



Brain and Behaviour – S2

PSYC 304 – Dr. Todd Kamensek



Announcements

1. FINAL EXAM – August 15, 7pm Swing 121 (or on Zoom)
2. Thank you for a wonderful 2 semesters, you did it!
 - As I said at the beginning of the course, this is a challenging course, but your hard work has not gone unnoticed. Way to go! I hope that the material has been memorable!
 - It has been a pleasure being your lecturer!
3. Departmental instructor/course survey – Available until Aug 11th
 - But you have 10 minute to complete now!
 - 10000 thank you's for completing!

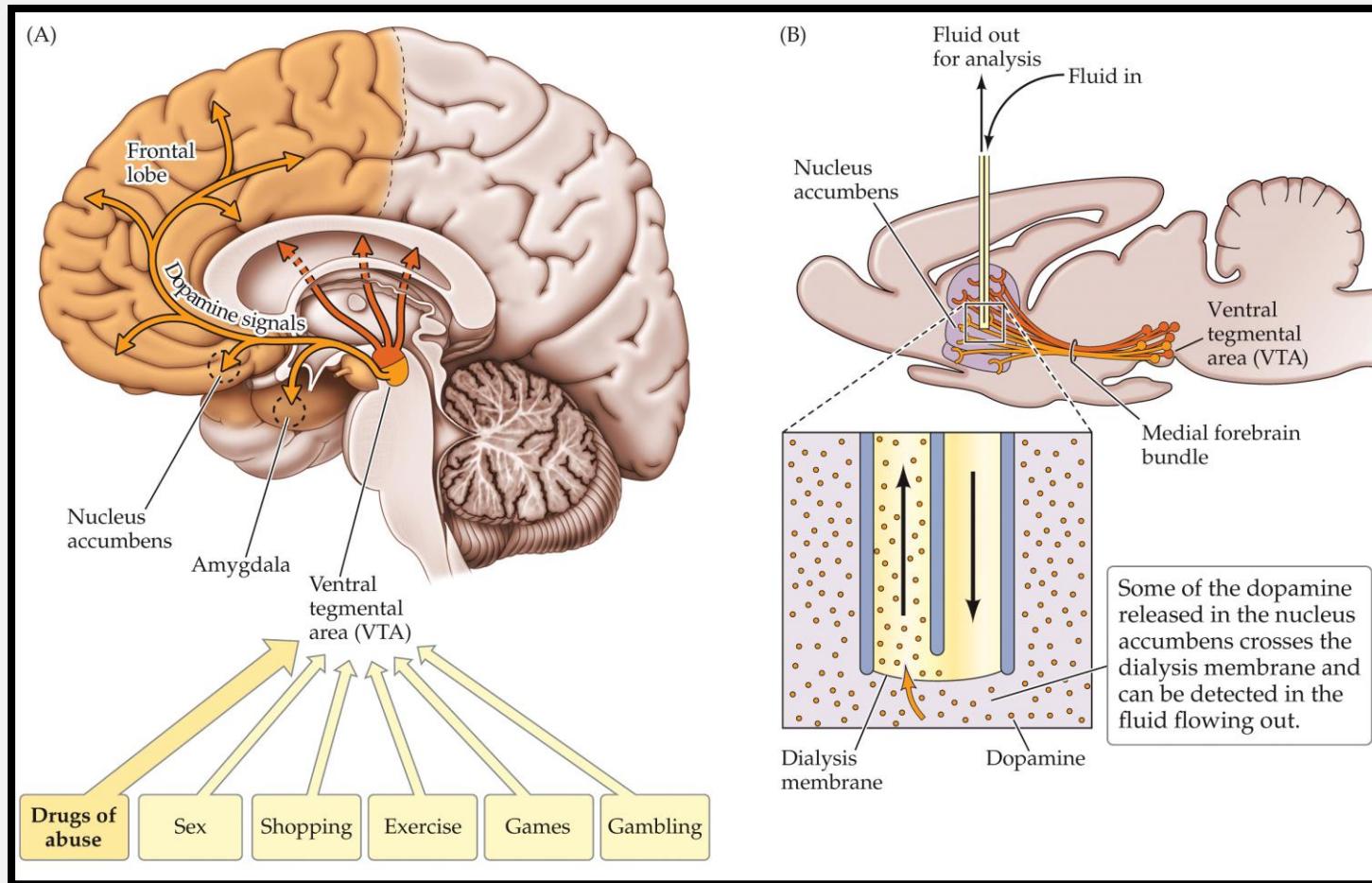
Substance Abuse and Addiction

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.

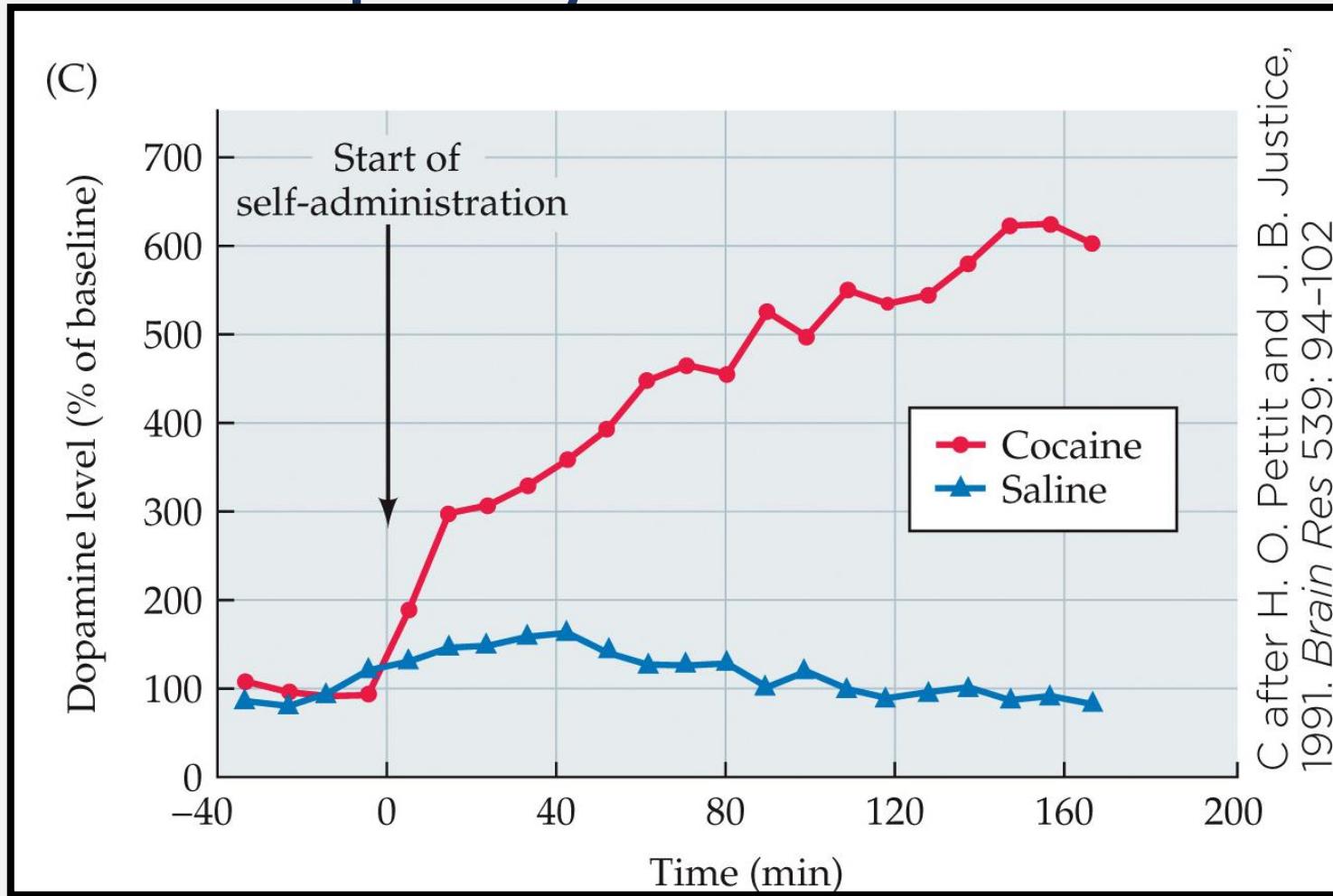
Substance Abuse and Addiction

Mesolimbic reward pathway



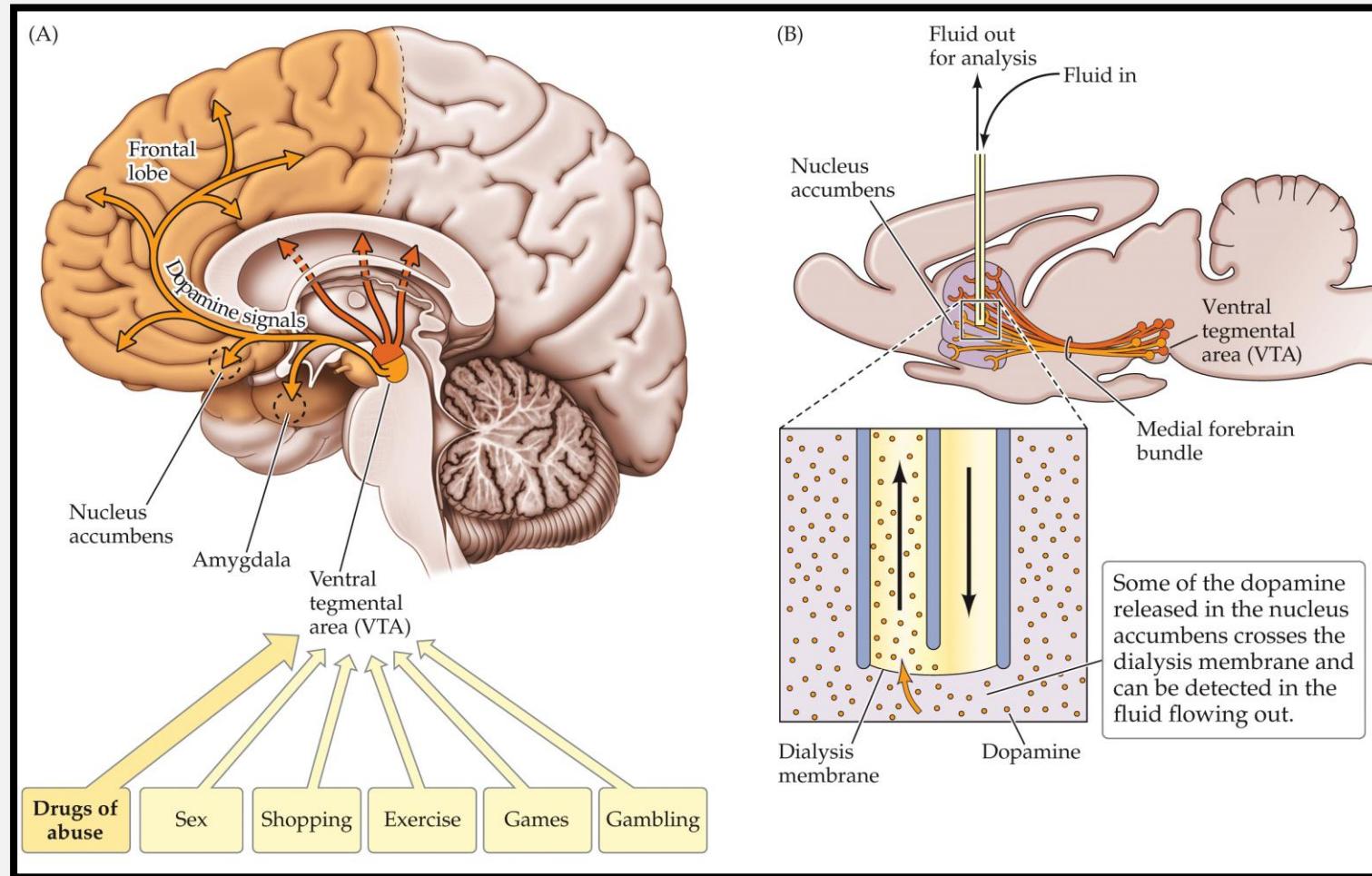
Substance Abuse and Addiction

Mesolimbic reward pathway



Substance Abuse and Addiction

Mesolimbic reward pathway





Test of sufficiency

Mesolimbic Dopamine Neuron Stimulation and the Progression to Addiction

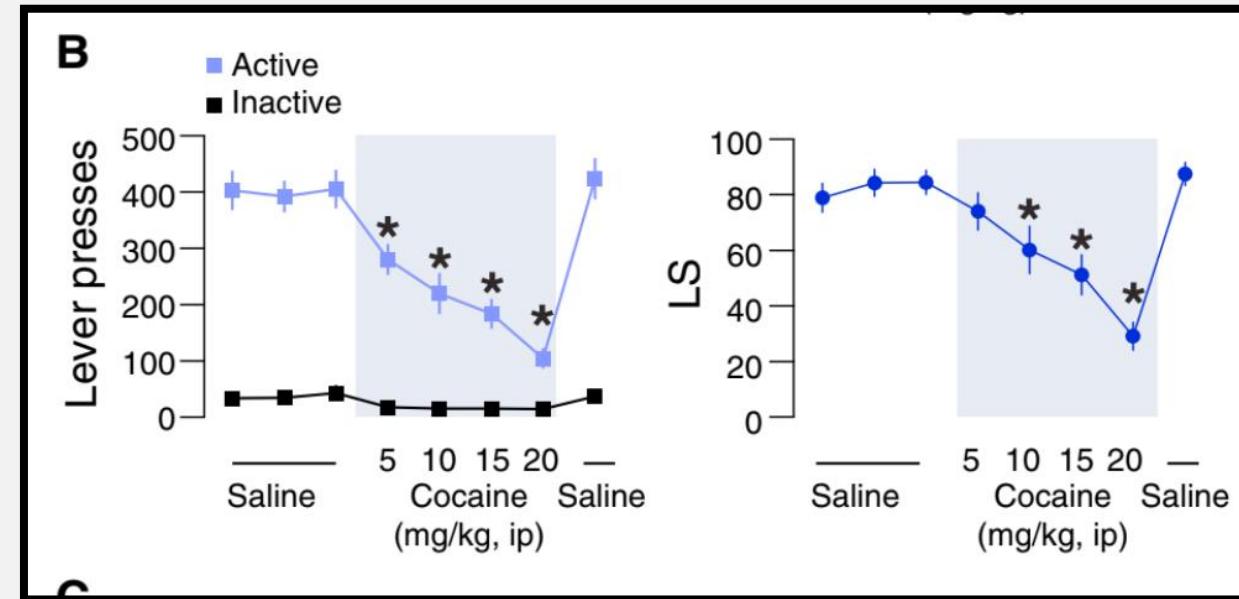
Pascoli et al., 2015

- **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 compulsion 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
 - From first press to laser stim – rats pressed furiously (futile effort as on the first press activates the laser) – accounted for 30% of lever presses and thought to reflect impulsive responses

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?

