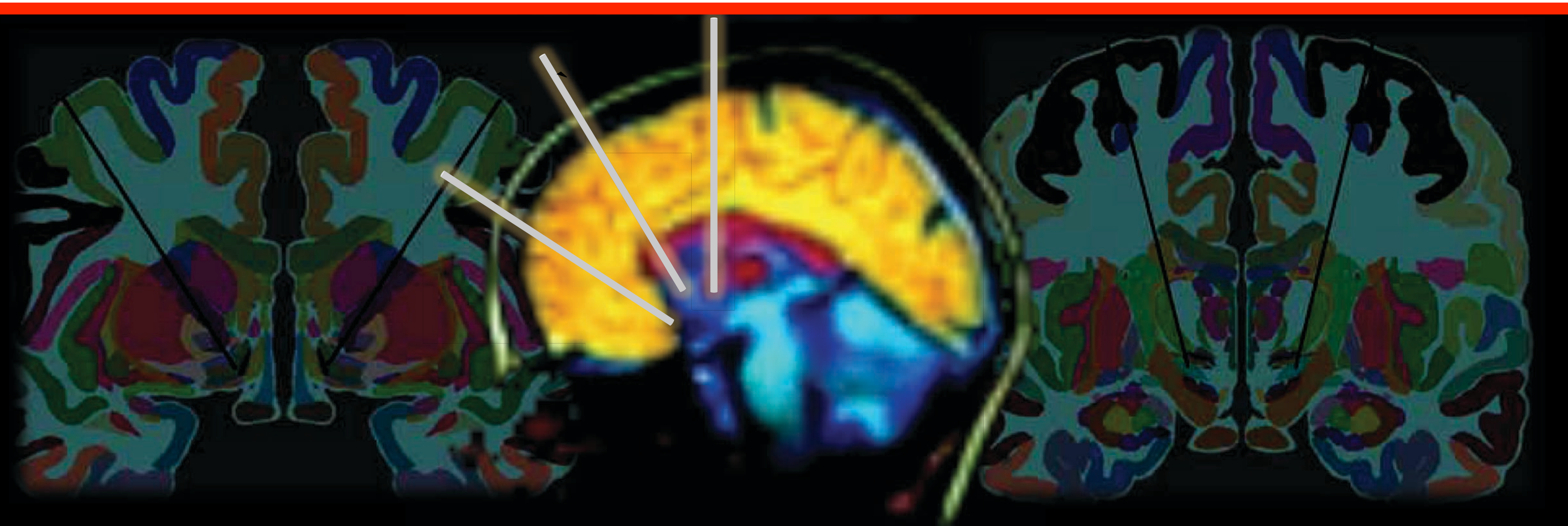
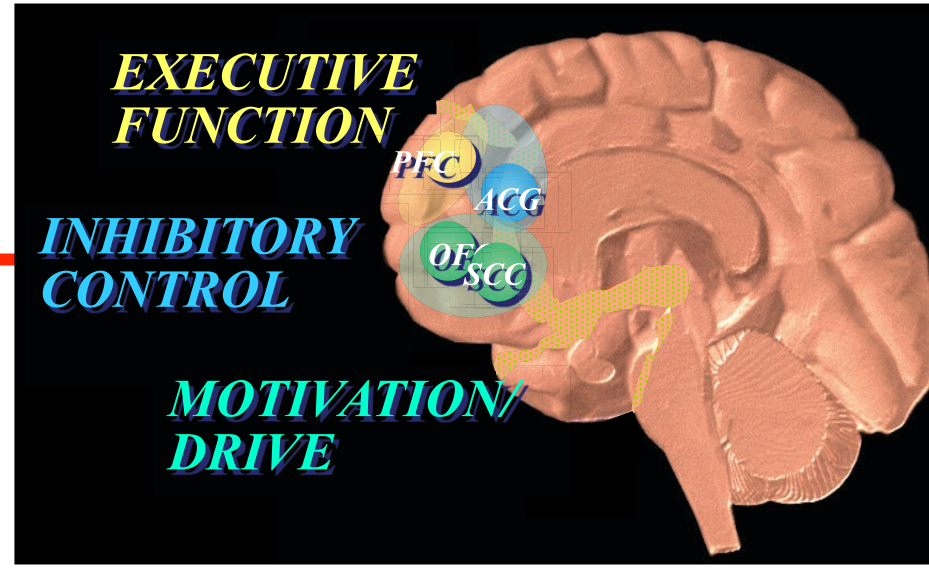
Brain Stimulation & New Therapeutic Perspectives In

ADDICTION

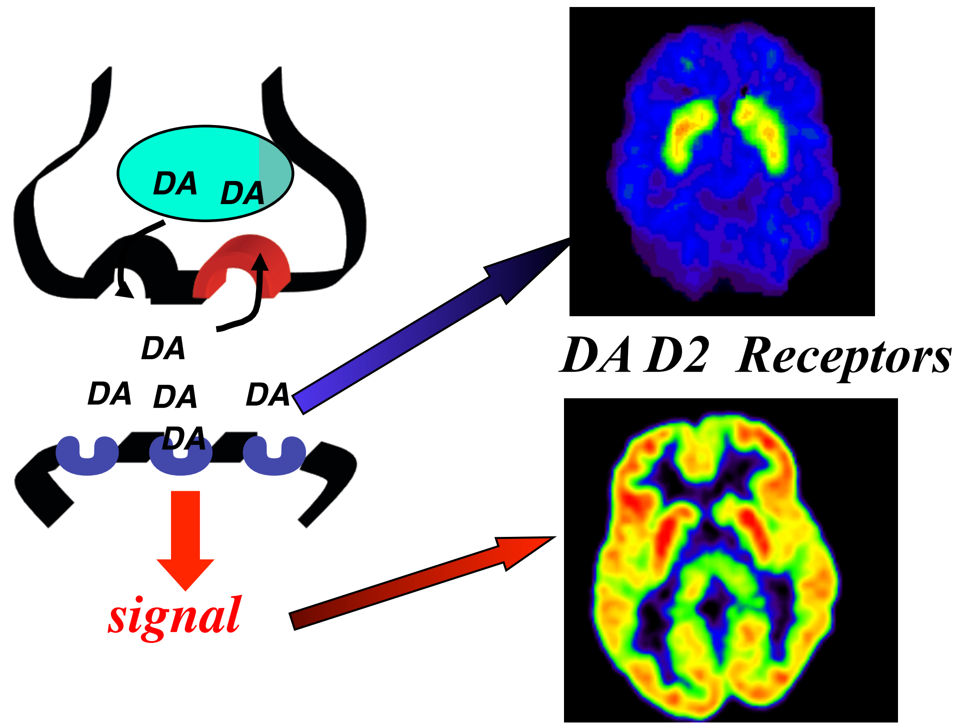


Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse
National Institutes of Health

Effects of Chronic Drugs on Brain Function

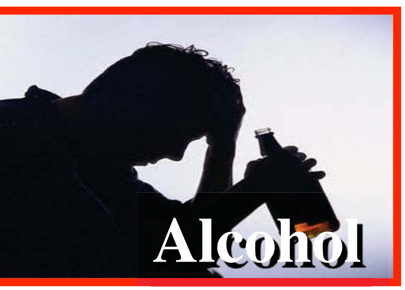


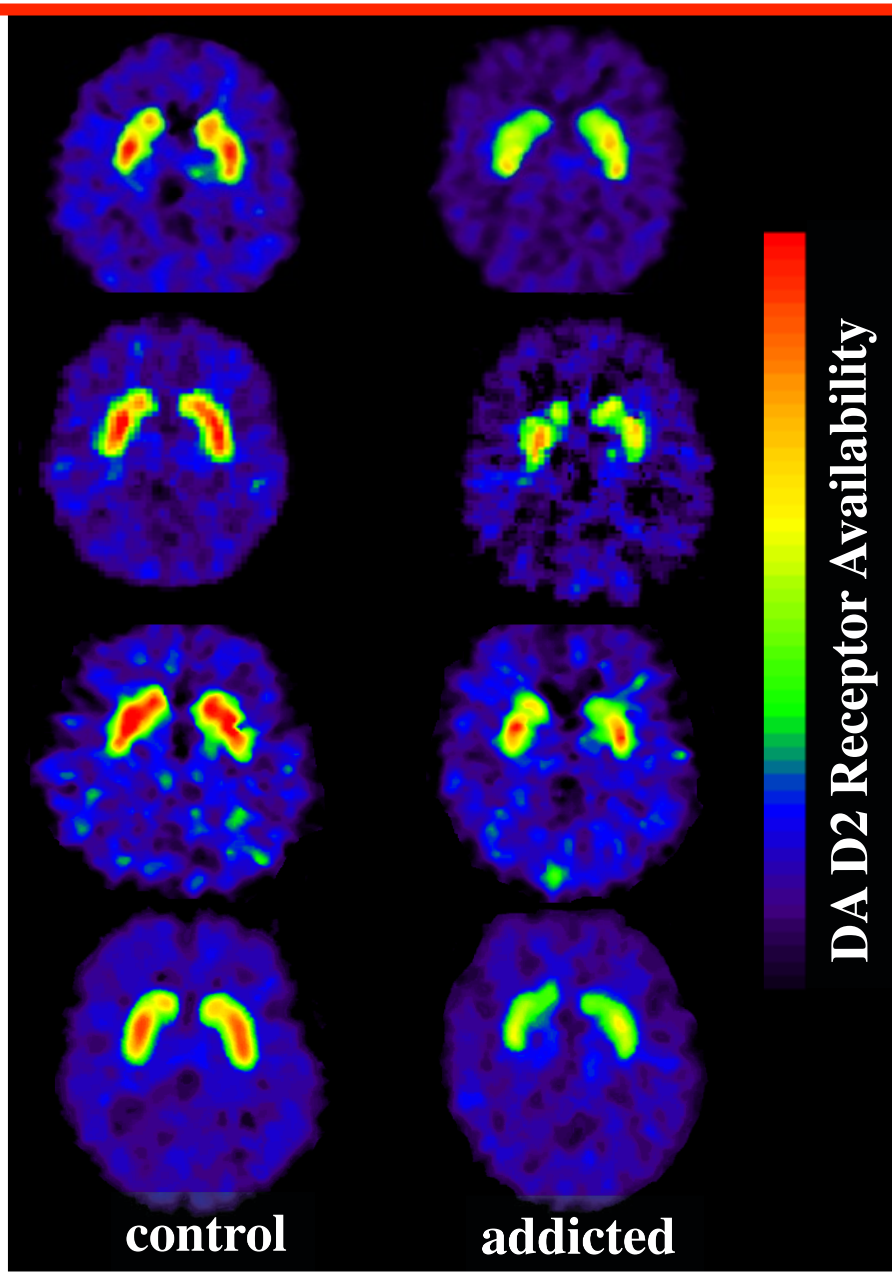
Here we tested if, in addicted subjects, changes in DA function were linked with disruption of brain function as assessed by multiple tracer studies that evaluated in the same subject dopamine D2 receptors and brain glucose metabolism (marker of brain function).

