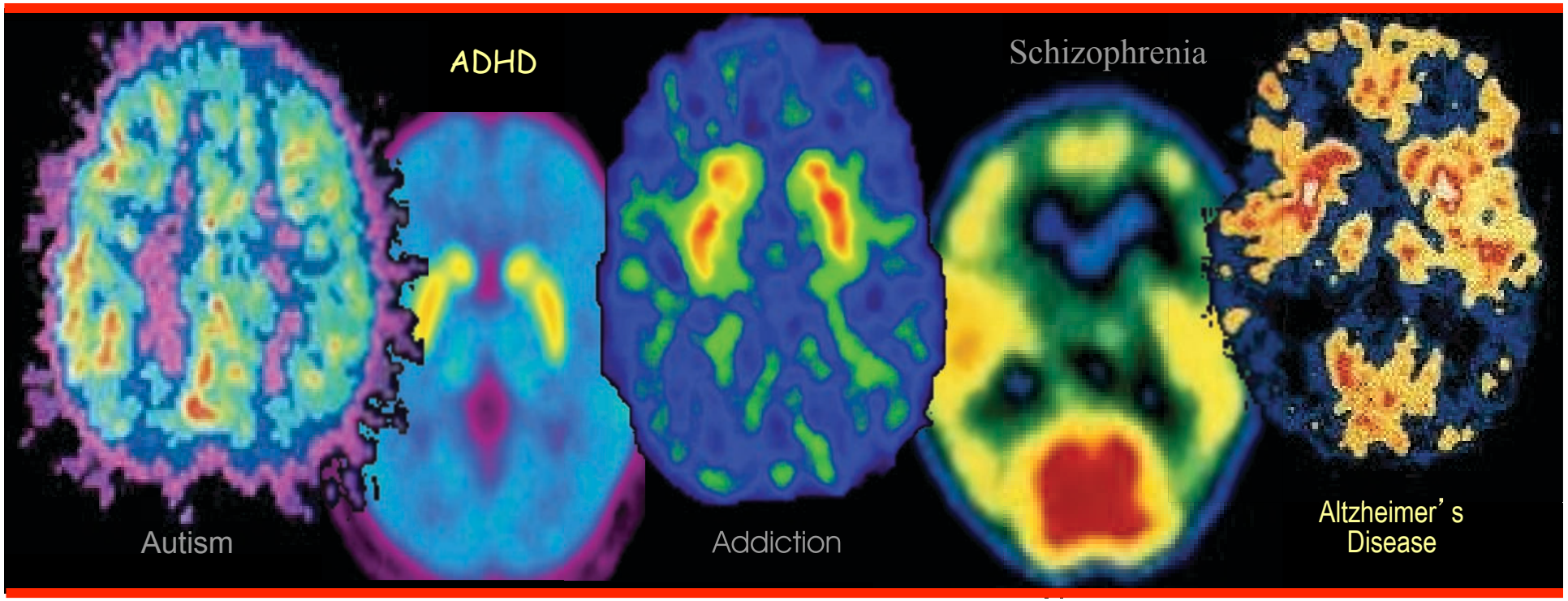
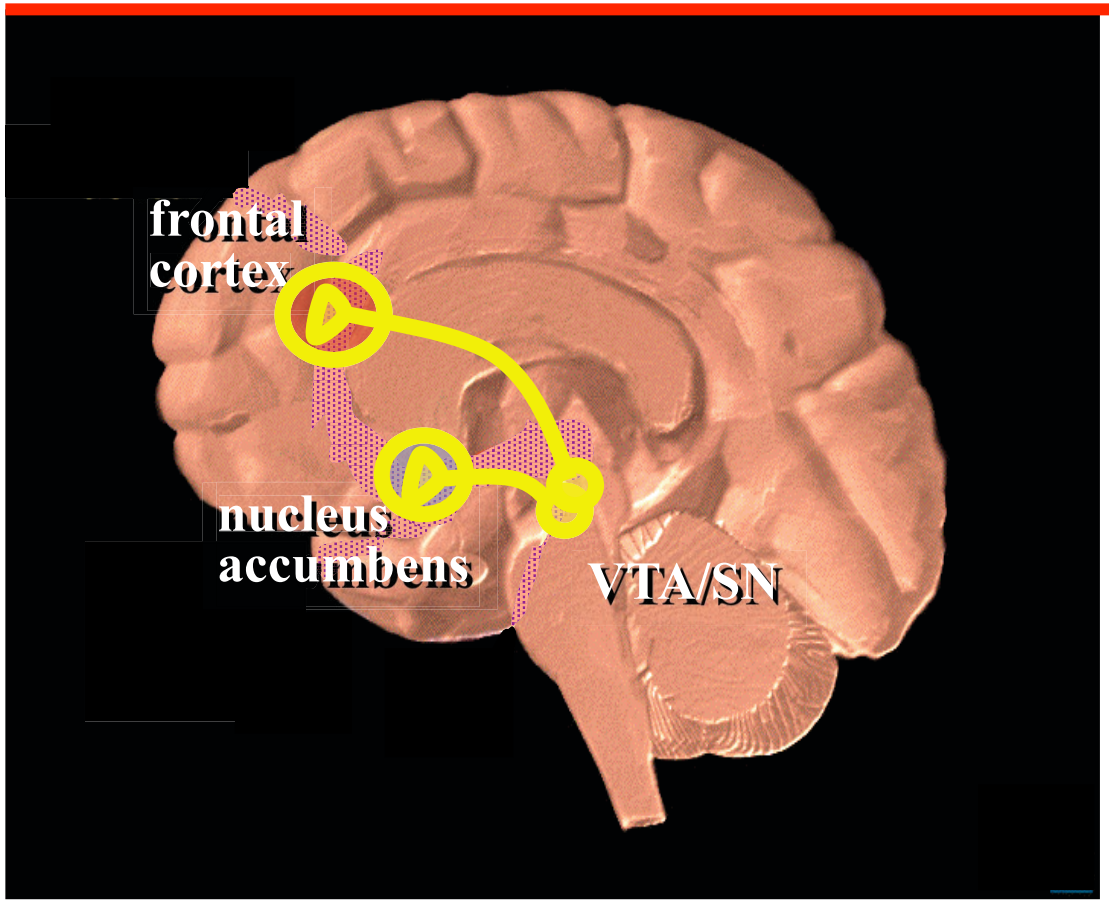
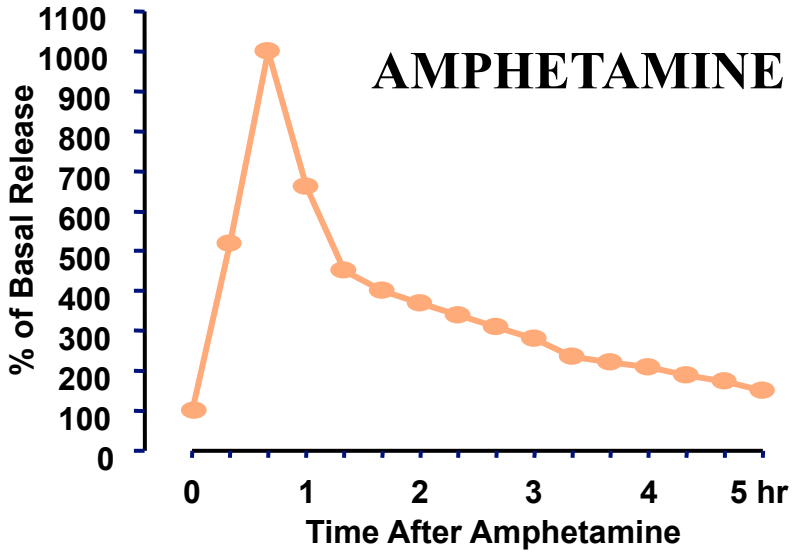
The Role of
NEUROIMAGING
In Diagnostic and Clinical Practice

