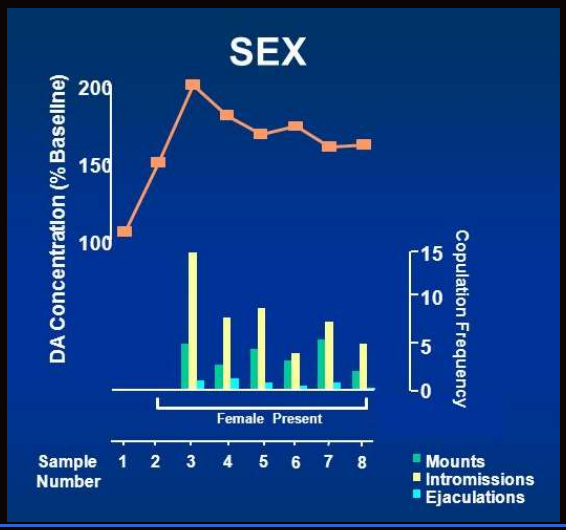
- More than 30 areas of the brain are active during the event, including those involved in touch, memory, reward and even pain
- PFC becomes more active during orgasm, whether it's achieved through physical touch or thought alone
- PFC evidently "shuts off" during orgasm – especially a region of the orbitofrontal cortex (OFC), which is involved in the process of self-control



1. Reference: Rutgers University and the University of Groningen in the Netherlands

Natural rewards elevate dopamine levels[1,2]





1. DiChiara et al., J. Neuroscience, 1999

2. Fiorino and Phillips, J. Neuroscience, 1997

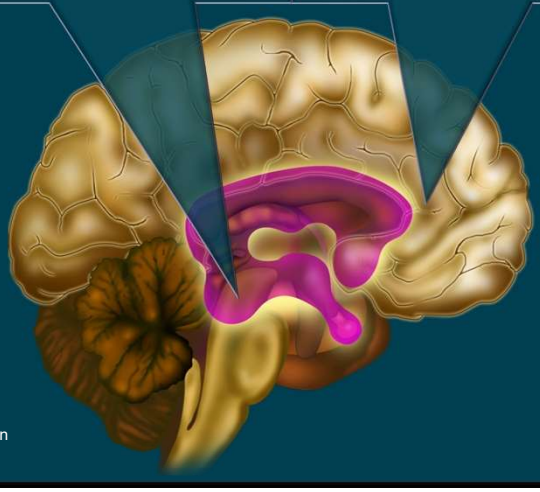
Treatment: the target areas

Limbic Region

Role: Reward, Emotions, *Drive Generation*
Intervention: Pharmacotherapy

Pre Frontal Cortex

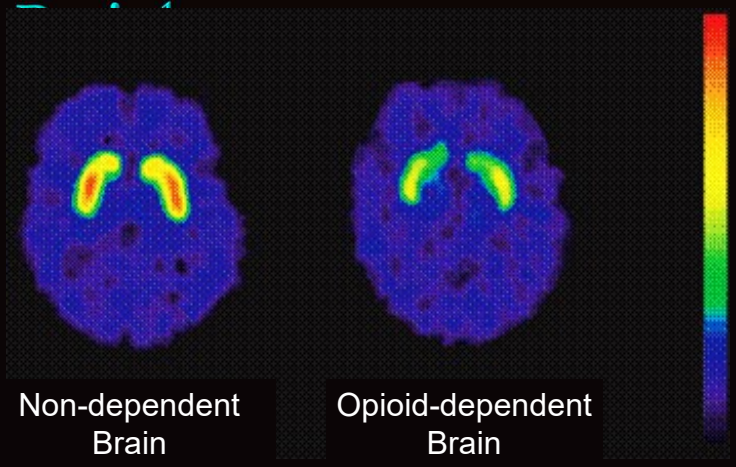
Role: *Decision Making, Impulse Control, Judgment*
Intervention: *Counseling, Mutual Support*



When limbic regions are "hijacked" by addiction the intent becomes "nefarious".

When the frontal cortex "succumbs" to addiction it "loses its strength".

