



Mood Disorders

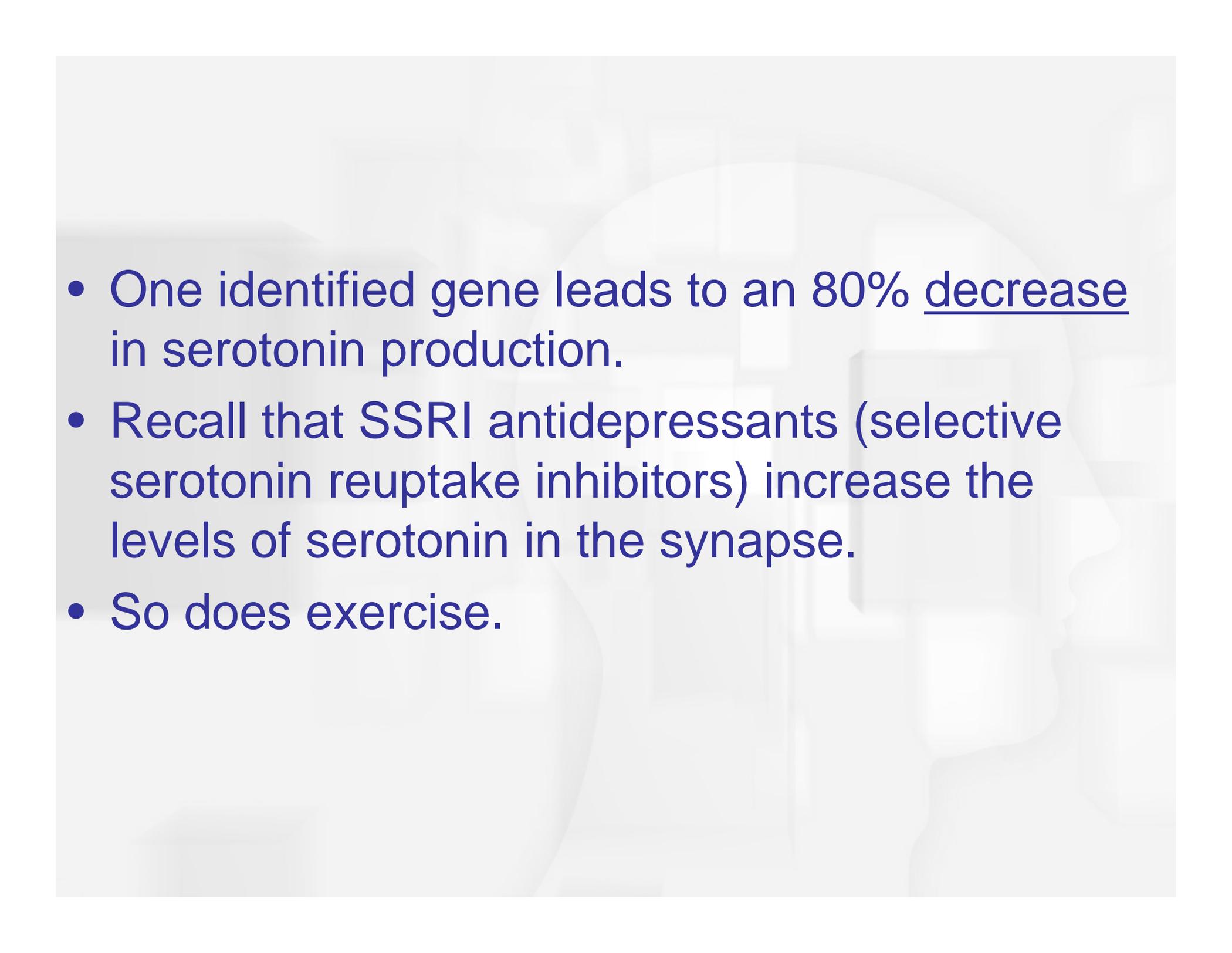
Mood Disorders

- **Major depression** - feeling sad and helpless every day for weeks at a time; includes the following characteristics:
 - Little energy.
 - Feelings of worthlessness.
 - Suicidal thoughts.
 - Feelings of hopelessness.
 - Difficulty sleeping.
 - Difficulty concentrating.
 - Little pleasure from sex or food.

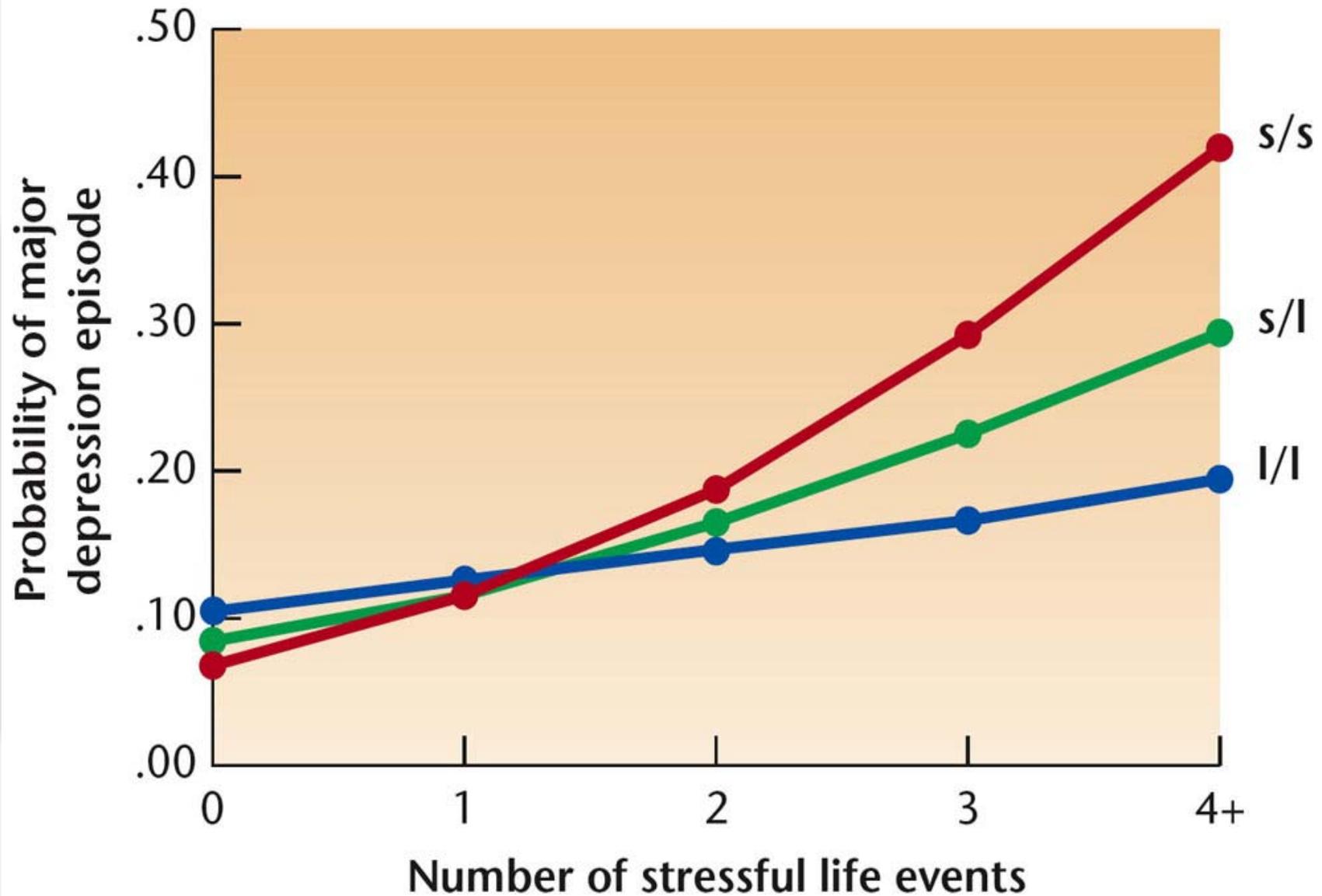
- Similar symptoms can result from hormonal problems, head injuries, brain tumors, or other illnesses.
- They often exist with other disorders: schizophrenia, substance abuse, anxiety, or Parkinson's disease.
- Absence of happiness is a more reliable symptom than increased sadness.
- It occurs at any age.
- It is twice as common in women.
- About 10% of all people will experience it in their lifetime.

