



# **Schizophrenia and Autism**

# Schizophrenia

- **Schizophrenia:** characterized by deteriorating ability to function in every day life and some combination of the following:
  - Hallucinations.
  - Delusions.
  - Thought disorder.
  - Movement disorder.
  - Inappropriate emotional expression.

# Schizophrenia

- **Positive symptoms:** characteristics that are present, but should not be.
  - Hallucinations (almost always auditory)
  - Delusions of grandeur or persecution
  - Disordered thought processes (thoughts skip from one topic to another)
  - Bizarre (strange) behaviors

# Schizophrenia

- **Negative symptoms:** characteristics that should be present, but are not.
  - Social withdrawal
  - Little emotion
  - Loss of pleasure
  - Reduced motivation; poor focus on tasks
  - Reduced speech and movement
- Negative symptoms are usually stable over time and difficult to treat.

# Schizophrenia

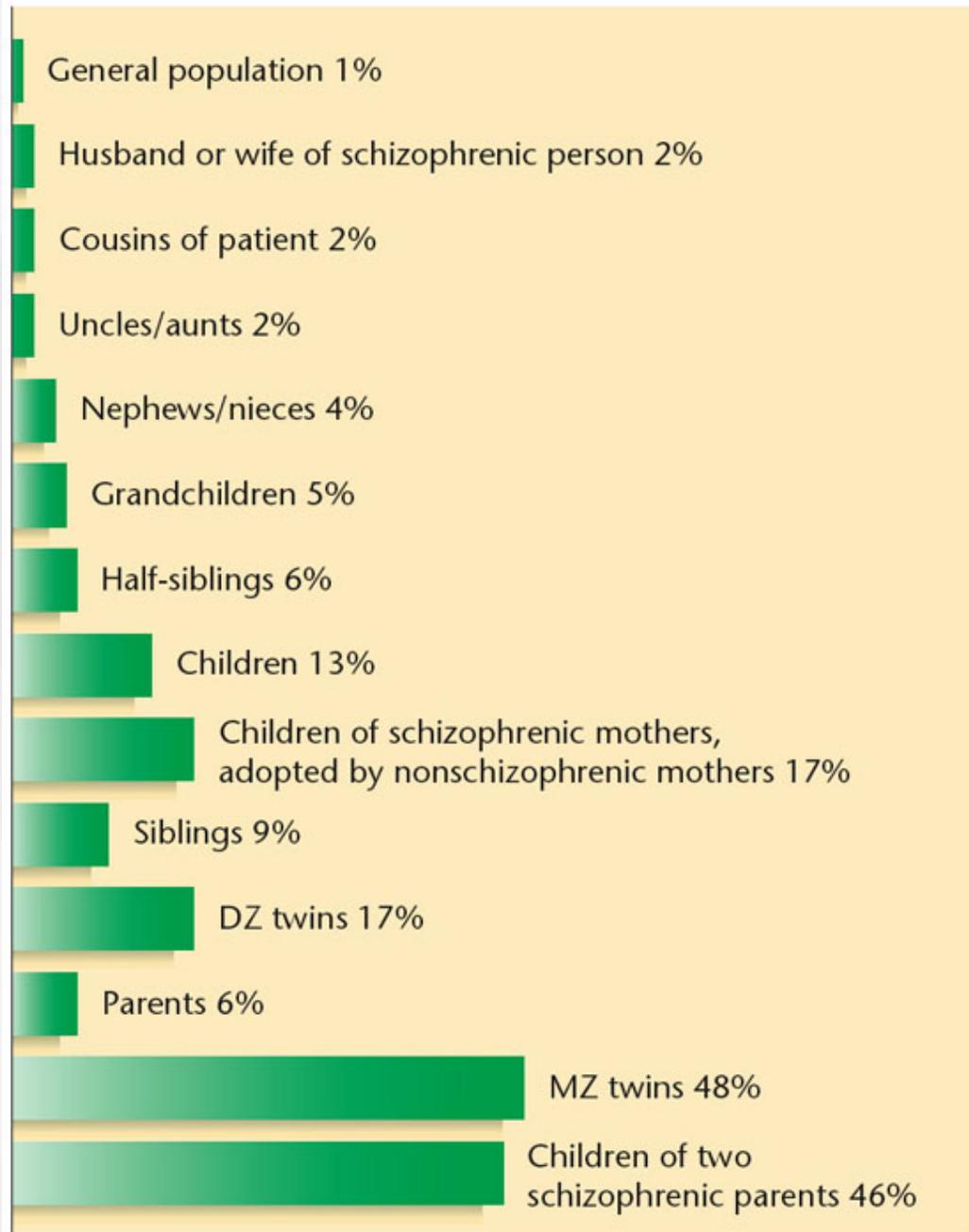
- Causes are not well understood but include a large biological component.
- Symptoms vary greatly.
  - **Acute** - condition has a sudden onset and good prospect for recovery.
  - **Chronic** - condition has a gradual onset and a long-term course.

# Schizophrenia

- Schizophrenia affects about 1% of the world's population and ranges in severity.
- Occurs in all parts of the world, but is 10 to 100 times more common in the United States and Europe than in third-world countries.
- More common in men than in women by a ratio of about 7 to 5.
- More severe and earlier age of onset for men (early 20's versus late 20's).
- Likelihood increases as the age of the father increases.

- Twin studies suggest a genetic component.
- Monozygotic twins have a much higher **concordance** rate than dizygotic twins.
- But monozygotic twins only have a 50% concordance rate.
  - Other factors may explain the difference.
- Greater similarity between dizygotic twins than siblings suggests a prenatal/postnatal environmental effect.
- Schizophrenia probably depends on a combination of genes or different genes in different families.

### Percent developing schizophrenia



## Twin studies

- Why does one twin become schizophrenic and the other does not?
  - Lower birth weight
  - More physiological distress
  - More submissive, tearful, sensitive
  - Impaired motor coordination

# Schizophrenia

- One study identified a gene linked to high levels of negative symptoms.
- Perhaps genetic research should focus on specific aspects of schizophrenia rather than schizophrenia in general.
- Schizophrenia probably results from environmental factors in addition to biological factors.

# Schizophrenia

- **Prenatal risk factors:**
  - Poor nutrition of the mother during pregnancy.
  - Premature birth.
  - Low birth weight.
  - Complications during delivery.
- Head injuries in early childhood are also linked to increased incidence of schizophrenia.

# Schizophrenia

- Mother/child blood type differences increase the likelihood of schizophrenia.
- If the mother has a Rh-negative blood type and the baby is Rh-positive, the child has about twice the probability of developing schizophrenia.