Drug Dependence Causes Changes in



Non-dependent Brain

Opioid-dependent Brain

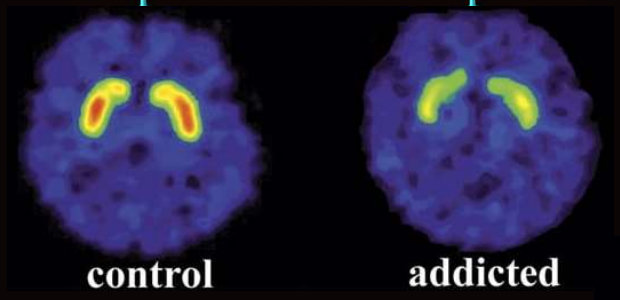
PET scan images

The lack of red in the opioid-dependent brain shows that chronic opioid use has reduced dopamine D2 receptor concentration.

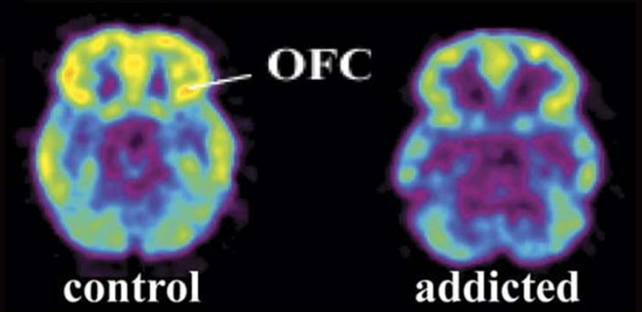
Similar finding occur with other addictive drugs.

1. Wang GJ et al. *Neuropsychopharmacology.* 1997;16(2):174-182.

Dopamine D2 receptors[1]

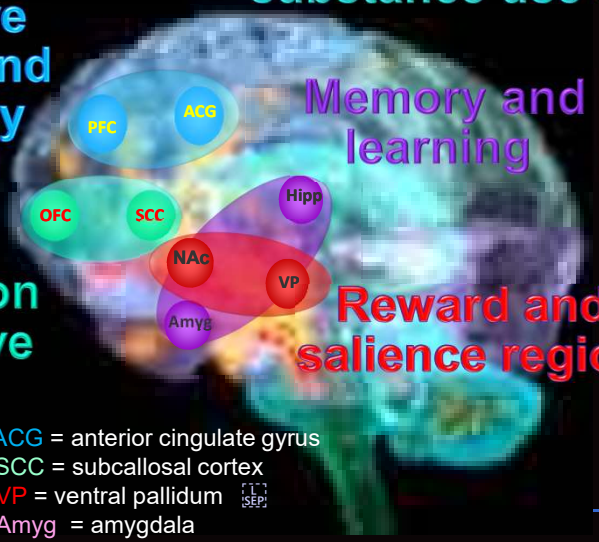


Brain glucose metabolism



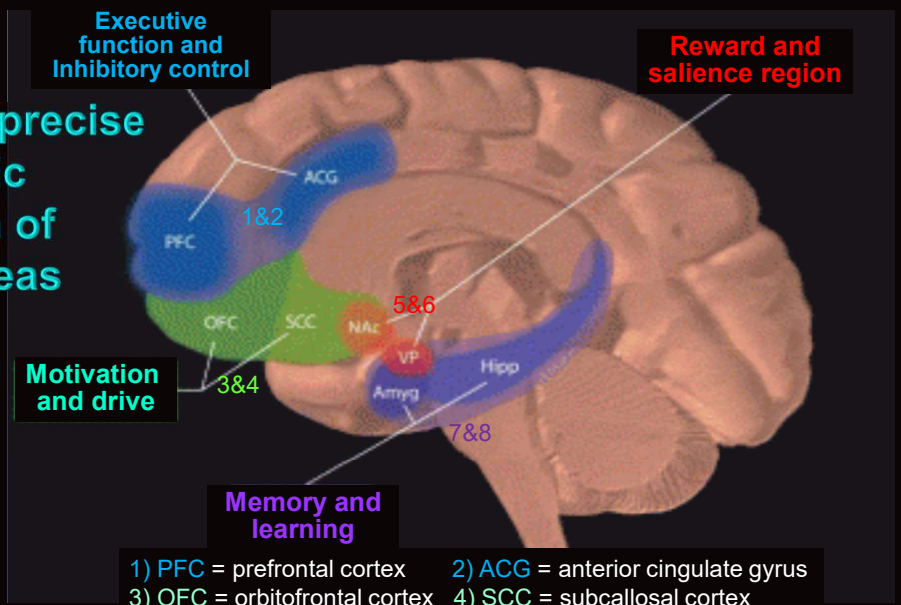
1 Ref: Volkow, et, al, PNAS Vol. 108 | No. 37