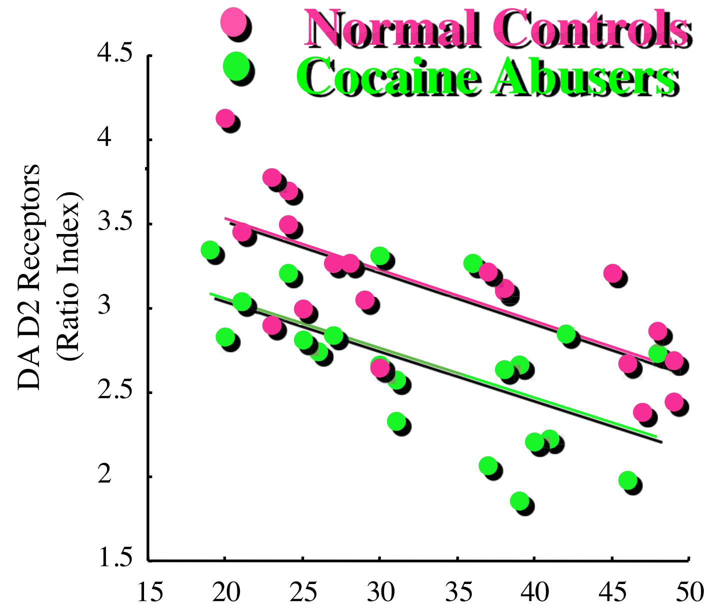


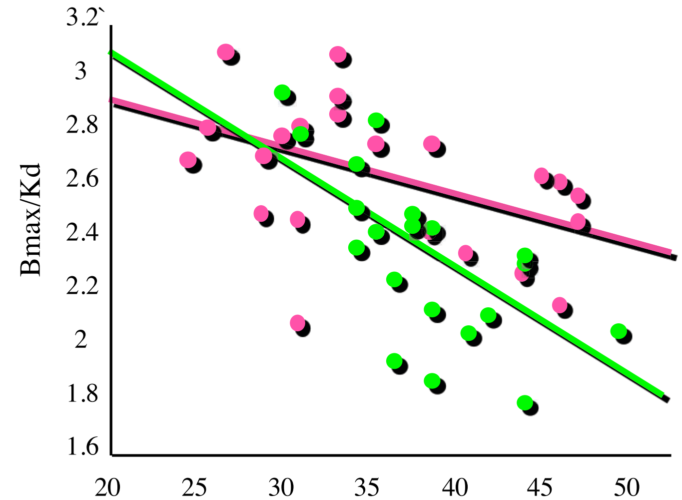
Metabolism

Dopamine D2 Receptors are Lower in Addiction



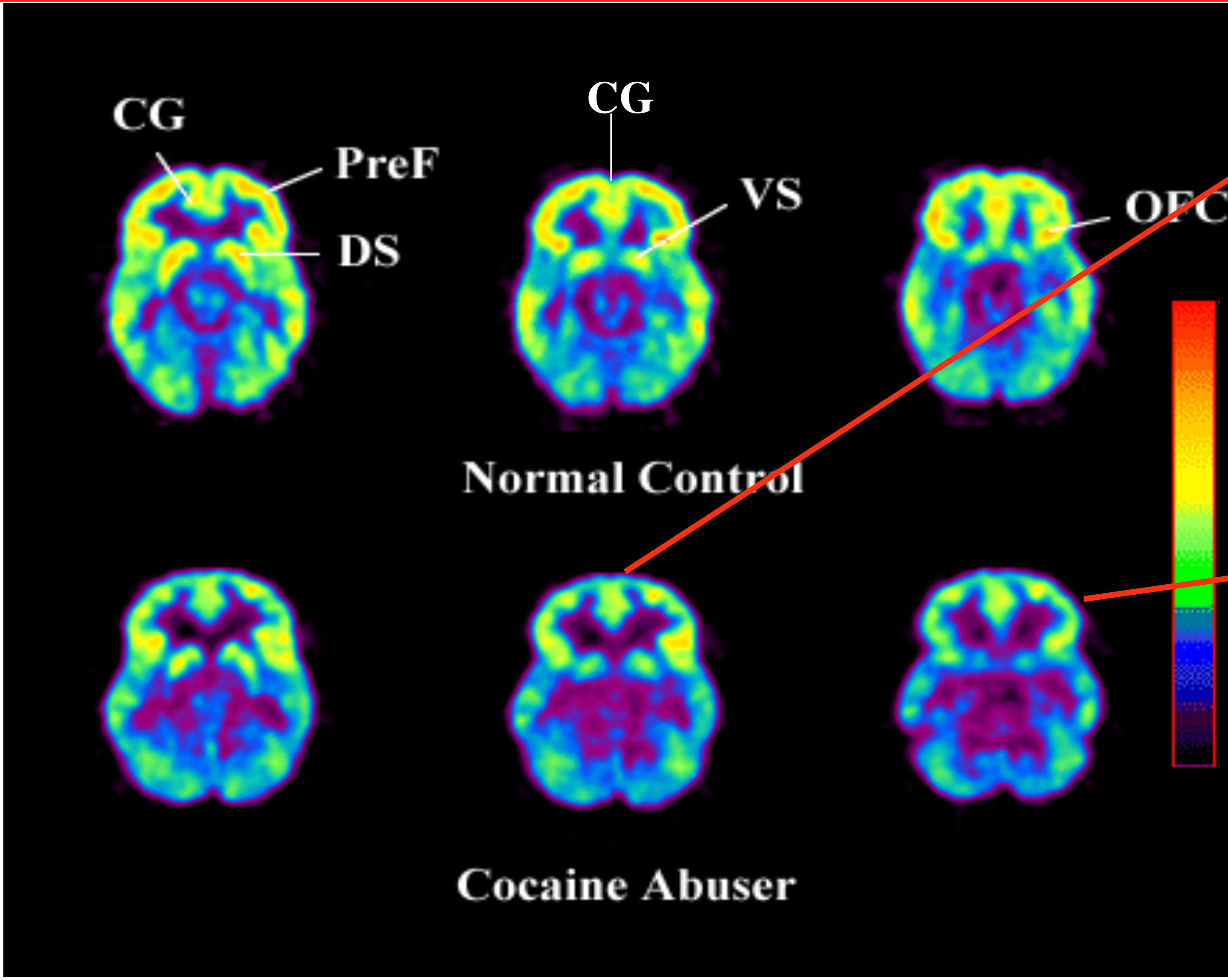




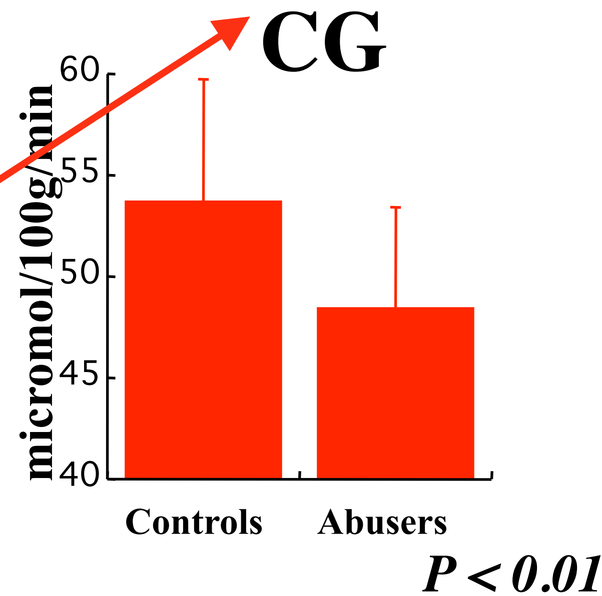


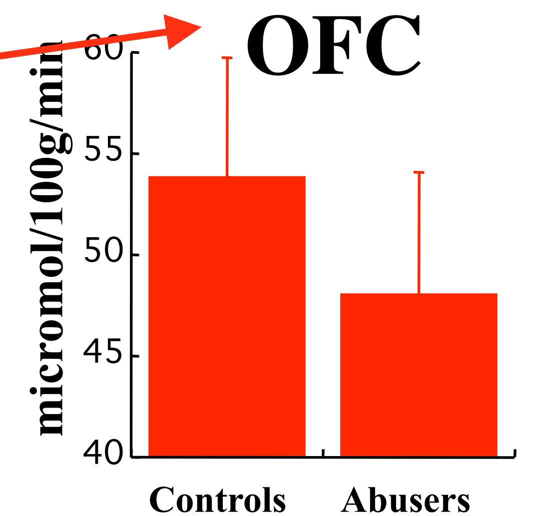
Volkow et al., Neuro Learn Mem 2002.

Brain Glucose Metabolism
in Cocaine Abusers (n=20) and Controls (n=23)

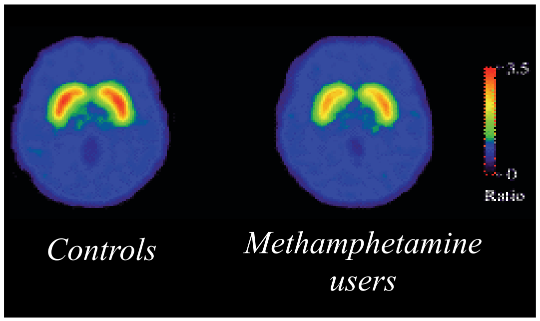


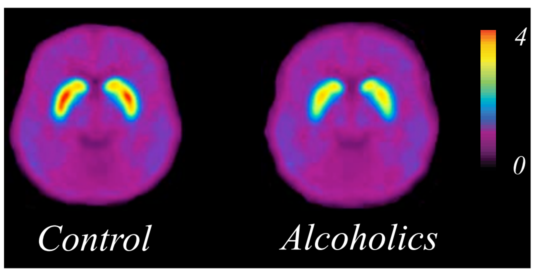
Volkow et al., AJP 156:19-26, 1999.