Mood Disorders

- There is a moderate degree of heritability.
 - 60% concordance for monozygotic twins
 - 20% for dizygotic twins
 - Not a single-gene defect
- Some of the genes are also associated with anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), drug addiction, migraine headaches, and several other conditions.
- Risk is increased in relatives of women with early-onset depression (before 30).

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- One identified gene leads to an 80% decrease in serotonin production.
 - Recall that SSRI antidepressants (selective serotonin reuptake inhibitors) increase the levels of serotonin in the synapse.
 - So does exercise.

- Another gene codes for the serotonin transporter protein.
 - It controls the ability of the axon to transport the neurotransmitter back into the axon after its release.
- Inheritance of the “short form” of the gene from both parents increases the likelihood of depression after stressful events.
 - The gene may alter the way people react to stressful events.



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s/s: short/short form of serotonin transporter; s/l: short form from one parent, long form from other parent; l/l: long form from both.

Fig. 15-6, p. 460

Hormones

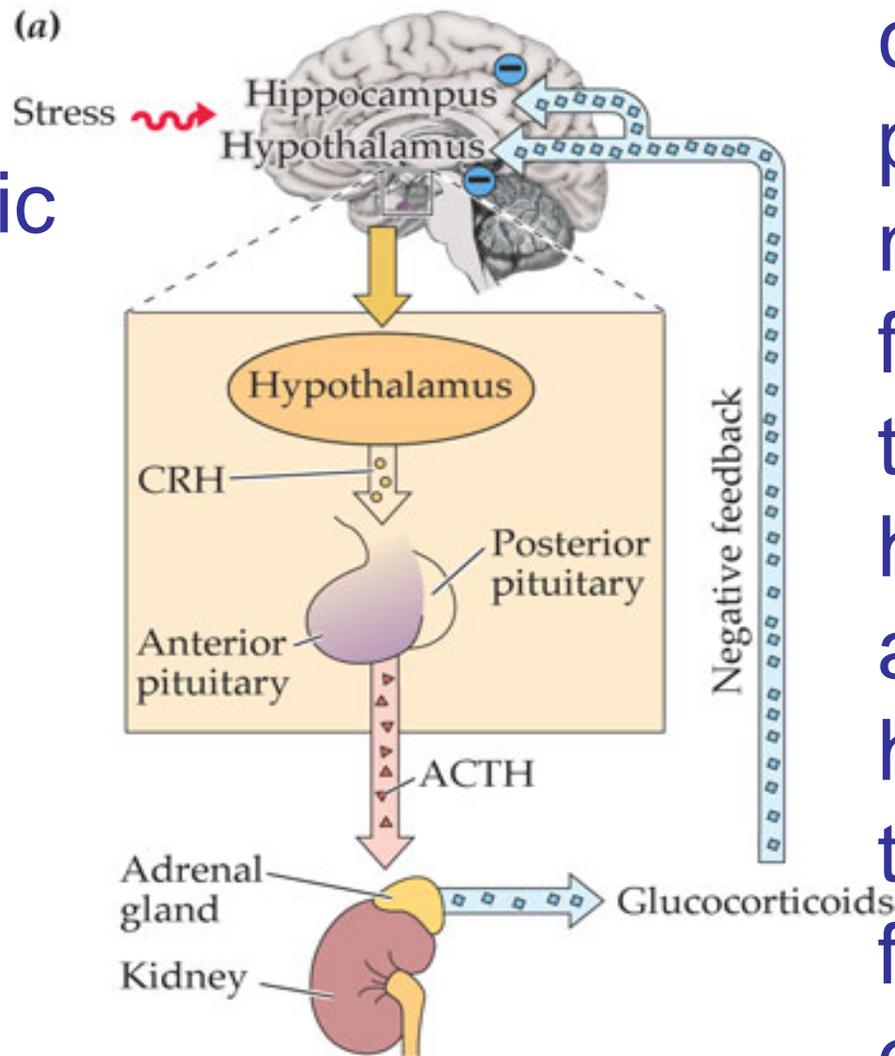
- Hormones are also involved with depression.
- A likely trigger for an episode of depression is stress and the release of cortisol.
- Prolonged elevated levels exhaust the body's energies (use up stored glycogen & break down muscle protein) and impair sleep and the immune system.
 - This sets the stage for an episode of depression.

Hormones

- **Postpartum depression**
- Affects ~20% of women and most recover quickly.
- ~1 in 1000 enter a serious, lengthy depression.
- More common among women who:
 - have suffered depression at other times.
 - experience severe discomfort during the times around menstruation.
- May be associated with a drop in estrogen and progesterone levels or with decreased levels of a progesterone metabolite.

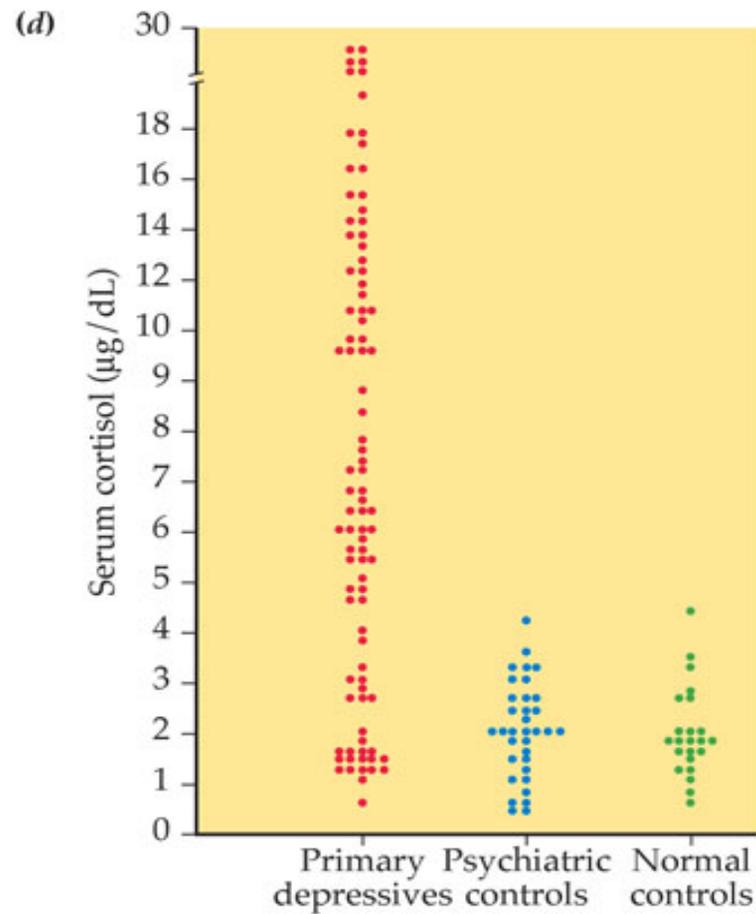
Cortisol is often increased in depressed people.

