

SCHIZOPHRENIA

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I. Symptoms of Schizophrenia

- Psychotic Symptoms (Positive Symptoms)
 - delusions
 - hallucinations
- Deficit Symptoms (Negative Symptoms)
 - flat affect
 - apathy
 - distractibility
 - social withdrawal
- Language Symptoms
 - loosening of associations
 - impoverished speech
- Non-Specific Symptoms
 - impairment in role functioning
 - peculiar behavior
 - poor hygiene and grooming
 - lack of insight regarding illness

II. Definition/Diagnostic Criteria/Course/Psychometrics

- DSM-IV
 - A. Two characteristic symptoms present for a significant portion of a month (or less with treatment):
delusions/hallucinations/disorganized speech, grossly disorganized behavior/flat affect, apathy or poverty of speech
 - B. Decline in functioning (work, social relations, self-care)
 - C. Continuous signs of the disturbance for at least six months. This can include prodromal or residual phase with negative or non-specific symptoms, or milder versions of psychotic symptoms, such as odd beliefs or disturbed perceptions
 - D. Affective disorder (manic, depressive) not present or comparatively brief
 - E. Substance abuse or general medical condition not causing the symptoms

- Validity of Definition

- A. Many other definitions and no "gold standard"
- B. DSM-IV Criteria predict a poor-prognosis group (vs. other psychotic illnesses)

- Course: Usually chronic and undulating, with a plateau of disability, but can improve in later life. Acute-onset cases can have a better course.

- Psychometric Examination

Mild reduction (8-10 points) in IQ
mainly performance IQ

Poor performance on Wisconsin Card Sort Test
which requires the development of concepts
on the basis of experience

III. Epidemiology

- A. 0.8% lifetime prevalence
- B. More than 1,000,000 afflicted in U.S.A.
- C. Men = Women, but onset earlier in men
- D. All countries, but some cultural isolates with elevated rates (Northern Sweden, Western Ireland)

IV. Subjective Experience of Schizophrenia

- Pre-psychosis

Increased awareness, alertness

- Psychosis

Expansion of meaning, apprehensiveness

Confusion, fear

Conviction

- Post-psychosis

Stigma and Rejection

Denial of illness

Withdrawal

Discouragement, Depression, Suicidal feelings

V. "Illness" vs. "Way of Being"

- Evidence for Way of Being

Behavioral/mental, thus intangible

vs. tangible medical/physical illnesses

In some cultures, some psychotic states are normative

- Evidence for Illness
 - Effective biological treatment (weak evidence)
 - Severe disability, with gross qualitative alteration of functioning
 - Stereotyped presentation across all cultures, and recognized as illness in them
 - Can be reliably diagnosed with same criteria across cultures
 - Can be mimicked by drugs and physical disorders: amphetamines, steroids, Lupus, frontal tumors, Addison's Disease
- Can be approached/investigated as an illness

VI. Disease vs. Syndrome; One Process or Multiple

- Schizophrenia is probably a clinical syndrome (e.g., congestive heart failure, nephrotic syndrome), with diverse etiologies. Specific subtypes not yet established, but this is an effort of current research.
- Schizophrenia has multiple processes, or sub-sets of symptoms identifiable by factor analysis
 - positive (psychotic) symptoms - delusions, hallucinations
 - negative symptoms - affective flattening, apathy, social withdrawal,
 - cognitive/language symptoms - loose associations, impoverished speech
 These different processes can be studied independently. They could represent different etiologic factors or the same factor affecting different brain areas.

VII. Search for a Biology of Schizophrenia:

A: Genetics: Familial, but does not correspond to Mendelian patterns (e.g. 8-10% risk in the children of a schizophrenic parent, concordance rates in monozygotic twins 45-50%). Perhaps polygenetic.

