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

Some Mechanisms of Drug Action

**Agonistic Drug Effects**

- Drug increases the synthesis of neurotransmitter molecules (e.g., by increasing the amount of precursor).
- Drug increases the number of neurotransmitter molecules by destroying degrading enzymes.
- Drug increases the release of neurotransmitter molecules from terminal buttons.
- Drug binds to autoreceptors and blocks their inhibitory effect on neurotransmitter release.
- Drug binds to postsynaptic receptors and either activates them or increases the effect on them of neurotransmitter molecules.
- Drug blocks the deactivation of neurotransmitter molecules by blocking degradation or reuptake.

**Antagonistic Drug Effects**

- Drug blocks the synthesis of neurotransmitter molecules (e.g., by destroying synthesizing enzymes).
- Drug causes the neurotransmitter molecules to leak from the vesicles and be destroyed by degrading enzymes.
- Drug blocks the release of the neurotransmitter molecules from terminal buttons.
- Drug activates autoreceptors and inhibits neurotransmitter release.
- Drug is a receptor blocker; it binds to the postsynaptic receptors and blocks the effect of the neurotransmitter.
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

**Red line is how much pleasure they got from the morphine**

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

In this condition, lever gave placebo. The red line indicates how much addicts reported liking what they received.

In this condition, lever gave very low doses of morphine.

Slightly higher dose of morphine given.

Higher dose of morphine given.
Blue line is how many times they pressed the morphine lever.

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

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Red line is how much pleasure they got from the morphine.

Even at the lowest doses (but not at 0 where there really is no morphine), they rapidly press the lever for 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.
<table>
<thead>
<tr>
<th>Substance users in America</th>
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<tbody>
<tr>
<td>Number of Alcohol Users</td>
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<td>Number of Tobacco Users</td>
</tr>
<tr>
<td>Number of Illegal Drug Users</td>
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<tr>
<td>TOTAL</td>
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</table>

<table>
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<tr>
<th>Annual social cost of substance abuse in America</th>
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</thead>
<tbody>
<tr>
<td>Cost of Alcohol Abuse</td>
</tr>
<tr>
<td>Cost of Tobacco Abuse</td>
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<tr>
<td>Cost of Illegal Drug Abuse</td>
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<tr>
<td>TOTAL</td>
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</table>

<table>
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<tr>
<th>Annual substance-related deaths in America</th>
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<tr>
<td>Alcohol-Related Deaths</td>
</tr>
<tr>
<td>Tobacco-Related Deaths</td>
</tr>
<tr>
<td>Illegal Drug-Related Deaths</td>
</tr>
<tr>
<td>TOTAL</td>
</tr>
</tbody>
</table>
Dose-Response Curve

After this point, increasing doses do not produce a stronger effect.
Dose-Response Curves for the Analgesic and Depressant Effects of Morphine

- Dose-response curve for the analgesic effect of morphine
- Dose-response curve for the depressive effect of morphine on respiration
- Margin of safety
Response vs Dose Graph

The graph depicts a curve that rises to a peak and then falls off, illustrating the relationship between dose and response.

Key Points:
- The x-axis represents the dose.
- The y-axis represents the response.
- The curve shows an optimal dose range where the response is maximized.
- Beyond this optimal range, the response decreases.

This type of graph is often used in pharmacology to determine the effective dose range for a drug.
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 effects
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
MEMORIZE THIS

www.pubmed.gov

And go to the site!!!
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

Abstract

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

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
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<tr>
<th>Demographic variables</th>
<th>Drinkers vs. abstainers (ref.)</th>
<th>Heavy vs. moderate drinkers (ref.)</th>
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<td>Education (ref. = less than HS)</td>
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<td>College or more</td>
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No details required from this slide

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<td>0.19</td>
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<td>1.65</td>
<td>(.48, 5.68)</td>
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<td>1.24</td>
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<tr>
<td>Community Churches</td>
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<td>(.90, 3.89)</td>
<td>.079</td>
<td>0.76</td>
<td>(.32, 1.83)</td>
<td>.522</td>
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<td>Jehovah’s Witness</td>
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<td>(.51, 2.55)</td>
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<td>0.89</td>
<td>(.53, 1.51)</td>
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<td>Catholic</td>
<td>1.74</td>
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<td>.000</td>
<td>1.52</td>
<td>(1.15, 2.01)</td>
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<td>(.85, 1.84)</td>
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<td>.888</td>
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<td>(.69, 2.01)</td>
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<td>(.49, 1.62)</td>
<td>.657</td>
<td>0.31</td>
<td>(.15, .62)</td>
<td>.004</td>
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</table>
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?
DRUG SENSITIZATION

Rate of Drug Sensitization

Drug Challenge

Shift in Dose-Effect Curve

Repeated Treatments

Dose of Drug

Fake data
Psychomotor Sensitization

Real data

(data from Anagnostaras & Robinson, 1996)
Blue line is how many times they pressed the morphine lever

Red line is how much pleasure they got from the morphine

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

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

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


Clinical Pharmacology Branch (R.J.L., K.L.P., R.A.M., F.D., J.E.H.) and Preclinical Pharmacology Branch (C.W.S., J.L.K., S.R.G.), National Institute on Drug Abuse, Addiction Research Center, Baltimore, Maryland; Behavioral Pharmacology Research Unit (K.L.P.), Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, Maryland; and Division of Addiction Research & Treatment (R.J.L.), Department of Mental Health Sciences, Hahnemann University, Philadelphia, Pennsylvania

Accepted for publication August 29, 1991

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

Genetically transmitted disease
Clumsines, 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

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 $\rightarrow$ retardation
Enz deficiency – phenylalanine $\rightarrow$ normal
Enz sufficiency $\pm$ phenylalanine $\rightarrow$ 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 \(\rightarrow\) changes in sex behavior

Photo credit: © Eric Isselée
Brain Development
Problem: How do you build a nervous system?

~100 billion neurons \((10^{11} \text{ neurons})\)
  \(\times\) 1000 synapses per neuron

= 100 trillion synapses \((10^{14} \text{ synapses})\) or
  or 100,000,000,000,000 synapses

How many genes? About half for brain
1. Neurogenesis/cell proliferation

- This cell will differentiate into a neuron.
- This cell undergoes a second round of mitosis.
Adult neurogenesis
2. Migration

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
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

Growth cone

Lamellipodium  Filopodia

Target cells
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

At first

Loss of an axon

Sprouting to fill vacant synapses
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 $\rightarrow$ High licking rat adult offspring
Low licking rat moms $\rightarrow$ 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
Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood

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 $\rightarrow$ behavior  
Behavior $\rightarrow$ brains

Understanding developmental mechanisms leads to interventions
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