

Schizophrenia

("the graveyard of neurophysiologists")

Positive vs. Negative Symptoms

Positive symptoms are things that are present that should not be. Negative symptoms are things that are absent that should be present. Notice that the negative symptoms are not unique to schizophrenia. Many of them sound like things that might occur in depression, for example.

- **Positive symptoms**

- hallucinations (usually auditory)
- delusions (paranoid, grandiose, control)
- disordered thinking or incoherence (thought disorder)
- strange mannerisms

- **Negative symptoms**

- flattened affect (absence of emotion)
- apathy, anhedonia, poverty of speech
- stupor, catatonia
- social withdrawal
- deterioration of personal habits

Cognitive Symptoms

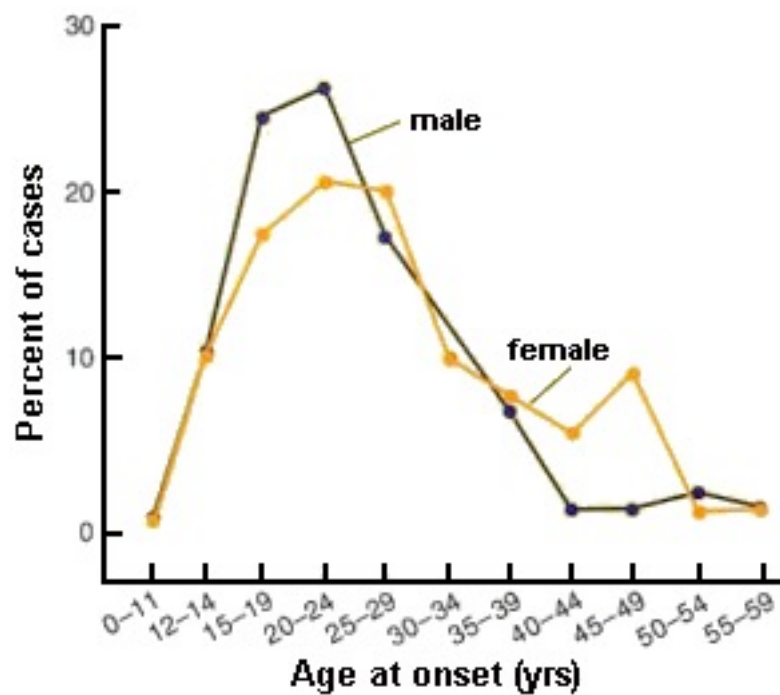
- Most of these are losses so also qualify as negative symptoms. Notice how much they resemble symptoms of frontal lobe damage.
 - difficulty in sustaining attention
 - low psychomotor speed
 - deficits in learning and memory
 - poor abstract thinking
 - poor problem solving

Statistics

- Lifetime risk vs. incidence vs. prevalence
 - about 1% of both men and women will be diagnosed with schizophrenia at sometime during their lives (lifetime risk)
 - about 100,000 new diagnoses will be made in the U.S. this year (incidence)
 - currently there are about 2.2 million people in the U.S. who have been diagnosed with schizophrenia (prevalence)

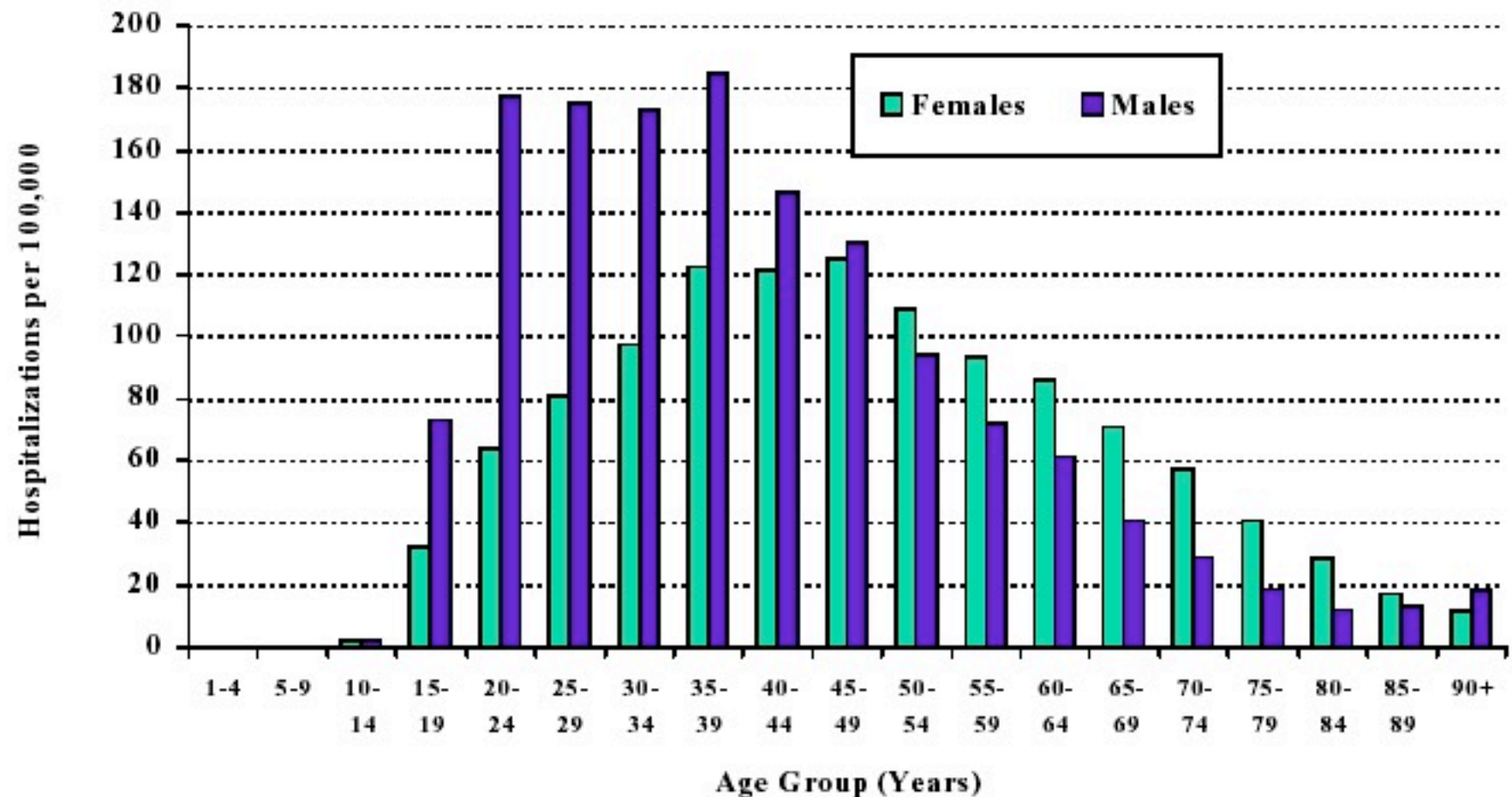
First Diagnosis

Usually occurs in late adolescence or young adulthood, somewhat earlier for males than for females.



(Adapted from Häfner H., Riecher-Rössler A., an der Heiden W., Maurer K., Fätkenheuer B., and Löffler W. *Psychological Medicine*, 1993, 23, 925-940.)

Hospitalizations for schizophrenia* in general hospitals per 100,000 by age group, Canada, 1999/2000



* Using most responsible diagnosis only

Source: Centre for Chronic Disease Prevention and Control, Health Canada using data from Hospital Morbidity File, Canadian Institute for Health Information

Course

- Typically the negative symptoms develop first, often during adolescence. These were at one time called “prodromal” symptoms.
- The cognitive symptoms begin to occur soon afterwards.
- Some years later (about 2-5 yrs.) the positive symptoms appear.
- It’s the positive symptoms that bring people to the attention of psychiatrists! (Nobody notices you if you’re withdrawn and apathetic, but if you’re wandering down the street hallucinating and raving about people who are out to get you, that’s going to attract attention!)

The Rule of Quarters

- About one-quarter of people diagnosed will improve to the point that they can be considered cured.
- About one-quarter will show some improvement.
- About one-quarter will show no improvement.
- And about one-quarter (mostly those with prominent negative symptoms) will continue to deteriorate.

Schizophrenia and Public Health

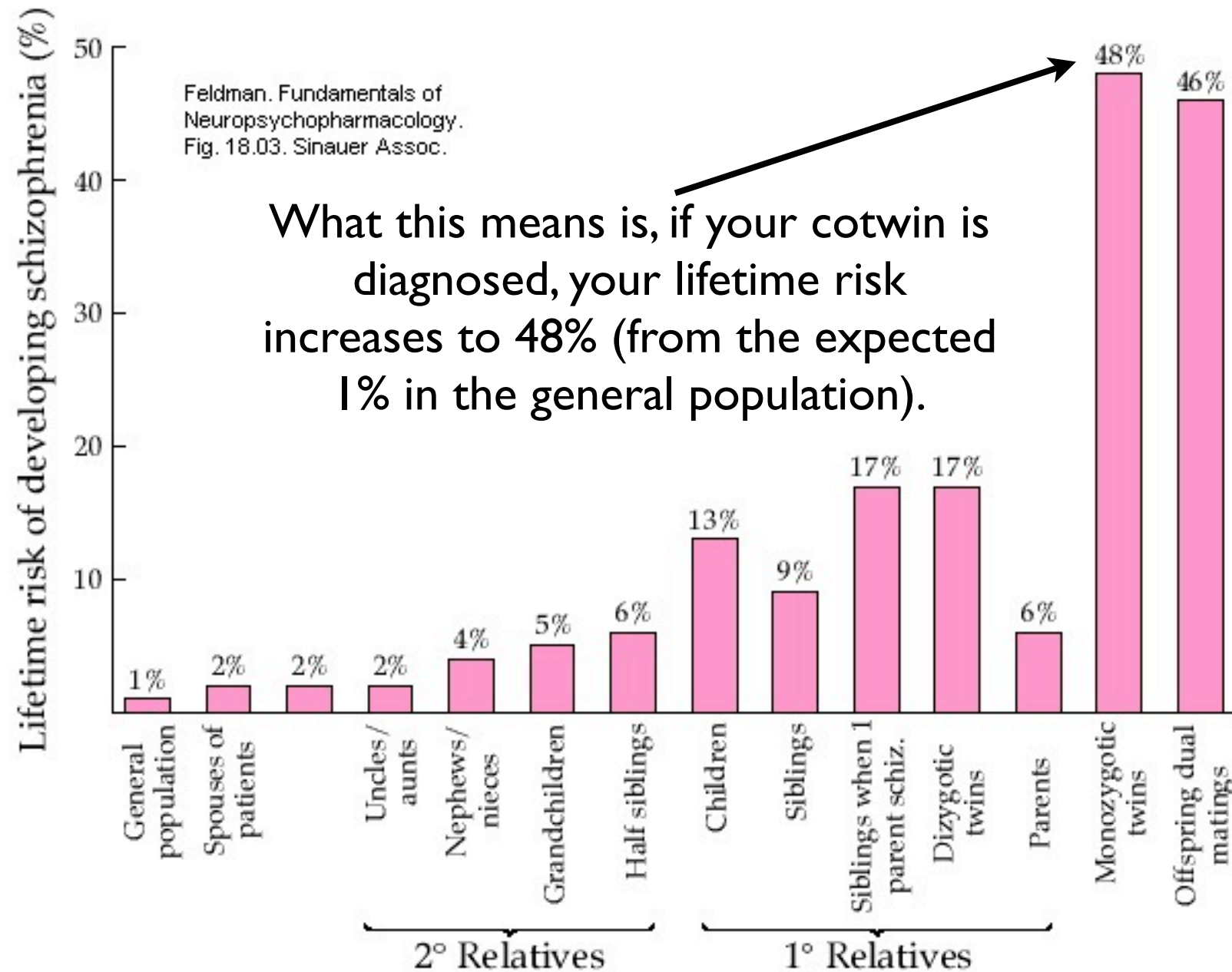
While schizophrenia is not the most common of psychiatric and neurological disorders, it strikes young and is chronic, which makes it a serious public health problem.