B: Brain Imaging and Neuropathology

- Brain Anatomy

Findings: Ventricular and temporal lobe abnormalities

CT and MRI

enlarged lateral ventricles, evident in the early stages of illness, and even when relatively small may be enlarged compared to "expected size" (twin studies)
decreased temporal lobe gray matter
smaller hippocampus

Neuropathology.

increased size of ventricles,
smaller hippocampus (H) reduced tissue mass in nearby areas especially parahippocampal (PH) gyrus,

Brain appears atrophied, but may be dysplastic, not atrophic
sulci as well as ventricles enlarged
no gliosis
evidence of failure of cellular migration

- Interpreting the anatomical findings regarding the temporal lobe:

- Normal functions of the temporal lobe:
memory, learning, "emotion"
- Electrical stimulation of temporal cortex can produce "hallucinations" (Penfield)
- Temporal lobe disorders, especially temporal lobe epilepsy, can produce "schizophrenia," with more positive symptoms than negative symptoms

- Imaging of Brain Function

- Methods

Positron Emission Tomography (PET)
Regional Cerebral Blood Flow (rCBF)

- Findings

- Initial PET findings link psychosis with lower functioning of the hippocampus area.
- rCBF studies show reduced activity of dorsolateral prefrontal cortex, most evident with an activation task, the Wisconsin Card Sort

- Interpreting the functional studies of frontal cortex:

- Lesions of prefrontal cortex in humans produce

negative symptoms and schizophrenia-like neurological, and neuropsychological abnormalities

- Primate lesions of dorsolateral prefrontal cortex produce a specific deficit on the Delayed Response Task. "Only when internalized or inner models of reality are used to govern behavior is the prefrontal cortex preeminently engaged."

-Interpreting the anatomic and functional studies:

The positive symptoms of schizophrenia may be produced by a disturbance in the medial temporal lobe limbic system structures), and the negative symptoms may be produced by a disturbance in the prefrontal cortex.

C: Neurochemistry

- Dopamine
Projections to the striatum (caudate, putamen), and to limbic system and to prefrontal cortex
- Cortical-Striatal-Thalamic-Cortical System
Importance of dopamine in reducing the filtering of sensations and impulses (i.e., high dopamine = more awareness and more impulsiveness).
- Dopamine hypothesis: Increased dopaminergic activity produces schizophrenic psychosis

Findings:

- antipsychotic drugs block dopamine, specifically D2 receptors
 - drugs which enhance dopamine (amphetamines, cocaine, L-dopa) can exacerbate psychoses
 - PET Studies have shown that schizophrenic patients release more dopamine when stimulated by amphetamine
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- Revised dopamine hypothesis #1: Decreased dopaminergic input to the frontal cortex produces negative symptoms and decreased feedback causes increased dopaminergic activity in the limbic system and striatum, producing psychosis

Findings linking dopamine deficiency to prefrontal dysfunction:

- Blocking Dopamine receptors (D1) produces a specific impairment of the delayed response task in primates.
 - In rodents, interrupting dopamine input to prefrontal cortex leads to an increase in dopamine output to all brain areas (probably through a feedback loop regulating dopamine output).
- Revised dopamine hypothesis #2: Damaged areas of the cortex lead to diminished glutamate and GABA control of dopamine, so that control of the dopamine system is lost and it becomes overactive under stress.

Findings

- In patients, hippocampal volume predicts prefrontal blood flow during the Wisconsin Card Sort Task (links Temporal Lobe status to prefrontal dysfunction)
- Some drugs that act on glutamate, such as PCP or Ketamine, also produce psychosis
- Some direct evidence of diminished glutamate in schizophrenic patients

D: Summary of the Biological Studies of Schizophrenic Patients

- Neuropathology and CT/MRI studies report temporal lobe abnormalities (hippocampus, parahippocampal gyrus) that may result from abnormal brain development
- Functional brain imaging studies report decreased functioning of the prefrontal cortex
- Neurochemical and neuropharmacological studies propose dopamine excess as a cause of psychosis, and perhaps dopamine deficiency, or cortical/glutamate dysfunction, as a cause of negative symptoms

