Schizophrenia

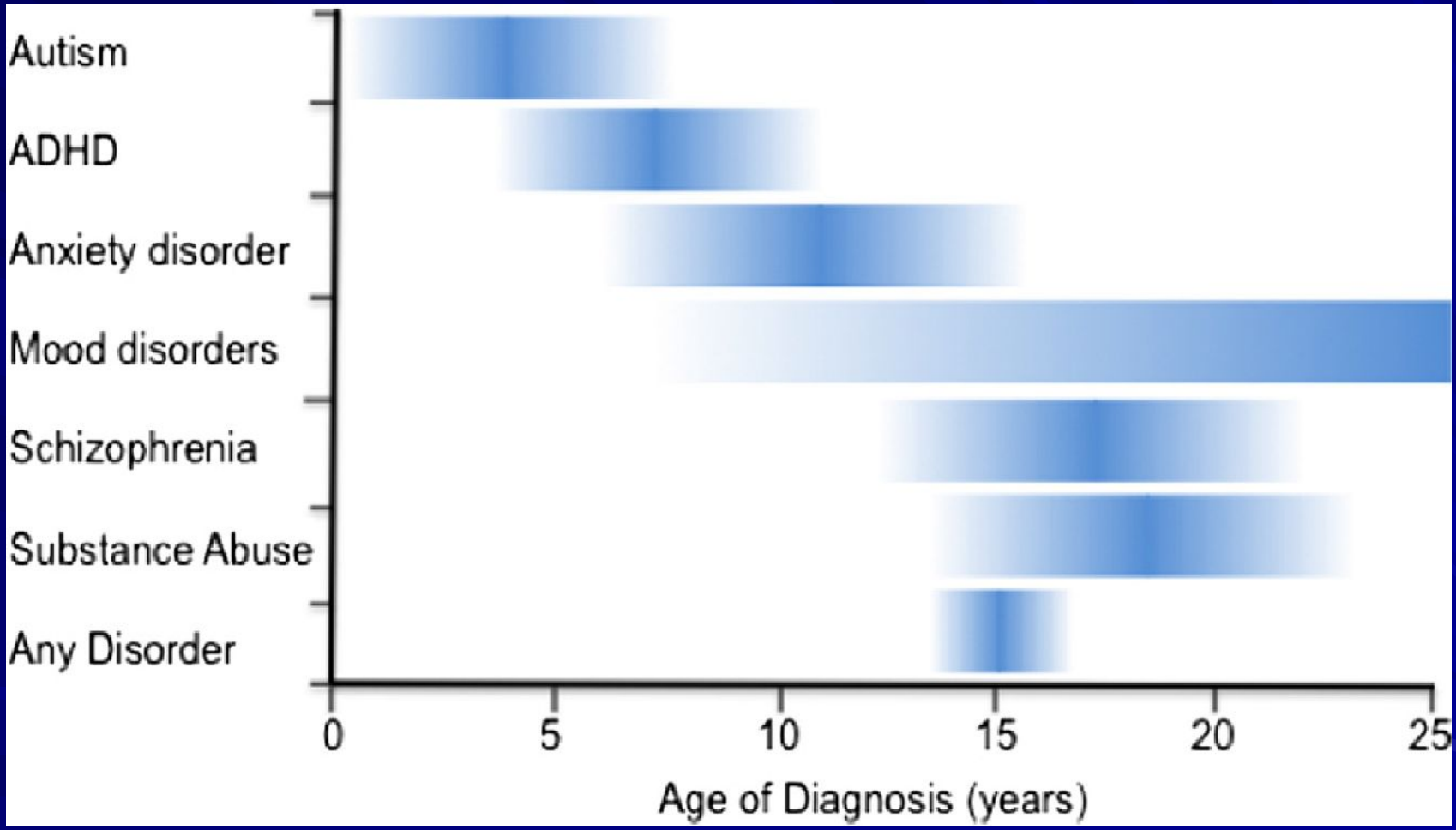
- Brain disorder of aberrant synaptic plasticity – “disconnection syndrome”
- Prevalence – 1% throughout the world
- Equally affect men and women
- Usually identified in second/third decade of life
- Progressive chronic course
- Complex clinical phenotype: positive, negative, disorganized, cognitive symptoms
- Causes substantial functional impairment

	Schizophrenia	
Family studies	Familial inheritance Two parents -50% One parent -10%	
Genetics	Concordance rate: monozygotic – 50%; dizygotic-10%. Common variants (SNPs); CNVs	
Age-at-onset	Adolescence/early adulthood	
Male/Female	Age-at-onset 2.5y earlier in men	
Social-economic status	Low	
IQ	Low	
Obstetric complications	Yes	
Excess of winter/spring birth	Yes	
Early childhood trauma	Yes	

