No Free Lunch

With Addictive Drugs

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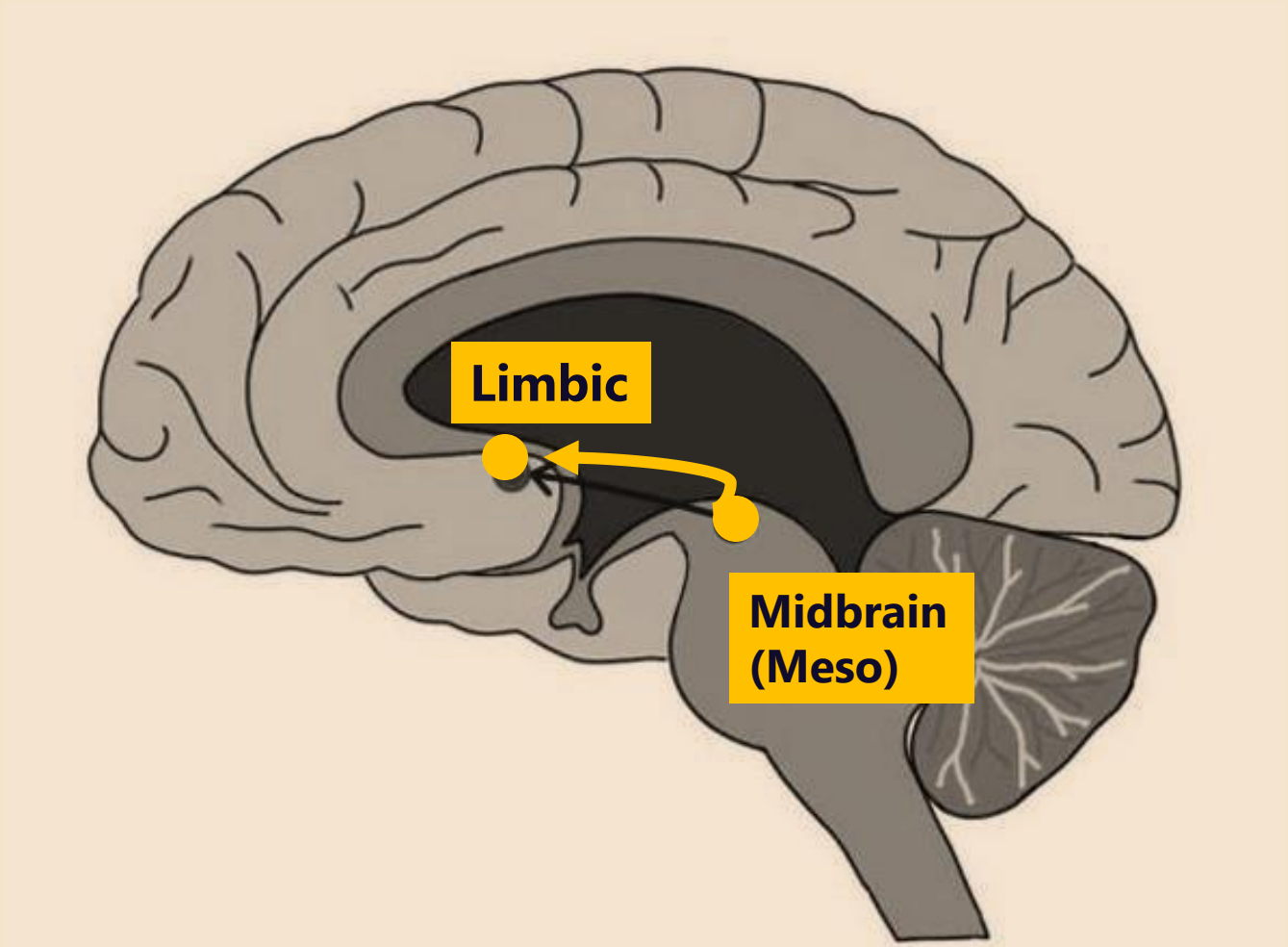
‘Wired’ to use mind-altering drugs

- Since prehistoric times
- Universal among humans
- Ubiquitous in the animal kingdom
- Role of dopamine “reward pathways”

Mesolimbic Dopamine Pathway



Mesolimbic Pathway

- Evolved through natural selection
- Promotes eating and reproduction
- Co-opted by all drugs of abuse
  - Drugs are often more potent than natural reinforcers
  - We control dose and delivery
  - Excess use dampens sensitivity

Addiction

- Overpowering desire or need (compulsion) to acquire and continue taking the drug
- Tendency to increase the dose (tolerance)
- Psychic and (generally) a physical dependence
- Detrimental effect on the individual and on society
- Denial of drug problem