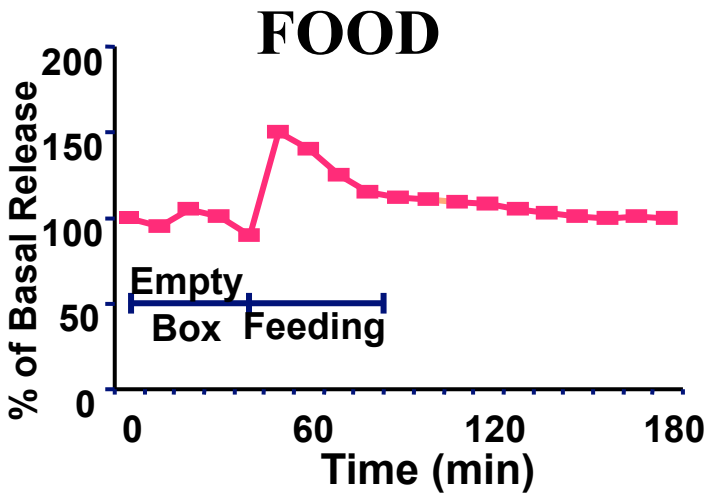


Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse
National Institutes of Health

Natural & Drug Reinforcers Increase Dopamine in NAc



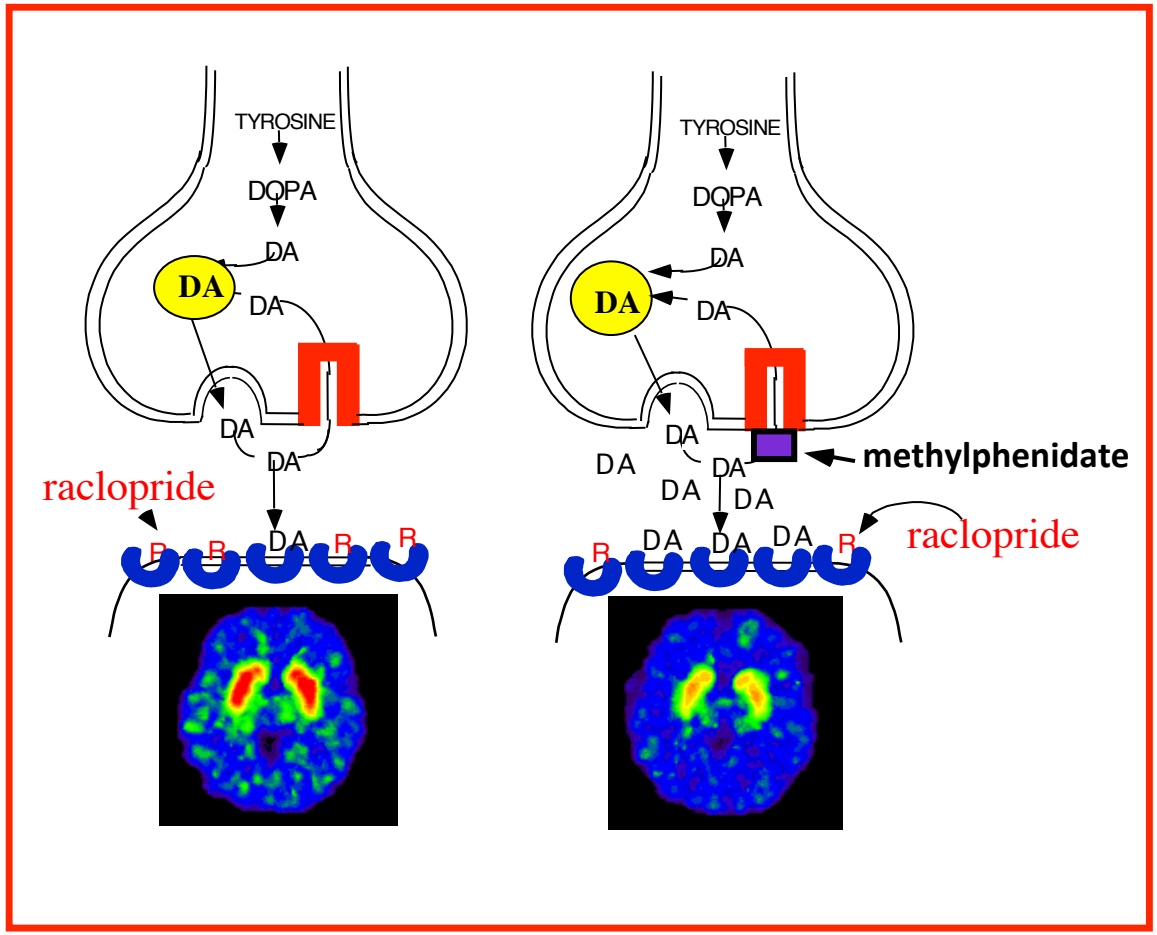




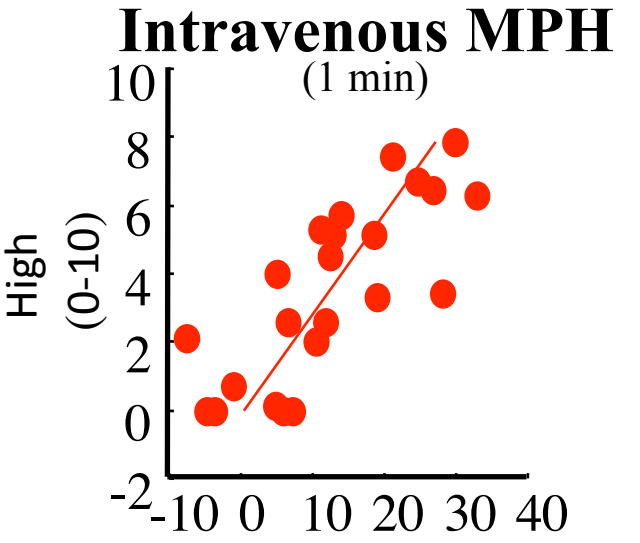
Di Chiara et al.

Drugs of abuse increase DA in the Nucleus Accumbens, which is believed to trigger the neuroadaptions that result in addiction

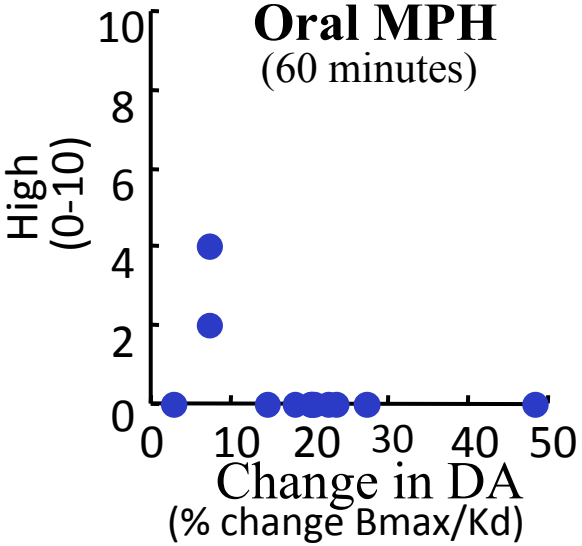
DA & the Rewarding Effects of Drugs in Humans

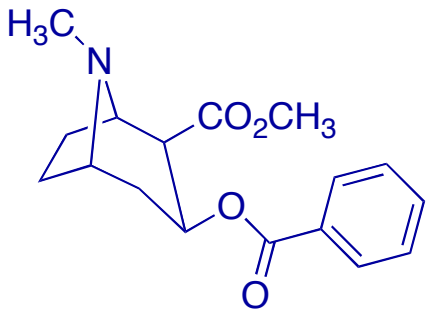


DA increases induced by intravenous but not by oral administration of MPH were associated with the "high". WHY?