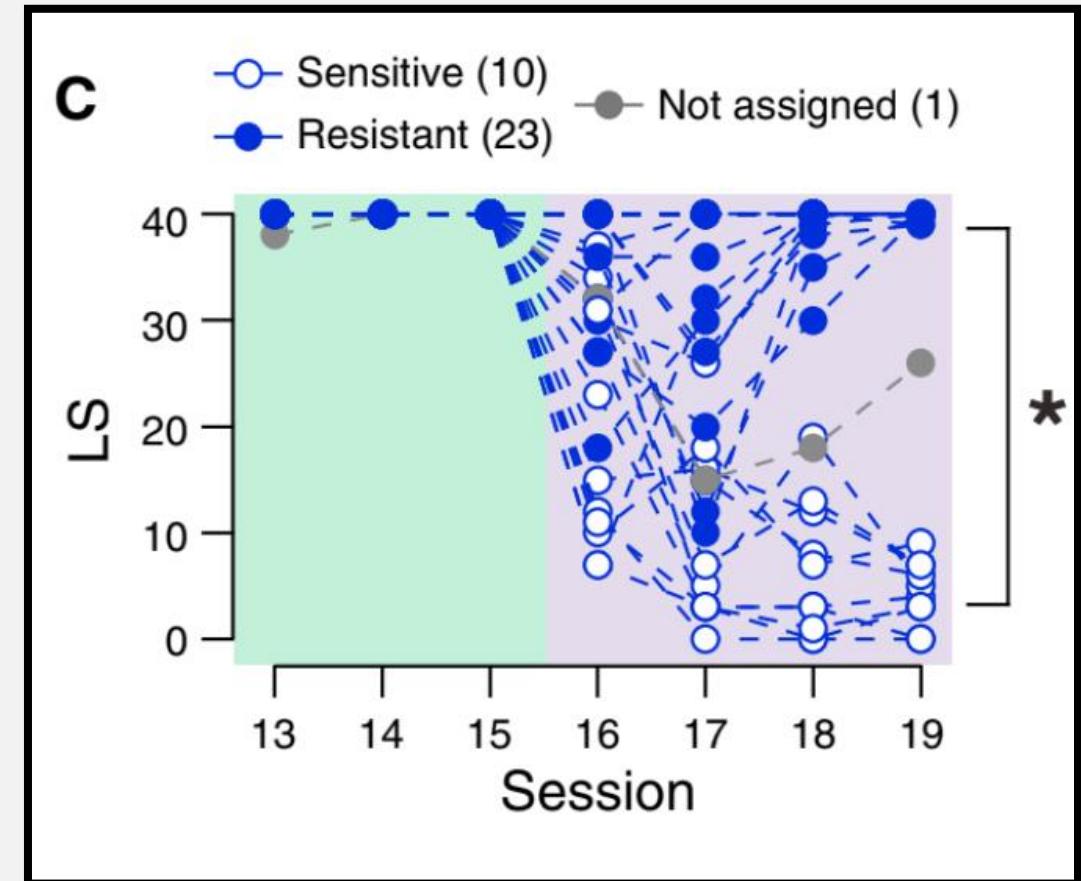
- 30 days after training – return to operant box
- Pressing the lever – activates the cue light, but not the laser
- High rate of lever pressing in the experimental group of mice (those with optogenetic mutation that leads to activation of the VTA neurons from the laser)!
- Synaptic plasticity resistant 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 behaviours



The addicted brain

What we have learned so far

- We see that the reward/pleasure circuits in the brain become hijacked into biasing an individual towards using, especially when exposed to environmental cues associated with previous drug use.
- Dopamine seems to be a key player, however not in the fashionable & historical “pleasure neurotransmitter” sense, rather dopamine helps the brain predict when rewarding goals are within reach.
 - Dopamine is not required to feel pleasure (Berridge & Robinson, 2016)
 - Mesolimbic sensitization following drug use (which tends to be more powerful when the drug is more rapidly delivered to the CNS) increases dopamine release in response to drug related cues. Pathway highly resistant to change.
- Downregulation of dopamine receptors
 - Leads to increased tolerance
 - Motivation for less rewarding behaviour is reduced (natural rewards do not have the same effect as they used to)

The addicted brain

What we have learned

- At the same time, D2 dopamine downregulation in the prefrontal cortex
 - Reduces executive function, which means...
 - Lack of planning and organization
 - Increased perseveration and impulsivity
 - Preference for immediate rewards, reduced self control, shift from goal directed behaviour to rigid, inflexible habitual or impulsive behaviour

Substance Abuse and Addiction

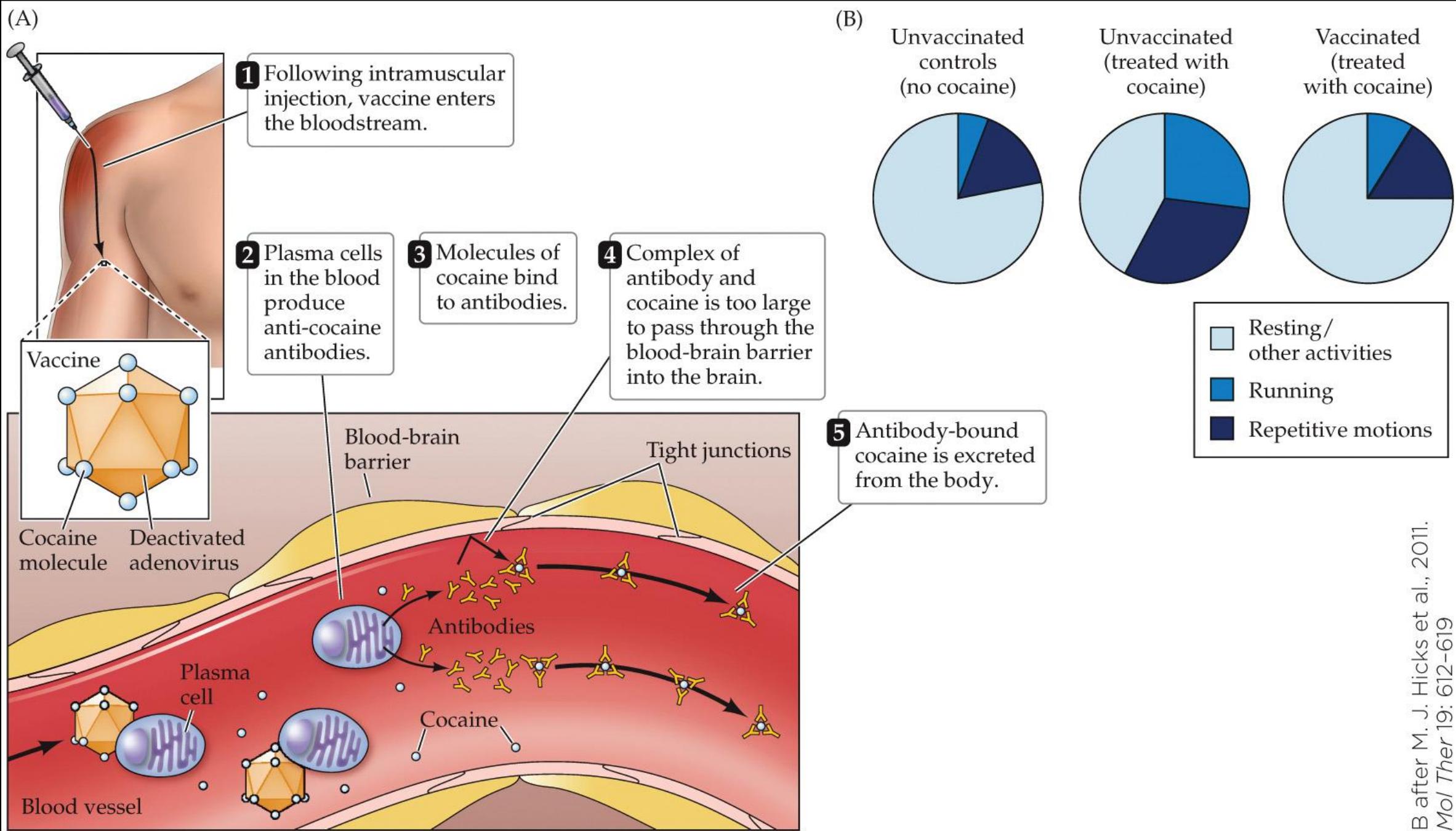
Many factors figure in an individual's susceptibility to addiction:

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

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

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B after M. J. Hicks et al., 2011.
Mol Ther 19: 612-619



End of drugs and addiction



Psychopathology

Learning objectives

1. Identify the most common symptoms of schizophrenia.
2. Discuss the strong influence of both genes and the environment on the chances of developing schizophrenia.
3. Describe several of the major brain differences of people with schizophrenia versus controls.
4. Review the possible neurochemical bases of schizophrenia and discuss several classes of antipsychotic drugs and their mechanisms of action.

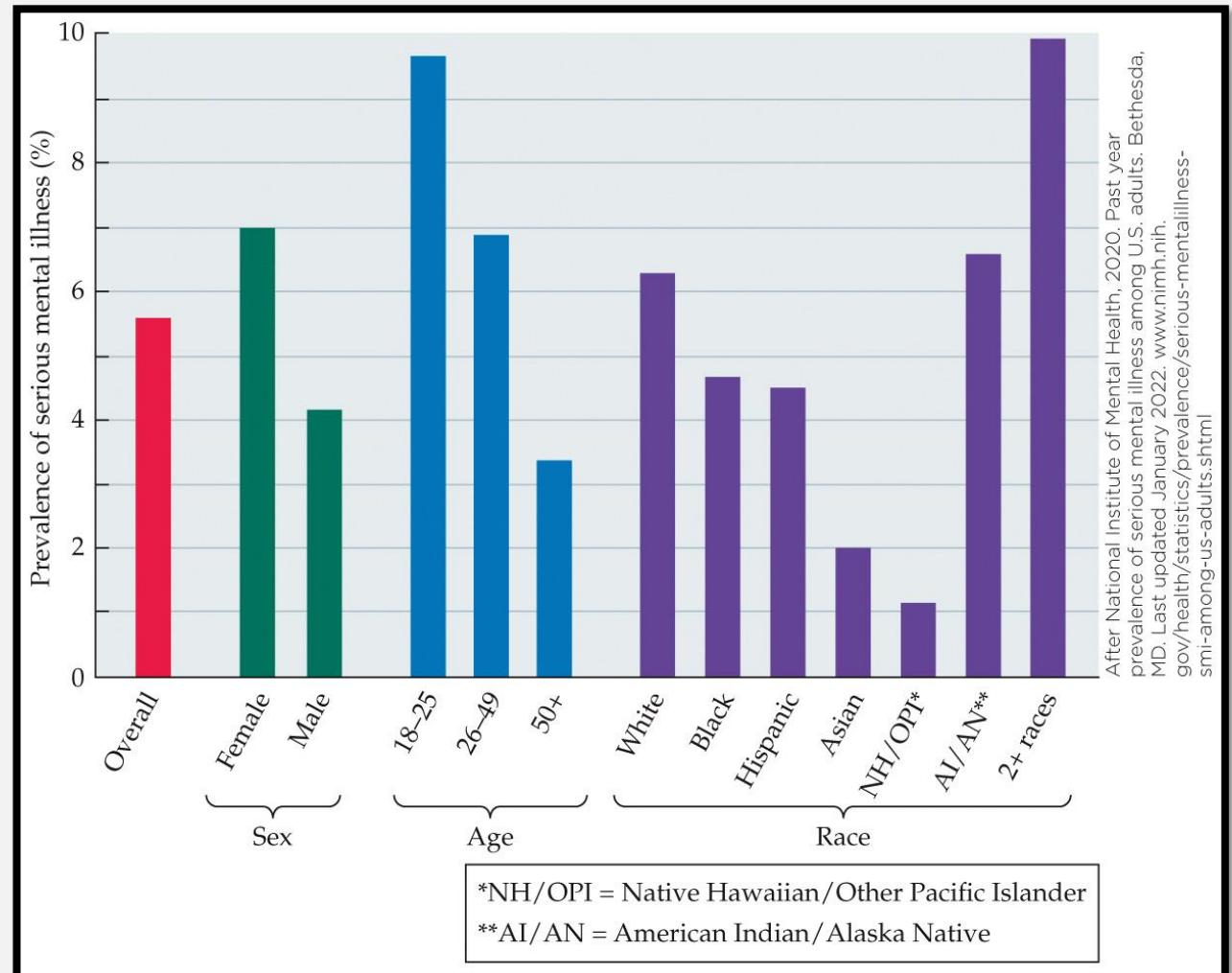
Introduction

- ***Biological perspective*** in psychiatry started in the early 20th century, when thousands of people in mental hospitals suffered from *paralytic dementia*.
- Postmortem studies implicated syphilis; the disease is now known as *syphilitic psychosis*, easily cured by antibiotics.

Introduction

Psychiatric disorders

- are diagnosed on the basis of behavioral symptoms.
- **Epidemiology** studies patterns of disease in a population.
- About one-third of the U.S. population reports symptoms of a psychiatric disorder at some point in life.



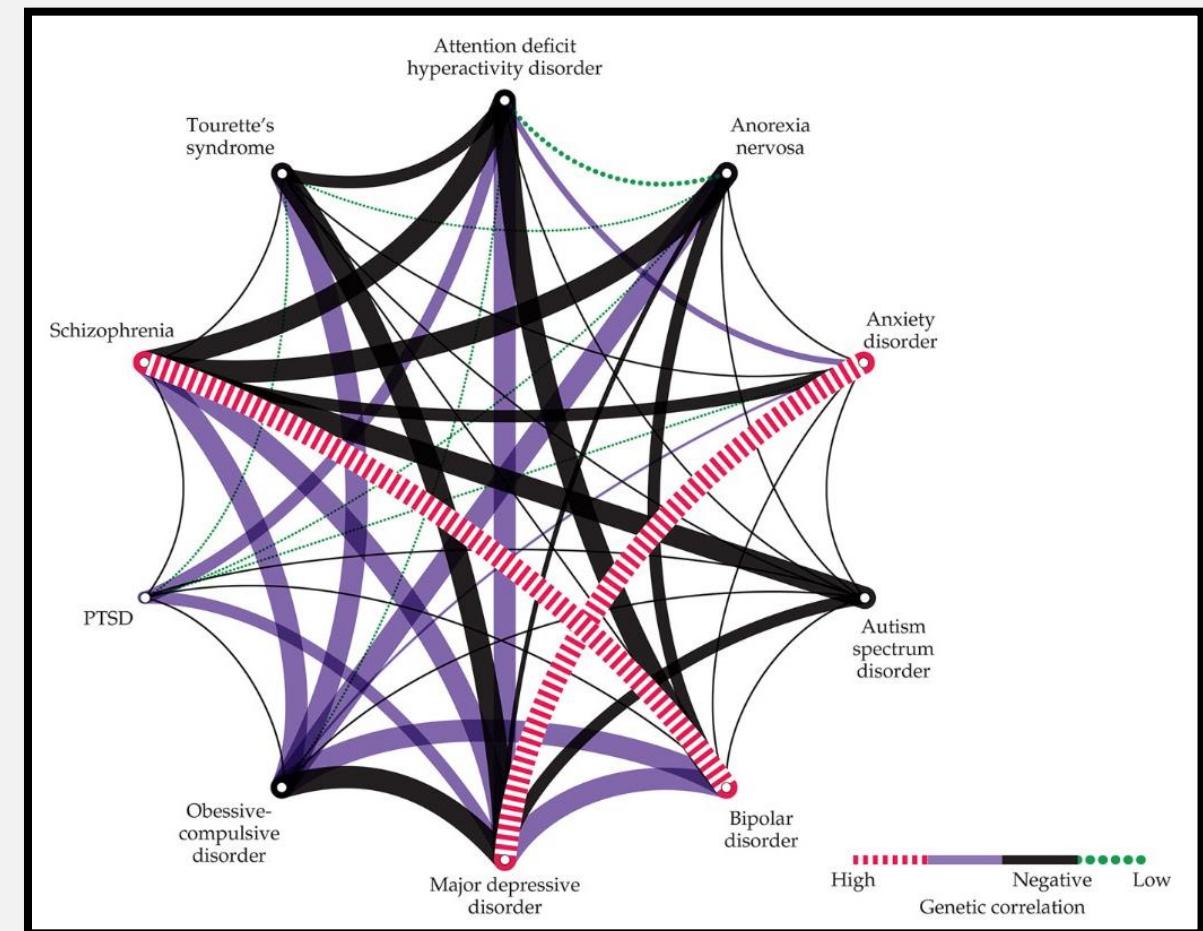
Prevalence world vs. NA

Disorders	Worldwide (%)	North America (%)
Any mental disorder	12.3	15.4
Anxiety disorders (including OCD and PTSD)	3.8	5.6
Depressive disorders	3.4	4.3
ADHD	1.1	2.1
Bipolar disorder	0.49	0.62
Autism spectrum	0.37	0.64
Schizophrenia	0.29	0.42