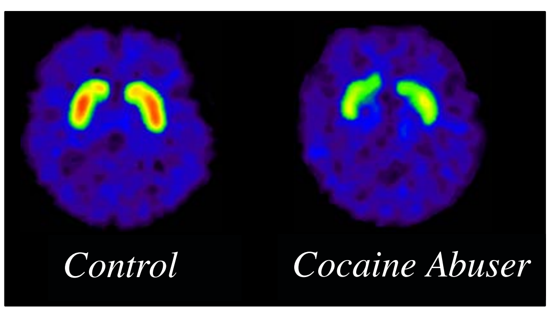


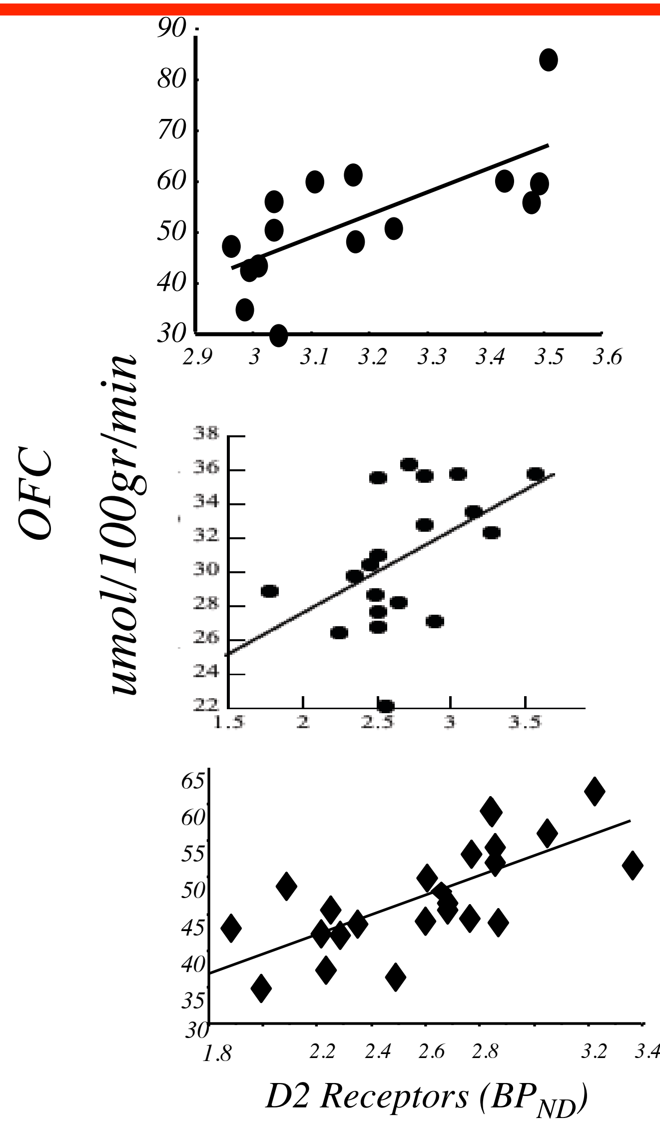
Decreased Dopamine Signaling (through D2R) in Addiction is Associated with Decreased Activity in OFC (BA 25, 11, 47) and ACC (BA 24, 32)



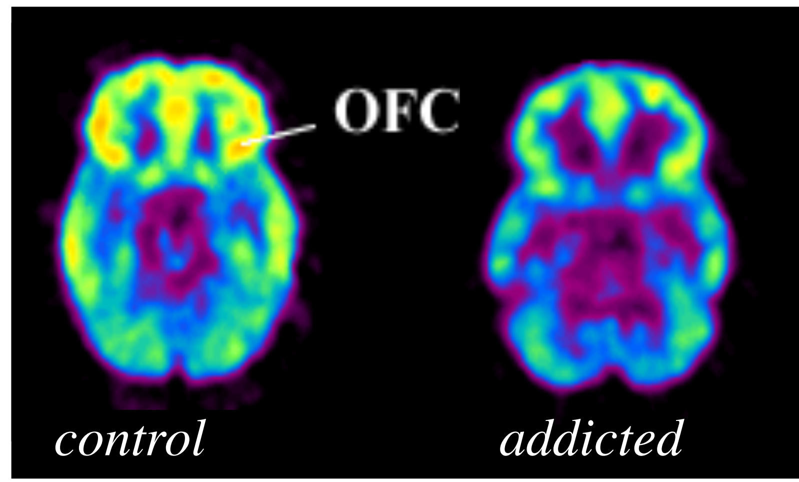


DA D2 receptors

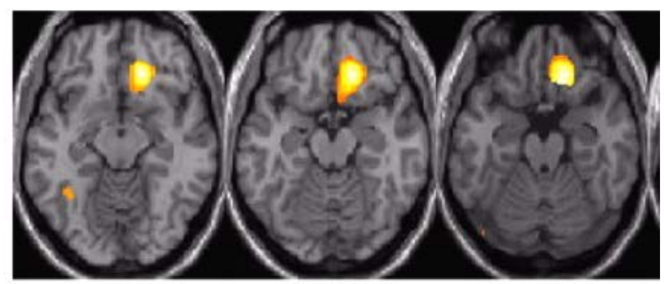




Brain glucose metabolism



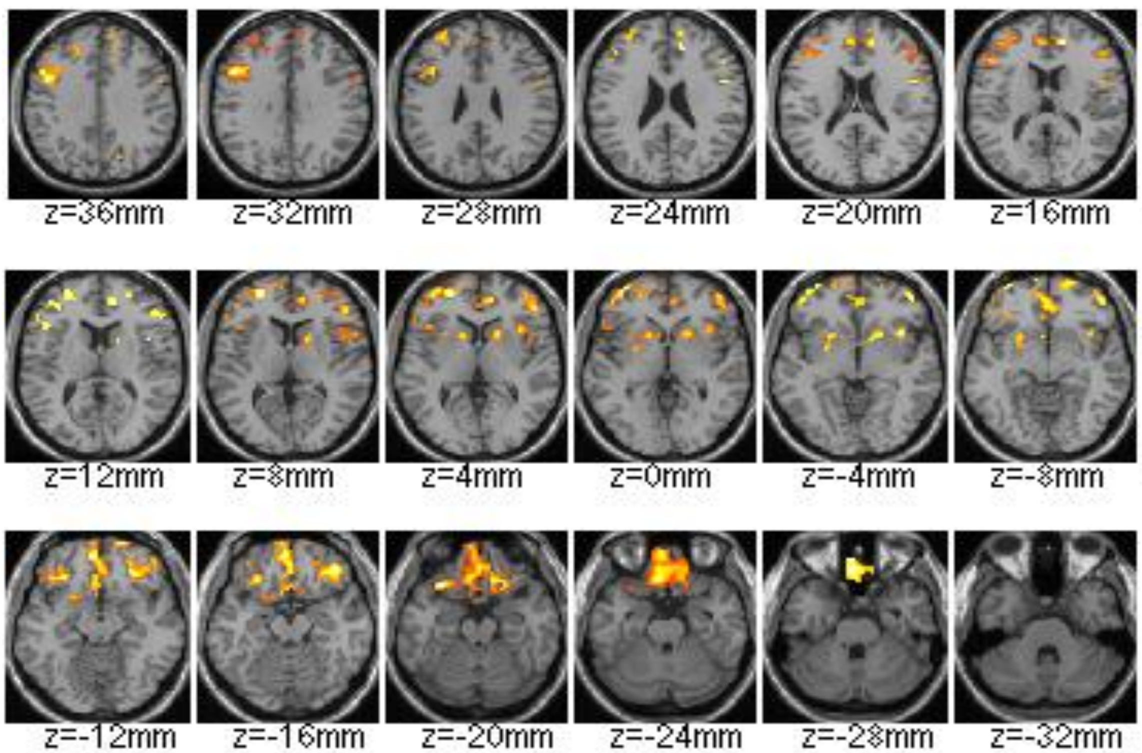
Metabolism Controls > Cocaine Abusers



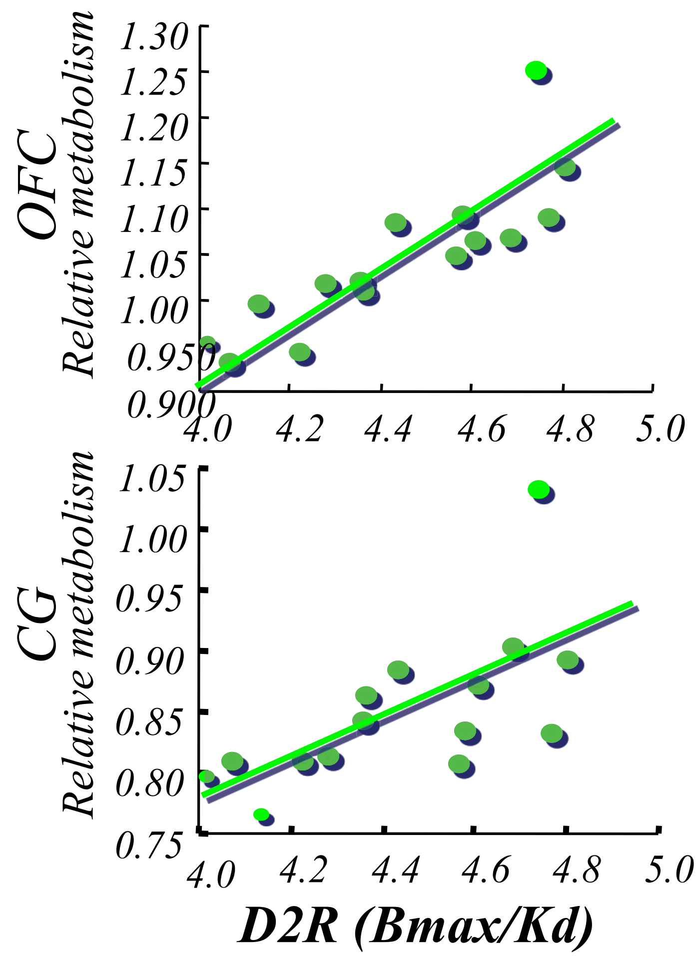
P <0.005

Volkow et al., PNAS 2011

DA D2 Receptors and Relationship to Brain Metabolism in Subjects with Family History for Alcoholism