Brain circuits involved in survival and substance use disorders



1) PFC = prefrontal cortex 2) ACG = anterior cingulate gyrus
3) OFC = orbitofrontal cortex 4) SCC = subcallosal cortex
5) NAc = nucleus accumbens 6) VP = ventral pallidum
7) Hipp = hippocampus 8) Amyg = amygdala

A more precise anatomic location of the 8 areas



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What is the goal addiction treatment?

Emotional Sobriety?

Remission?

Rehabilitation?

Recovery

Abstinence?

Sobriety?

Personal Health?

Perhaps recovery is: the process of being motivated to seek new healthy rewards, having learned better ways to cope with life's stressors, having the capacity to regain control over cravings and impulses (all 8 centers).

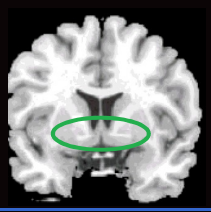
Alcohol Dependence and *Neuroscience* [1]

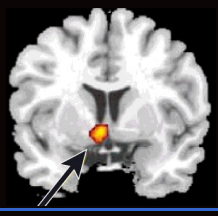
fMRI images of brain's reward system

- *Social drinkers*
- *Neutral cues vs. Alcohol cues*
- *Alcohol dependent* (non-treatment seeking)

Social drinkers

Alcohol Dependent Individuals





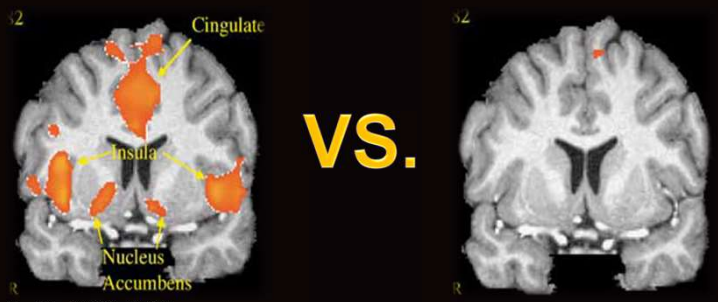
Reference:
1. Myrick, et al. Arch Gen Psychiatry. 2008;65:466-475.

The cues can activate multiple areas of the brain [1,2,3,4]

fMRI imagery of the brain's reward system demonstrates that:

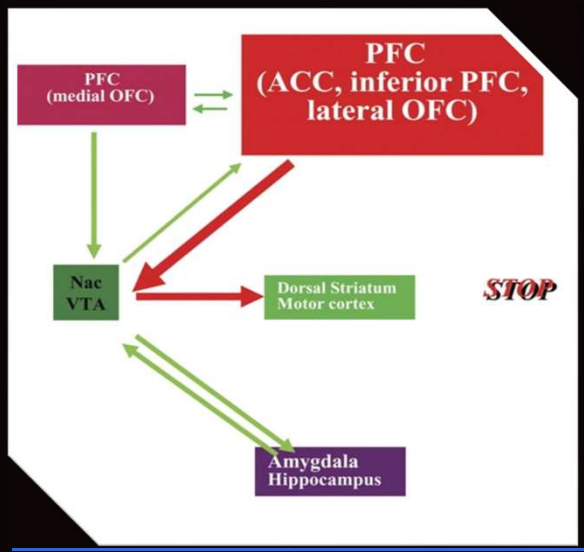
- Alcohol cues activate the brain in alcohol-dependent individuals compared with social drinkers[1]
- These findings may lead to better interventions for the treatment of alcohol dependence[4]