Genome wide association studies

Genomic screening and correlation

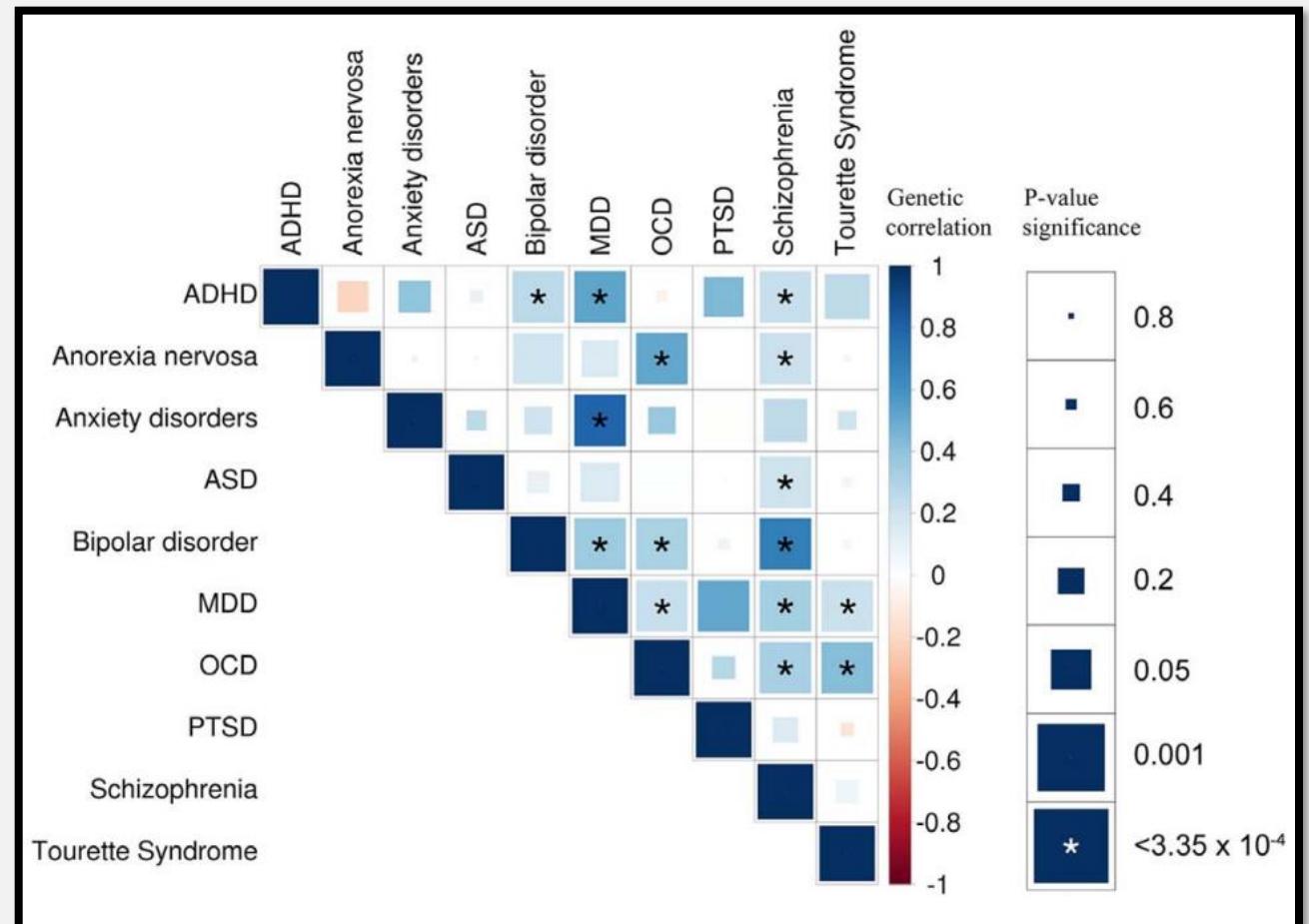
- Investigate genetic overlap of people with various psychiatric disorders
- Schizophrenia and bipolar disorder have a strong genetic correlation (50% genetic overlap)
- Anxiety and depression also highly correlated



Genetic correlations

Genomic screening and correlation

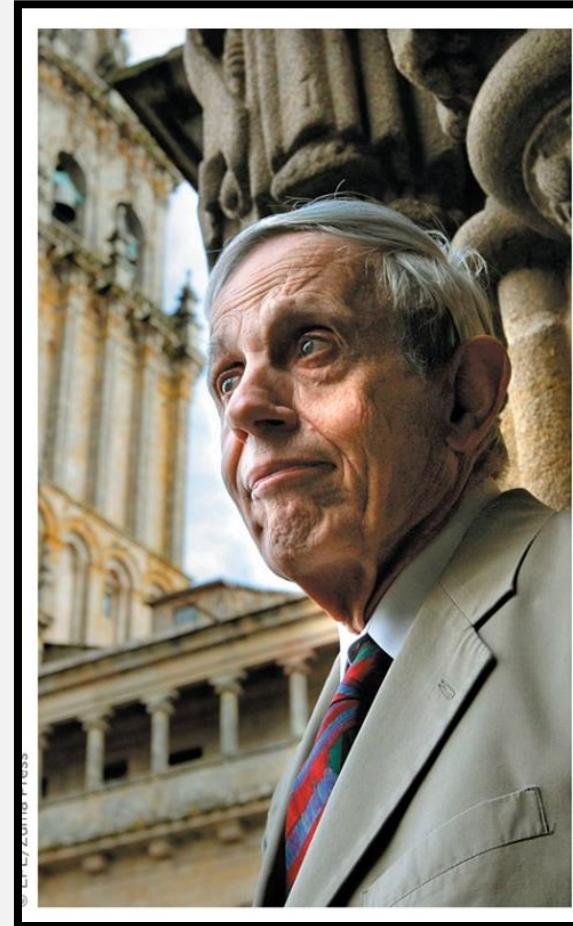
- Same information, different visualization!



Psychiatric Disorders: Schizophrenia

Schizophrenia

- affects approximately 1% of the population.
- **Disorganized thinking** or impaired logical, fragmented, disconnected thought is a key symptom
- **Other symptoms:** hallucinations, personalized delusions, changes in affect (emotion), cognitive impairments.
- Imaged here: Mathematician John Nash



Psychiatric Disorders: Schizophrenia

Positive symptoms:

- abnormal behaviors that are gained—hallucinations, delusions, excited motor behavior.
- The hallucinations are almost always purely auditory.

Negative symptoms

- result from lost functions—slow thought and speech, emotional and social withdrawal, blunted affect.

Cognitive impairments

- Memory problems, poor attention, difficulty making plans, reduced decision-making capacity, poor social cognition.

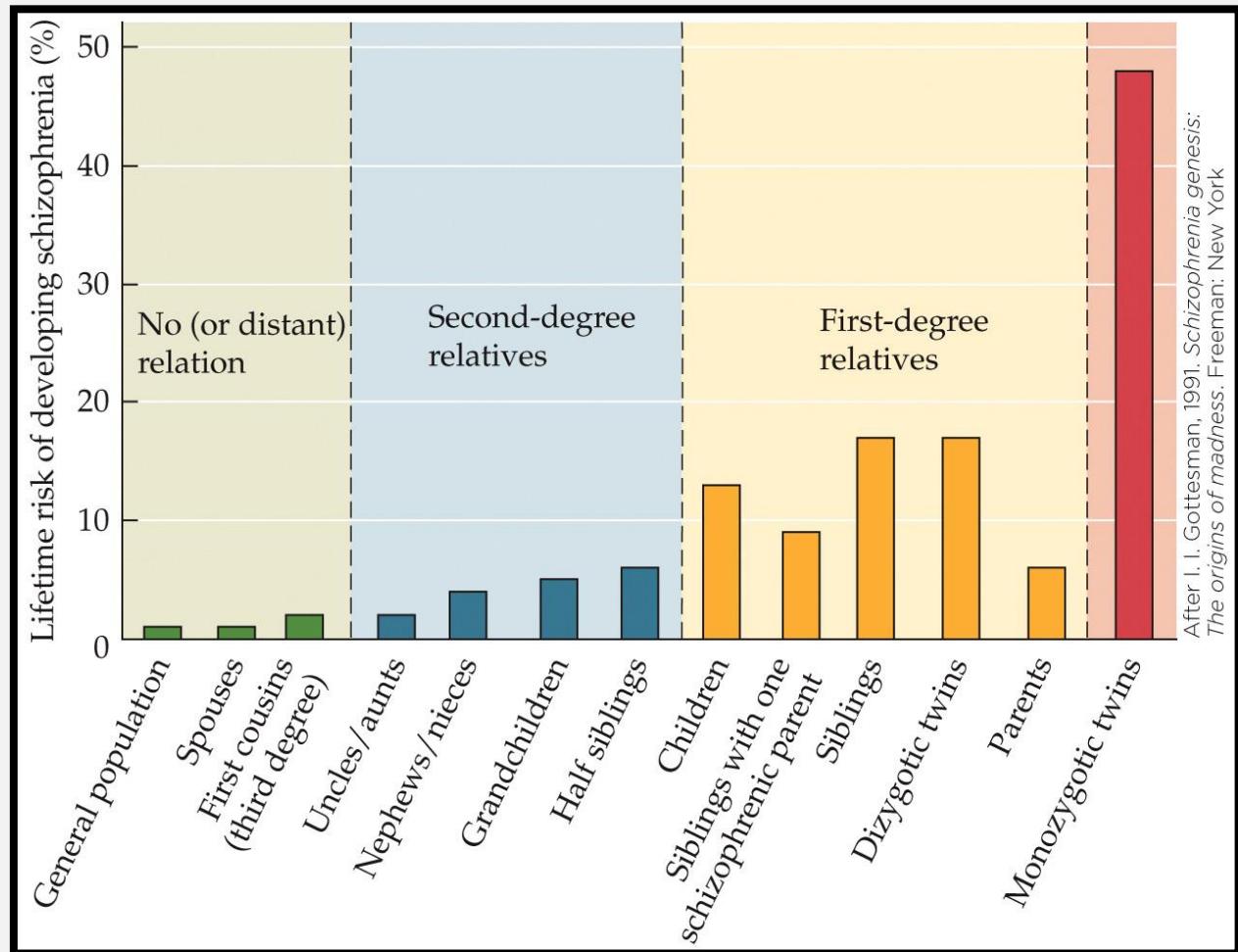
Psychiatric Disorders: Schizophrenia

Schizophrenia

- is partly heritable, but many genes play a role.
- Family, twin, and adoptive studies show a higher incidence among biological relatives.
- **Monozygotic** (identical) twins share identical genes
- **Dizygotic** (fraternal) have half of their genes in common.

Psychiatric Disorders: Schizophrenia

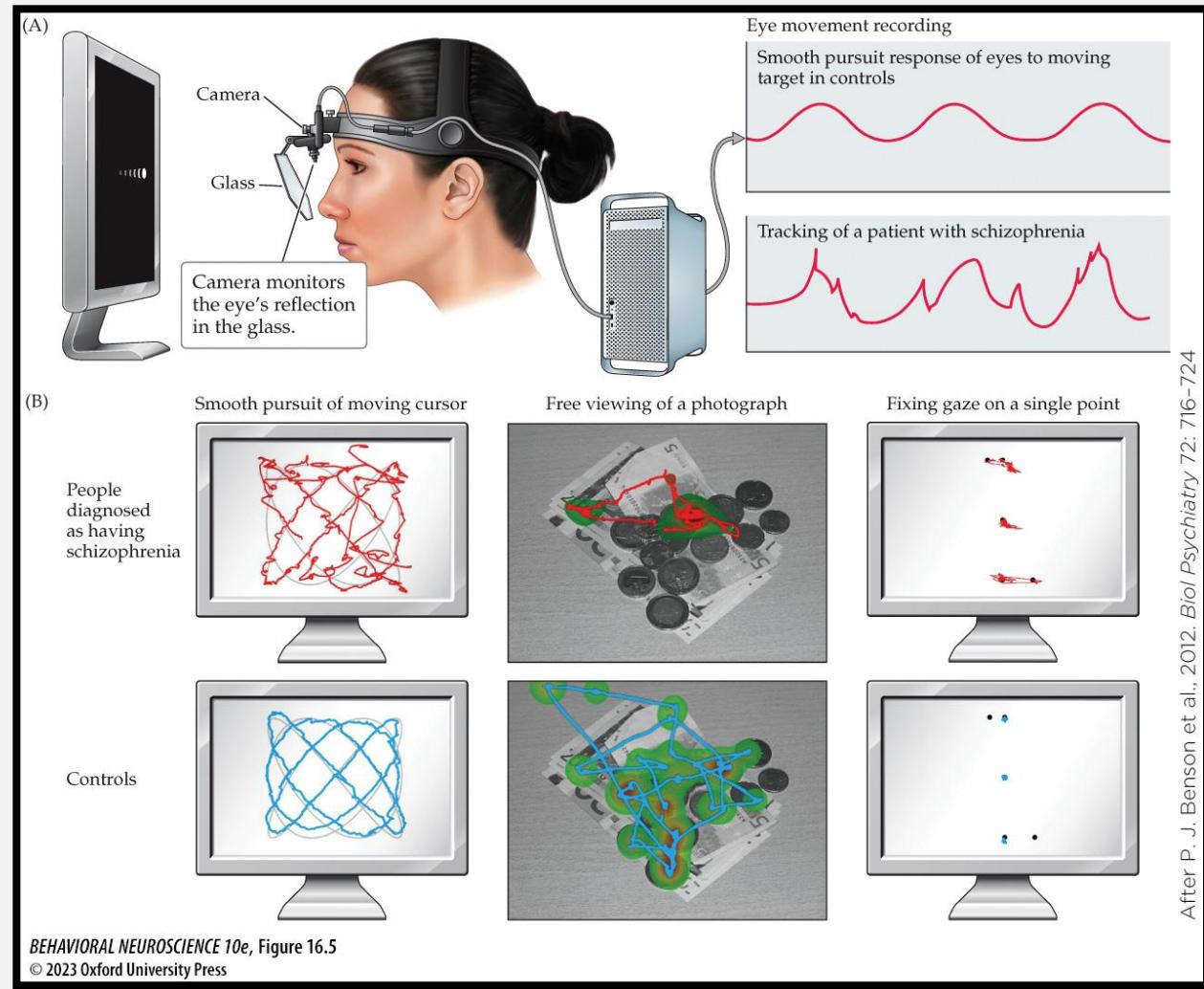
- If both twins suffer from schizophrenia, they are **concordant** for the disease.
- If only one member of a pair has it, they are **discordant**.
- For identical twins, concordance rate is 50%, pointing to a genetic factor.
- Rate of discordance suggests that other factors also contribute.



Psychiatric Disorders: Schizophrenia

Schizophrenia

- may have an associated **endophenotype**: behavioral or physical characteristics that accompany an inherited susceptibility to a disorder.
- These can be objectively measured by various neuropsychological tests, eg., differences in eye movements.



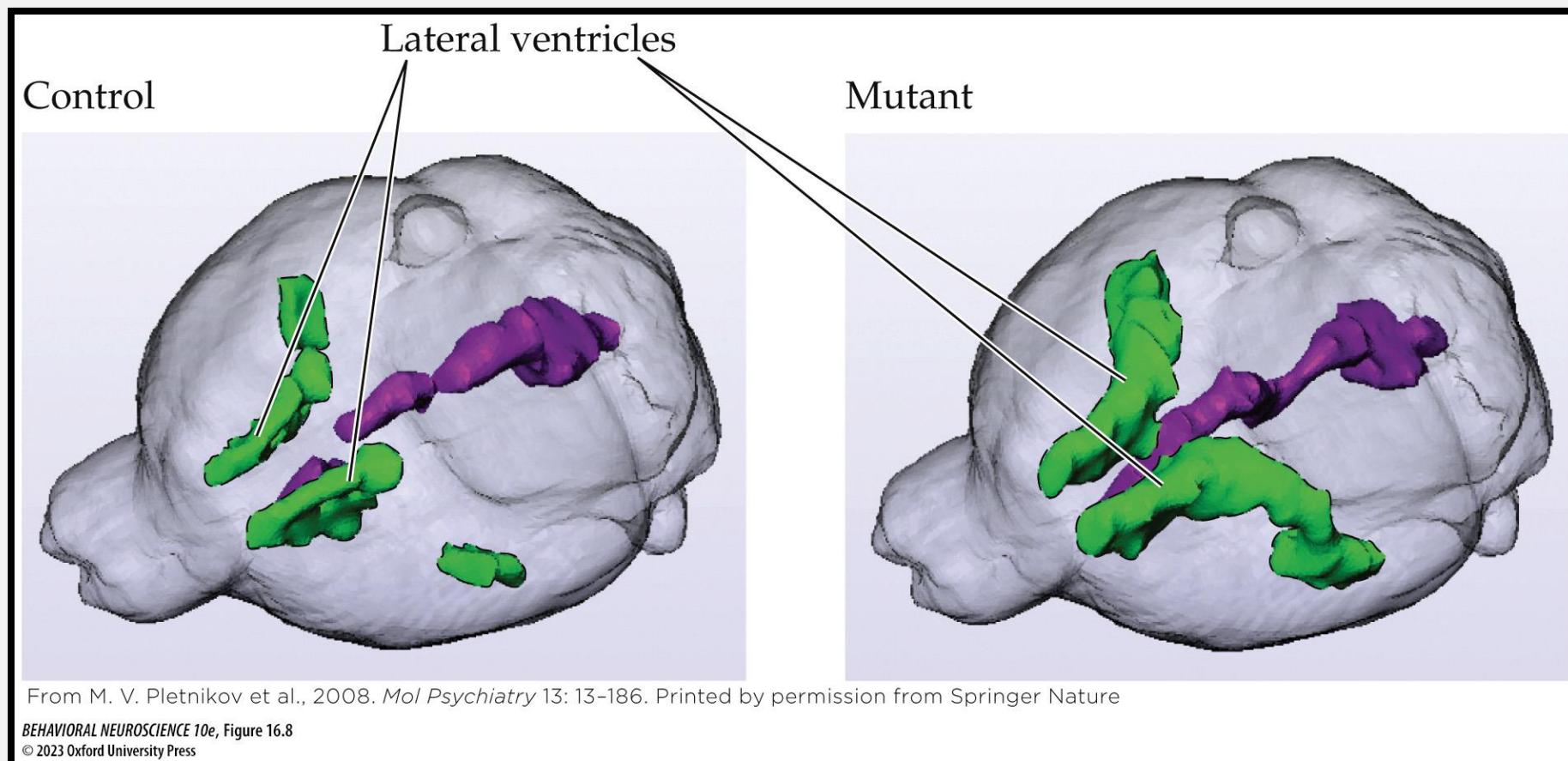
Psychiatric Disorders: Schizophrenia

Genetic factors

- No single gene causes or increases susceptibility to schizophrenia.
- A few genes have been identified as abnormal in some schizophrenics; several are involved in synapse rearrangement.
- Paternal age is an **epigenetic factor**: older fathers are more likely to have a child with schizophrenia.