# Schizophrenia

- Certain viral infections may also contribute.
- The **season-of-birth effect** refers to the tendency for people born in winter to have a slightly (5% to 8%) greater probability of developing schizophrenia.
  - Greater effect in far northern or southern latitudes.
  - Might be explained by nutritional factors or increased likelihood of viral infections

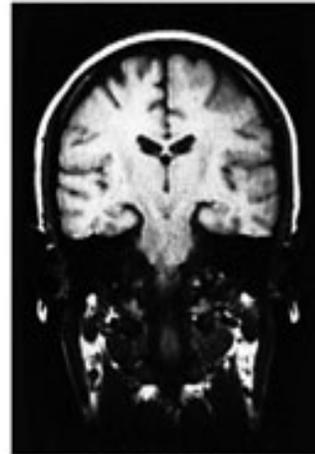
# Schizophrenia

- Mild brain abnormalities:
  - Strongest deficits in the left temporal and frontal lobes.
  - Larger than normal ventricles.
    - Especially common in those with complications during birth.
- Areas that mature slowly such as the dorsolateral prefrontal cortex.
  - Schizophrenics have deficits in working memory.

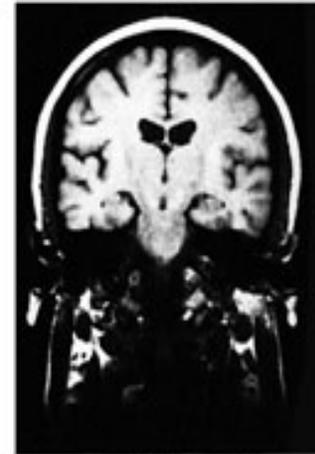
Larger than normal lateral ventricles: rest of brain must be smaller.

Large ventricles correlate with more negative symptoms.

MRI brain images of twins discordant for schizophrenia  
35-year-old female identical twins