Alcohol-Dependent Individuals | Social Drinkers

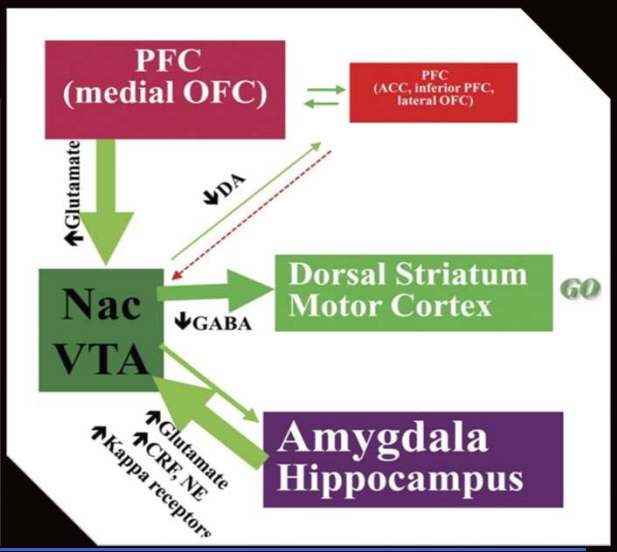


References
1. Myrick H et al. *Arch Gen Psychiatry*. 2008;65:466-475.
2. Anton RF. *N Engl J Med*. 2008;359:715-721.
3. Dackis C et al. *Nat Neurosci*. 2005;8:1431-1436.
4. Myrick H et al. *Neuropsychopharmacology*. 2004;29:393-402.

Non-Addicted Brain



Addicted



Main classes of drugs of abuse, their main molecular targets, and some of the mechanisms by which they increase dopamine in nucleus accumbens[1]

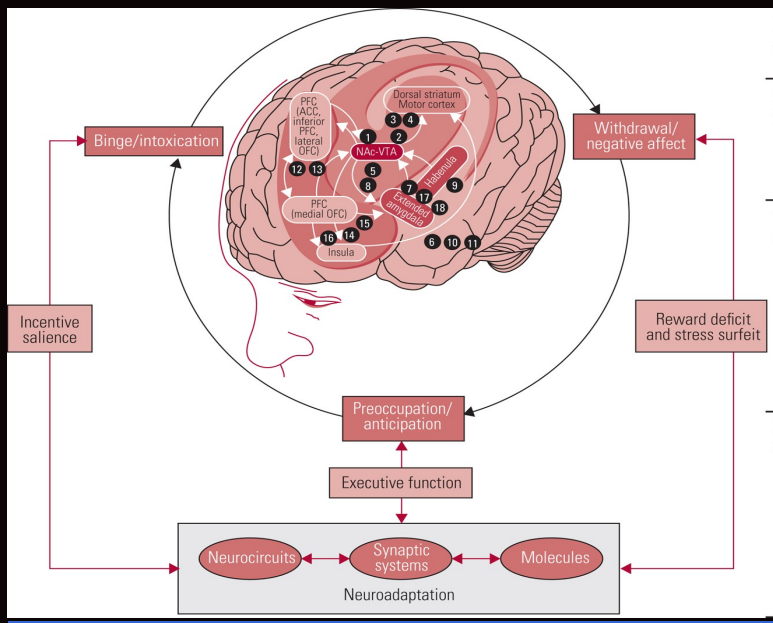
Drug	Target	Mechanism for dopamine increases
Stimulant drugs (cocaine, amphetamine, methamphetamine)	Dopamine transporter	Blocks dopamine transporter on the terminals of dopamine projecting neurons from ventral tegmental area to nucleus accumbens (cocaine) or releases dopamine from the vesicles of dopamine terminals (methamphetamine and amphetamine).
Opioids (heroin, opioid analgesics)	μ-opioid receptor	Ventral tegmental area dopamine neurons by inhibiting GABA interneurons that contain μ-opioid receptor in the ventral tegmental area or directly activates nucleus accumbens neurons that contain μ-opioid receptor.
Nicotine (cigarettes and other tobacco products)	Nicotinic receptors (predominantly α4β2 subtype)	Directly activates ventral tegmental area dopamine neurons by stimulating their nicotine receptors and indirectly activates them by stimulating the nicotine receptors in glutamatergic terminals to ventral tegmental area dopamine neurons.
Alcohol and inhalants	Multiple targets, including GABA and glutamate receptors	Facilitates GABAergic neurotransmission, which may disinhibit ventral tegmental area dopamine neurons from gamma amino butyric acid interneurons or may inhibit glutamate terminals that regulate dopamine release in nucleus accumbens.
Cannabinoids (marihuana)	Cannabinoid CB1 receptors	Regulates dopaminergic signaling through CB1R in nucleus accumbens neurons and in gamma amino butyric acid and glutamate terminals to nucleus accumbens.

