Reading Today 3.3

Main points

1. Drugs alter function of endogenous chemical systems

2. Drugs of abuse induce long and short-term effects

3.Addiction may reflect sensitization of drug "wanting"

Study questions:

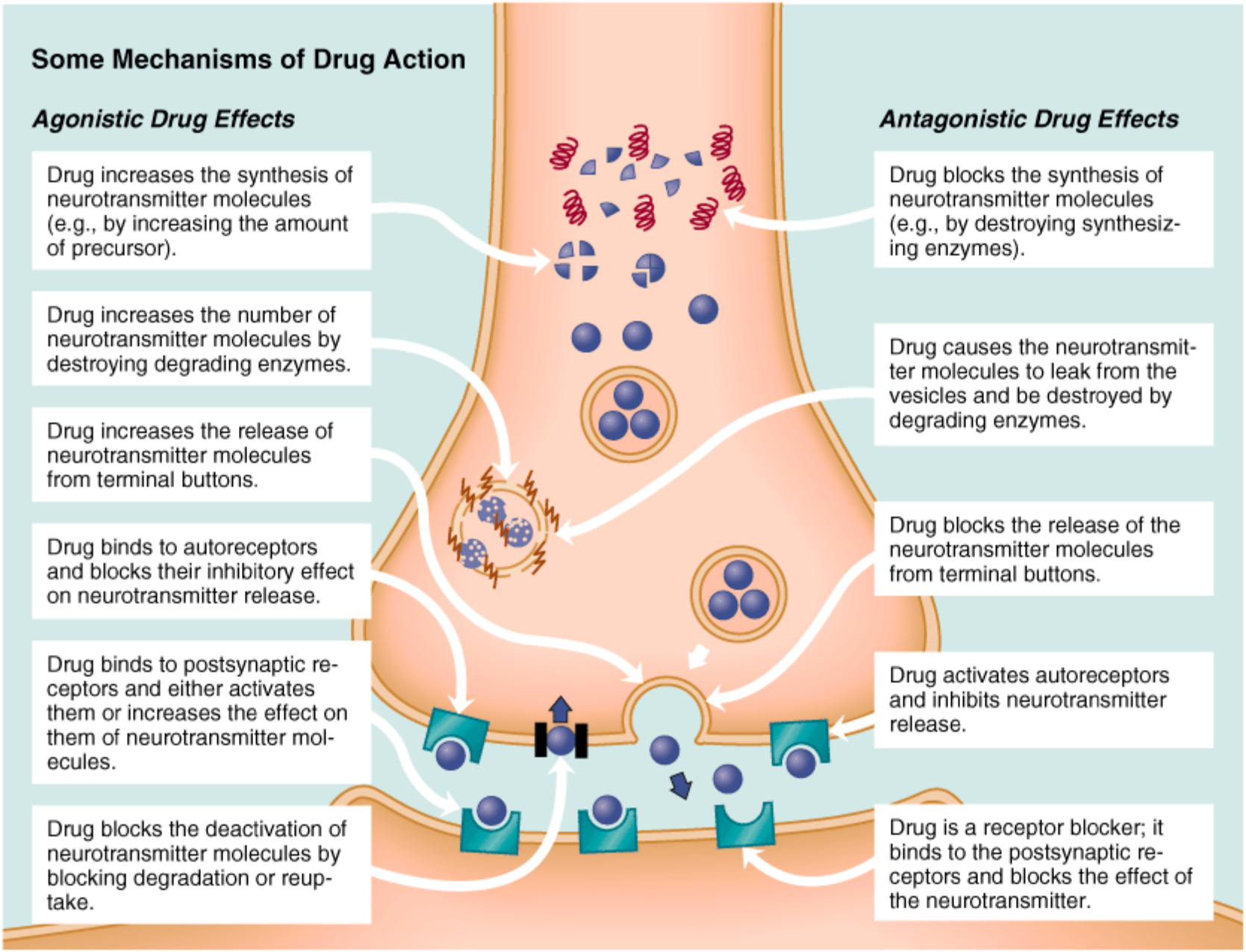
1.How does the study of heroin addicts support the idea that drugs simultaneously affect multiple brain systems that underlie our feelings and behavior?

2.What factors affect how much a person responds to a given amount of a drug on any one occasion?

Quiz Wednesday

- First 30-40 minutes of class
- No make-ups
- 20-25 multiple choice questions
- Material through today's lectures
- Heavy focus on understanding of vocabulary lists on website
- Study questions on midterm – NOT ON QUIZ

▶ Mechanisms of Drug Effects



Presynaptic Agonists

1. Stimulate release
   a. L-Dopa is DA precursor; Parkinson's disease
      DA does not go through BBB, L-Dopa does

   b. Amphetamine releases DA, NE

2. Prolong NT
   a. AChE inhibitors/myasthenia gravis

   b. Cocaine blocks reuptake of DA, NE

   c. Prozac (fluoxetine) blocks reuptake of 5-HT

Postsynaptic Agonists

1. Mimic NT
   a. Apomorphine*** activates postsynaptic D2 receptors

   b. Nicotine attaches to ACh R and has same effect

   c. heroin stimulates mu R for analgesia, euphoria

2. Facilitate receptor binding
   Benzodiazepines (Valium, Librium)

   Bind to site on GABA receptors

Presynaptic Antagonists

1. Suppress release/storage of NT

    a. botulinum toxin inhibits ACh release

    b. autoreceptors (stimulation can prevent release)
    e.g. apomorphine***
        D2 agonist (stimulates DA release)
        More selective for pre-synaptic than post-synaptic

Postsynaptic Antagonists

1. Block receptors and prevent ion channels from opening

   Epileptogenic drugs (bicuculline, picrotoxin) block site on GABA R

   Anti-narcotic drugs (naloxone) block opiate receptors
   prevent opiate overdose

   Curare blocks ACh receptors

Self test question

A drug that caused neurons to release DA would be considered a …

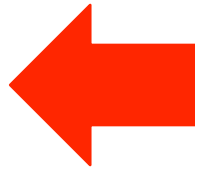
A. Presynaptic agonist

B. Presynaptic antagonist

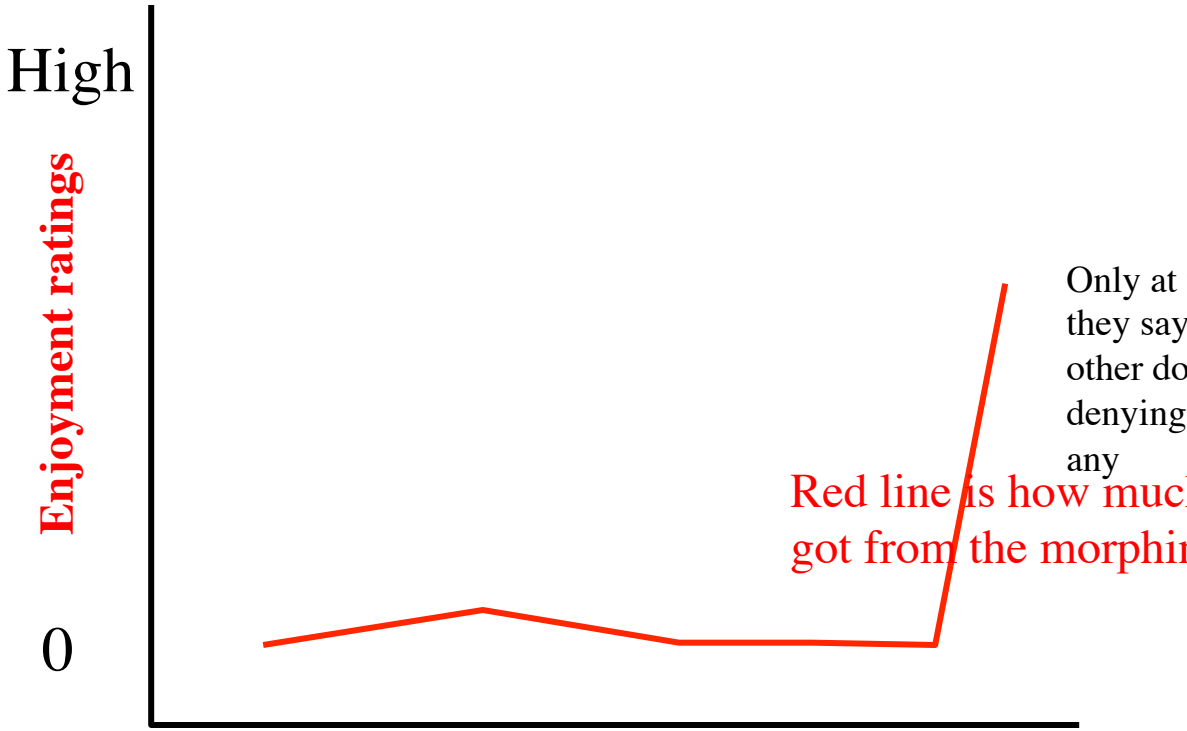
C. Postsynaptic agonist

D. Postsynaptic antagonist

E. I don't know

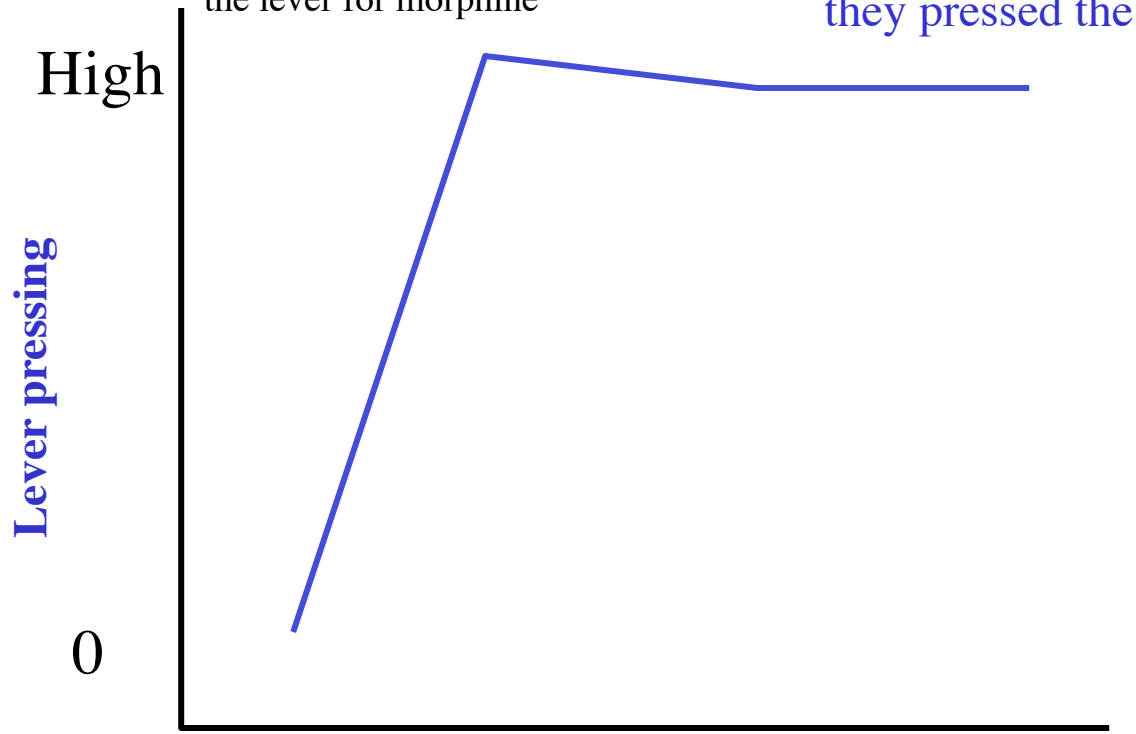


5 men with past daily i.v. heroin use; not currently dependent
If pressed lever 3000 times, would get an injection of 0-30 mg morphine



Even at the lowest doses (but not at 0 where there really is no morphine), they rapidly press the lever for morphine

Blue line is how many times they pressed the morphine lever



In this condition, lever gave placebo

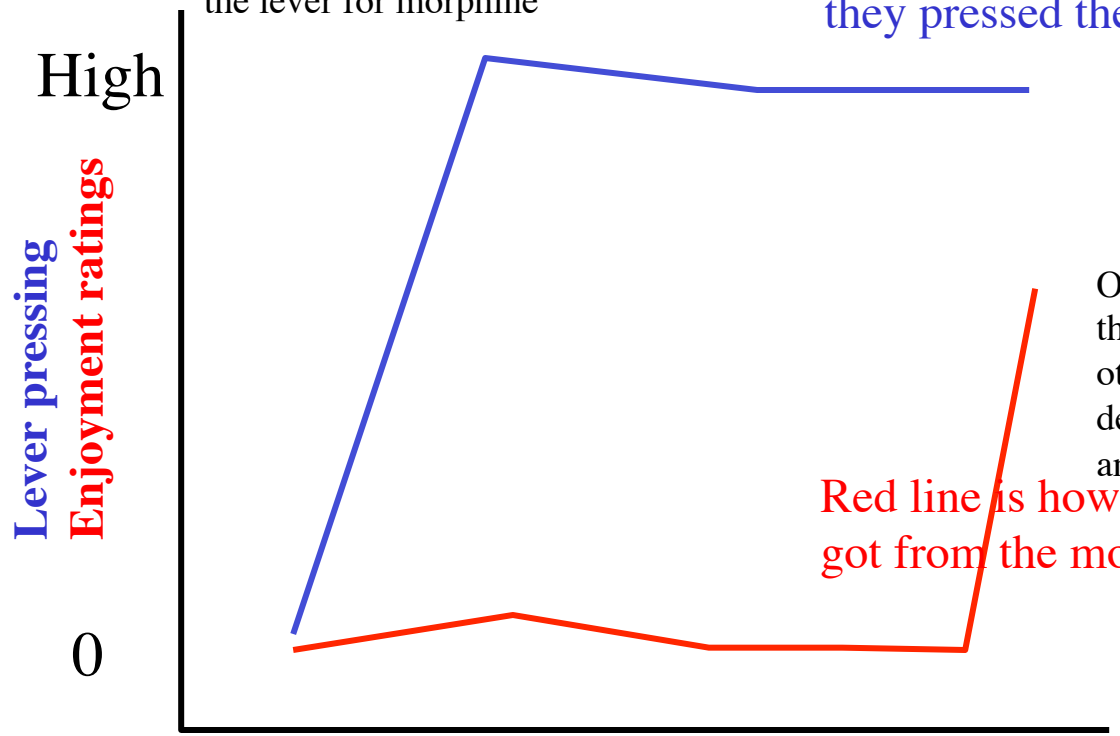
In this condition, lever gave very low doses of morphine. The red line indicates how much addicts reported liking what they received

Slightly higher dose of morphine given

Higher dose of morphine given

Even at the lowest doses (but not at 0 where there really is no morphine), they rapidly press the lever for morphine

Blue line is how many times they pressed the morphine lever



Only at the highest dose are they saying they enjoy it -- at other doses they are even denying that they are getting any

Red line is how much pleasure they got from the morphine

In this condition, lever gave placebo

In this condition, lever gave very low doses of morphine. The red line indicates how much addicts reported liking what they received

Slightly higher dose of morphine given

Higher dose of morphine given

Substance users in America

Number of Alcohol Users	120 million
Number of Tobacco Users	72 million
Number of Illegal Drug Users	20 million
TOTAL	120 million + *(some people use multiple substances)*