Laws of Psychopharmacology

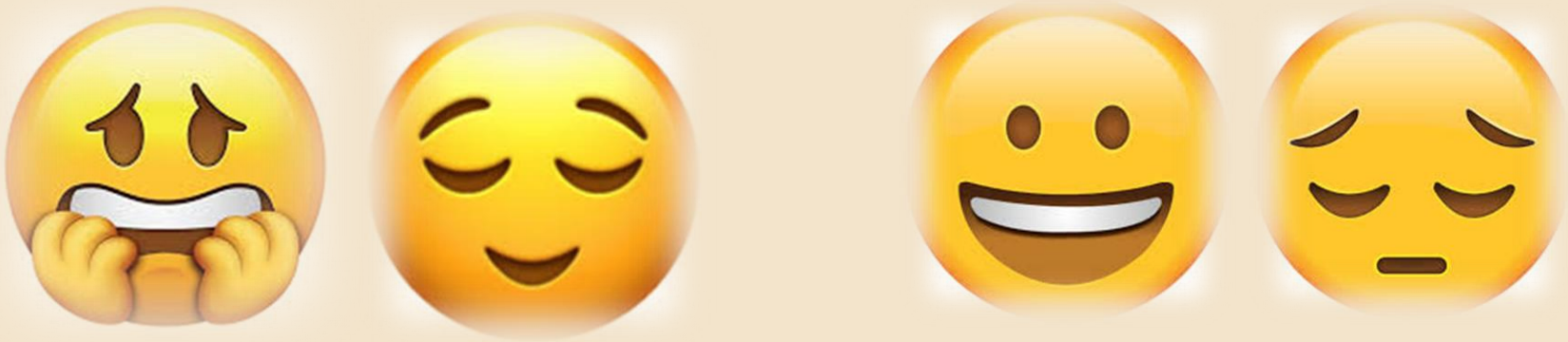
I. Drugs only act by changing the rate of what is already going on

II. All drugs have side effects

III. Whatever effects the drug produces, the brain counteracts by producing the opposite

Oppoent Process Theory

Richard Solomon & John Corbit adapt the idea of homeostasis to **emotional/affective states**