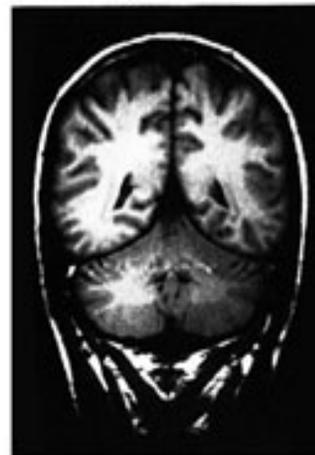


Well

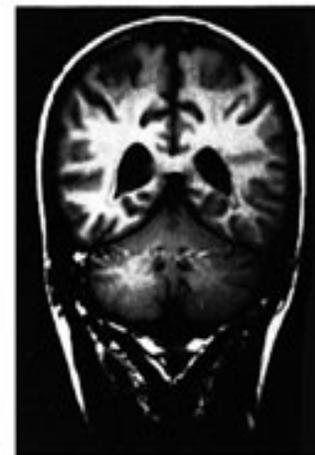


Affected

28-year-old male identical twins

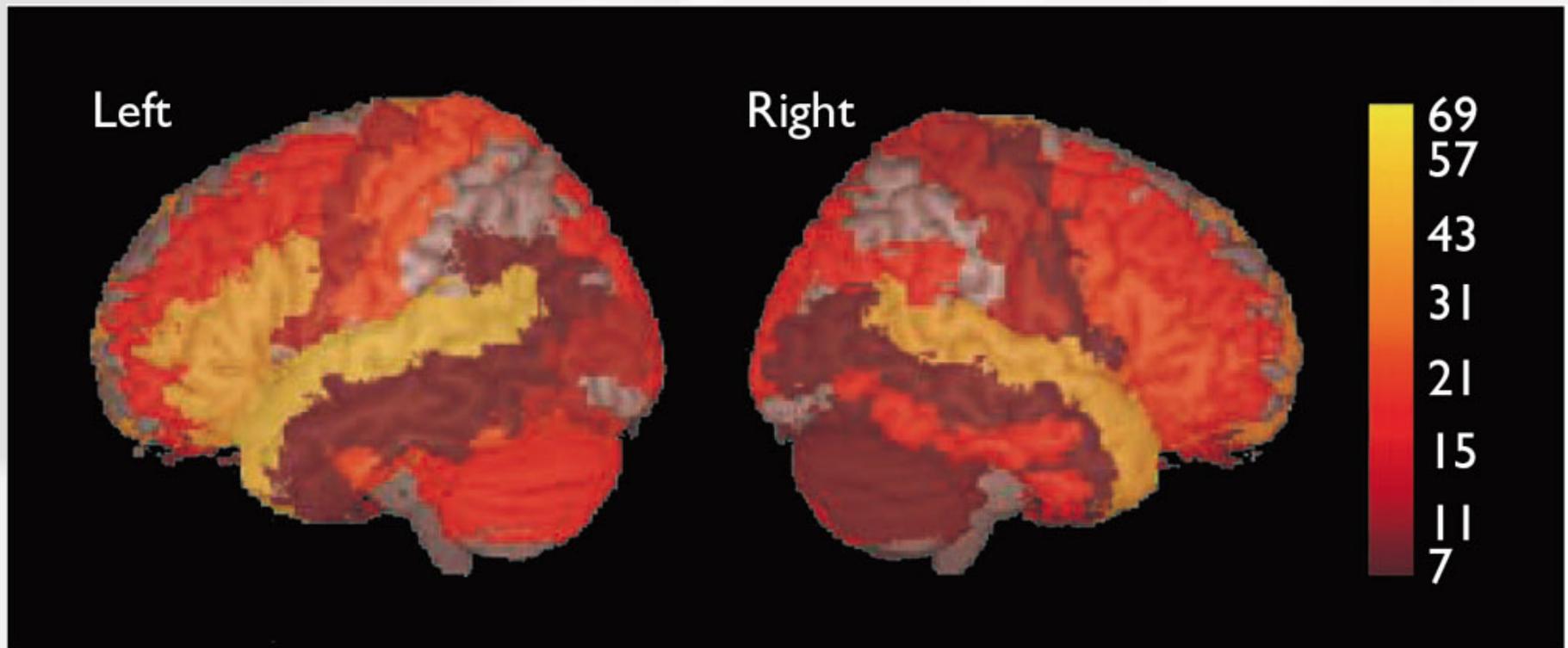


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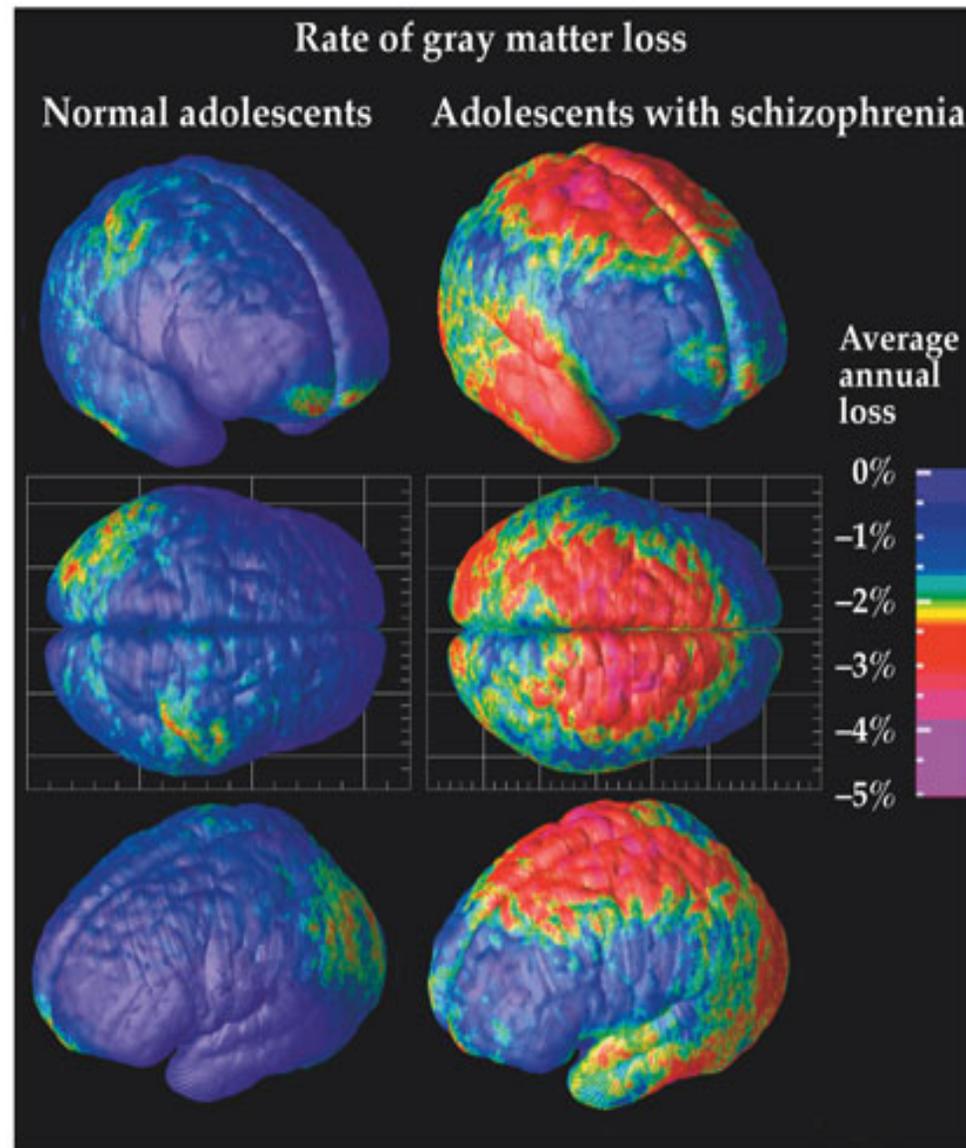


Affected

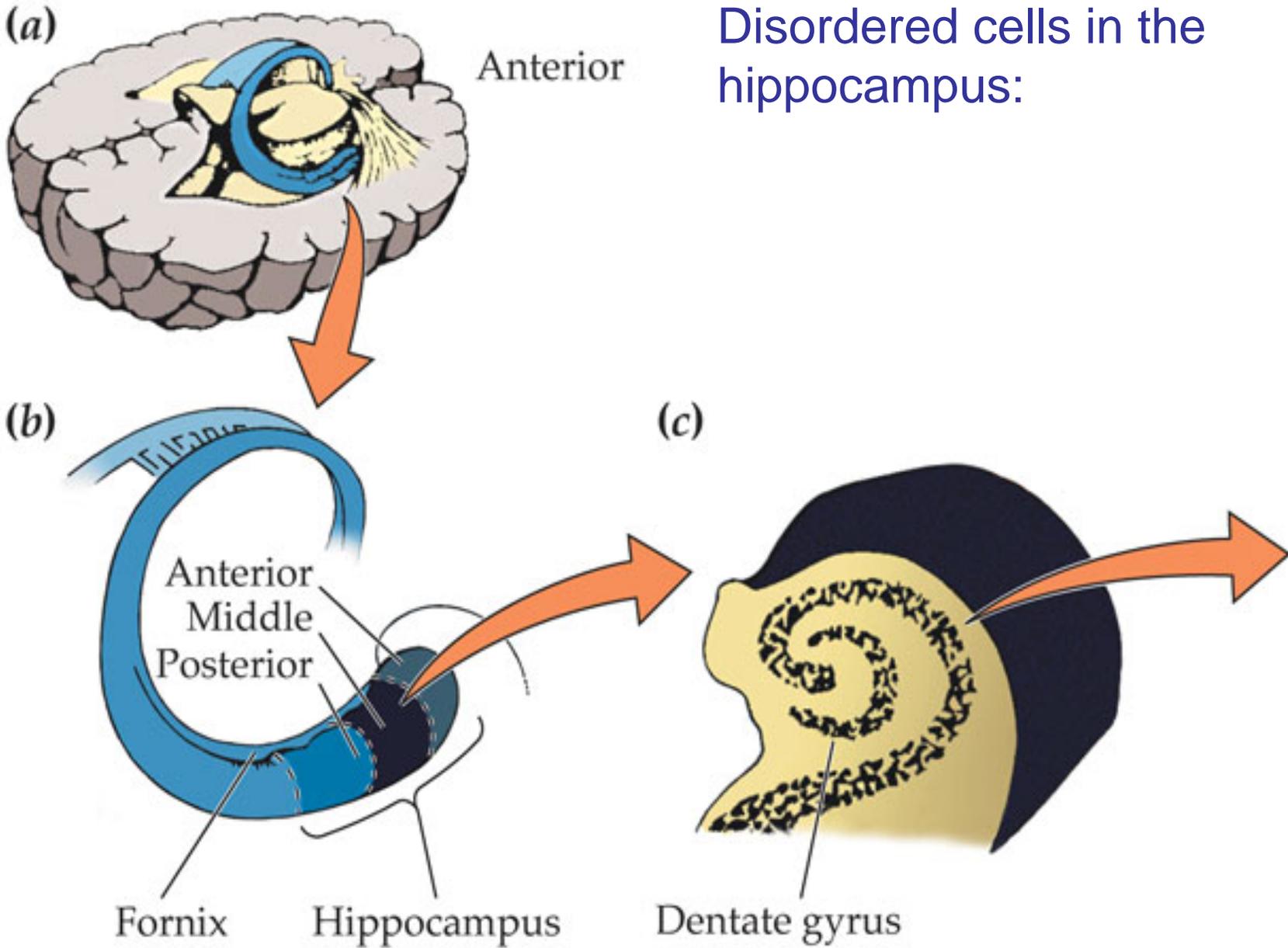
**Cortical areas showing decreased volume in schizophrenics:  
Yellow areas show most deficits, red show less.**