Environmental factors

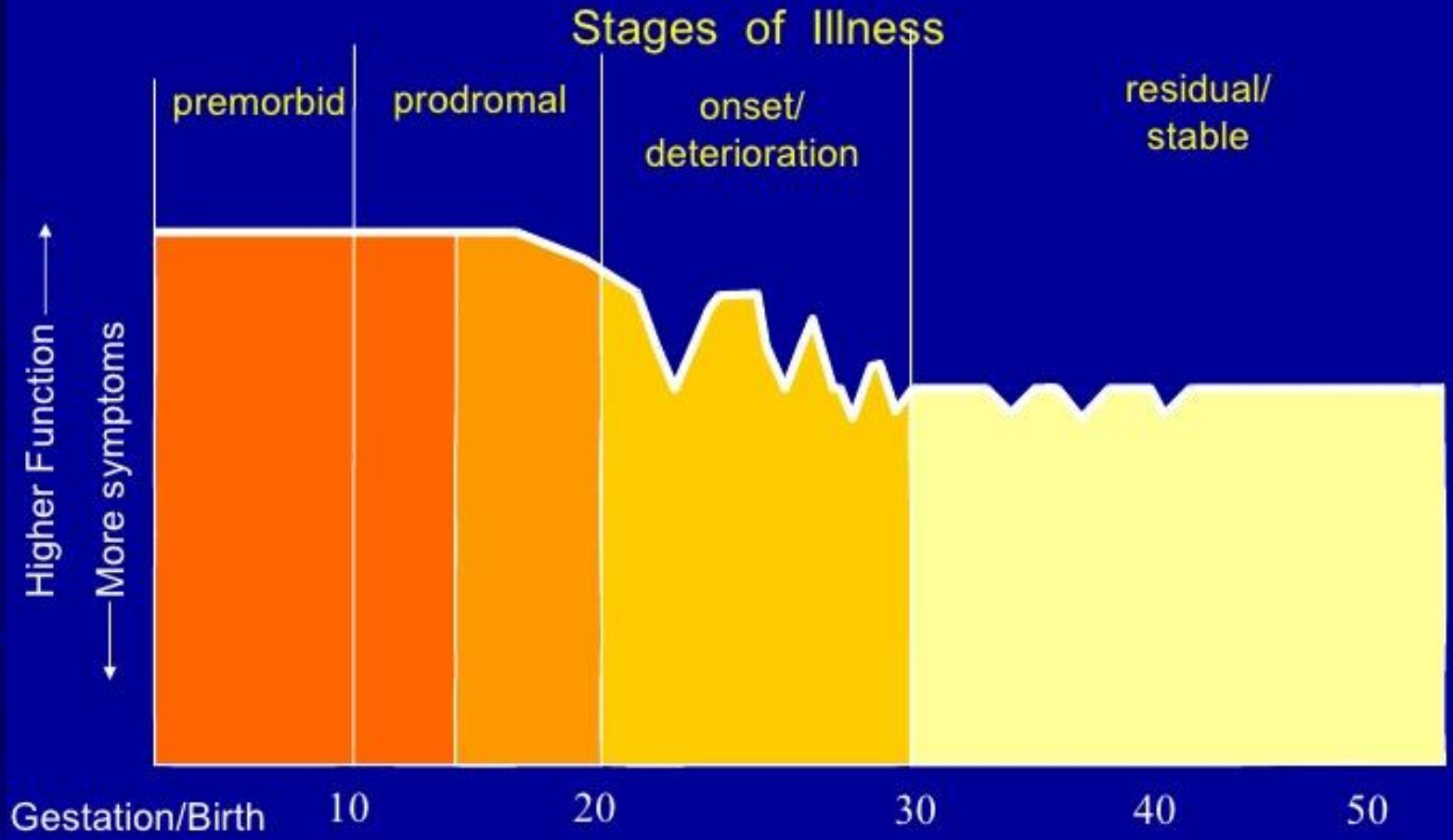
	Schizophrenia	
Urban upbringing	Yes	
Migration	Yes	
Cannabis	Yes	
Advanced parental age	Yes	
Reproductive output	Low	
Brain structural abnormalities	More severe; present in premorbid/prodromal phases	
Cognitive dysfunction	Generalized deficit; presents in prodrome	