Correlations between Metabolism and D2R *P <0.005*

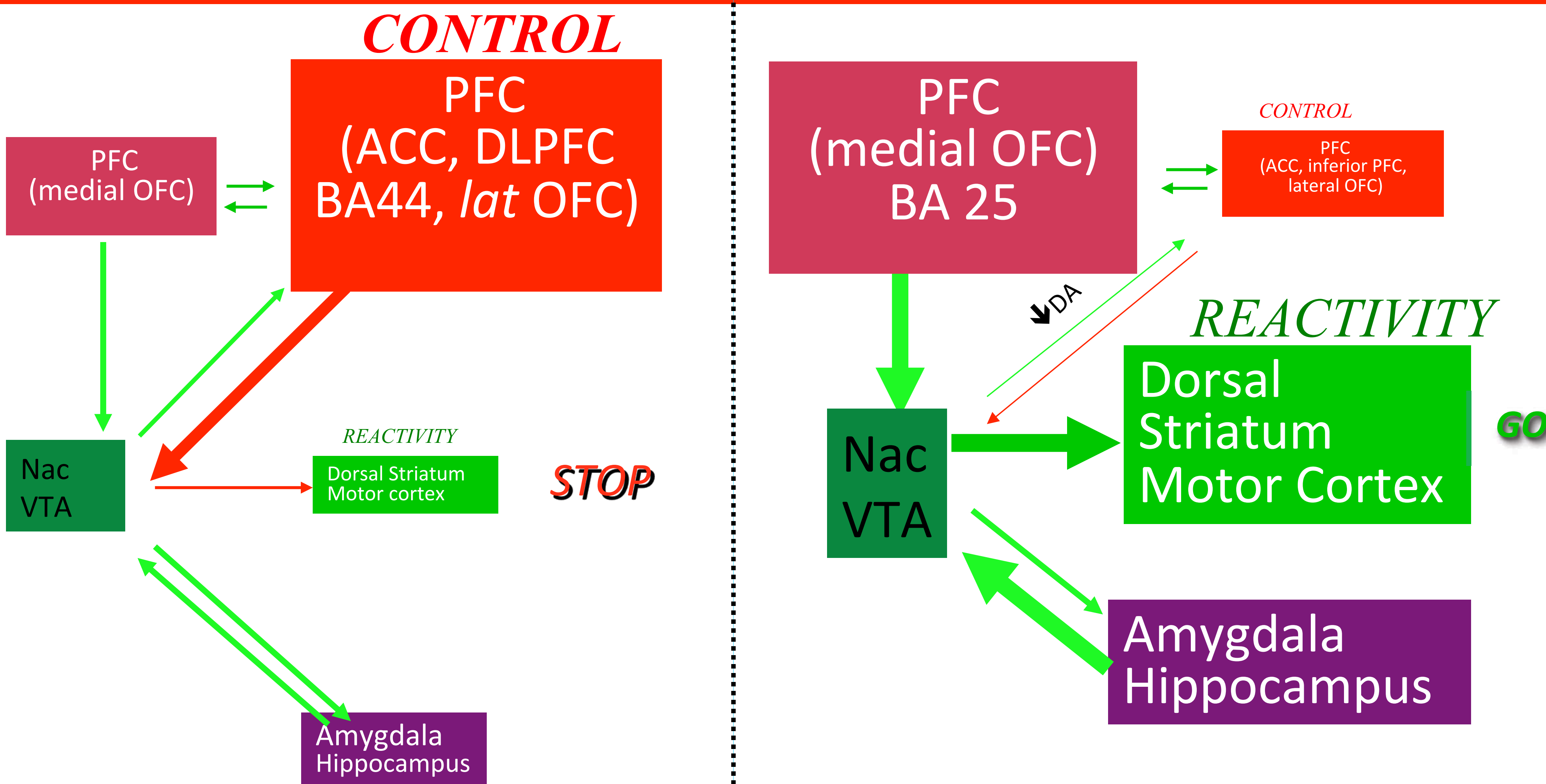


Volkow et al. Arch Gen Psychiatry 2006.

DA D2R are associated with metabolism in PREFRONTAL regions the disruption of which results in IMPULSIVITY and COMPULSIVITY

Non-Addicted Brain

Addicted Brain

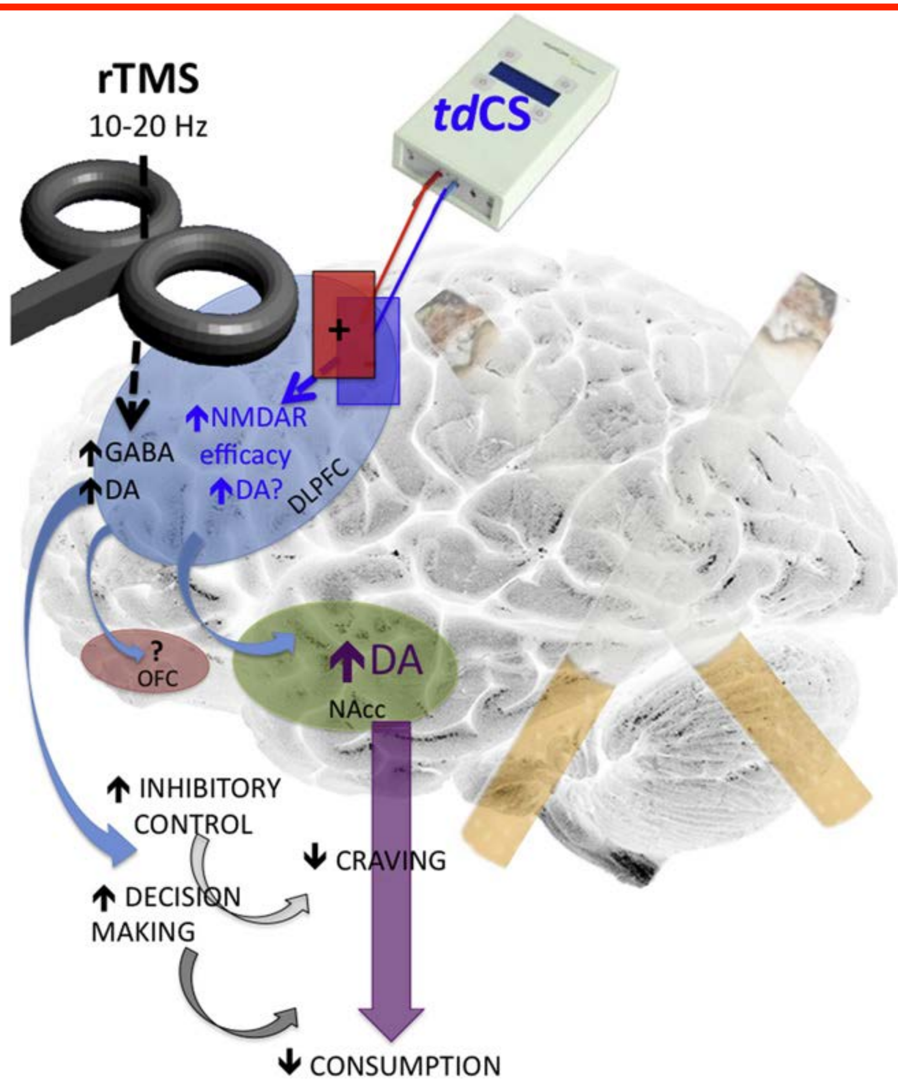


Controlled behavior

Automatic behavior

Volkow et al PNAS 2011

Potential Mechanisms of Action of Repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (tdCS) on Tobacco Addiction



Wing VC et al., Brain Stimulation 2012.

Non-Invasive Brain Stimulation, Smoking & Reward

Studies Reporting the Effects of rTMS and tDCS on Smoking, Related Craving, and Dopaminergic Reward

Author (year)	Tx (days)	MT (%)	Stimulation type	TMS freq	Stimulated	Side	Cues	Result
Amiaz (2009)	10	100	rTMS	10 Hz	DLPFC	L	Images	Reduced cue induced cravings & consumption
Eichhemmer (2003)	4 (2 Sham)	90	rTMS	20 Hz	DLPFC	L	None	Reduced cigarette consumption
Johann (2003)	2	90	rTMS	High	DLPFC		None	Reduced craving
Rose (2011)	3	90	rTMS	10 Hz	SFG	L	View lit Cigarette	Increased cue induced craving, reduced gen craving
						L	Cig smoke	Reduced craving
Soo Cho & Strafella (2009)	1	100	rTMS	10 Hz	DLPFC	L	None	DA release in ipsilateral ACC and mOFC
						R	None	None
Strafella (2001)	1		rTMS	10 Hz	DLPFC	L	None	DA release in ipsilateral caudate nucleus
Strafella (2003)	1	90	rTMS	10 Hz	M1	L	None	DA release in ipsilateral caudate nucleus
Boggio (2009)	5		tDCS		DLPFC	L-anodal R-cathodal	Video, cig handling	Decreased cue induced craving
Fregni (2008)	1		tDCS		DLPFC	L-anodal R-cathodal	Video, cig handling	Decreased cue induced craving
						R-anodal L-cathodal	Video, cig handling	Decreased cue induced craving
Grundey (2012)	1		tDCS		ADM (orbit As reference)	ADM-anodal Orbit-cathodal	Abstinence	Control: no sig increase with nic increased excitability
						Orbit-anodal ADM-cathodal	Abstinence	Control: reduced excitability with nic: effects abolished

Fraser PE et al., Front Psych 2012;3:79.