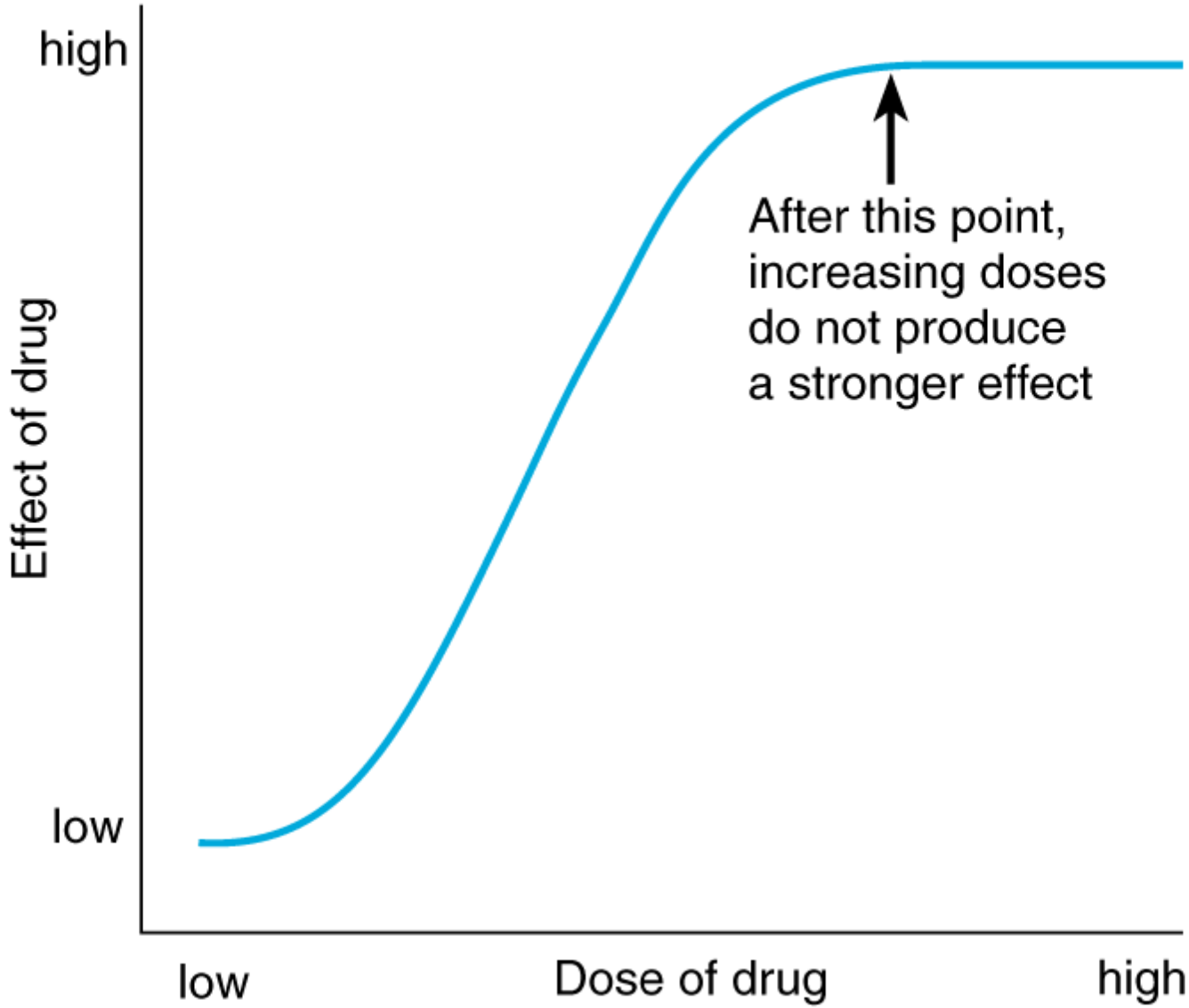
Annual social cost of substance abuse in America

Cost of Alcohol Abuse	$110 billion *(illness, deaths, medical costs, crime)*
Cost of Tobacco Abuse	$138 billion *(medical costs, death, illness)*
Cost of Illegal Drug Abuse	$110 billion *(crime, illness, deaths, medical costs)*
TOTAL	$358 billion

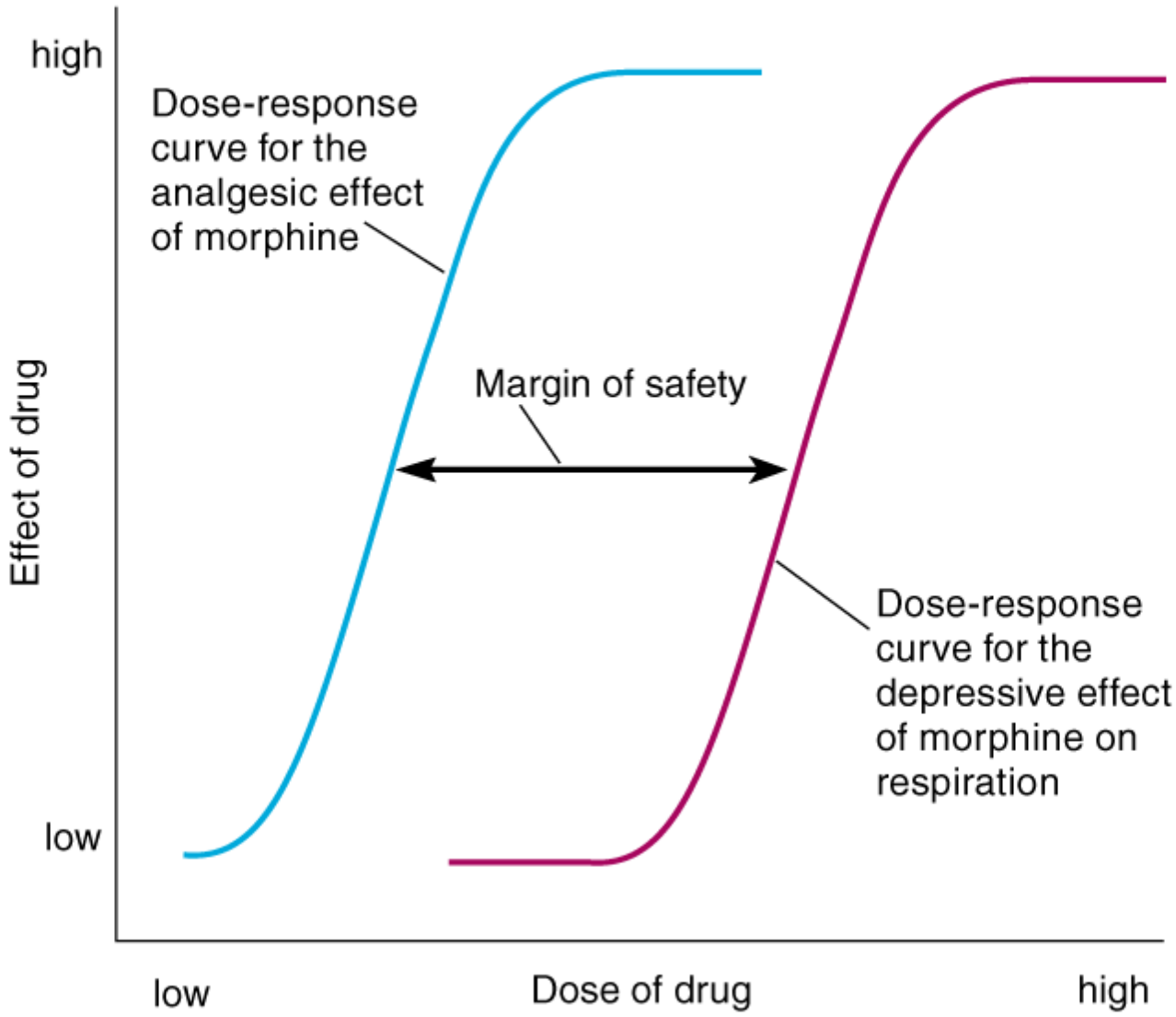
Annual substance-related deaths in America

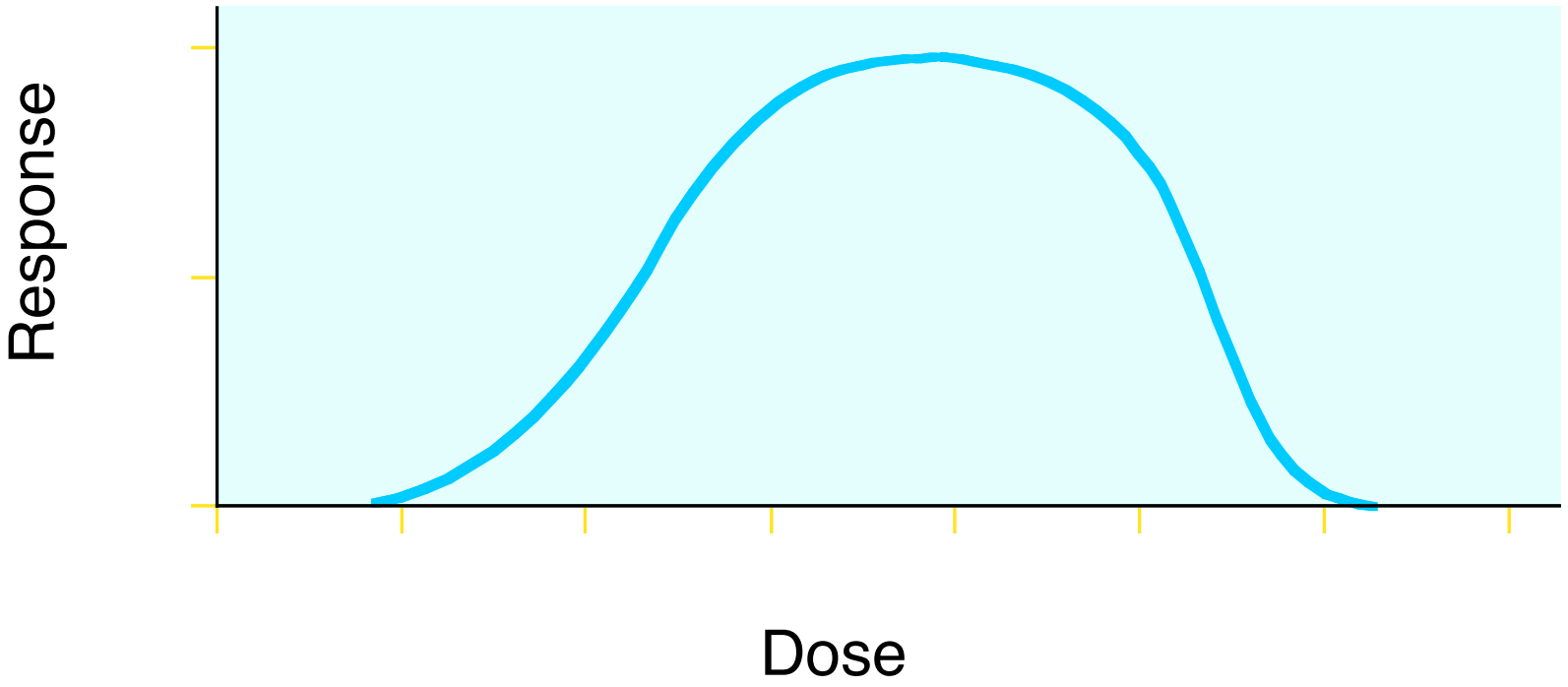
Alcohol-Related Deaths	110,000
Tobacco-Related Deaths	430,000
Illegal Drug-Related Deaths	16,000
TOTAL	556,000

► Dose-Response Curve



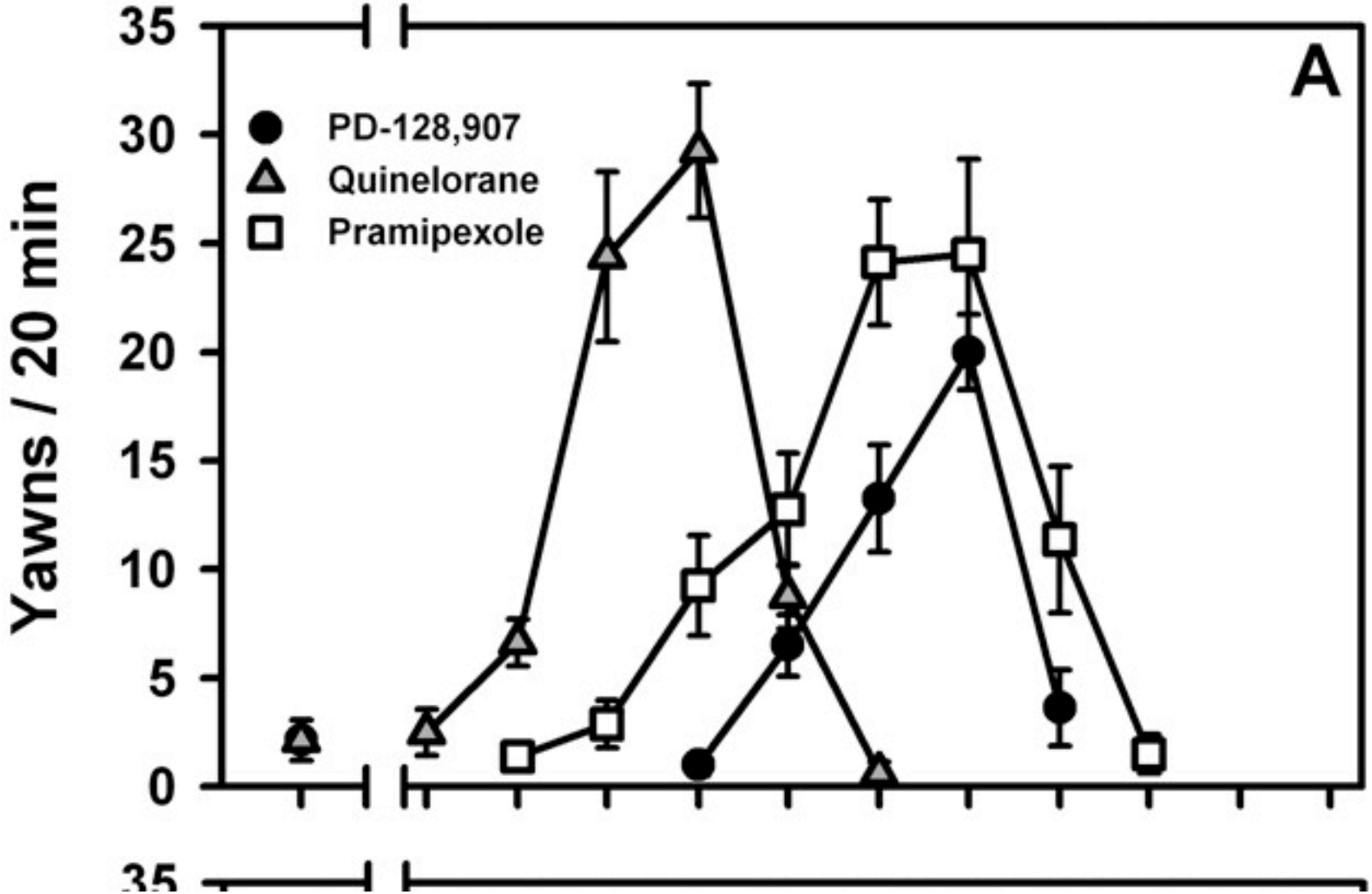
► Dose-Response Curves for the Analgesic and Depressant Effects of Morphine




Response
Dose

Dopamine Agonist-Induced Yawning in Rats: A Dopamine D3 Receptor-Mediated Behavior

Gregory T. Collins, Jeffrey M. Witkin, Amy H. Newman, Kjell A. Svensson, Peter Grundt, Jianjing Cao, and James H. Woods



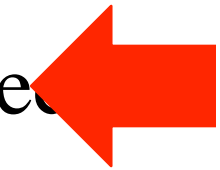
Self test question

Identify the ***FALSE*** statement about dose response curves (DRCs)?

A. They plot drug effects and drug dose

B. More potent drugs have DRCs shifted to the left

C. Higher doses always produce larger effe



D. They have various shapes

E. They may reflect actions on different receptors

Alcohol -- VERY COMPLEX PHARMACOLOGY

Binds …

- ACh R
- GABA R
- 5-HT R
- NMDA R (important glutamate Rs)

***Alters DA too

postsynaptic agonist (like benzodiazepines)
facilitates postsynaptic GABA receptors
"sobriety pill" - benzodiazepine receptor antagonist

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And go to the site!!!

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Dihydromyricetin As A Novel Anti-Alcohol Intoxication Medication

Yi Shen,[1] A. Kerstin Lindemeyer,[1] Claudia Gonzalez,[1] Xuesi M. Shao,[2] Igor Spigelman,[3] Richard W. Olsen,[1] and Jing Liang[1]

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Abstract

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Alcohol use disorders (AUD) constitute the most common form of substance abuse. The development of AUD involves repeated alcohol use leading to tolerance, alcohol withdrawal syndrome (AWS), physical and psychological dependence, with loss of ability to control excessive drinking. Currently there is no effective therapeutic agent for AUD without major side-effects. Dihydromyricetin (DHM, 1 mg/kg, i.p. injection), a flavonoid component of herbal medicines, counteracted acute alcohol (EtOH) intoxication, and also withdrawal signs in rats including tolerance, increased anxiety and seizure susceptibility; DHM greatly reduced EtOH consumption in an intermittent voluntary EtOH intake paradigm in rats. $GABA_A$ receptors ($GABA_A$Rs) are major targets of acute and chronic EtOH actions on the brain. At the cellular levels, DHM (1 μM) antagonized both acute EtOH-induced potentiation of $GABA_A$Rs and EtOH exposure/withdrawal-induced $GABA_A$R plasticity, including alterations in responsiveness of extra- and post-synaptic $GABA_A$Rs to acute EtOH, and most importantly, increases in $GABA_A$R α4 subunit expression in hippocampus and cultured neurons. DHM anti-alcohol effects on both behavior and CNS neurons were antagonized by flumazenil (10 mg/kg *in vivo*, 10 μM *in vitro*), the benzodiazepine (BZ) antagonist. DHM competitively inhibited BZ-site [^{3}H]flunitrazepam binding (IC_{50}, 4.36 μM), suggesting DHM interaction with EtOH involves the BZ-sites on $GABA_A$Rs. In summary, we determined DHM anti-alcoholic effects on animal models, and determined a major molecular target and cellular mechanism of DHM for counteracting alcohol intoxication and dependence. We demonstrated pharmacological properties of DHM consistent with those expected to underlie successful medical treatment of AUD; therefore DHM is a therapeutic candidate.

