Brain and Behaviour – S2

PSYC 304

Announcements

- ***FINAL EXAM – AUGUST 15, 7pm SWING 121 (or Zoom)***
- ***Reading CLUB 4A and 4B – AUGUST 5th (Due the 6th by midnight)***
- ***Don't forget your tweets!***
- ***Midterm 3 grades are out – Avg – 75%***
    - ***Looks like we found the sweet spot!***
    - ***Great work!***
    - ***Midterm 3 review – next Thursday (last 30 minutes of class.***

Learning objectives

1. Summarize the ways in which drugs alter presynaptic processes, with examples.
2. Summarize drug effects on postsynaptic processes, with examples.
3. Define autoreceptors and explain their function, using caffeine as an example.
4. Describe the processes that terminate transmitter action at synapses
5. Summarize the two major types of antipsychotic medications, and review their pharmacological actions.
6. Discuss the major types of actions of drugs for treating depression and anxiety, with examples.
7. Review the discovery of opiates and their major actions in the brain. Using the opiate receptors as examples, discuss the significance of the discovery of orphan receptors in the brain

Neuroactive drugs

Mental disorders

- Neuroscience breakthroughs over the past 70 years – revolutionized psychiatry and freed millions of people from institutionalized care

Antipsychotics:

- class of drugs used to treat schizophrenia.

First-generation antipsychotics:

- selective dopamine D_2 antagonists.

Second-generation antipsychotics:

- dopaminergic activity; block some serotonin receptors.

Neuroactive drugs

Antidepressants

- treat depression.
- Monoamine oxidase (MAO) inhibitors prevent breakdown of monoamines at the synapses.
- Accumulating monoamines and prolonging their activity is a major feature of antidepressants.

Neuroactive drugs

Tricyclic antidepressants

- increase norepinephrine and serotonin at synapses by blocking their reuptake.

Selective serotonin reuptake inhibitors (SSRIs)

- like Prozac or Zoloft allow serotonin to accumulate in synapses, with fewer side effects than tricyclics.

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

- additionally inhibit reuptake of norepinephrine.

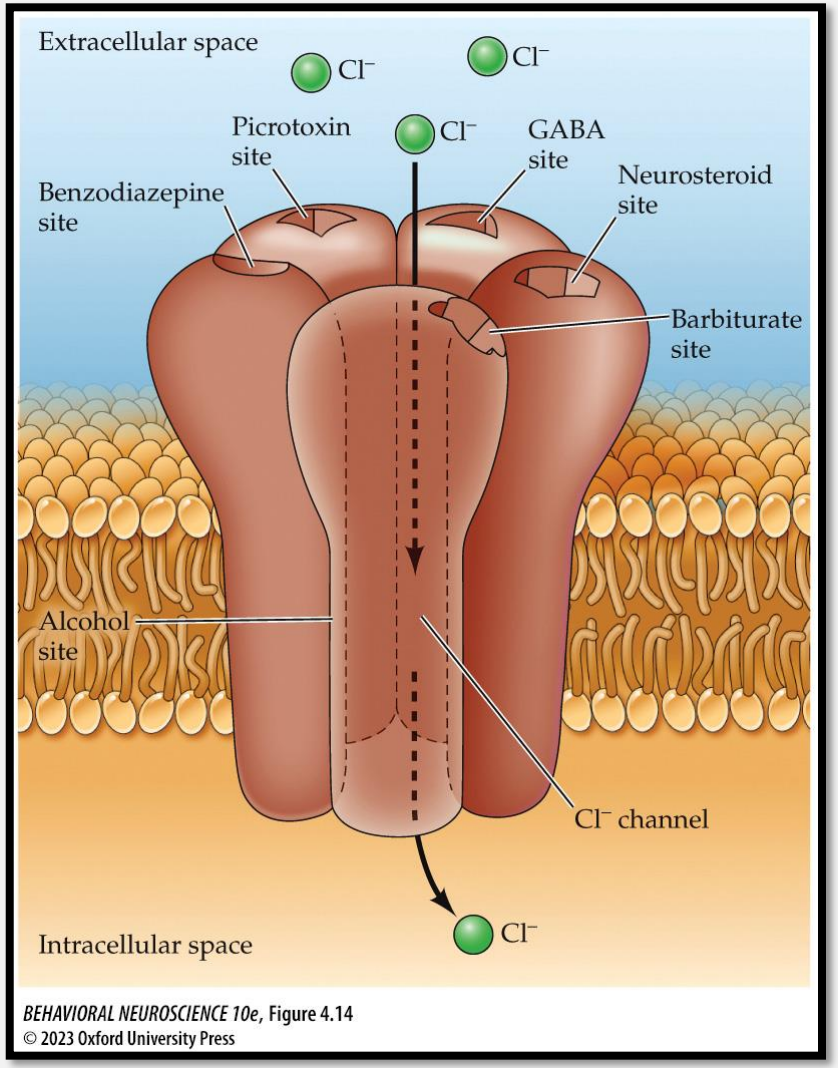
Neuroactive drugs

Depressants

- drugs that reduce nervous system activity.
- **Anxiolytics** (tranquilizers)
- **Barbiturates –** originally developed to reduce anxiety, promote sleep and prevent seizures (but are addictive and easily overdosed)
- **Benzodiazepine agonists** act on $GABA_A$ receptors and enhance the inhibitory effects of GABA (more specific and safer than barbiturates)
- *Alprazolam (Xanax) and Lorazepam (Ativan)*

Neuroactive drugs

- GABA receptors have several binding sites that enhance or inhibit GABA's effects.
- Benzodiazepines bind at an **orphan receptor**—no known endogenous ligand.
- **Allopregnanolone** acts on a different $GABA_A$ receptor; is elevated during stress and is calming.
- Other **neuro-steroids** may act on $GABA_A$ sites.