SUMMARY OF THE BIOLOGY OF SCHIZOPHRENIA

We do not have a firm understanding of the etiology or of the pathophysiology of schizophrenia. However, we do know the following:

1. Schizophrenia runs in families. For example, 10% of the children of a schizophrenic parent will have schizophrenia themselves. Studies of identical twins show that approximately 50% of the identical co-twins of a schizophrenic patient will have schizophrenia. From these studies, and others, including studies of adopted-away children, we believe that a predisposition to develop schizophrenia can be inherited, but that certain additional pathogenic factors are often necessary to produce the illness.

2. Schizophrenia alters brain structure, and impairs brain function.

- A. The most replicated structural abnormality is an increase in the size of the cerebral ventricles. All ventricles have been found to be enlarged, especially the lateral ventricles. The sulci of the cortex are also enlarged. The brain thus looks atrophied, in ways similar to those produced by normal aging. However, there is no microscopic evidence of neurons dying or of scar formation (gliosis) in this illness. Thus, many believe that these abnormalities are produced by abnormal development of the CNS, and not by atrophy.

B. There is a very active search going on to discover what specific parts of the brain are most abnormal or undeveloped. The studies thus far have most often shown that the temporal lobe, especially the medial portion of the temporal lobe, is often abnormal. The hippocampus is an important structure in this area, as is the parahippocampal gyrus. Both of these structures have been found to be smaller or anatomically disrupted in neuropathological and MRI studies.

C. There are many ways of examining the function of the brain, and many ways in which the brains of schizophrenics have been found to function abnormally:

- the brain imaging techniques, such as regional cerebral blood flow (rCBF) and positron emission tomography (PET) scans, have shown decreased levels of neuron activity in both the prefrontal cortex and in the hippocampus of schizophrenic patients.

- other physiological tests, done by using cortical evoked potentials, show that schizophrenic patients' brains respond differently to certain stimuli. They appear to have a difficulty in automatically filtering out irrelevant stimuli and in focusing their attention on the most important stimuli. Though these latter studies do not help us identify what part of the brain is abnormal, the impairments may help us understand why schizophrenic patients have difficulty with certain psychological tests,

such as the Wisconsin Card Sort Test, and the difficulties patients have in thinking and talking in a direct, coherent fashion.

3. Many of the symptoms of schizophrenia, especially the positive symptoms (hallucinations, delusions, loose associations), improve when patients are treated with anti-psychotic medications. These medications are thought to work primarily by blocking dopamine D₂-type receptors. Also, drugs which release dopamine in the brain, such as cocaine and amphetamine, can cause psychosis. We believe that something might be wrong with the dopamine system in schizophrenic patients, or in those brain systems which influence dopamine. Though all dopamine cell bodies are located near each other in a small portion of the midbrain, these neurons project to many different portions of the brain. The medications block the dopamine post-synaptic receptors in all these areas, and it is not clear whether their therapeutic action comes from blocking all, or from blocking only a certain area of the dopamine projections. The bulk of the dopamine projections go to the striatum (caudate and putamen) which itself sends projections to the thalamus. By blocking the dopamine input into the striatum, the actions of the thalamus, which include filtering, could be improved. Also, dopamine goes to the limbic system (hippocampus and amygdala). This system is responsible for emotion and the interpretation of perceptions. By blocking dopamine going to this system, it is possible that the medications decrease emotion and improve the accuracy of perceptions.

Though drugs which block dopamine are helpful in the treatment of schizophrenia, it is possible that certain areas of the brain may be getting too little dopamine in this disorder. Animal and human studies have shown that too little dopamine going to the frontal lobes can produce abnormalities similar to those found in schizophrenia, e.g., poor performance on the Wisconsin Card Sort Test, and other tests requiring "working memory." Dopamine going to the frontal lobes primarily acts on dopamine D₁-type receptors, which are not blocked by most anti-psychotic medications.