Age of onset and peak of mental disorders

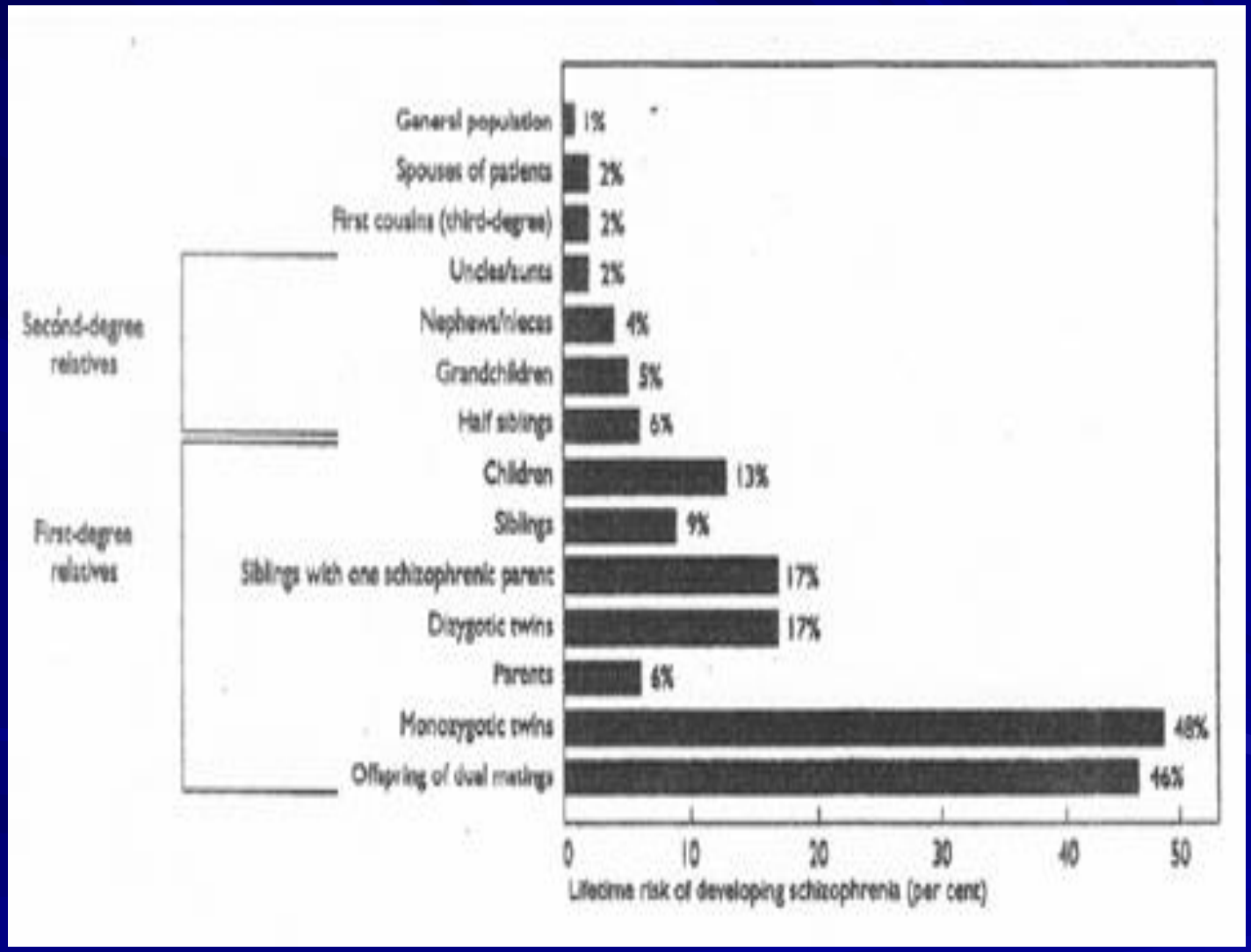


Nat Rev Neurosci (2), & 2008

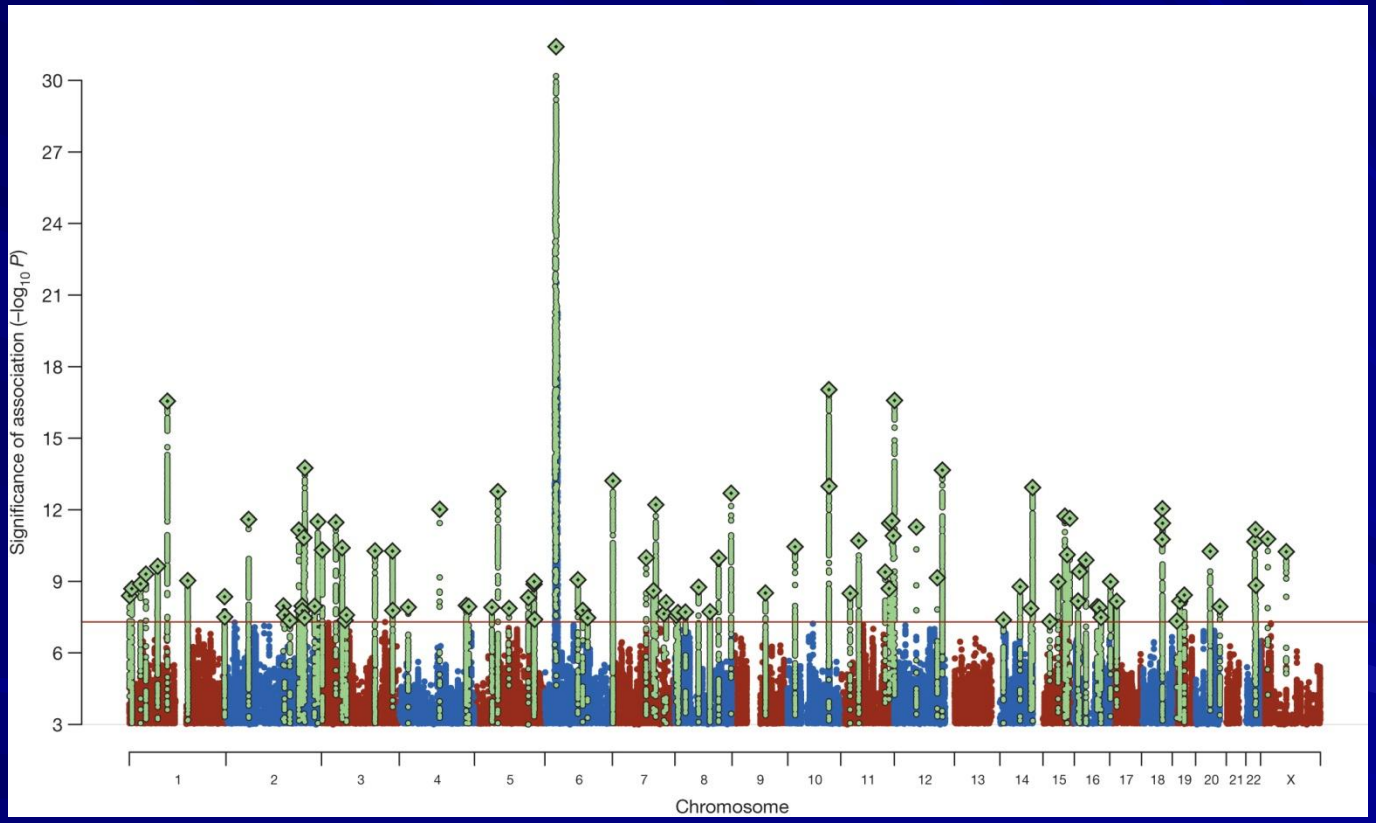
Course of Schizophrenia



Schizophrenia: inheritance



Manhattan plot showing schizophrenia associations



S Ripke *et al. Nature* 1-7 (2014)

Subdivision of Symptoms into Three Dimensions

- Psychotic
  - Delusions
  - Hallucinations
- Disorganized
  - Disorganized speech
  - Disorganized behavior
  - Inappropriate affect
- Negative
  - Poverty of speech
  - Avolition
  - Affective Blunting
  - Anhedonia

Types of Hallucinations

- Auditory
- Visual
- Tactile
- Olfactory

Types of Delusions

- Persecutory
- Grandiose
- Religious
- Jealous
- Somatic

DSM-5 Criteria for Schizophrenia: The Basics

- Characteristic symptoms for one month
- Social/Occupational Dysfunction
- Overall Duration > 6 months
- Not attributable to mood disorder
- Not attributable to substance use or general medical condition

Differential Diagnosis

- Mood Disorders
- Nonpsychotic personality disorders
- Substance-induced psychotic disorders
- Psychotic disorders due to a general medical condition (i.e., “organic” disorders)

Drugs That May Induce Psychosis

- Amphetamines
- Marijuana
- Hallucinogens
- Cocaine
- Cannabis

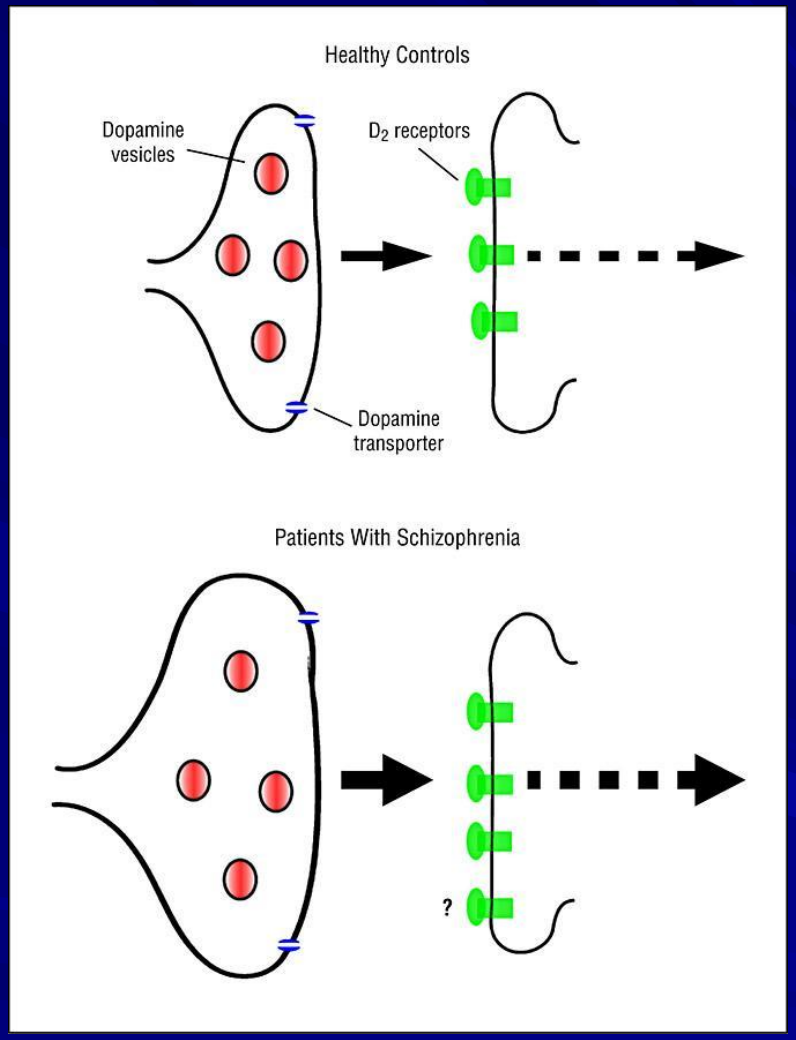
Medical Conditions That May Present with Psychosis