Dihydromyricetin As A Novel Anti-Alcohol Intoxication Medication

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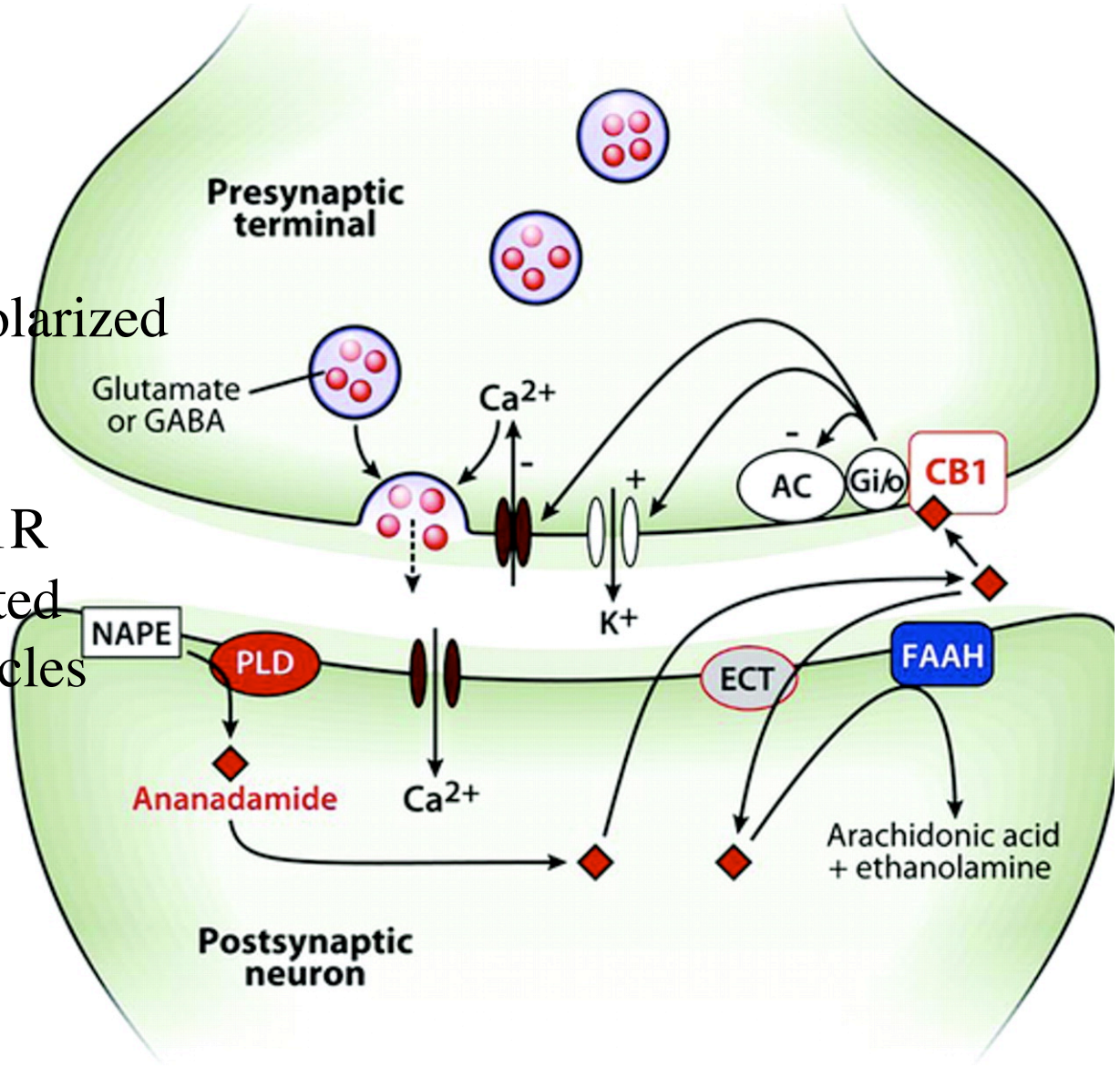
Alcohol use disorders (AUD) constitute the most common form of substance abuse. The development of AUD involves repeated alcohol use leading to tolerance, alcohol withdrawal syndrome (AWS), physical and psychological dependence, with loss of ability to control excessive drinking. Currently there is no effective therapeutic agent for AUD without major side-effects. Dihydromyricetin (DHM, 1 mg/kg, i.p. injection), a flavonoid component of herbal medicines, counteracted acute alcohol (EtOH) intoxication, and also withdrawal signs in rats including tolerance, increased anxiety and seizure susceptibility; DHM greatly reduced EtOH consumption in an intermittent voluntary EtOH intake paradigm in rats. $GABA_A$ receptors ($GABA_ARs$) are major targets of acute and chronic EtOH actions on the brain. At the cellular levels, DHM (1 μM) antagonized both acute EtOH-induced potentiation of $GABA_ARs$ and EtOH exposure/withdrawal-induced $GABA_AR$ plasticity, including alterations in responsiveness of extra- and post-synaptic $GABA_ARs$ to acute EtOH, and most importantly, increases in $GABA_AR$ α4 subunit expression in hippocampus and cultured neurons. DHM anti-alcohol effects on both behavior and CNS neurons were antagonized by flumazenil (10 mg/kg *in vivo*, 10 μM *in vitro*), the benzodiazepine (BZ) antagonist. DHM competitively inhibited BZ-site [^{3}H]flunitrazepam binding (IC_{50}, 4.36 μM), suggesting DHM interaction with EtOH involves the BZ-sites on $GABA_ARs$. In summary, we determined DHM anti-alcoholic effects on animal models, and determined a major molecular target and cellular mechanism of DHM for counteracting alcohol intoxication and dependence. We demonstrated pharmacological properties of DHM consistent with those expected to underlie successful medical treatment of AUD; therefore DHM is a therapeutic candidate.

1. The problem is defined
2. Drug, dose, source
3. List of effects related to intoxication
4. How it affects receptors
5. What drugs prevent its effects to say more about receptor action
6. Worth evaluating in humans
7. Not yet reported

Marijuana

- THC (tetrahydrocannabinol)
- cannabanoid receptors (CB1, CB2)
- anandamide, 2-AG
- very novel mechanism of action

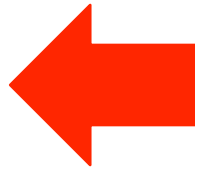
1. Presynaptic cell fires
2. Post-synaptic cell depolarized
3. Anandamide released
4. Goes BACKWARDS
5. Binds presynaptic CB1R
6. Presynaptic cell inhibited
7. Post-synaptic cell recycles



Self test question

Smoking marijuana will produce what response?

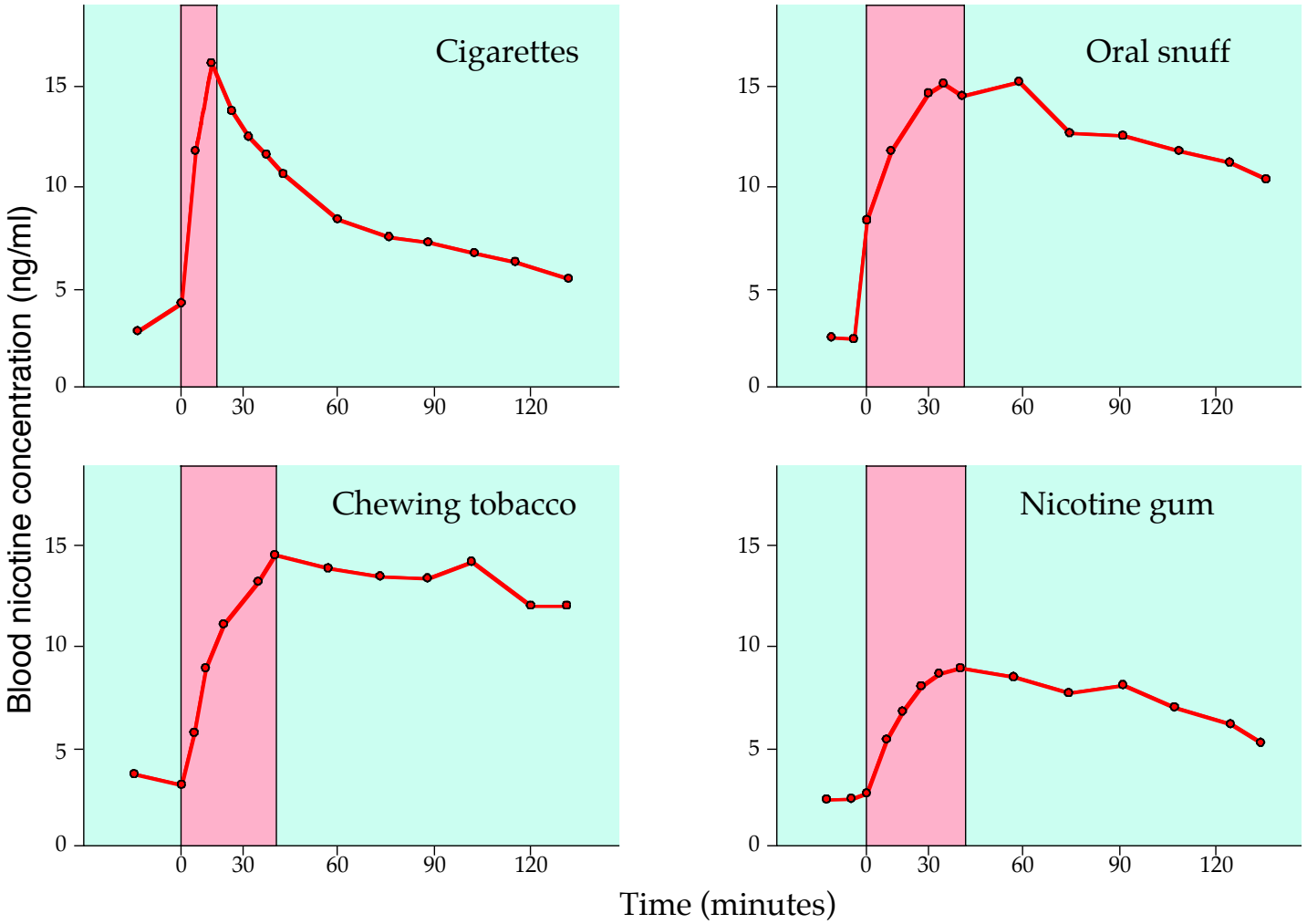
A. Post-synaptic release of endocannabinoids
B. Post-synaptic binding of CB receptors
C. Reduce GABA or glutamate release



Not all drugs are addictive/abused

need hedonic value

Route of administration affects addictive potential



Complementary models

1. Moral model

2. Physical dependence

3. Reward-based models

Table 2
Multiple logistic regression of demographic and religion variables for predicting drinking patterns: adjusted

	Drinkers vs. abstainers (ref.)		
	Adjusted odds ratio	95% confidence interval	*p*-Value
A. Demographic variables			
Gender (ref. = women)	1.22	(1.07, 1.38)	.002
Age (ref. = 29 or younger)			.000
30–39	0.77	(.64, .92)	.005
40–59	0.57	(.47, .68)	.000
50–59	0.51	(.42, .62)	.000
60+	0.40	(.31, .51)	.000
Income (ref. = $ 30,000/less)	1.57	(1.37, 1.80)	.000
Married (ref. = not married)	0.85	(.73, .98)	.015

Odds Ratio: roughly, how many times more like (>1) or less likely (<1) an outcome will occur for a group. Compared to the likelihood of a woman being a drinker, a man is 1.22 times more likely to be one.

p-Value: probability this difference is due to chance. < 0.05 considered significant result

L. Michalak et al. / Drug and Alcohol Dependence 87 (2007) 268–280

Table 2
Multiple logistic regression of demographic and religion variables for predicting drinking patterns: adjusted odds ratios

	Drinkers vs. abstainers (ref.)			Heavy vs. moderate drinkers (ref.)		
	Adjusted odds ratio	95% confidence interval	*p*-Value	Adjusted odds ratio	95% confidence interval	*p*-Value
A. Demographic variables						
Gender (ref. = women)	1.22	(1.07, 1.38)	.002	3.49	(2.92, 4.16)	.000
Age (ref. = 29 or younger)			.000			.000
30–39	0.77	(.64, .92)	.005	0.66	(.53, .83)	.000
40–59	0.57	(.47, .68)	.000	0.47	(.37, .60)	.000
50–59	0.51	(.42, .62)	.000	0.26	(.19, .34)	.000
60+	0.40	(.31, .51)	.000	0.14	(.09, .22)	.000
Income (ref. = $ 30,000/less)	1.57	(1.37, 1.80)	.000	0.95	(.78, 1.16)	.551
Married (ref. = not married)	0.85	(.73, .98)	.015	0.65	(.54, .77)	.000
Ethnicity (ref. = Black)			.000			.115
White	1.37	(1.13, 1.66)	.005	1.22	(.92, 1.60)	.153
Hispanic	0.74	(.56, .97)	.018	1.44	(1.00, 2.07)	.048
Other	0.71	(.51, .98)	.019	1.56	(1.00, 2.44)	.034
Education (ref. = less than HS)			.000			.000
High school graduate	1.53	(1.22, 1.92)	.000	0.90	(.65, 1.24)	.451
Some college	1.93	(1.53, 2.45)	.000	0.64	(.47, .887)	.002
College or more	2.31	(1.80, 2.97)	.000	0.44	(.31, .62)	.000
Employment (ref. = employed)			.000			.098
Unemployed	0.68	(.54, .84)	.000	1.02	(.76, 1.36)	.890
Retired	0.70	(.54, .92)	.004	1.08	(.69, 1.69)	.708
Homemaker	0.66	(.49, .90)	.002	0.62	(.39, .98)	.014

No details required from this slide

B. Religion variables						
Proscription	0.59	(.51, .69)	.000	0.78	(.63, .95)	.006
Religiosity	0.67	(.60, .75)	.000	0.79	(.70, .89)	.000
Preference (ref. = No Religion)			.000			.000
Mormon	0.13	(.07, .23)	.000	1.50	(.51, 4.45)	.383
Assembly of God	0.40	(.11, 1.40)	.046	0.19	(.01, 4.09)	.146
Seventh Day Adventists	0.47	(.16, 1.37)	.081	0.28	(.05, 1.59)	.229
European Free Church	0.59	(.29, 1.18)	.084	0.20	(.04, .88)	.031
Church of God	0.31	(.16, .64)	.000	1.65	(.48, 5.68)	.352
Churches of Christ	0.71	(.34, 1.49)	.306	0.83	(.29, 2.35)	.728
Muslim	0.17	(.07, .38)	.000	0.59	(.11, 3.10)	.498
Pentecostal	0.38	(.21, .68)	.000	0.80	(.25, 2.55)	.611
Baptist	0.74	(.56, .98)	.015	1.58	(1.12, 2.22)	.004
Protestant/miscellaneous denominations	0.44	(.26, .73)	.000	1.20	(.47, 3.06)	.589
United Churches of Christ	0.94	(.50, 1.76)	.806	0.57	(.22, 1.47)	.245
Christian/no denomination	1.02	(.71, 1.48)	.890	1.80	(1.12, 2.88)	.005
Protestant/no denomination	0.80	(.56, 1.15)	.152	0.80	(.50, 1.28)	.276
Methodist	1.19	(.85, 1.65)	.234	1.24	(.82, 1.88)	.206
Community Churches	1.87	(.90, 3.89)	.079	0.76	(.32, 1.83)	.522
Jehovah's Witness	2.26	(1.24, 4.10)	.009	1.14	(.51, 2.55)	.710
Presbyterian	1.30	(.82, 2.07)	.188	0.89	(.53, 1.51)	.654
Catholic	1.74	(1.35, 2.26)	.000	1.52	(1.15, 2.01)	.001
Lutheran	2.12	(1.36, 3.29)	.000	1.25	(.85, 1.84)	.202
Episcopal	0.97	(.59, 1.61)	.888	1.18	(.69, 2.01)	.562
Jewish	0.89	(.49, 1.62)	.657	0.31	(.15, .62)	.004

2. Physical dependence model: Alleviate unpleasant withdrawal symptoms

Tolerance = requires larger doses for same effect
Down-regulation of receptors, faster metabolism
Conditioned compensatory responses

Tolerance may gated by environment
OD in new environments

Withdrawal symptoms
Occur in absence of the drug
generally opposite produced by the drug itself

Problems with this model:
why do users get hooked initially?
addictions to cocaine without withdrawal symptoms
addicts sometimes quit to reverse tolerance

Psychological addiction - compulsion in absence of withdrawal symptoms

3. Reward models: drugs of abuse are "rewarding"

Reward (heavily dependent on dopamine) that reinforces behavior

Electrical stimulation of medial forebrain bundle (MFB)