Opponent Process Theory

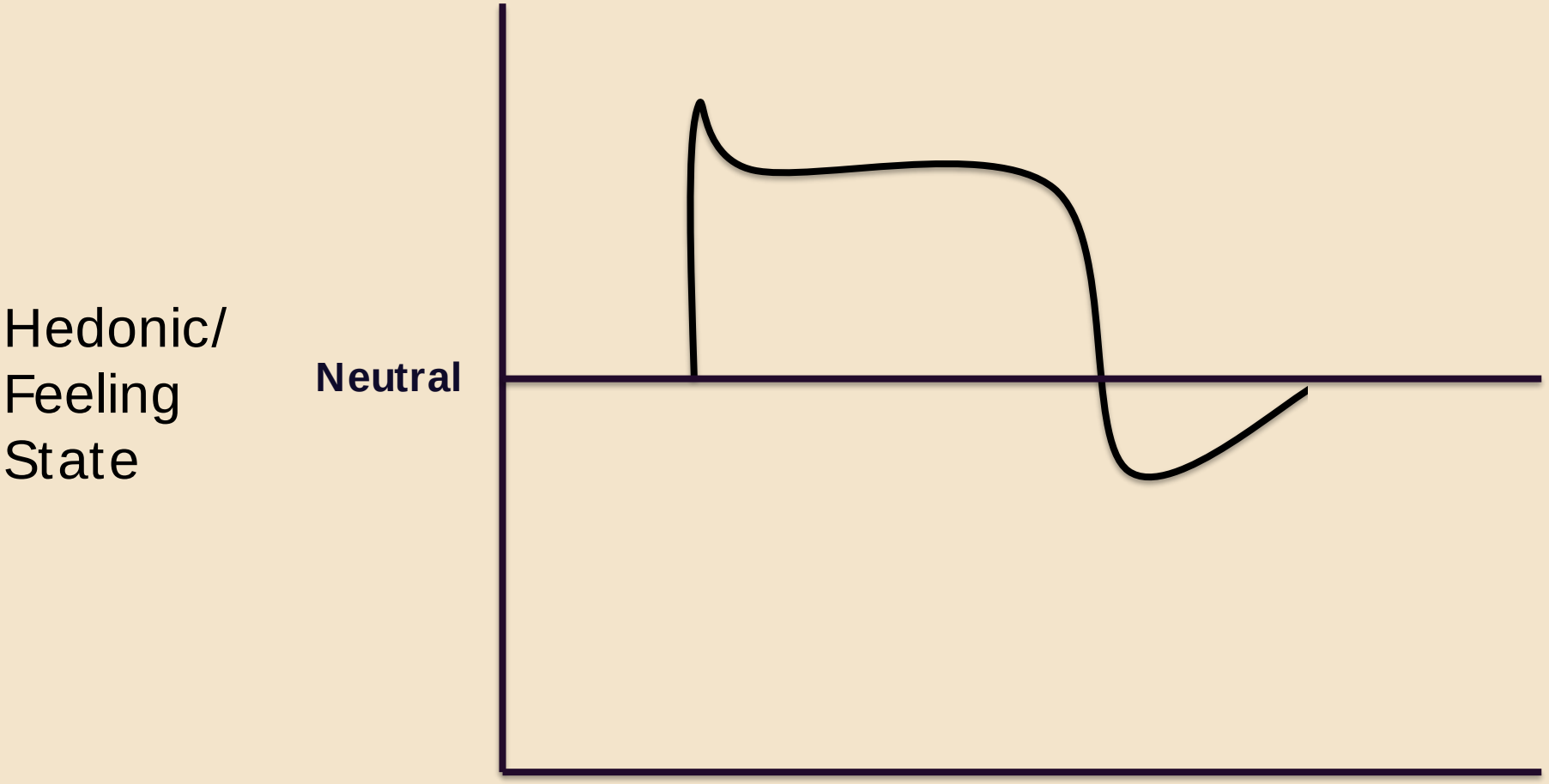
Solomon & Corbit

Proposed that

any stimulus that alters brain functioning to affect the way we feel will elicit a response by the brain that is exactly opposite to the effect of the stimulus.

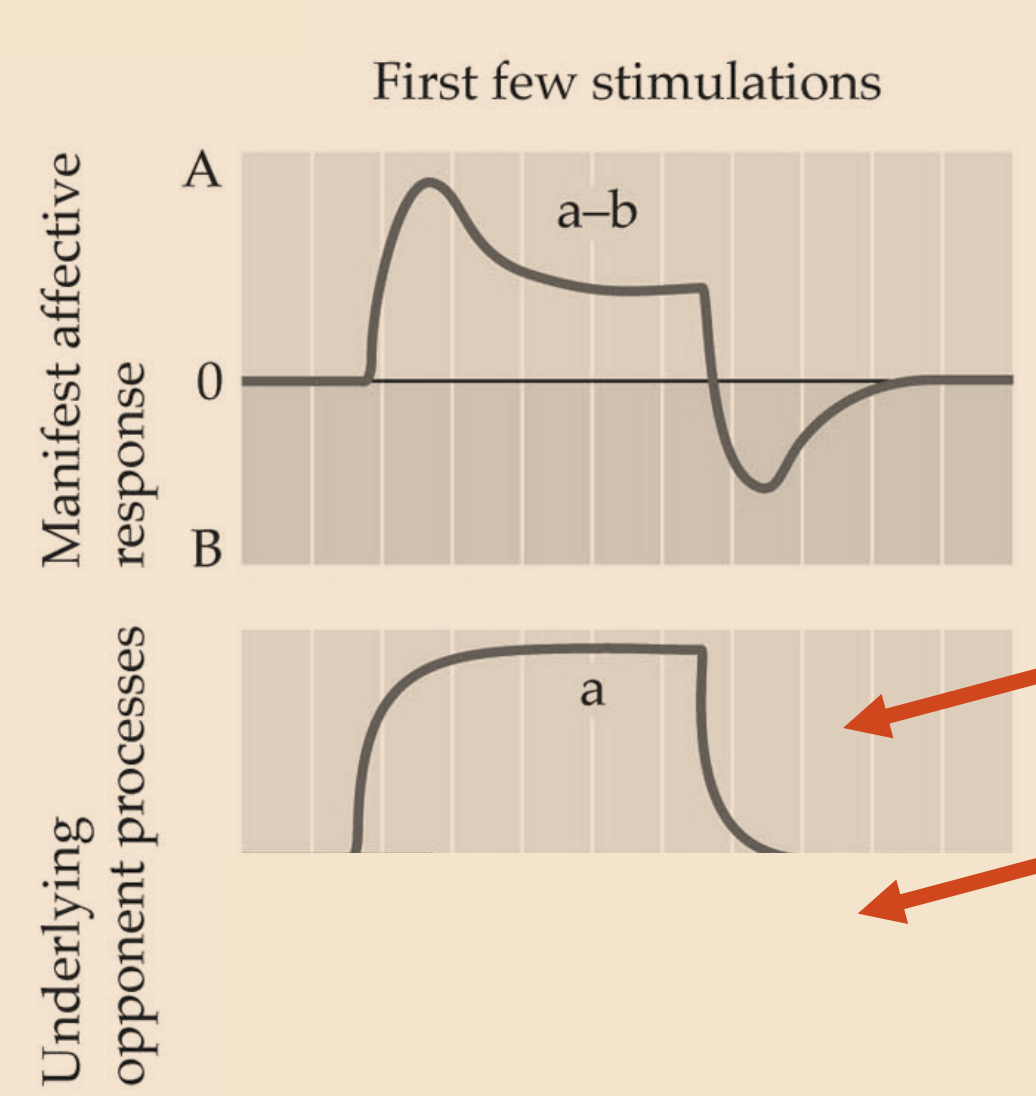
An Opponent-Process Theory of Motivation, Richard L. Solomon & John D. Corbit. Psychological Review, Vol. 81, No. 2, pp. 119-145, 1974.