- Temporal lobe epilepsy
- Tumor
- Stroke
- Trauma
- Endocrine/metabolic abnormalities
- Infections
- Multiple Sclerosis
- Autoimmune diseases

The Dopamine Hypothesis

- Psychosis (schizophrenia?) is due to excessive dopaminergic tone
- Psychotic symptoms are relieved by blockade of dopamine receptors with neuroleptic medications

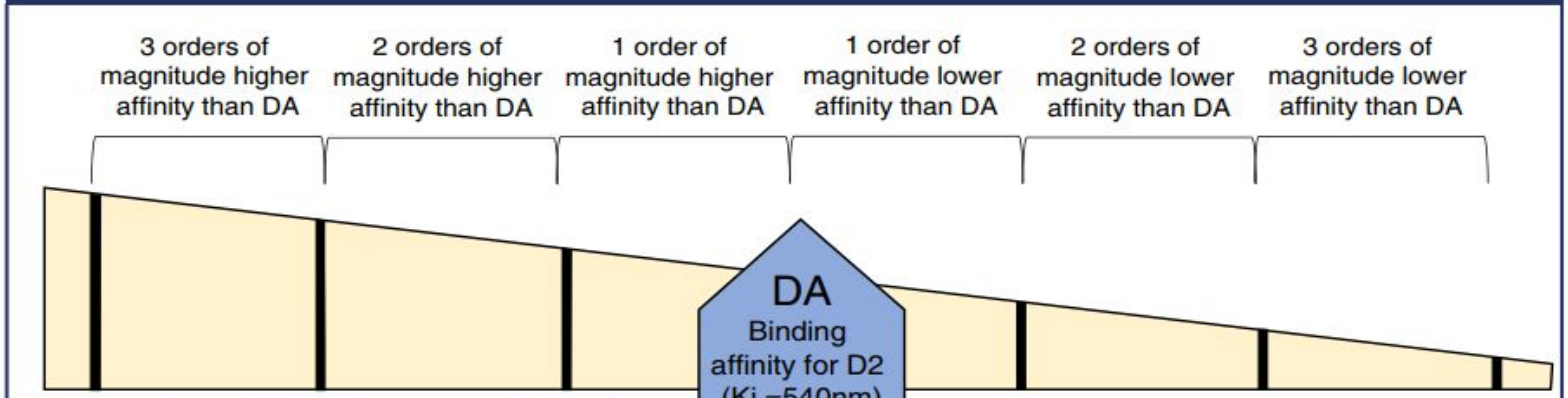
Schematic diagram summarizing the findings from our meta-analyses of dopamine function in schizophrenia



Howes, O. D. et al. Arch Gen Psychiatry 2012;0:archgenpsychiatry.2012.169v1-11.

ARCHIVES OF GENERAL PSYCHIATRY

Figure 4. This figure shows the relative affinities of drugs for psychosis and mood for D2 receptors compared to the affinity of dopamine itself for D2 receptors. All agents have equal or higher affinity for the D2 receptor than does dopamine itself. Many agents have higher or much higher affinities for D2 compared to dopamine.



Blonanserin binding affinity for D2 (0.14nM)

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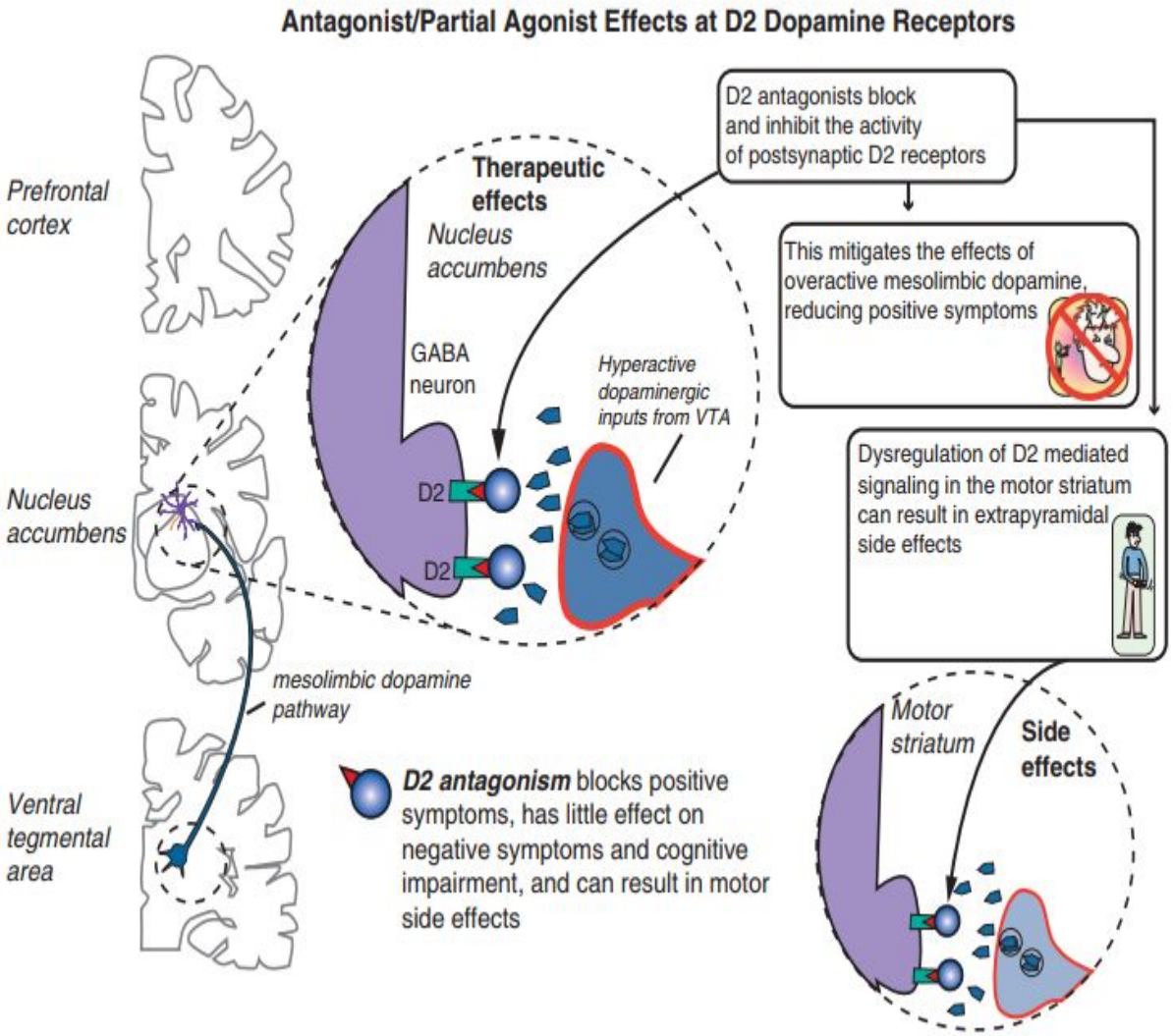
Iloperidone binding affinity for D2 (8.3nM)