If it turns out to be true that there is too much dopamine in some areas of the brain of schizophrenic patients and perhaps too little going to other areas of the brain, this seeming paradox has been better understood since we have discovered that in animals decreasing the dopamine input to the frontal cortex (by making lesions of that dopamine system) leads to an increased amount of dopamine going to other areas of the brain. This is probably because of alterations in a feedback loop coming from prefrontal cortex to the dopamine cell bodies.

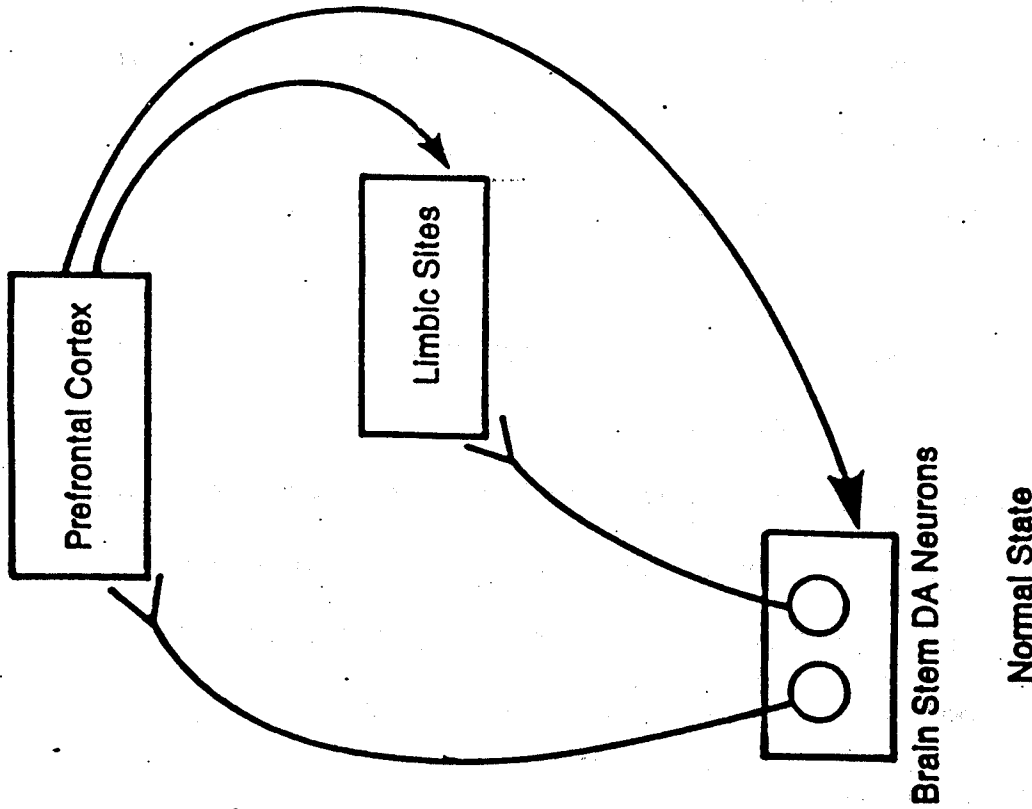
4. We have searched for a unifying theory of the etiology of schizophrenia which would be consistent with all the above findings and explain why and how the brain functions abnormally in this disorder. We do not have enough information to be sure of any such theory, and there is no agreement on one.

a. We know, as described above, that damage to or reduced function of the prefrontal cortex could produce the negative symptoms of schizophrenia and, through feedback mechanisms, this could produce dopamine flooding into other areas, and psychosis. We do not know, however, what causes the prefrontal cortex not to function well. We are not at all sure that decreased dopamine going to the prefrontal cortex starts this whole illness process.

b. The anatomical abnormalities in the hippocampus are quite striking, and need to be incorporated into our theory. One investigator has shown that the degree of abnormality in the hippocampus can actually predict the degree of functional abnormality in the prefrontal cortex. We know that the hippocampus sends information to (i.e. influences) the prefrontal cortex. Therefore, one possibility is that the damaged hippocampus causes the prefrontal cortex dysfunction, and one or both of these areas might affect the dopamine system through glutamate and GABA releasing axons.