Processes Associated with PFC Disrupted in Addiction

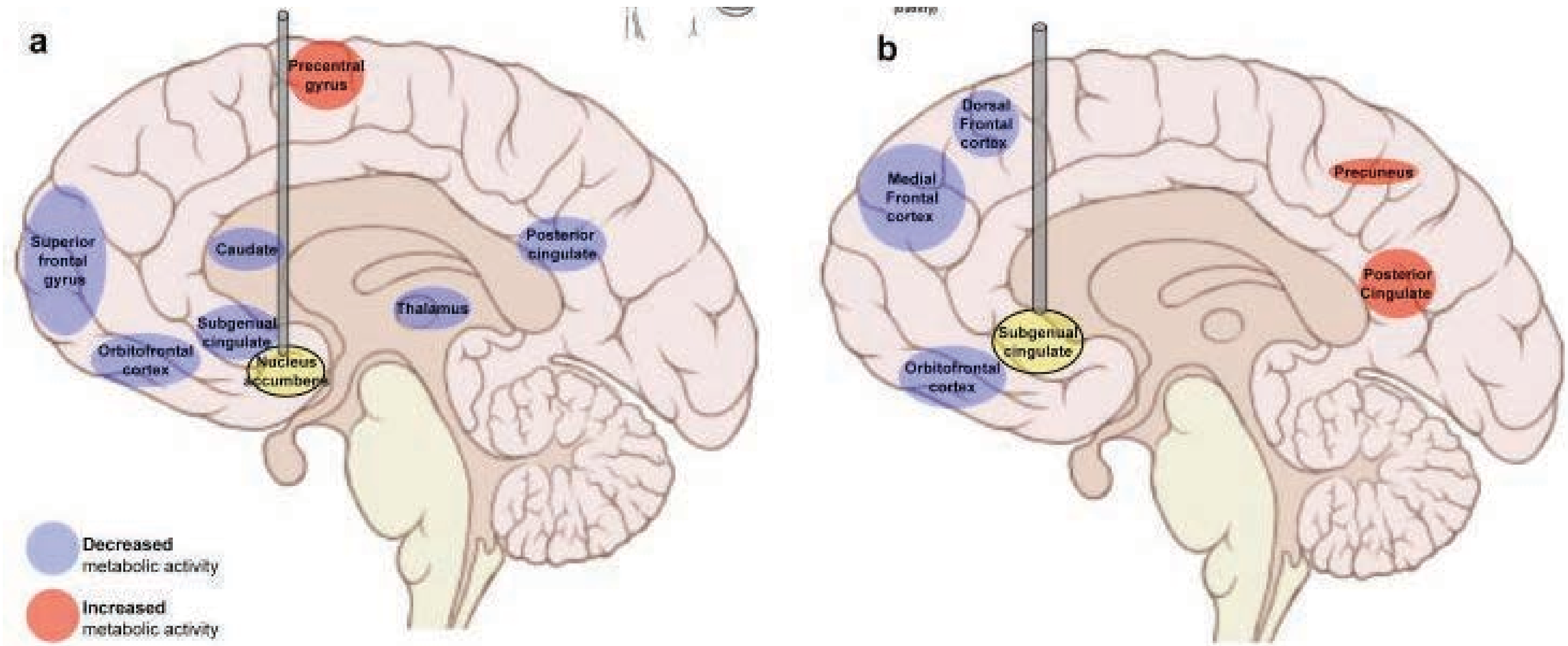
Process	Possible disruption in addiction	Probable PFC region
Self-control and behavioural monitoring: response inhibition, behavioural coordination, conflict and error prediction, detection and resolution	Impulsivity, compulsivity, risk taking and impaired self-monitoring (habitual, automatic, stimulus-driven and inflexible behavioural patterns)	DLPFC, dACC, IFG and vlPFC
Emotion regulation: cognitive and affective suppression of emotion	Enhanced stress reactivity and inability to suppress emotional intensity (for example, anxiety and negative affect)	mOFC, vmPFC and subgenual ACC
Motivation: drive, initiative, persistence and effort towards the pursuit of goals	Enhanced motivation to procure drugs but decreased motivation for other goals, and compromised purposefulness and effort	OFC, ACC, vmPFC and DLPFC
Awareness and interoception: feeling one's own bodily and subjective state, insight	Reduced satiety, 'denial' of illness or need for treatment, and externally oriented thinking	rACC and dACC, mPFC, OFC and vlPFC
Attention and flexibility: set formation and maintenance versus set-shifting, and task switching	Attention bias towards drug-related stimuli and away from other stimuli and reinforcers, and inflexibility in goals to procure the drug	DLPFC, ACC, IFG and vlPFC
Working memory: short-term memory enabling the construction of representations and guidance of action	Formation of memory that is biased towards drug-related stimuli and away from alternatives	DLPFC
Learning and memory: stimulus–response associative learning, reversal learning, extinction, reward devaluation, latent inhibition (suppression of information) and long-term memory	Drug conditioning and disrupted ability to update the reward value of non-drug reinforcers	DLPFC, OFC and ACC
Decision making: valuation (coding reinforcers) versus choice, expected outcome, probability estimation, planning and goal formation	Drug-related anticipation, choice of immediate reward over delayed gratification, discounting of future consequences, and inaccurate predictions or action planning	lOFC, mOFC, vmPFC and DLPFC
Salience attribution: affective value appraisal, incentive salience and subjective utility (alternative outcomes)	Drugs and drug cues have a sensitized value, non-drug reinforcers are devalued and gradients are not perceived, and negative prediction error (actual experience worse than expected)	mOFC and vmPFC

Goldstein & Volkow Nature Rev Neurosci 2011

Deep Brain Stimulation (DBS) in Refractory Depression

Nucleus Accumbens

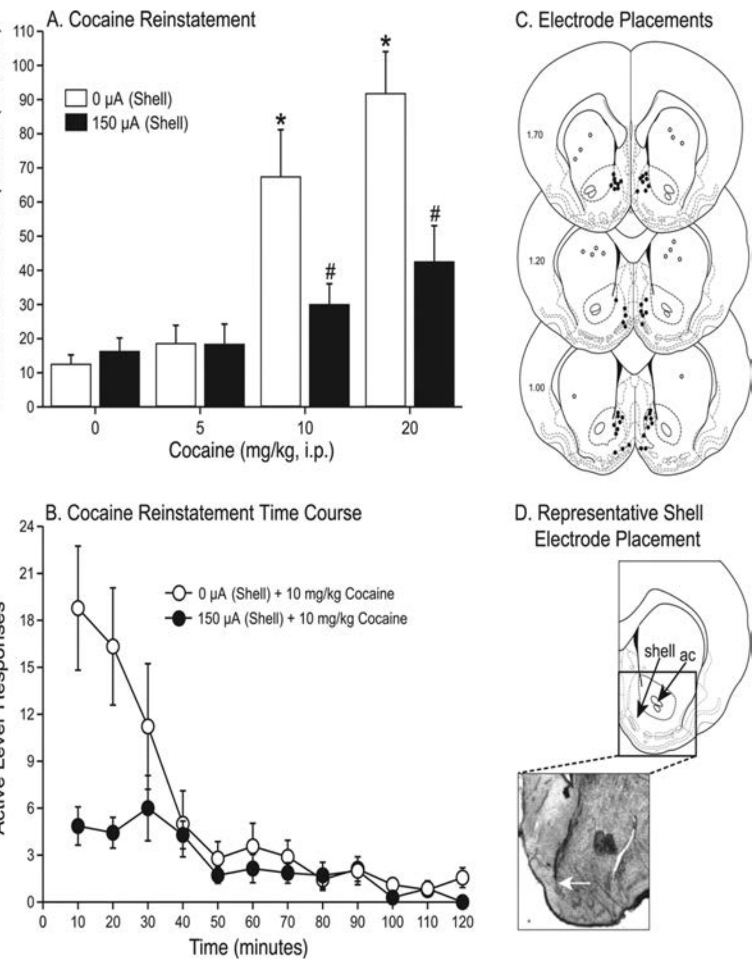
BA 25



Krishnan and Nestler. Am J Psychiatry 2010

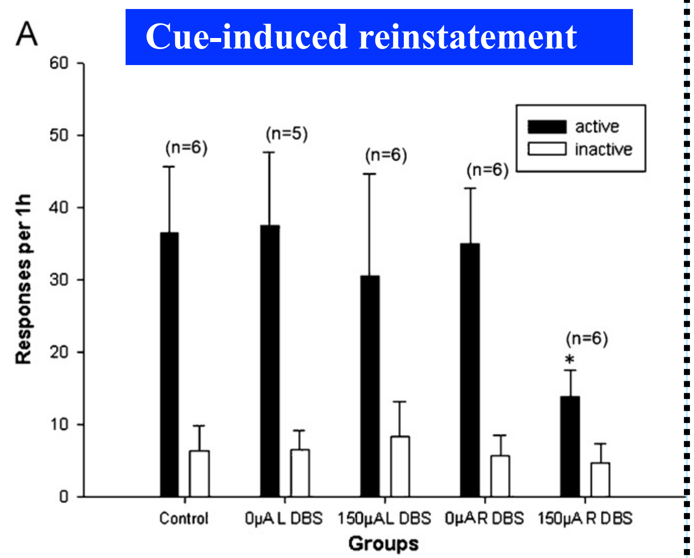
DBS in Nucleus Accumbens and in BA 25 for treatment-resistant depression results in clinical improvement and in decreases in activity in several PFC and subcortical regions

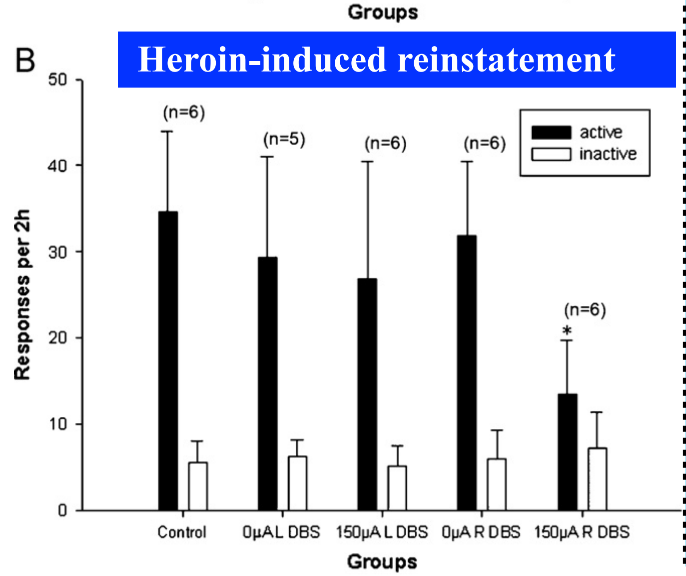
DBS of the NAc Shell Attenuated Cocaine Reinstatement of Drug Seeking In Rats



Vassoler FM et al. J. Neurosci. 2008;28:8735-39.

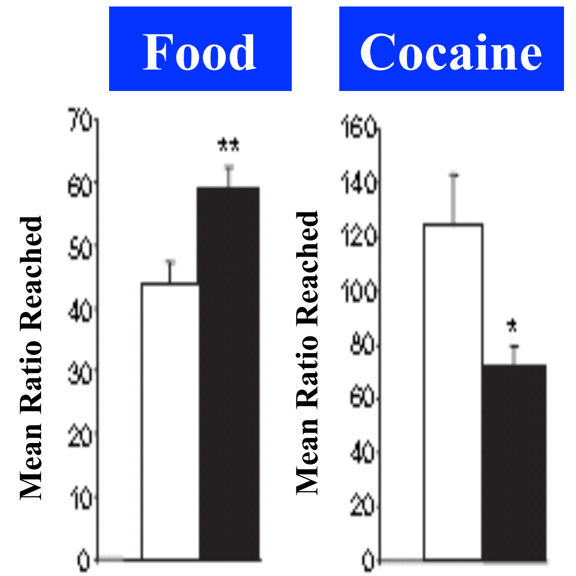
Unilateral DBS of the NAc Core Attenuated Heroin Reinstatement of Drug Seeking in Rats





Guo L et al., Drug Alc Depend 2012.