Olanzapine binding affinity for D2 (30.8nM)

Clozapine binding affinity for D2 (147nM)

Quetiapine binding affinity for D2 (437nM)

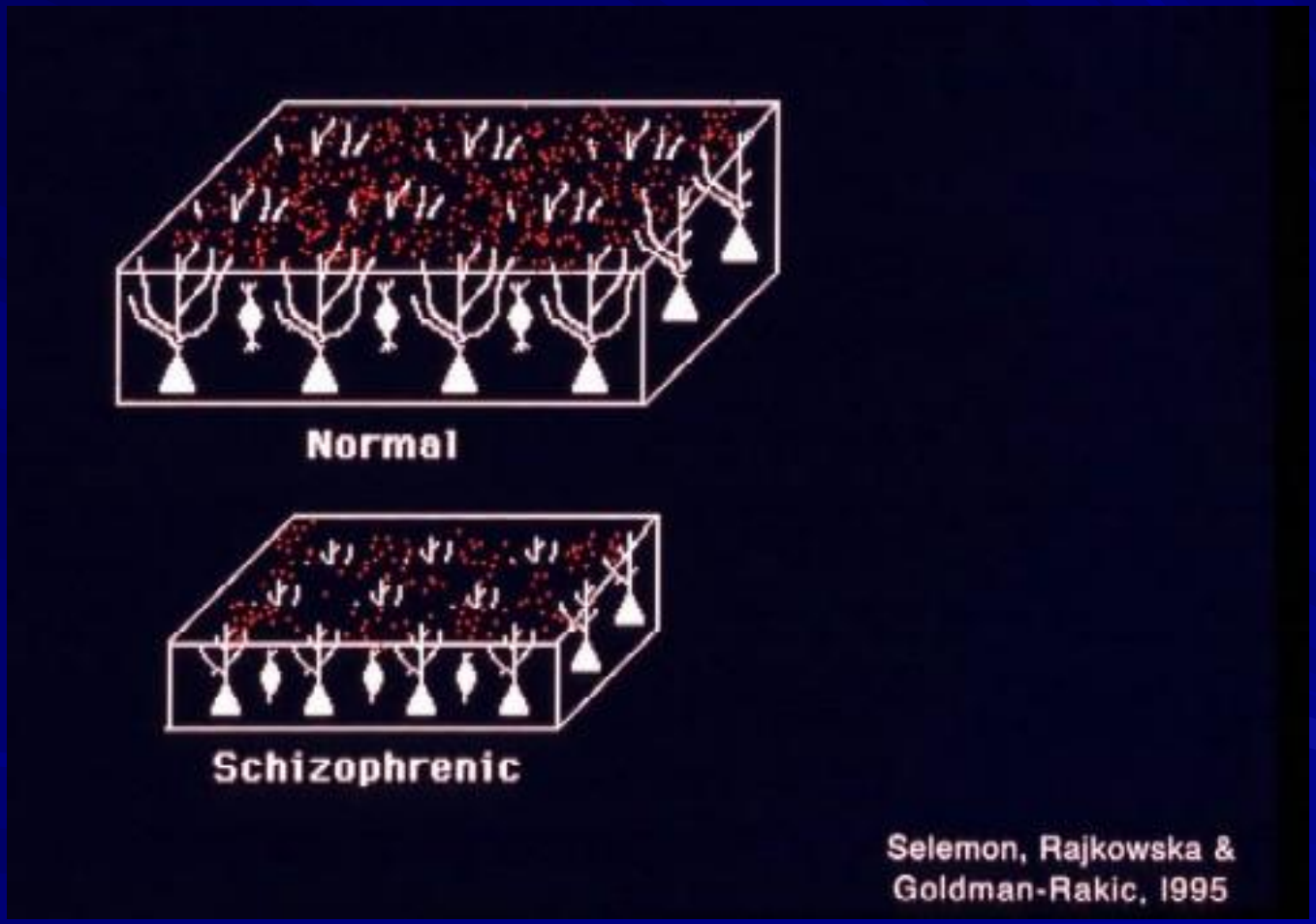
Figure 7. Antagonist/partial agonist effects at D2 dopamine receptors are illustrated here. These are well-known antipsychotic actions at D2 receptors in the nucleus accumbens, and also motor side effects at D2 receptors in the motor striatum.