5. In order for us to understand the etiology and pathophysiology of schizophrenia, many more research studies in patients, and basic research studies of brain systems in animals and humans, must be done. It would also be of great benefit to discover specific genes which increase the predisposition to schizophrenia, so that we could understand what the biological functions and impact of those genes would be.

EFFECT OF PREFRONTAL DOPAMINE DEAFFERENTATION



Normal State

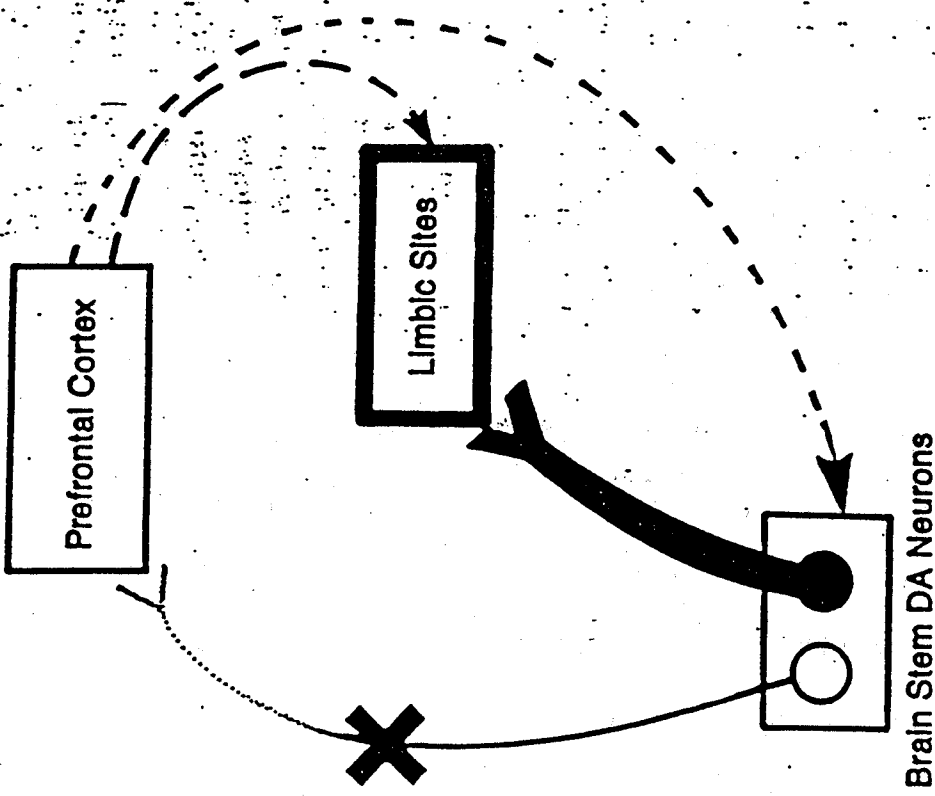


Fig 2.—Schematized interactions between mesolimbic and mesocortical dopamine systems in normal state (left) and after selective lesioning of dopamine input to prefrontal cortex (right), based on the work of Pycocock et al.⁵⁷ Broken line indicates that specific effect of lesion on corticolimbic feedback (eg, decreased inhibition or increased excitation) is unknown. DA indicates dopamine.