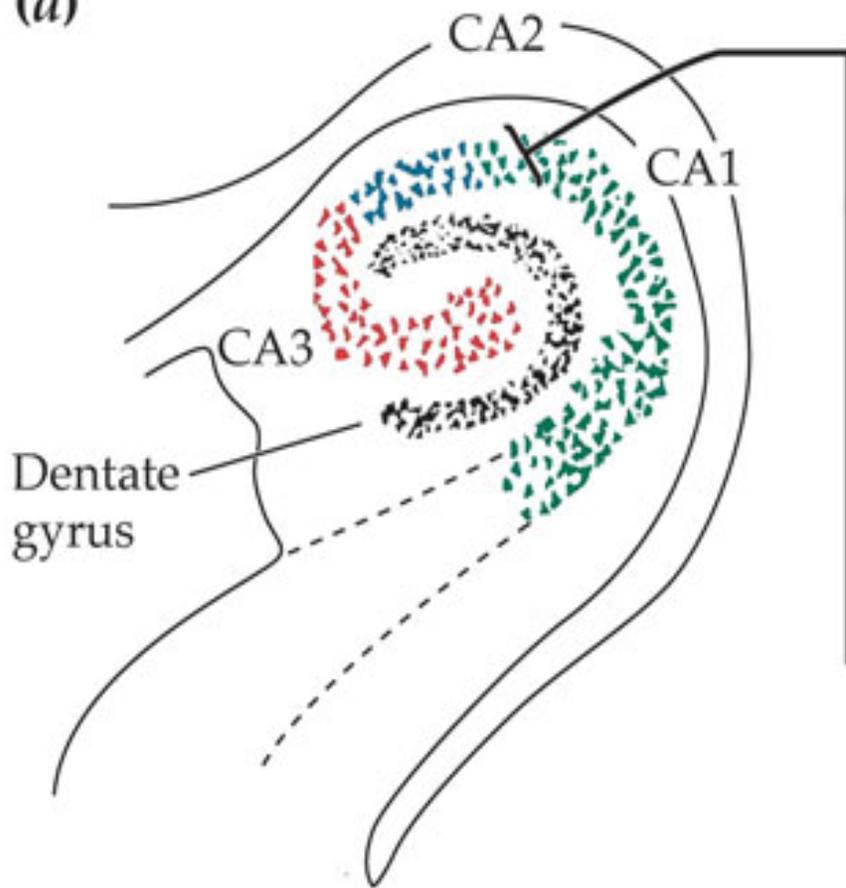
# Increased loss of gray matter in schizophrenics during adolescence



# Disordered cells in the hippocampus:



(d)



(e)

Organized



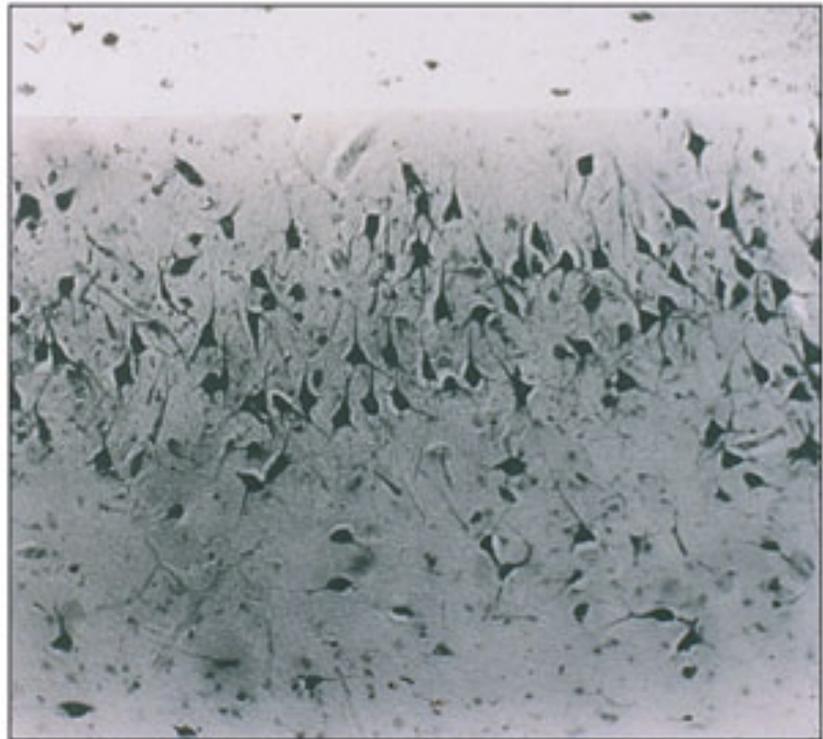
Disorganized



**(f) Normal control**



**(g) A patient with schizophrenia**



# Schizophrenia

- At a microscopic level, schizophrenics have smaller cell bodies than usual, especially in the hippocampus and prefrontal cortex.
- There is lower than normal activity throughout the left hemisphere, suggesting subtle changes in early development.

## Structural changes in brain

- Shrinkage of part of the cerebellum
- Thicker corpus callosum
- Frontal lobes
  - Dendrites have fewer branches
  - Measures of frontal function impaired

## Functional changes in brain

- Hypothesis: Impaired function in frontal lobes
  - If one twin is schizophrenic and the other is not, there is low frontal blood flow only in the affected twin

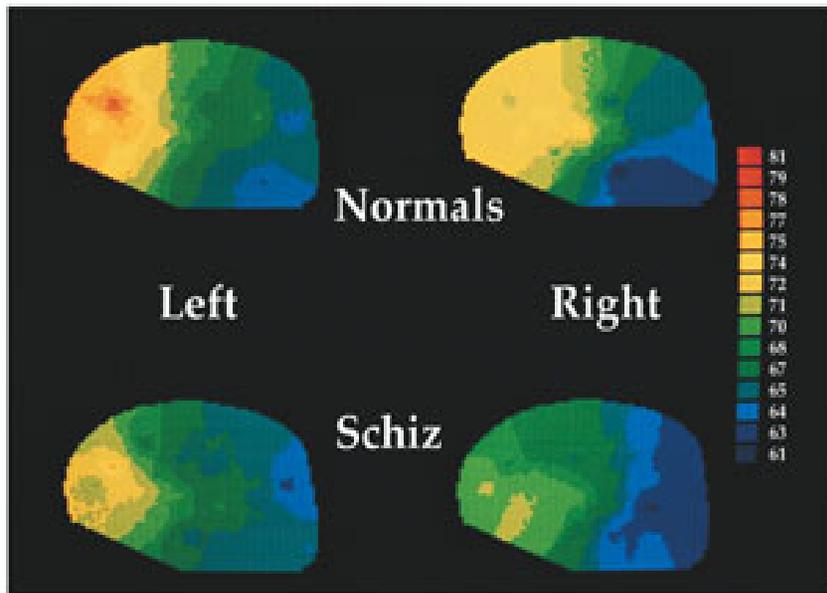
# Functional changes in brain

- Wisconsin card sorting task
  - Cards have several types of figures, several colors of figures, and a different number of figures on each card.
  - Task: sort EITHER by color, OR by shape, OR by number of figures on a card.
  - Schizophrenics can't shift attention to the other criterion