- all anxiety disorders: 19.1 million people in the U.S.
 - social phobia: 5.3 million people
 - PTSD: 5.2 million people
 - generalized anxiety disorder: 4 million people
 - OCD: 3.3 million people
- all depression: 14.4 million people
 - dysthymia: 10.9 million people
- Alzheimer's disease: 5 million people
- schizophrenia: 2.2 million people
- Parkinson's disease: 1 million people

Heritability: twin studies

MZ (identical) twins have a very high concordance rate (i.e., if one twin is diagnosed, the other is also very likely to be) of almost 50%. DZ (fraternal or nonidentical) twins have a much lower concordance rate (17%) but still much higher than would be expected from randomly paired individuals. This is the pattern you would expect from a heritable disease. That schizophrenia is heritable is not surprising.

Most things are. What it tells us is, “look for the genes.”



Heritability: adoption studies

- Kety et al. (1968) - in Denmark
 - looked for index cases of schizophrenia who had been adopted very early in life
 - adoptive families had the expected 1% risk of schizophrenia
 - biological families had a much higher risk
 - family environment is a much less important predisposing factor than genes - schizophrenia is not the result of having a “schizophrenogenic mother” as the neofreudians thought (your parents do not make you crazy!)

Heritability: morbid risk

This study was the “last nail in the coffin” of people who refused to believe that schizophrenia was a heritable disorder. G & B looked at the children of twins who were discordant (only one had been diagnosed with schizophrenia). The MZ twins are genetically identical, so if there are “schizophrenia genes,” they should be passing them on at a similar rate whether diagnosed or not, and they did (17%). DZ twins are not genetically identical and, therefore, should not be passing the “schizophrenia genes” on at a similar rate, and they did not (17% vs. 2%).

- **Gottesman and Bertelsen (1989)**
- looked at the children of discordant twins

MZ schizo.	MZ nonschizo.	DZ schizo.	DZ nonschizo.
16.8%	17.4%	17.4%	2.1%

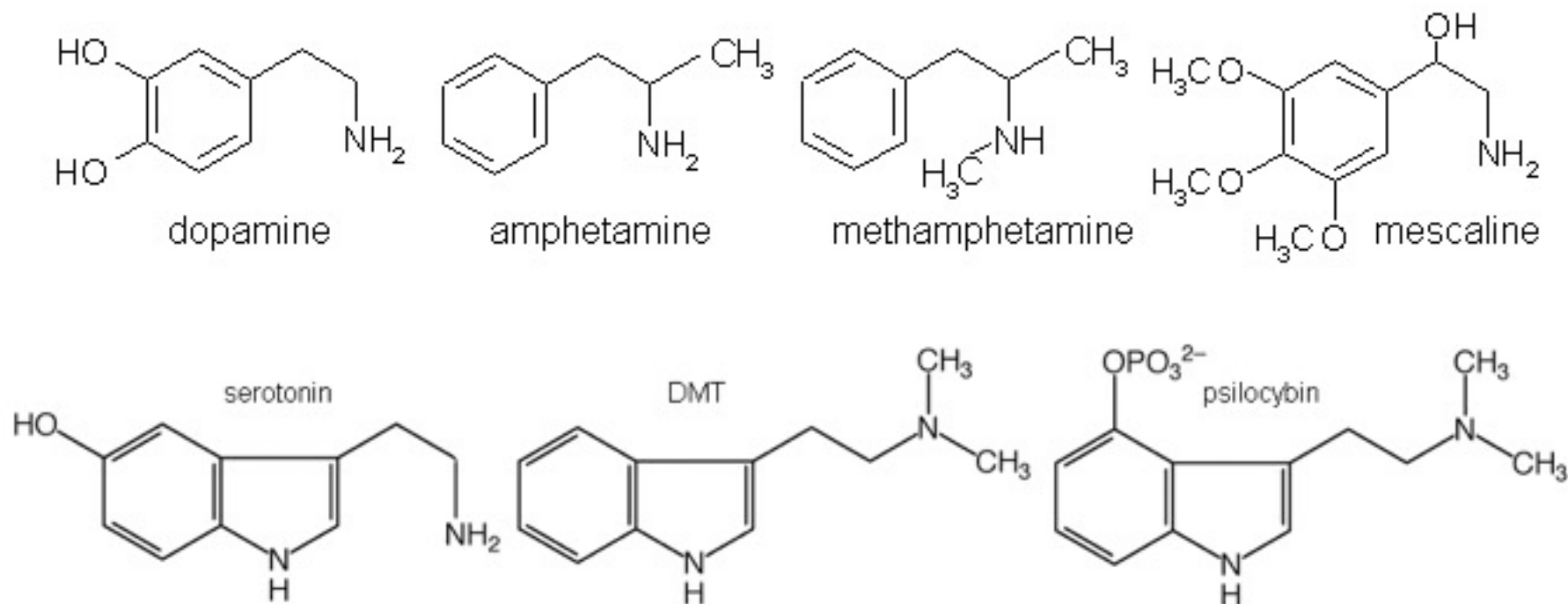
- carrying a schizophrenia gene does not necessarily mean a person will become schizophrenic

Congenital Factors

- schizophrenic individuals without a family history are likely to have experienced complications at childbirth
- there is considerable evidence that a maternal viral infection at certain times during pregnancy can predispose the infant to developing schizophrenia (this is NOT the viral theory of schizophrenia, which I'll mention later)

Methylation Theory in a Nutshell

The dopamine theory is the leading biological theory of schizophrenia, as I'm sure you know from other classes, but it is not the only game in town! The methylation theory, popular in the 1960s and 70s, said that schizophrenia results at least initially from an abnormal metabolism in the body that turns normally occurring amino acids that we get in the diet, and ordinarily convert to neurotransmitters like dopamine and serotonin, into hallucinogenic substances such as mescaline-like substances and DMT, which are very similar in chemical structure to the normally occurring neurotransmitters. This theory lost favor because in order for this to occur the necessary enzymes must be present, and they could not be convincingly found.



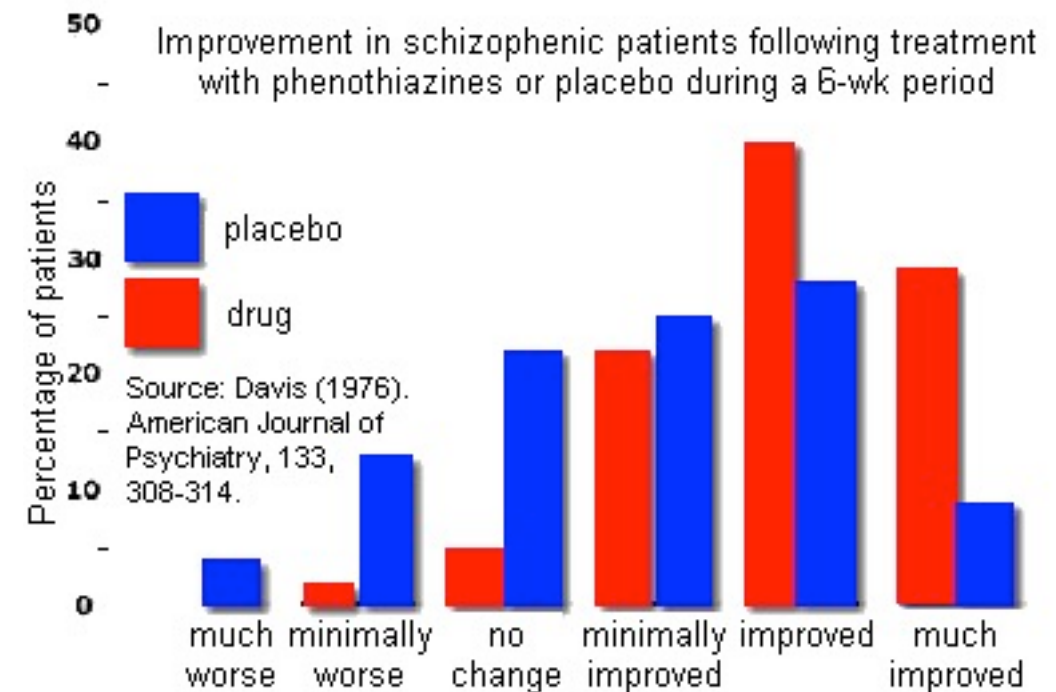
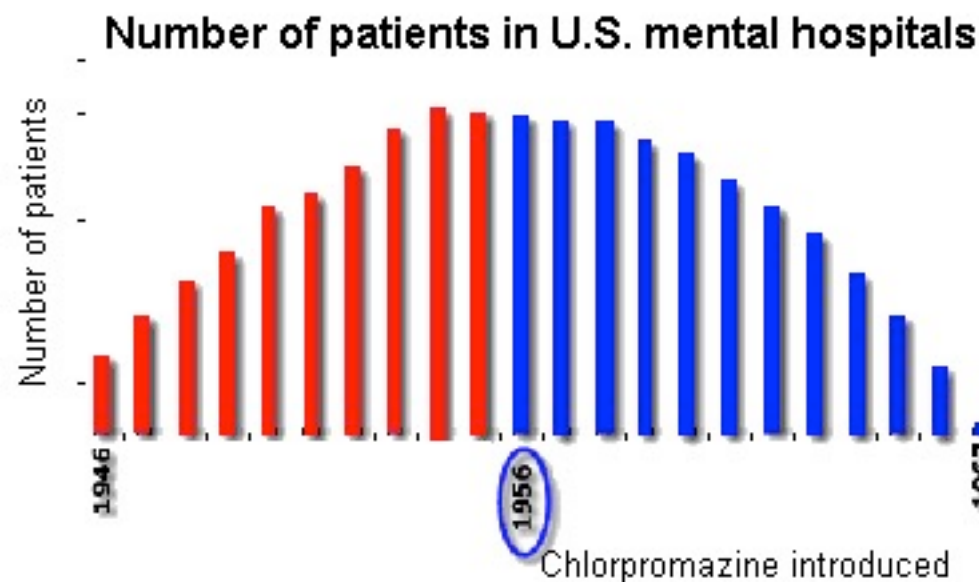
A 20th-century artist, Louis Wain, who was fascinated by cats, painted these pictures over a period of time in which he developed schizophrenia. The pictures mark progressive stages in the illness and exemplify what it does to the victim's perception.

(We will return to this bizarre idea later in these lectures.)