Psychiatric Disorders: Schizophrenia

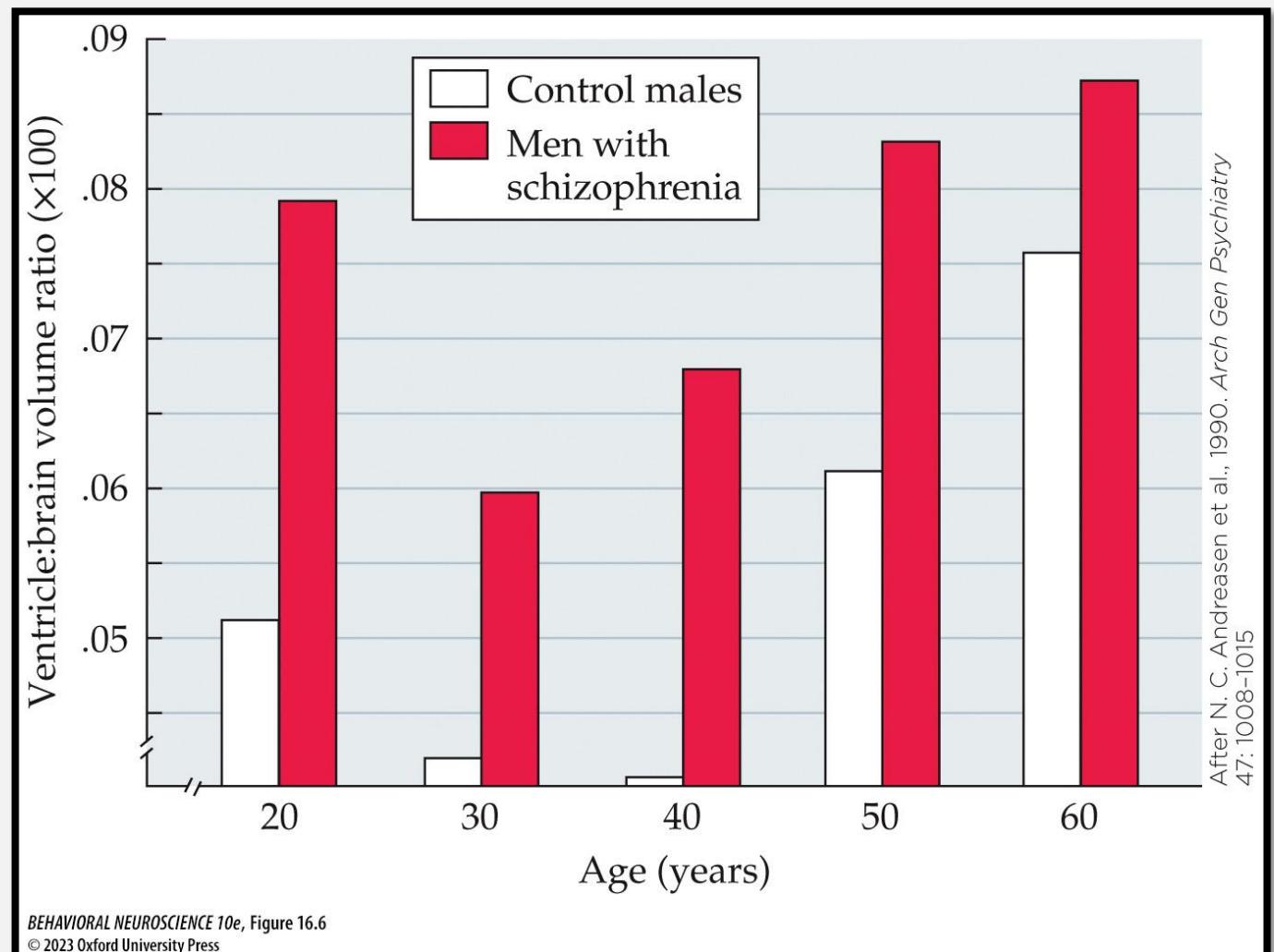
- mice with mutated *DISC1* (an abnormal gene associated with schizophrenia) develop enlarged lateral ventricles.



Psychiatric Disorders: Schizophrenia

Cerebral Factors

- Brains of many schizophrenic patients show consistent structural changes: cerebral ventricles are enlarged, especially lateral ventricles.
- Ventricle enlargements – predicts later development of schizophrenia in adolescents
- Also have poorer responses to antipsychotic drugs

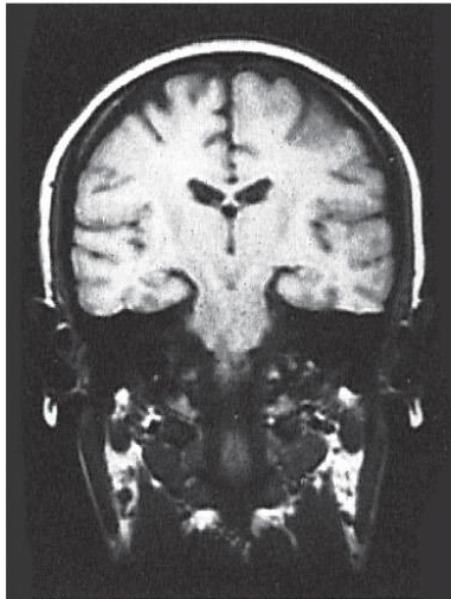


Psychiatric Disorders: Schizophrenia

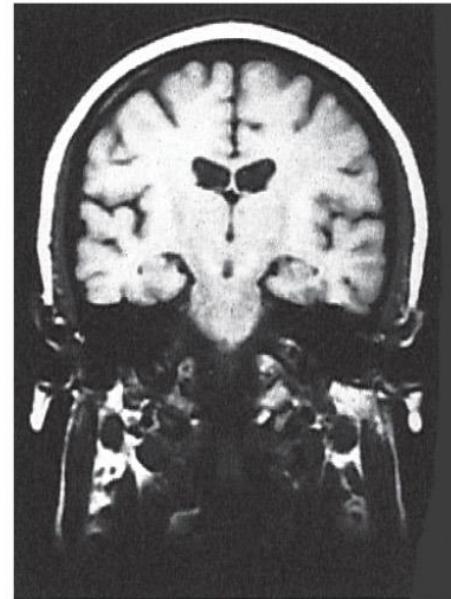
- Twins with schizophrenia have decidedly enlarged lateral ventricles.

MRI brain images of twins discordant for schizophrenia

35-year-old female identical twins

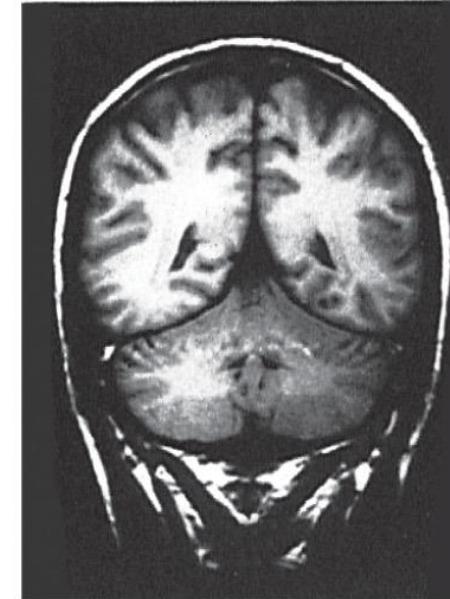


Well

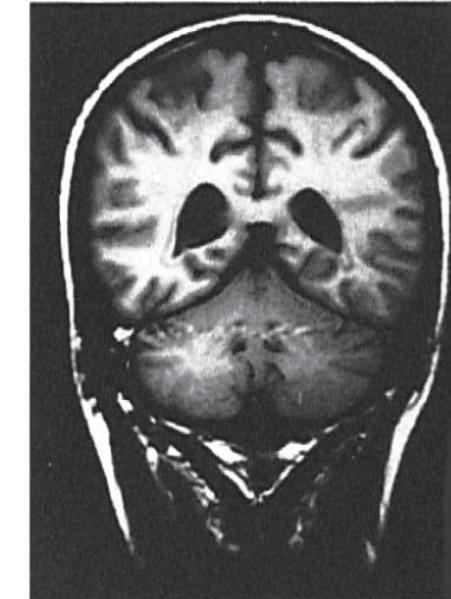


Affected

28-year-old male identical twins



Well

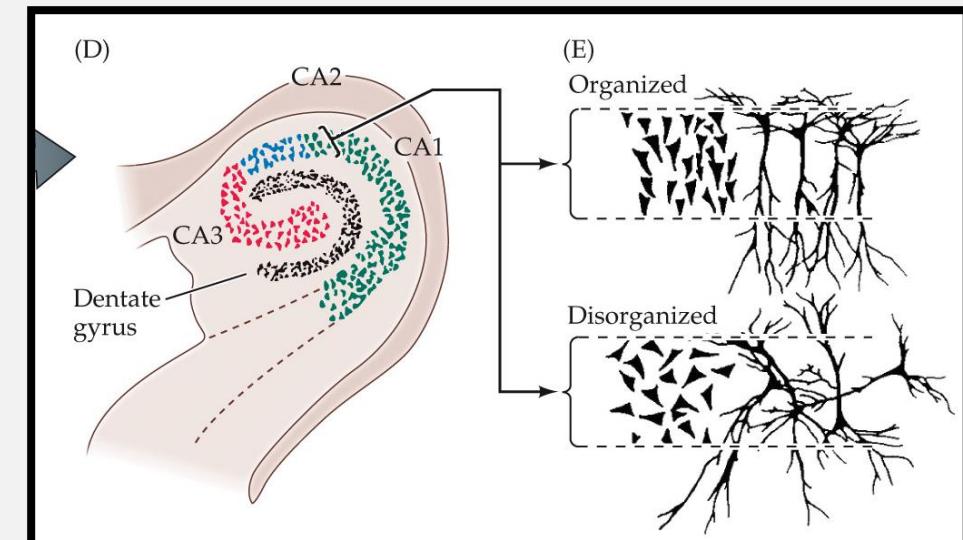
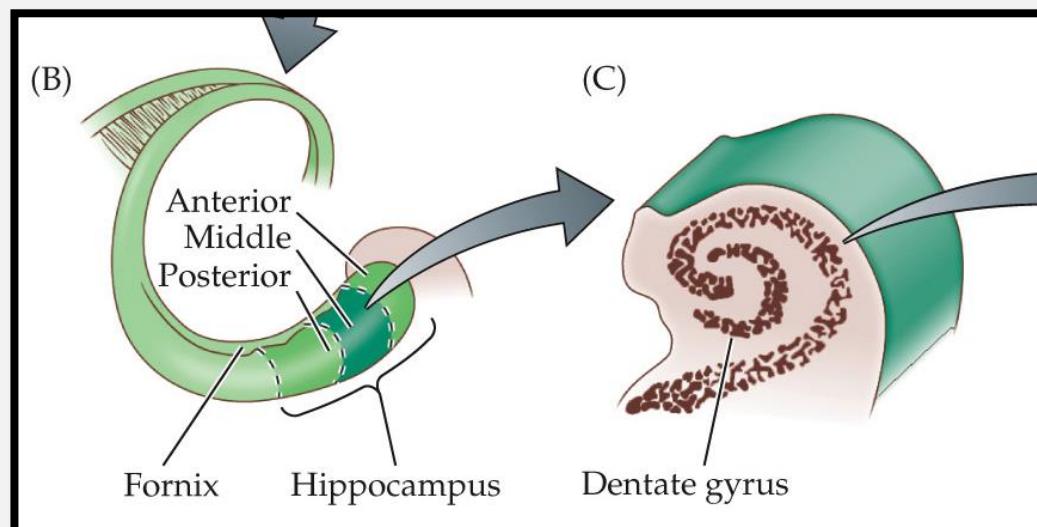


Affected

From E. F. Torrey et al., 1994. *Schizophrenia and manic depressive disorder*. Basic Books: New York; MRIs courtesy of E. Fuller Torrey and Daniel Weinburger

Psychiatric Disorders: Schizophrenia

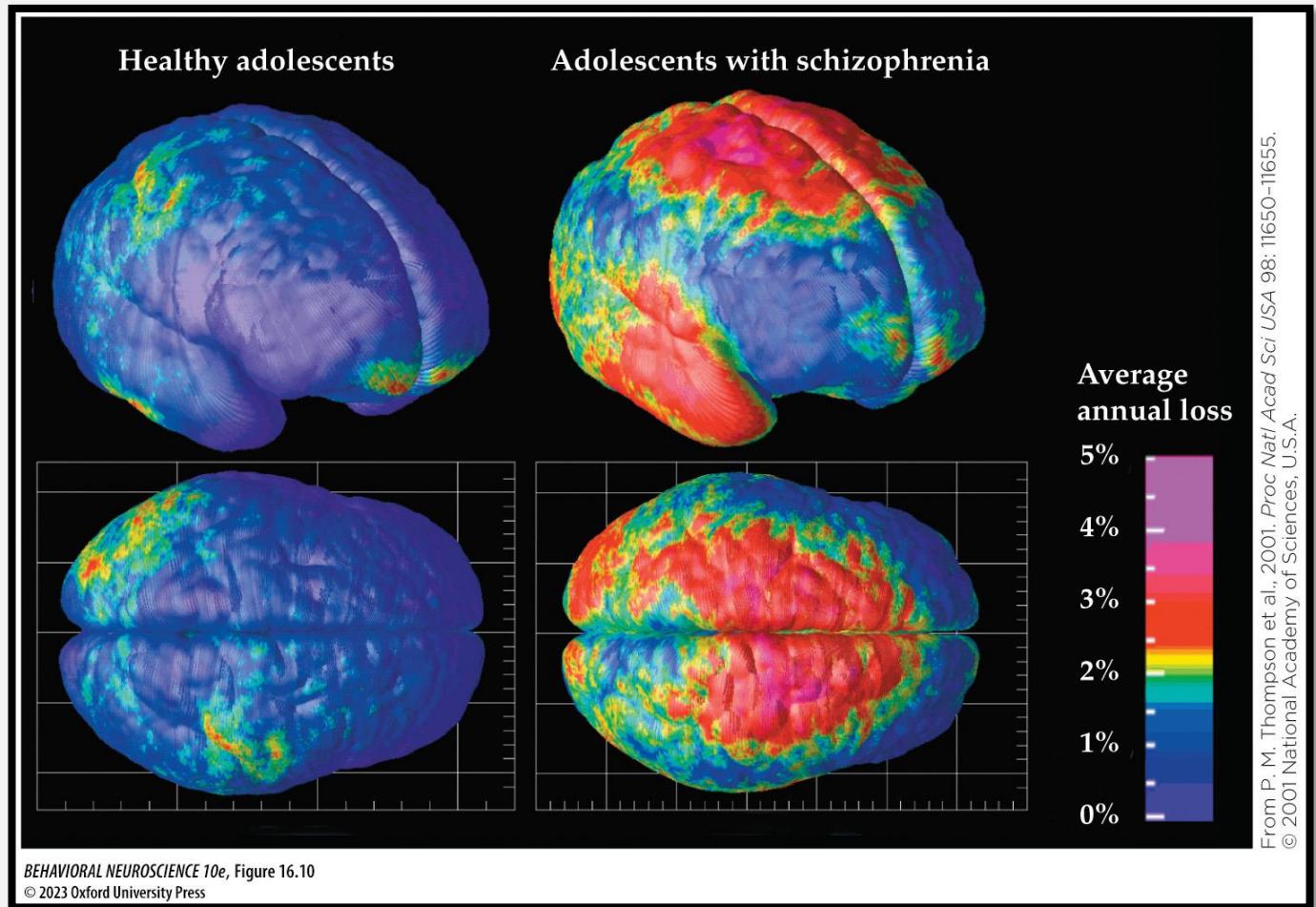
- The hippocampus and amygdala are smaller in schizophrenics than in most people.
- In schizophrenics, pyramidal cells of the hippocampus have a disorganized arrangement; probably occurs during early cell development.
- There may be abnormalities in activity of limbic networks extending from the hippocampus to other limbic structures.