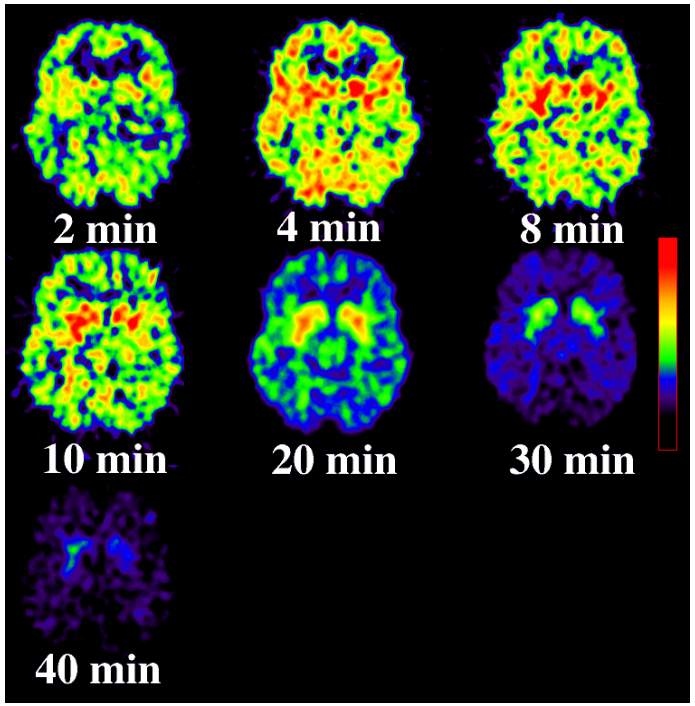


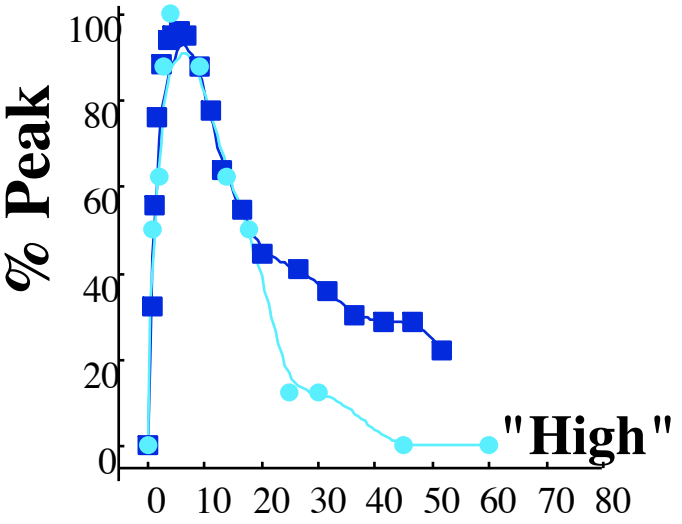
Volkow et al., JPET 291:409-415, 1999.