Brain Regions Showing Replicable Neuropathological Abnormalities

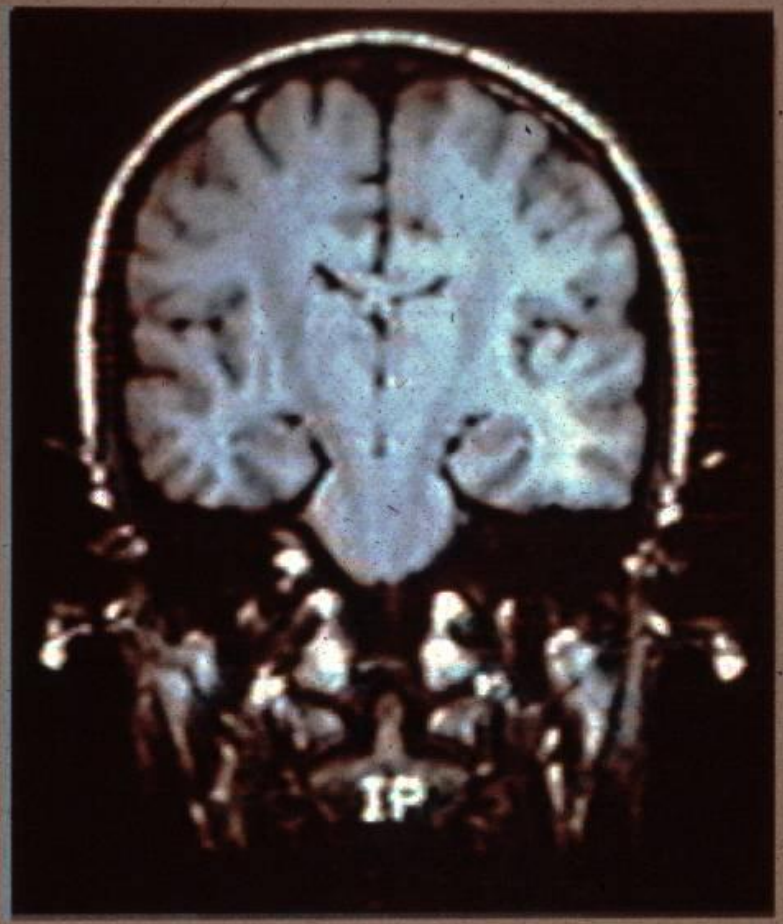
- Temporolimbic regions
- Thalamus
- Prefrontal cortex

Neuropil in Frontal Cortex

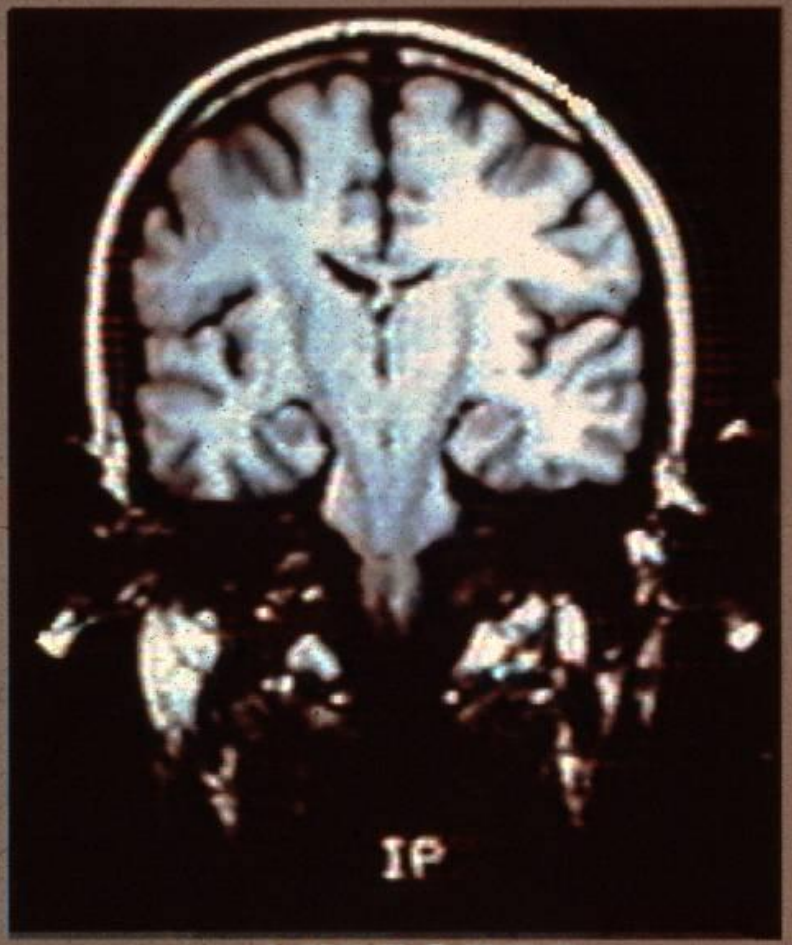


SCHIZOPHRENIA IN MONOZYGOTIC TWINS

Pair no. 1: 27 year old females



UNAFFECTED



AFFECTED

Criterion A: Characteristic Symptoms

- At least two of the following, each present for a significant portion of time during a one month period (or less if successfully treated):
- (1) delusions
- (2) hallucinations
- (3) disorganized speech (e.g., frequent derailment or incoherence)
- (4) grossly disorganized or catatonic behavior
- (5) negative symptoms, I.e., affective flattening, alogia, or avolition

Gender Differences

- Males have an earlier age at onset, a poorer premorbid history, more negative symptoms, a poorer outcome, and more prominent brain abnormalities as measured in neuroimaging studies
- Women have more prominent affective symptoms and a better outcome

Important Epidemiolgical Observations

- Prevalence is not highly variable over time or over geographical areas
- Found in all cultures
- More common and/or severe in males than females
- Persists in the population despite decreased fertility

Bleuler's Fundamental Symptoms

- Associations
- Affective Blunting
- Avolition
- Autism
- Ambivalence
- Attention

Schneider: The Psychotic Experience

- Interested in pathognomonic symptoms
- "First Rank Symptoms" (FRS)
  - E.g., voices commenting
  - Voices arguing
  - Thought insertion
- Involve a loss of the sense of autonomy of self, or "ego boundaries"

Characteristic Symptoms

- Schneider: specific types of delusions and hallucinations
- Bleuler: fragmented thinking, inability to relate to external world
- Kraepelin: emotional dullness, avolition, loss of inner unity

Criterion B: Social/Occupational Dysfunction

- For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations or self-care is markedly below the level achieved prior to the onset
- OR when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement

Criterion C: Overall Duration

- Continuous signs of the disturbance persist for at least six months
- This six-month period must include at least one month of symptoms that meet criterion A (i.e., active phase symptoms), and may include periods of prodromal or residual symptoms
- During these prodromal or residual period, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in criterion A present in an attenuated form (e.g.
  odd beliefs, unusual perceptual experiences)