Stress →
release of a
hypothalamic
hormone →
pituitary
release
ACTH →
stimulates
the adrenal
gland to
secrete
cortisol.

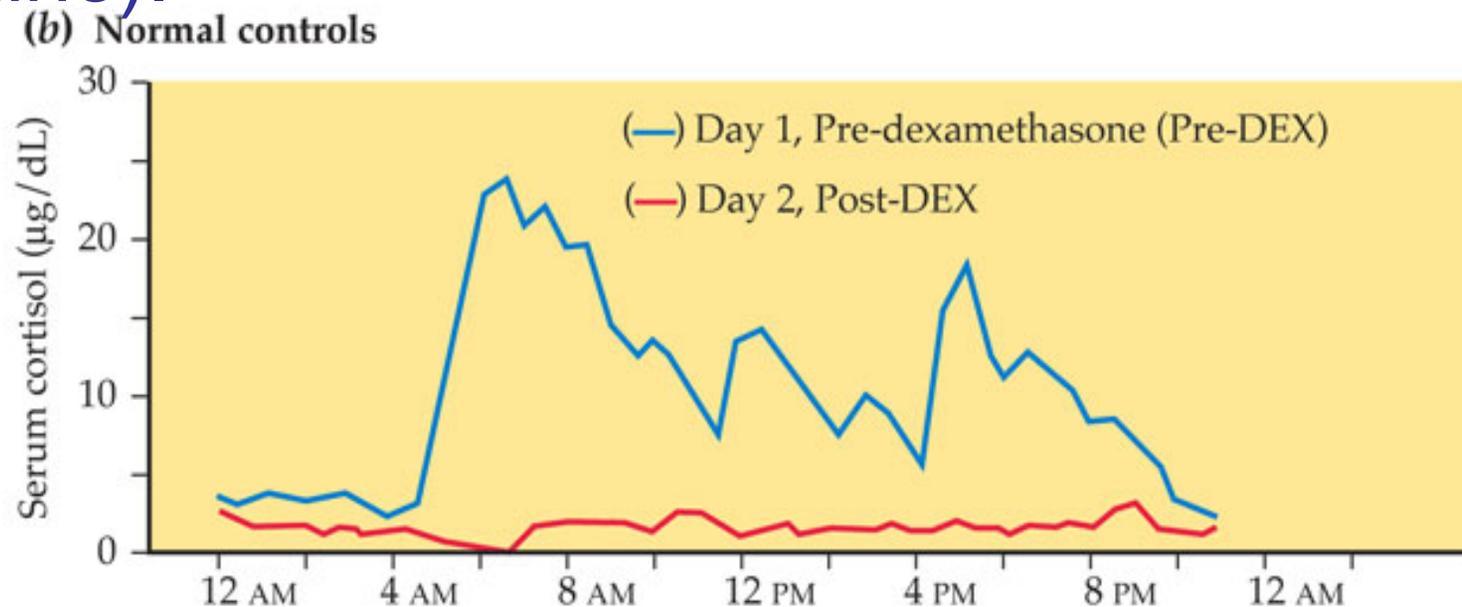


Normally,
cortisol
provides
negative
feedback to
the
hypothalamus
and
hippocampus
to decrease
further release
of cortisol.

Cortisol is increased in depressed patients

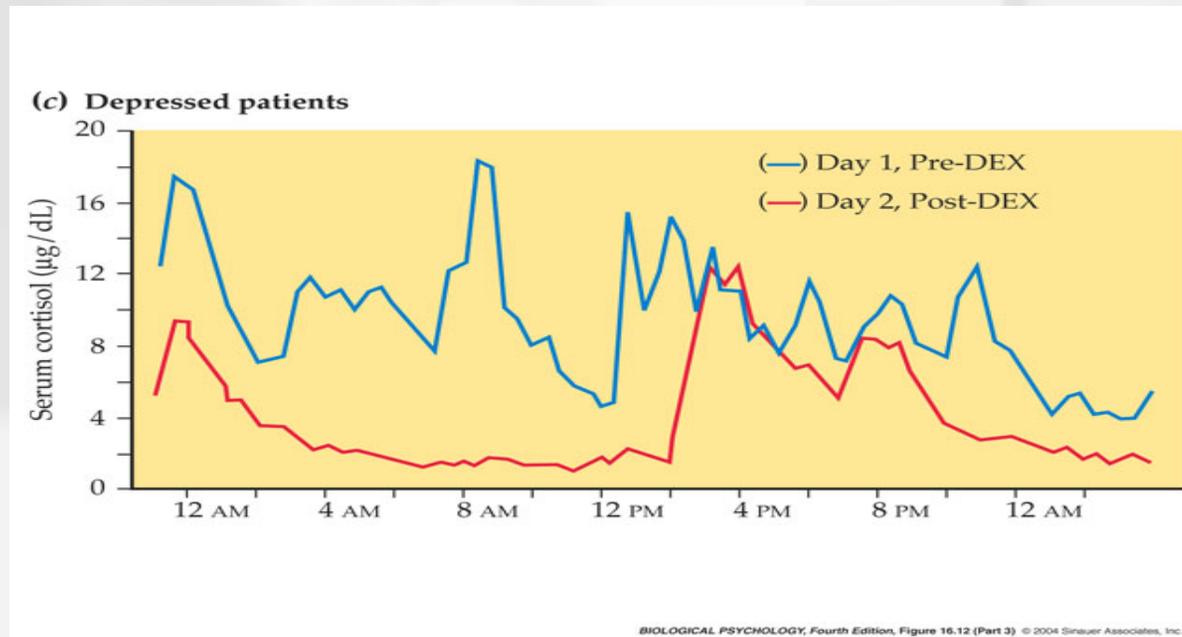


In normal people, cortisol has several peaks during the day (blue line). Injection of a potent glucocorticoid provides so much negative feedback that cortisol levels are very low all day (red line).



(A glucocorticoid is a hormone from the adrenal cortex that regulates glucose.)

In depressed people the glucocorticoid decreases cortisol in the morning, but by afternoon, levels are close to normal. Therefore, there is less negative feedback in depressed people.



Effects of high cortisol levels:

- Increased cell death in hippocampus
 - Brief cortisol exposure increases activity in the hippocampus and helps one remember an acute stressor.
 - The hippocampus provides negative feedback on cortisol levels.
 - Lengthy high levels increase cell death and decrease the formation of new neurons.