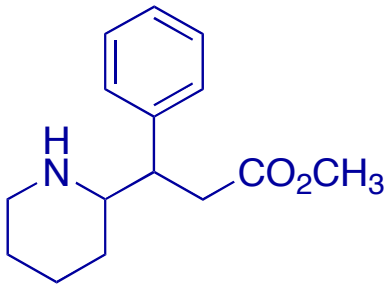




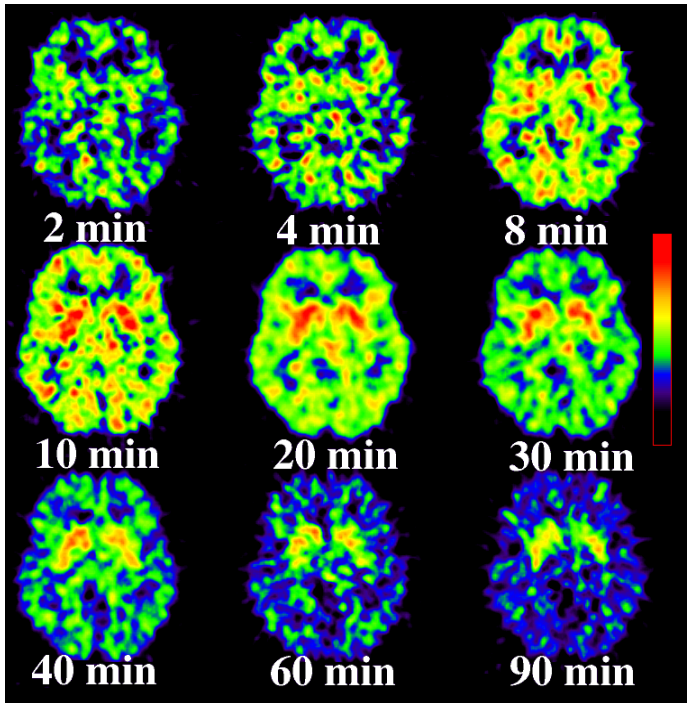
[11C]Cocaine

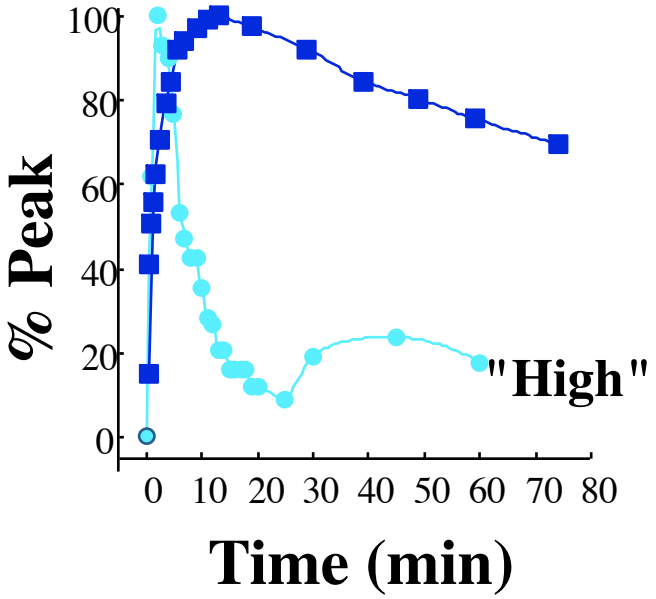




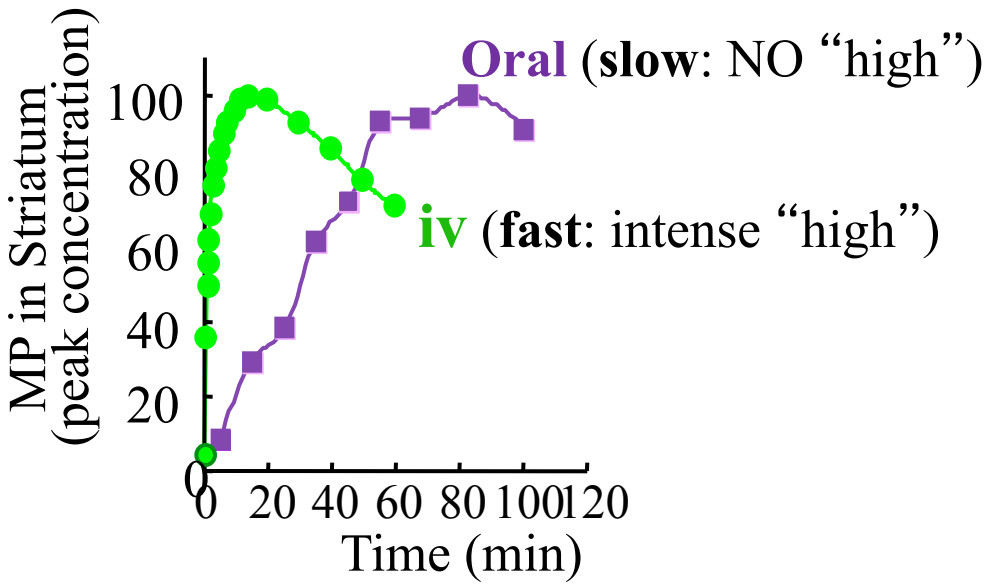


[11C]Methylphenidate





Pharmacokinetics of Oral and iv MPH in Baboon Brain

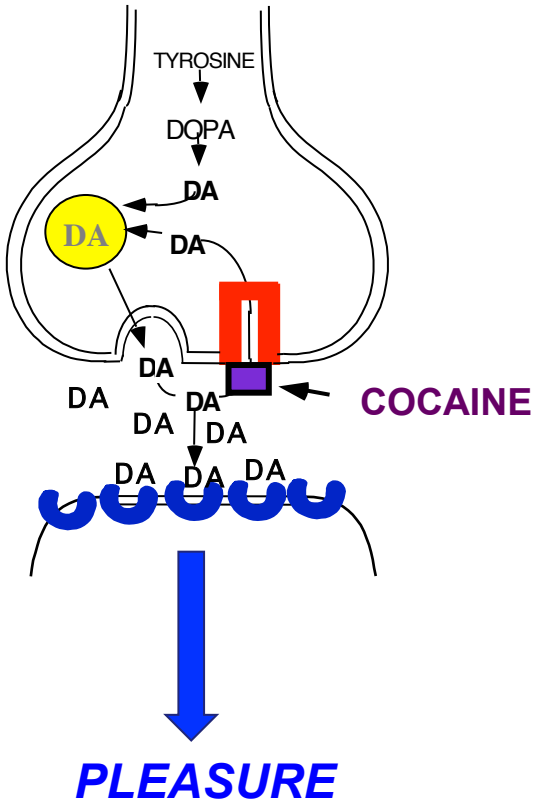


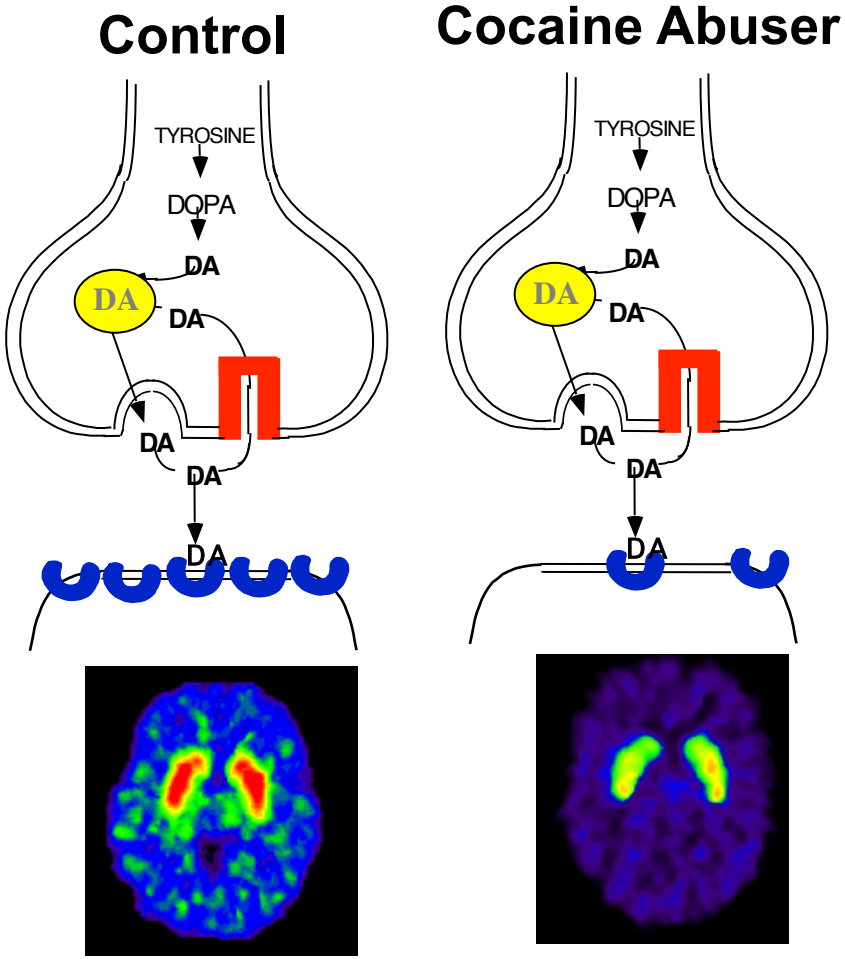
Thus reinforcing effects of drugs are due to FAST DA increases that emulate phasic DA cell signaling (15-30 Hz), which is implicated in reward and conditioning rather than tonic DA cell signaling (2-10 Hz), which is implicated in cognitive, motivational and motoric systems.