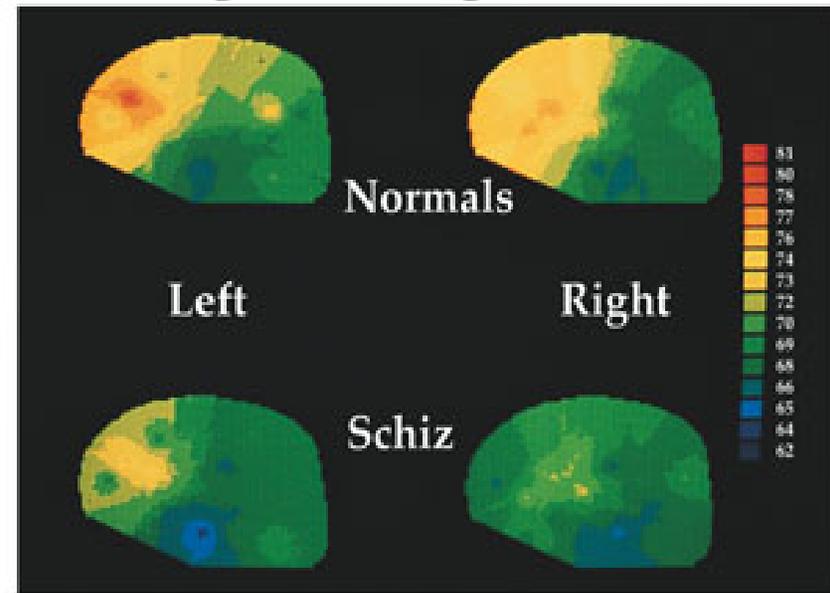
## Decreased frontal activity in schizophrenia

- Functional imaging: frontal lobe activity lower at rest, especially in right hemisphere; activity does not increase during the task.

(a) At rest



(b) During card-sorting task

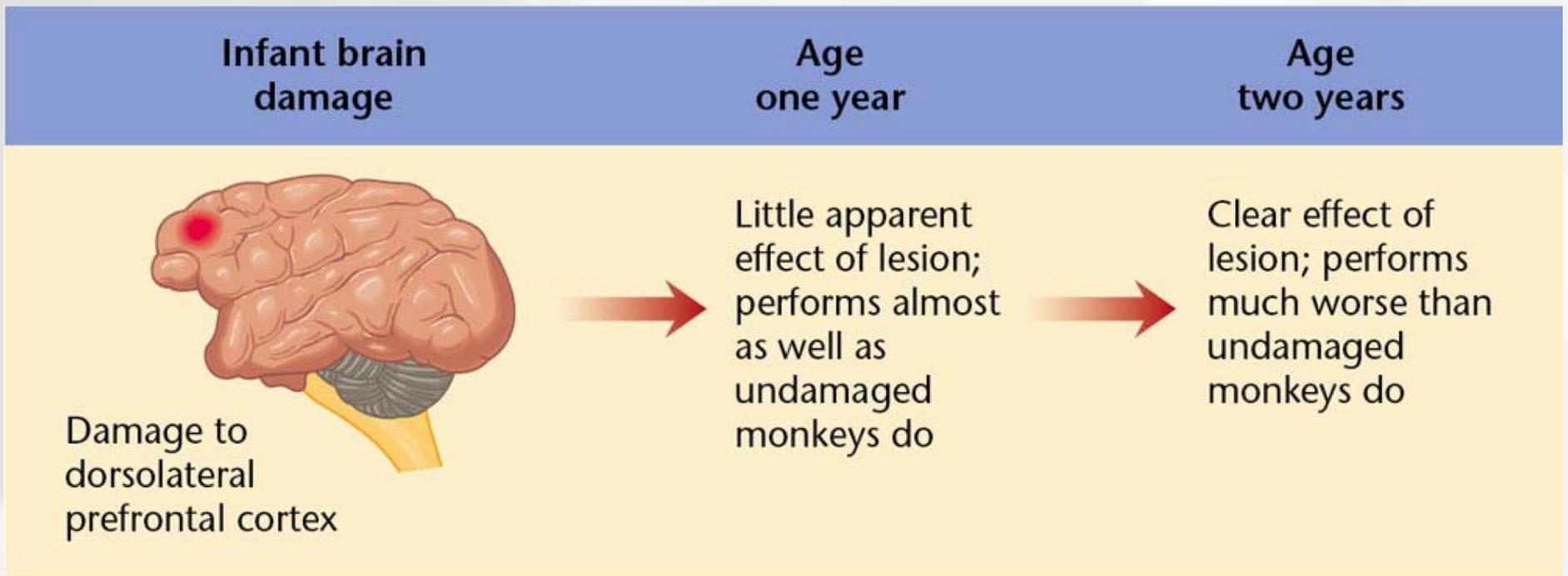


- Drug treatment increased activation of frontal lobes

# Schizophrenia

- Schizophrenia typically develops **after the age of 20**, but many show signs at an earlier age.
  - Deficits in attention, memory and impulse control.
- Prefrontal cortex damage may not result in signs of damage until later.
  - It matures slowly and does not do much at an earlier age.

# Delayed effects of brain damage in infant monkeys



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# Dopamine hypothesis of schizophrenia

- Amphetamine (increases dopamine release) in very high doses → paranoia, delusions, auditory hallucination.
- It also worsens symptoms of schizophrenia.
- Its effects are blocked by a dopamine antagonist.
- All typical antipsychotic drugs block dopamine D2 receptors and lessen positive symptoms.
- Schizophrenics appear to have more D2 receptors occupied by dopamine.

## **Limitations of the dopamine hypothesis**

- Direct measurement of dopamine and its metabolites indicate generally normal levels in people with schizophrenia.
- Antipsychotic drugs block dopamine within minutes but effects on behavior gradually build over 2 to 3 weeks.

## **The glutamate hypothesis of schizophrenia**

- Proposes that the problem is due to deficient activity at glutamate receptors.
  - Especially in the prefrontal cortex.