Effects of high cortisol levels:

- The result is a vicious circle: High cortisol → cell death in the hippocampus → less negative feedback → higher cortisol.
- Depressed people often have bad memory and difficulty reasoning because of hippocampus damage.

Effects of antidepressants on neurogenesis

- The major class of antidepressants are Selective Serotonin Reuptake Inhibitors (SSRIs, example: Prozac).
- SSRIs increase the production of Brain-Derived Neurotrophic Factor (BDNF), which increases neurogenesis, cell survival, and number of dendrite branches in the hippocampus. (“Neurotrophic” means “growing neurons.”)
- As a result, rats given an SSRI had better negative feedback and were less fearful in a stressful situation.

Changes in brain activity

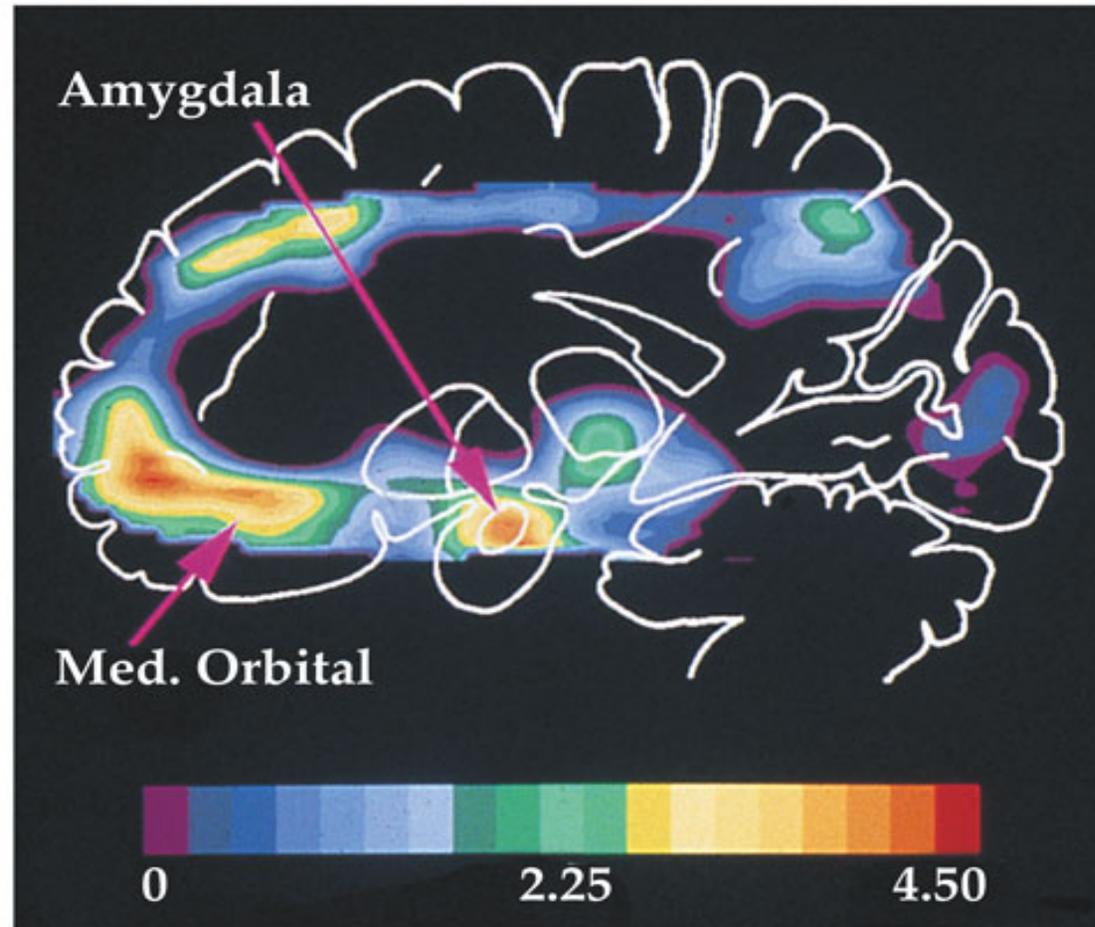
- Depression is associated with the following changes in brain activity:
 - **Decreased** activity in the **left** prefrontal cortex.
 - **Increased** activity in the **right** prefrontal cortex.
 - Also increased activity in the amygdala.
- Many people become seriously depressed after left-hemisphere damage.
- Occasionally, people with right hemisphere damage become manic.

Increased blood flow to frontal lobes, amygdala, and anterior cingulate cortex

Increased activity in right frontal lobes → “obsessing” (recurring negative thoughts).

Increased activity in amygdala → anxiety

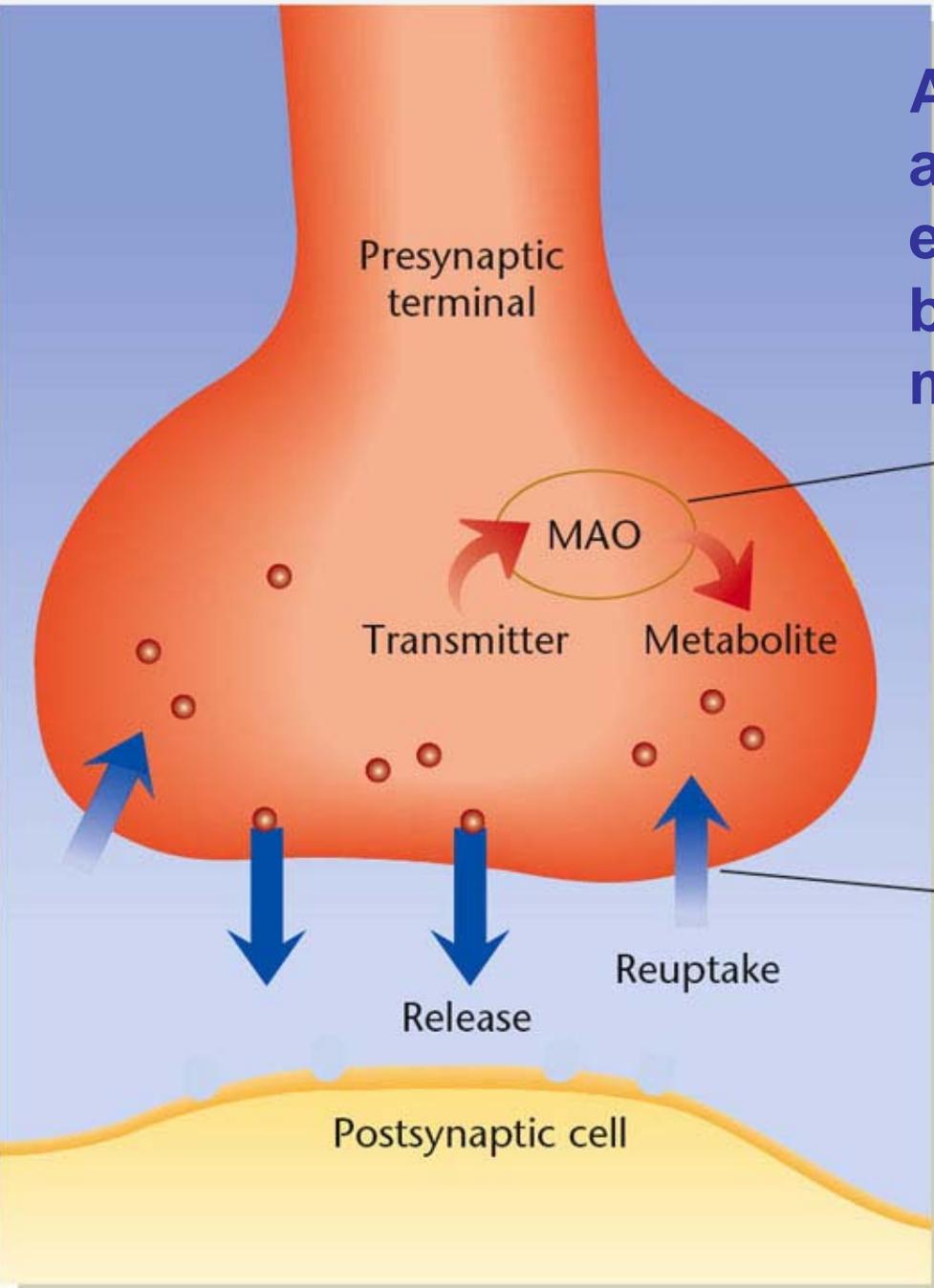
Increased activity in anterior cingulate cortex → sadness, anxiety