IMPLICATIONS: Drug Development

Repeated Drug Use Changes the Brain

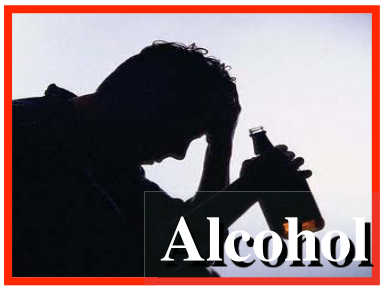
Weakens the Brain Dopamine System

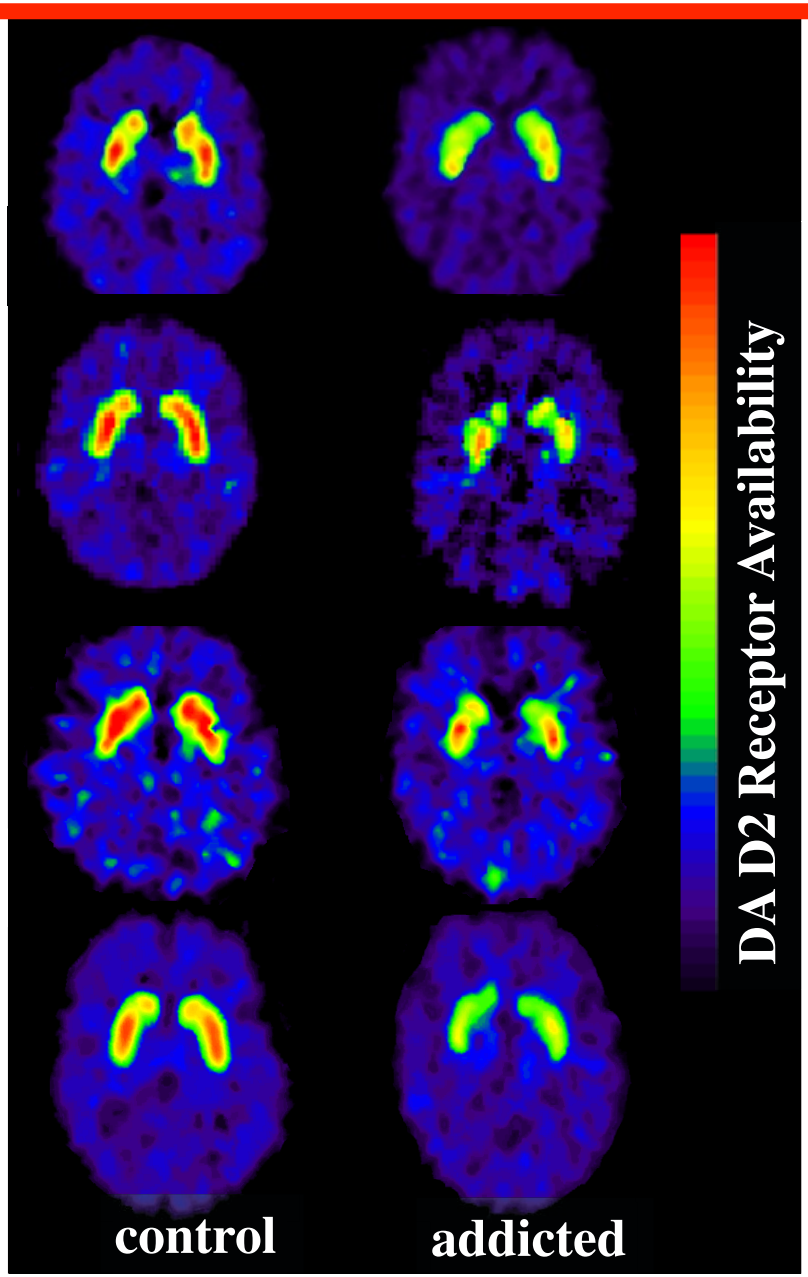


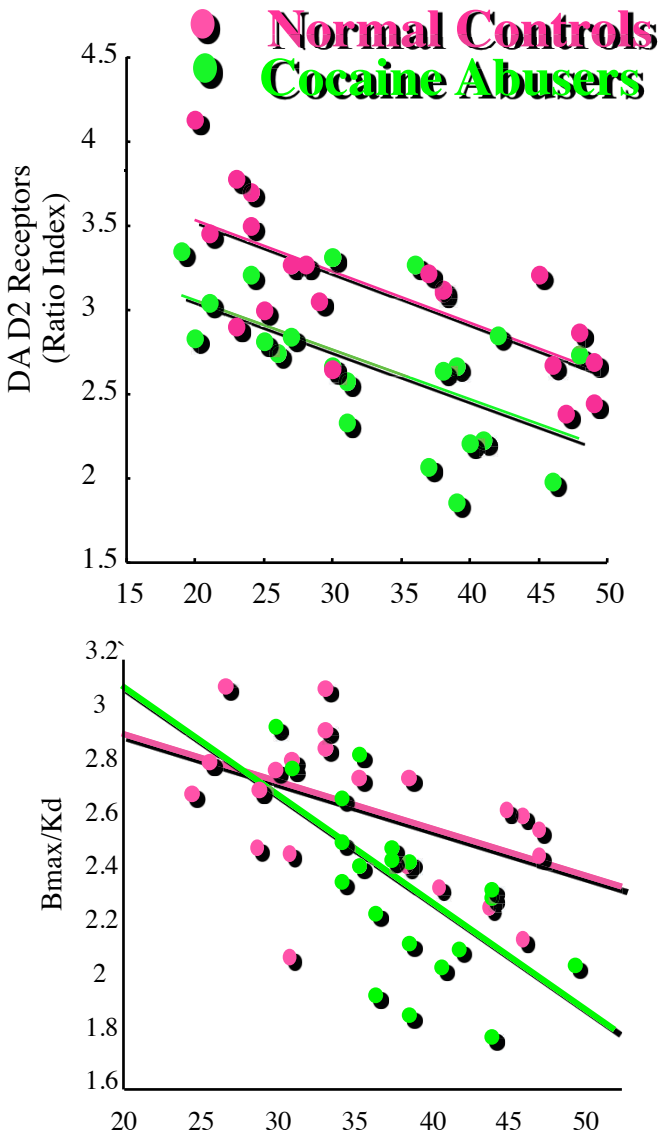


REPEATED USE OF COCAINE OR OTHER DRUGS REDUCES LEVELS OF DOPAMINE D2 RECEPTORS`

Dopamine D2 Receptors are Lower in Addiction



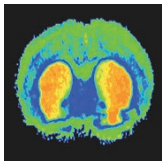




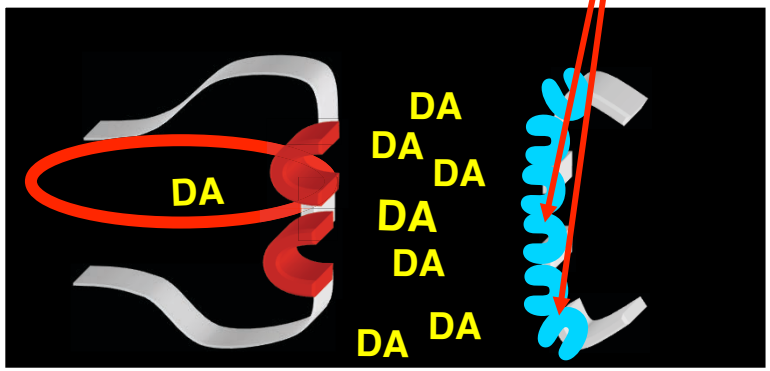
Volkow et al., Neuro Learn Mem 2002.

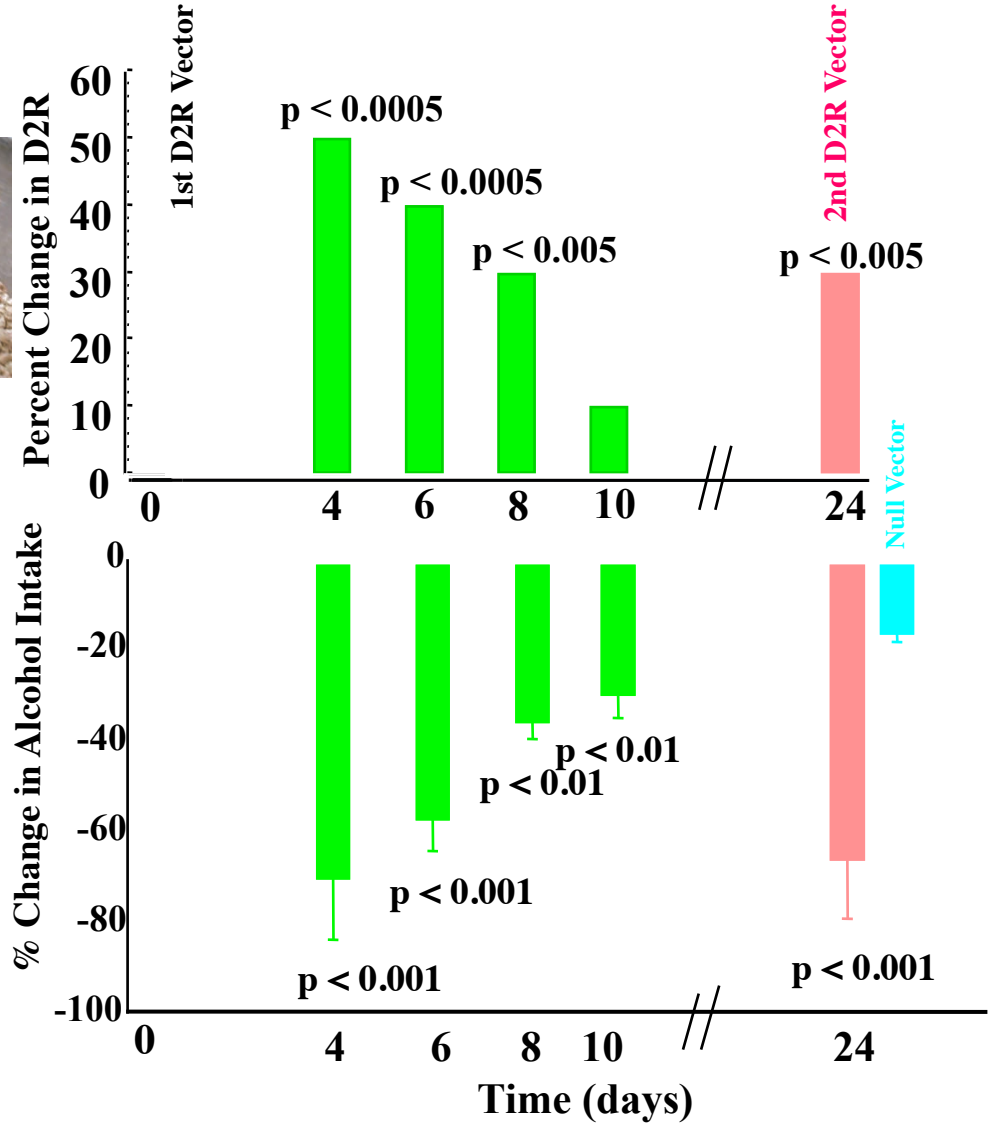
Effects of Tx with an Adenovirus Carrying a DA D2 Receptor Gene into NAc in DA D2 Receptors

Overexpression of DA D2 receptors reduces alcohol self-administration



Thanos, et al., J Neurochem,, 2001.