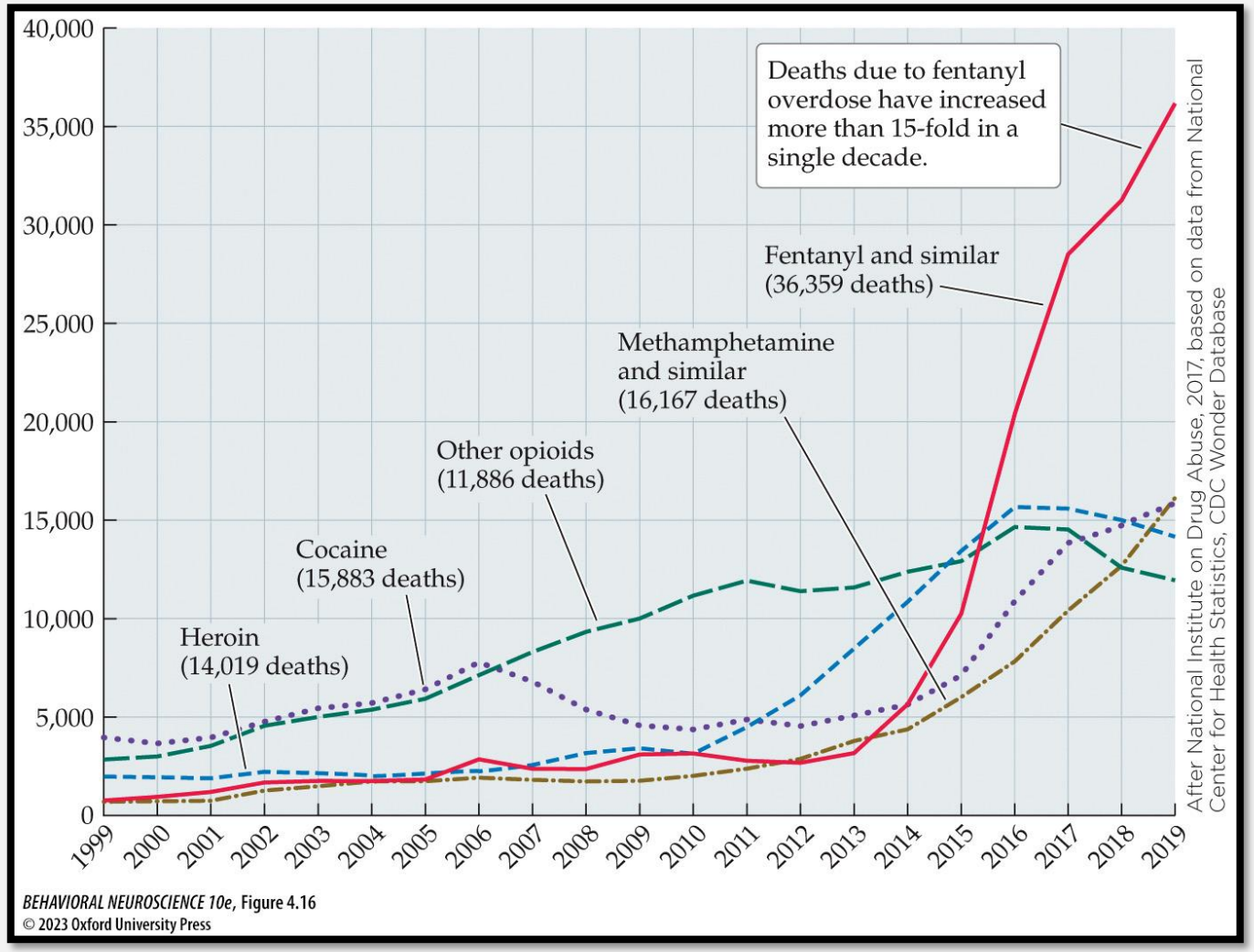


BEHAVIORAL NEUROSCIENCE 10e, Figure 4.14

Neuroactive drugs

Opiates

- **Opium** (from poppy seedpods) contains **morphine**, an **analgesic** (painkiller).
- Morphine, **heroin**, oxycodone (OxyContin) and fentanyl are all highly addictive.
- Accidental fentanyl overdose is a growing epidemic.



Neuroactive drugs

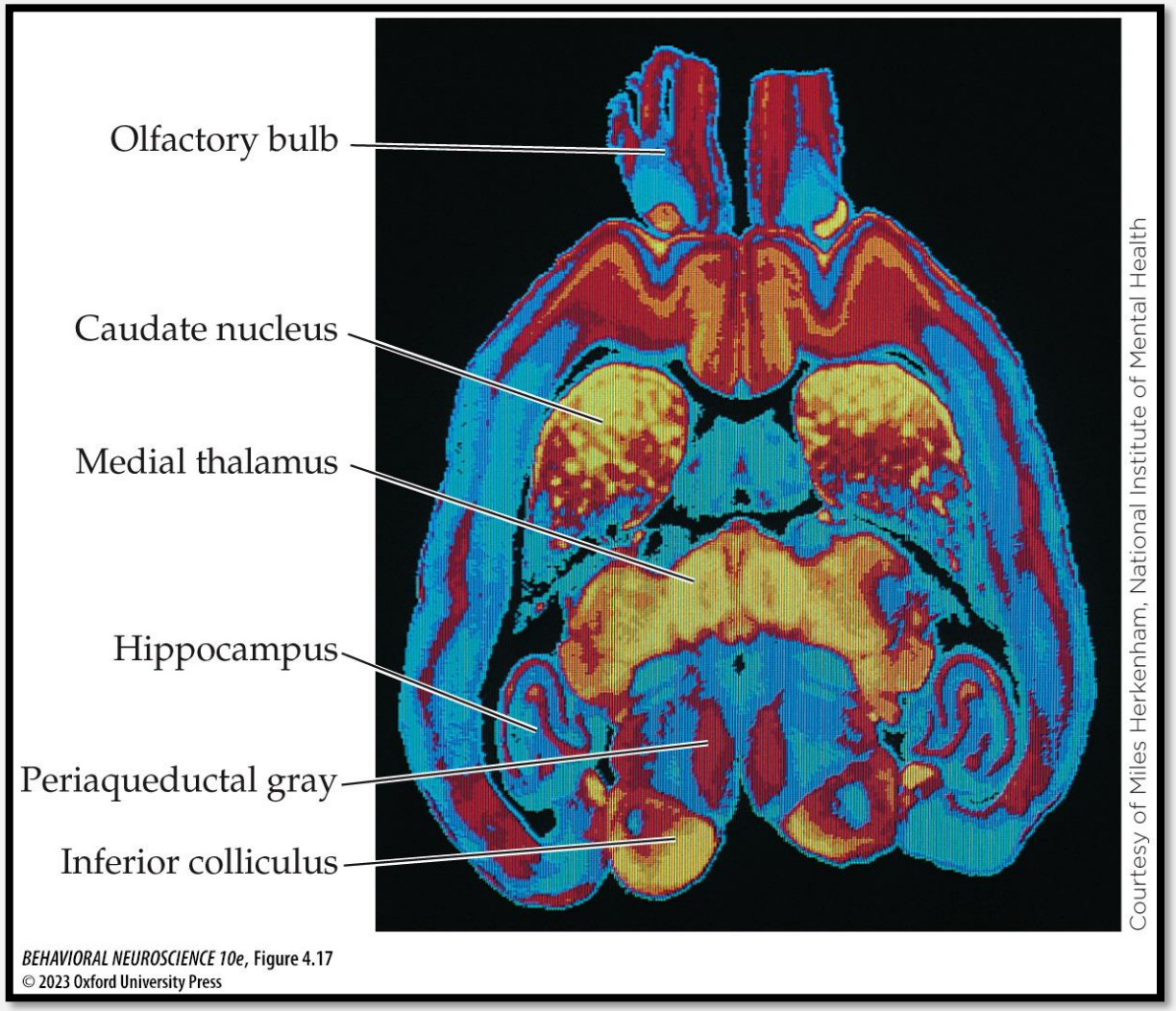
Opiates

- bind to **opioid receptors** in the brain, especially the locus coeruleus and the **periaqueductal gray**.