Neurochemical theories

- Monoamine hypothesis: Depression results from low levels of monoamine transmitters (dopamine, norepinephrine, serotonin).
 - The earliest antidepressants inhibited the enzyme that breaks down all monoamines.
 - Therefore, inhibiting that enzyme would prolong all monoamines in synapses.

All major antidepressants affect either reuptake or breakdown of monoamine transmitters.



MAOIs block the enzyme MAO, prevent it from breaking transmitters into inactive metabolites

Tricyclic drugs and SSRIs block reuptake

The case for serotonin (5-hydroxytryptamine, 5-HT)

- Suicide victims often have lower levels of serotonin or its metabolites in brain.
- People with a variant gene for either the serotonin transporter or one type of serotonin receptor are more susceptible to depression.
- Selective serotonin reuptake inhibitors (SSRIs) are more effective than most other antidepressants.

SSRIs

- SSRIs are more effective than drugs that increase all monoamines, and have fewer side effects.
- They increase neurogenesis in the hippocampus.
- They increase production of brain steroids, especially a metabolite of progesterone that stimulates GABA receptors and decreases anxiety.
- Psychotherapy + SSRI is more effective than either alone.

Mood Disorders

- In some depressed people, neurons in the hippocampus and the cerebral cortex shrink.
 - This may be due to high levels of cortisol.
- Behavioral effects of antidepressant drugs probably depend on slow changes in the brain:
 - Drug → release of BDNF → neuron growth and survival in hippocampus.
 - This provides better negative feedback to decrease cortisol.

Regular exercise

Effective on mild to moderate depression.

Increases release of serotonin & BDNF

Mimics effects of SSRIs

Also increases release of opioid neurotransmitters (effects are like opiates).



Problems with the serotonin hypothesis

- Time course of SSRIs: The drug acts at synapses within hours, but it takes weeks to improve depression.
- Only ~1/2 are “cured”; ~ 20% show no improvement.
- No evidence that they work in children or adolescents, and they may increase the likelihood of suicide in adolescents.

Other treatments

- **Electroconvulsive therapy (ECT)**: an electrically induced seizure, used for the treatment of severe depression.
- Used with patients who did not respond to antidepressant medication or are suicidal.
- Applied every other day for two weeks.
- Side effects include memory loss.
 - Memory loss is minimized if shock is localized to the right hemisphere.
 - Induces release of monoamine transmitters

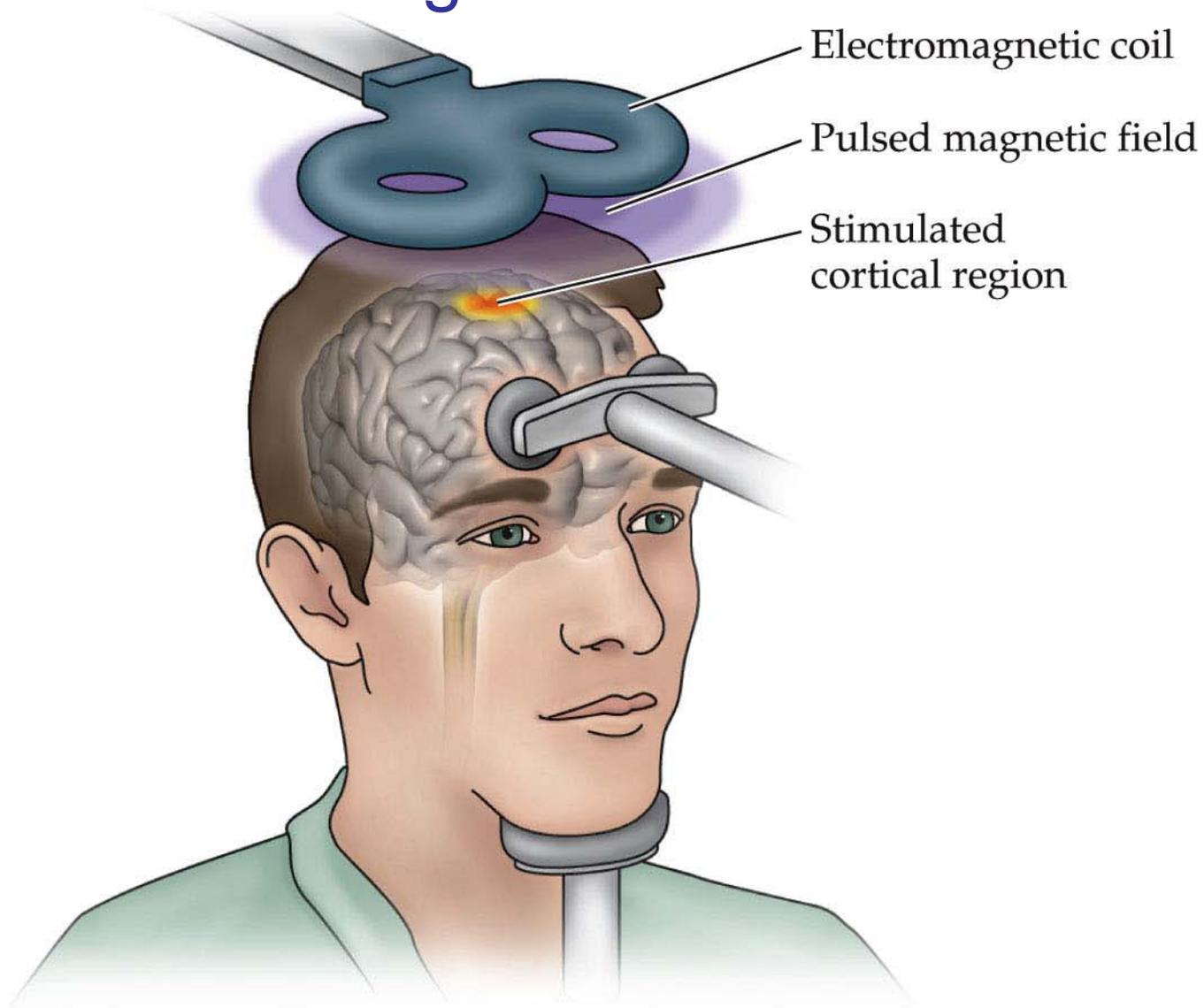
Mood Disorders

- A drawback of ECT: the high risk of relapse.
- Animal studies suggest that it alters gene expression in the hippocampus and frontal cortex, including genes for neurotrophins (like BDNF).