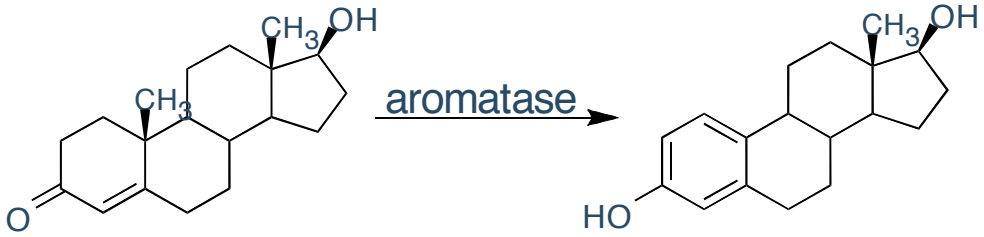


IMPLICATIONS: Treatment development

Nicotine

… More than just effects on Dopamine circuitry

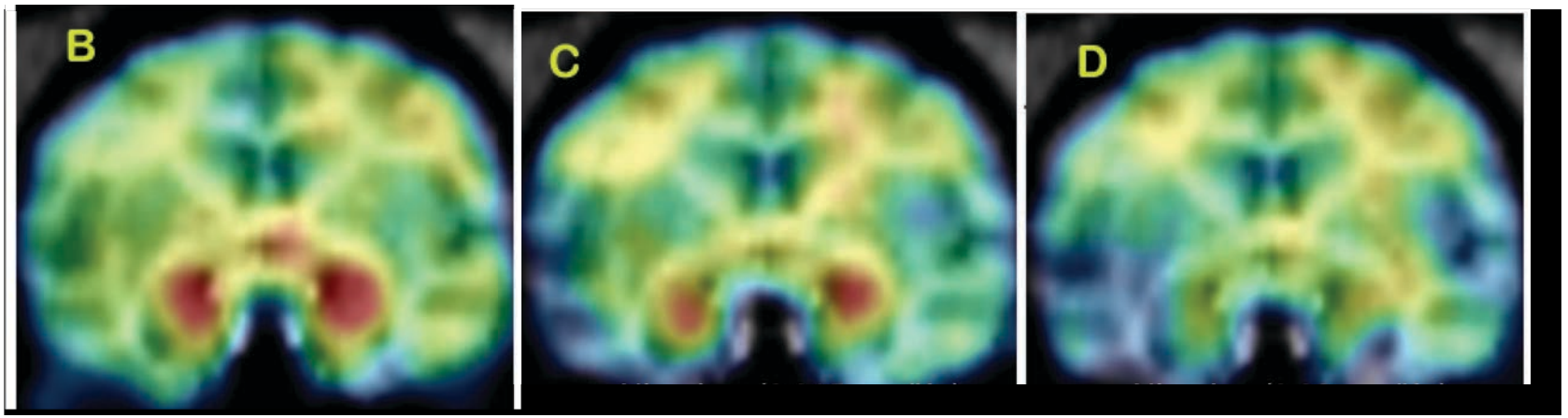
Aromatase* **(Estrogen synthase, CYP19A1)**



testosterone 17β-estradiol

- **Mediates sexual differentiation of the brain during development (Wu et al., Cell 139, 139: 61, 2009)**
- **Elevated in brain injury (neuroprotective effects of estrogen)**

Acute nicotine dose dependently inhibits aromatase in baboon at concentrations relevant to smoking *(Biegon et al., Biological Psychiatry , 2010)*.



Baseline 0.015 mg/kg 0.03 mg/kg

IMPLICATIONS:

Female smokers show hypo-estrogenic effects including early menopause

Fetal development

Tobacco Smoke

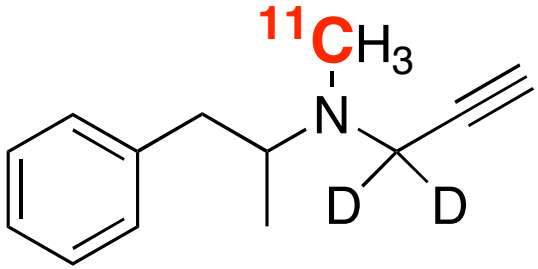
… More than just nicotine

4000 chemical compounds in smoke

Monoamine Oxidase (MAO)

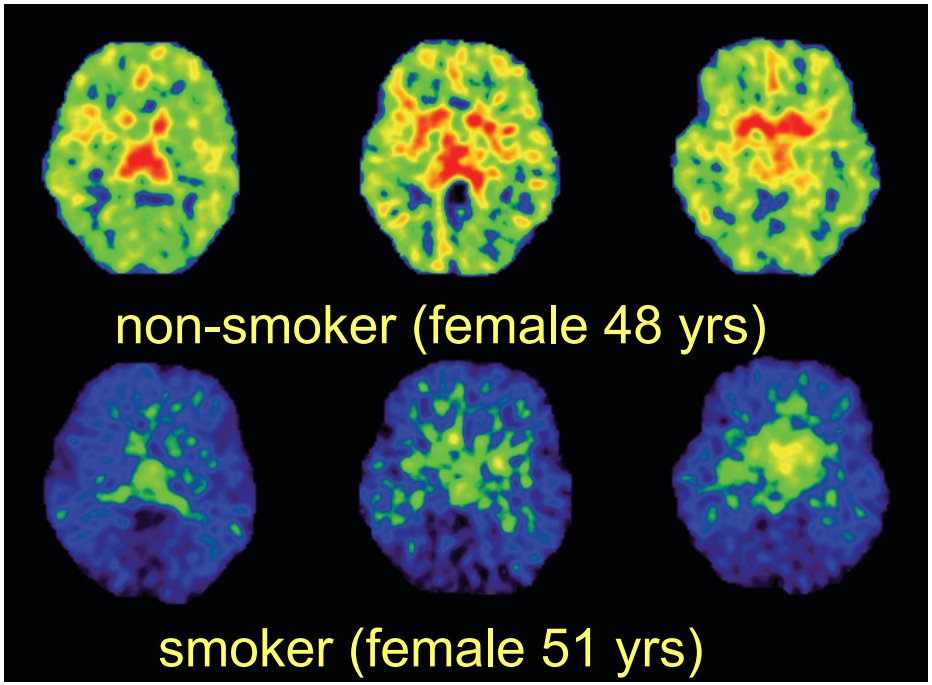
Breaks down neurotransmitter like dopamine (reward), serotonin (mood) and norepinephrine (arousal)