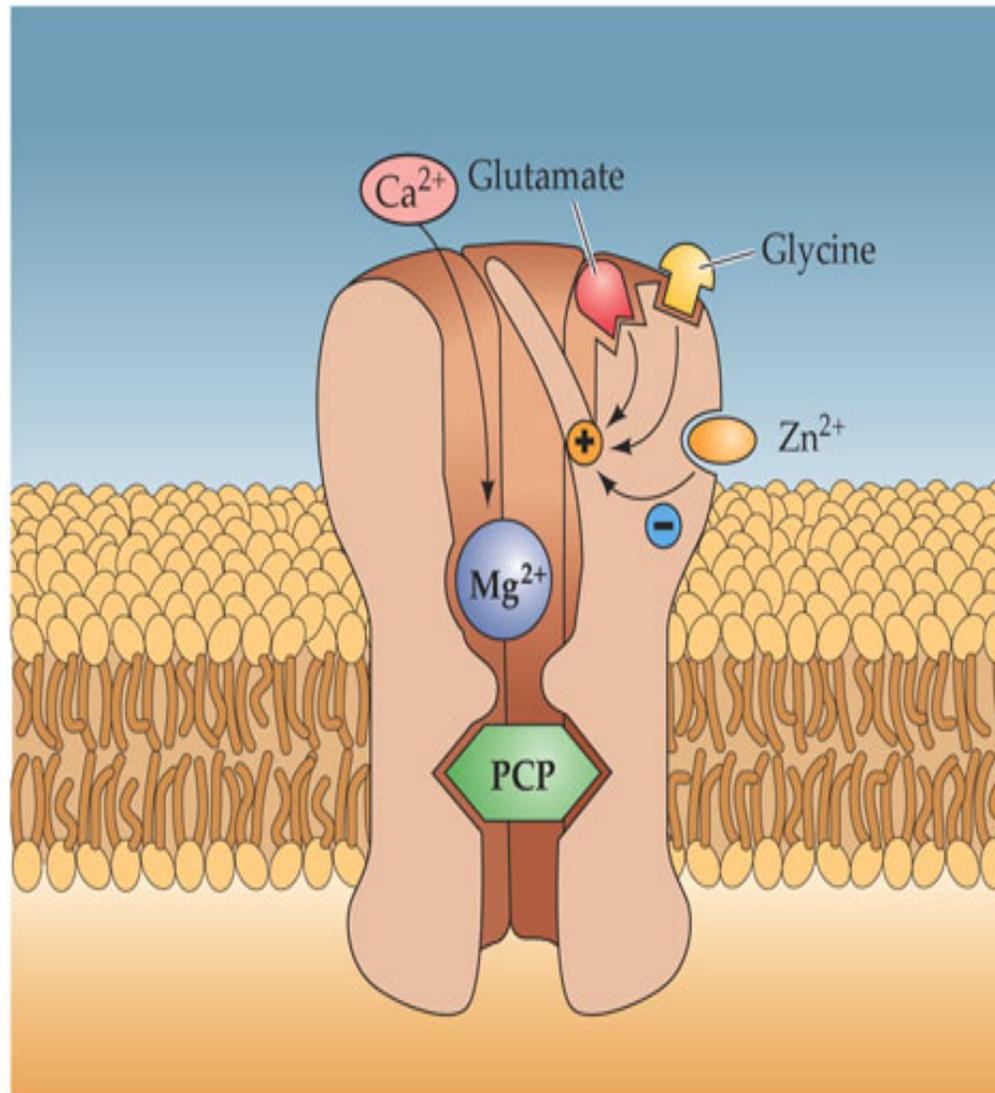
## Glutamate hypothesis

- There is some evidence that schizophrenics have lower than normal release of glutamate and fewer receptors in the prefrontal cortex and hippocampus.
- Further support comes from the effects of a drug (phencyclidine, PCP).
  - Inhibits the one type of glutamate receptors.
  - Produces positive and negative symptoms at high doses.

PCP blocks the glutamate receptor and → auditory hallucinations & other symptoms of schizophrenia.

Glycine (an amino acid) also binds to the receptor and facilitates glutamate binding.

(b) A model of PCP action on the NMDA receptor



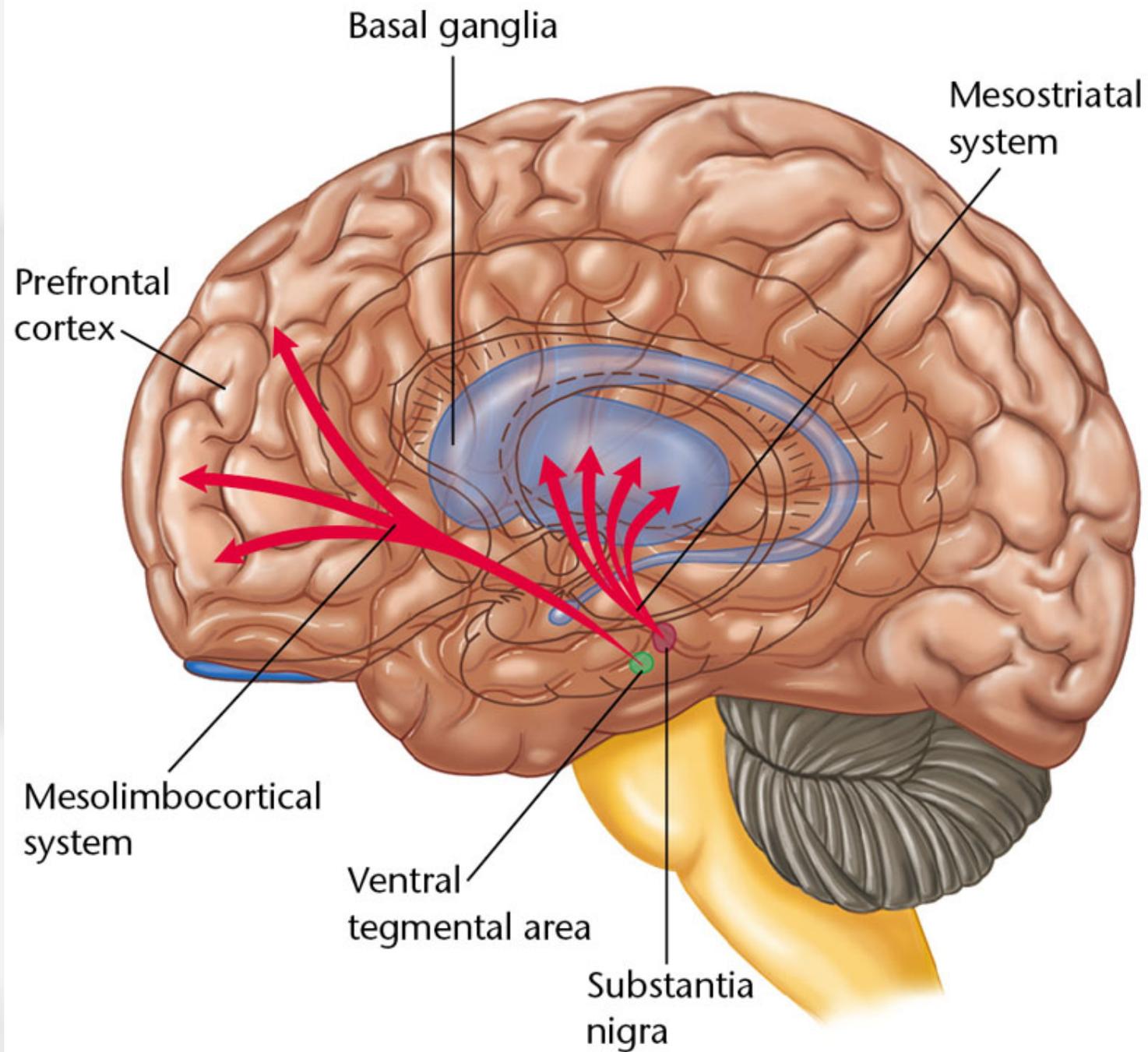
## **Glutamate hypothesis**

Glycine alone is not clinically effective, but it improves effects of other drugs.

There have also been promising effects in a trial of a slow-acting glutamate agonist.

# Schizophrenia

- The **mesolimbic system**: a set of neurons that project from the midbrain to the limbic system and frontal lobes.
  - It is the site where drugs that block dopamine synapses produce their benefits.
- Typical antipsychotic drugs also block dopamine in a nearby dopamine tract that controls motor movements.
  - The result is tremors and other involuntary movements.