Psychiatric Disorders: Schizophrenia

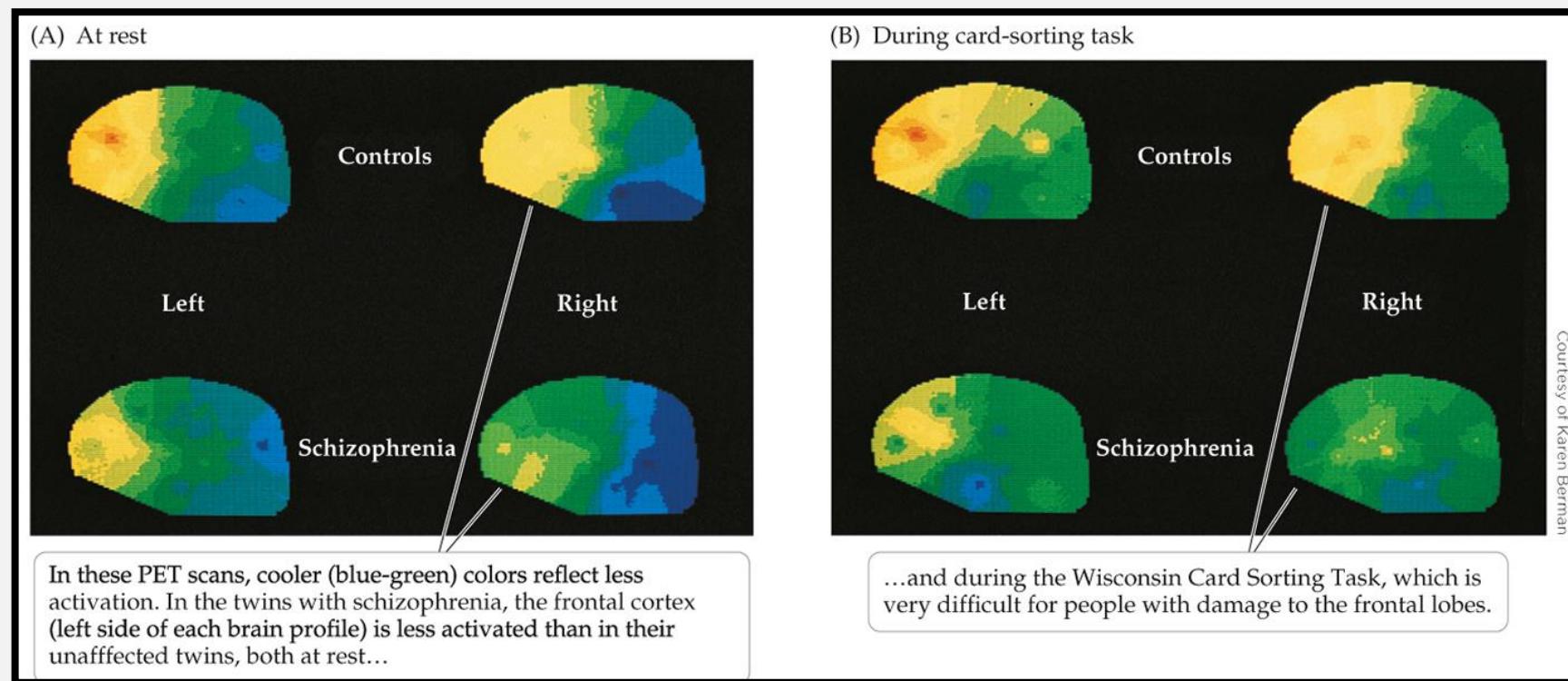
Cerebral Factors

- The corpus callosum in people with schizophrenia has altered structure and function.
- Studies show a loss of gray matter in the frontal lobes in adolescents.



Psychiatric Disorders: Schizophrenia

- PET shows reduced metabolic activity in the frontal lobes.
- **Hypo-frontality hypothesis:** schizophrenia may be caused by under activation of the frontal lobes.



Psychiatric Disorders: Schizophrenia

Treatment

- In the 1930s, psychiatrists performed **lobotomies** to treat schizophrenia.
- Today, **psychosurgery** is very rare, involves much smaller lesions, and is a last resort for disorders such as epilepsy.
- By the 1950s, schizophrenics were treated with **chlorpromazine** (thorazine)—reduced positive symptoms.

Psychiatric Disorders: Schizophrenia

Treatment

- **Antipsychotic** drugs work by blocking dopamine D₂ receptors.
- **Dopamine hypothesis**: schizophrenia results from excess synaptic dopamine or dopamine receptors.
- Support came from amphetamine abusers who develop symptoms similar to schizophrenia. Amphetamine promotes release of dopamine and blocks its reuptake.

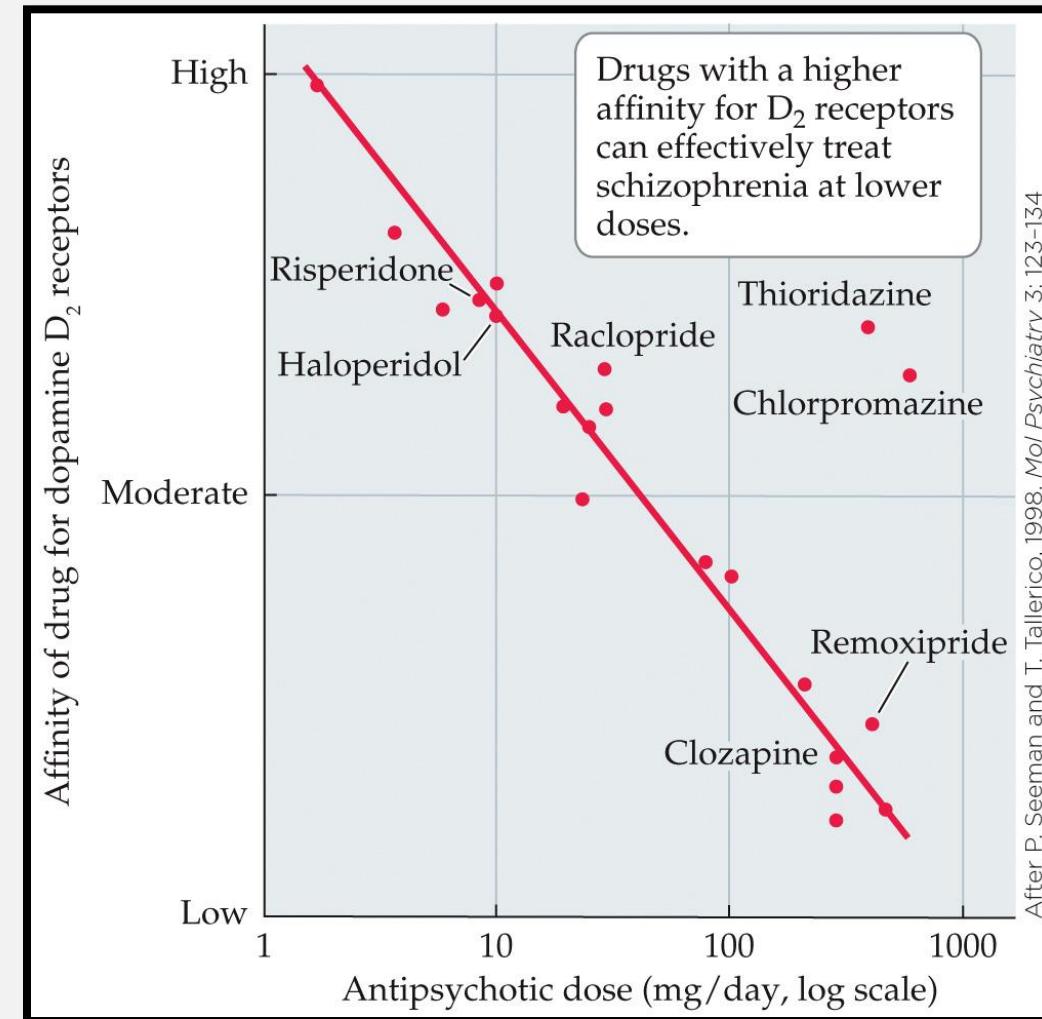
D2 receptors

- Found primarily in striatum prefrontal cortex, limbic system
- Modulate effects of dopamine
 - 1. Act to inhibit dopamine release (Autoreceptor; negative feedback; prevent excessive DA release)
 - 2. Involved in executive function, inhibitory control, cognitive flexibility.

Psychiatric Disorders Take an Enormous Toll

Treatment

- **First-generation antipsychotics** are D₂ receptor antagonists.
- Clinically effective dose can be predicted from affinity for D₂ receptors.
- Haloperidol has a great affinity for D₂ receptors than chlorpromazine and is now used widely.



Psychiatric Disorders: Schizophrenia

Problems with the dopamine hypothesis:

- Drugs block D₂ receptors (hours) much faster than symptoms are reduced (weeks).
- Some patients do not respond to dopamine antagonists at all.

Psychiatric Disorders: Schizophrenia

Antipsychotic drugs

- have long-term effects, such as **dyskinesia**—distortion in voluntary movement.
- **Tardive dyskinesia** is characterized by repetitive movements involving the face, mouth, lips, and tongue.
- **Super-sensitivity psychosis** can emerge when drug doses are lowered; reflects upregulation of receptors during treatment.



Photographs courtesy of Steven J. Frucht

Psychiatric Disorders: Schizophrenia

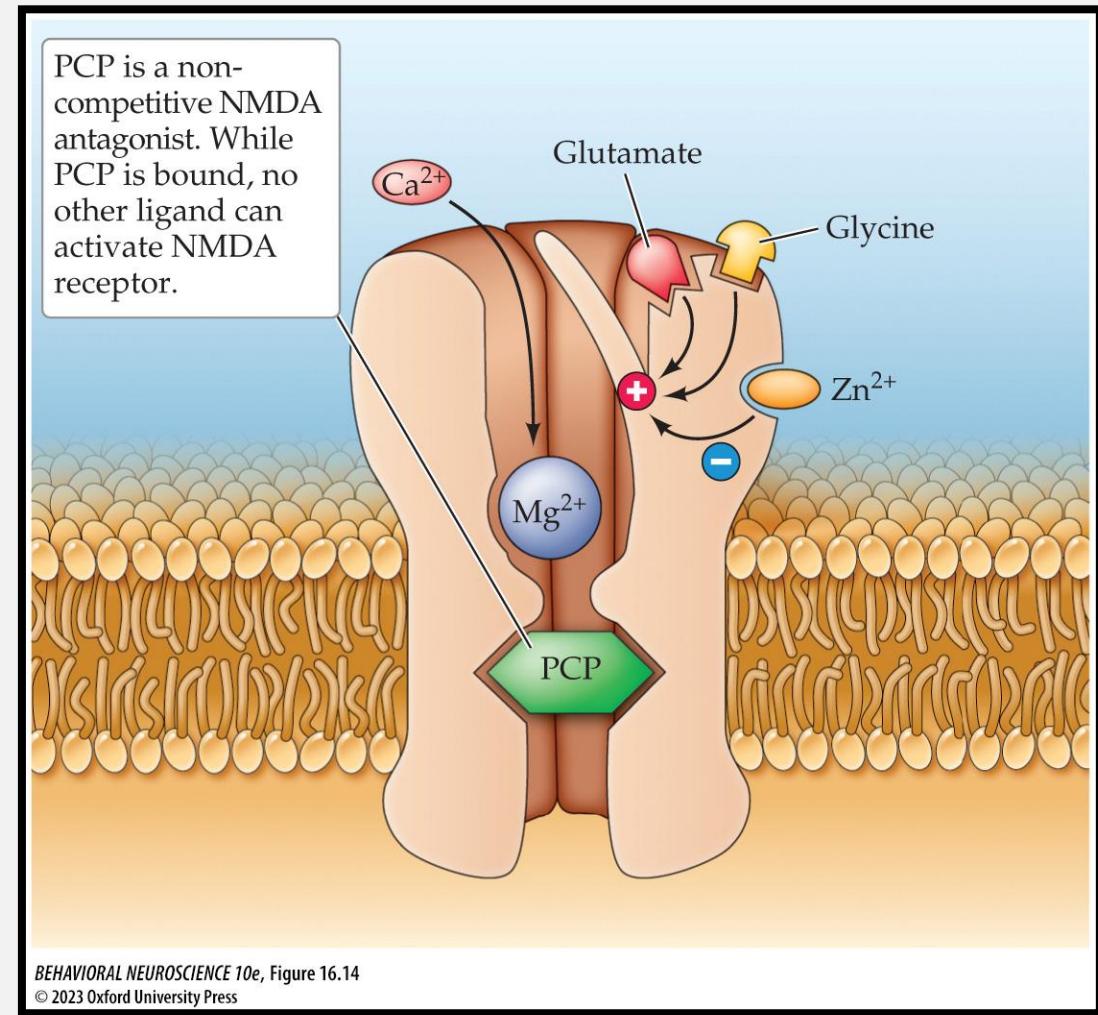
Second-generation antipsychotics

- have affinity for other receptors.
- **Clozapine** blocks serotonin receptors as well as D₂ (and D4) receptors.
- Weak antagonism in the mesolimbic pathways can help alleviate positive symptoms.
- It can increase dopamine release in the frontal cortex (unique regional effects: typical antipsychotics decrease DA release here) – more effective in treating negative symptoms.
- Second-generation drugs are less likely to cause motor side effects, but some research shows that they are no more effective than first-generation and are more likely to cause weight gain.

Psychiatric Disorders: Schizophrenia

Phencyclidine (PCP, or angel dust)

- is a **psychotomimetic**, producing both positive and negative symptoms of schizophrenia.
- PCP acts as a NMDA receptor antagonist and prevents glutamate from acting normally.
- Other NMDA receptor antagonists, like **ketamine**, produce effects similar to PCP.



Psychiatric Disorders: Schizophrenia

Glutamate hypothesis:

- schizophrenia is caused by under activation of glutamate receptors.
- Possibly accounts for the reduction in frontal cortex activity (*hypo frontality*).
- Compounds that increase glutamatergic activity cause seizures, so these compounds are not an option to treat schizophrenia.

Psychiatric Disorders: Schizophrenia

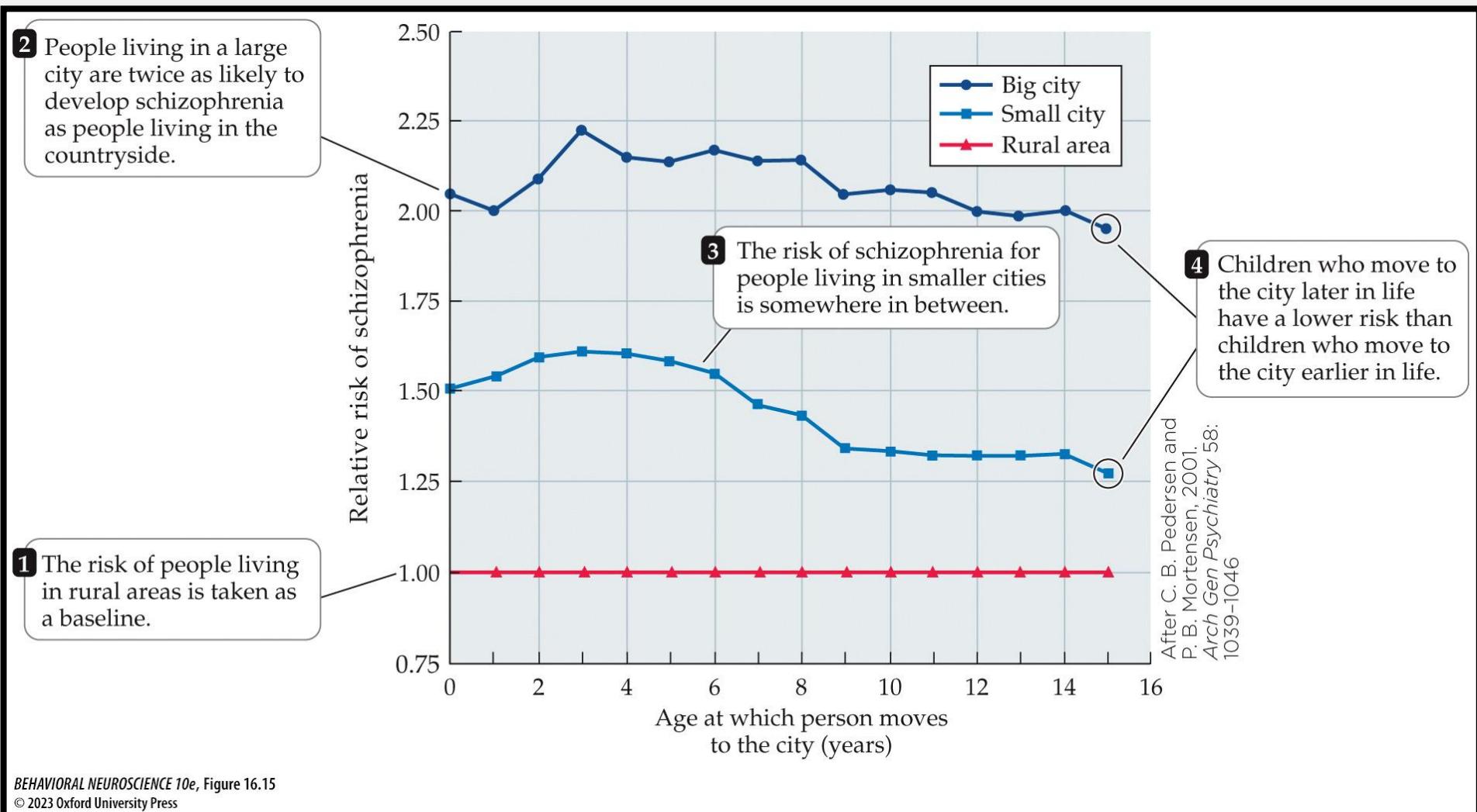
Psychobiological model

- Stressful events increase the risk of developing schizophrenia:
- Usually appears in adolescents or young adults—puberty, going off to college, etc.
- Prenatal stress—exposure to influenza, low birth weight or lack of oxygen at birth
- Stress of city living