The Dopamine Theory

(evidence in favor)

- all drugs known to alleviate the positive symptoms of schizophrenia are DA (dopamine) receptor blockers in the brain
- chlorpromazine (Thorazine) was the first

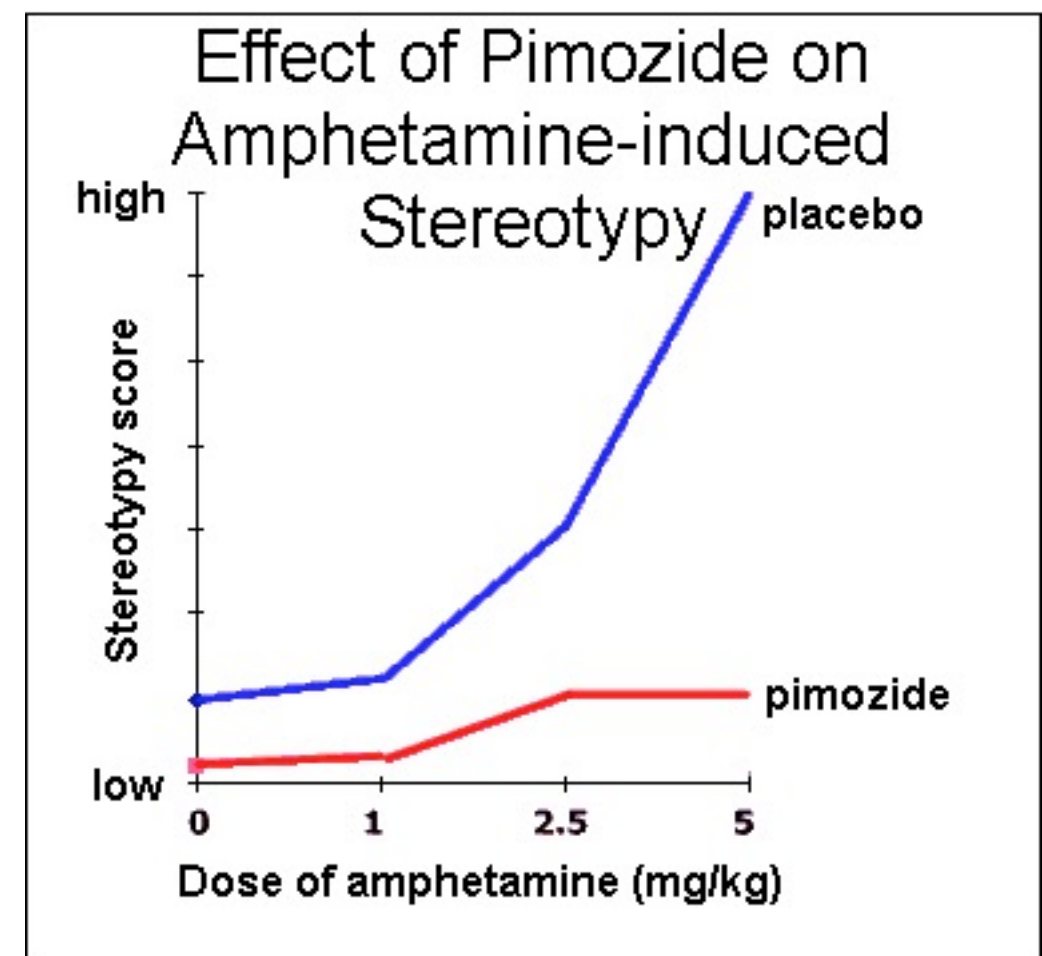
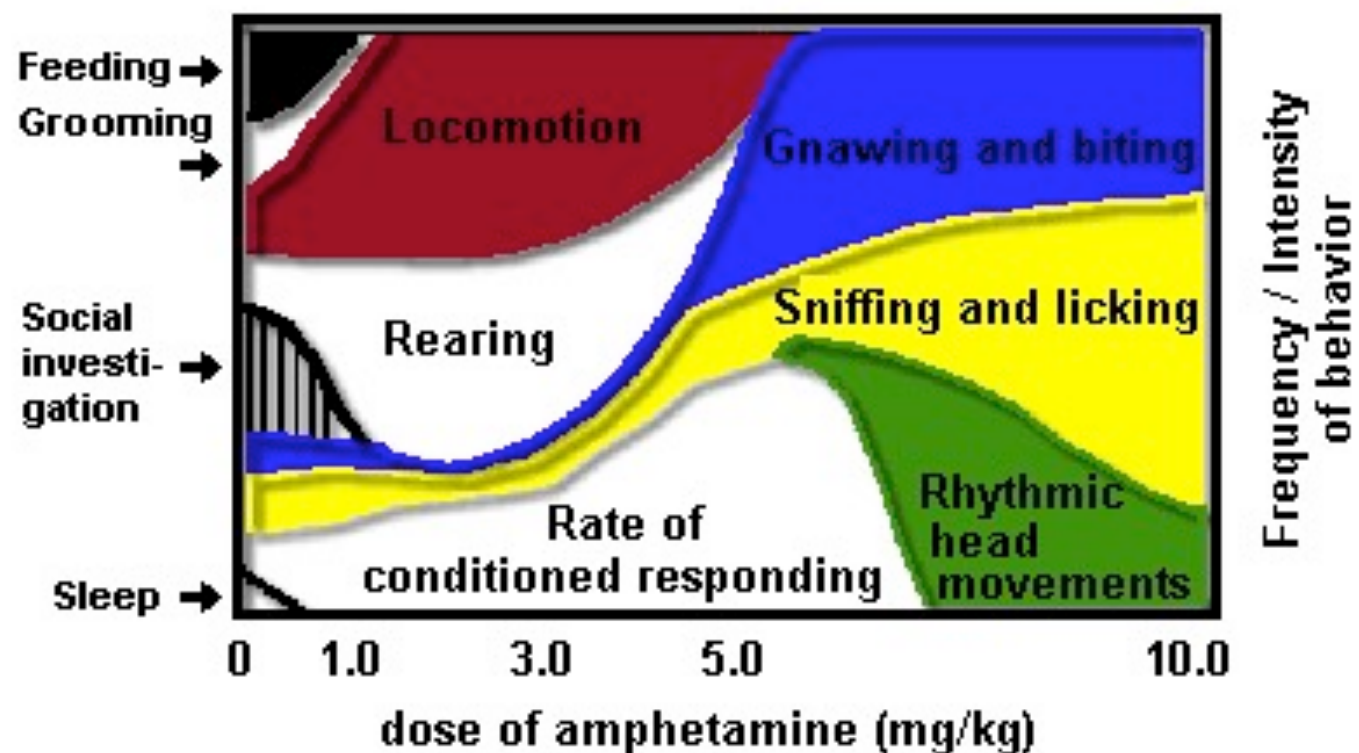


Dopamine Theory (cont)

- These drugs do not cure schizophrenia, they only alleviate the positive symptoms. (Like taking aspirin for a headache or insulin for diabetes.)
- Most (but not all) of these drugs produce motor side effects.
- Parkinsonian symptoms - known to be due to DA deficiency
- tardive dyskinesia (later)

Dopamine Theory (cont)

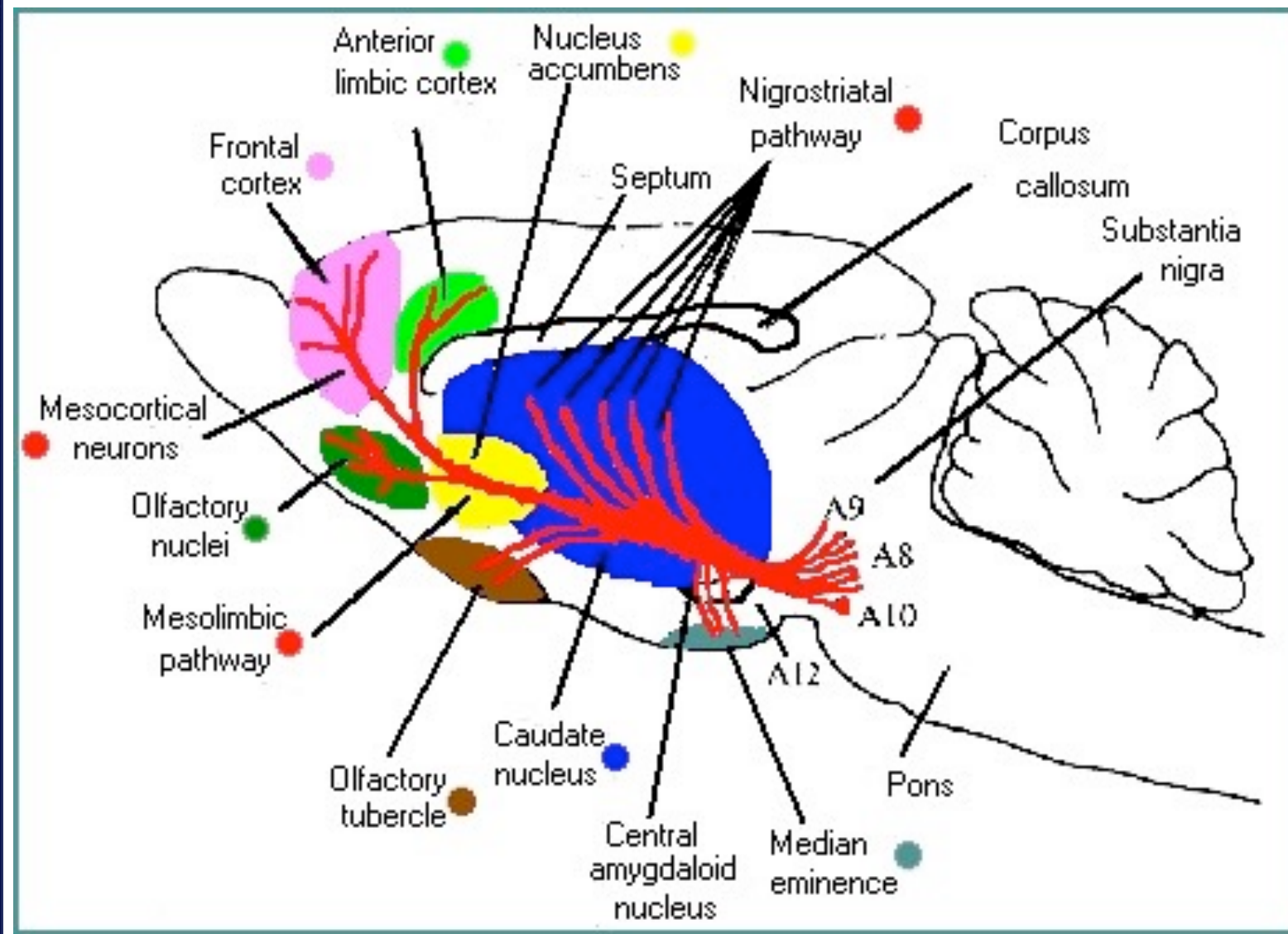
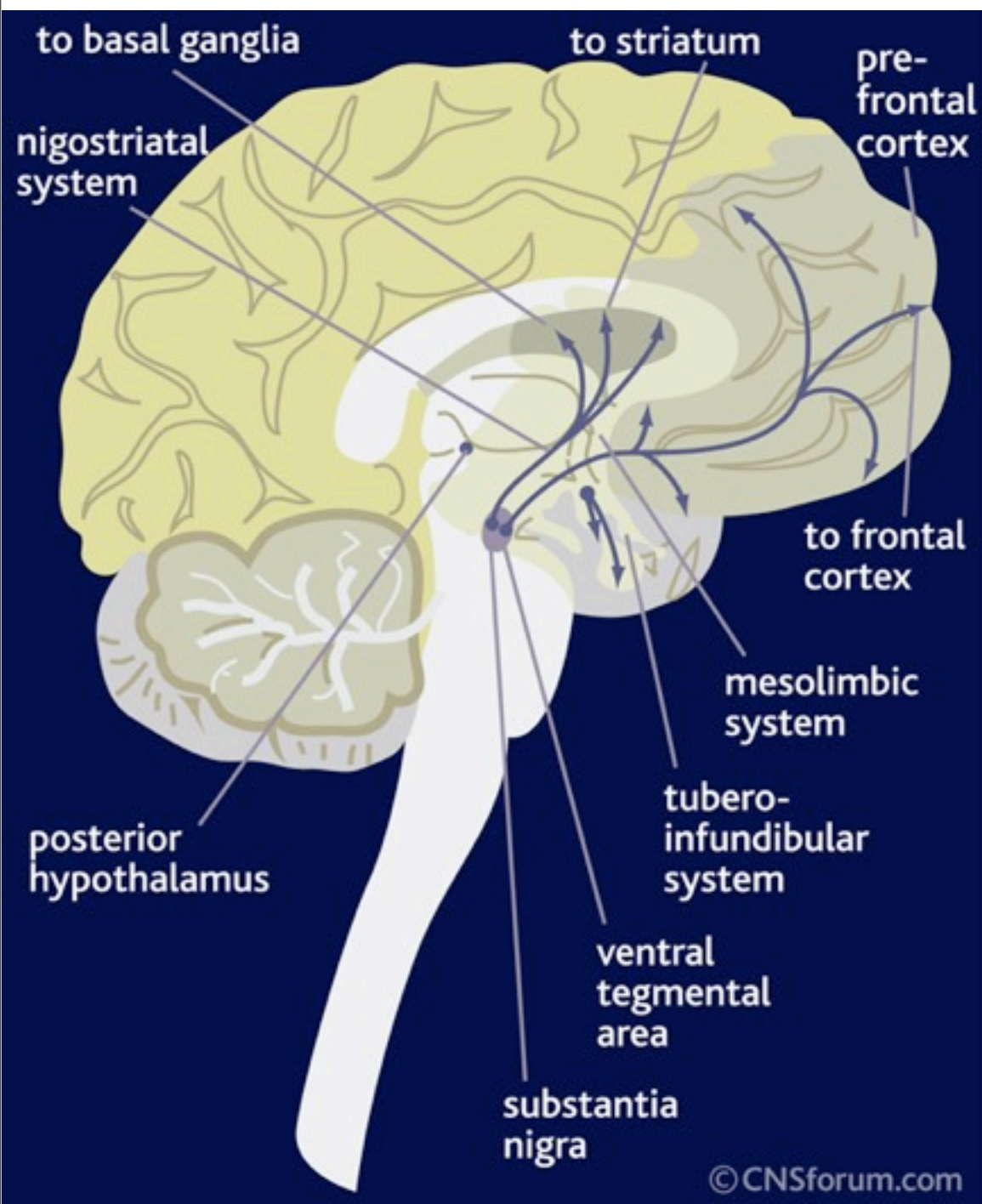
- The ability to block amphetamine-induced stereotypy in rats was once used as an animal assay for antipsychotic drugs. We know that amphetamine-induced stereotypy is due to excessive DA activity in the brain.