Other treatments

- “Transcranial magnetic stimulation” is another treatment for depression: intense magnetic field is applied to the scalp, to stimulate the neurons.
- Rapidly changing magnetic fields induce weak electric currents in tissue
- It is like ECT in its level of effectiveness.
- Exact mechanisms of its effects are unknown, but it does alter metabolism of monoamines.

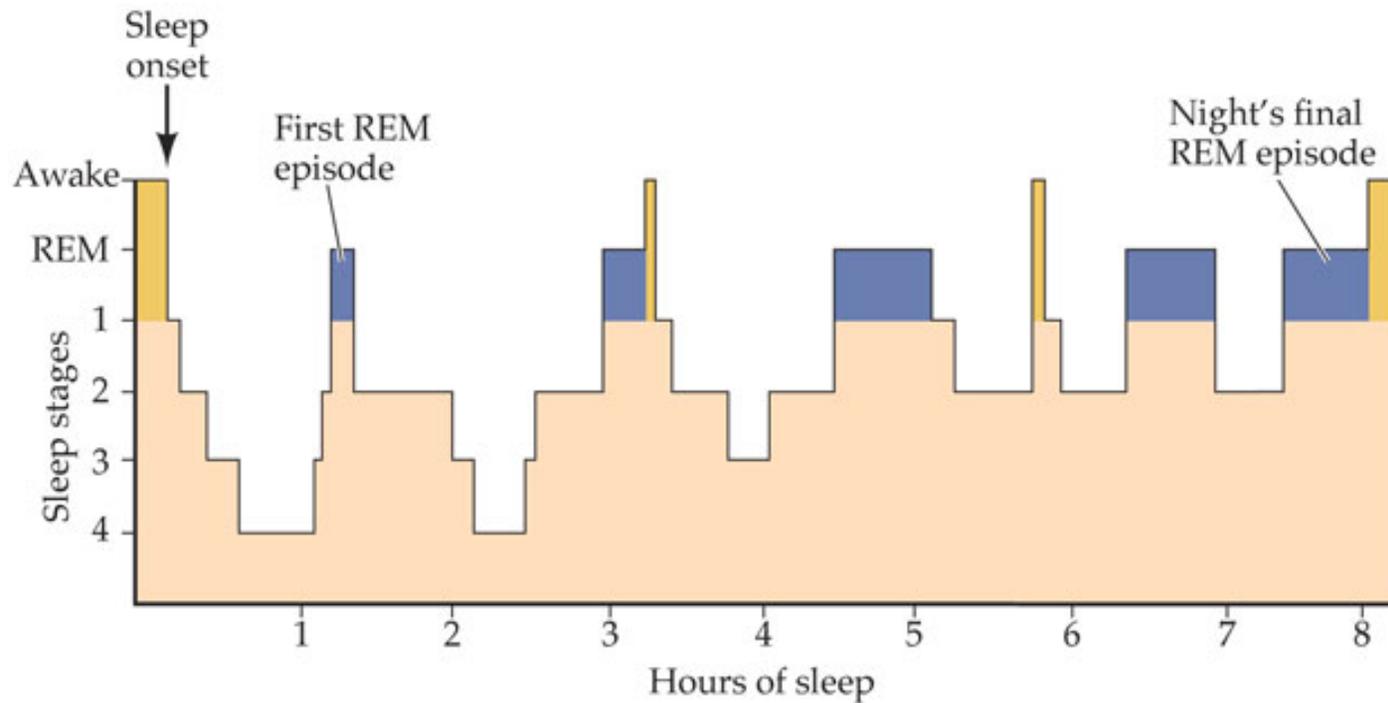
Transcranial magnetic stimulation



Sleep Patterns

- Disruption of sleep patterns is common in depression.
 - Depressed people usually fall asleep but awaken early and are unable to get back to sleep.
 - They enter REM sleep within 45 minutes (rather than the usual 90 minutes) and have an increased number of eye movements during REM sleep.