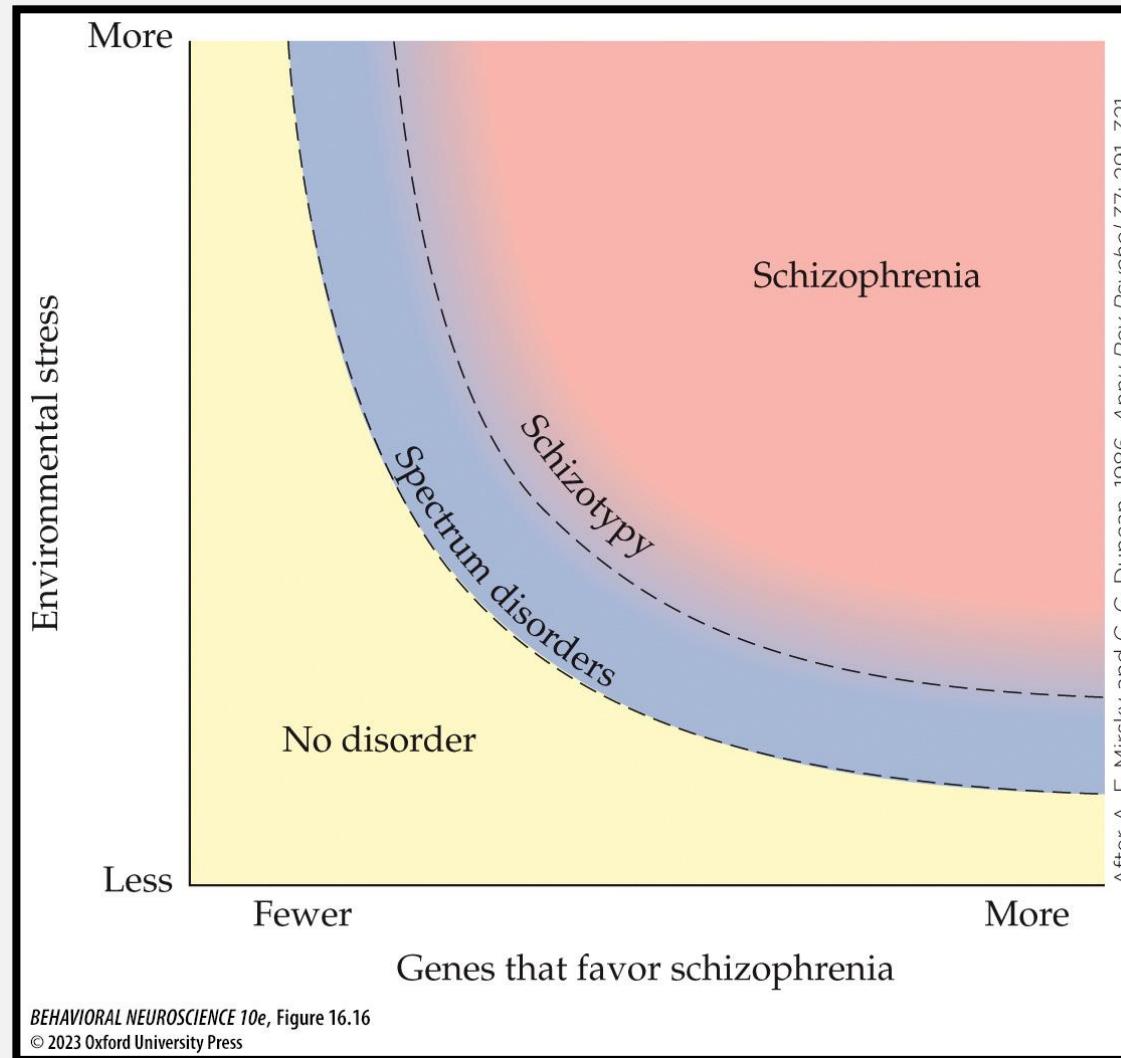
Modern view:

- schizophrenia is caused by the interaction of genetic factors and stress.

City living

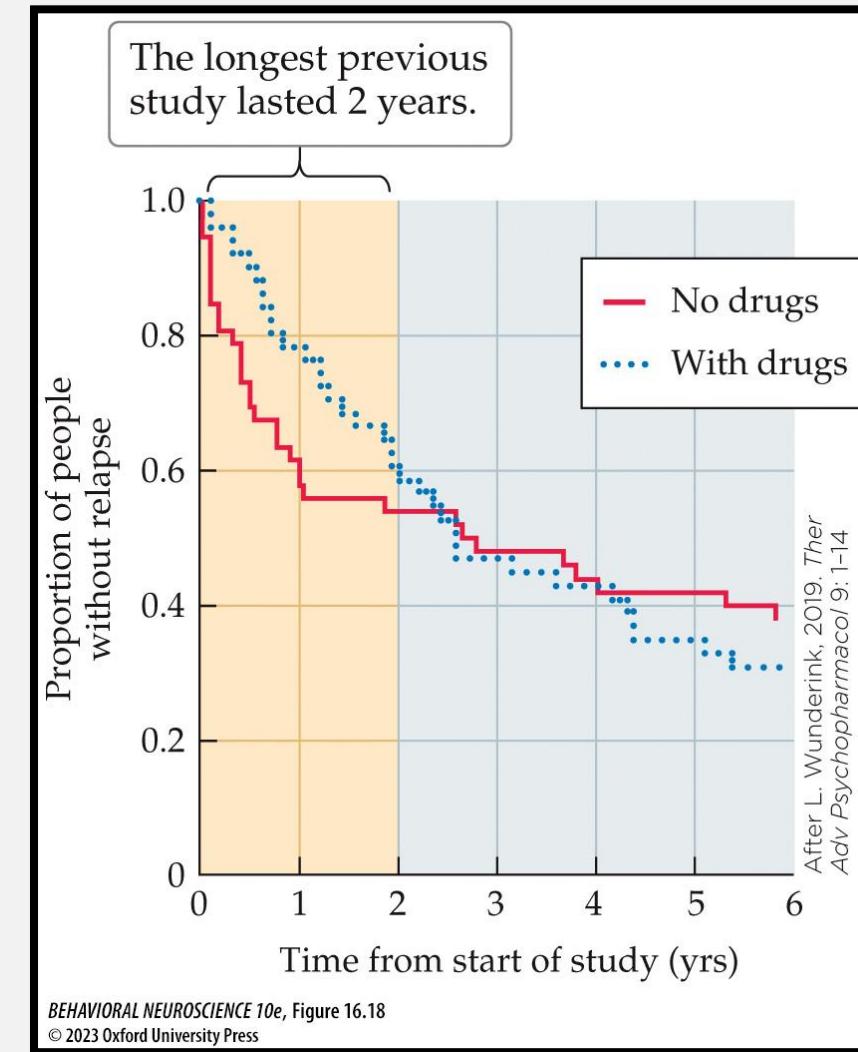


Environmental & genetic interaction



Psychiatric Disorders: Schizophrenia

- Controversy over long-term use of antipsychotic drugs:
- Programs that provide only medication are less successful than those that wean people from medication and help them become reintegrated in society, and relapses are less common.
- Cognitive behavioral therapy (CBT) helps people reduce stress and helps them feel less disturbed by the voices they hear.





Break

Learning objectives

1. Define depression and discuss depression's relationship to suicide risk.
2. Discuss the evidence that depression can be inherited.
3. Identify known neurophysiological correlates of depression.
4. Summarize the major clinical interventions used to treat depression, and catalog the main pharmacological modes of action of antidepressant medications.
5. Discuss ways in which sex differences, sleep, and hormone levels may all contribute to mood disorders.
6. Describe bipolar disorder in terms of its cardinal symptoms and relation to the other major psychiatric illnesses.
7. Summarize treatment options for bipolar disorder and their probable mode of action.
8. Discuss the genetic and physiological components of bipolar disorder, including differences between the sexes
9. Discuss the symptoms, causes, and possible physiological bases of posttraumatic stress disorder (PTSD).
10. Describe the symptoms, causes, and various treatments of obsessive-compulsive disorder (OCD).

Mood Disorders: Depression

Depression

- is the most prevalent mood disorder.
- Characterized by unhappy mood, loss of interests, low energy and appetite, difficulty concentrating, restless agitation
- Lets talk about the DSM-5 on the board.
- Can occur with no readily apparent stress and last for months.
- May lead to suicide.
- Studies suggest that if the first attempt is averted, a second attempt becomes very unlikely.

Mood Disorders: Depression

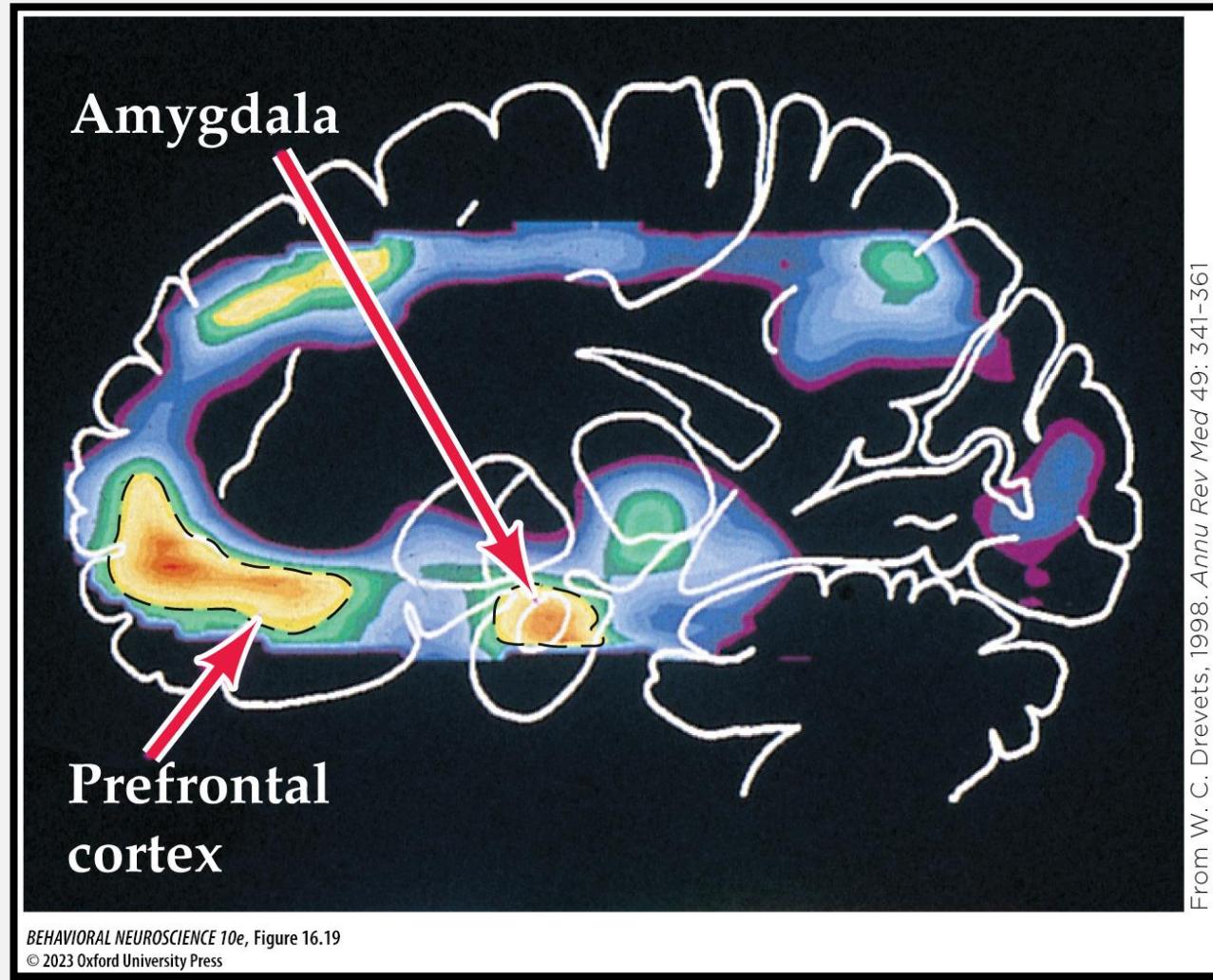
Depression

- has strong hereditary links, shown by twin and adoptive studies. Many genes contribute.
- Higher concordance in monozygotic twins than dizygotic twins whether reared together or apart.
- Genome studies – no single gene, subset of D2 receptor genes seem to be important.

Mood Disorders: Depression

PET scans of depressed people show

- Increased blood flow in prefrontal cortex and amygdala
- Decreased blood flow in parietal and posterior temporal cortex and anterior cingulate
- Hippocampal volume reduction & reduced activation during memory tasks (contributor or impacted?)





Treatment of depression?

Mood Disorders: Depression

Some treatments for depression:

- **Electroconvulsive therapy (ECT)**: induced seizures are used to treat severe, drug-resistant depression.
- **Repetitive transcranial magnetic stimulation** and **vagal nerve stimulation**.
- **Deep brain stimulation (DBS)**: mild electrical stimulation of brain sites through a surgically implanted electrode.
- **Personalized DBS** – automatic stimulation of key pleasure centers 100s times per day in previously identified marker areas for depression (pace-maker for the brain)
- **Exercise?**

Mood Disorders: Depression

Most common treatments

- are drugs that affect monoamine transmitters.
- **What NTs are monoamines?**

Monoamine hypothesis:

- insufficient activity of monoamines at synapses.
- First antidepressants were inhibitors of **monoamine oxidase (MAO)**, the enzyme that normally inactivates the monoamines: norepinephrine, dopamine, and serotonin.
- ECT may ease depression by releasing monoamines.
- Antipsychotic drugs like **reserpine** which depletes dopamine, norepinephrine and serotonin levels in the brain can lead to profound depression

Mood Disorders: Depression

Second-generation tricyclics

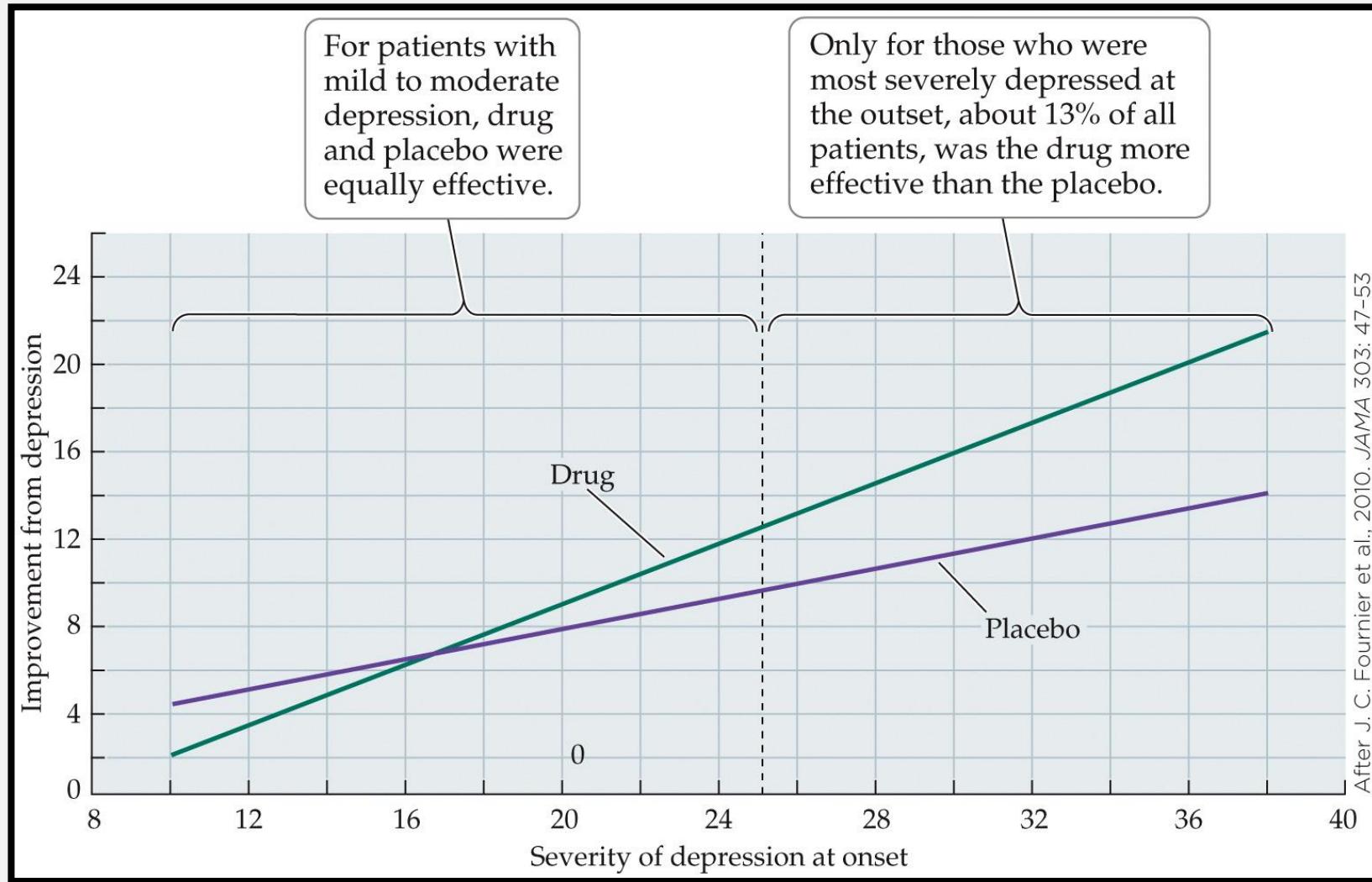
- inhibit reuptake of monoamines.
- **Selective serotonin reuptake inhibitors (SSRIs)** e.g., Prozac, are more effective with fewer side effects.
- **Serotonin-norepinephrine reuptake inhibitors (SNRIs)** may not be significantly better than SSRIs. Both take weeks to have an effect.
- Ongoing research with...
- **Ketamine** – NMDA receptor antagonist
- **Psilocybin and LSD** Serotonin receptor subtype agonist

Mood Disorders: Depression

In general, antidepressants are effective

- but the overall beneficial effects are modest.
- Undesirable side effects can prompt people to stop taking them.
- In some placebo-controlled trials, a significant proportion of people taking the placebo also report feeling better.