Dopamine Theory (cont)

- Eventually, neuroleptic drugs were developed that did not block amphetamine-induced stereotypy (e.g., clozapine), and that also did not produce typical Parkinsonian side effects.
- What's up with that?
- These drugs do “block” DA receptors, but not in the nigrostriatal system.
- It's generally believed that the mesolimbic and mesocortical pathways are the important ones in schizophrenia.

Dopamine Pathways



Dopamine Theory (cont)

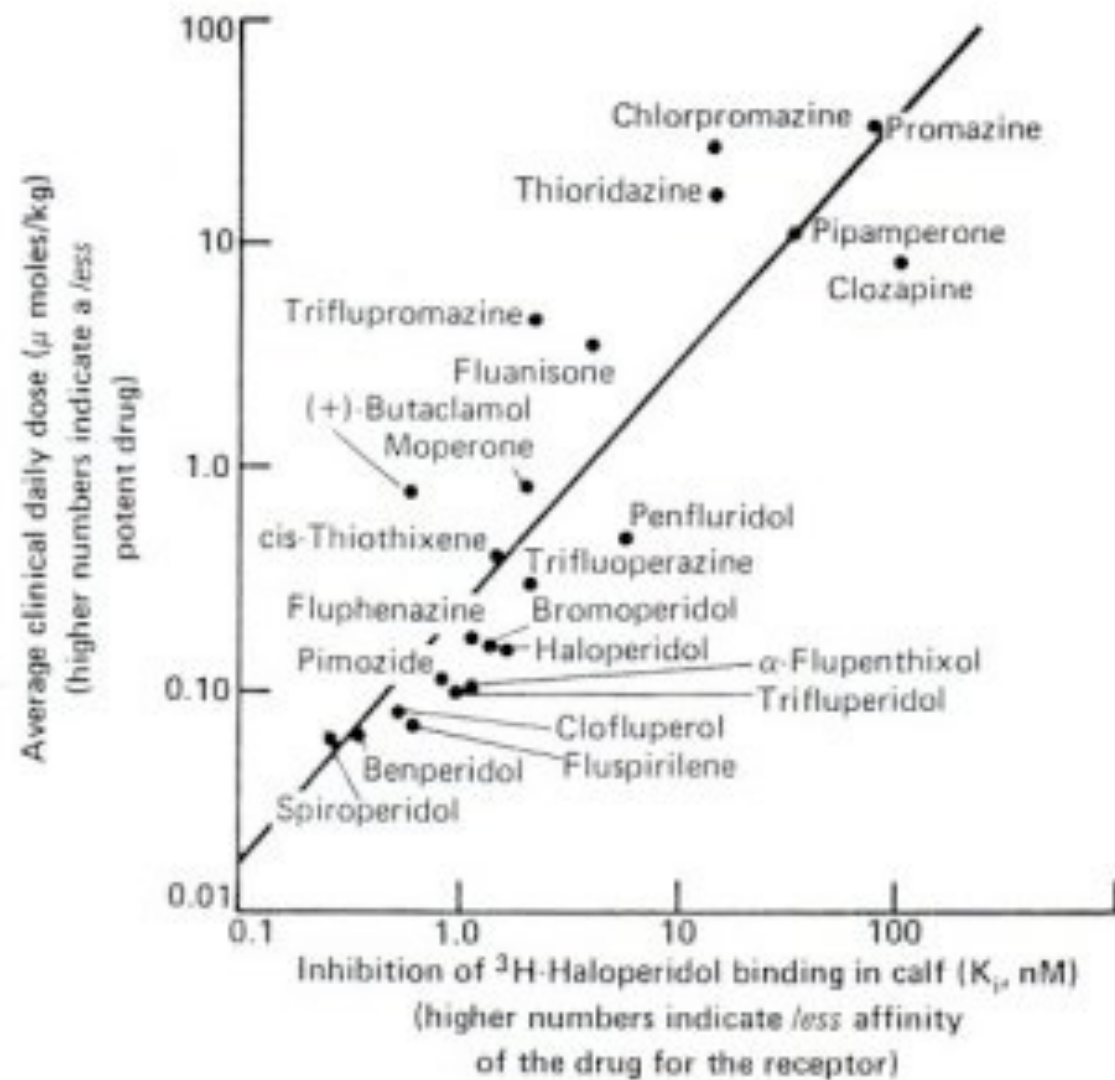


FIGURE 20.4 The relationship between the ability of an antipsychotic drug to inhibit binding of ^3H -haloperidol with cell membranes extracted from calf caudate nucleus and the dose of the drug that is needed to achieve a therapeutic result. (From Snyder, S. H. *Journal of Continuing Education in Psychiatry*, 1978, 39, 21–31.)

- The potency of the drugs in relieving symptoms is strongly correlated with the drug's ability to block DA receptors (Snyder et al., 1978).
- This means the therapeutic effect of these drugs is almost certainly due to their ability to block DA receptors. (But stay tuned--there may be more to this story.)

Dopamine Theory (cont)

- DA agonists (amphetamine, cocaine, l-dopa) produce positive psychotic symptoms.
- amphetamine psychosis - a condition that resembles paranoid schizophrenia very closely and that is due to repeated abuse of stimulants such as amphetamine
- if taken by someone who is already psychotic, they make the endogenous psychosis worse
- treated with neuroleptics such as chlorpromazine
- but LSD does not - schizophrenic patients given LSD can tell the difference between the drug effect and their endogenous psychosis

Dopamine Theory (cont)

- autopsy studies - 10 of 12 studies found increased numbers of DA receptors in the neostriatum
- PET scanning studies are split about 50:50
 - almost all examine the neostriatum because it is large and easy to localize
 - not all studies use drug-free patients, and neuroleptic drugs themselves can increase the number of DA receptors
- recent reviews are pessimistic - there may be modest increases in D2 receptor densities, but they probably play little role in the disease process

Dopamine Theory (cont.)

- functional imaging studies
 - measured DA release (in the striatum) in response to a dose of amphetamine
 - significantly greater in schizophrenic subjects than in normal controls

Dopamine Theory: Problems

- About 1/3 of patients do not respond to neuroleptics, which are most effective at alleviating positive symptoms.
- but PET scans show drugs still block DA receptors in nonresponders
- negative symptoms may be produced by a different disease process
- prominent negative symptoms give a particularly poor prognosis

Dopamine Theory: Problems

- Neuroleptics begin blocking DA receptors within minutes, but the therapeutic effect of the drugs is delayed for days or weeks.
- This may be due to up-regulation of the DA system when drugs are given that block DA receptors. (I.e., when you do something to the brain with a drug, the brain will try to thwart you by counteracting the action of the drug. If you block DA receptors, the brain turns up the amount of DA released onto receptors that are not blocked.)
- Or perhaps it's due to the primary pathology not being in the DA system.

Dopamine Theory: Problems

- tardive dyskinesia - perhaps the most serious problem with the DA theory
- tardive = “developing late” (unlike the Parkinsonian side effects, which begin almost immediately), dyskinesia = “abnormal movements”
- this is the most serious side effect of neuroleptic treatment - occurs in about 10% of long-term treatments and is permanent

- thought to be due to a permanent increase in DA receptor density in the neostriatum
- characterized by choreiform and athetotic movements (quick jerky movements and writhing movements that the person cannot control)
- but why is there no “tardive schizophrenia”? (i.e., why does the schizophrenia not get worse with time if DA receptor density is being increased by the meds?)

- four possible answers:
 - there may be! - patients taken off meds not only relapse eventually, but according to some studies become even more severely psychotic
 - there may be a fundamental physiological difference in the DA target cells in the neostriatum (where movement disorders are caused) and target cells in the nucleus accumbens, limbic system, and cortex (where schizophrenia is caused) - but probably not

- four possible answers (cont.)
- tardive dyskinesia may not result from neuroleptic medications but may be part of the disease process itself
- Emil Kraepelin's description (next page) - the problem with trying to understand what schizophrenia looks like these days is that almost all patients are medicated, and so it's hard to tell what is due to the psychosis and what is due to the meds; so to get a better idea of what schizophrenia looks like without the meds, scientists resort to old textbooks like Kraepelin's, written over 100 years ago, long before the meds existed
- Now don't be going to your other professors and saying that Dr. King told us tardive dyskinesia is part of schizophrenia and not a side effect of the meds. I'm not saying that. I'm merely suggesting the possibility! (This was actually first suggested by Carlson, but he has removed it from his textbook, and I suspect I know why!)

Dementia Praecox = dementia developing early (as opposed to Senile Dementia, which is dementia developing in old age)

DEMENTIA PRÆCOX

AND

PARAPHRENIA

BY

PROFESSOR EMIL KRAEPELIN OF MUNICH

TRANSLATED BY

R. MARY BARCLAY, M.A., M.B.

From the Eighth German Edition of the "Text-Book of Psychiatry,"
vol. II., part II., section on the Endogenous Dementias

EDITED BY

GEORGE M. ROBERTSON, M.D., F.R.C.P. (EDIN.)