Effect of Any Addictive Drug



From Solomon & Corbit, 1974

Two Process Underlie Drug Effects



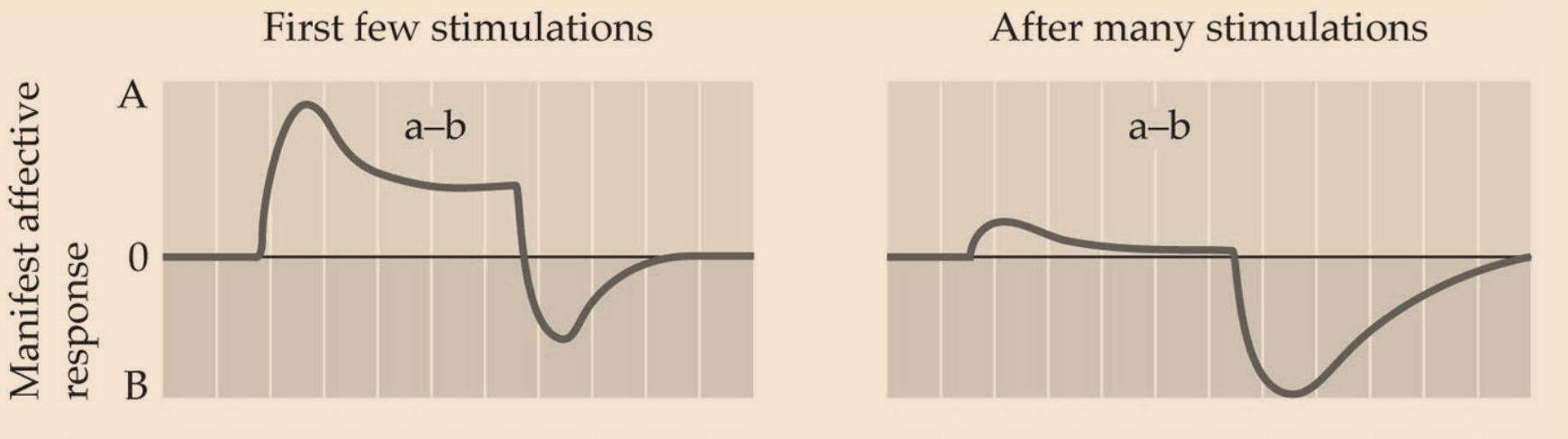
"a process"

- Direct result of the drug acting in the brain

"b process"

- brain's
- i.e. dopamine release, receptor interactions
- compensatory response to drug
- i.e., receptor downregulation

Drug-Induced Changes in Affect



"b process"adapts

- Earlier, larger, longer
- Learns to anticipate drug/"a process"

Adaptive 'b process' → Relapse

- **Elicited by drug Paraphernalia**
- **Using buddies**
- **Time of day or week**
- **Emotional states**
- **$**
- **Weather, music or other broad contextual cues**

3 Causes of Relapse

- **"Taste" of drug** ***(b process)***
- **Cues associated with drug** ***(b process)***
- **Stress**

Narcotics

- Used for thousands of years
- Opium is from the opium poppy
- 1803 active ingredient isolated and named **Morphine** after the god of dreams, Morpheus.
- 1853 syringe and hollow needle invented.

Opiate Effects and Withdrawal

"a process"	"b process"
Analgesia	Pain and irritability
Respiratory depression	Panting and yawning
Euphoria	Dysphoria and depression
Relaxation and sleep	Restlessness and insomnia
Tranquilization	Fearfulness and hostility
Decreased blood pressure	Increased blood pressure
Constipation	Diarrhea
Pupil constriction	Pupil dilation
Hypothermia	Hyperthermia
Drying of secretions	Tearing, runny nose
Reduced sex drive	Spontaneous ejaculation