Criterion D: Schizoaffective and Mood Disorder Exclusion

- Schizoaffective Disorder and Mood Disorder with Psychotic Features have been ruled out because of either:

  (1) No major depressive or manic episodes have occurred concurrently with the active phase symptoms; or

  (2) If mood episodes have occurred during active phase symptoms, their total duration has been brief relative to the duration of the active and residual periods

Criterion E: Substance / General Medical Condition Exclusion

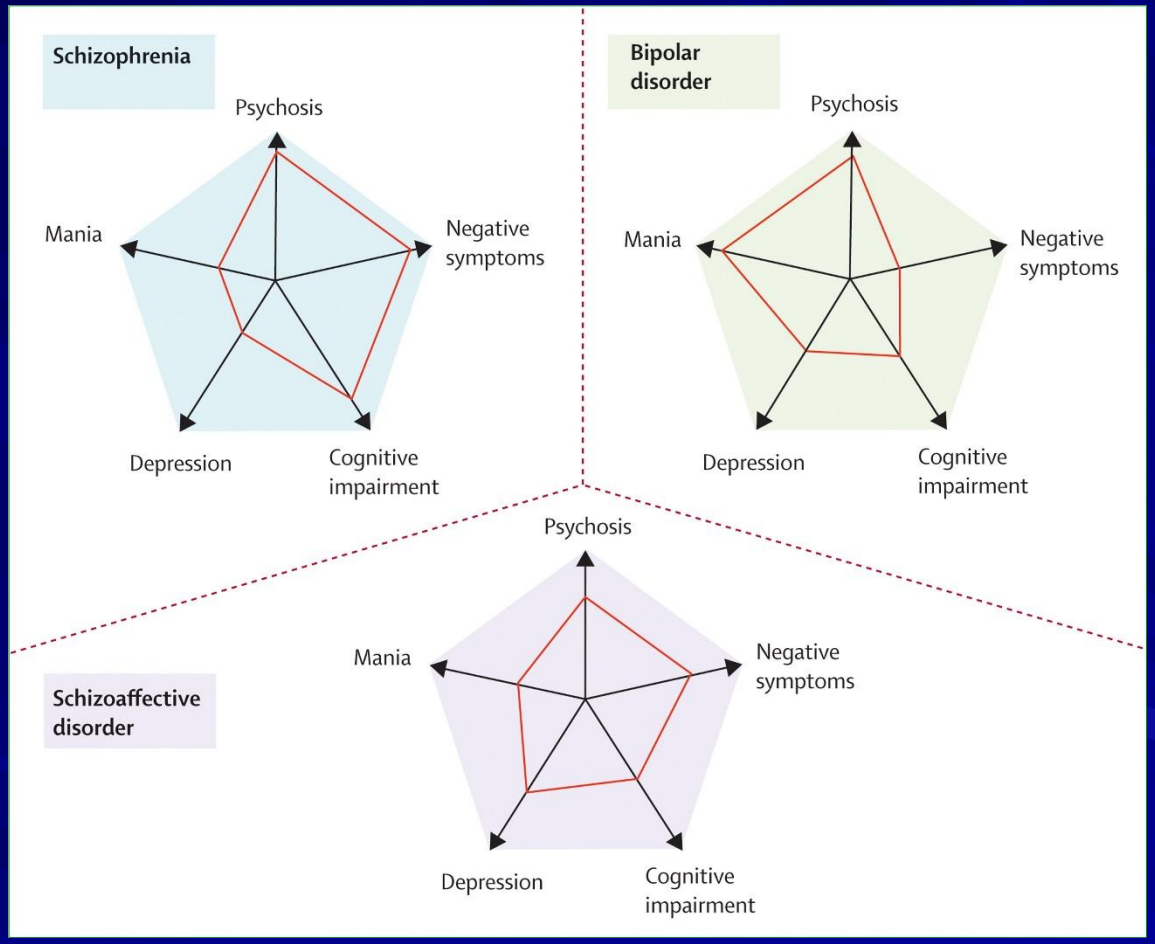
The disturbance is not due to the direct effects of a substance (e.g., drugs of abuse, medication) or a general medical condition

DSM 5: Categories of Psychosis

- Schizophreniform Disorder
- Schizophrenia
- Brief Psychotic Disorder
- Schizoaffective Disorder
- Delusional Disorder
- Shared Psychotic Disorder
- Psychotic Disorder due to a General Medical Condition
- Substance-Induced Psychotic Disorder
- Psychotic Disorder Not Otherwise Specified

Poor Outcome: Predictors

- Prominent negative symptoms
- Early age of onset
- Insidious onset
- Poor premorbid adjustment
- Low educational achievement
- Low parental social class
- Male gender


Schizophrenia
Psychosis
Mania
Negative symptoms
Depression
Cognitive impairment
Bipolar disorder
Psychosis
Mania
Negative symptoms
Depression
Cognitive impairment
Schizoaffective disorder
Psychosis
Mania
Negative symptoms
Depression
Cognitive impairment

Lower Social Class in Schizophrenia

- Consistently observed in patients
- Lower social class is a result—not a cause—of the illness
- Social class of parents does not differ from the general population
- Lower social class is due to “downward drift,” not to social deprivation, poor nutrition, or inadequate access to health care