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FASCIMILE 1919 EDITION



ROBERT E. KRIEGER PUBLISHING CO. INC.
HUNTINGTON, NEW YORK

1971

This is an almost perfect description of tardive dyskinesia, written long before antipsychotic meds existed!

patients (6 per cent. of the men, 3 per cent. of the women) spasms or fainting fits had occurred previously in youth, about which it must for the present remain doubtful whether any connection with the psychic disorder may be ascribed to them. Some patients had suffered from chorea. Urstein records seizures in 8 per cent. of the men and in 19 per cent. of the women. In one case I saw the development of a profound catatonia after the existence for many years of undoubted epileptic seizures to which then hysteroid seizures were added. And otherwise hysteroid spasms and paralyses are often observed besides aphonia, singultus, sudden erection, local contractures, and similar phenomena.

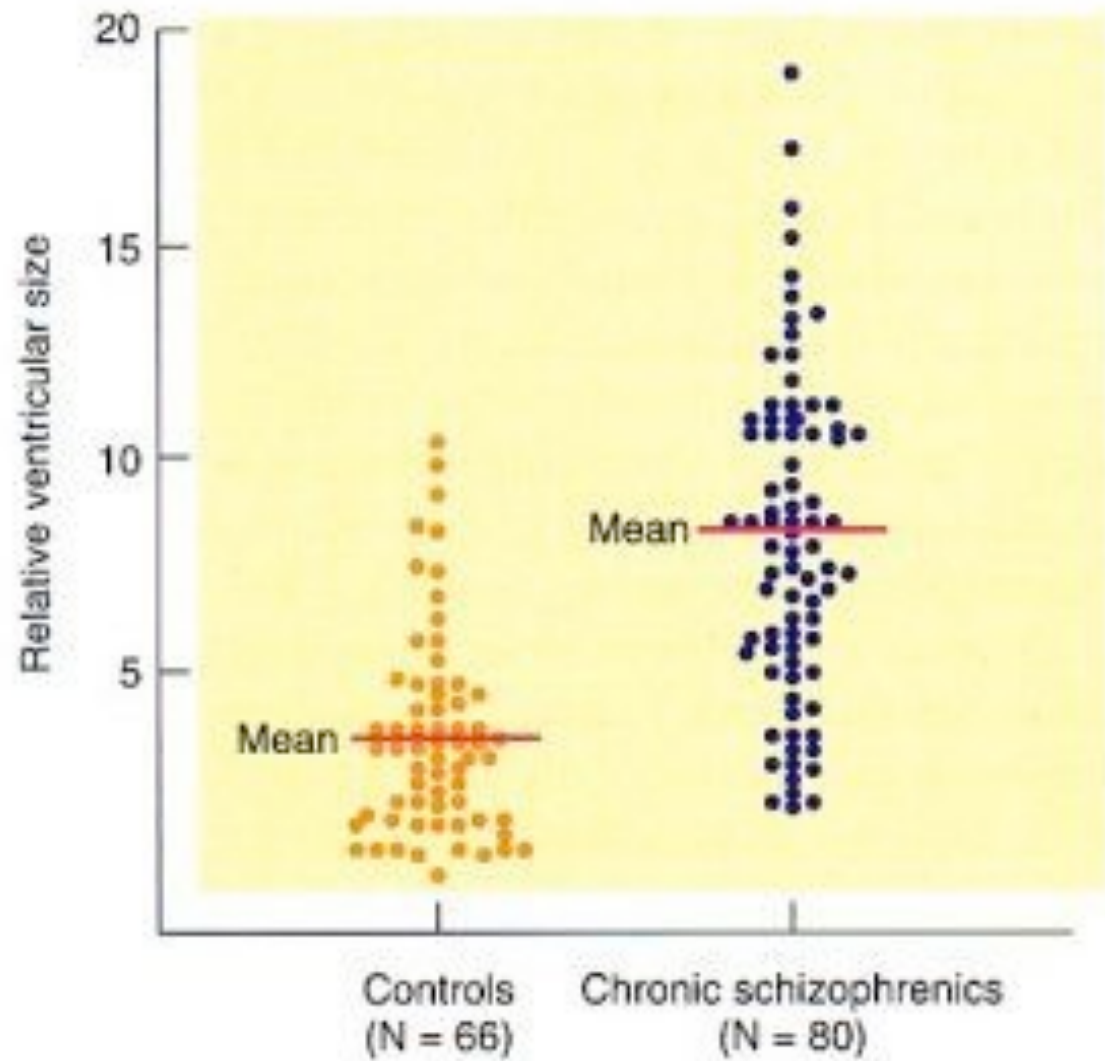
The **spasmodic phenomena** in the musculature of the face and of speech, which often appear, are extremely peculiar disorders. Some of them resemble movements of expression, wrinkling of the forehead, distortion of the corners of the mouth, irregular movements of the tongue and lips, twisting of the eyes, opening them wide, and shutting them tight, in short, those movements which we bring together under the name of making faces or *grimacing*; they remind one of the corresponding disorders of choreic patients. Nystagmus may also belong to this group. Connected with these are further, smacking and clicking with the tongue, sudden sighing, sniffing, laughing, and clearing the throat. But besides, we observe specially in the lip muscles, fine lightning-like or rhythmical twitchings, which in no way bear the stamp of voluntary movements. The same is the case in the tremor of the muscles of the mouth, which appears sometimes in speaking and which may completely resemble that of paralytics. In a great number of patients I observed distinct twitchings of the musculature of the mouth on tapping the lower branches of the facial nerves. Occasionally one sees uneven muscle-tension on the two sides of the face temporarily or for a longer time, on which Hüfler has laid stress. The out-spread fingers often show fine tremor. Several patients continually carried out peculiar sprawling, irregular, choreiform, outspreading movements, which I think I can best characterise by the expression "athetoid ataxia."

Aphasia.—In two cases it was possible during a state of dull stupor to demonstrate distinct aphasic disorders. The patients were unable to recognise and to name the objects laid in front of them although they could speak and were evidently exerting themselves to give the required information. Repeatedly after long consideration the wrong names came out. The disorder disappeared again after a few hours.

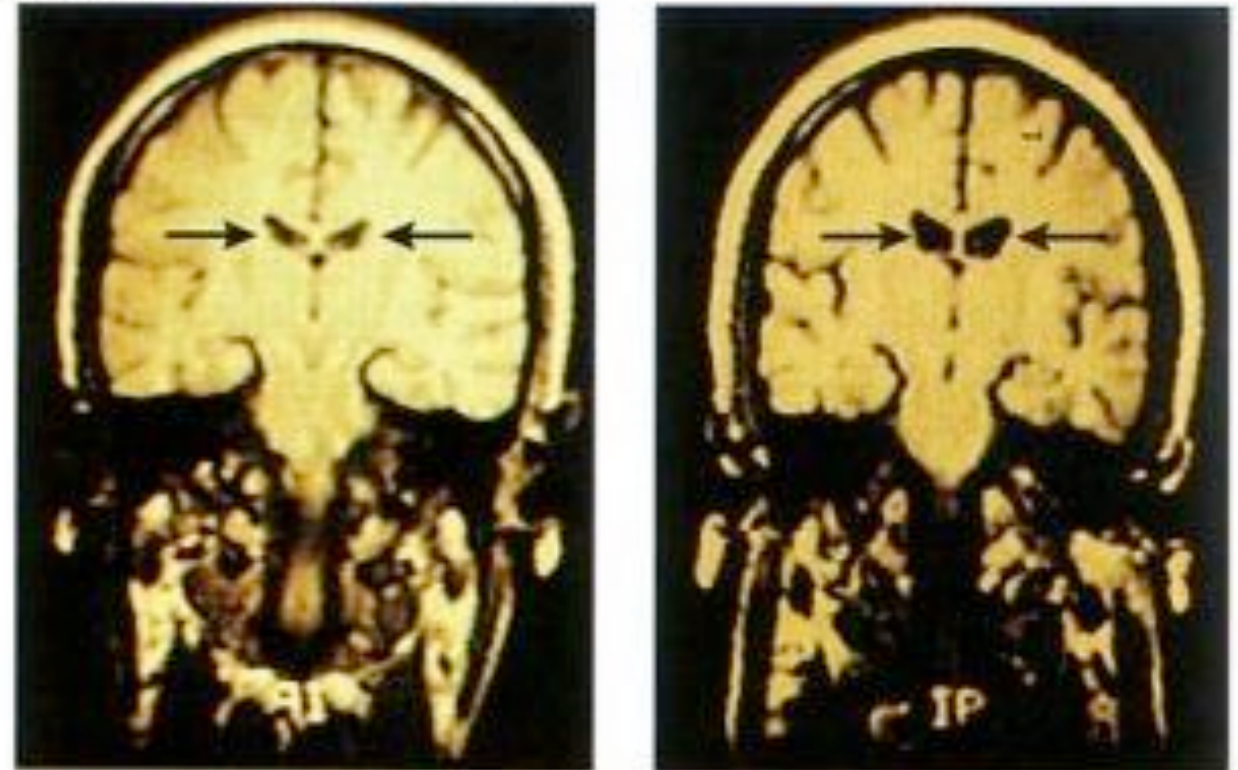
- tardive dyskinesia (cont.)
- the 4th possibility would have to be that the DA theory is wrong
- Atypical antipsychotic medications such as clozapine don't cause tardive dyskinesias (although they are not side-effect free either!).
 - side effects of atypical antipsychotics - tremor, weight gain, dizziness, headache, chest pain and pounding heart, nausea, blurred vision, sweating, seizures, confusion, high blood sugar, kidney damage

Schizophrenia as a Neurological Disorder

- soft neurological signs - most schizophrenic patients have neurological symptoms such as strange eye movements, unusual reflexes, and strange body movements (up to and including catatonia)
- there is evidence of general brain atrophy, which is esp. severe in cases predominantly characterized by negative symptoms (next slide)



Relative ventricular size in chronic schizophrenics and controls.
 (From Weinberger, D. R., and Wyatt, R. J., in *Schizophrenia as a Brain Disease*,
 edited by F. A. Henn and H. A. Nasrallah. New York: Oxford University Press,
 1982. Reprinted with permission.)