Another Example…

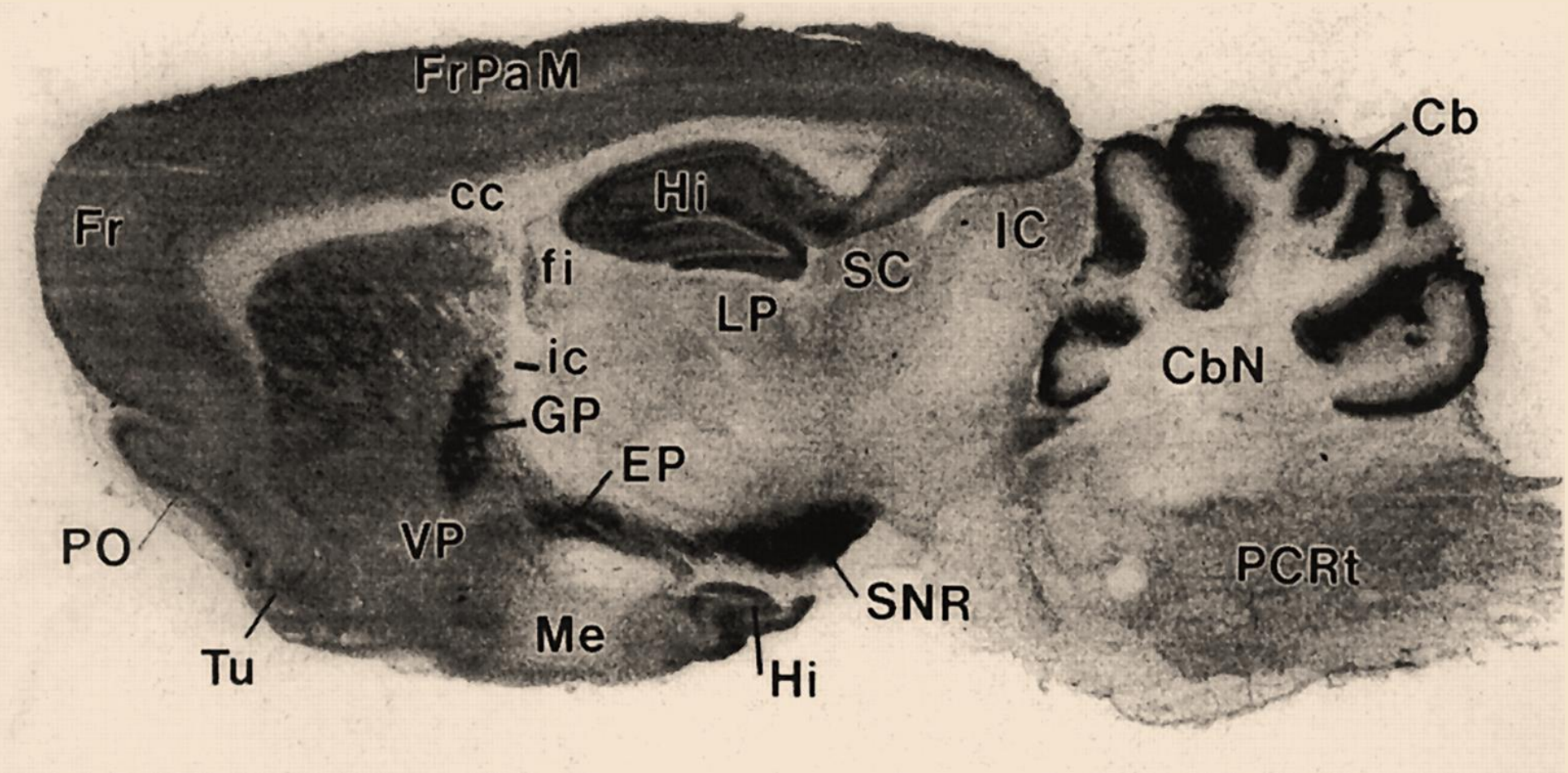
The Journal of Neuroscience, February 1991, *11*(2): 563–583

Characterization and Localization of Cannabinoid Receptors in Rat Brain: A Quantitative *in vitro* Autoradiographic Study

Miles Herkenham,[1] Allison B. Lynn,[1] M. Ross Johnson,[2] Lawrence S. Melvin,[3] Brian R. de Costa,[4] and Kenner C. Rice[2]

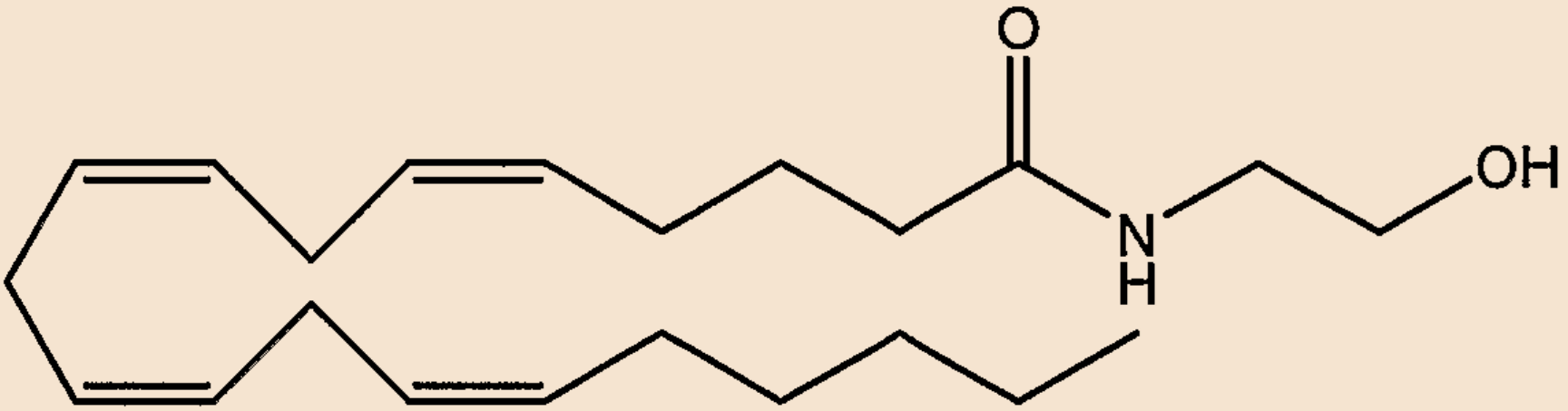
[1]Section on Functional Neuroanatomy, National Institute of Mental Health, Bethesda, Maryland 20892, [2]Glaxo Incorporated, Research Triangle Park, North Carolina 27709, [3]Pfizer Incorporated, Central Research, Groton, Connecticut 06340, and [4]Laboratory of Medicinal Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland 20892