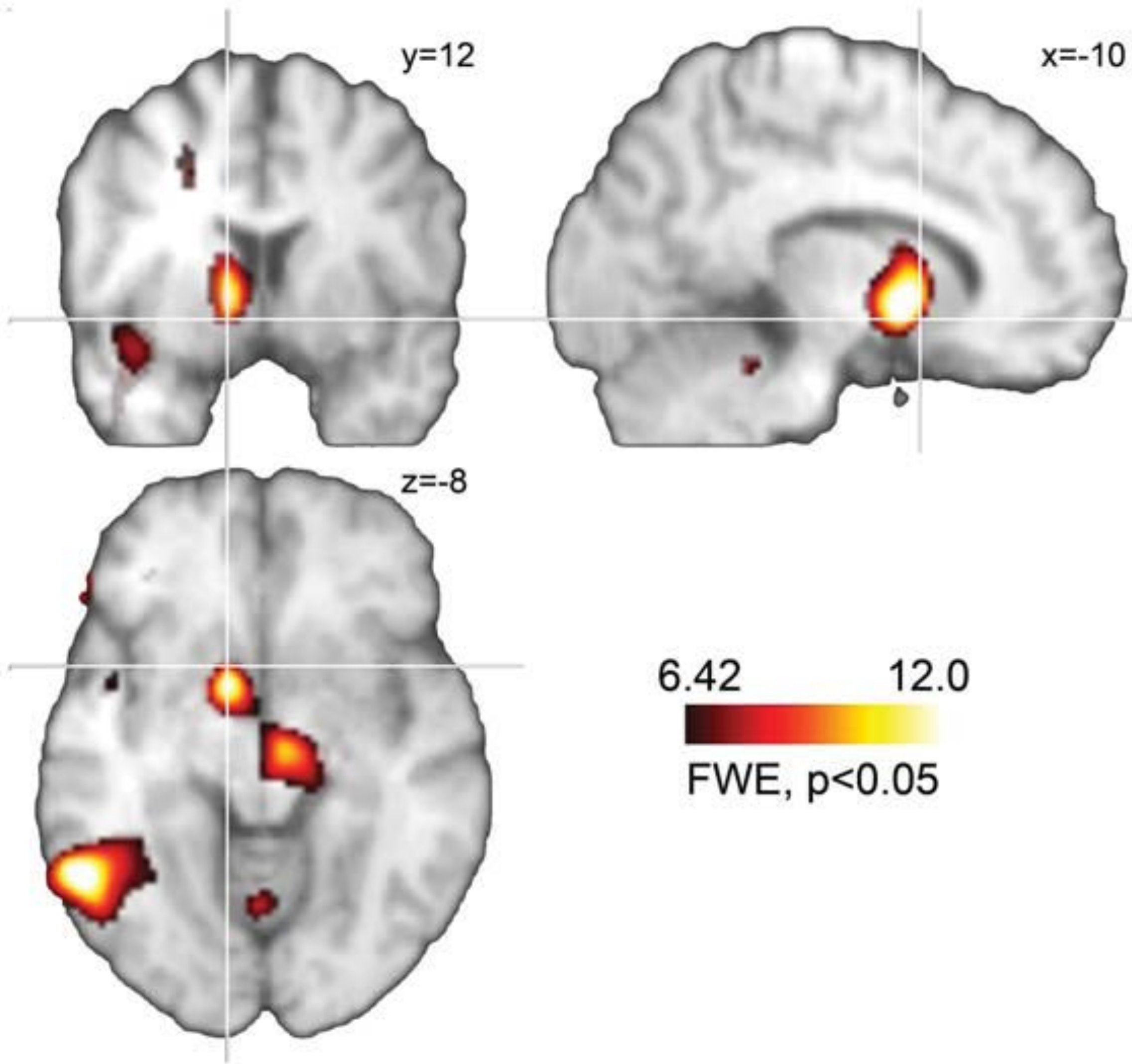
Effects of STN DBS On Willingness of the Animals to Produce An Effort To Obtain Food Or Cocaine



Rouaud T et al., PNAS 2010; 107(3): 1196-1200 .

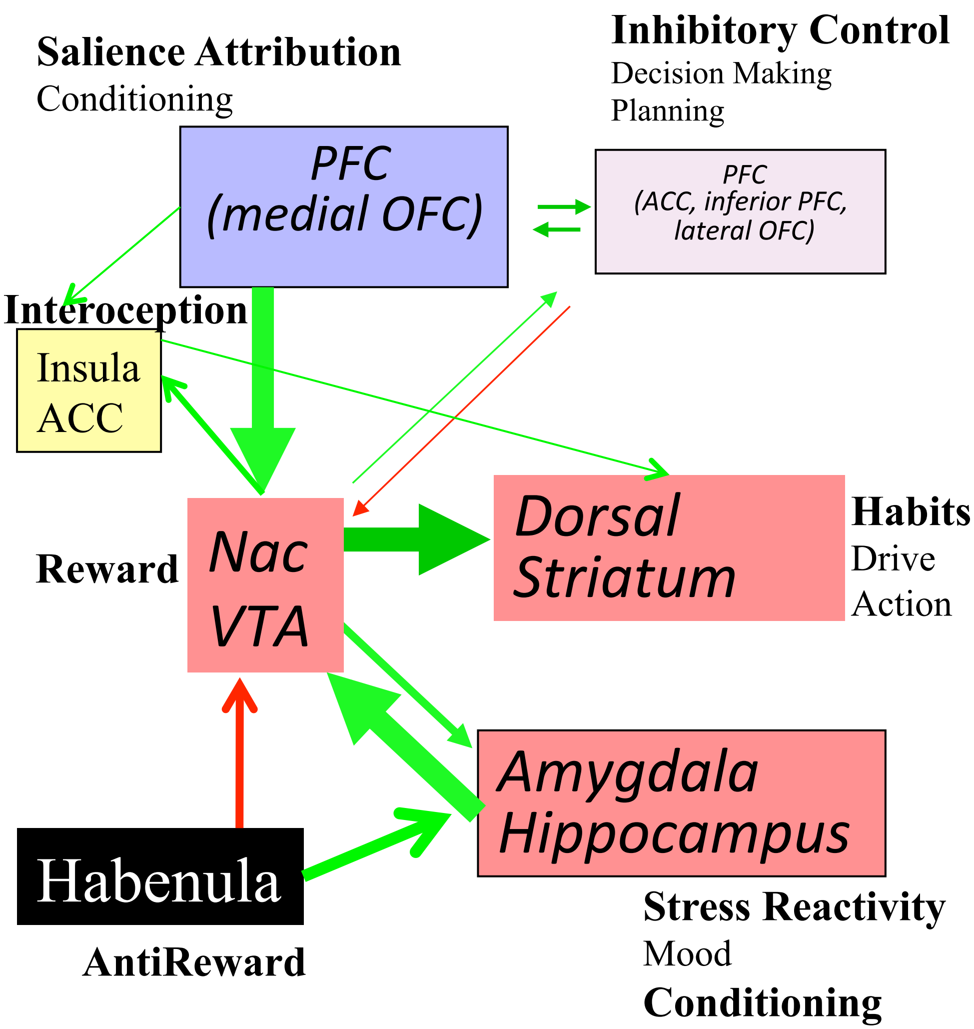
Contrast Image for the Comparison DBS On. DBS Off.

Crosshair Position Indicates the Location of the Nucleus Accumbens



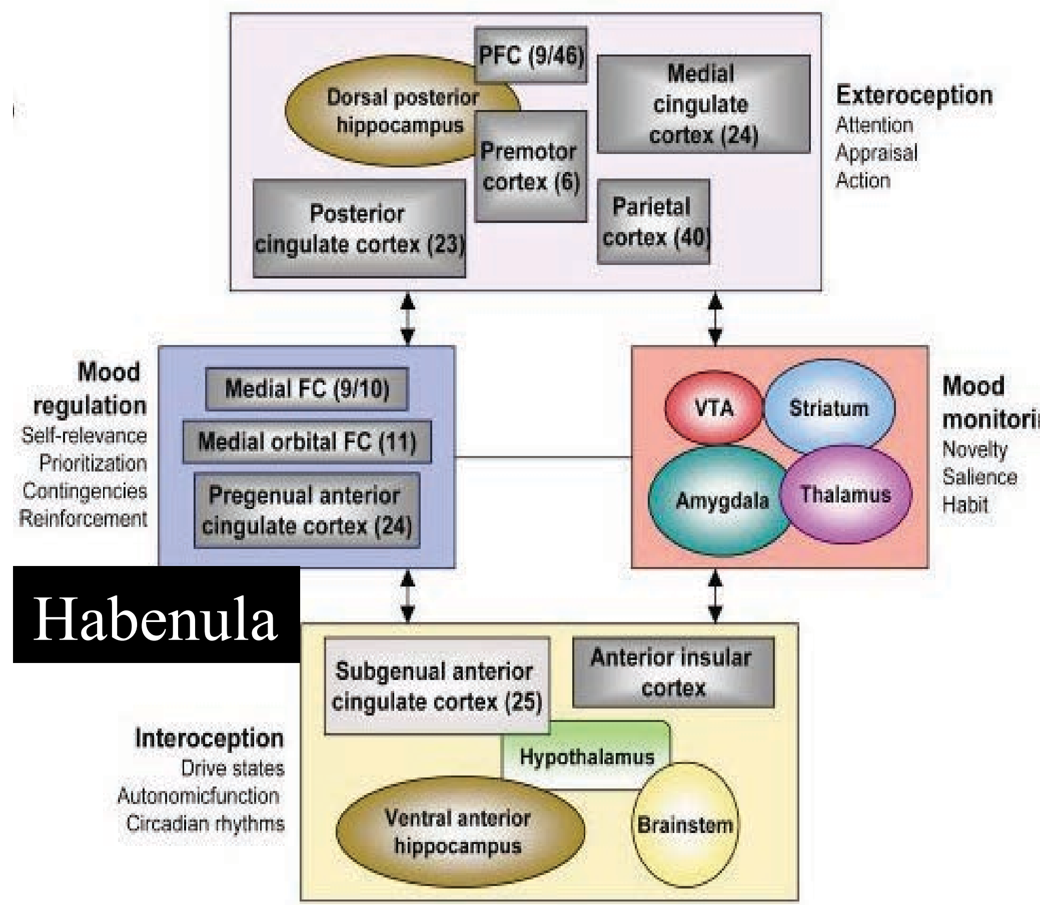
Heldmann M et al., PLoS ONE 2012; 7(5): e36572.