Endogenous opioids

- peptides produced in the body that bind to opioid receptors:

- **Enkephalins**
- **Endorphins**
- **Dynorphins**



Neuroactive drugs

Opioids

- 3 main kinds of receptors – all metabotropic
- Antagonists – Naloxone (Narcan), naltrexone – rapidly reverse effects of opiates, rescue people from overdose
- Also blocks rewarding aspects of drugs – helpful to treat addiction
- Naltrexone – approved treatment of alcohol use disorder – blocks the euphoria from alcohol – suggests that alcohol mediates the release of endogenous opioids, which brings pleasure

Break

Learning objectives

1. Identify the main active ingredients in cannabis, their sites of action in the brain, and their roles in behavioral processes.
2. Compare and contrast the main families of stimulant drugs, and explain how they interact with neurons, their major effects, and risks they pose to human health.
3. Review the modes of action of alcohol in the brain.
4. Discuss the prevalence of alcohol use disorders, negative effects on the brain, and changes in the brain in people recovering from severe alcohol use disorder.
5. Define psychedelic drugs, and highlight the ways in which the major psychedelics have different or shared actions in the brain
6. Provide a formal definition of substance abuse, and distinguish between mild, moderate, and severe forms.
7. Summarize the major theoretical models of substance abuse.
8. Describe some individual differences that affect susceptibility to addiction.
9. Review leading categories of treatments for addiction, briefly explaining the logic of each

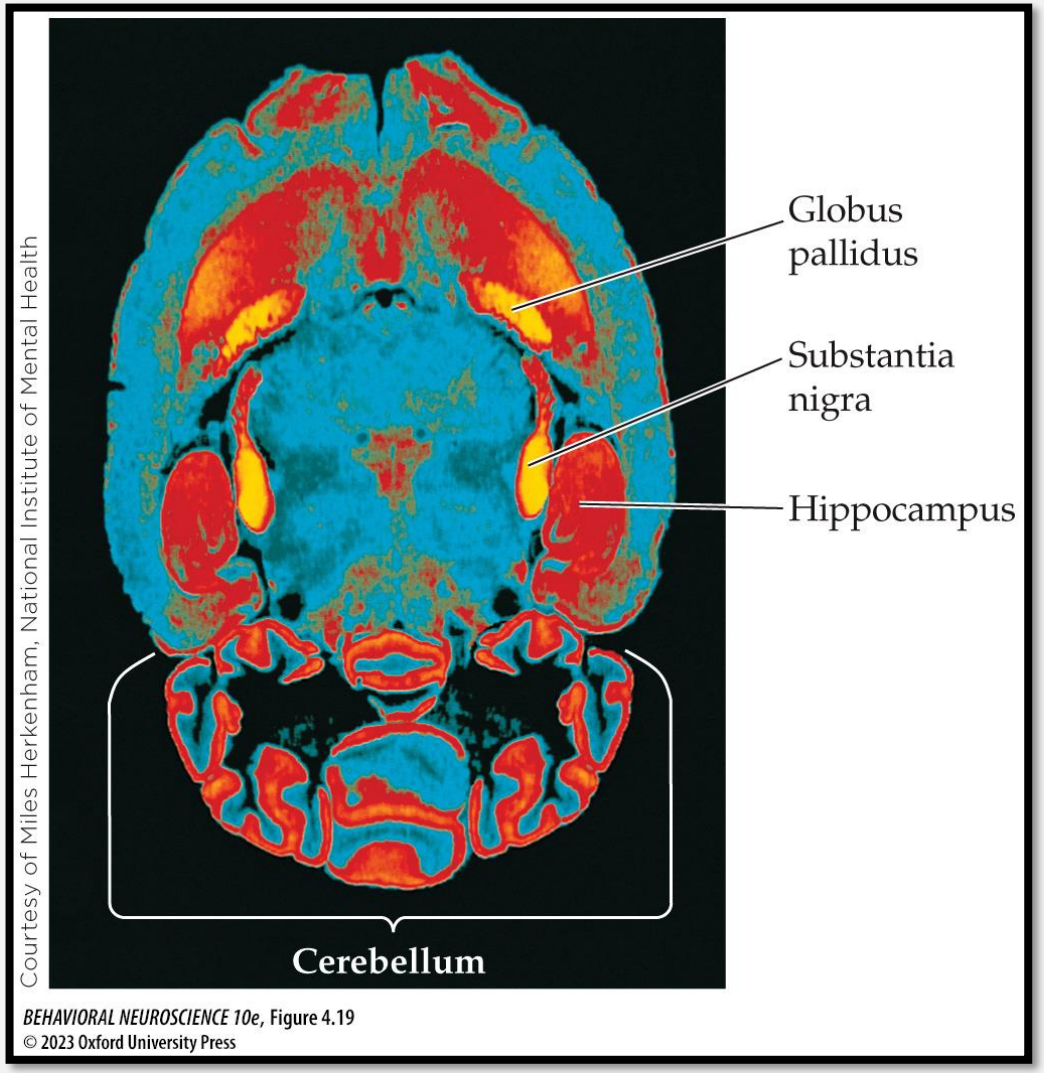
Consciousness altering drugs

Cannabis

- is derived from *Cannabis sativa.*

Active ingredients include:

- **9-tetrahydrocannabinol** (**THC**) produces the psychoactive effect
- **Cannabidiol** (**CBD**)
  - Cannabinoid receptors in the brain are concentrated in the substantia nigra, hippocampus, cerebellar cortex, and cerebral cortex.



Consciousness altering drugs

- Two kinds of cannabinoid receptors (both are G protein-coupled metabotropic receptors):
- Endogenous endocannabinoid: anandamide.

CB_1 receptors

- are only found in the CNS; mediate the rewarding properties of cannabinoids.
- Activation – reduce NT release from the presynaptic neuron (works in retrograde fashion.

CB_2 receptors

- are prominent in the immune system and periphery
- Activation – modulates nociceptive signaling (reduction of pain), regulates inflammation (reduces cytokine release, reduces immune cell migration and activation) which can help with nausea.

Consciousness altering drugs

Stimulants

- increase nervous system activity.

Nicotine:

- acts as an agonist on nicotinic ACh receptors; increases heart rate, blood pressure, and intestinal activity; highly addictive

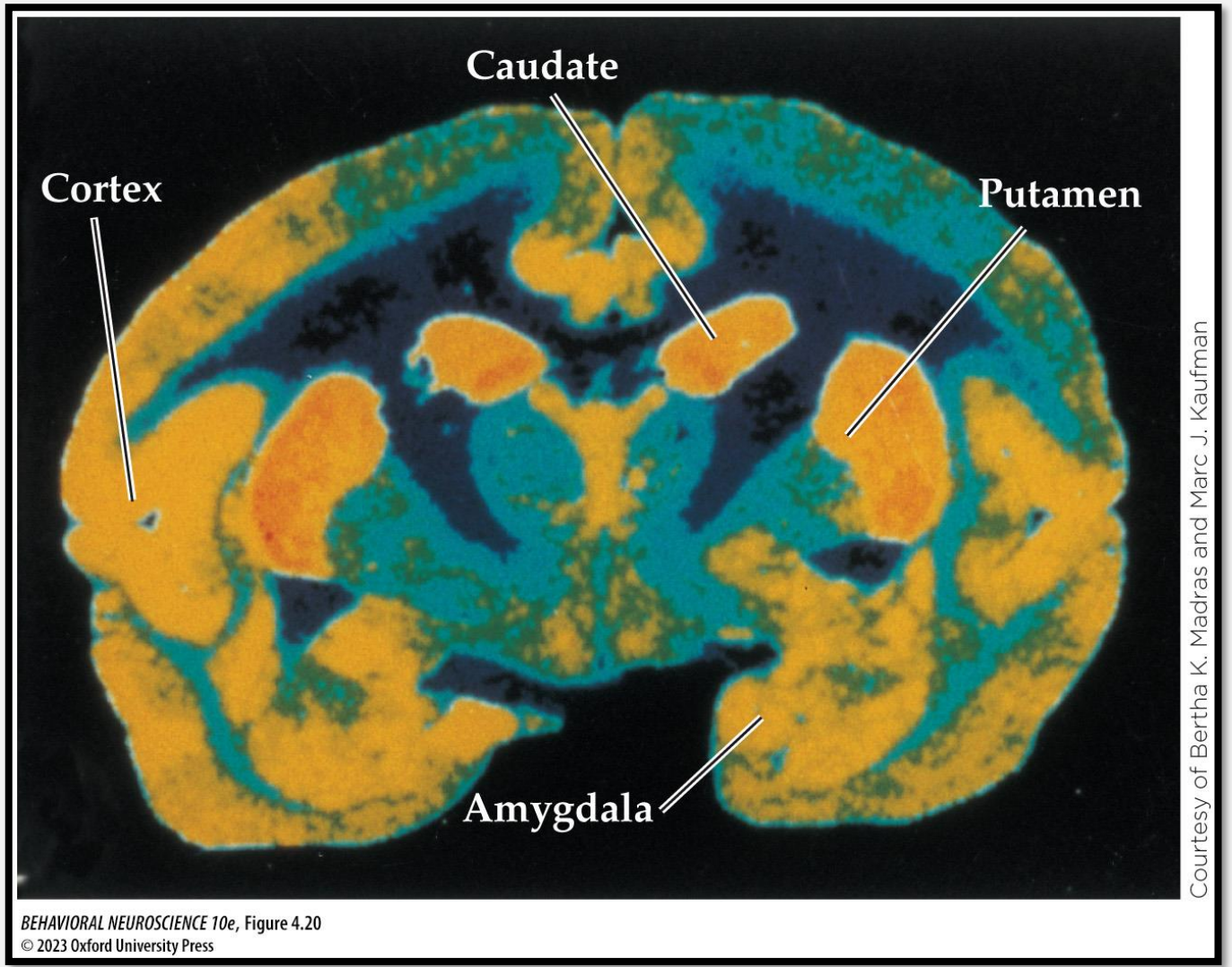
Cocaine:

- purified extract from the coca shrub; blocks monoamine transporters, especially for DA, slowing reuptake.
- *Crack* cocaine is smoked and enters the brain more rapidly.

Consciousness altering drugs

Cocaine:

- Binding sites in the monkey brain



BEHAVIORAL NEUROSCIENCE 10e, Figure 4.20

Consciousness altering drugs

Tolerance and sensitization to cocaine

- **Early –** tolerance via downregulation of dopamine receptors (following overstimulation of the dopamine system
- **Following chronic use –** the brain becomes more responsive to the drugs effects, especially in the reward pathway.
    - **How could a drug cause tolerance and sensitization??**

Consciousness altering drugs

Amphetamine and methamphetamine:

- synthetic; resemble catecholamine transmitters, boost their effects:

1. Induce release of these transmitters even in the absence of action potentials
2. Potentiate release in the presence of action potentials.
3. block reuptake
4. Inhibit breakdown of the transmitters

Consciousness altering drugs

Short-term effects of amphetamines

- include alertness, euphoria, and stamina.

Long-term use

- leads to sleeplessness, weight loss, and general deterioration of mental and physical condition.
- Prolonged use may lead to symptoms that resemble those of paranoid schizophrenia: compulsive, agitated behavior and irrational suspiciousness.

Consciousness altering drugs

Alcohol

- effects are biphasic—an initial stimulant phase followed by a depressant phase.

Alcohol activates $GABA_A$ receptors

- At low concentrations ethanol activates specific subunits of GABAA receptors
- Leads to release of **dopamine** in the mesolimbic pathway – stimulant and euphoric effects of alcohol
- At larger concentrations, alcohol increases inhibitory effects; contributes to social disinhibition and loss of motor coordination.

Alcohol at 2 doses

Low doses

- Binds GABAa receptors of interneurons which typically provide inhibition to the VTA and block release of dopamine to the nucleus accumbens (mesolimbocortical pathway) – This system is tightly controlled and therefore sensitive to small changes
- These interneurons have GABA A receptors with highly ethanol sensitive subunits
- This inhibition of the inhibitory interneurons leads to disinhibition of the dopamine system and the feeling associated with **stimulants** – slight euphoria, giddiness, more talkativeness, more sociable

Alcohol at 2 doses

High doses

- More widespread inhibitory effects (against a more robust arousal network)
- GABA A enhancement inhibits
    - pre-frontal cortex – reduced executive function
    - cerebellum (reduced balance and coordination)
    - Strong cortical inhibition – sedation/drowsiness
- NMDA inhibition (non-competitive antagonist) at higher doses
    - Memory impairment – no LTP!
    - Cognitive slowing – prefrontal cortex
    - Motor impairment – reduced excitation to motor systems

Consciousness altering drugs

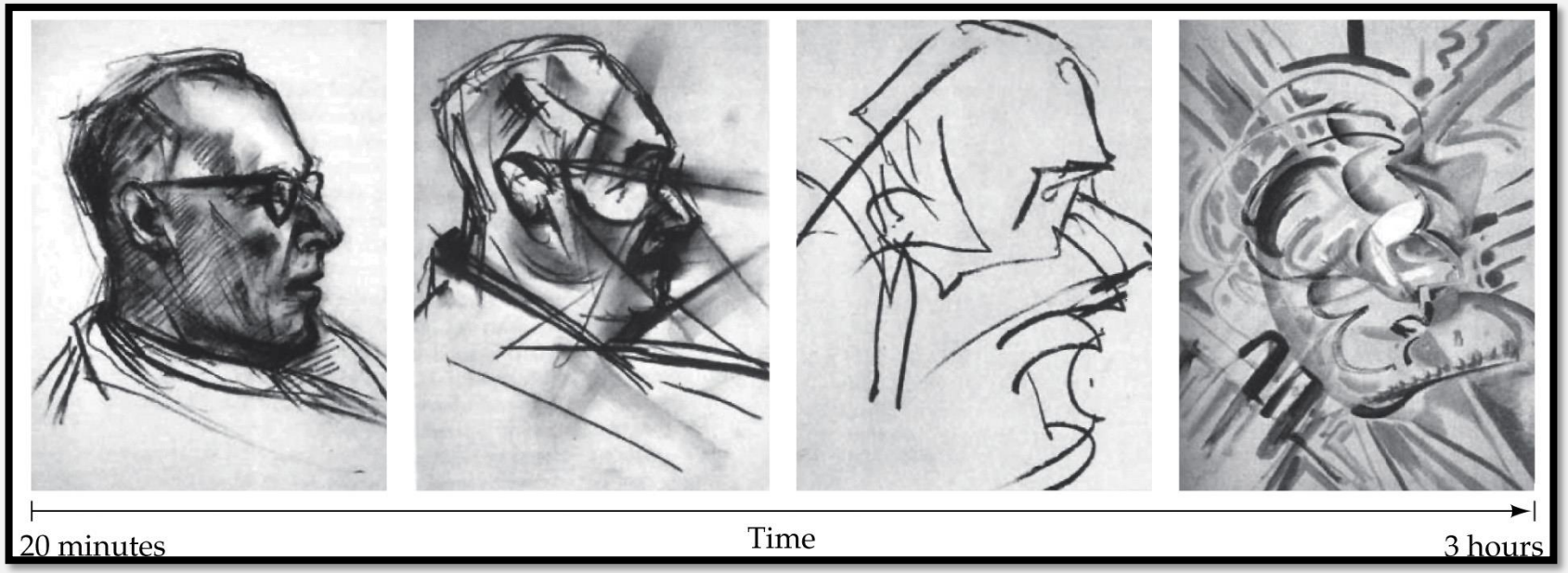
Hallucinogens

- Alter sensory perception and produce peculiar experiences.
- **LSD** *(acid)*, mescaline (*peyote*), and psilocybin *(magic mushrooms)* have mainly visual effects.