1 Adapted from the National Academy of Sciences · March 2011

GABA=gamma amino butyric acid

Drug	Primary target	Acute effect	Key neuroadaptation with chronic consumption
Stimulants			
Cocaine	DAT	↑Dopamine	↓Dopaminergic activity
Amphetamine	DAT + MAO ↑Synaptic vesicle release	↑Dopamine	↓Dopaminergic activity
Nicotine	Nicotinic ACh receptor on dopaminergic VTA neurons	↑Dopamine	↓Dopaminergic activity
Sedatives/depressants			
Alcohol	GABA Glutamate	↑$GABA_A$ function ↓NMDA function	↓$GABA_A$ function ↑NMDA function
Benzodiazepines	GABA	↑GABA function	Unclear, likely reduced $GABA_A$ function
GHB	$GABA_B$ receptors, GHB receptors	↑GABA function	Unclear
Cannabis	CB_1 receptors	↑Dopamine via modulation of GABAergic input to dopaminergic neurons; modulates opioid systems	↓CB_1 receptor activity
Opiates: morphine, heroin, codeine, etc.	Mu opioid receptors	Stimulates opioid receptors (μ is key), indirectly increases dopamine via modulation of GABAergic input to dopaminergic neurons	Reduced sensitivity of μ opioid receptor, reduced noradrenergic activity

Adapted from Lingford-Hughes Reference Lingford-Hughes, Watson and Kalk2010

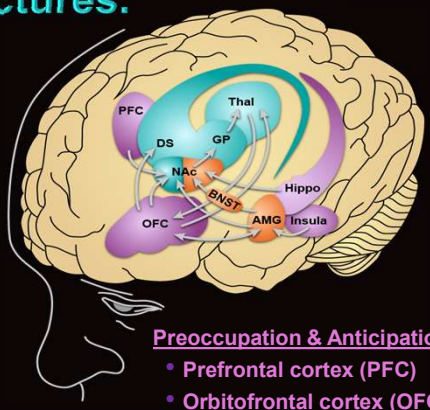


Functional domain	Circuit	Brain region	Neuro-transmitter
Binge/ intoxication	1	VTA	Glutamate
	2	VTA	GABA
	3	dStr	Dopamine
	4	dStr	Glutamate
Withdrawal/ negative affect	5	VTA	CRF
	6	Amyg(Ce)	CRF
	7	BNST	Noravrenaline
	8	NAc	Dynorphin
	9	Habenula	ACh
	10	Amyg(Ce)	NPY
	11	Amyg(Ce)	EC
Preoccupation/ anticipation	12	PFC	Glutamate
	13	PFC	GABA
	14	Hippo	Glutamate
	15	Amyg(B)	Glutamate
	16	BNST	CRF
	17	BNST	Norepinephrine
	18	Insula	CRF

Ref: G. Koob and N. Volkow 2016

What drives the addiction process? [1] 3 sets of brain structures.

Is it a carrot on a stick?



Is it a whip from behind?

Euphoria, Binge & Reward

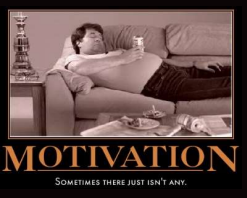
- Nucleus (anterior) accumbens (NAc)
- Dorsal striatum (DS)
- Globus pallidum (GP)
- Thalamus (Thal)
- Ventral pallidum (VP)

Preoccupation & Anticipation

- Prefrontal cortex (PFC)
- Orbitofrontal cortex (OFC)
- Hippocampus (Hippo)
- Insula (Insula)