Placebo effect



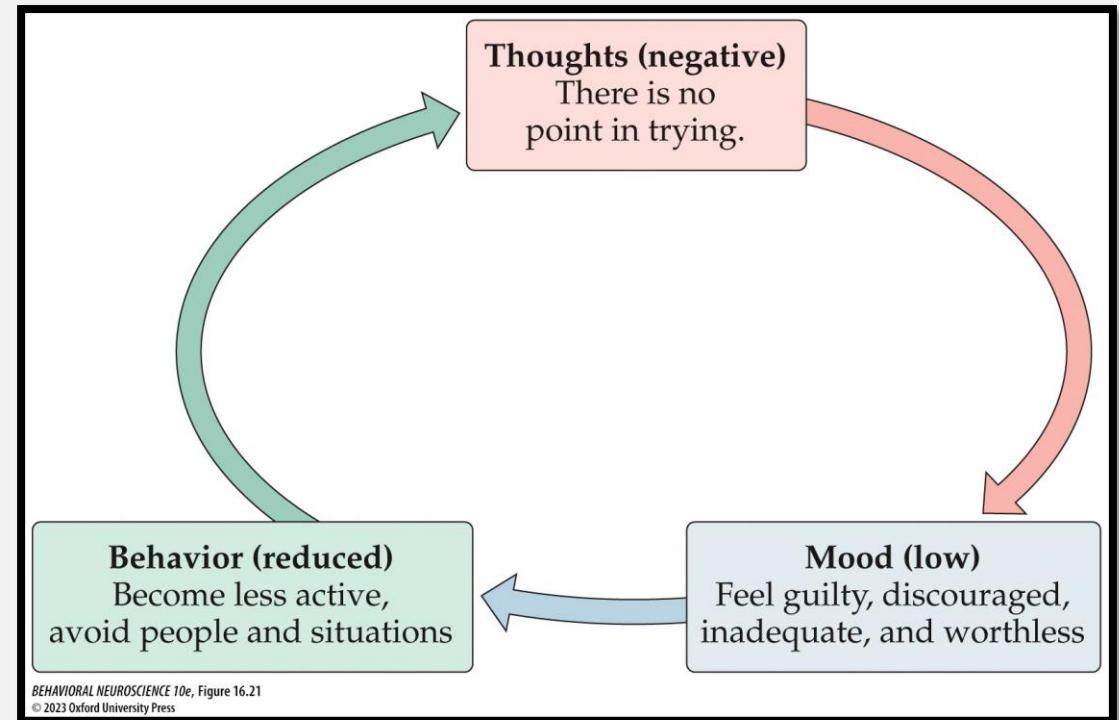
Mood Disorders: Depression

Risks of SSRI use include

- Increased risk of suicide in youths
- Synergy with other drugs, triggering **serotonin syndrome**.

Cognitive behavioral therapy (CBT)

- aimed at correcting negative thinking, reducing stress, and improving interpersonal relationships—is about as effective as SSRI treatment.



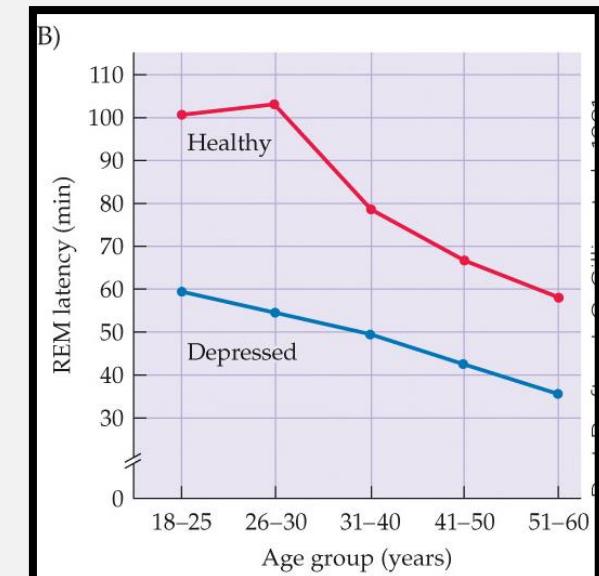
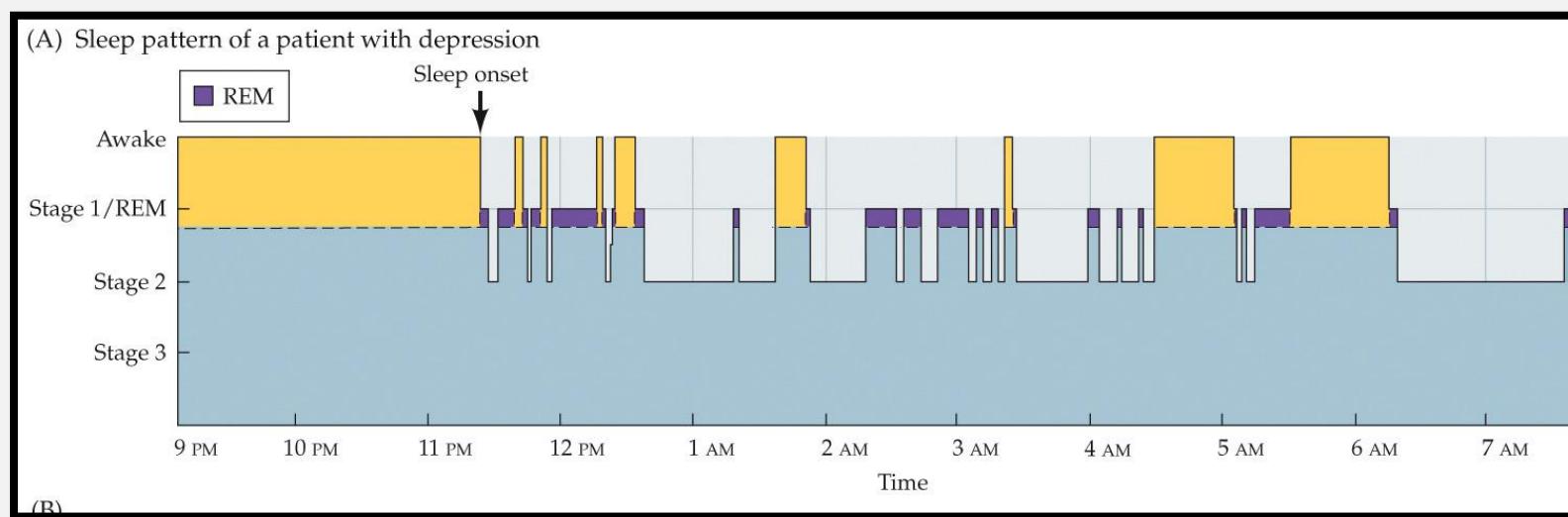
Genetics

- Hundreds or thousands of genes are implicated in each of the major psychiatric disorders.
- Researchers are using genetic screens to predict which drugs will be most effective for an individual.
- Some of the variability in patients' responses to particular drugs can be explained by a collection of **genetic polymorphisms**.

Mood Disorders: Depression

Sleep and depression

- Difficulties with sleep are common in depression, and EEGs of depressed people show abnormalities:
- Reduced stage 3, increased stage 1 and 2; they enter REM much earlier.
- Latency to REM sleep correlates with the severity of depression.



Mood Disorders: Bipolar Disorder

Bipolar disorder

- is characterized by periods of depression alternating with expansive mood, or mania.
- Brain imaging shows more activity during manic bouts.
- Has some similarities with schizophrenia, including enlarged ventricles. Changes probably include subcortical limbic structures, such as the amygdala, hippocampus, cingulate, and frontal cortex.

Bipolar Disorder

Cyclothymia:

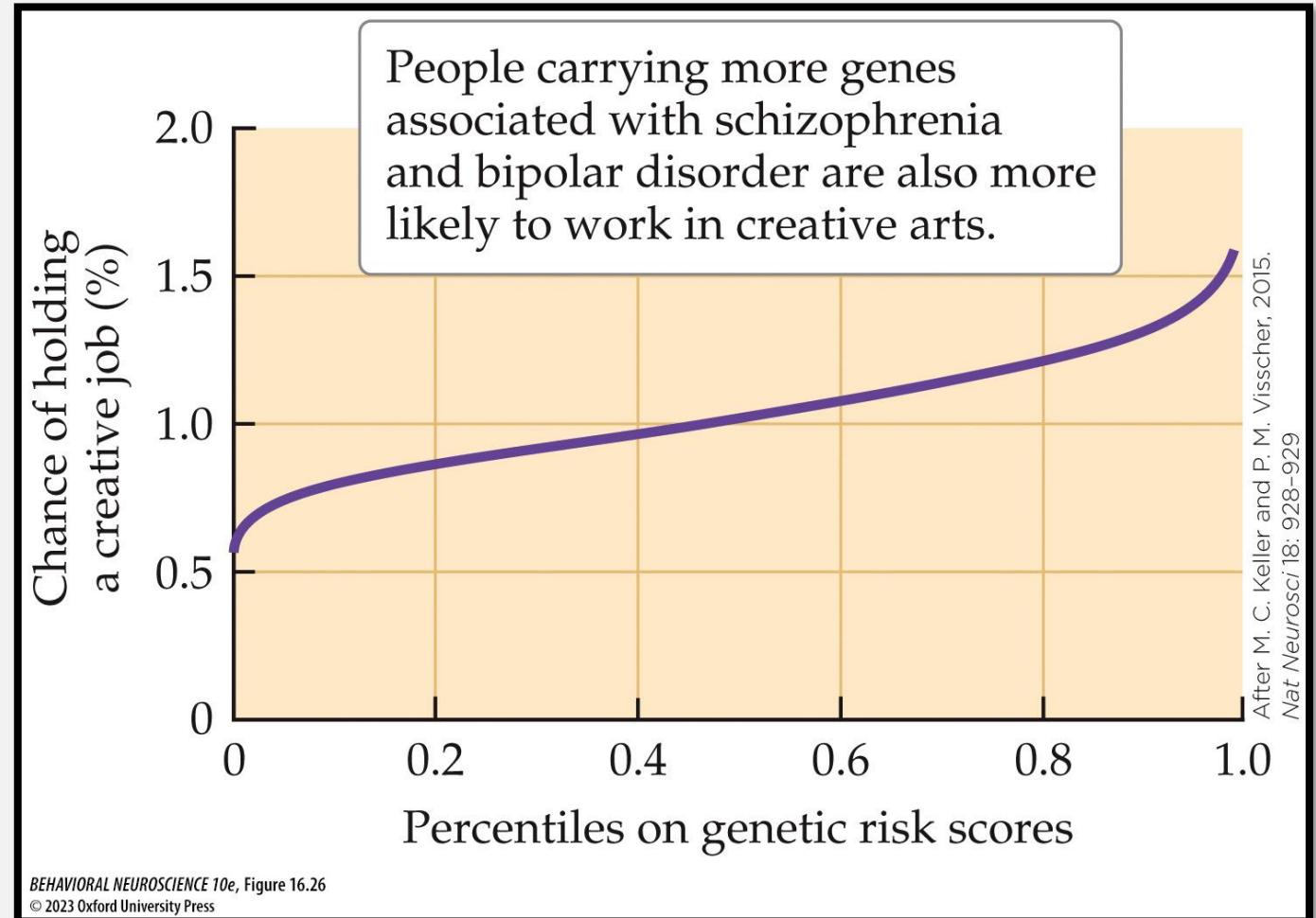
- milder, subclinical state—patients cycle between dysthymia (mild depression) and hypomania (increased energy).

Lithium

- is used to treat bipolar disorder; mechanism is unknown.
- Widespread actions in the brain
- Interacts with the circadian clock
- Boosts BDNF activity

Bipolar Disorder

- Males and females are equally affected.
- Many genes affect probability of developing bipolar disorder; one is the gene that encodes BDNF. Many also increase risk of schizophrenia.
- People who are susceptible to schizophrenia and bipolar disorder are more likely to be creative, artistic types.



Anxiety

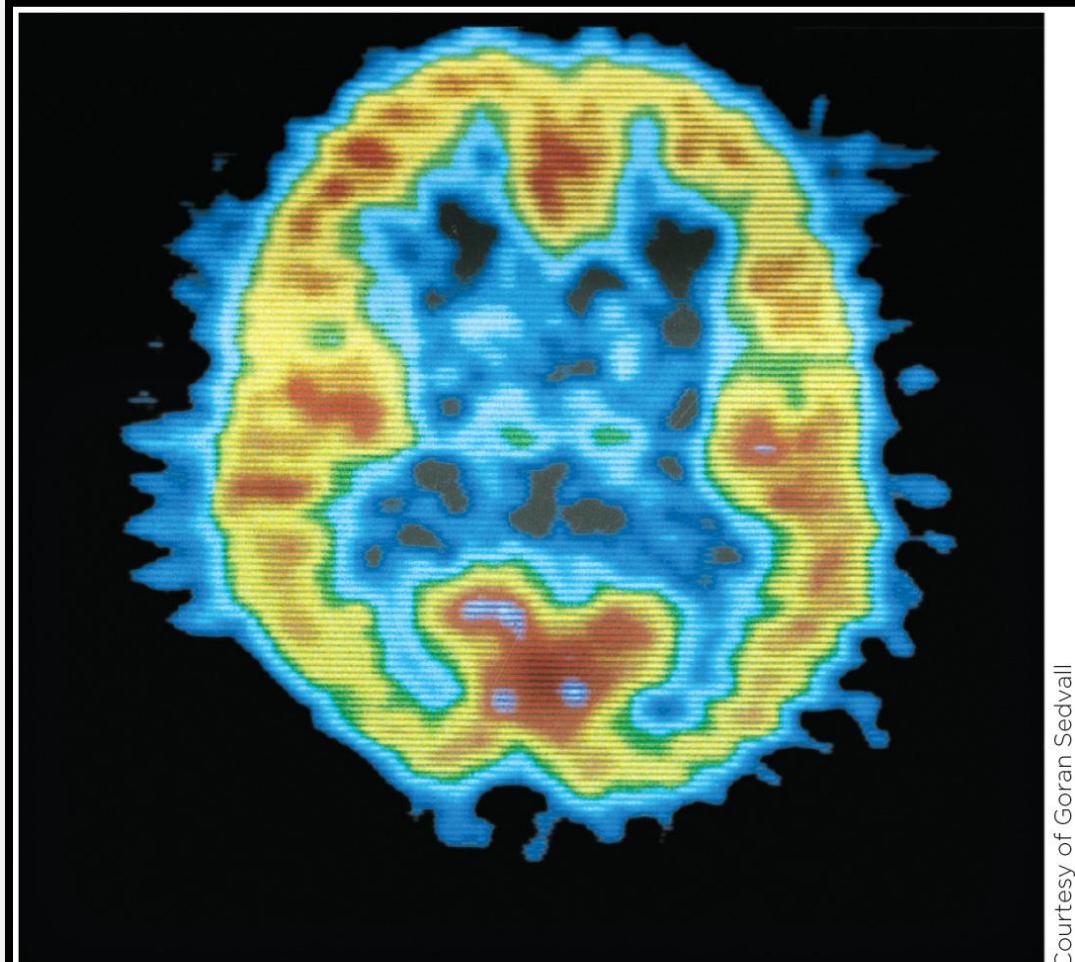
Anxiety disorders:

- psychological disorders that include recurrent panic and generalized anxiety.
- **Phobic disorders:** intense irrational fears centered on an object, activity, or situation that a person avoids.
- *Panic disorders:* recurrent transient attacks of intense fearfulness.
- *Generalized anxiety disorder:* persistent, excessive anxiety and worry.