CB1 Receptors: A surprise!

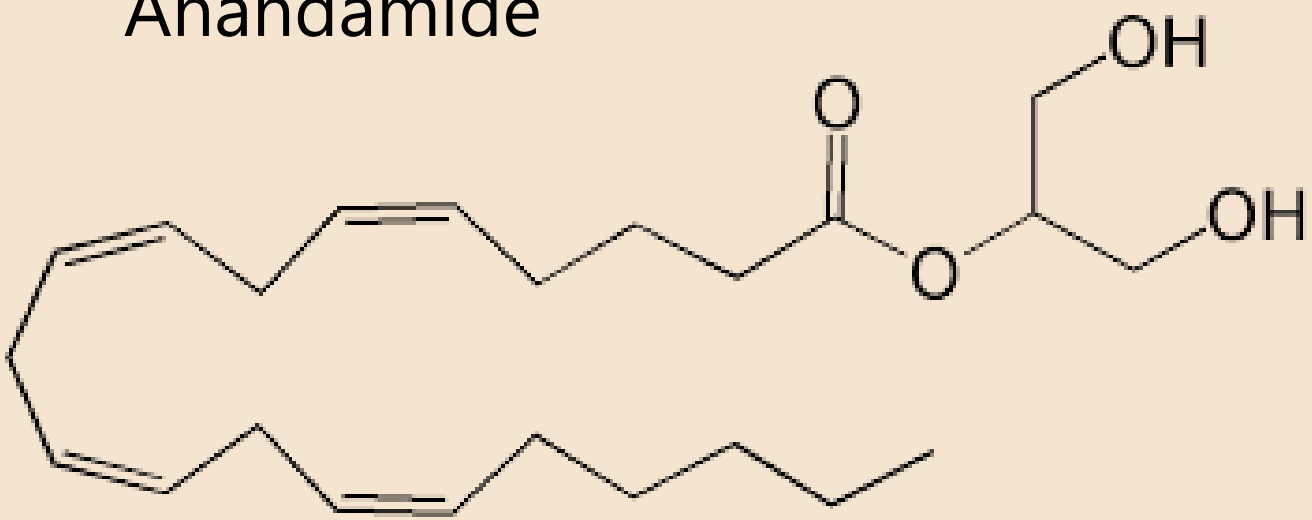


Herkenham et al., 1991, *Journal of Neuroscience*

Endocannabinoids



Anandamide



2-Arachidonoylglycerol or 2-AG

Flooding the Fields

Acute Effects of Marijuana