Consciousness altering drugs

Hallucinogens

- have diverse actions, including on the noradrenergic (mescaline), serotonergic (mescaline, psilocybin, and LSD), Ach (muscarine), and opiate (*Salvia*) systems.
- LSD acts as a serotonin agonist or partial agonist, especially on 5-HT_{2A} receptors, found in high concentrations in the visual cortex.



Functional classes of drugs

Dissociative drugs

- produce feelings of depersonalization and detachment from reality in moderate doses.

Ketamine *(Special K)*

- blocks NMDA receptors in the prefrontal cortex.
- High doses produce transient hallucinogenic effects and psychotic symptoms

Functional classes of drugs

MDMA (*Ecstasy*):

- hallucinogenic amphetamine derivative; increases serotonin levels and changes dopamine and oxytocin levels.
- Effects are positive emotions, empathy, sense of well-being, colorful visual phenomena.
- Chronic use causes depression and memory disturbances and alters structure and function of serotonergic neurons.

Substance Abuse and Addiction

Substance abuse and addiction

- afflicts millions of people and disrupts the lives of families, friends, and associates.
- **Social costs** include expenses for medical and social services, lost work hours, increase crime associated with illicit drugs, children damaged by parents' substance abuse behavior.

Substance Abuse and Addiction

Addiction

- is defined as substance use disorder (SUD) in the *DSM-5*.
- Criteria for diagnosis is the same for all substances, including alcohol, opioids, stimulants, tobacco, cannabis, hallucinogens, etc.

Models of drug abuse

Moral Model:

- abuse is due to failure of moral character or lack of self control.
- Little evidence that morality-based programs affect abuse rates.

Disease Model:

- addiction is considered to be a disease that requires medical treatment.
- But there is no evidence of physical or biochemical abnormalities.

Substance Abuse and Addiction

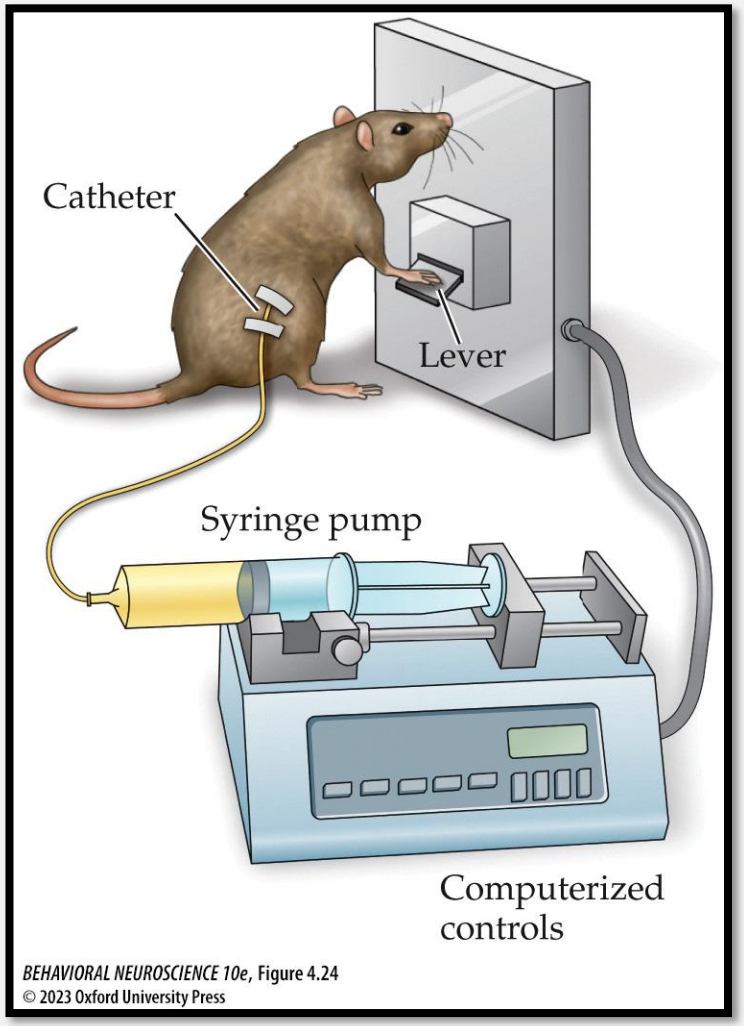
Physical Dependence Model:

- abusers continue to use drugs to avoid withdrawal symptoms.
- But some people become addicted before physical dependence develops
- some addictive drugs such as cocaine don’t produce withdrawal symptoms.

Substance Abuse and Addiction

Positive Reward Model vs. Physical dependence model:

- drug abuse and addiction are due to powerful reinforcement.
- Self-administration experiments using animals shows that addiction can occur in the absence of physical dependence or withdrawal symptoms.
- Self administration of morphine (so there is no physical dependence)
- Cocaine – do not produce market withdrawal symptoms compared to morphine lead to record setting levels of lever pressing.