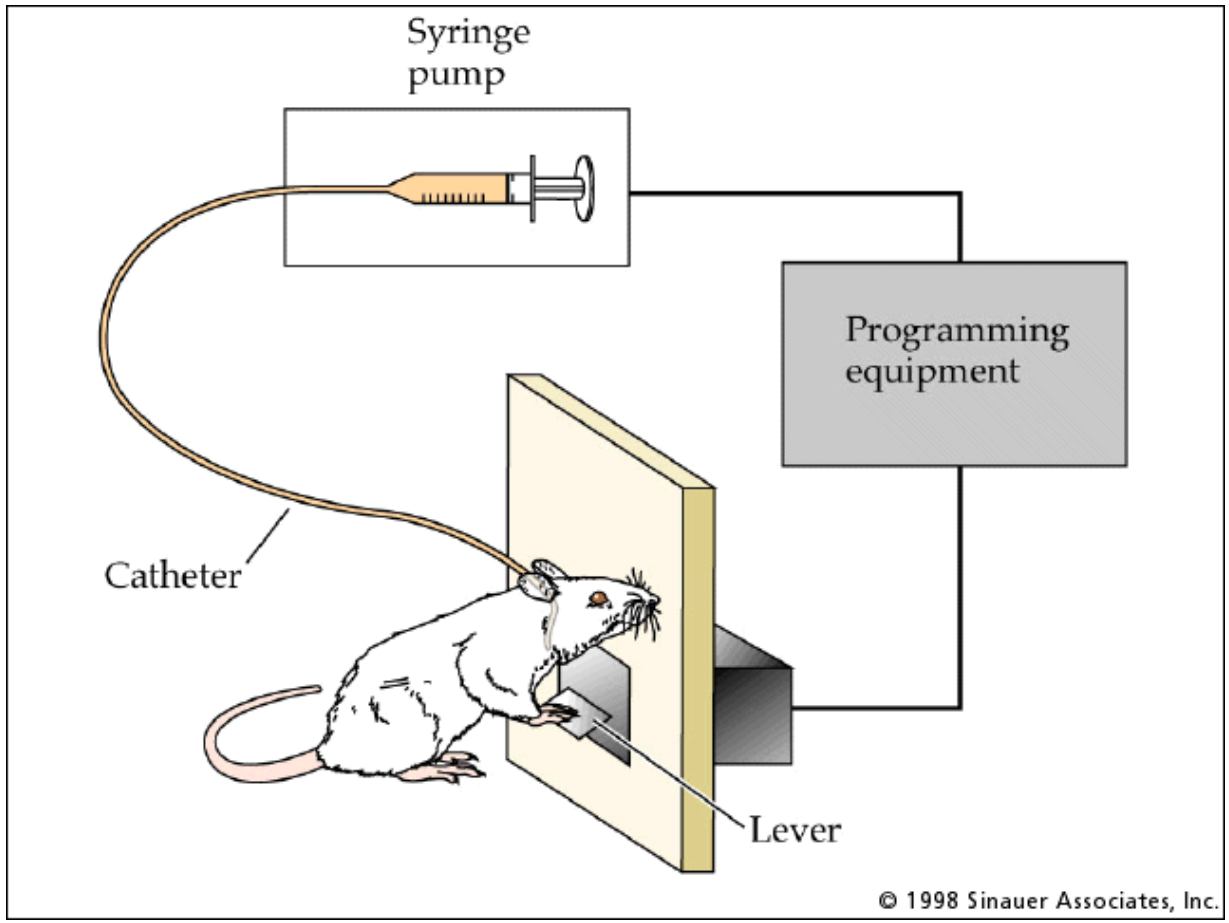
Many stimuli reinforce behavior
Food
Sex
Animals will
self-administer drugs
form conditioned place preferences -- learned preference for location of reward
All of these rewards increase DA in nucleus accumbens

Lesions inhibit self-administration in animals
Surgery in humans done in China ~2000-2004 but stopped for ethical reasons/side effects

Reward and pleasure are different things

Wanting versus liking

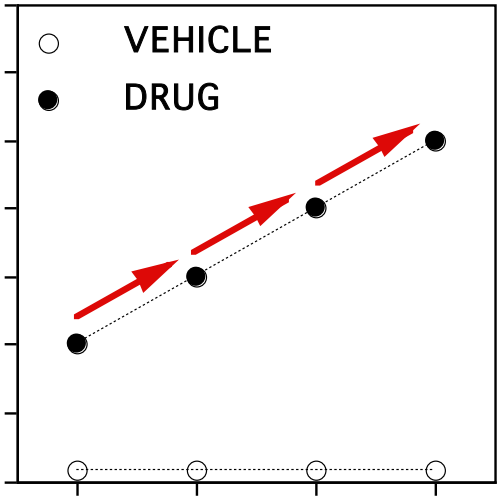
Can get animals to take drugs, but very time-consuming
Other "proxy" variables related to drug-taking?



Fake data

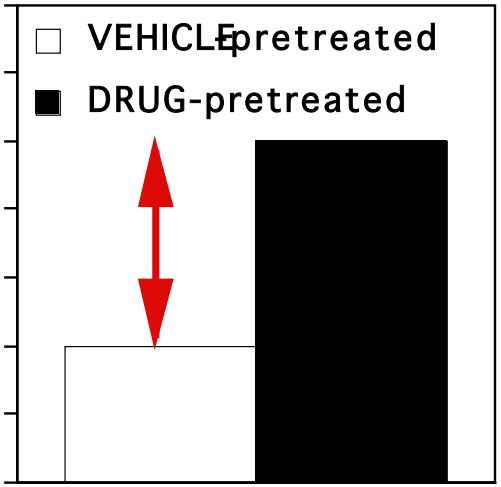
DRUG SENSITIZATION

Rate of Drug Sensitization

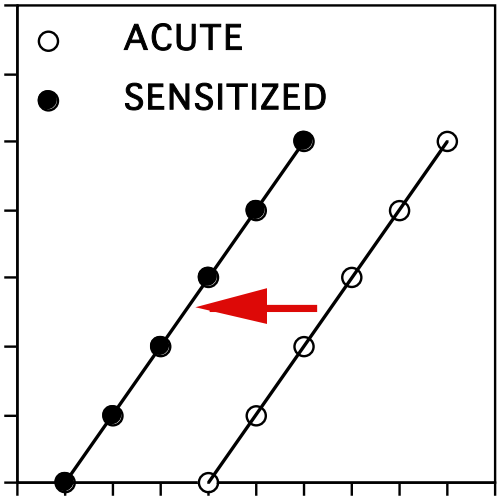


Repeated Treatments

Drug Challenge



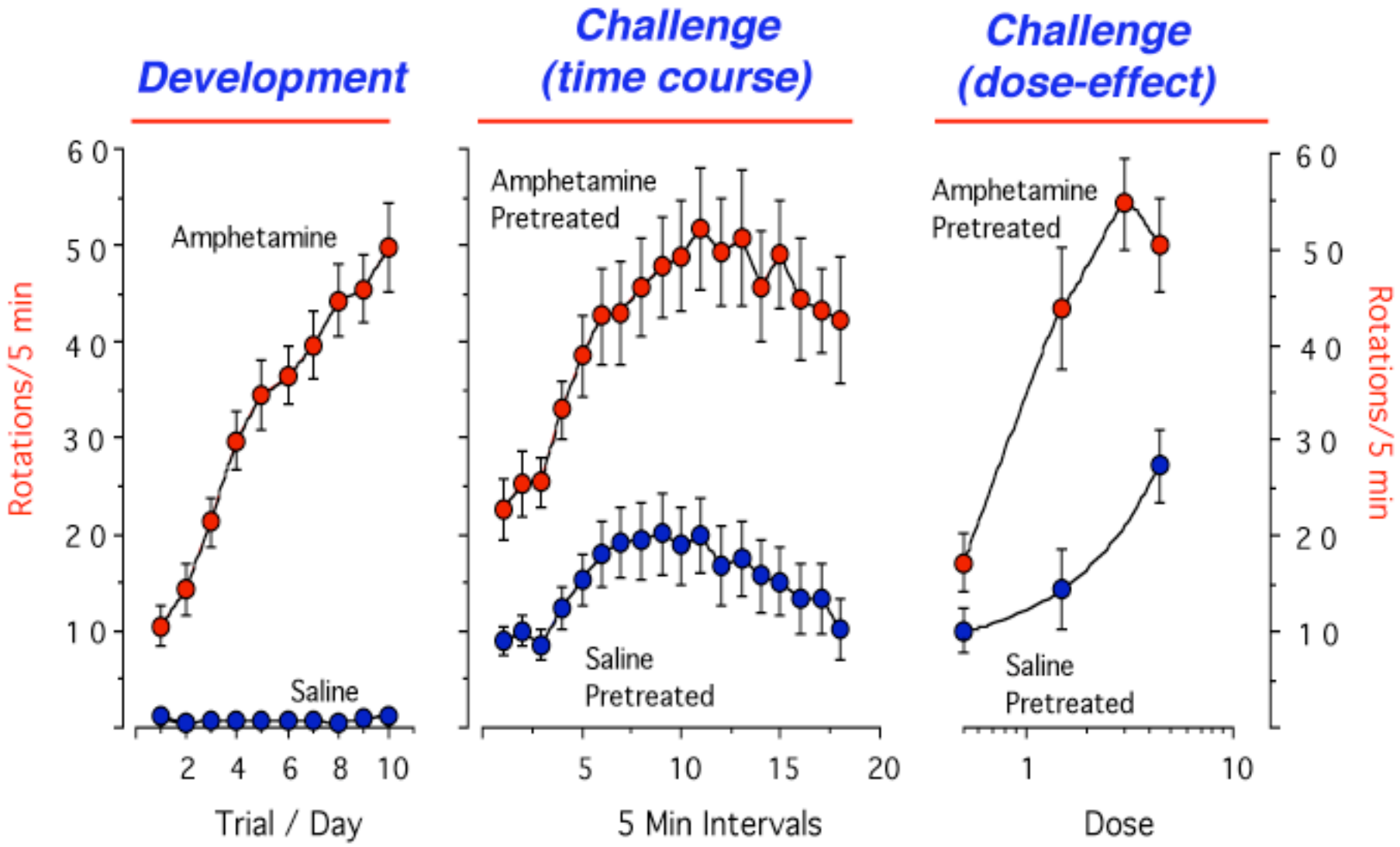
Shift in Dose-Effect Curve



Dose of Drug

Real data

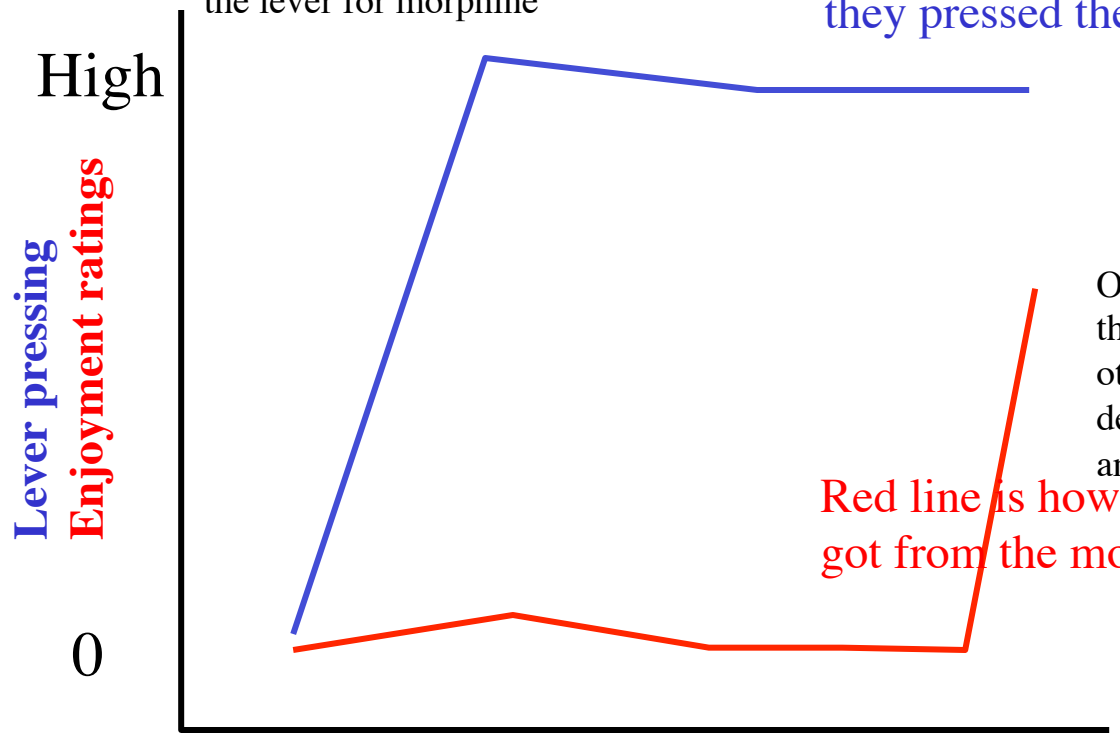
Psychomotor Sensitization



(data from Anagnostaras & Robinson, 1996)

Even at the lowest doses (but not at 0 where there really is no morphine), they rapidly press the lever for morphine

Blue line is how many times they pressed the morphine lever



Only at the highest dose are they saying they enjoy it -- at other doses they are even denying that they are getting any

Red line is how much pleasure they got from the morphine

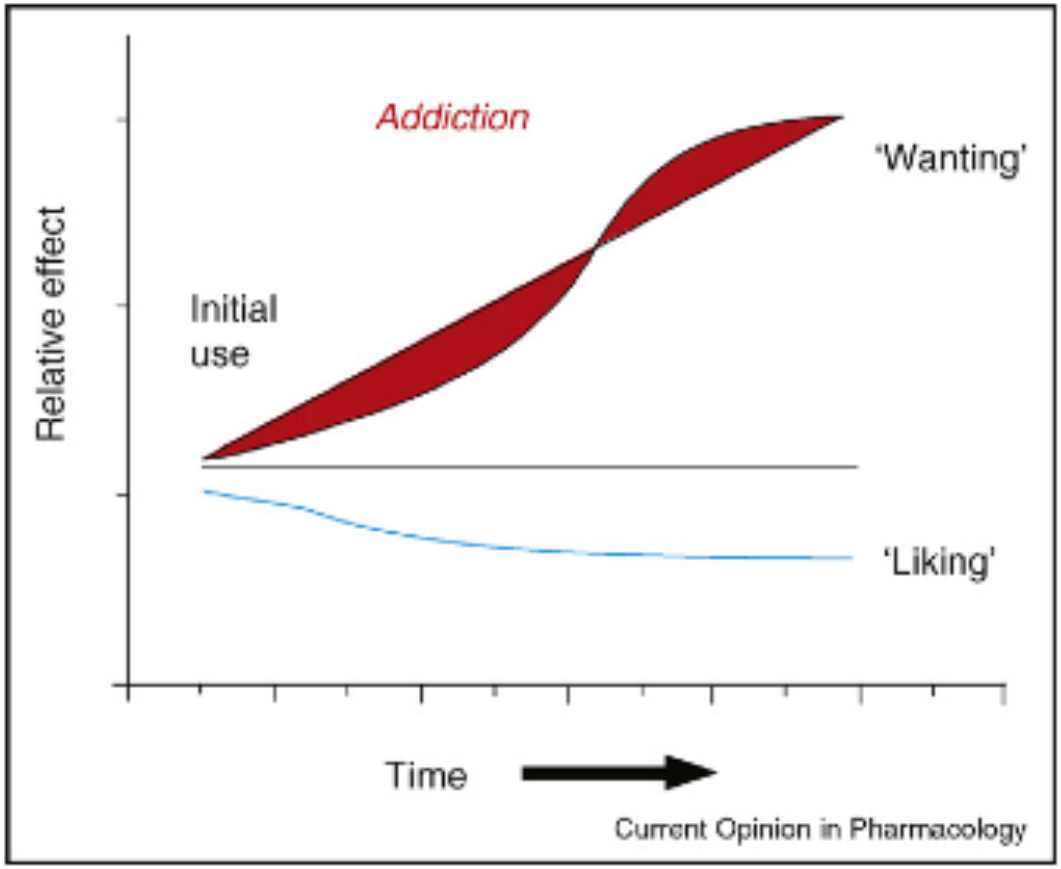
In this condition, lever gave placebo

In this condition, lever gave very low doses of morphine. The red line indicates how much addicts reported liking what they received

Slightly higher dose of morphine given

Higher dose of morphine given

Figure 5



Incentive-sensitization model of addiction. Schematic model of how 'wanting' to take drugs may grow over time independently of 'liking' for drug pleasure as an individual becomes an addict. The transition from casual drug use to compulsive addiction is posited to be owing to drug-induced sensitization of mesocorticolimbic mechanisms of incentive salience. Modified from [42].