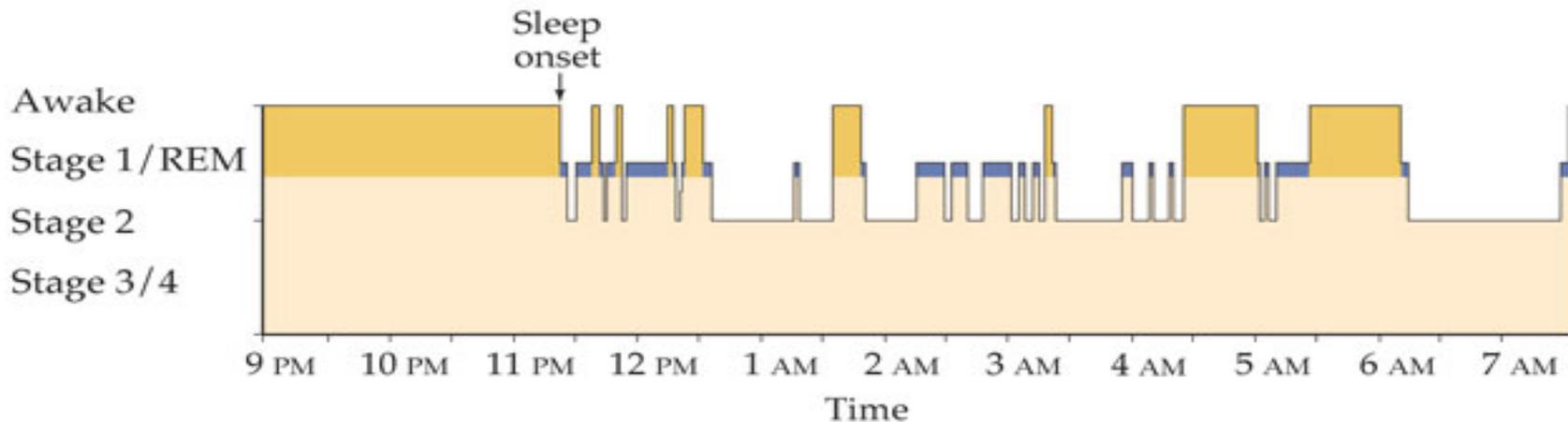
Normal sleep pattern



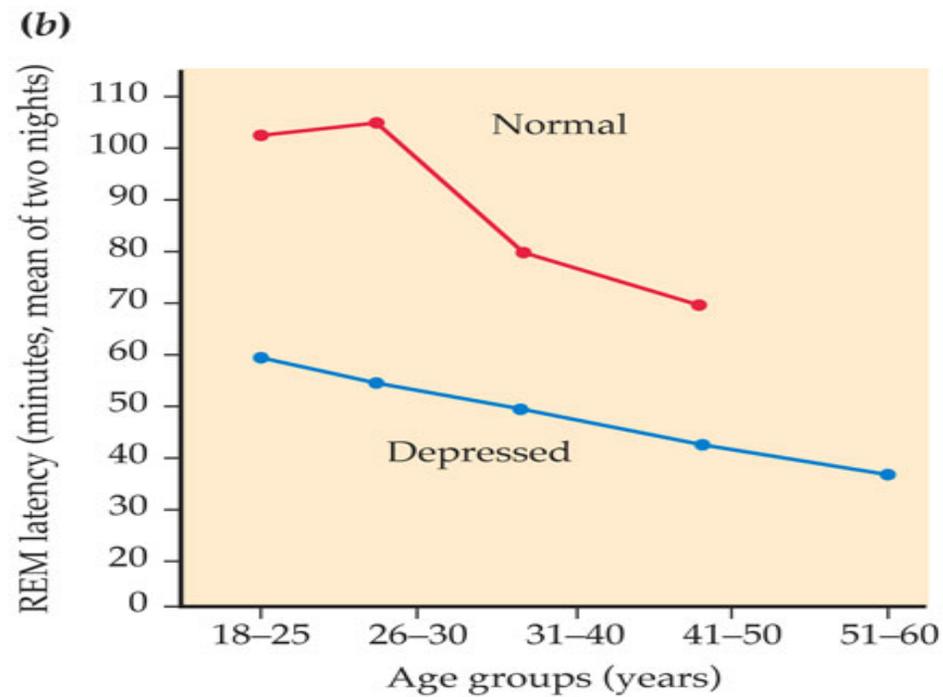
Sleep pattern in depression

Long time to fall asleep; lack of stages 3 & 4; earlier onset of REM and more REM, especially early in the night

(a) Sleep pattern of a patient with depression



Early entry into REM in depressed people



Altering sleep patterns sometimes helps depression

- Most depressed people are phase-advanced in their sleep cycles.
- 3 wks of REM deprivation improved depression
- Several antidepressant drugs suppress REM.
- Some people are helped temporarily by total sleep deprivation for 1 night.
- Others are helped by going to bed from 5 pm to midnight for a week & gradually going back to normal sleep times.

Summary of Depression

- Symptoms
 - Sad & helpless; feel worthless
 - Loss of interests, energy, appetite
 - Agitated; Contemplate suicide
 - Can't concentrate
 - Little or no pleasure from eating or sex
- High cortisol → damage hippocampus
 - Decreased negative feedback; damages memory

- Daily biological rhythms are phase advanced.
- Genetic predisposition (not just one gene)
- Women > men
- Treatments
 - SSRIs, other drugs that inhibit breakdown or transport of monoamine transmitters.
 - SSRIs → BDNF → new neuron survival
 - ECT and transcranial magnetic stimulation
 - REM deprivation; Don't sleep for 1 night; Go to bed earlier
 - Glucocorticoid antagonist

Mood Disorders

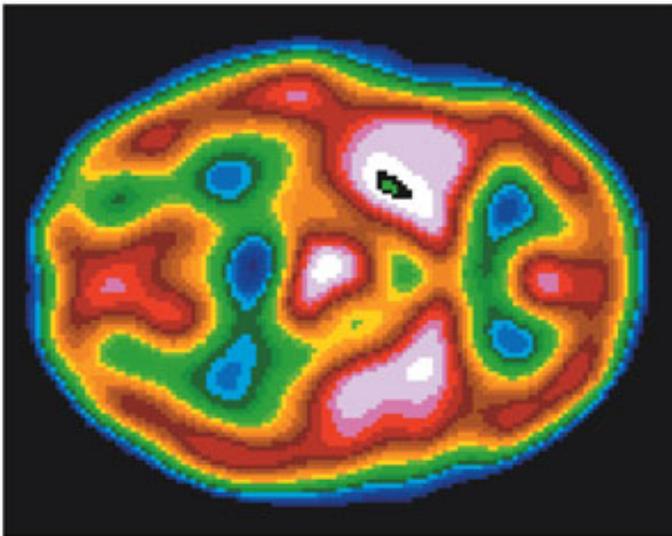
1. **Unipolar disorder**: alternating states of normality and depression.
2. **Bipolar disorder** (manic-depressive disorder): alternating states of depression and mania.
 - **Mania** - restless activity, excitement, laughter, self-confidence, rambling speech, and loss of inhibition.

Mood Disorders

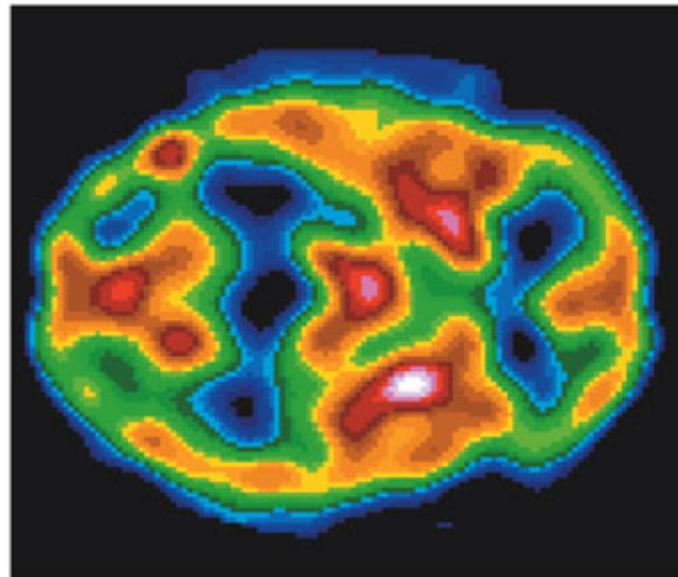
- **Bipolar disorder I** - full blown episodes of mania.
- **Bipolar disorder II** - much milder manic phases (hypomania) in which anxiety and agitation are the primary symptoms.
- Affects approximately 1% of people.
- Average age of onset: early 20's.
- Brain's use of glucose increases during periods of mania and decreases during periods of depression.