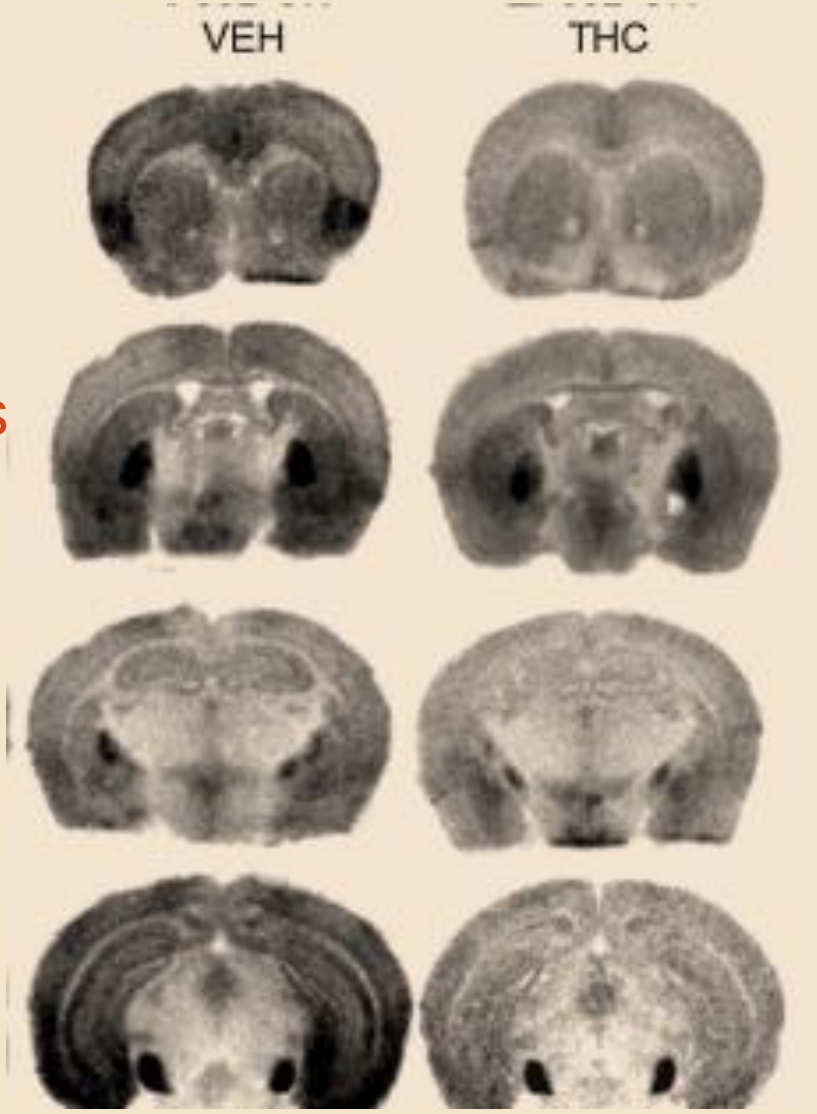
Makes stimuli more rich and meaningful

Stimulates pleasure, relaxation

- Impairs memory
- Slows response time
- Causes critical tracking errors

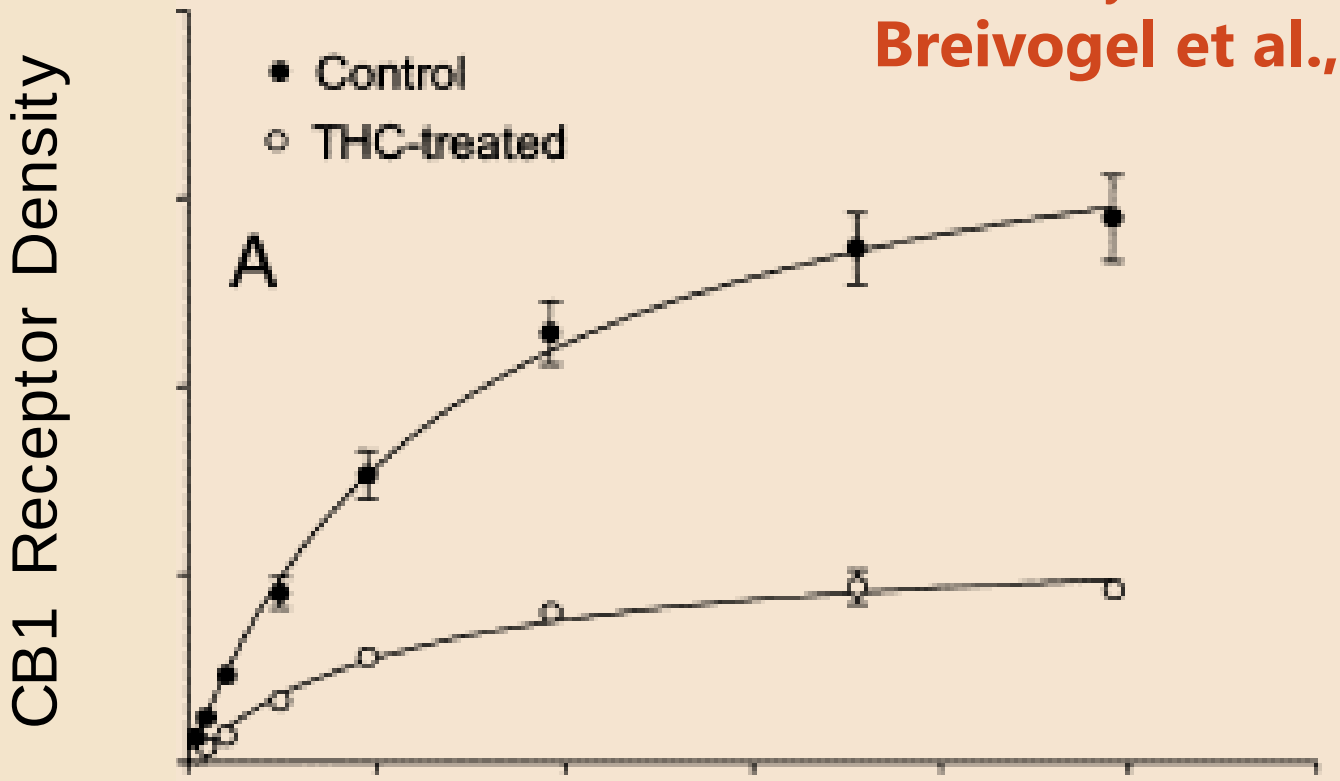
b process!