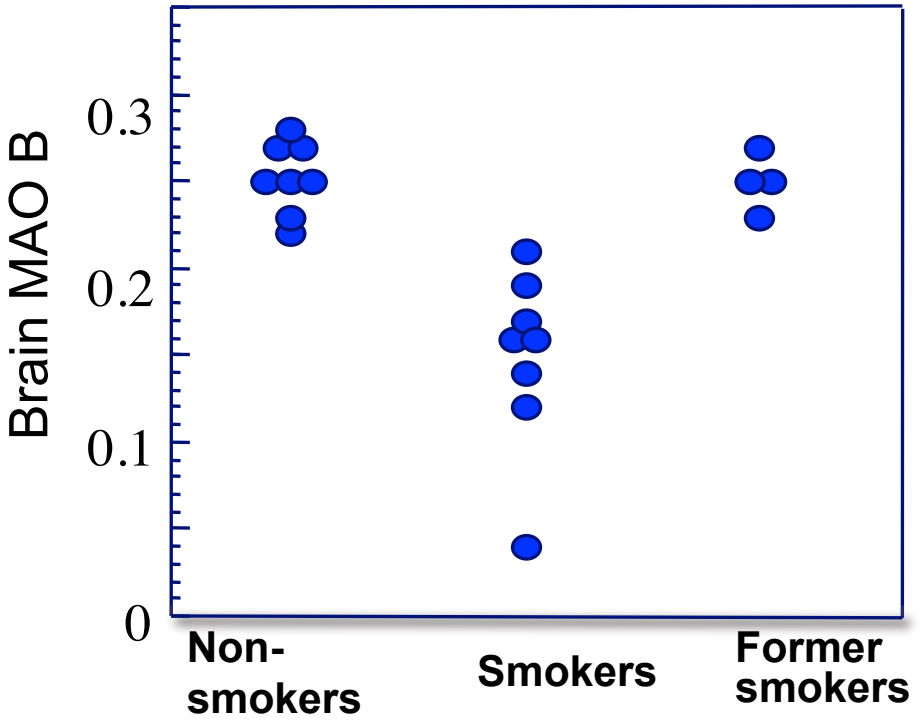
MAO inhibitor drugs are used to treat depression and Parkinson's disease



[11C]Deprenyl

Smoking inhibits MAO B in the human brain





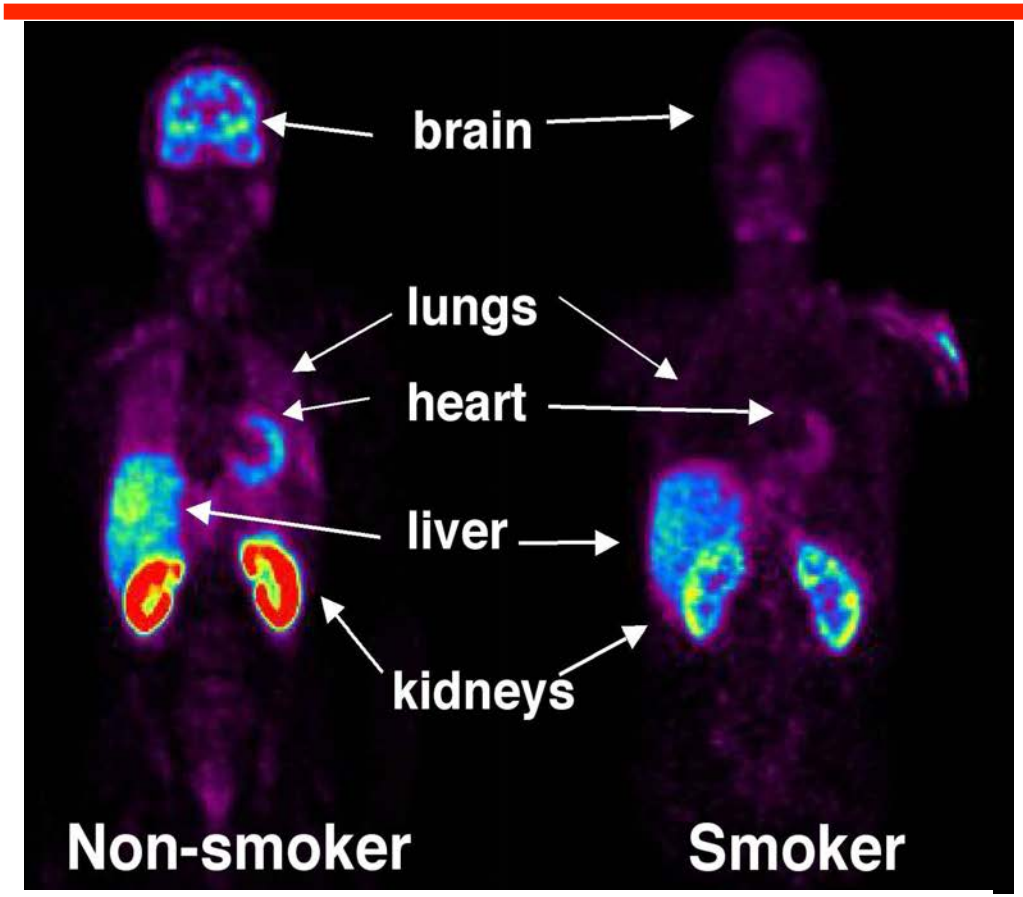
Low brain MAO in smokers is caused by the tobacco smoke and not by biology or genetics

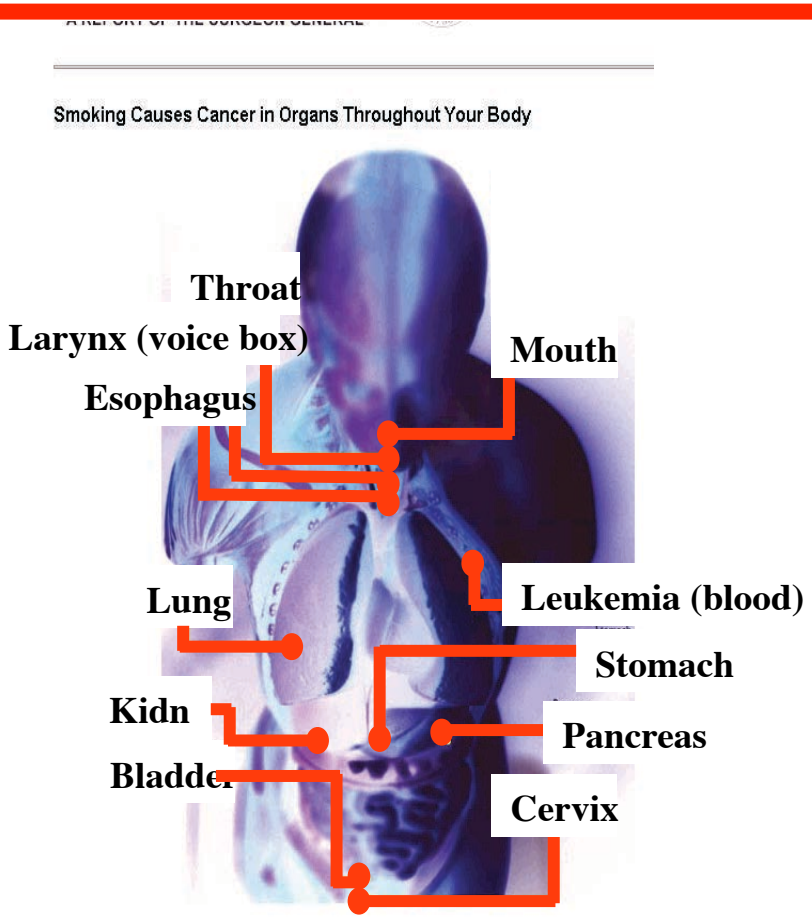
IMPLICATIONS:

Could this contribute to smoking?

Fetal development?