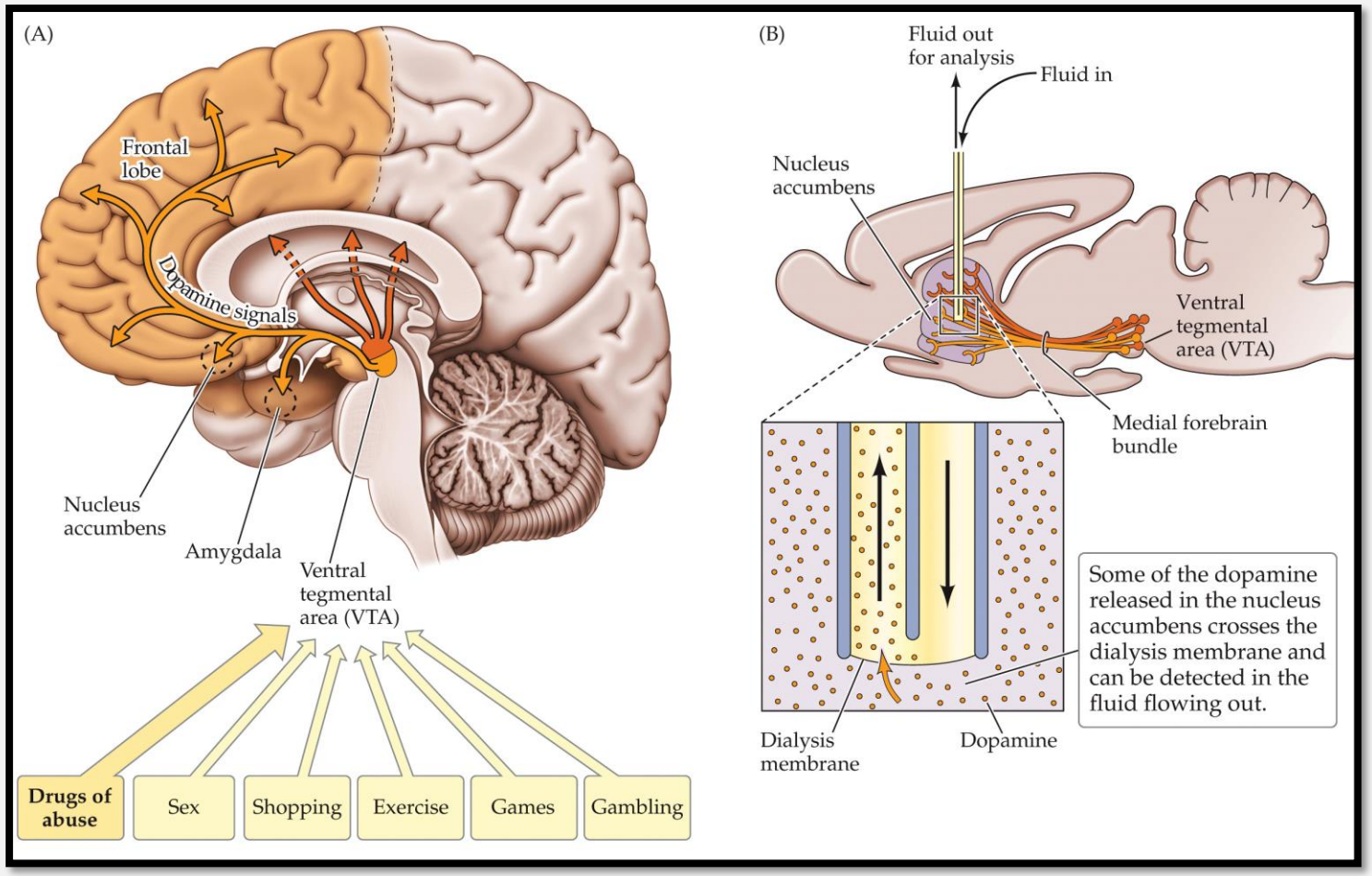
Substance Abuse and Addiction

Dopamine

- Many addictive drugs cause dopamine release in the **nucleus accumbens**.
- Some axons that terminate here originate in the ventral tegmental area (VTA) and are involved in the reward pathway.
- The addictive power of drugs may come from stimulating this pathway.