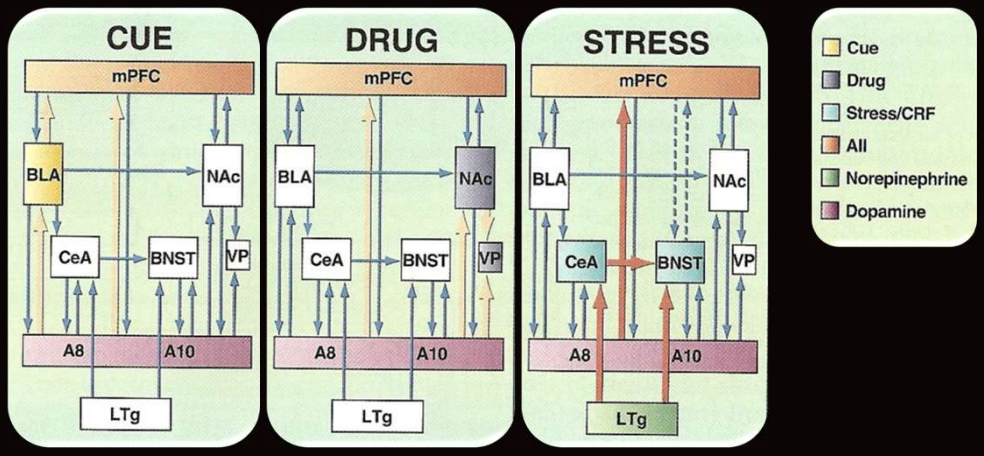
Withdrawal and Negative Affect

- Central amygdala (AMG)
- Bed nucleus of the stria terminalis (BNST)
- Nucleus (posterior) accumbens (NA_C)
- Habenula



1. Koob GF, Volkow ND. *Neuropsychopharmacology*. 2010;35(1):217-238.

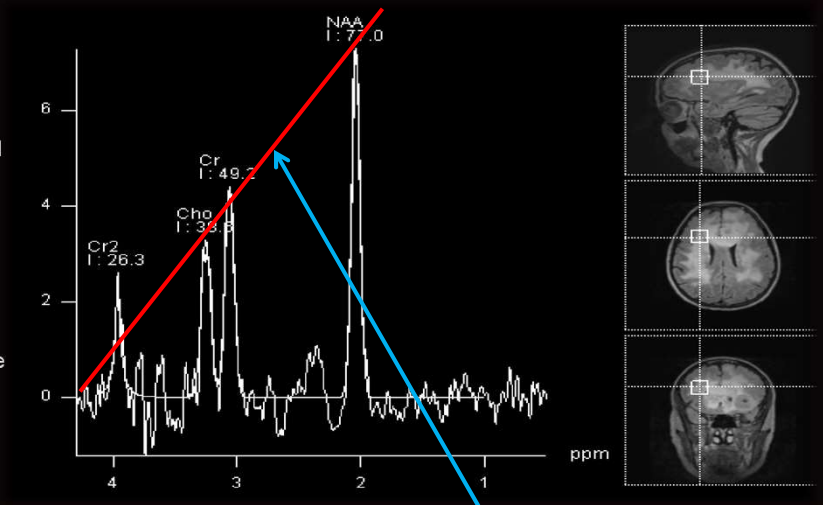
What are the known underlying mechanisms of relapse and why are some prescribed medications are a risk? [1]



Reference:
1. Shaham *et al., 2003*

Magnetic Resonance Spectroscopy (MRS) [1]

- Safe (No X-Rays)
- Noninvasive
- Provides a snapshot of the neurochemistry within a defined volume of interest
- Significantly increases the accuracy and specificity of conventional MR imaging in differentiating between disease states
- MRS enables us to characterize cellular constituents such as N-acetyl aspartate or choline, as well as gamma-aminobutyric acid (GABA) and glutamate[2]