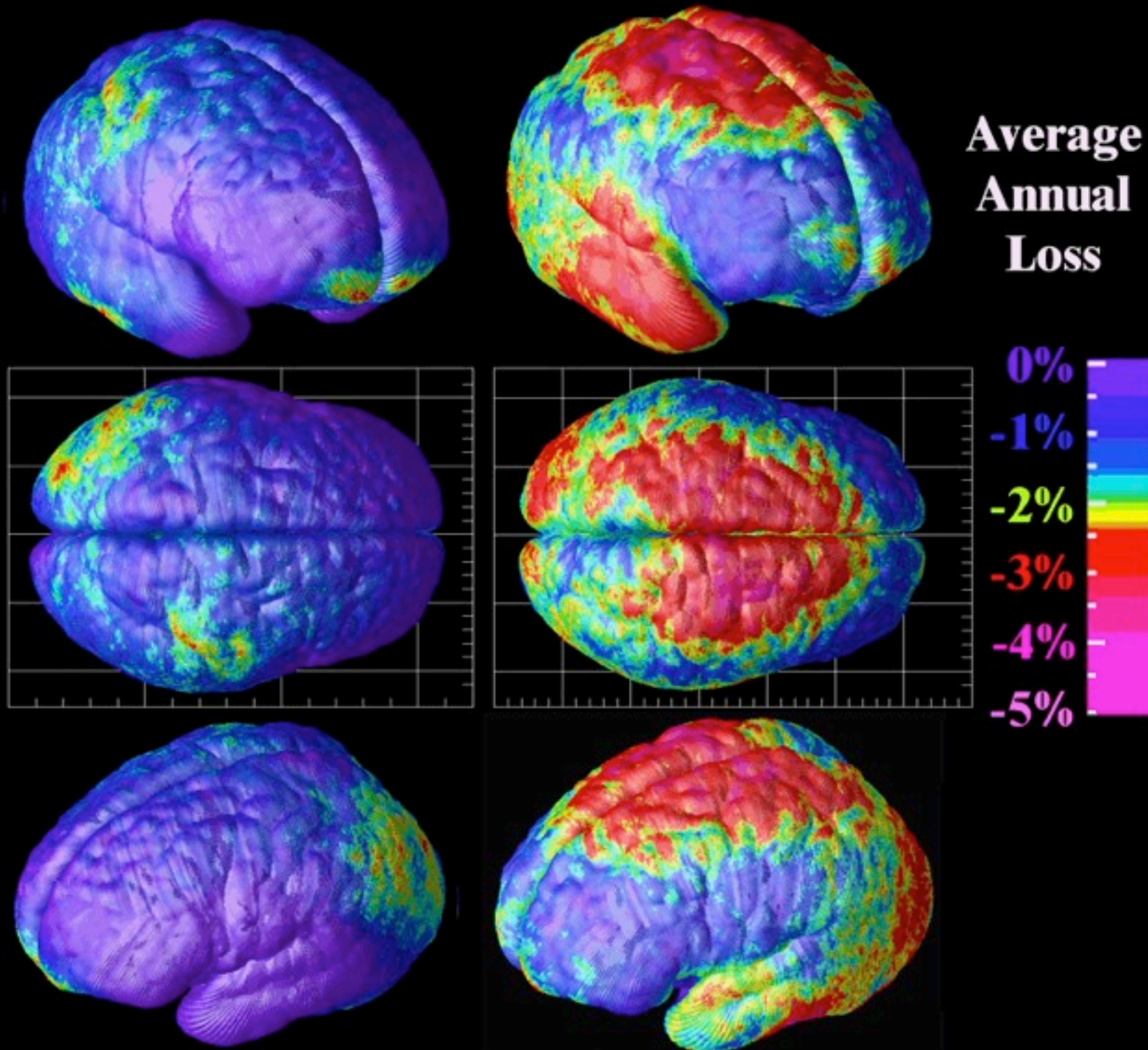


The usual signs of degeneration are seen in scans of schizophrenics: enlarged ventricles and sulcuses gapping open.

Rate of Gray Matter Loss

**Normal
Adolescents**

**Schizophrenic
Subjects**

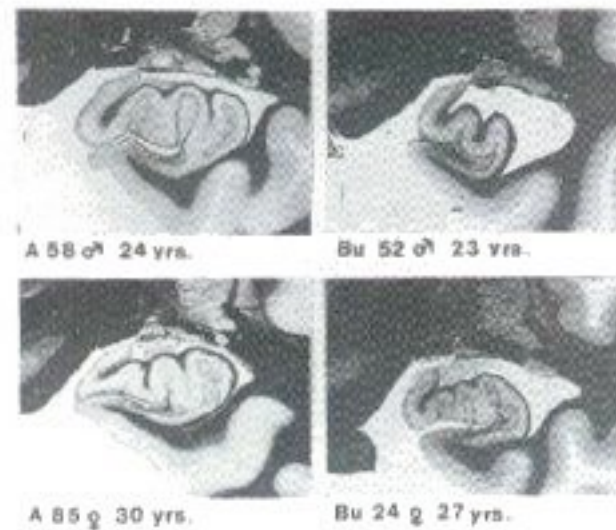


Thompson et al., 2000

During the last stages of brain development in late adolescence, neurons and synapses are “pruned” away when they don’t seem to be “doing the right thing.” This process is more severe in adolescents who have been or will be diagnosed with schizophrenia.

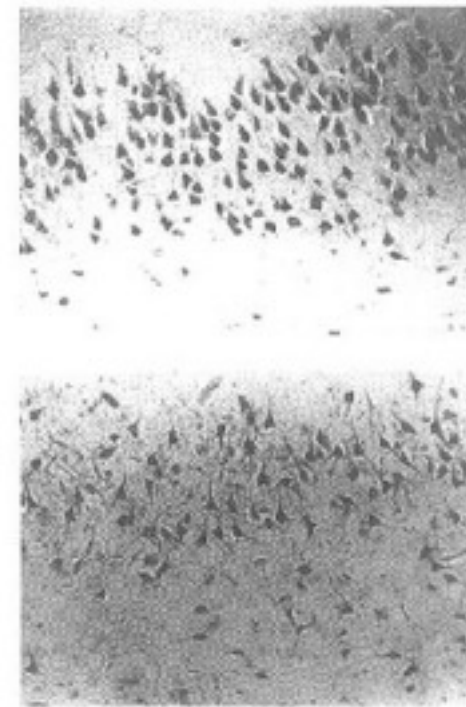
Schizophrenia as a Neurological Disorder

- Classical anatomical methods, as well as modern scanning methods, have revealed shrinkage and abnormal structure in the hippocampus.



Hippocampus of normal people (left) and people with schizophrenia (right).

Source: Bogerts et al. (1985)

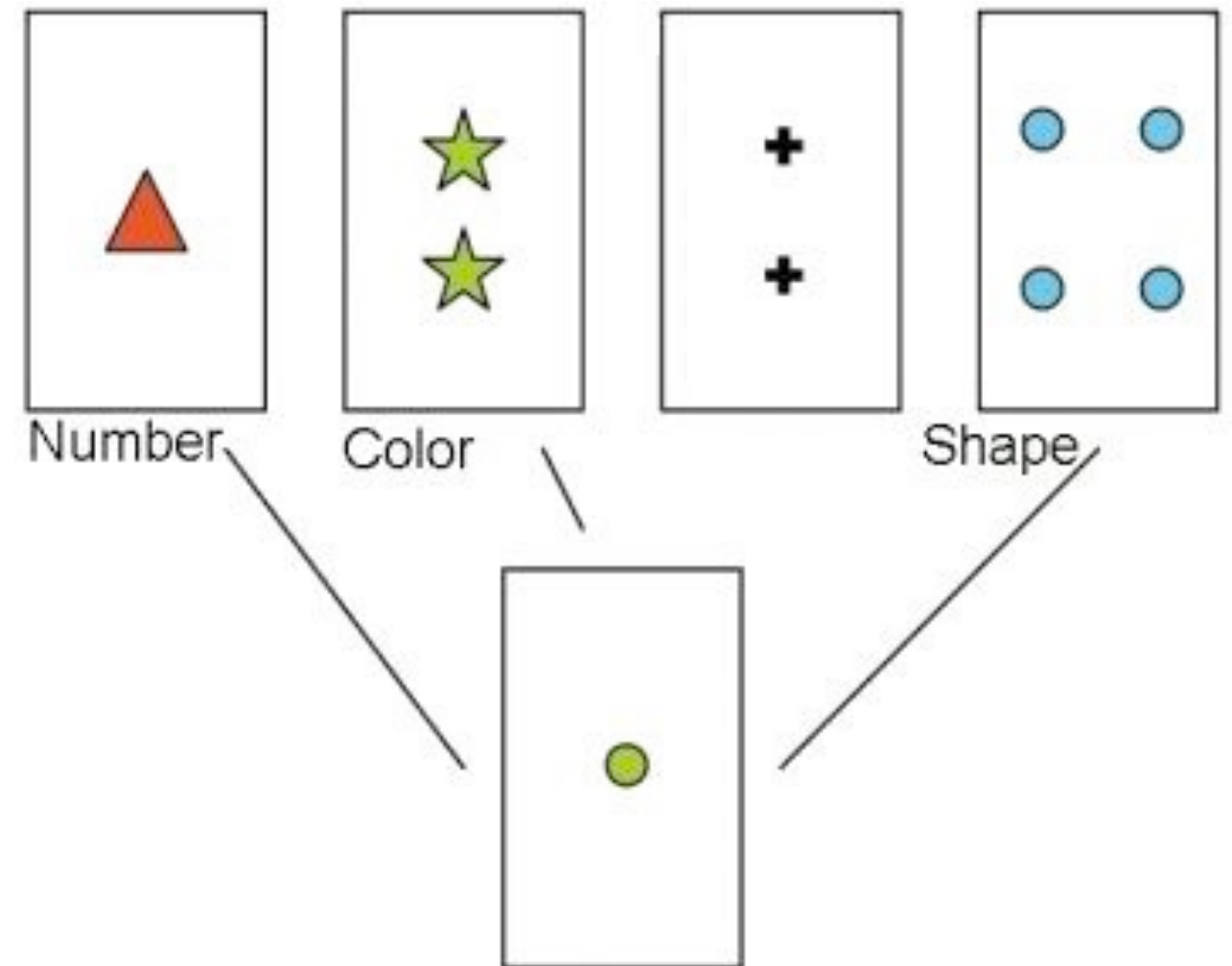


Hippocampal cytoarchitecture of normal people (top) and people with schizophrenia (bottom).

Source: Arnold Scheibel

Schizophrenia as a Neurological Disorder

- hypofrontality
 - PET scanning studies reveal abnormalities in the basal ganglia and dorsolateral prefrontal cortex (DLPFCx)
 - the Wisconsin Card Sort Test also reveals deficient functioning in the DLPFCx (Weinberger et al., 1986)
 - more on this later



Hilger E, Kasper S Journal für Neurologie, Neurochirurgie und Psychiatrie 2002; 3 (4): 17-22 ©

The task here is to match the selected card (bottom) to one of the target cards. Notice the match can be made several different ways, and it is up to the subject to figure which is correct. Most people can do this in a few trials, but then the rules are changed, and the subject now has to figure out the new rule. Damage in the DLPFCx impairs their ability to do so. Schizophrenics perform poorly on this test.