Brain activity in manic vs. depressive episode

Manic



Depressive



Heritability for bipolar disorder

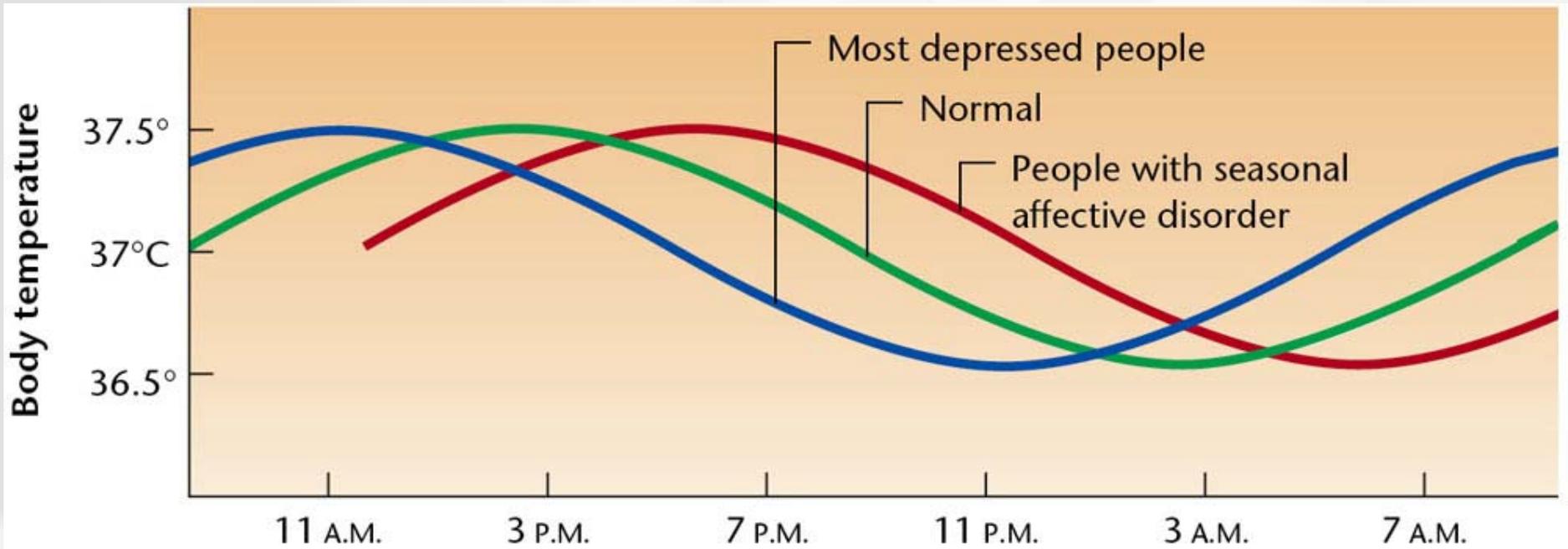
- Twin studies: monozygotic twins: 50% concordance rate.
- Dizygotic twins, brothers, sisters or children: 5 – 10% concordance rate.
- Several genes are somewhat more common in people with the disorder.
- Genes increase the risk but do not cause the disorder.
- Enlarged ventricles suggest decreased brain volume
- Larger amygdala than normal

Treatments for bipolar

- :
- 1. Lithium - a salt that stabilizes mood and prevents relapse in mania or depression
- 2. Drugs - anticonvulsant drugs
 - Usually prescribed for bipolar II.
- These drugs work by blocking the synthesis of a chemical that is produced during brain inflammation.

Seasonal Affective Disorder (SAD)

- A form of depression that regularly occurs during winter.
- Patients with SAD have phase-delayed sleep and temperature rhythms, whereas most depressed people have phase-advanced patterns.
- Treatment includes the use of very bright lights in the morning.
- The most likely explanation is that the light affects serotonin synapses and alters circadian rhythms.



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Fig. 15-13, p. 468

Light treatment for SAD



Light therapy for SAD

Attention-Deficit Hyperactivity Disorder (ADHD)

- ADHD is typically diagnosed during childhood.
- Symptoms:
 - Inattention and/or hyperactivity
 - Forgetfulness
 - poor impulse control or impulsivity
 - distractibility.
- ADHD is a persistent and chronic condition for which no medical cure is available, although medication and therapy can treat symptoms.

Attention-Deficit Hyperactivity Disorder (ADHD)

- ADHD is usually diagnosed in children, but about 60% of children diagnosed with ADHD retain the condition as adults.
- ADHD is highly inheritable (75% concordance). However, one-fifth of all cases are estimated to be caused by trauma or toxic exposure.
- Treatments usually involve a combination of medications, behavior modification, life style changes, and counseling.

ADHD

- Magnetic resonance imaging (MRI) has shown a developmental lag of 3 to 5 years in development of the prefrontal cortex and temporal lobe.
 - Prefrontal cortex: control and focus thinking, attention and planning, suppress inappropriate actions and thoughts
 - Temporal lobe (& hippocampus): remember things from moment to moment
- However, motor cortex actually matures faster!
 - Fidgetiness (restlessness)

ADHD

- There appears to be lower production of dopamine throughout the brain in ADHD subjects.
- However, one form of ADHD appears to result from sensory overstimulation, due to a disorder of ion channels in the peripheral nervous system.
- Other studies have shown decreased glucose utilization, either throughout the brain during a specific task or only in the prefrontal lobes.

Possible causes of ADHD

- Genes
- Smoking
- Lead exposure
- Complications during pregnancy or birth
- Heavy cell phone usage by the mother!
- Head injuries
- Food additives in a minority of children
- Impaired parental attachment or abuse

Treatment of ADHD

- Ritalin or similar drugs that increase dopamine levels are the main treatment.
 - This especially helps to activate the prefrontal cortex, which can inhibit lower centers that promote impulsiveness.
 - Concerns that Ritalin may increase later drug addiction have not been supported. There is actually a decrease in drug addiction in those who took Ritalin.
- Omega-3 fatty acids, zinc, and magnesium may have some benefits.

Prognosis

- Many ADHD children are socially aggressive.
- Even ADHD kids with average to above average intelligence show "chronic and severe under achievement".
- 46% of those with ADHD in the United States have been suspended from school and 11% expelled.

Prognosis

- Although the motoric hyperactivity declines in adulthood, attention problems remain.
- 37% of those with ADHD do not get a high school diploma even though many of them receive special education services.
- Almost half of all ADHD students never finish high school. In the United States, less than 5% of individuals with ADHD get a college degree, compared to 28% of the general population.

Summary

- People with major depression find that almost nothing makes them happy. Depression occurs as a series of episodes.
- Depression shows a strong family tendency, especially for relatives of women with early-onset depression.
- Depression is associated with decreased activity in the left hemisphere of the cortex and with increased activity in the right prefrontal lobe, amygdala, and anterior cingulate cortex.

Summary

- Several kinds of antidepressant drugs are in wide use. Some block reuptake or breakdown of monoamine transmitters. Either type increases the amount of transmitters in the synapses. However, they produce bad side effects.
- SSRIs block reuptake of serotonin and are the most effective, with fewest side effects.
- Atypical antidepressants include a glucocorticoid antagonist and drugs that affect reuptake of dopamine and norepinephrine.

Summary

- Antidepressants alter synaptic activity quickly, but their effects on mood build up over weeks.
- The behavioral effects of antidepressant drugs probably depend on slow changes in the brain. They increase release of BDNF, which promotes neuron growth and survival.
- Exercise also increases BDNF and helps to relieve moderate depression.

Summary

- Other therapies for depression include psychotherapy, electroconvulsive therapy, and altered sleep patterns.
- People with bipolar disorder alternate between depression and mania. Bipolar disorder has a probable genetic basis. Effective therapies include lithium salts and certain anticonvulsant drugs.

Summary

- Seasonal affective disorder (SAD) is marked by recurring depression during the winter. Exposure to bright lights, especially in the morning, is usually an effective treatment. It may also help people with other kinds of depression.
- ADHD is characterized by impulsiveness, hyperactivity, and difficulty concentrating.

Summary

- ADHD has a high degree of heritability, but can also be caused by smoking during gestation, lead exposure, or complications during pregnancy or delivery.
- It is associated with delayed development of the prefrontal cortex and temporal lobes.
- It is treated primarily with drugs, such as Ritalin, that increase dopamine levels. This results in activation of the prefrontal cortex, which can control impulsivity.