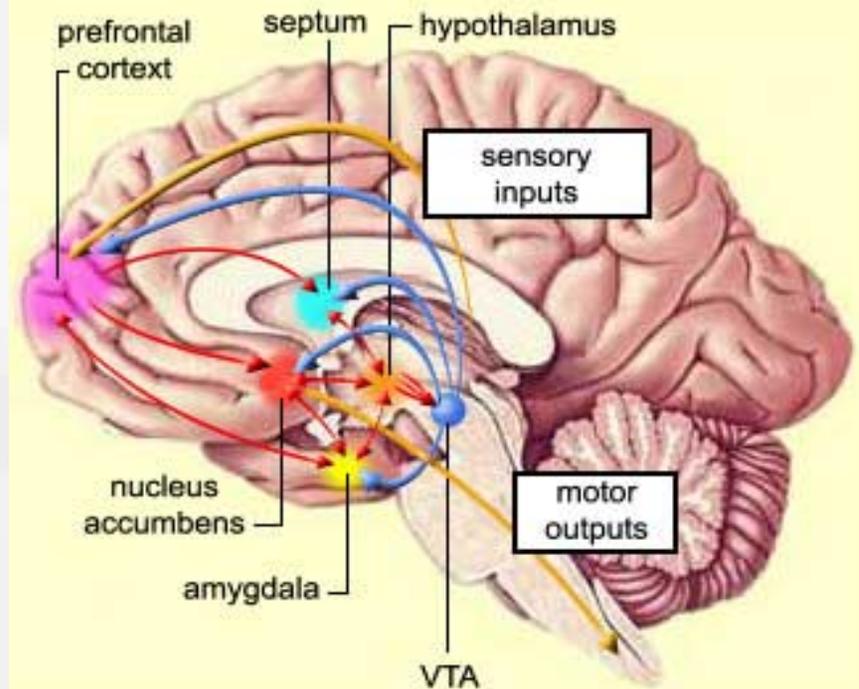


# Schizophrenia

- **Second-generation antipsychotics** (atypical antipsychotics): treat schizophrenia but seldom produce movement problems.
- They are more effective at treating the negative symptoms and are now more widely used.
- They have less effect on dopamine receptors and more strongly block a type of serotonin receptors.

# Reconciliation between dopamine and glutamate hypotheses

- Frontal lobes normally inhibit dopamine release in the mesolimbic tract (important for motivation and repetitive thoughts)
- Maybe decreased frontal activity results in too much dopamine in mesolimbic tract, which leads to positive symptoms of schizophrenia.



# Schizophrenia

- Schizophrenia cannot be explained by a single gene or single transmitter.
- Dopamine and glutamate may play important roles in schizophrenia to different degrees in different people.
- Schizophrenia involves multiple genes and abnormalities in dopamine, glutamate, serotonin and GABA.

# Schizophrenia Summary

- Brains are smaller in schizophrenics, and hippocampus cells are disordered.
- Prefrontal cortex (PFC) is less active.
- Normally PFC inhibits dopamine activity in the mesolimbic tract; this would inhibit impulses and irrelevant thoughts.
- Therefore, if we could increase activity in the PFC this would increase glutamate's inhibitory effects on mesolimbic dopamine release and decrease positive symptoms.

# Summary

- Positive symptoms of schizophrenia (those present in schizophrenics but not normal people) include hallucinations, delusions, inappropriate emotions, bizarre behaviors, and thought disorder.
- Negative symptoms (behaviors present in normal people but absent in schizophrenics) include deficits of social interaction, emotional expression, and speech.

# Summary

- Studies of twins and adopted children imply a genetic predisposition to schizophrenia. However, the adoption studies do not distinguish between roles of genetics and prenatal environment.
- No single gene has been found that is strongly linked to schizophrenia. Perhaps it depends on multiple genes.

## Summary

- According to the dopamine hypothesis, schizophrenia is due to excess dopamine activity. The main support for this hypothesis is that drugs that block dopamine receptors reduce positive symptoms, and drugs that increase dopamine can induce positive symptoms.
- However direct measurements of dopamine and its receptors have not strongly supported this hypothesis. Also the time course for effects on symptoms is later than effects on the receptors.

## Summary

- According to the glutamate hypothesis, the problem is deficient glutamate activity. Evidence supporting this view is that phencyclidine, which blocks NMDA glutamate receptors, produces both positive and negative symptoms of schizophrenia, especially in people predisposed to schizophrenia.

# Summary

- Prolonged use of antipsychotic drugs may produce tardive dyskinesia, a movement disorder. Second-generation antipsychotic drugs relieve both positive and negative symptoms without producing tardive dyskinesia. Most psychiatrists now prescribe these drugs.

# Autism

- **Autism** is a disorder of brain development that impairs social interaction and communication.
- There is a milder form of the disorder, called Asperger syndrome.

## Autism symptoms

- Stereotypy:** purposeless movement, such as hand flapping, head rolling, or body rocking.
- **Compulsive behavior:** follows strict rules, such as arranging objects in a certain way.
- **Resistance to change;** for example, insisting that the furniture not be moved.
- **Ritualistic behavior:** performance of daily activities the same way each time.
- **Self injury:** movements that injure or can injure the person, such as biting oneself.

**Repetitive stacking of objects can be a symptom of autism.**



# An autistic boy and the precise line of toys he made



# Autism

- 0.5% to 10% of people with Asperger's syndrome show unusual abilities, ranging from memorizing trivia to the rare talents of *idiot savants*.
- Autistic people do not make eye contact. When they do look at someone's face, it is almost always at the mouth.
- One study used fMRI to show that the amygdala is over-activated when autistic people try to look at someone's eyes.