Schizophrenia as a Neurological Disorder

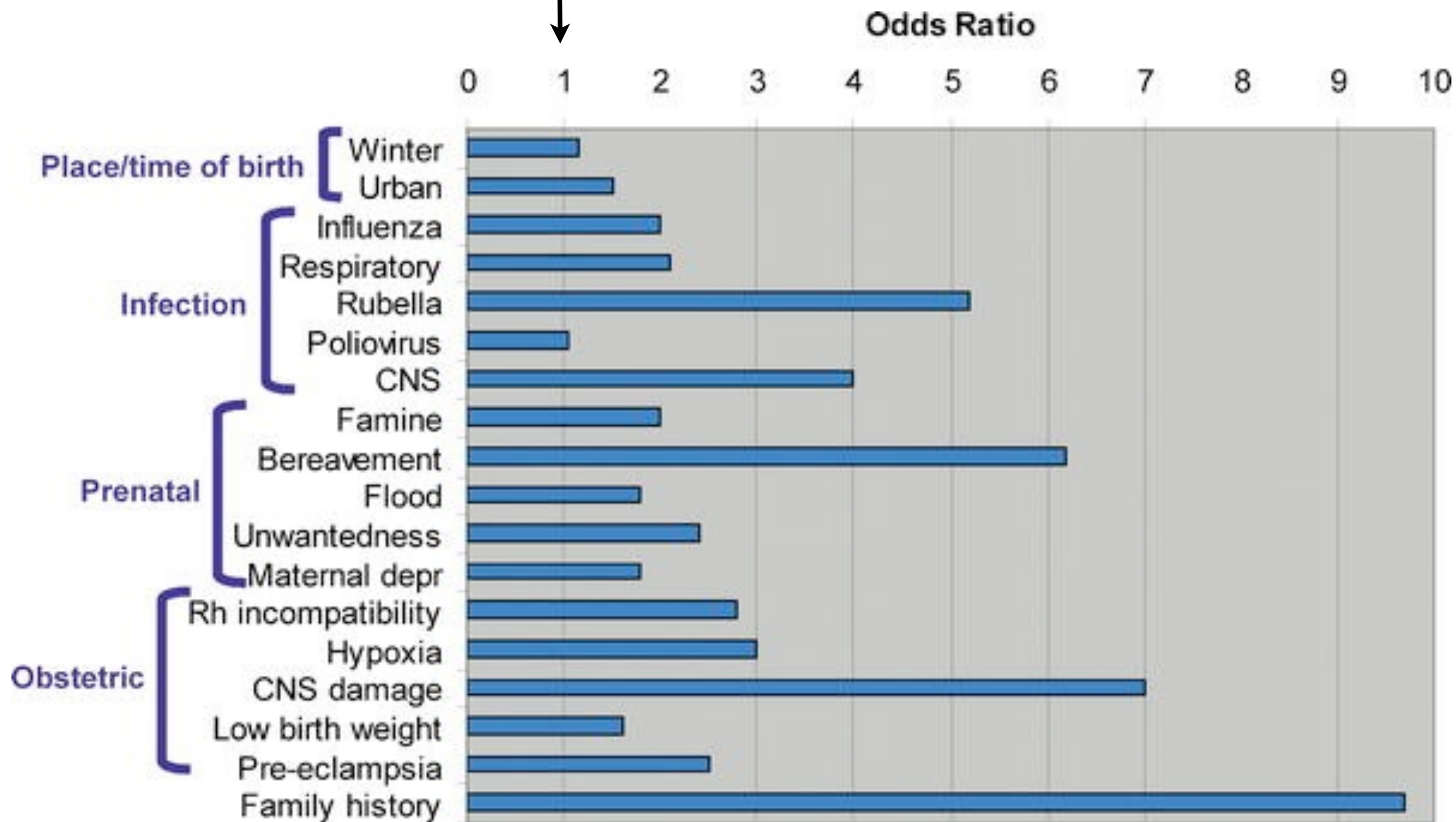
- Is the damage done by a virus? (This is the viral theory and the evidence is strongly against it.)
- Viral infections of the brain can certainly cause brain damage and behavioral disturbances.
 - AIDS related dementia
 - rabies
- However, there is no direct evidence of a viral infection.
- There is absolutely NO evidence that schizophrenia is in any way contagious!

Epidemiology

- schizophrenia is linked to:
 - season of birth - there is a slight increase in the likelihood of developing schizophrenia for people born in late winter and early spring (seasonality effect)
 - perhaps due to flu infection of mother during second trimester (a critical period for brain development)
 - babies born a few months after an influenza epidemic are also at increased risk
 - population density - 3 times increased risk for people who live in a large city vs. a rural area
 - prenatal malnutrition
 - prenatal maternal stress
 - obstetric complications
- all this points to the likelihood of disordered brain development being a key factor

Epidemiology

Odds ratio of 1 means no increased risk due to this factor. OR > 1 means the risk of being diagnosed with schizophrenia is increased.



The Emerging Story

- Abnormal brain development is strongly implicated.
 - prenatally
 - during and shortly after puberty when important changes are occurring in the brain
 - loss of cortical grey matter is normal during adolescence - “pruning”
 - however, it is more severe in future schizophrenic individuals
- The dorsolateral prefrontal cortex is strongly implicated.
 - hypofrontality (again)
 - may be important especially in the development of negative symptoms

Hypofrontality

- activation of the DLPFCx is deficient in specific cognitive tasks - esp. those involving working memory

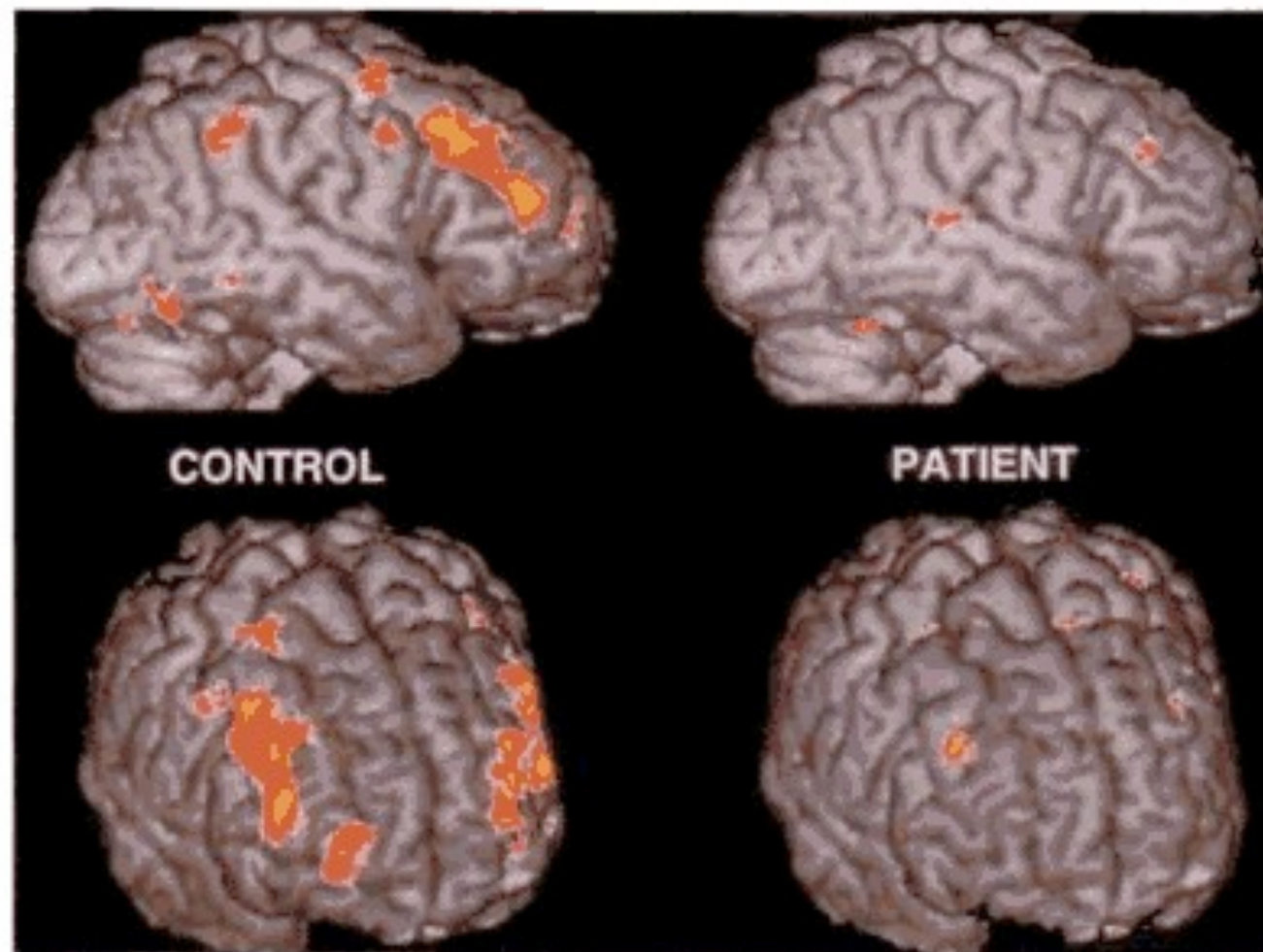


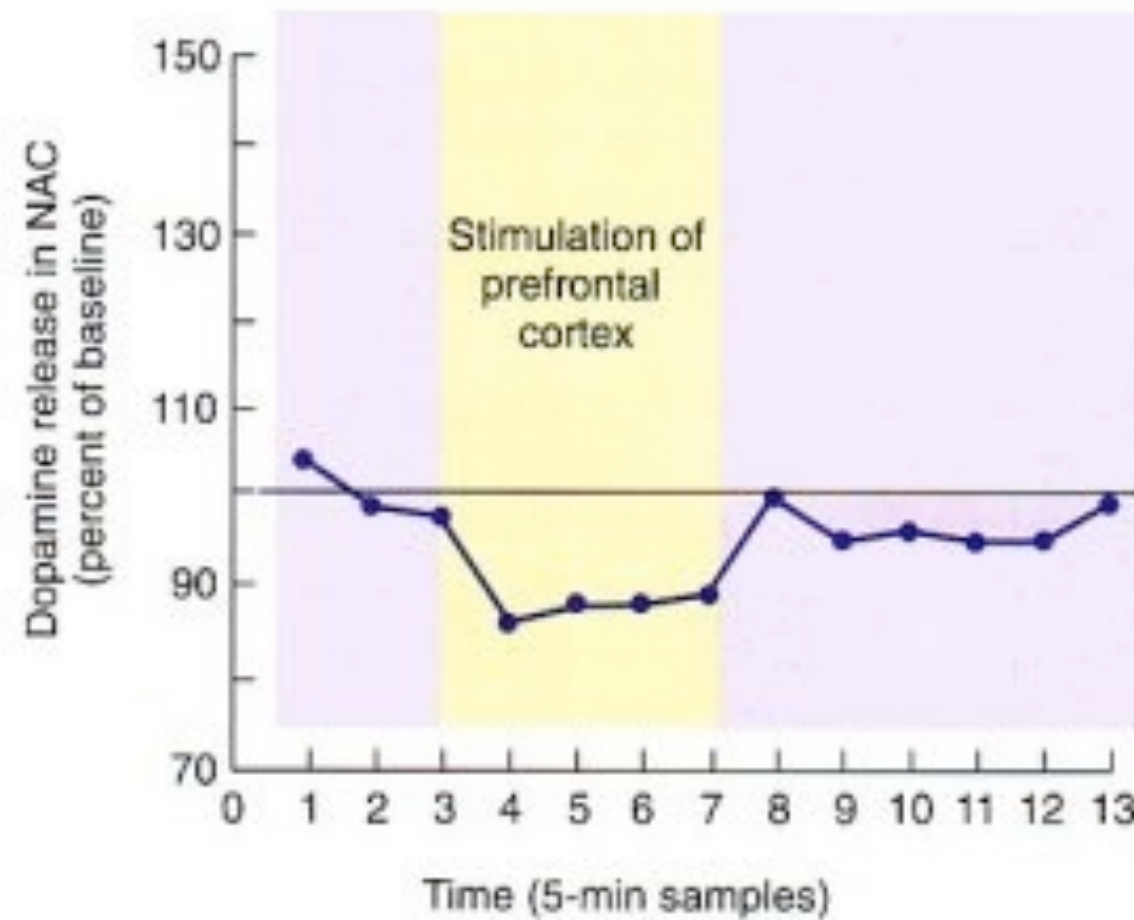
Fig. 5.3. Cognitive activation maps (areas in red and yellow) overlaid on a rendered brain in a patient with schizophrenia and a normal control during a working memory task. There is a reduction in blood flow in the dorsolateral prefrontal cortex in the patient with schizophrenia (right) compared to the control.

Source: Bremner, 2005.

Hypofrontality

- DLPFCx deficits seem to be correlated with small hippocampal size (Weinberger et al., 1992)
- studies in rats show that 6-OHDA lesions in the DA synapses in the DLPFCx increase the activity of DA synapses in the neostriatum and nucleus accumbens
- while electrical stimulation (activation) of the DLPFCx decreases DA release in the nucleus accumbens

effect of electrical stimulation



Effects of electrical stimulation of the prefrontal cortex on the release of dopamine in the nucleus accumbens (NAC), as measured by microdialysis.