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The Reinforcing and Subjective Effects of Morphine in Post-Addicts: A Dose-Response Study

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ABSTRACT

The reinforcing and subjective effects of morphine were determined in five human volunteers with histories of i.v. heroin abuse. Subjects responded under a second-order schedule of i.m. injection. Under this schedule, every 100 lever presses produced a brief stimulus light [fixed ratio (FR) 100:s]; the 30th completion of the FR 100 requirement turned on the light for 15 min and the subject received an i.m. injection of morphine [FR 30 (FR 100:s)]. Once each weekday morphine or placebo was available under this schedule. Each drug dose was available for 1 week. Under these conditions placebo did not maintain responding; 3.75 mg of morphine maintained responding in four of five subjects, and higher morphine doses (7.5, 15 and 30 mg) maintained responding in all five subjects. Subjective effects were measured concurrently: these included measures of drug liking, the Morphine Benzedrine Group scale of the Addiction Research Center Inventory, drug detection and identification. Subjects did not report subjective effects different from placebo for the lowest dose of morphine; the intermediate doses of morphine produced inconsistent effects, and the highest dose of morphine occasioned reports of drug liking and "dope" identifications. These results indicate that there can be a significant dissociation of the reinforcing and the subjective effects of opioids, which has implications for theories of opioid abuse, particularly those assuming that the reinforcing effects are causally related to the euphoric effects of opioids. Furthermore, these results confirm that measures of reinforcing effects and measures of subjective effects do not necessarily lead to identical predictions when used to assess the liability for abuse of a substance.

Article posted on website (optional reading)

Self test question

According to the model of Berridge and Robinson, addiction reflects the wanting undergoes _____ and liking undergoes _____.

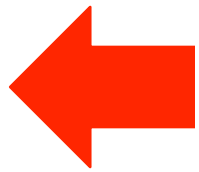
A. Habituation; tolerance

B. Potentiation; sensitization

C. Agonism, antagonism

D. Habituation; sensitization

E. Sensitization; tolerance



Summary

- Myriad cellular “sites of action”
- Myriad long and short-term effects on “systems”
- Systems are “dynamic”

Development

Main points:

1. EVERY BEHAVIOR HAS A HISTORY THAT RENDERS IT SUSCEPTIBLE TO INTERVENTION

2. BRAIN AND BEHAVIOR AFFECTED BY MULTIPLE PROCESSES THAT OVERLAP IN TIME

Study Questions:

1. Evaluate the statement that "having a gene for behavior X means that it is inevitable a person will exhibit behavior X."

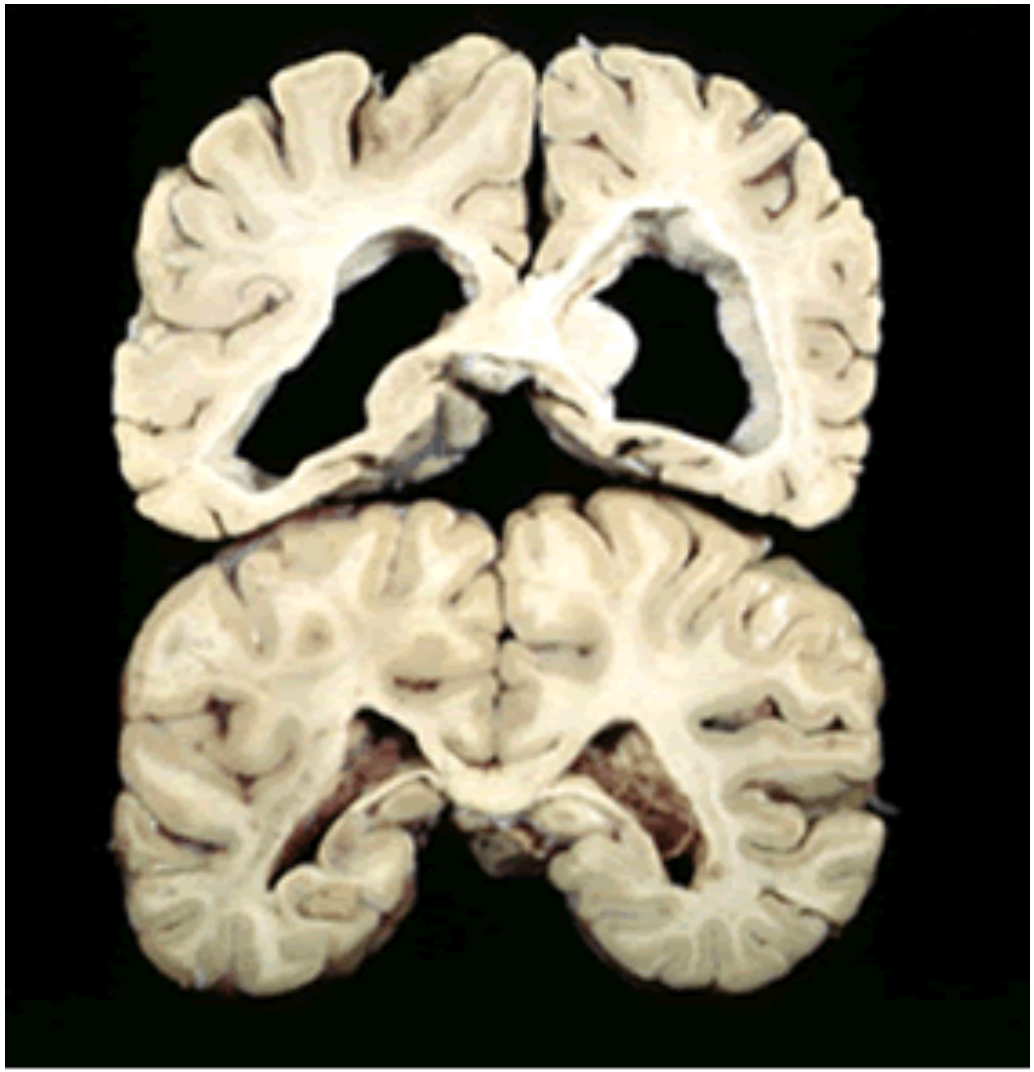
2. Describe a number of developmental processes that might influence how large a neural structure is in adulthood.

Story 1: Huntington's Disease

THE DNA AGE
Facing Life With a Lethal Gene
AMY HARMON March 18, 2007

Genetically transmitted disease
Clumsiness, twitching
Becomes jerking
Intellectual deterioration
BG destruction (GABA cells)
Single gene on #4 mutated
Dominant
Not known why cells in BG deteriorate when all cells make it
Why hits after 40-50?

Ms. Moser at 13 in a family photo with her grandfather, who had Huntington's disease.



The human brain, showing the impact of HD on brain structure in the basal ganglia region of a person with HD (top) and a normal brain (bottom).

http://kobiljak.msu.edu

Story 2: Phenylketonuria (PKU)

Genetic autosomal recessive

Decreased neuron size, dendrite length, spine density, layering

95% have IQs < 50

Boy with untreated PKU

Because a child with PKU lacks the normally functioning enzyme necessary to break down phenylalanine (PHE), it accumulates in the blood and body tissues.

This excess PHE can prevent normal brain development and result in mental retardation.

Jared Compiano, a normal healthy boy with PKU, poses with his siblings Hannah and Nathan.

Enz deficiency + phenylalanine → retardation
Enz deficiency – phenylalanine → normal
Enz sufficiency ± phenylalanine → normal

Story 3: Testosterone and sexual development

Rats grow up to show sex differences in sex behavior
Males have more Testosterone (T) early in life than females
Give female rats T early in life they act more masculine in some respects
By what mechanisms does T directly cause this?

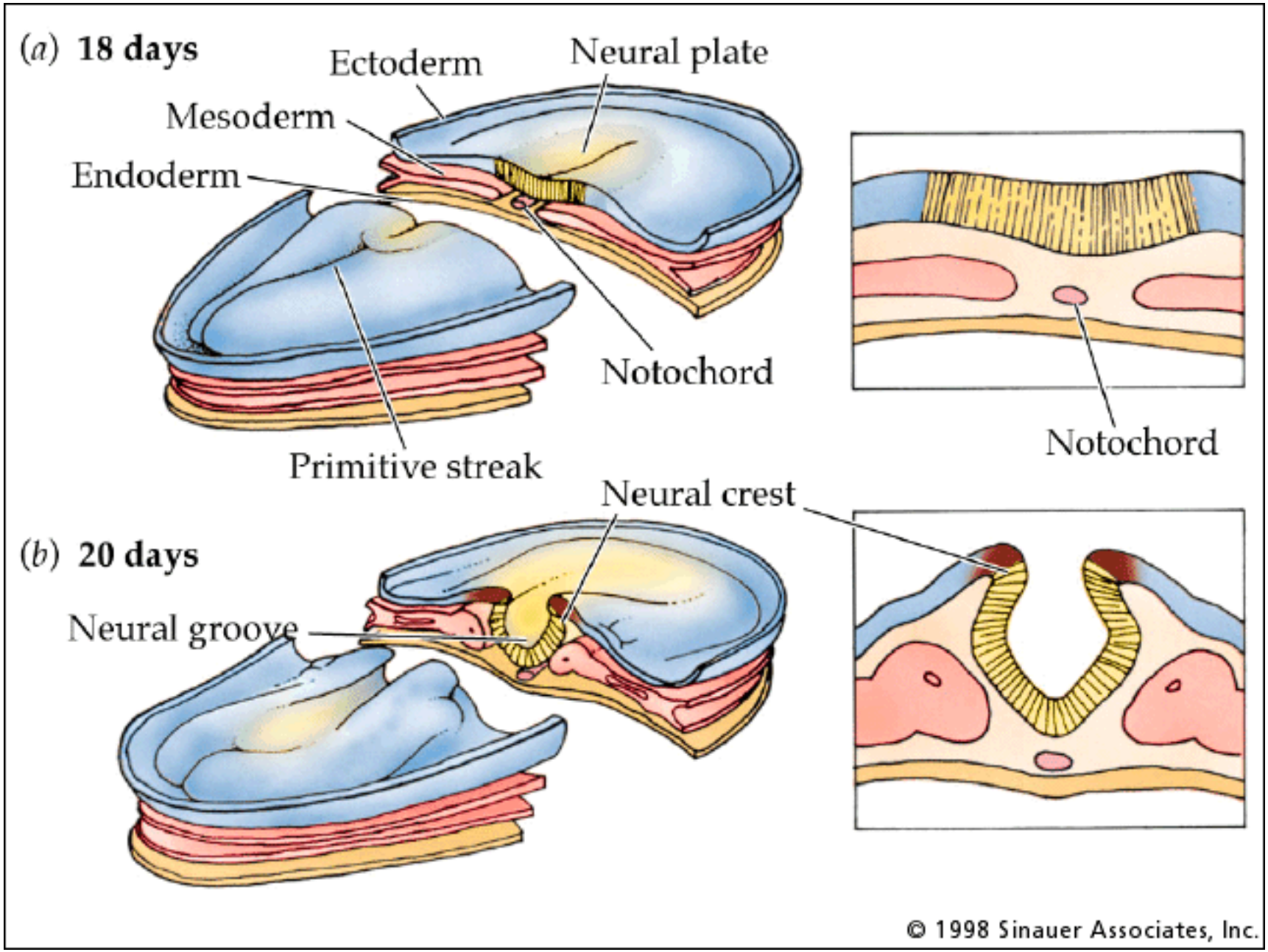
Here's ONE interesting mechanism
Mom treats M and F rats differently
- Licks anogenital region of Ms > Fs
- Decides based on T residues in urine
- Trick her into licking Fs > Ms → changes in sex behavior

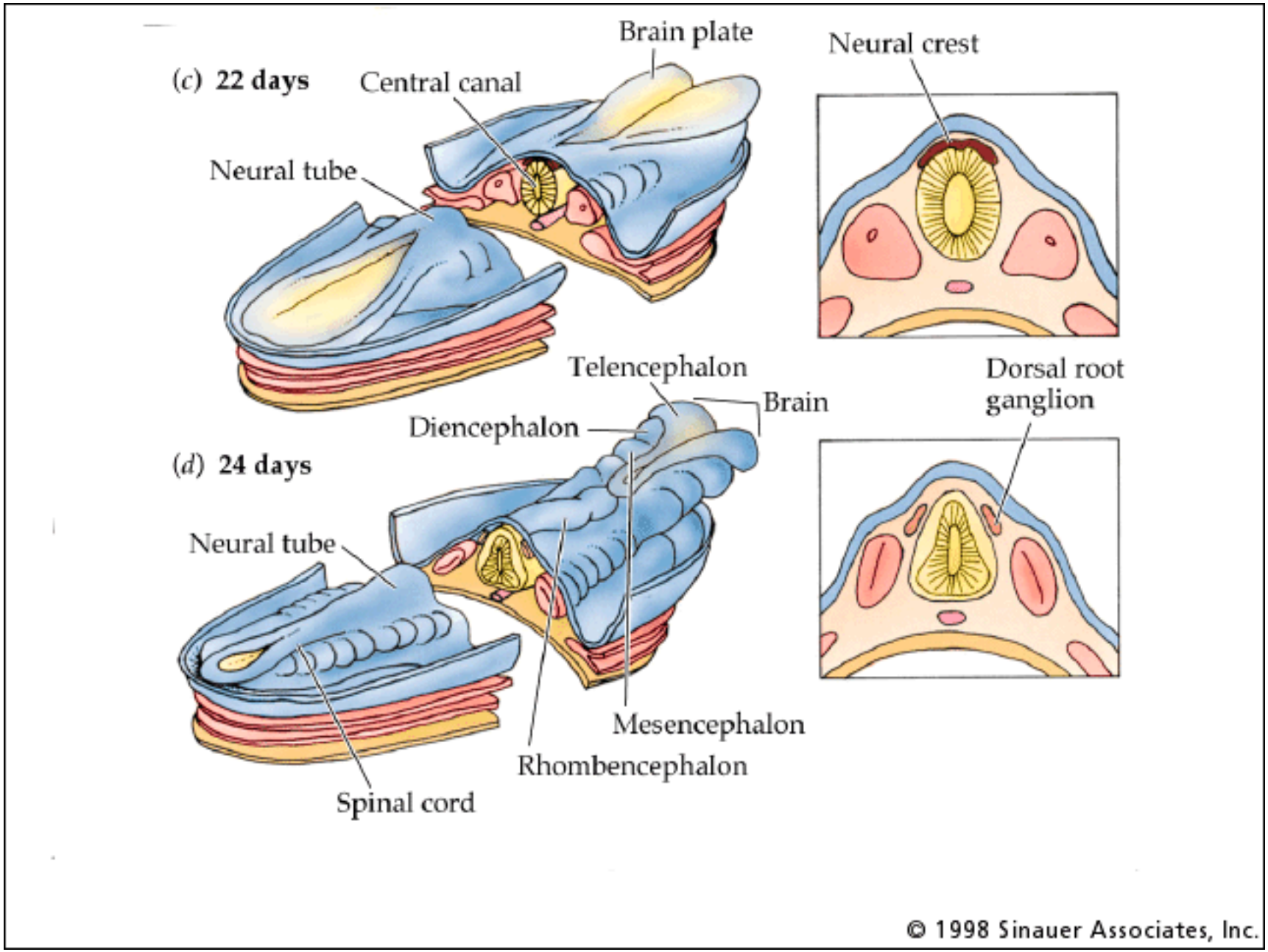
Photo credit: © Eric Isselée

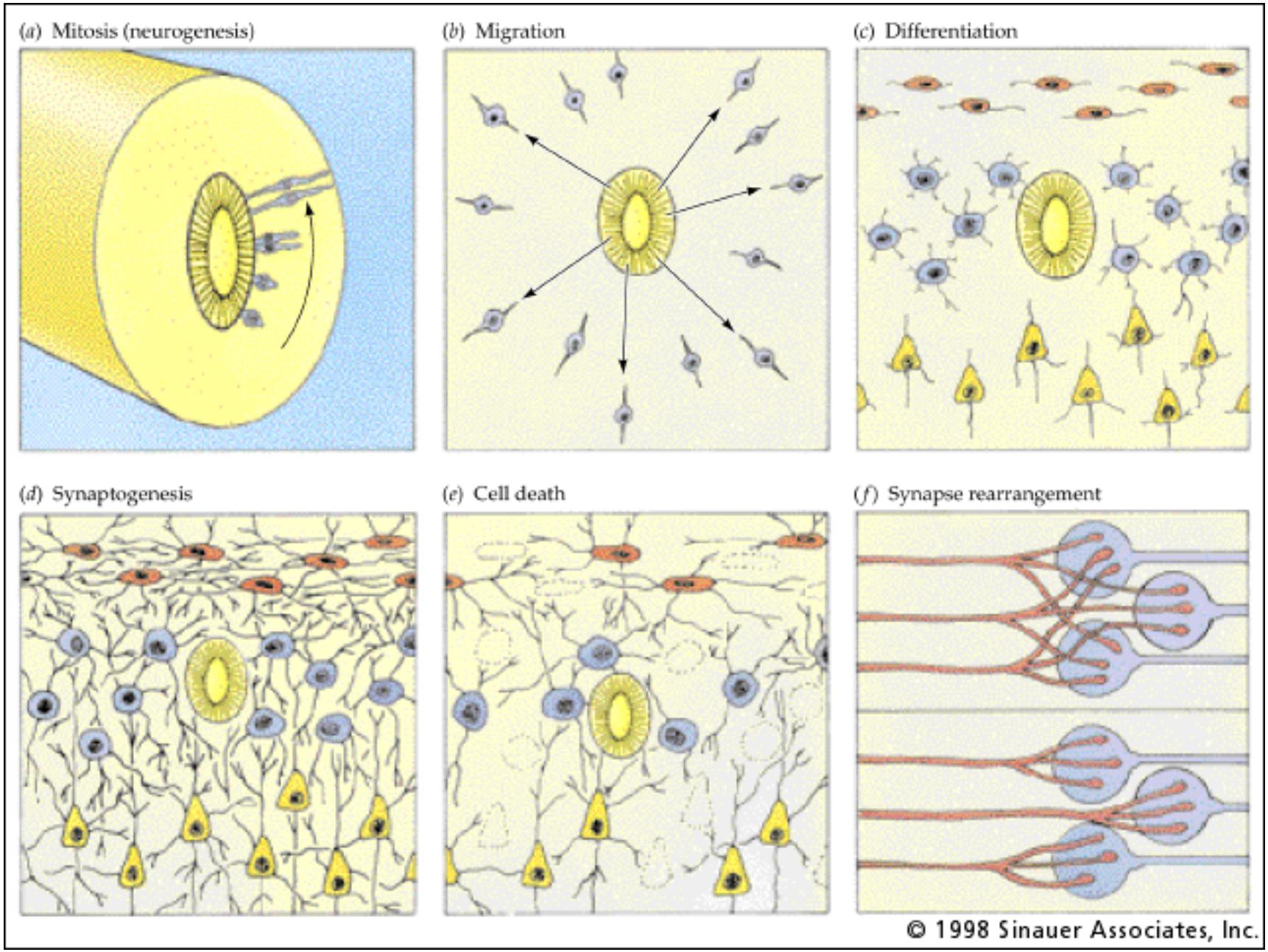
Brain Development
Problem: How do you build a nervous system?