Anxiety

Benzodiazepines

- are **anxiolytic** (anxiety reducing) drugs used to treat anxiety, e.g., Valium.
- They bind to GABA receptors and enhance GABA's inhibitory actions by increasing the flow of Cl^- ions into cells (non competitive agonist).
- Serotonin 5-HT_{1A} receptor agonists and SSRIs are also used to treat anxiety.



BEHAVIORAL NEUROSCIENCE 10e, Figure 16.27
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Trauma related disorders

Posttraumatic stress disorder (PTSD):

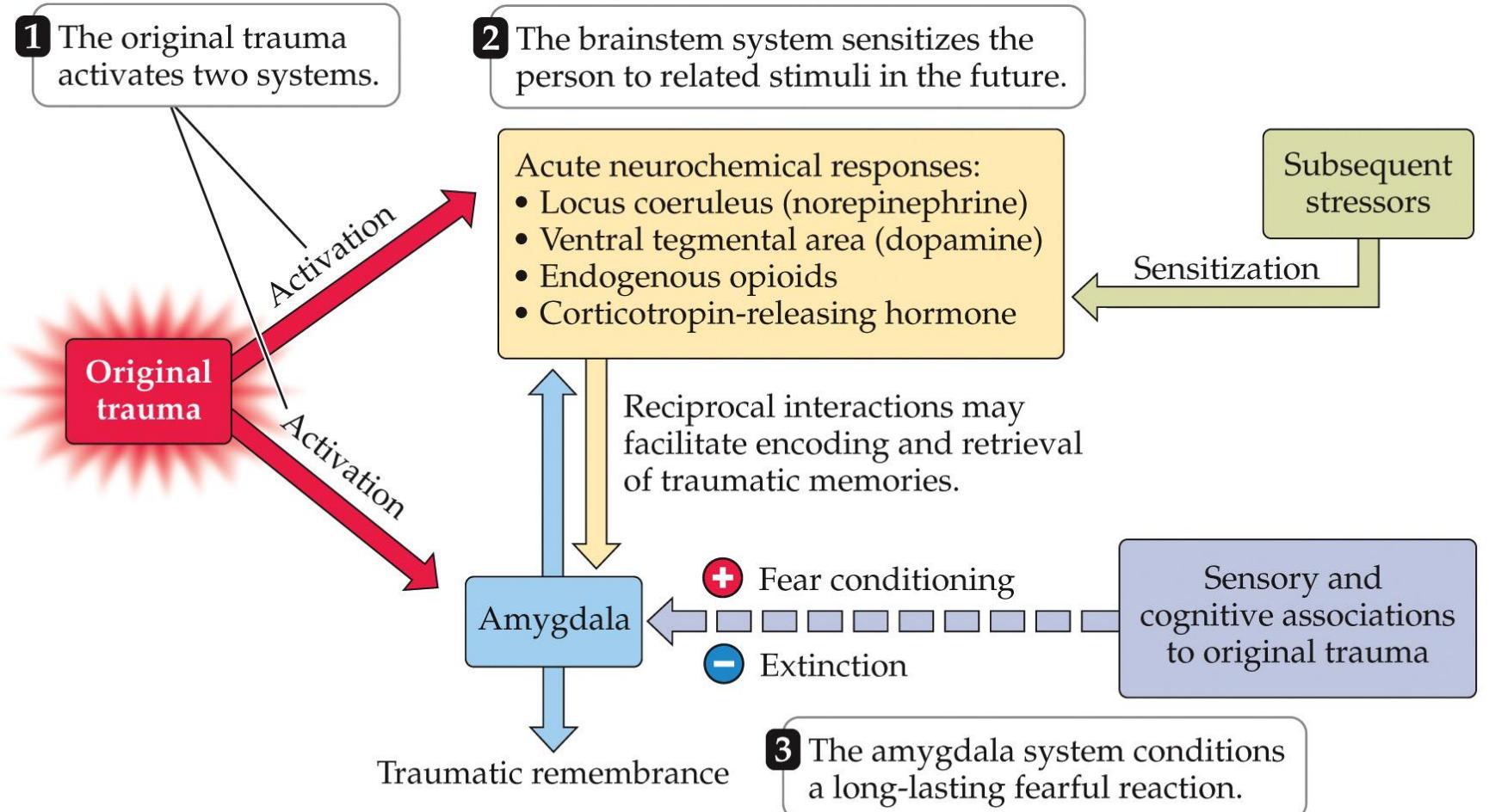
- memories of horrible events repeatedly plague the victim.
- Memories are easily reawakened by stressful circumstances and even seemingly benign stimuli; triggers fear and general autonomic activation.
- Victims may also have amnesia, flashbacks, and deficits in short-term memory.

Trauma-Related Disorders

PTSD victims

- have decreased volume in the right hippocampus; may be a risk factor.
- People learn to avoid stimuli associated with the original trauma, a type of **fear conditioning**.
- PTSD may involve a failure to forget. Projections to the amygdala may lose effectiveness in suppressing fear.

Neural model of PTSD



After D. S. Charney et al., 1993. *Arch. Gen. Psychiatry* 50:295

Compulsive-Related Disorder

Obsessive-compulsive disorder (OCD):

- recurring, repetitive acts that are carried out without rhyme, reason, or the ability to stop, despite recognizing that the behaviors are abnormal.

In OCD patients:

- Routine acts become compulsions
- Recurrent thoughts become obsessions

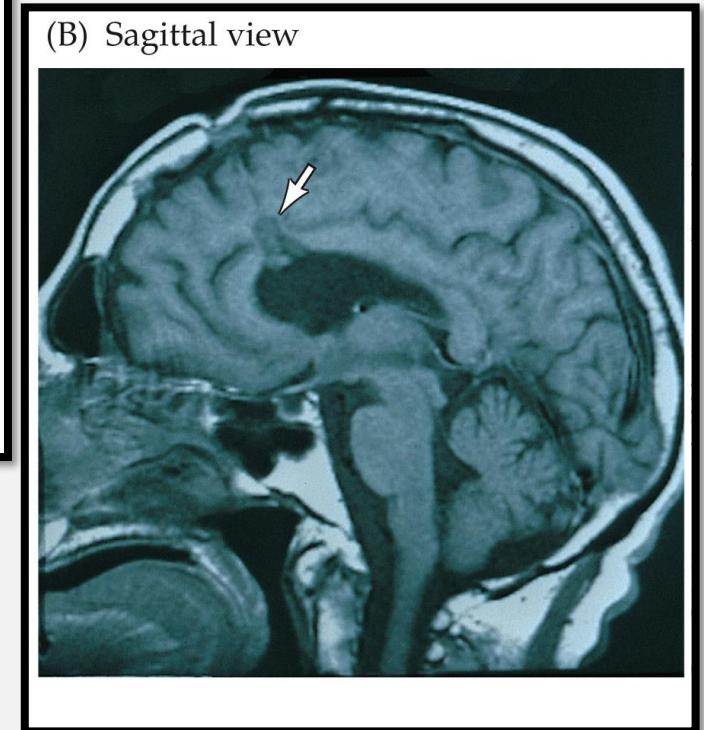
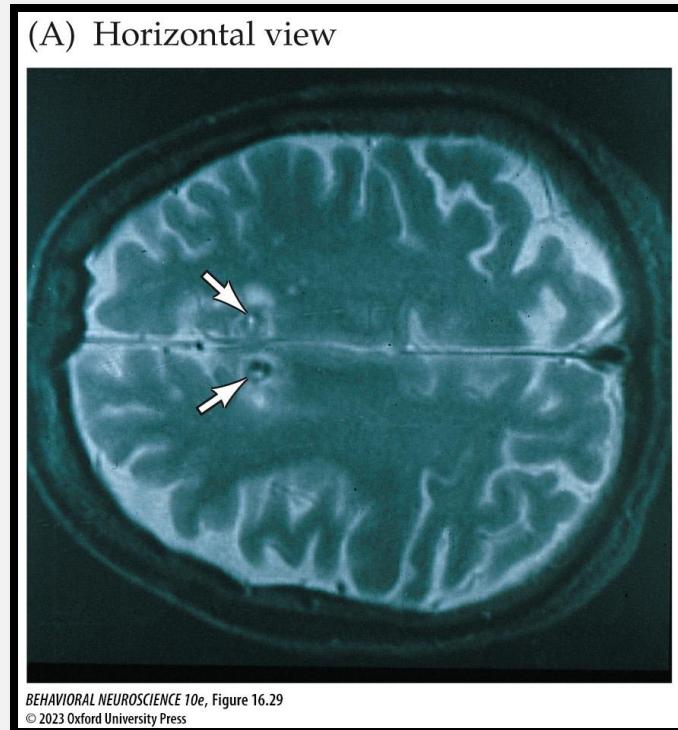
Compulsive-Related Disorder

OCD patients

- have increased metabolic rates in orbitofrontal cortex, cingulate cortex, and caudate nuclei.
- OCD responds to SSRIs in most cases; suggests serotonin dysfunction plays a major role.
- Overactivity of a circuit from prefrontal cortex to striatum to thalamus and back may underlie OCD.

Compulsive-Related Disorder

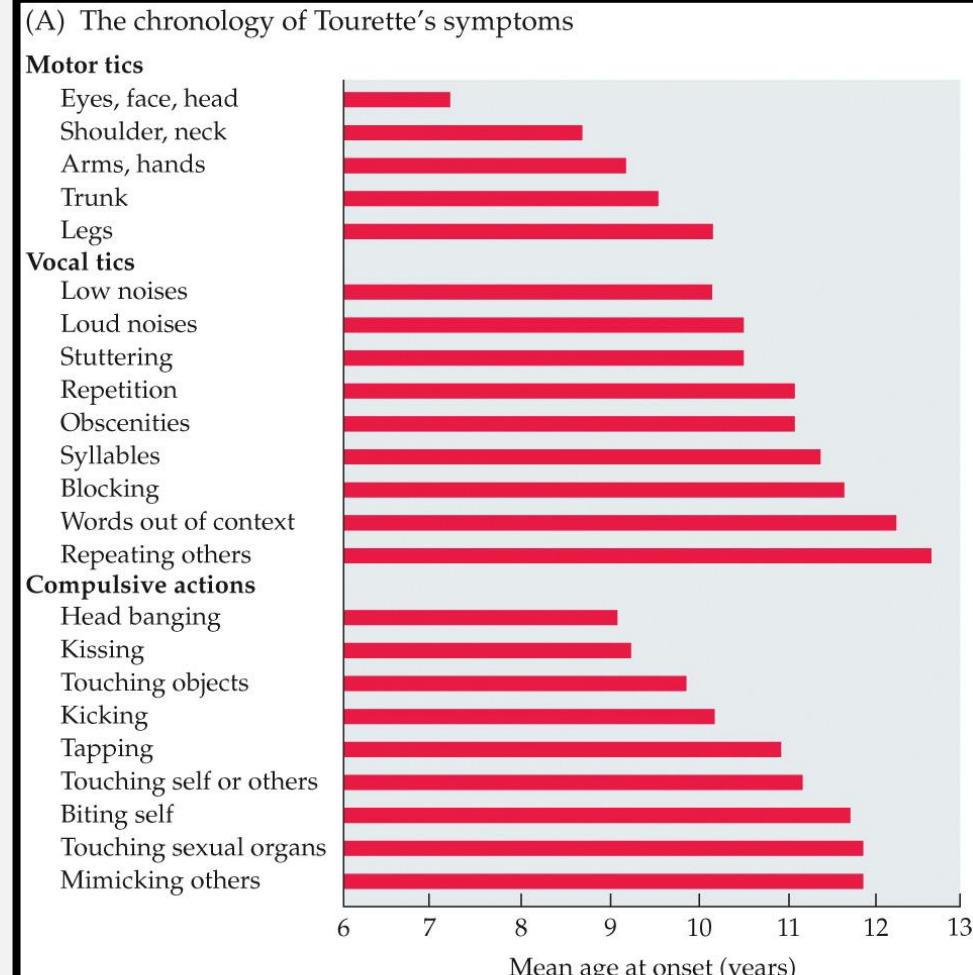
- *Cingulotomy* (surgical disruption of circuits in the cingulate cortex) benefits some severely disabled OCD patients.
- OCD has a heritable component, with many genes involved.
- Perinatal events and infections may trigger OCD—many children with OCD are producing antibodies to brain proteins.



Compulsive-Related Disorder

OCD & Tourette's syndrome

- OCD is often **co-morbid** with **Tourette's syndrome** and may be part of a spectrum of disorders.
- Patients have heightened sensitivity to tactile, auditory, and visual stimuli and an urge to emit verbal or phonic tics.
- It is diagnosed early, at 6–7 years; children may also exhibit attention deficit hyperactivity disorder (ADHD) or OCD.

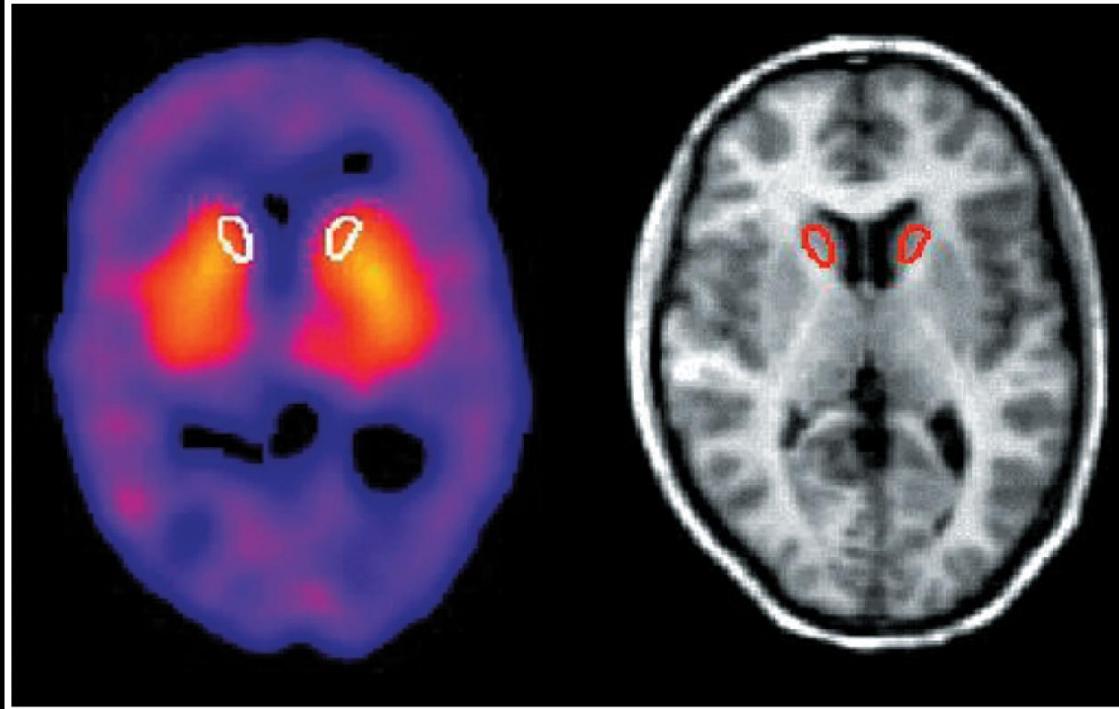


Compulsive-Related Disorder

Dopamine D₂ receptors

- are denser in the caudate nucleus of a Tourette's sufferer, as seen in twin studies.
- Differences in the dopaminergic system, especially in the basal ganglia, may be important.
- Haloperidol, a dopamine antagonist, is a primary treatment.

(B) D₂ receptor binding in Tourette's syndrome.
(Left) PET scan of D₂ binding. (Right) MRI scan illustrating the location of the caudate nuclei.





End