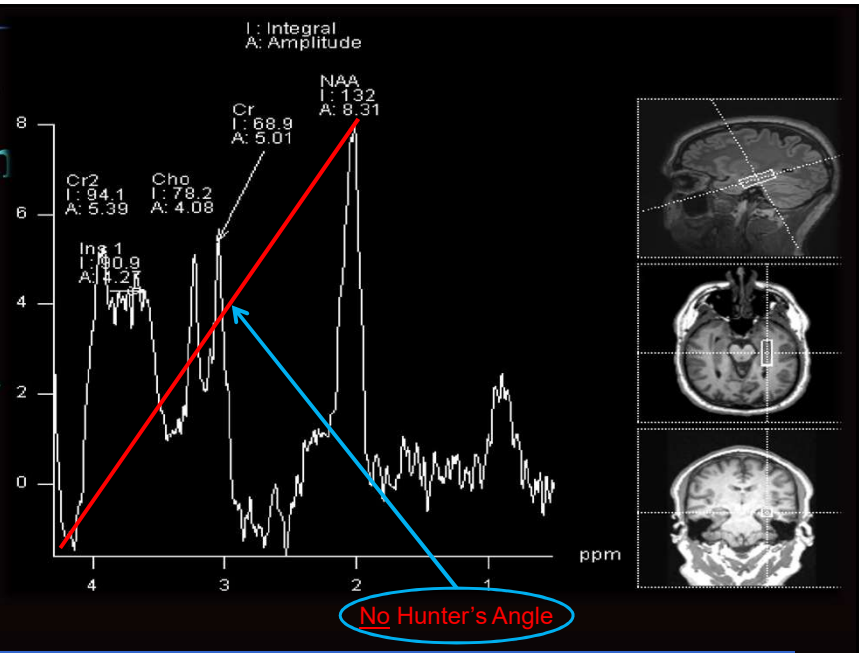


1 Images from BHF research in Jacksonville

2 Brain Sci. 2022, 12(7), 918; https://doi.org/10.3390/brainsci12070918

Case 28-year-old male with intractable seizures for 5+ years and depression. [1]

MR Spectroscopy
& MRI localization



1 Ref: Image from BHF research in Jacksonville

Myo-inositol peak and proportionally less NAA – consistent with Mesial Temporal Sclerosis

Some of the metabolites seen on MRS [1]

ppm	Metabolite	Properties
0.9-1.4	Lipids	Products of brain cell destruction
1.3	Lactate	Product of anaerobic glycolysis
2.0	N-acetylaspartate (NAA)	Neuron cell marker
2.2-2.4	Glutamine (Gtx)/GABA	Neurotransmitters
3.0	Creatine (Cr)	Energy metabolism
3.2	Choline (Cho)	Cell membrane marker
3.5	Myo-inositol (MI)	Glial cell marker, osmolyte, hormone receptor mechanisms
1.48	Alanine	Present in meningiomas

1. Ref: Ann N Y Acad Sci. 2010 February; 1187: 148–171.
doi: 10.1111/j.1749-6632.2009.05143.x

Magnetic Resonance Spectroscopic Imaging and Relevance to Substance Use Disorders[1]

Summary of anatomically related metabolite changes with drugs of abuse

	N-acetylaspartate	Choline	Creatine	myo-inositol
Amphetamine	___	___	___	Increase (TL) None (PFC)
Methamphetamine	Decrease (BG, FGM)	Increase (FGM)	Decrease (BG)	Increase (FGM, FWM)
MDMA	Decrease (FGM, HP) None (FGM, PWM, NC, HP, OCC)	___	___	Increase (PWM) None (FMG, PWM, OCC)
Cocaine	Decrease (FMG, TAH)	Increase (BG)	Increase (PWM)	Increase (FGM)

1. Ref: Ann N Y Acad Sci. 2010 February; 1187: 148–171.
doi: 10.1111/j.1749-6632.2009.05143.x

Magnetic Resonance Spectroscopic Imaging and Relevance to Substance Use Disorders[1]

Summary of reported neurotransmitter changes with drugs of abuse

	Glutamate	GABA
Methamphetamine	Decrease in frontal gray matter (Ernst & Chang, 2008)	_____
Cocaine	_____	Decrease in prefrontal cortex (Ke et. al., 2004) Decrease in OCC (Hetherington et al., 2000)
Opiates	Decrease in ACC (Yucel et al, 2007)	_____
Cannabis	Decrease in basal ganglia (Chang et al., 2006)	_____
Alcohol	Increase in ACC (Lee et al, 2007) Decrease in BG (Miese et al., 2006)	Decrease in OCC (Behar et al., 1999)
Nicotine	No change in HP (Galliant et al., 2008)	Decrease in OCC (Epperson et al., 2005)

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Magnetic Resonance Spectroscopic Imaging and Relevance to Substance Use Disorders [1]

Simplified summary of overlapping metabolite findings across drug classes

Metabolite	Decrease	Increase
N-acetylaspartate (NAA)	Methamphetamine, MDMA, Cocaine, Opiates, Cannabis, Alcohol, Nicotine, Toluene	Cocaine (acute administration)
Choline (Cho)	Cannabis, Alcohol	Methamphetamine, Cocaine, Alcohol
Creatine (Cr)	Methamphetamine	Cocaine, Cannabis, Alcohol
Myo-Inositol (MI)	_____	Amphetamine, Methamphetamine, MDMA, Cocaine, Alcohol, Toluene
Glutamate (Glx)	Methamphetamine, Opiates, Cannabis	Alcohol
GABA	Cocaine, Alcohol, Nicotine	____