~100 billion neurons (10^{11} neurons)
X 1000 synapses per neuron
= 100 trillion synapses (10^{14} synapses) or
or 100,000,000,000,000 synapses

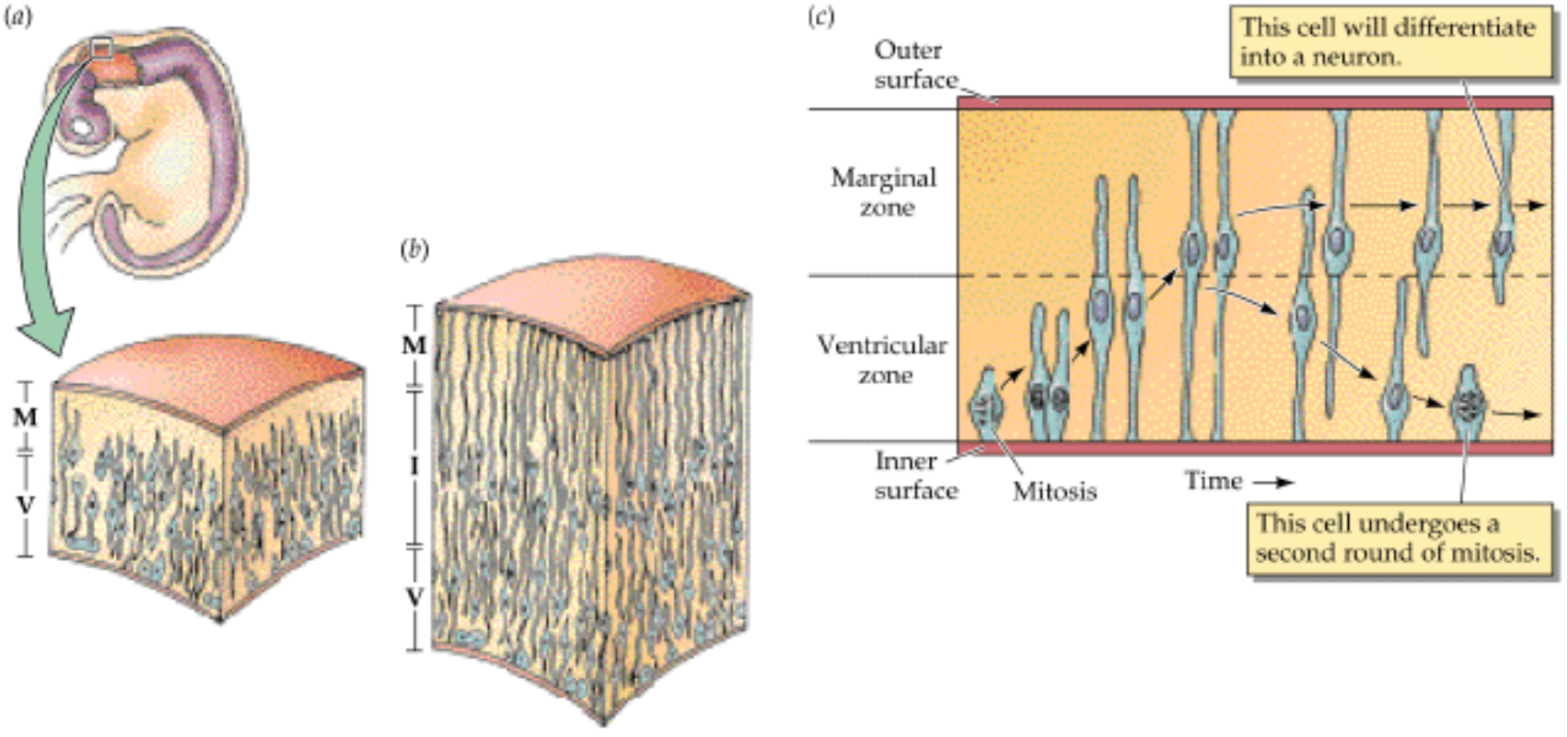
How many genes? About half for brain


(a) 18 days
Ectoderm
Neural plate
Mesoderm
Endoderm
Notochord
Primitive streak
Notochord
(b) 20 days
Neural crest
Neural groove
© 1998 Sinauer Associates, Inc.

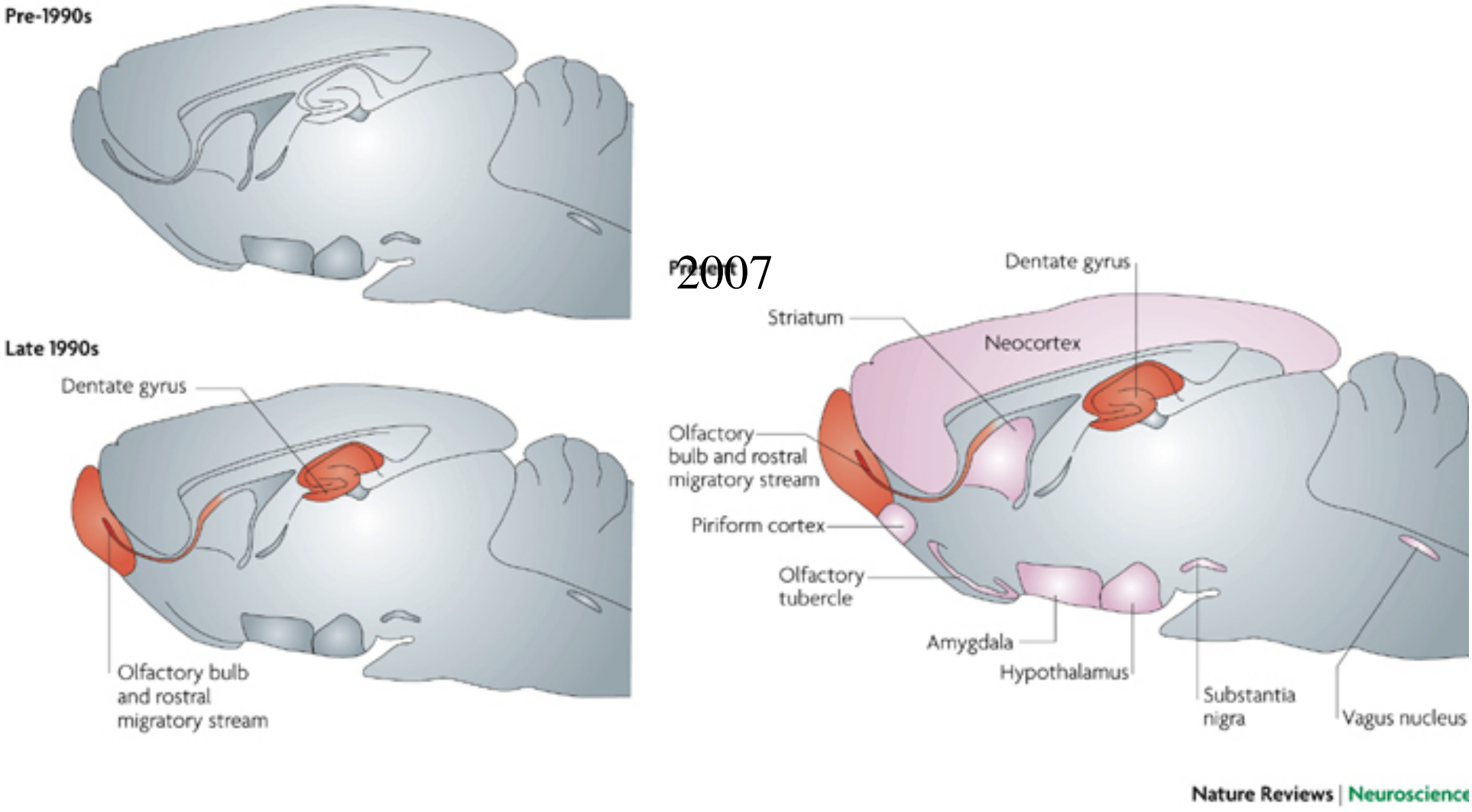




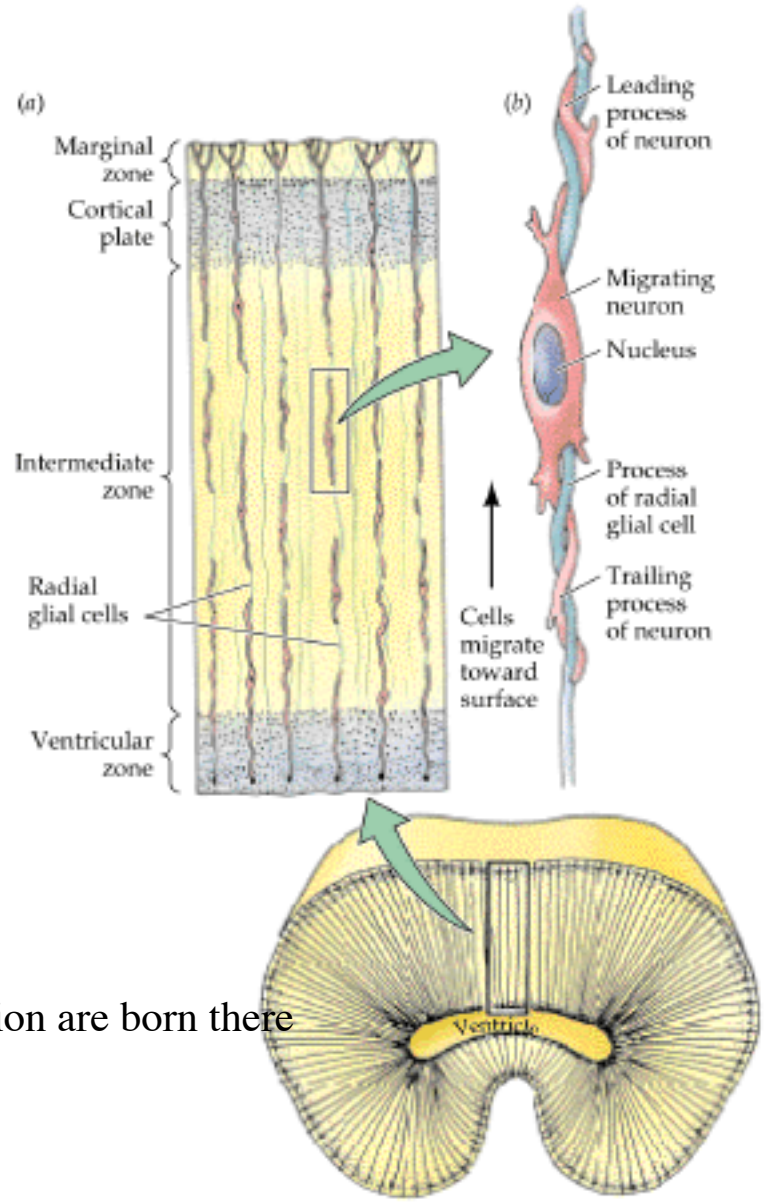
1. Neurogenesis/cell proliferation



Adult neurogenesis



2. Migration



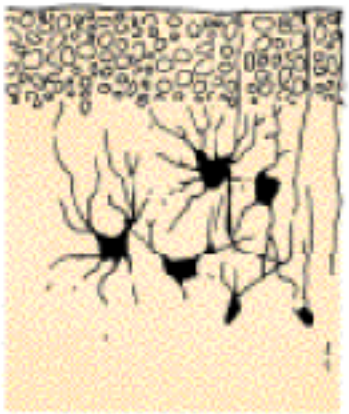
Radial glia
Cell adhesion molecu

Kallmann's syndrome:
- Infertility
- Loss of smelling sense
- Cells born in olfactory region don't migrate properly
- Cells controlling reproduction are born there

3. Differentiation – shape shown here

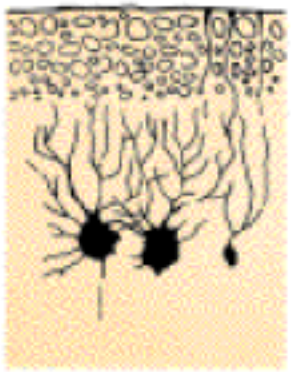
12th fetal week

15 weeks

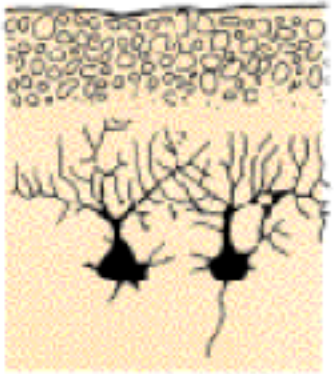


18 weeks

22 weeks



28 weeks



32 weeks

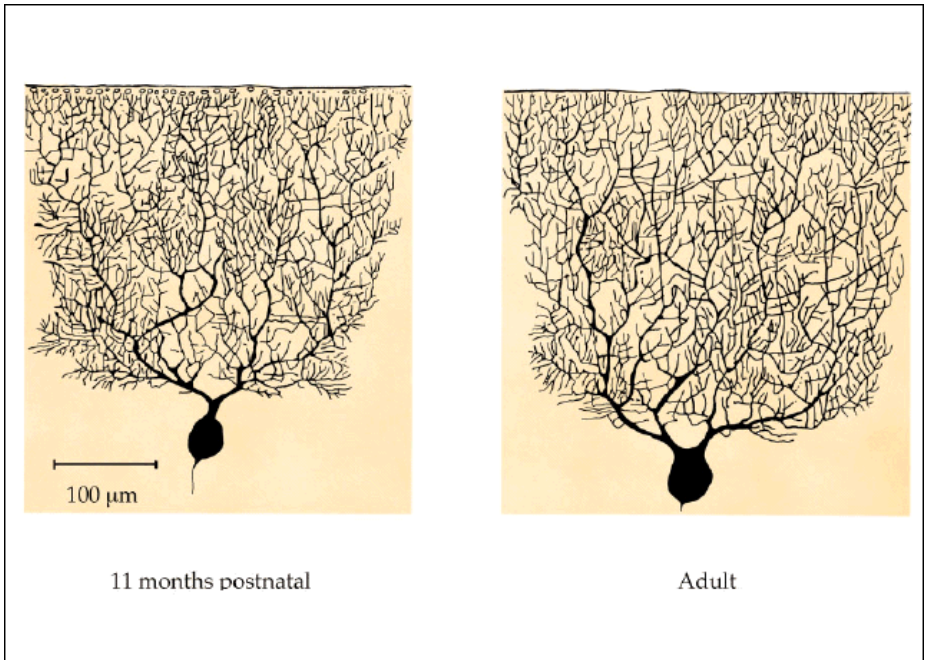
35 weeks

Birth

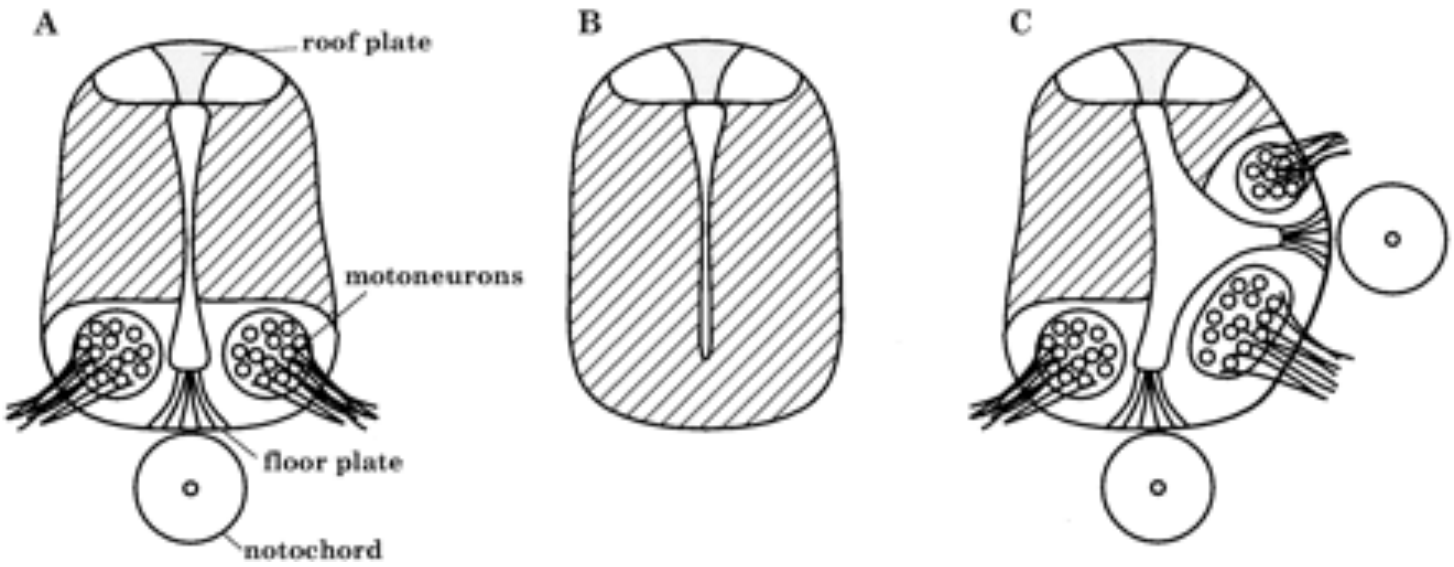
Differentiation – shape shown here

but also what NTs, Rs etc

some genes turned on; others turned off = epigenesis



Induction factors trigger differentiation



Notochord, sonic hedgehog, motor neurons

Self test question

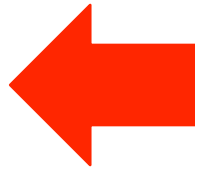
Which of the following should **NOT** be considered part of differentiation of a neuron?