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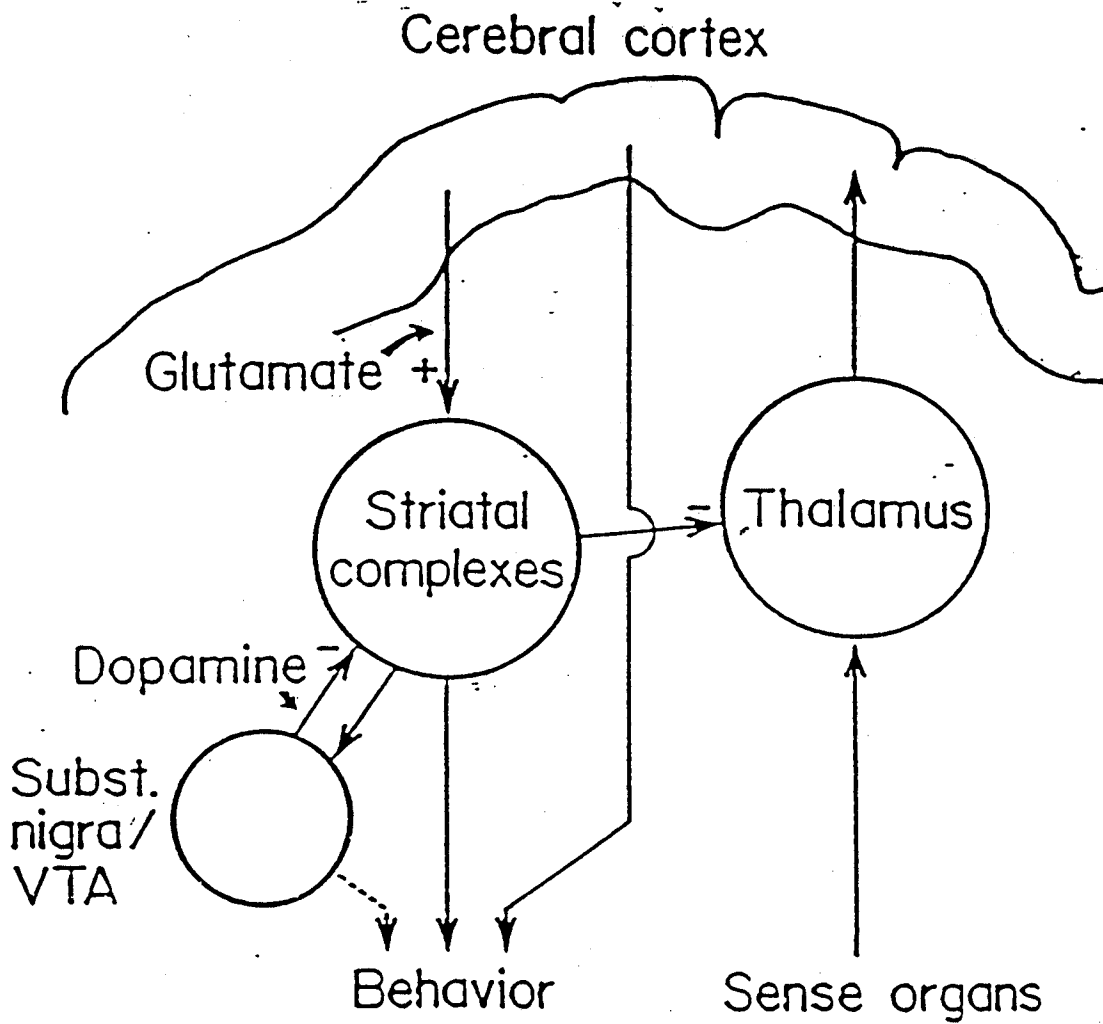


Figure 1. Schematic representation of the hypothesis that the cerebral cortex can protect itself from an overload of information and from hyperarousal by means of feedback loops engaging the striatal complexes and the thalamus (as well as the mesencephalic reticular formation, not indicated). The feedback loops are postulated to be modulated by the mesencephalostriatal dopaminergic pathways.