Circuit Model of Addiction

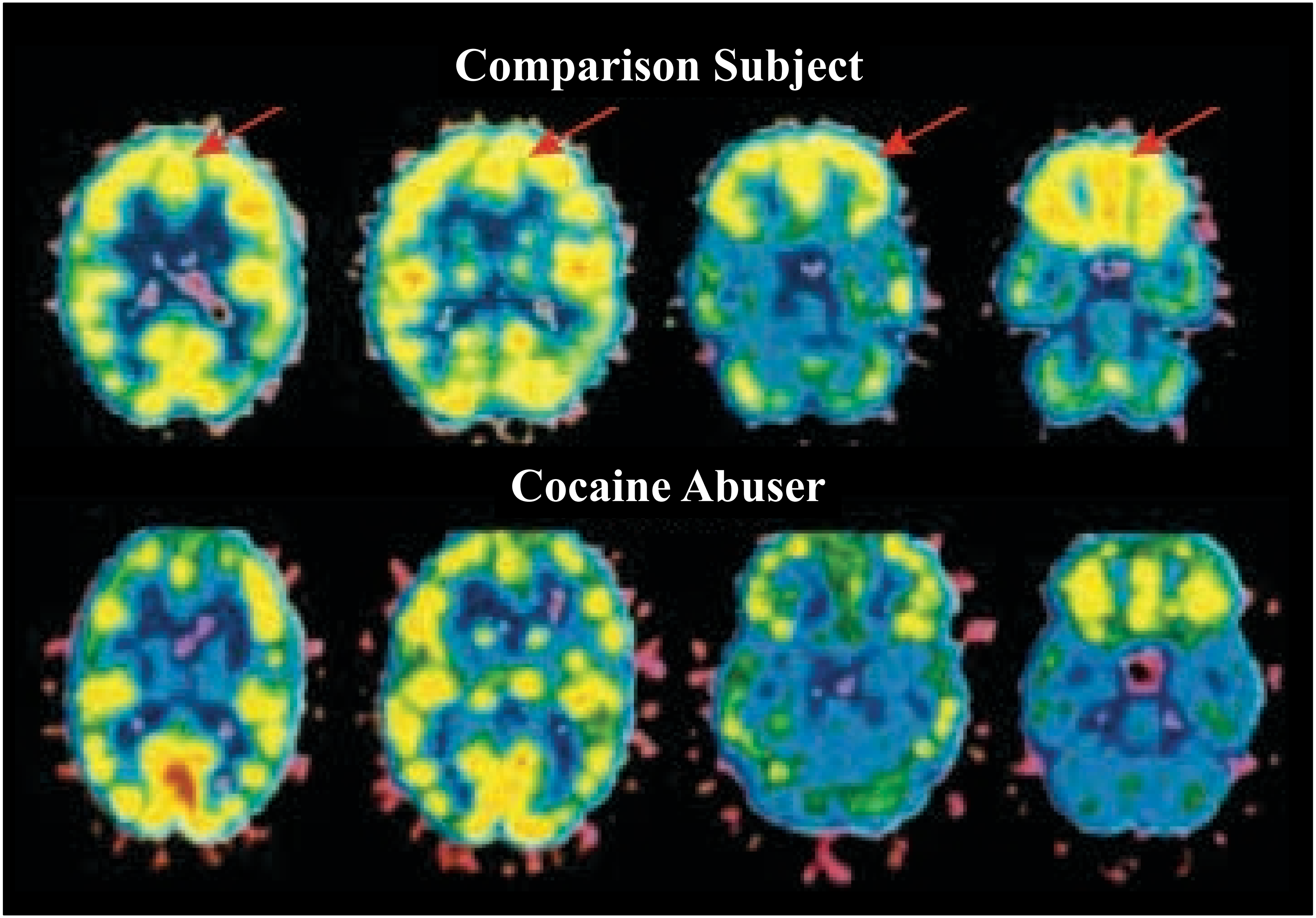


Volkow et al., PNAS 2011.

Circuit Model of Depression



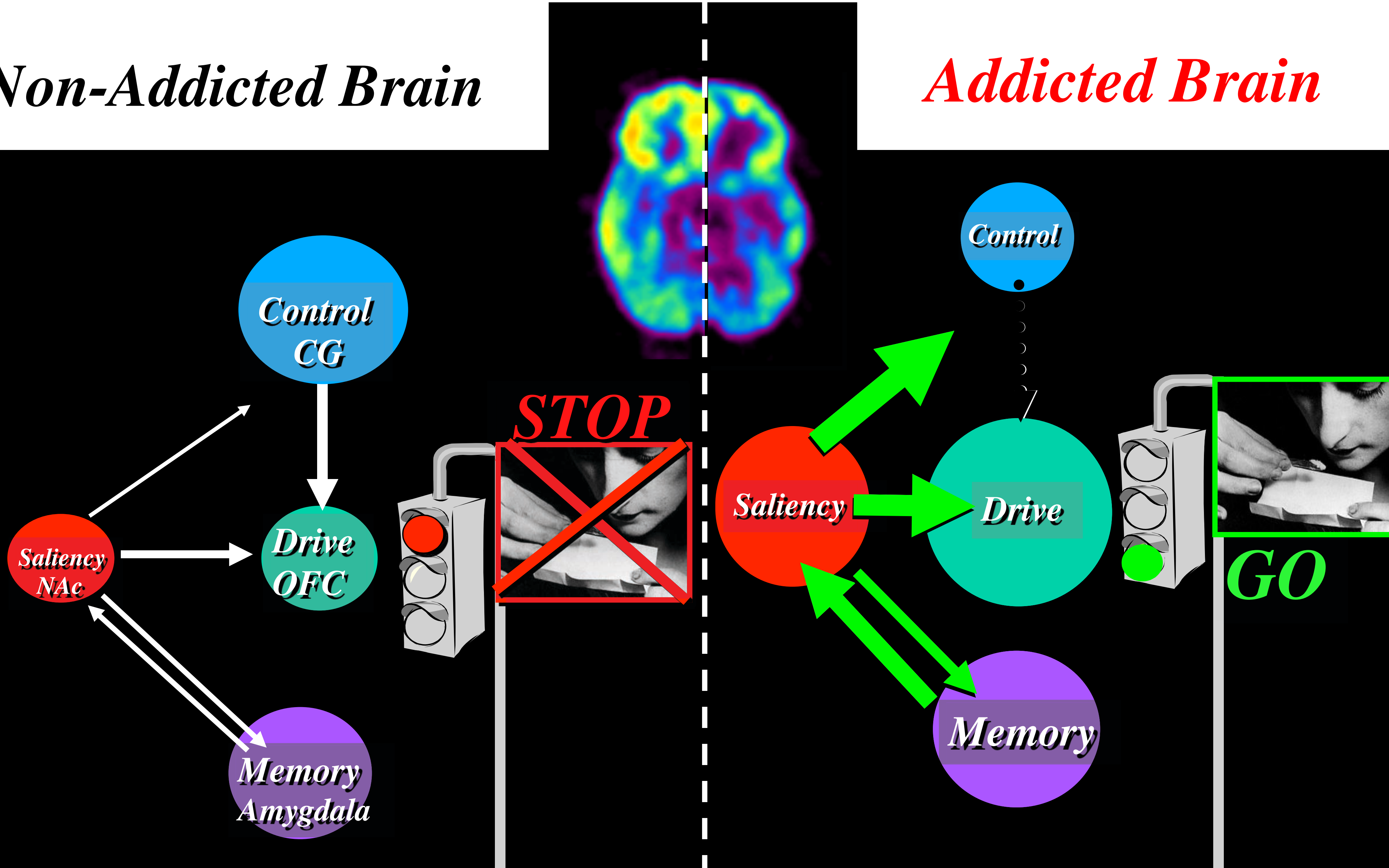
Mayberg J Clin Invest. 2009;119(4):717–725.



Goldstein RZ & Volkow ND. AJP 2002; 159: 1642-1652.

Non-Addicted Brain

Addicted Brain



Adapted from: Volkow et al., J Clin Invest 111(10):1444-1451, 2003.

BRAIN STIMULATION FOR ADDICTIVE DISORDERS

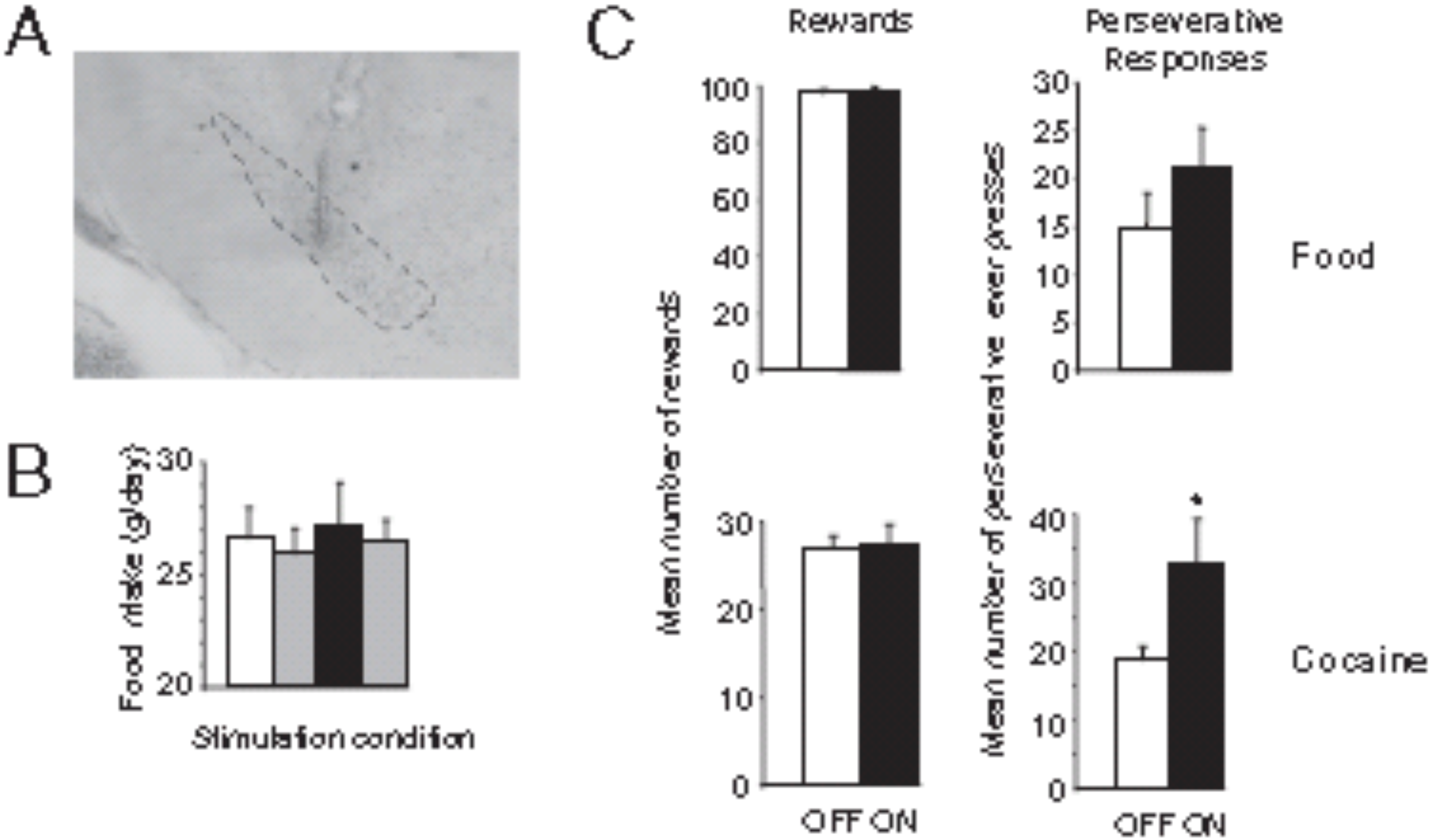
deep brain stimulation in animal models
transcranial magnetic stimulation in addition