A. Making enzymes for neurotransmitter synthesis

B. Growing dendritic branches

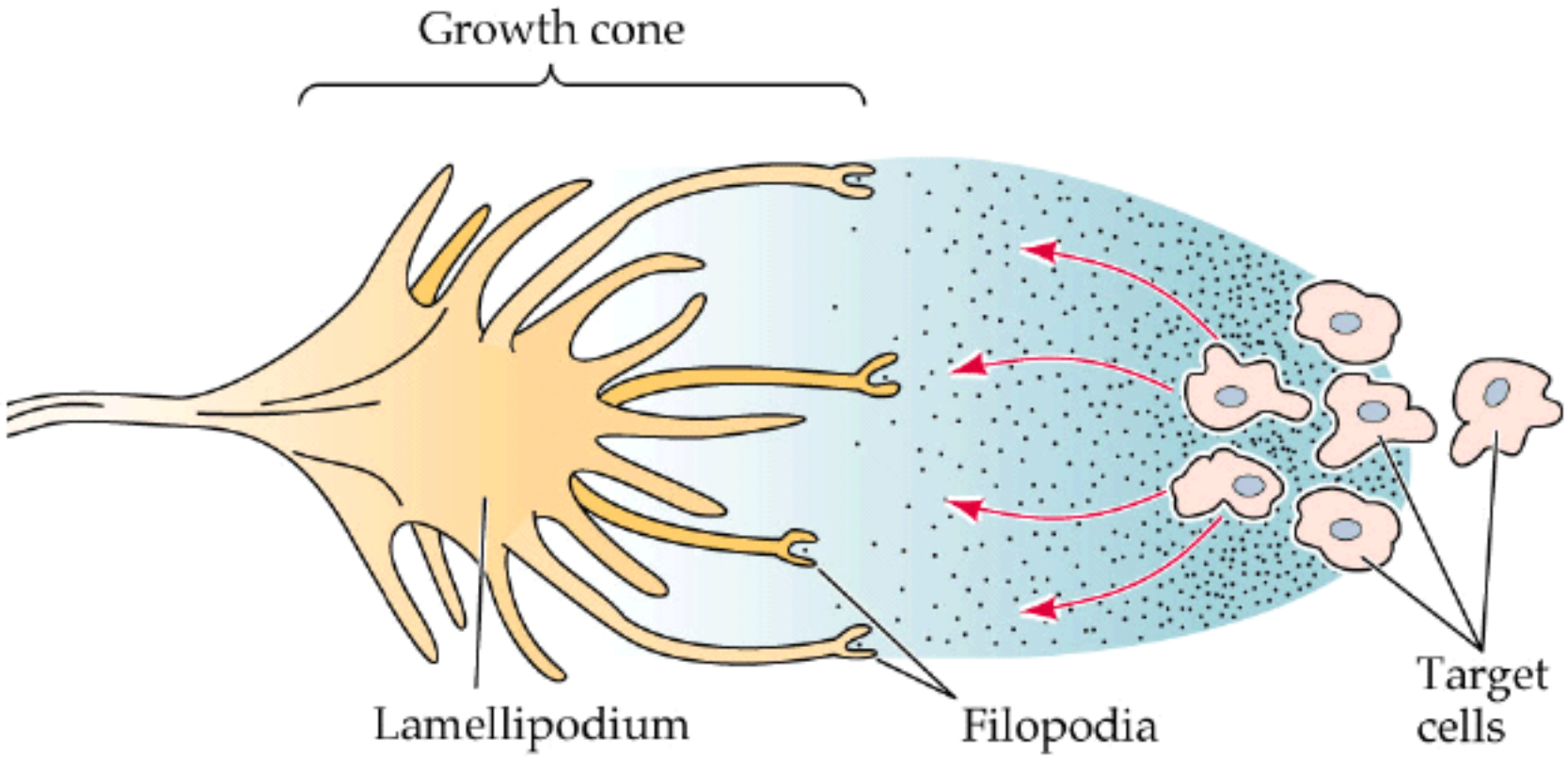
C. Making post-synaptic ligand receptors

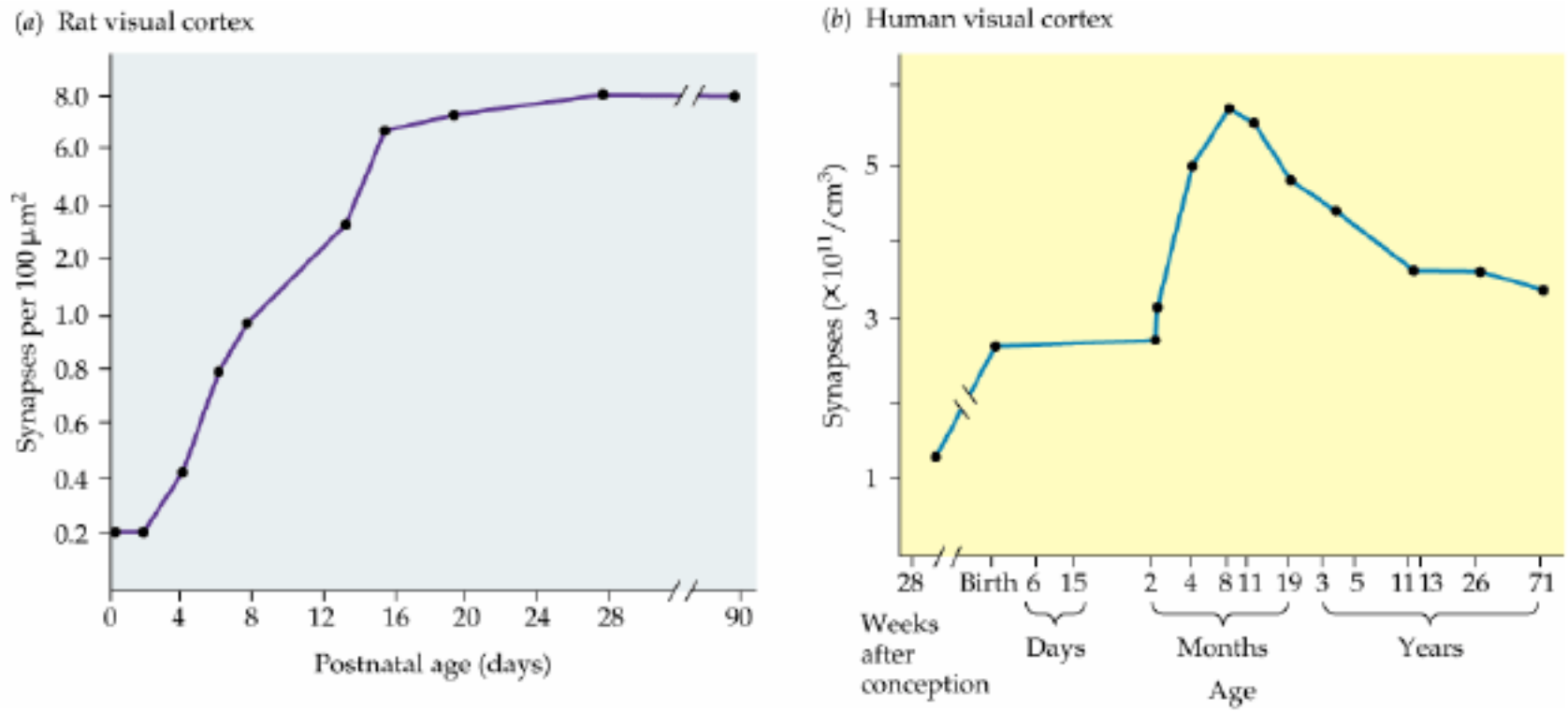
D. Temporal summation

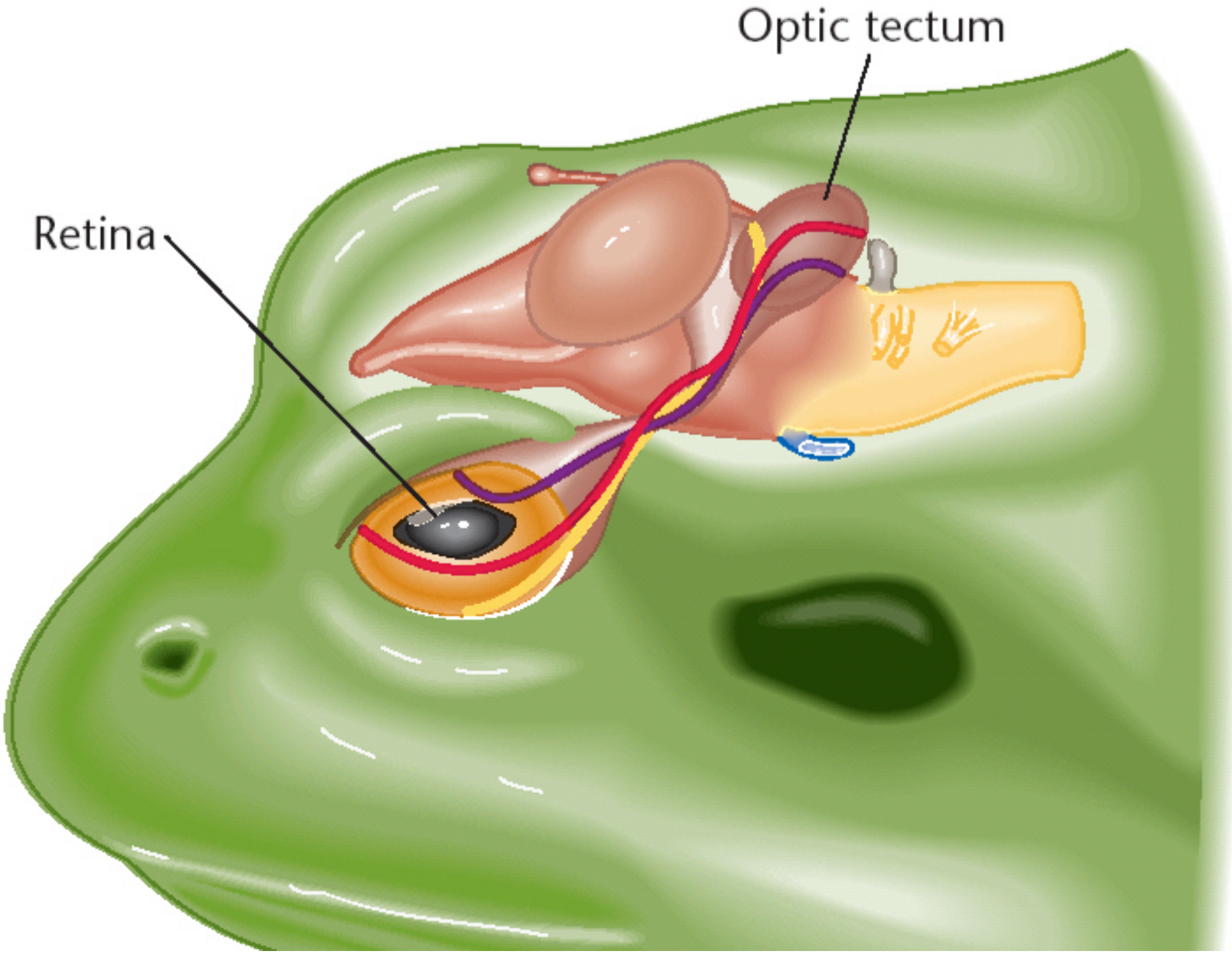


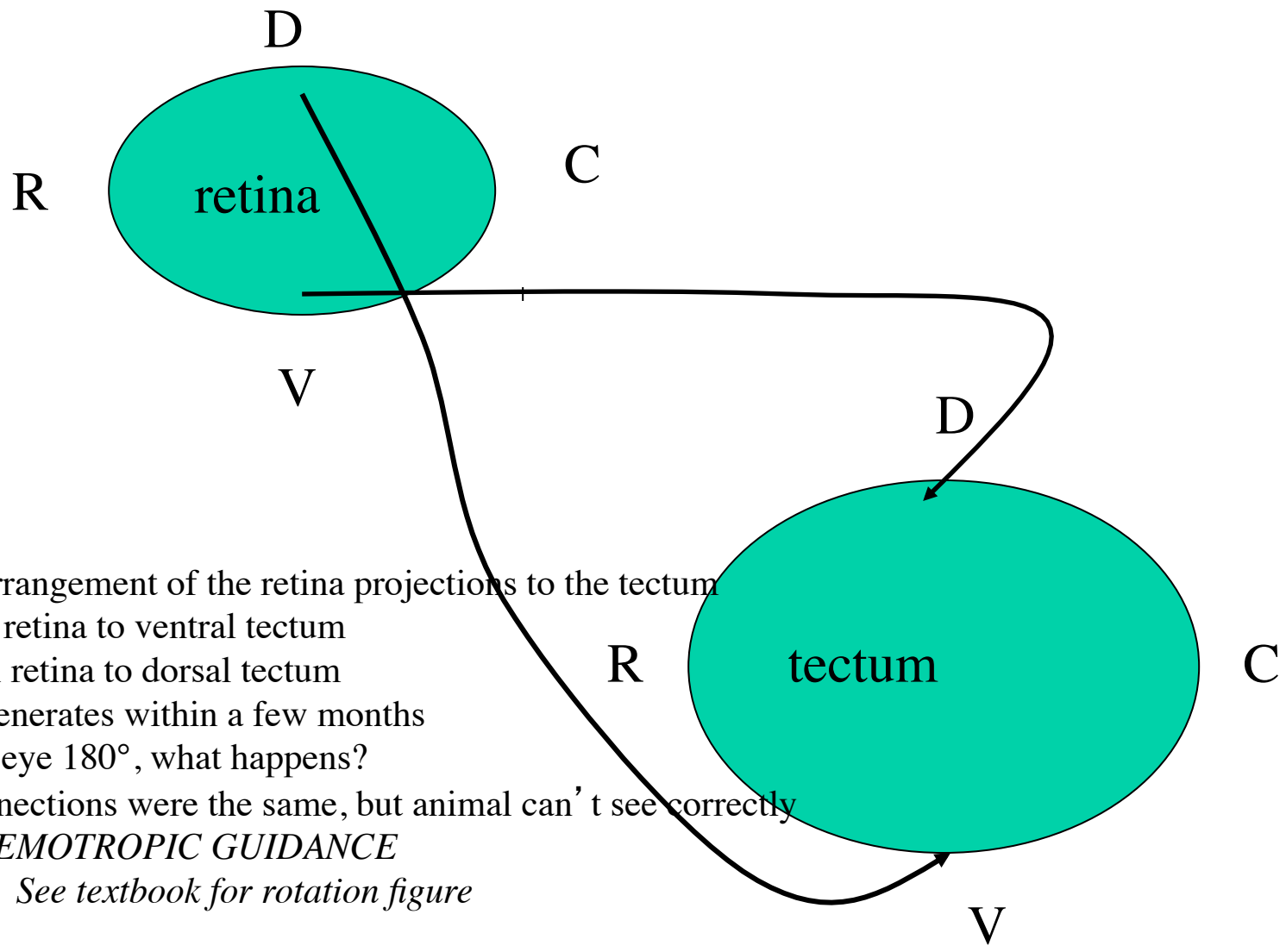
E. All are important parts of differentiation