(Adapted from Jackson, M. E., Frost, A. D., and Moghaddam, B. *Journal of Neurochemistry*, 2001, 78, 920-923.)

Hypofrontality

- PCP (“angel dust”) and ketamine (“special K”) decrease metabolic activity in the frontal lobes
- causes negative- and cognitive-like symptoms - probably due to a decrease in activity of dopamine and NMDA in the dorsolateral prefrontal cortex
- eventually, positive-like symptoms also begin

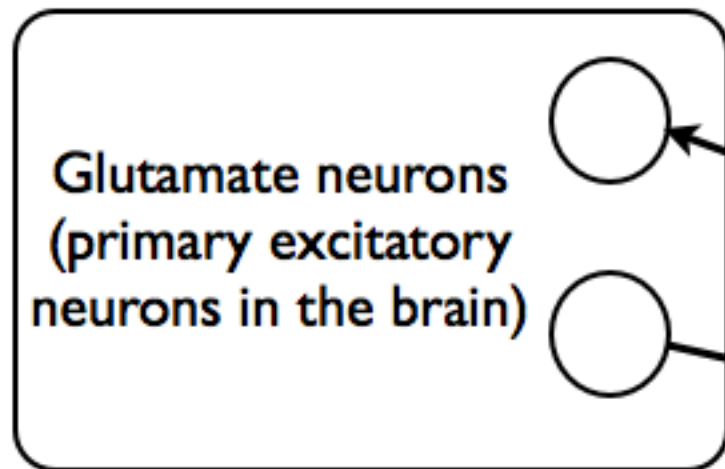
So Here's What Happens

- A developmental brain disorder, which becomes especially severe during adolescence, causes degeneration in the DLPFCx (hypofrontality).
- This results in a loss of glutamine (excitatory) neurotransmission into the ventral tegmental area of the mesencephalon.
- results in decreased activation of DA neurons that project back to the frontal lobe - a decrease in DA release (negative symptoms)
- also results in decreased activation of GABA interneurons...
- which normally inhibit the DA neurons that project into the nucleus accumbens - an increase in DA release (positive symptoms)

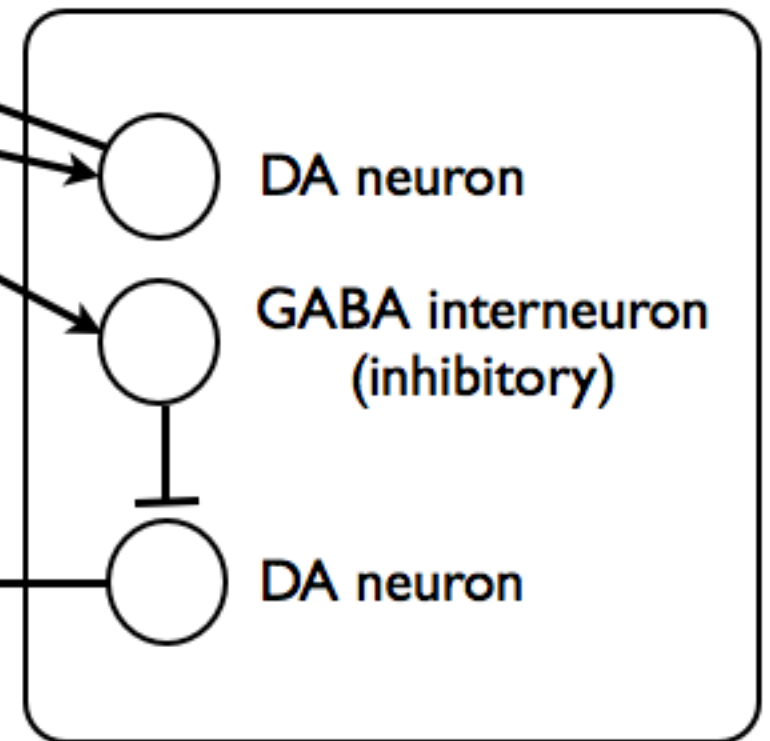
The Current Dopamine Theory

(per the text)

Dorsolateral Prefrontal Cortex (DLPFCx)



Ventral Tegmental Area (VTA)



decreased
(negative symptoms)

X
primary
disease
process

increased
(positive symptoms)

limbic and prefrontal cx

Nucleus Accumbens
(ventral striatum)

limbic system

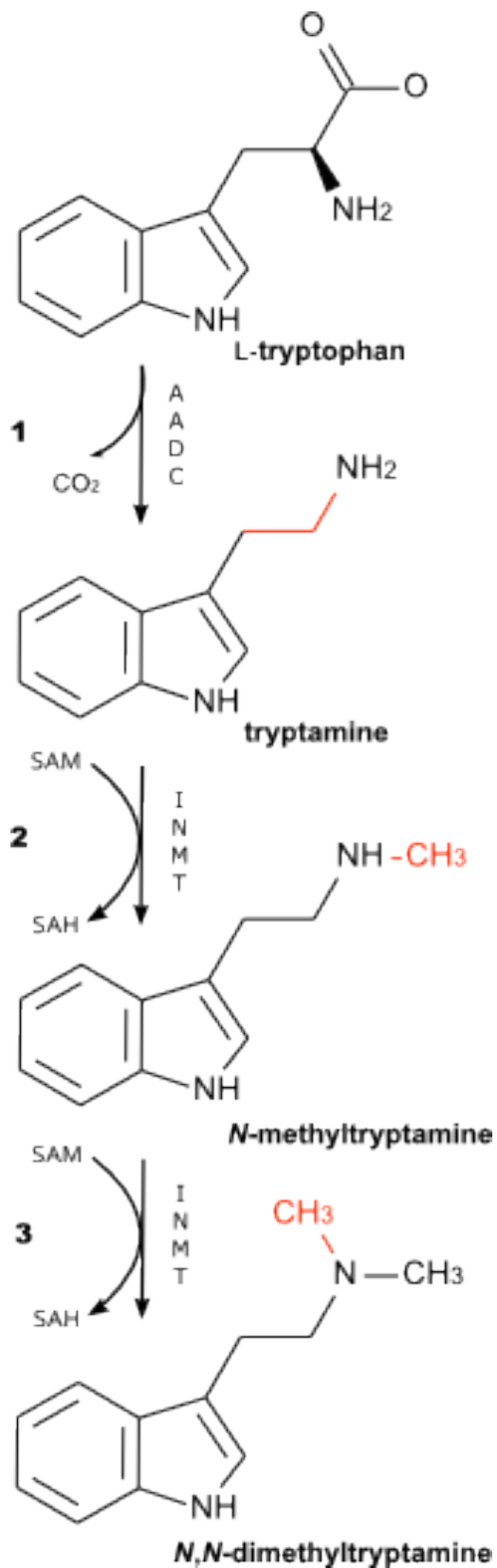
Clozapine, etc.

- Atypical antipsychotic meds like clozapine and aripiprazole increase DA activity in the frontal cx and decrease it in the nucleus accumbens.
- these drugs are called partial agonists
- bind to receptors but activate them less than the normal ligand (DA)
 - if DA is deficient (DLPFCx), this tends to increase activity of the receptors from previous levels
 - if DA is present in excess (nuc. accumbens), this tends to interfere with DA's ability to bind to receptors
- Thus, these drugs relieve the positive symptoms, as all antipsychotics do due to their antagonism of DA in the nuc. accumbens, but they also relieve the negative and cognitive symptoms due to their agonistic effect in the frontal lobes.

Just Hold the Phone a Minute!

- serotonin receptors and schizophrenia
 - remember the methylation theory?
 - LSD and other classic hallucinogens (mescaline, psilocybin, DMT, etc.) bind to 5-HT_{2A} receptors in the prefrontal cortex
 - there are clinical reports that psilocybin can cause a psychotic syndrome similar to the early stages of schizophrenia - ego-disorders, affective changes, thought disorder-like changes, perceptual alterations
(“we recently found that psilocybin in normal subjects produced a marked prefrontal activation associated with ego- and thought disorder comparable to that seen in acutely ill unmedicated or first episode schizophrenics” - Vollenweider, et al., 1998)
- do we make these things in our brain?

Just Hold the Phone a Minute!



- the enzymes necessary to produce DMT in the body were discovered in rabbit lung in 1961 (Julius Axelrod)
- reportedly found in human blood and urine in 1965 by German scientists - the catch: their analytical methods were questionable and probably not sensitive enough to detect the small amounts that would occur in humans
- this initiated a controversy that is ongoing - do we make this stuff in our brains?
- Internet confabulations aside, the evidence for that is weak - but there is some evidence that DMT may be a normal metabolite of tryptophan in pineal gland (2013/14)

Just Hold the Phone a Minute!

- antipsychotics, esp. the atypical antipsychotics such as clozapine, block the serotonin-2A receptors and turn off the psychotomimetic effects of LSD-like drugs quickly
- it has been proposed that blockade of these receptors may play a major role in the antipsychotic effects of these drugs
 - see next slide
- so things are getting interesting again!

Serotonin receptors : their key role in drugs to treat schizophrenia

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Abstract

Serotonin (5-HT)-receptor-based mechanisms have been postulated to play a critical role in the action of the new generation of antipsychotic drugs (APDs) that are usually referred to as atypical APDs because of their ability to achieve an antipsychotic effect with lower rates of extrapyramidal side effects (EPS) compared to first-generation APDs such as haloperidol. Specifically, it has been proposed by Meltzer et al. [J. Pharmacol. Exp. Ther. 251 (1989) 238] that potent 5-HT_{2A} receptor antagonism together with weak dopamine (DA) D₂ receptor antagonism are the principal pharmacologic features that differentiate clozapine and other apparent atypical APDs from first-generation typical APD. This hypothesis is consistent with the atypical features of quetiapine, olanzapine, risperidone, and ziprasidone, which are the most common treatments for schizophrenia in the United States and many other countries, as well as a large number of compounds in various stages of development. Subsequent research showed that 5-HT_{1A} agonism may be an important consequence of 5-HT_{2A} antagonism and that substitution of 5-HT_{1A} agonism for 5-HT_{2A} antagonism may also produce an atypical APD drug when coupled with weak D₂ antagonism. Aripiprazole, the most recently introduced atypical APD, and a D₂ receptor partial agonist, may also owe some of its atypical properties to its net effect of weak D₂ antagonism, 5-HT_{2A} antagonism and 5-HT_{1A} agonism [Eur. J. Pharmacol. 441 (2002) 137]. By contrast, the alternative “fast-off” hypothesis of Kapur and Seeman [Am. J. Psychiatry 158 (2001) 360] applies only to clozapine and quetiapine and is inconsistent with the “slow” off rate of most atypical APDs, including olanzapine, risperidone and ziprasidone. 5-HT_{2A} and 5-HT_{1A} receptors located on glutamatergic pyramidal neurons in the cortex and hippocampus, 5-HT_{2A} receptors on the cell bodies of DA neurons in the ventral tegmentum and substantia nigra and GABAergic interneurons in the cortex and hippocampus, and 5-HT_{1A} receptors in the raphe nuclei are likely to be important sites of action of the atypical APDs. At the same time, evidence has accumulated for the important modulatory role of 5-HT_{2C} and 5-HT₆ receptors for some of the effects of some of the current APDs. Thus, 5-HT has joined DA as a critical target for developing effective APDs and led to the search for novel drugs with complex pharmacology, ending the exclusive search for single-receptor targets, e.g., the D₃ or D₄ receptor, and drugs that are selective for them.

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