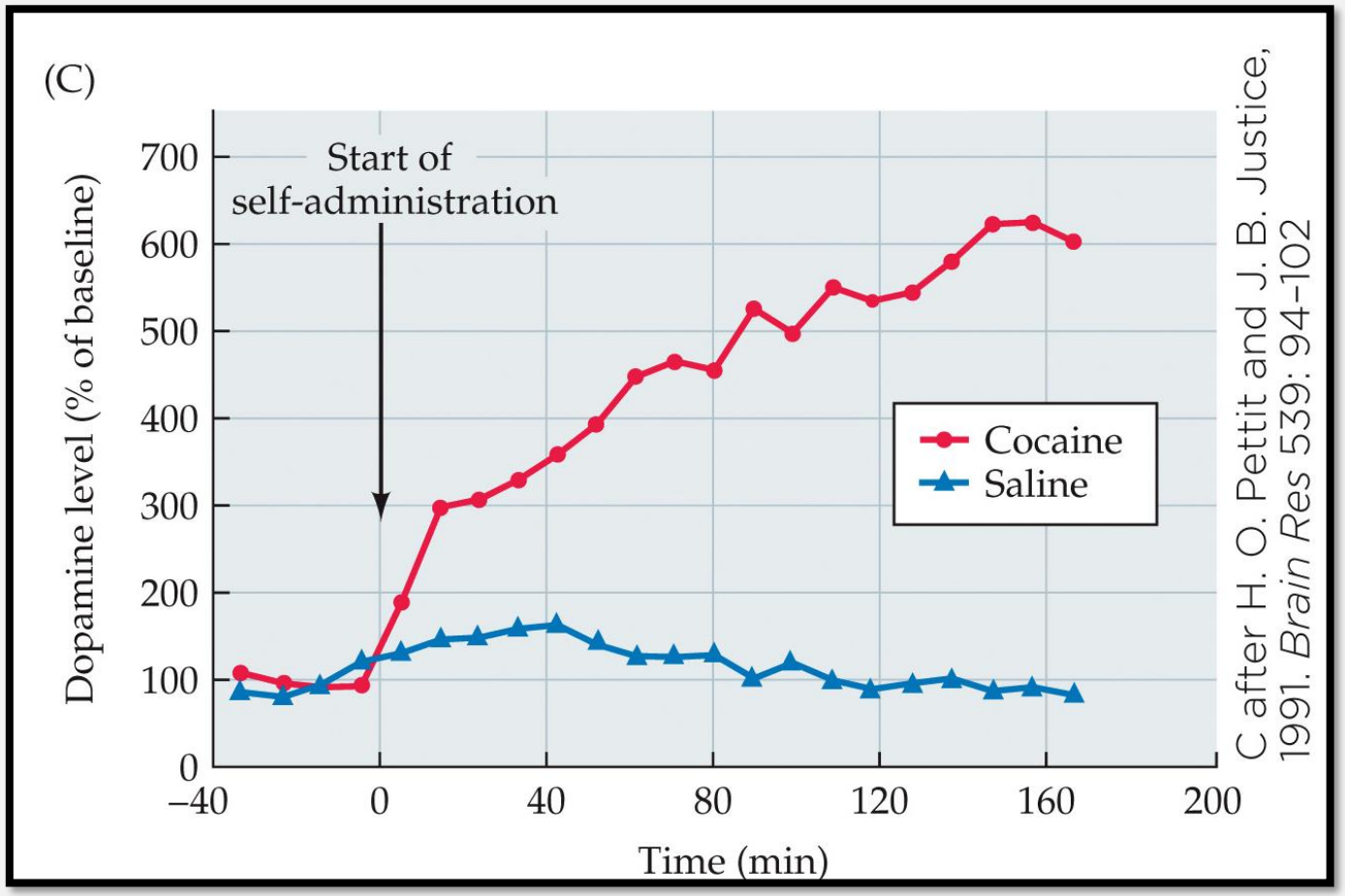
Substance Abuse and Addiction

Mesolimbic reward pathway



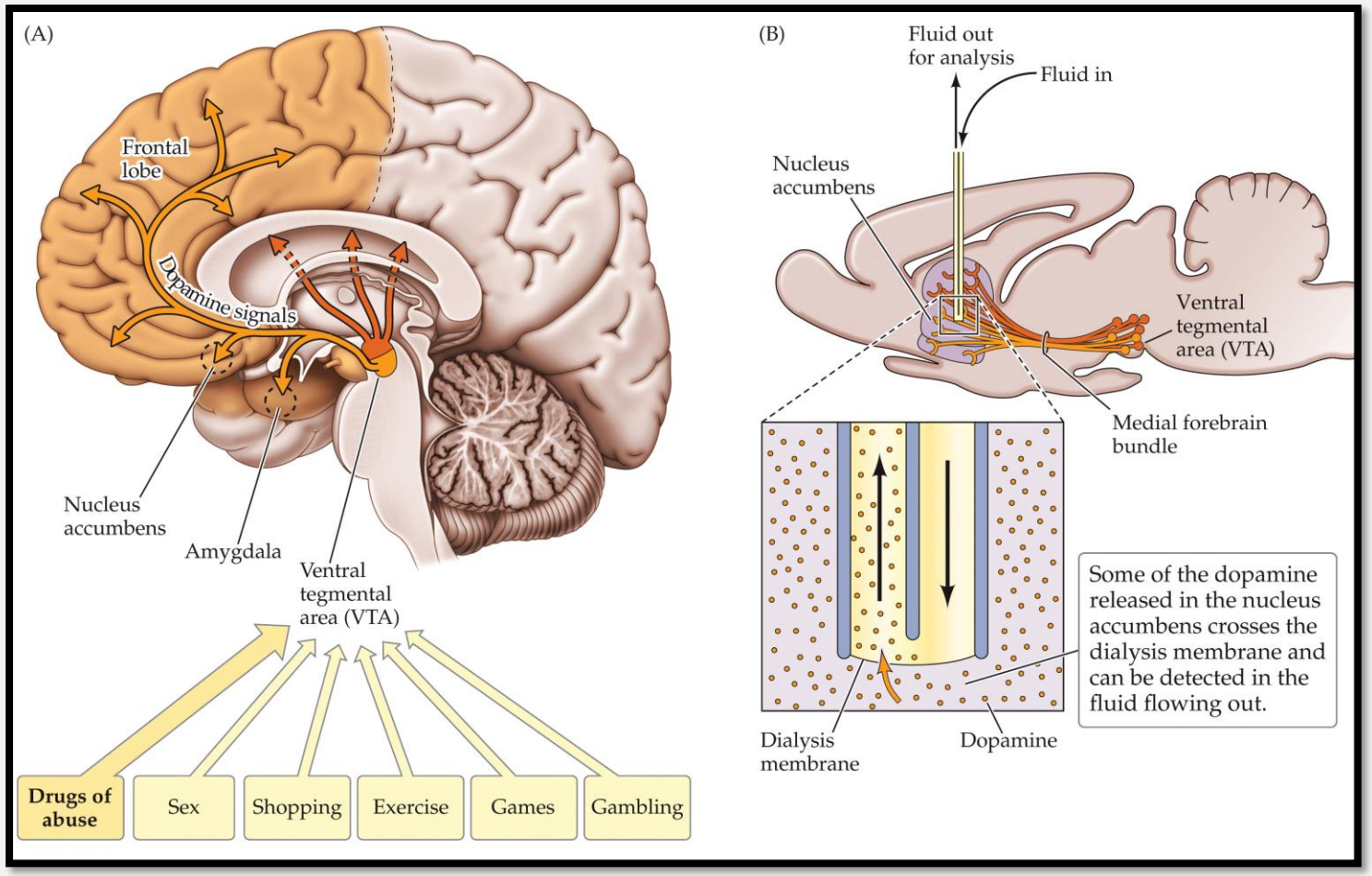
Substance Abuse and Addiction

Mesolimbic reward pathway



Substance Abuse and Addiction

Mesolimbic reward pathway



Time for reading club!

Test of sufficiency

Mesolimbic Dopamine Neuron Stimulation and the Progression to Addiction

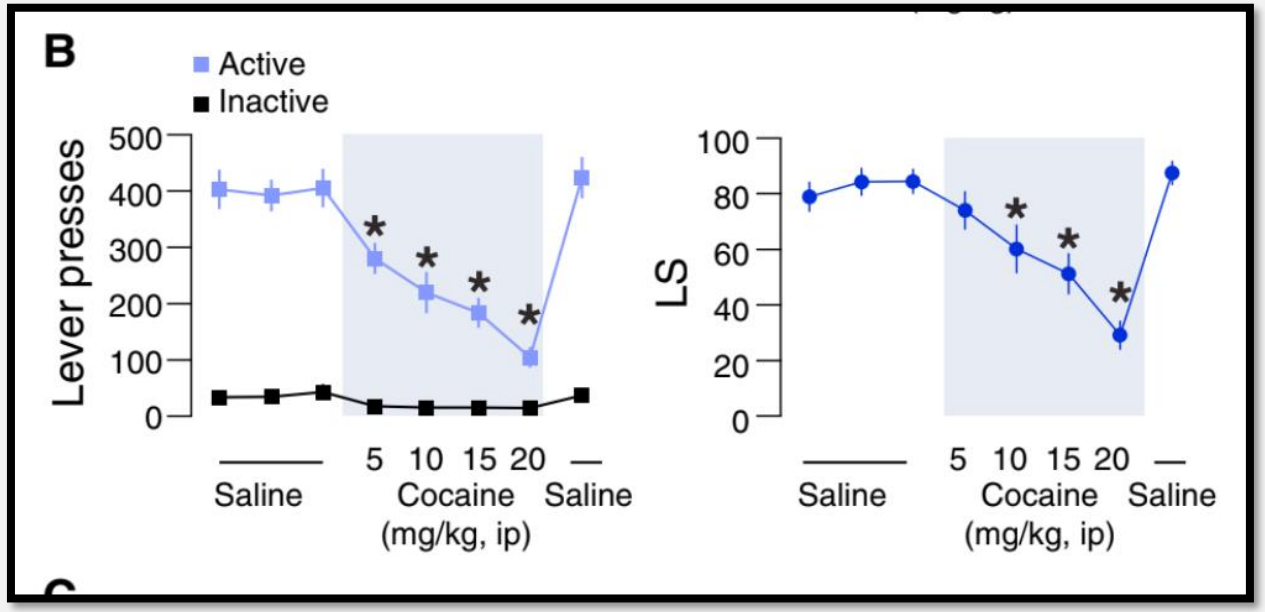
Pascoli et al., 2015

- **Research question:** Is artificial activation of the DA pathway sufficient in reinforcing "drug taking" behaviour and can this lead to addiction?
- Investigated whether DA neuron self-stimulation can induce two addictive-related behaviors—cue-associated reward seeking and compulsivity associated consumption despite negative consequences
- **Methods:**
- *Optogenetics* – laser induced activation of the DA pathway via lever press
- *12 days of lever presses* – 2 hours to get 80 laser stimulations
    - Laser stim follows a 5 second delay to lever press and occurs during a flashing cue light that lasts for 10 seconds
    - In the first few days the frequency of lever presses increased such that all 80 stimulations were complete in the first hour

Mesolimbic Dopamine Neuron Stimulation and the Progression to Addiction

Same pathway as addictive drugs?

- Baseline – trained animal will make 400 presses for 85 laser stimulations in 45 minutes
- With some cocaine administration – dose dependent performance decreases to 100 presses for 30 light stimulations (at highest dose)