Daily escalating doses for 6 days
Assess on Day 7
Lazenka et al., 2014



b process?

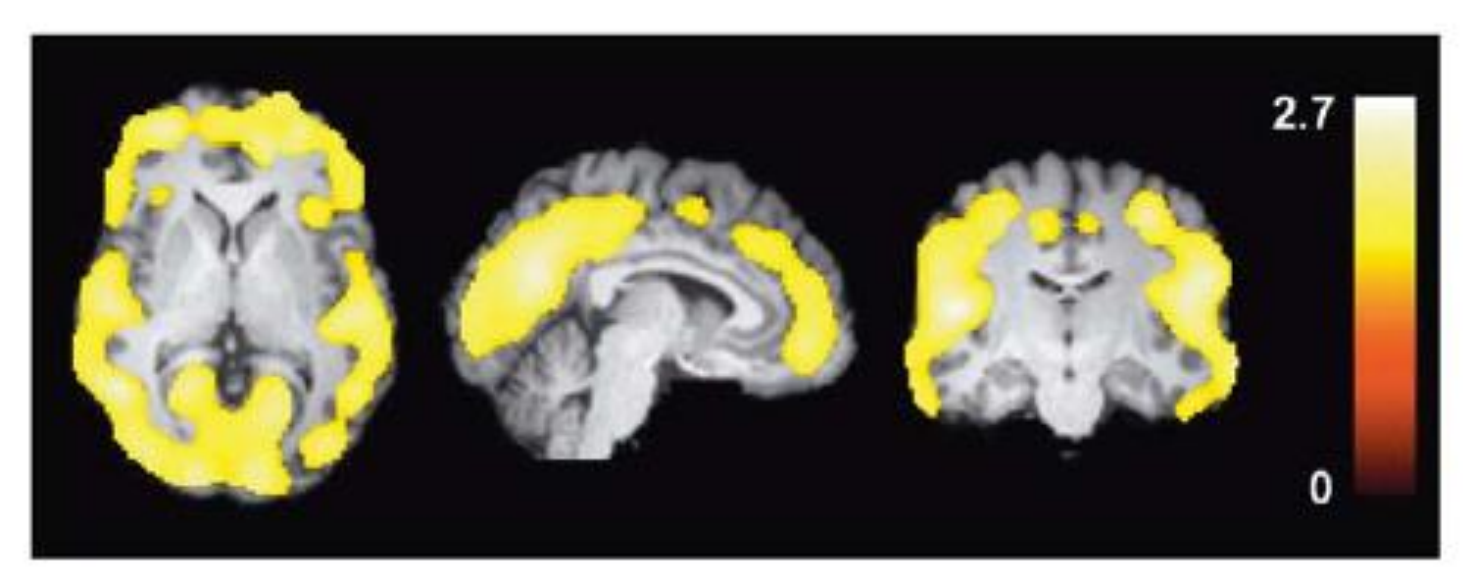
1 injection/day of THC
For 4 days
Breivogel et al., 2003



(Also cf: Sim-Selley, 2003, Critical Reviews in Neurobiology)

CB1 Downregulation in Humans

- Used PET scan to quantify CB1 receptors in 30 regular smokers and 28 controls
- Found about a 20% decrease in receptor density in users
- Subjects who smoked the longest had the most downregulation
- Receptors levels recover with abstinence



Hirvonen et al., 2012 *Molecular Psychiatry;* Also see: *Villares, 2007*

Heavy-smoking teens

- **Altered cortical structure** (Jacobus et al., 2015, Developmental Cognitive Neuroscience; Ganzer et al., 2016, Neuropsychological Review)
- **Downregulation of "pleasure pathway"** (e.g., Ellgren et al., 2007, Neuropsychopharmacology)
- **Increased risk of subsequent heroin addiction and alcoholism** (Ellgren et al., 2007; Panlilio & Justinova, 2018, Neuropsychopharmacology; Stopponi et al., 2014, Eur Neuropsychopharm)
- **Increased "negative emotionality"** (Volkow et al., 2014, PNAS)
- **7X more likely to attempt suicide** (Silins et al., 2014, Lancet)
- **Increased impulsivity** (Aston et al., 2016, Drug & Alcohol Dependence; Ganzer et al., 2016, Neuropsychological Review)
- **60% less likely to graduate high school** (Silins et al., 2014, Lancet)
- **Epigenetics?** (Szutorisz & Hurd, 2018, Neuroscience & Biobehavioral Reviews)

Adaptation (b process) to

Caffeine	→	Hypo-arousal (lethargy)
Alcohol	→	Reduced pleasure, anxiety, insomnia
Benzos	→	Anxiety, insomnia
Ecstasy	→	Depression

The brain adapts to any and every drug that alters its activity by producing the exact opposite state.