1. TMS
2. DBS
3. Electrical stimulation

clinical examples from depression where they have been used and examples from preclinical models if they exist

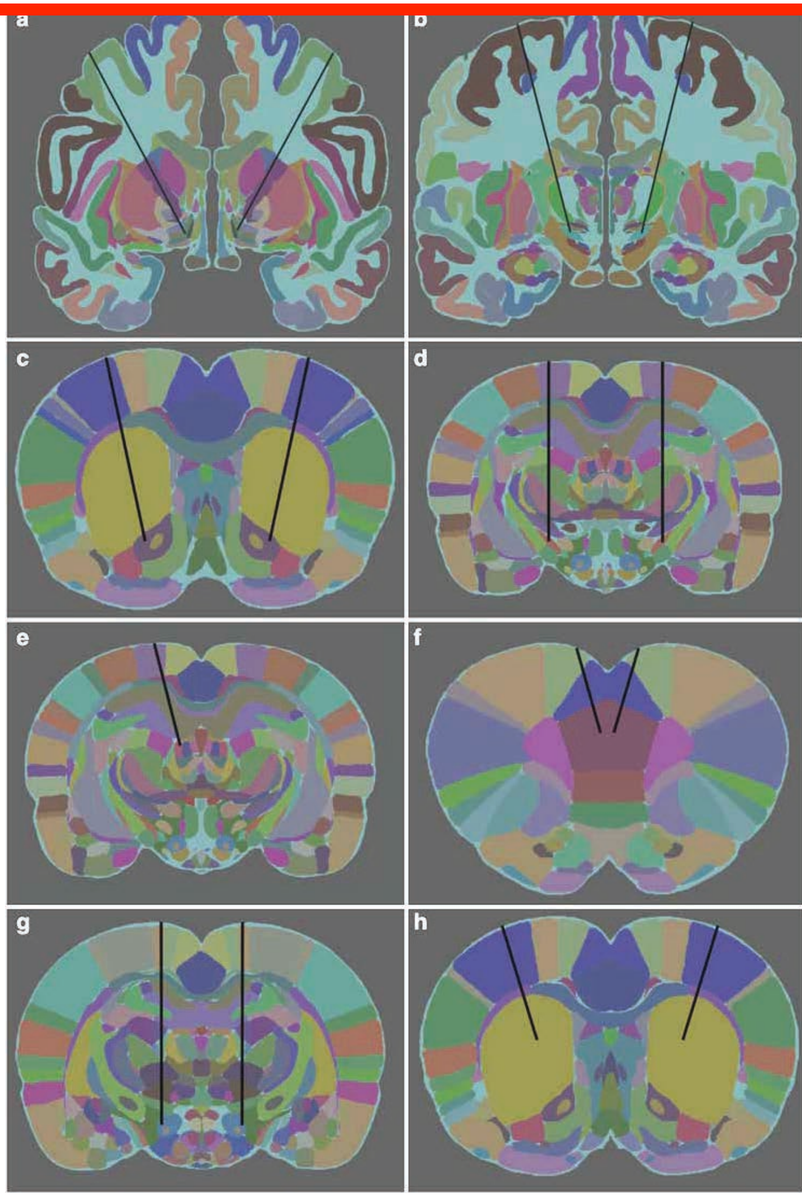
all of these treatment are predicated on specific regional brain abnormalities
good to have a diagram of areas in the brain that are disrupted in addiction and for which these treatments would be useful

Histology & Consummatory Behavior Under STN DBS



Rouaud T et al., PNAS 2010; 107(3): 1196-1200 .

Atlas Illustrations Show the Location of Electrode Placement In the Used Brain Areas For Both Animals and Humans



Human Brain:

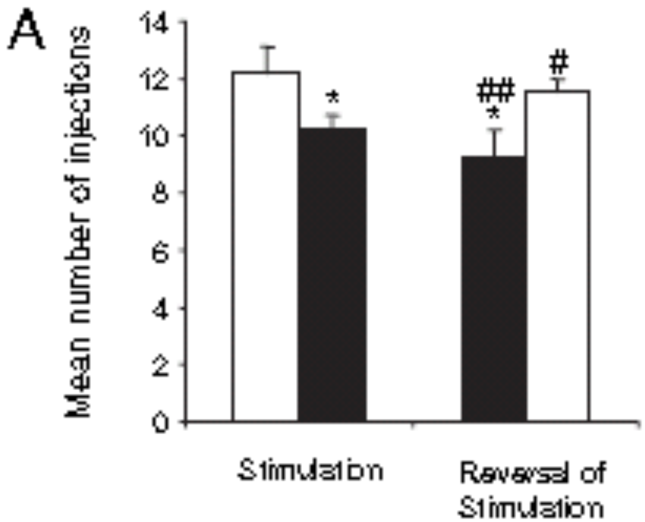
(a) bilateral nucleus accumbens (NAc)
(b) bilateral subthalamic nucleus (STN)

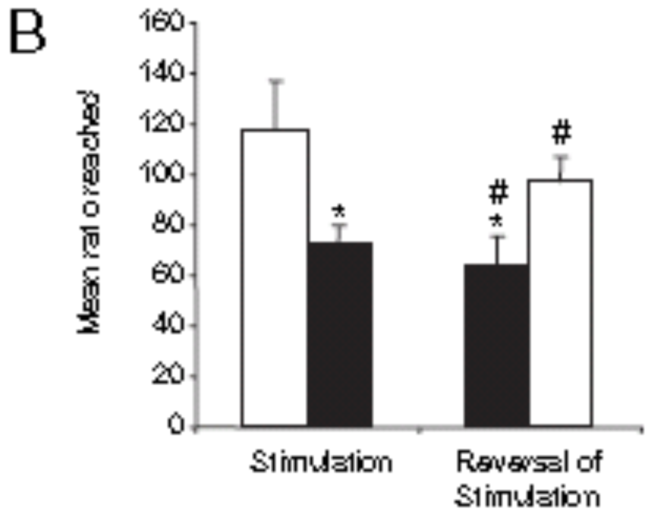
Rat Brain:

(c) bilateral NAc 1.2mm anterior to bregma
(d) bilateral STN 3.7mm anterior to bregma
(e) unilateral lateral habenula 3.8mm anterior to bregma
(f) bilateral medial prefrontal cortex 3.2mm anterior to bregma
(g) bilateral hypothalamus 2.5mm anterior to bregma
(h) dorsal striatum 1mm anterior to bregma

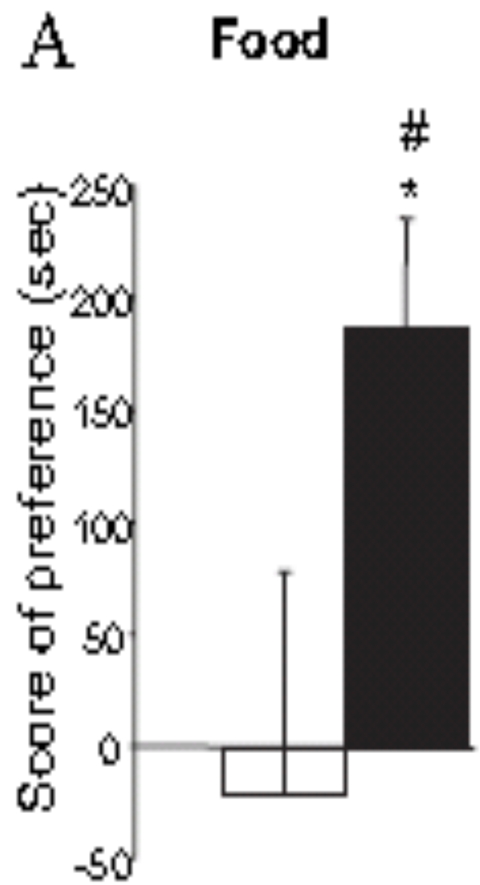
Brain Navigator release 2.0 (2009), Paxinos G and Watson C, editors-in-chief, Elsevier, Boston, MA, USA, *www.brainnav.com*
Luiguis J et al., Molecular Psychiatry 2012; 17: 572-583.

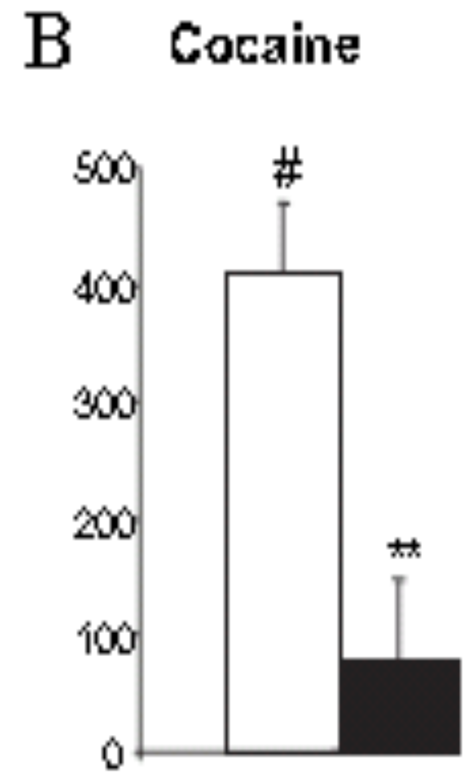
STN DBS Reversibility on its Behavioral Effects in the Progressive Ratio Task for IV Cocaine





Effects of STN DBS On Conditioned Place Preference for Food and for Cocaine





Rouaud T et al., PNAS 2010; 107(3): 1196-1200 .