Smoking does not just affect the BRAIN



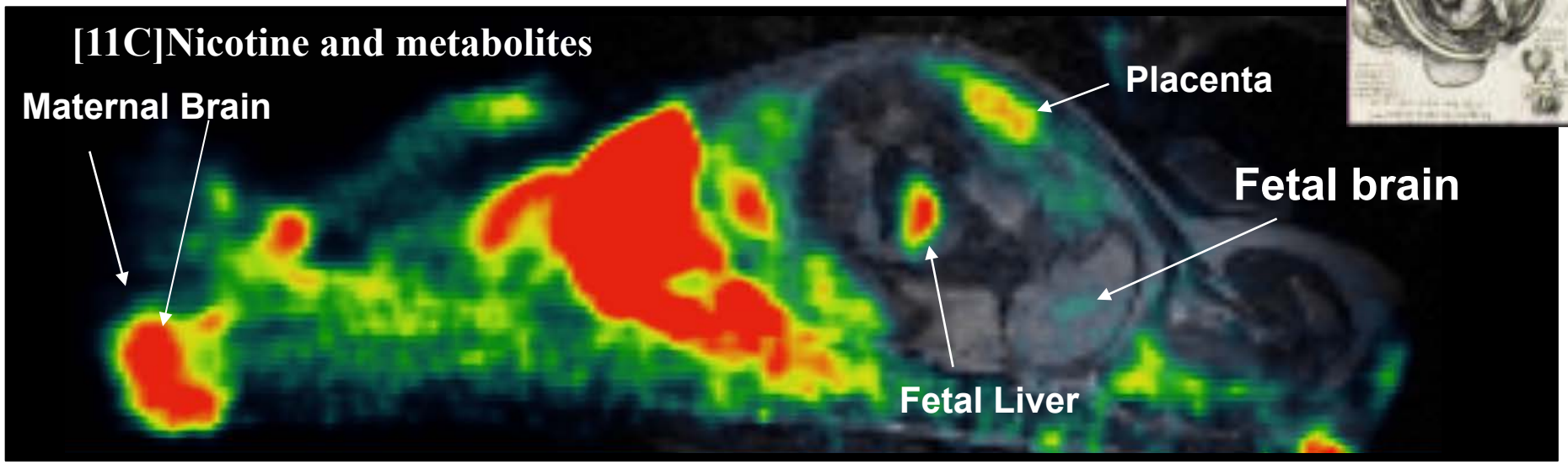


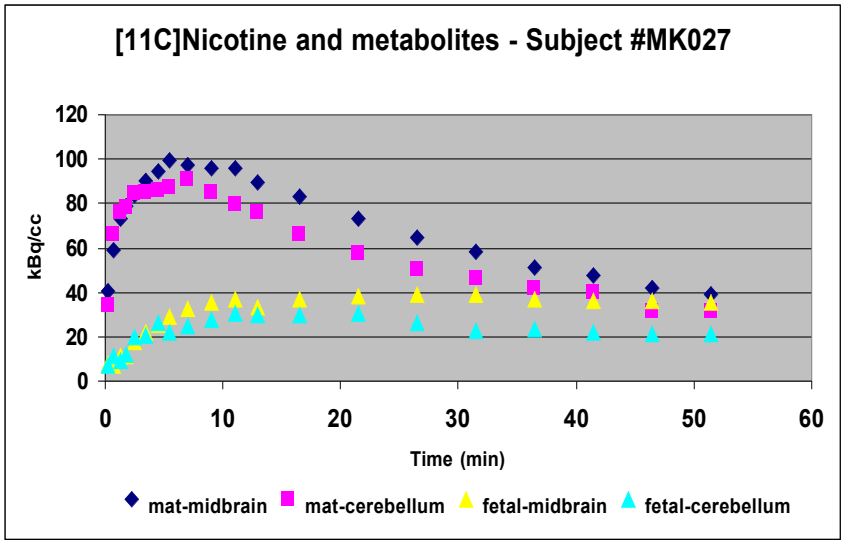
Smokers have 35-45% reduction in MAO B in heart, lungs, kidneys and spleen

Fowler et al PNAS 2003.

IMPLICATIONS: Mechanisms of tobacco toxicity

Nicotine Gets into the Fetus' Brain





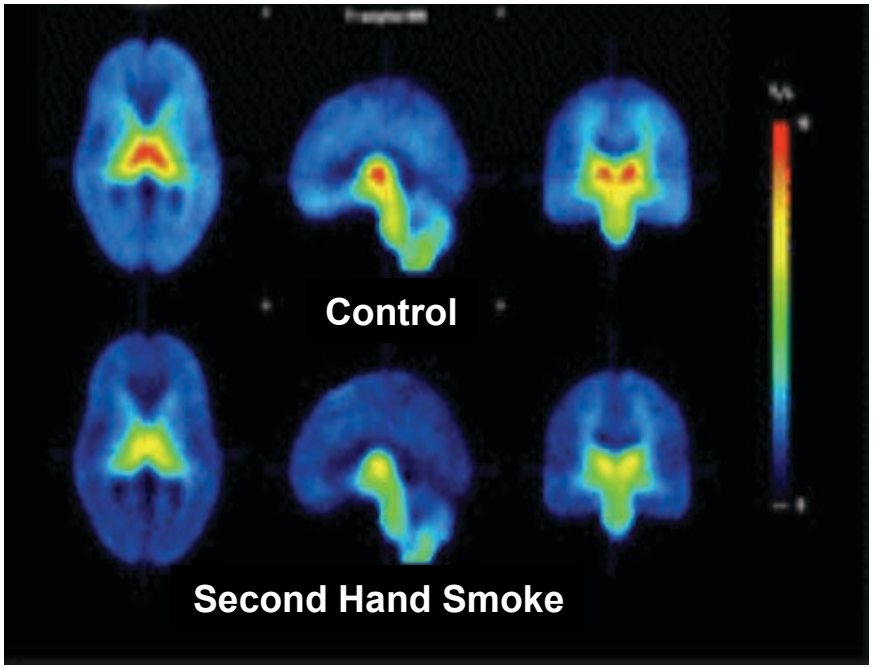
Benveniste et al., PNAS 2010

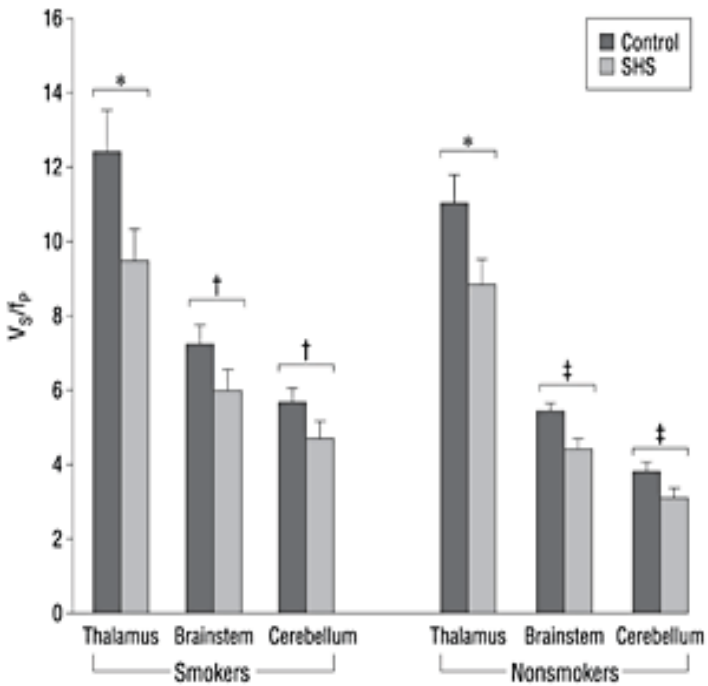
IMPLICATIONS: Understanding fetal toxicity

How about NRT as treatment during pregnancy?

Effect of Secondhand Smoke on Occupancy of Nicotinic Acetylcholine Receptors in Brain

Brody et al. Arch General Psych 2011.





-22% receptor occupancy

Secondhand smoke (SHS) decreased 2-FA binding demonstrating $\alpha_4\beta_2$* receptor occupancy.

IMPLICATIONS: Policy re: smoking in households with children