Mesolimbic Dopamine Neuron Stimulation and the Progression to Addiction

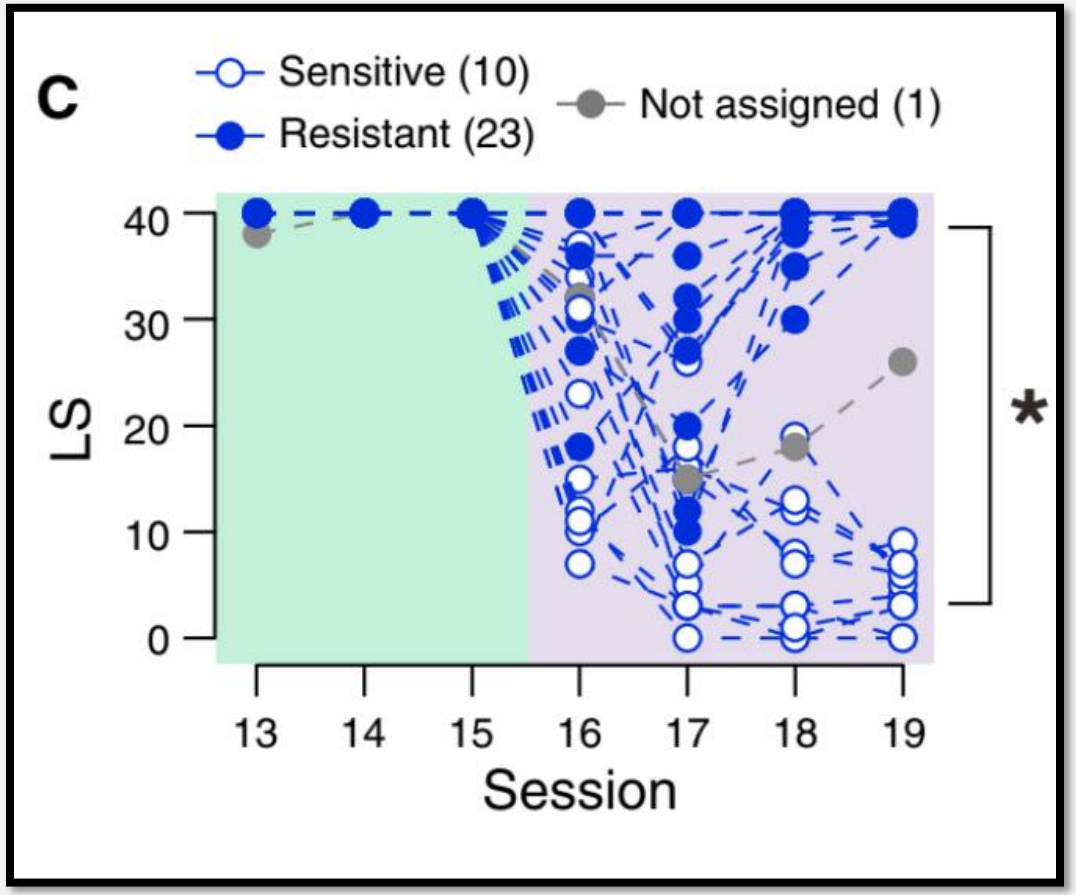
Relapse behaviour?

- 30 days after training – return to operant box
- Pressing the leaver – activates the cue light, but not the laser
- High rate of lever pressing in the experimental group of mice!
- Synaptic plasticity resistant to change in response to cue induced activation of the pathway following withdrawal.

Mesolimbic Dopamine Neuron Stimulation and the Progression to Addiction

Behaviour resistance to punishment?

- Give a foot shock every three lever presses
- 2 groups emerged
- *Sensitive* – punishment – reduced behaviour
- *Resistant* – punishment did not significantly reduce behaviour
- Individual differences in addictive behavours



The addicted brain

Substance Abuse and Addiction

Many factors figure in an individual's susceptibility to addiction:

- Biological—sex, genetic predisposition
- Family situation—family breakup, poor relationships, sibling drug users
- Personal characteristics—aggressiveness, emotional control
- Environmental factors—peer pressure, social factors

Substance Abuse and Addiction

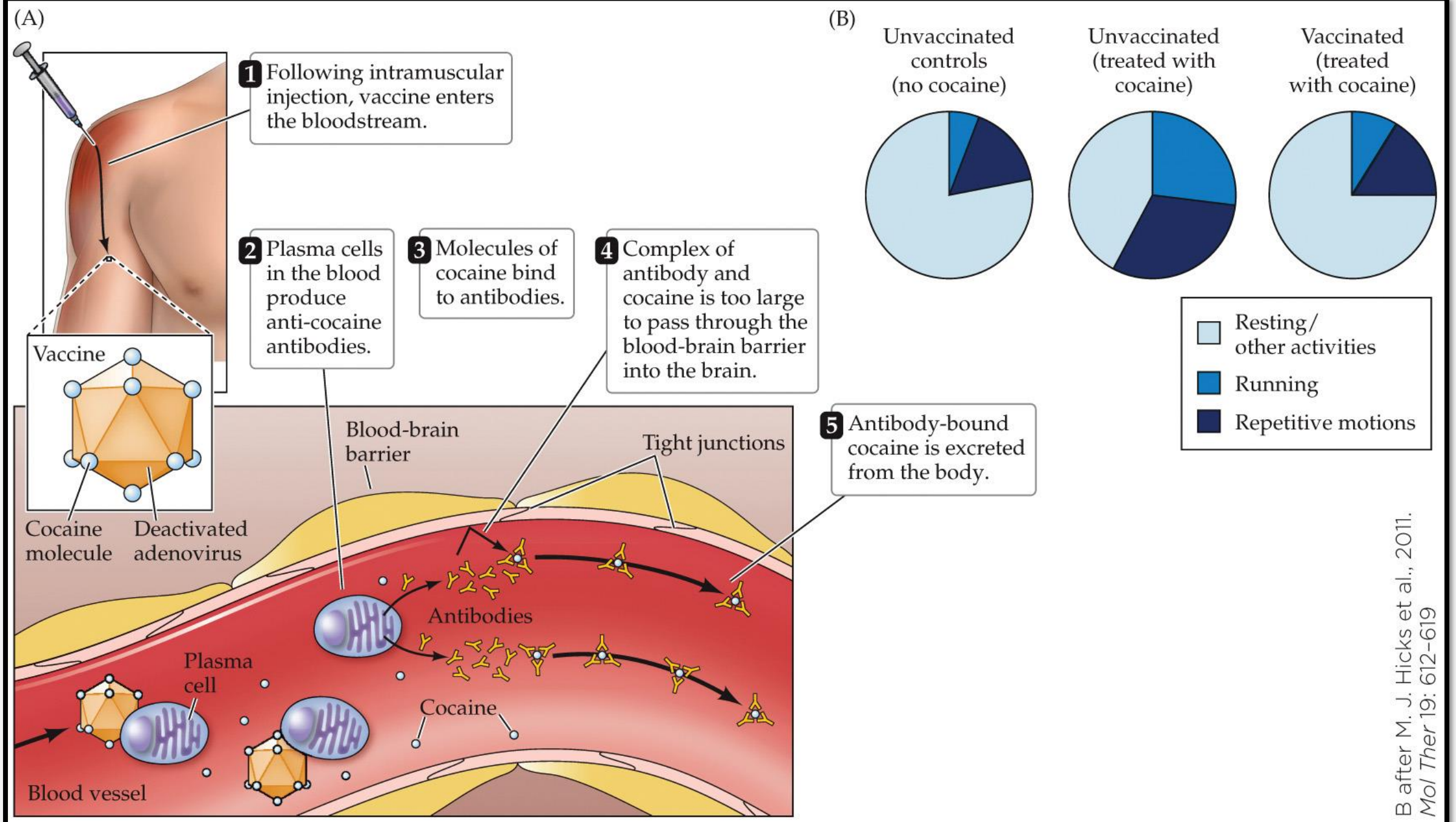
Cue-induced drug use (coming up in reading club)

- Environmental stimuli can become associated with the effects of drugs.
- increased likelihood of using a drug because factors are present that were also present when the drug was last used.

Substance Abuse and Addiction

Medications to treat drug abuse:

- Lessen the discomfort of withdrawal and drug craving
- Provide alternatives to the addictive drug
- Block action of the addictive drug
- Alter metabolism of the drug
- Block brain's reward system
- Vaccines may be effective in reducing the drug's reward and preventing addiction.



BEHAVIORAL NEUROSCIENCE 10e, Figure 4.27

End