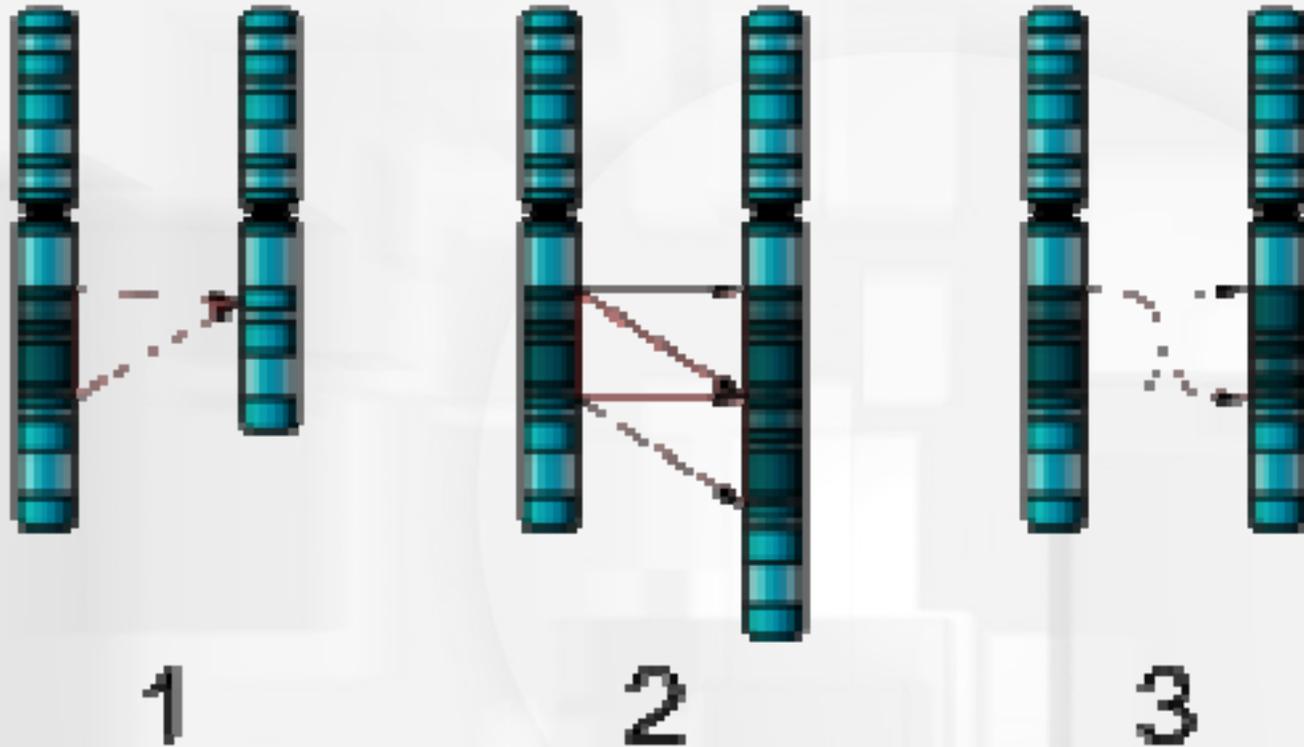
# Autism

- Autistic people may not prefer to be alone, but it is difficult for them to make friends.
- Especially those that have limited intelligence may have frequent emotional outbursts.
- About a third to a half of autistic individuals do not develop enough speech to meet their daily communication needs.
- As babies, they have delayed onset of babbling and unusual gestures.

# Autism

- Autism has a strong genetic basis, but no single gene is implicated.
- Incidence: 2 cases per 1,000 people for autism; 6 per 1,000 for Asperger's syndrome. There is a 4:1 male-to-female ratio.
- The number of people known to have autism has increased dramatically since the 1980s. However, that is at least partly due to changes in diagnosis. It is not clear whether the numbers have actually increased.

## Genetic Causes

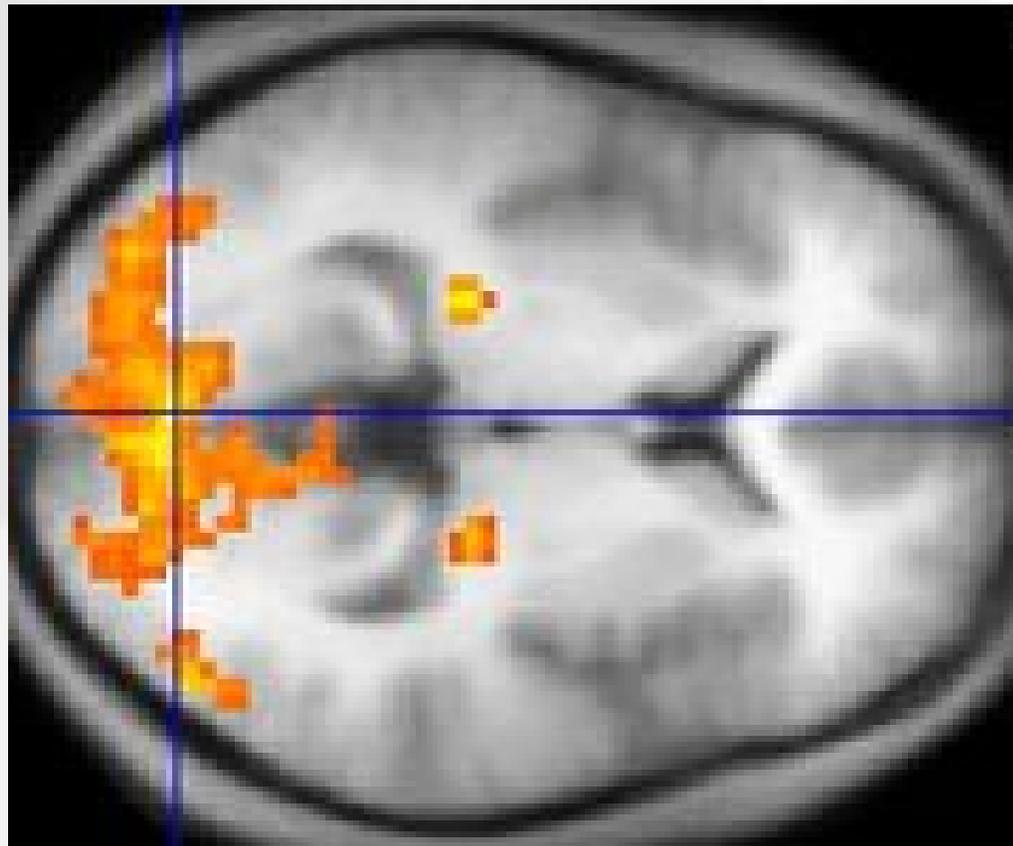


Deletion (1), duplication (2) and inversion (3) are chromosome abnormalities implicated in autism. Numerous cases may be highly heritable but not inherited: that is, the mutation that causes the autism is not present in the parental genome.

## Brain abnormalities

- Several neurotransmitter abnormalities have been detected in autism, especially increased blood levels of serotonin. Whether these lead to the behavioral abnormalities is unclear.
- Structural abnormalities in “mirror neuron” regions of the brain have been noted. However, individuals with autism have abnormal brain activation in many circuits.

A 2008 brain-imaging study found a specific pattern of signals in the [cingulate cortex](#) that differs in individuals with autism.



## Brain abnormalities

- Brain weight and volume and head circumference tend to be greater in autistic children.
- Several studies suggested that adults with autism have local overconnectivity within regions of the cortex and weak functional connections between the frontal lobes and the rest of the cortex.
- Therefore, the prefrontal cortex cannot direct thoughts and impulses.

## Brain abnormalities

- In normal people there is overproduction of neurons during gestation and early childhood. However, most of those die out because they do not make good functional connections.
- Perhaps the increased brain size in autistic people is due to abnormal local connections within cortical areas preventing the death of neurons that are not useful.
- Therefore, each area repetitively processes its own information, without interacting with other areas of the brain.

## Autism summary

- Autism has a strong genetic basis, but no single gene is implicated.
- The main symptoms are inability to have social interactions and repetitiveness.
- There is evidence for overgrowth in the brain, and increased connections within certain areas. However, there is underconnection between the frontal lobes and other areas.

## Autism summary

- This may result in obsessive, repetitive behaviors, which are not directed by the prefrontal cortex.
- In addition, there is increased anxiety when looking into someone's eyes. This anxiety is driven by overactivity in the amygdala.