4. Synaptogenesis





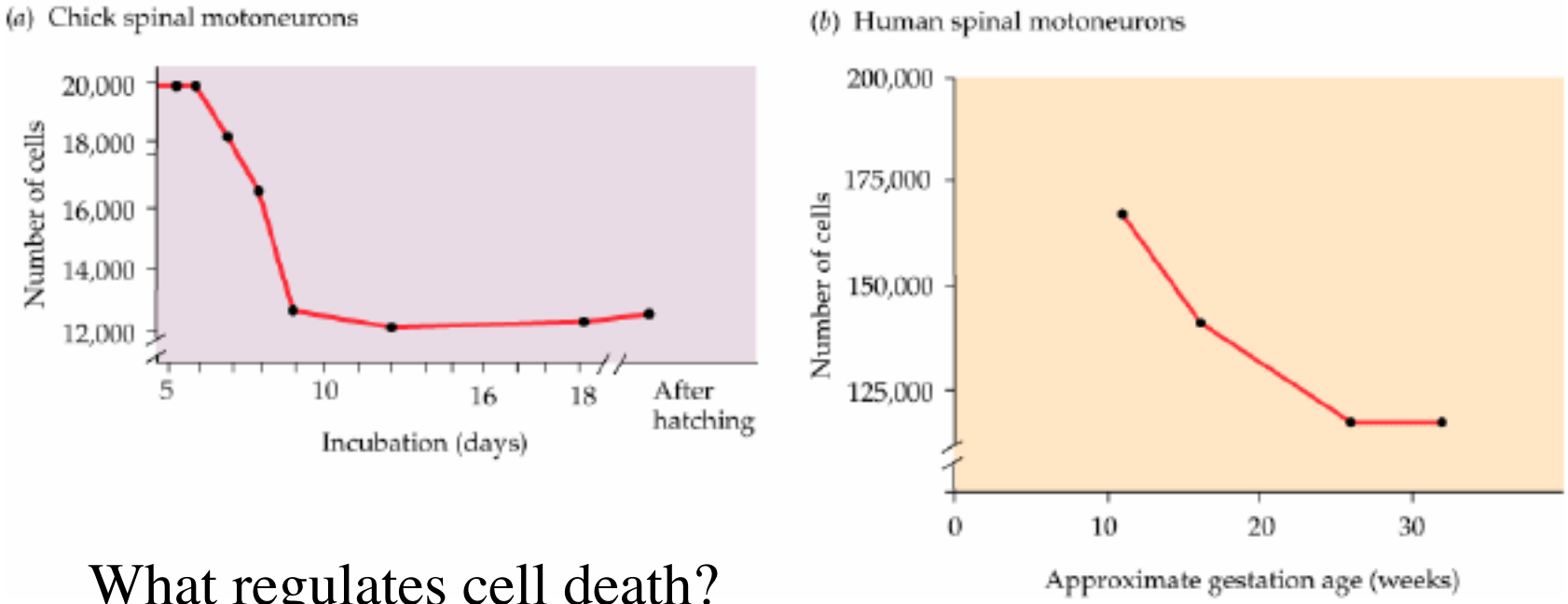

Optic tectum
Retina



Orderly arrangement of the retina projections to the tectum
- Dorsal retina to ventral tectum
- Ventral retina to dorsal tectum

If cut, regenerates within a few months
- Rotate eye 180°, what happens?
  - connections were the same, but animal can't see correctly
  - *CHEMOTROPIC GUIDANCE*
    - *See textbook for rotation figure*

5. Apoptosis/Cell death



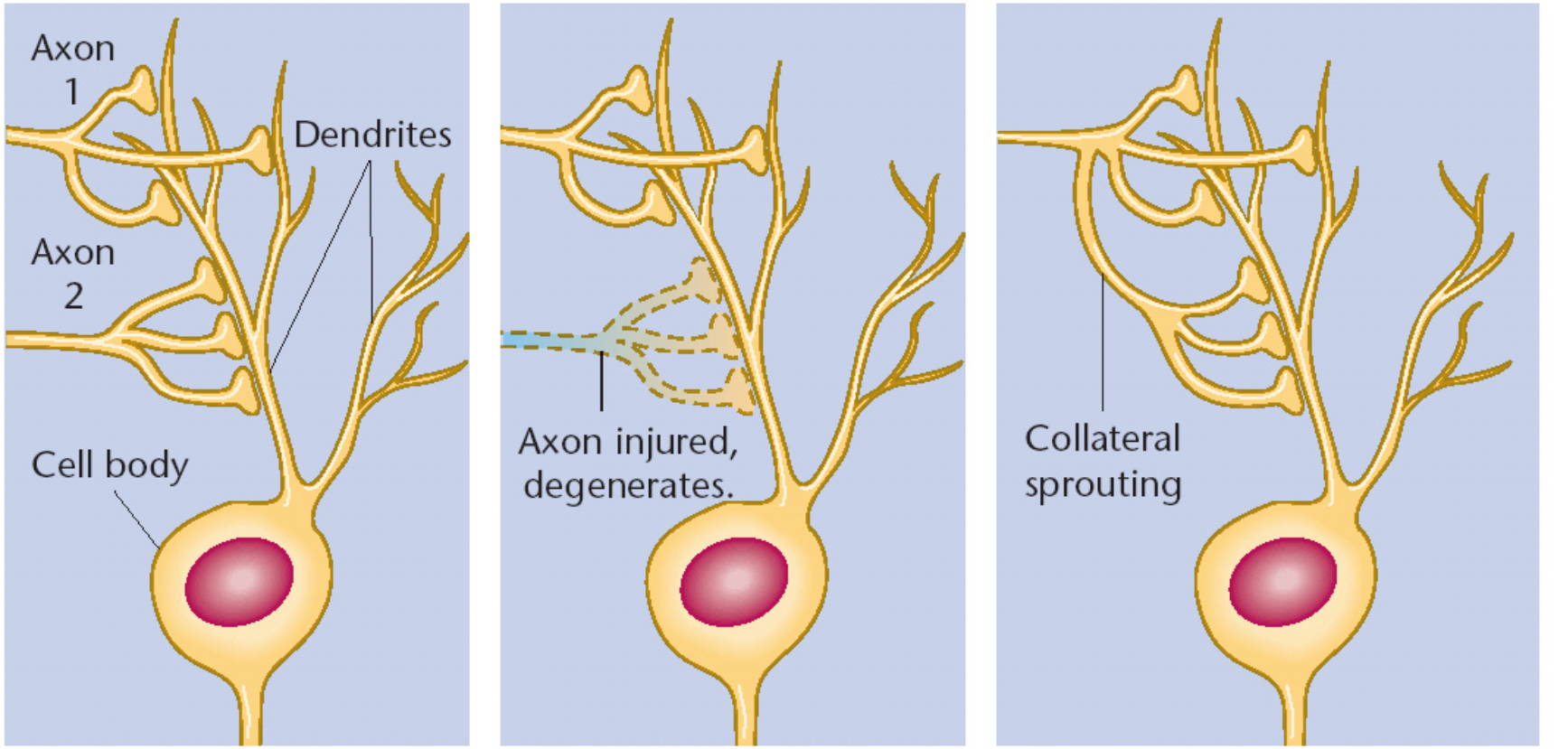
What regulates cell death?

size of target regulates neuron number

level of neurotrophic factors

NGF

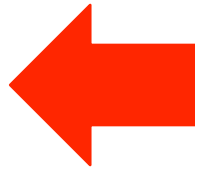
Synaptic remodeling



Self test question

What is the standard order of developmental processes?

A. Apoptosis, neurogenesis, synaptogenesis
B. Migration, synaptogenesis, apoptosis
C. Differentiation, apoptosis, migration
D. Synaptogenesis, migration, neurogenesis
E. None of the above



Development is interplay of

intrinsic factors – originating within organism (i.e., genes) and

extrinsic factors – those provided by environment

Enriched environments in rodents

Isolated housing, standard group housing, enriched housing

- Greater activity of AChE
- Heavier, thicker cortex, particularly visual cortex
- Larger neurons, more synapses
- Better learning
- Better recovery from brain damage

Super-impoverished environments in humans

- Orphanages etc

New *developments* …

Maternal licking early in life affects …

anxiety-related behaviors (open field test)

hormonal stress response

cognitive tasks

Passed on to next generation

High licking rat moms → High licking rat adult offspring
Low licking rat moms → Low licking rat adult offspring

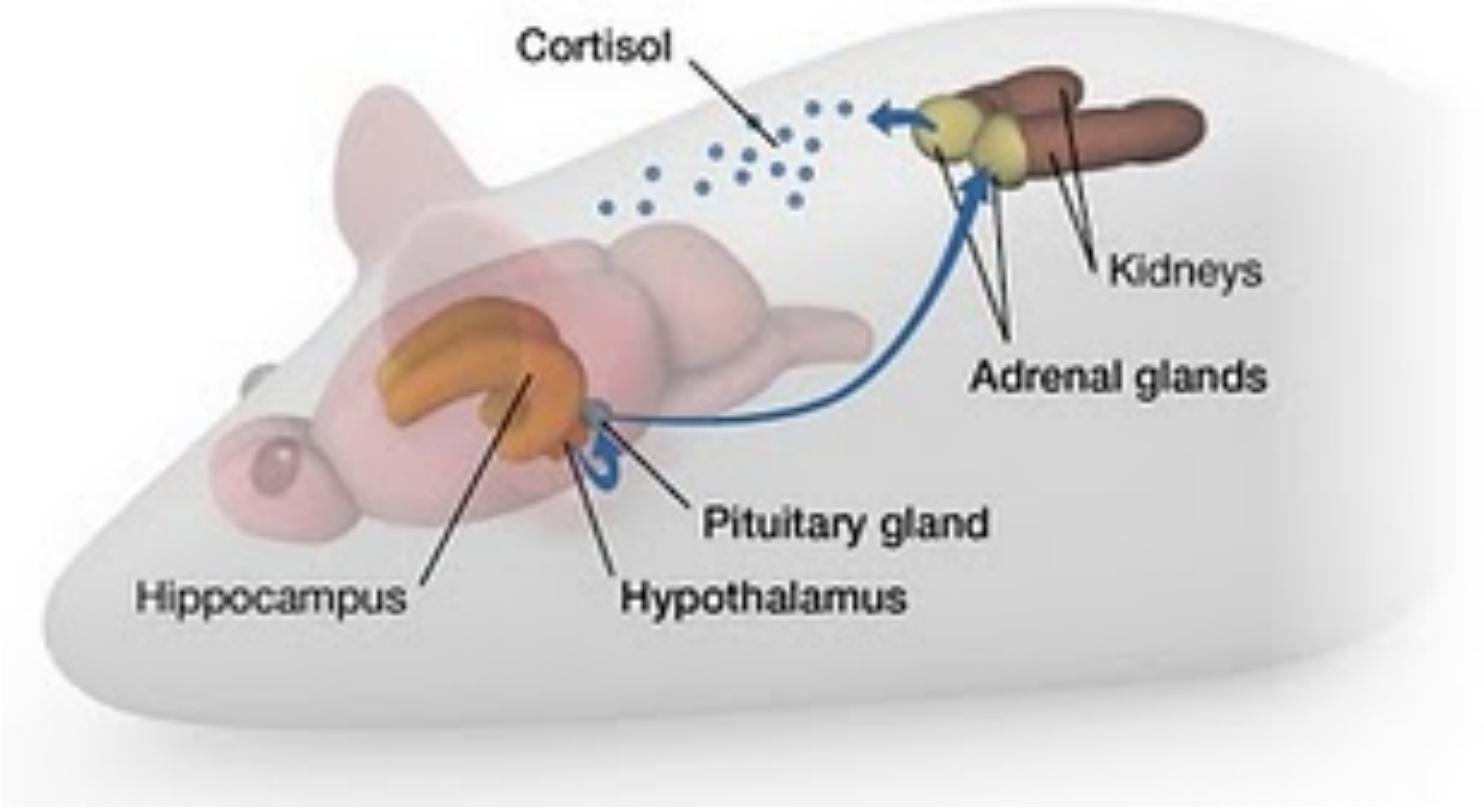
Reflect genetic differences between animals?????
Reflect differential treatment of animals???

Rat adoption studies – act like adopted mother
Maternal intervention studies – act like affected mother

Epigenetics – changes in gene EXPRESSION caused without changing the fundamental DNA sequence.

Can turn off genes with DNA methylation or histone deacetylation – referred to in New Yorker article

Glucocorticoid receptors in hippocampus



Self test question

What percentage of the genome do you think would have changed expression after being licked more as less as a young rat?

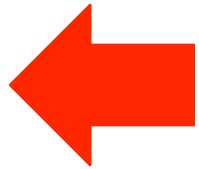
A. 0, because licking is environmental

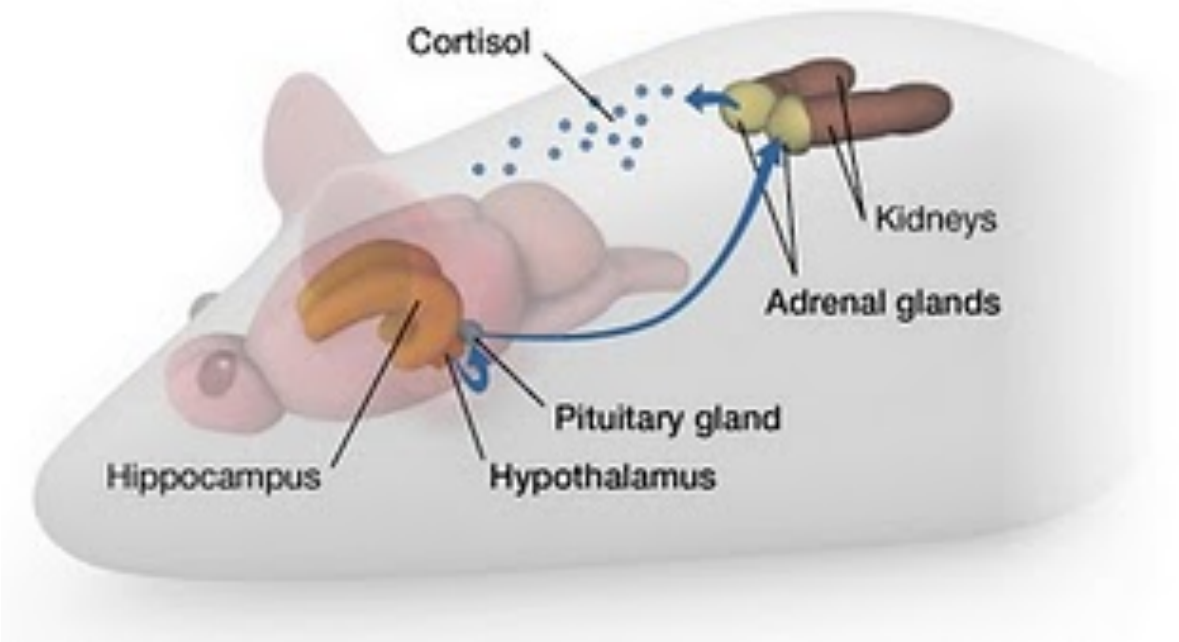
B. 0.01% (3 of 30,000)

C. 0.2% (60 of 30,000)

D. 0.5% (150 of 30,000)

E. 3% (1,000 of 30,000)





Compare high vs low-licked rats in adulthood
Microarray of gene expression in hippocampus (tests 30,000)

900 genes differed between groups!
Treated adults with drugs that alter epigenetic mechanisms
Reversed some behavior effects and some gene expression

Optional details for microarray study:

Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood

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Abstract

Early-life experience has long-term consequences on behavior and stress responsivity of the adult. We previously proposed that early-life experience results in stable epigenetic programming of glucocorticoid receptor gene expression in the hippocampus. The aim of this study was to examine the global effect of early-life experience on the hippocampal transcriptome and the development of stress-mediated behaviors in the offspring and whether such effects were reversible in adulthood. Adult offspring were centrally infused with saline vehicle, the histone deacetylase inhibitor trichostatin A (TSA), or the essential amino acid L-methionine. The animals were assessed in an unfamiliar open-field arena, and the hippocampal transcriptome of each animal was evaluated by microarray analysis. Here we report that TSA and methionine treatment reversed the effect of maternal care on open-field behavior. We identified >900 genes stably regulated by maternal care. A fraction of these differences in gene expression is reversible by either the histone deacetylase inhibitor TSA or the methyl donor L-methionine. These results suggest that early-life experience has a stable and broad effect on the hippocampal transcriptome and anxiety-mediated behavior, which is potentially reversible in adulthood.

Big lessons:

Mantra #2:
Brains → behavior
Behavior → brains

Understanding developmental mechanisms leads to interventions

Self test question

Thought question: what best describes the difference between gene effects in Huntington's and PKU?

A. Strength of the gene effect

B. The role of the environment

C. The interaction of gene and environment

D. How well we understand the gene effects

E. All of the above