1. Ref: Ann N Y Acad Sci. 2010 February; 1187: 148–171. doi: 10.1111/j.1749-6632.2009.05143.x

Summary of MRS Drugs of Abuse Findings [1, 2, 3]

- Research on alcohol, nicotine, cocaine, and cannabis addiction suggests that medications modulating GABA signaling may be effective in reducing addictive behaviors. [3]
- Reductions in NAA and elevations in MI were observed almost universally indicating that drugs of abuse in general have a profound impact on neuronal health, energy metabolism and inflammatory processes. [1]
- The next most common metabolite changes involved alterations in Cho and Cr, suggesting that methamphetamine, cocaine, cannabis, and alcohol negatively influence cell membrane turnover as well as energy maintenance. [1]
- Methamphetamine, opiates, cannabis, and alcohol were found to alter Glx to some extent, while GABA was reduced by cocaine, alcohol and nicotine, together suggesting that drugs of abuse adversely impact neurotransmission. [1]
- Nearly 40 peer-reviewed research articles that focused on the utility of MRS in alcohol, methamphetamine, 3,4-methylenedioxymethamphetamine, cocaine, opiates, opioids, marijuana, and nicotine use disorders were reviewed. The most consistent finding across substances was decreased N-acetylaspartate and choline levels with chronic alcohol, methamphetamine, and nicotine use. [2]

1. Ref: Ann N Y Acad Sci. 2010 February; 1187: 148–171. doi: 10.1111/j.1749-6632.2009.05143.x
2. Ref: Published August 17, 2015 Review Article Find in PubMed https://doi.org/10.1177/1078390315598606
3. Ref: Brain Sci. 2022, 12(7), 918 https://doi.org/10.3390/brainsci12070918

Lets use our knowledge and work together to help our participants and patients with substance use disorders using proper assessment, early interventions and appropriate treatments. This is in the best interest of everyone.

Quiz Questions

Which brain region is most involved in the irritable mood and negative affect associated with addictions?

1. Nucleus Accumbens
2. Extended Amygdala
3. Ventral Tegmental Area
4. Prefrontal Cortex
5. Lateral Dorsal Tegmentum

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Brain region(s) that account for disrupted inhibitory control that make it difficult for an addicted individual to refuse a drug is/are?

1. Cingulate gyrus, dorsolateral prefrontal and inferior prefrontal cortex
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3. Nucleus Accumbens
4. Substantia Nigra
5. Hippocampus

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Brain region(s) most associated with cravings even months after last use?

1. Orbitofrontal Cortex, Dorsal Striatum, Hippocampus, Insula
2. Ventral Tegmental Area
3. Pituitary Gland
4. Nucleus Accumbens & Ventral Pallidum
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Which of the following psychoactive substances directly increases the release of dopamine?

1. Alcohol
2. Stimulants
3. Opiates
4. Nicotine
5. Cannabis

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Following chronic consumption, psychoactive substances cause varying neuroadaptations. Chronic use of which substance primarily causes a decrease in $GABA_A$ receptor function while increasing the function of NMDA receptors?[1]

1. Nicotine
2. Cocaine
3. Opiates
4. Alcohol
5. Cannabis

1 verywellhealth.com

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For which class of drugs should benzodiazepines (i.e., with diazepam, chlordiazepoxide, or lorazepam) not to be used for detoxification?

1. Opiates
2. Benzodiazepines
3. Alcohol
4. Ketamine
5. GHB/GBL

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Thank you

A few Resources and Sources

- "Drug addiction as dopamine-dependent associative learning disorder" G Di Chiara
- Volkow, ND et al., Journal of Neuroscience 21, 9414-9418, 2001.
- American Society of Addiction Medicine (www.asam.org)
- NIDA (www.drugabuse.gov)
- NIAAA (www.NIAAA.nih.gov)
- Amer. Osteo. Acad. of Addiction Medicine (www.aoaam.org)

Thank you for listening

John C. Tanner, D.O., DABAM, DFASAM, FAOAAM, CCFC, MRO

Questions