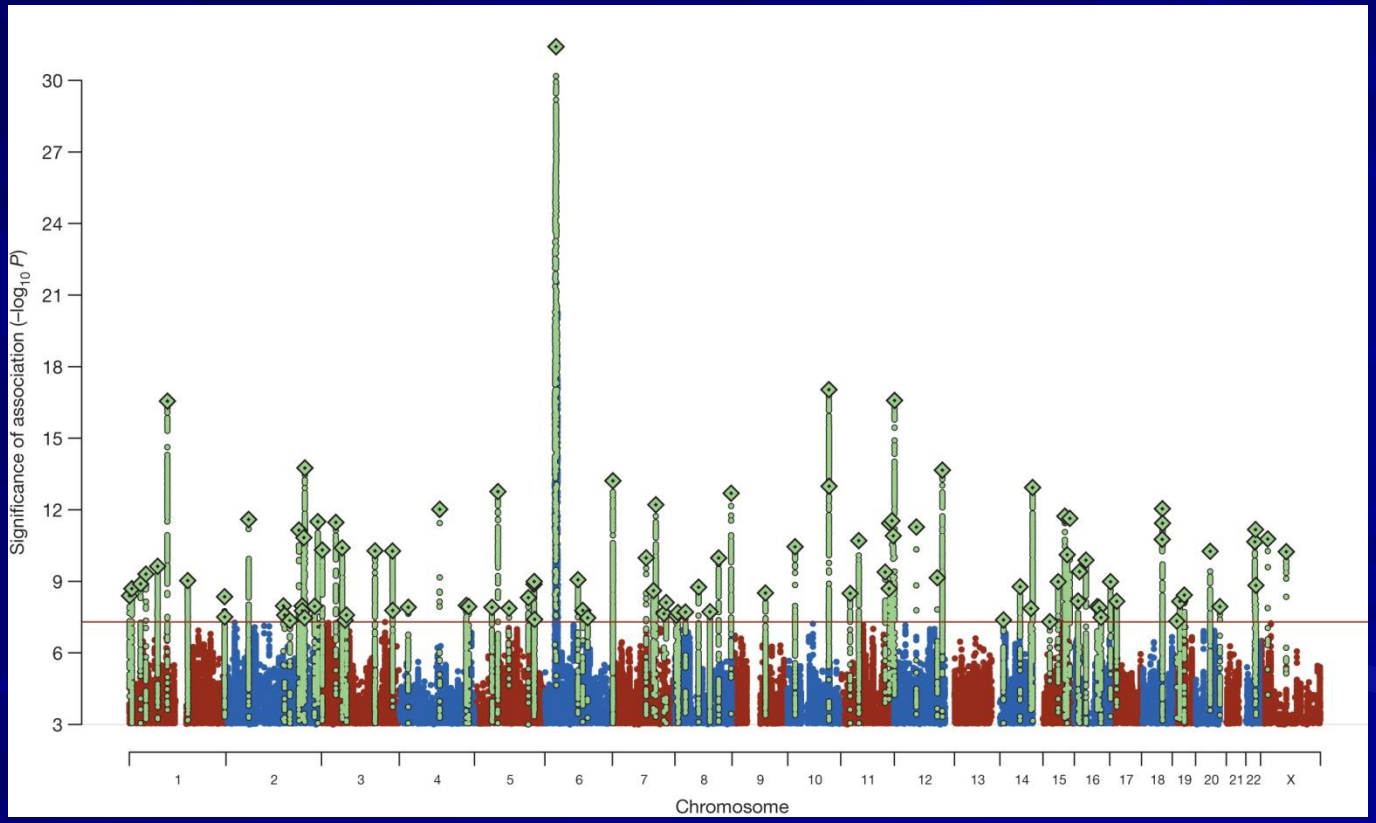
Genetic Questions

- Is the disorder familial?
- Relative contributions of genes and environment
- Mode of transmission
- Location of gene
- Function and products of gene
- Role of the products in illness mechanisms

Genetic Methods

- Family history studies
- Family studies
- Twin studies
- Adoption studies
- Linkage and association studies, candidate genes
- Molecular genetics—functional genomics, proteomics

Manhattan plot showing schizophrenia associations



S Ripke *et al. Nature* 1-7 (2014)

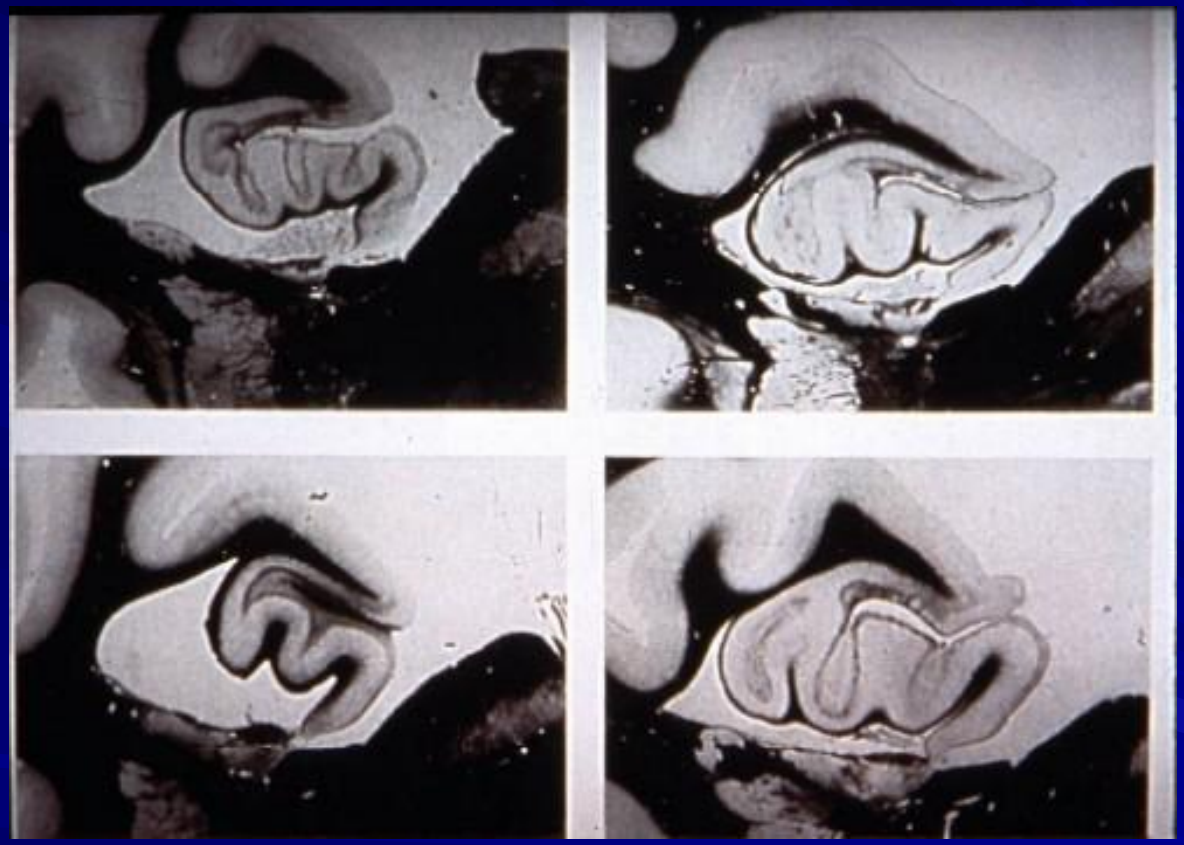
Family History and Family Studies

- Provide evidence for a modest level of familial transmission
- Morbid risk for parents: 5.6%
- Morbid risk for siblings: 10.1%
- Morbid risk for offspring: 12.8%
- Second degree relatives: 2.4-4.2%

Possible Reasons for Lack of Measurable Abnormalities

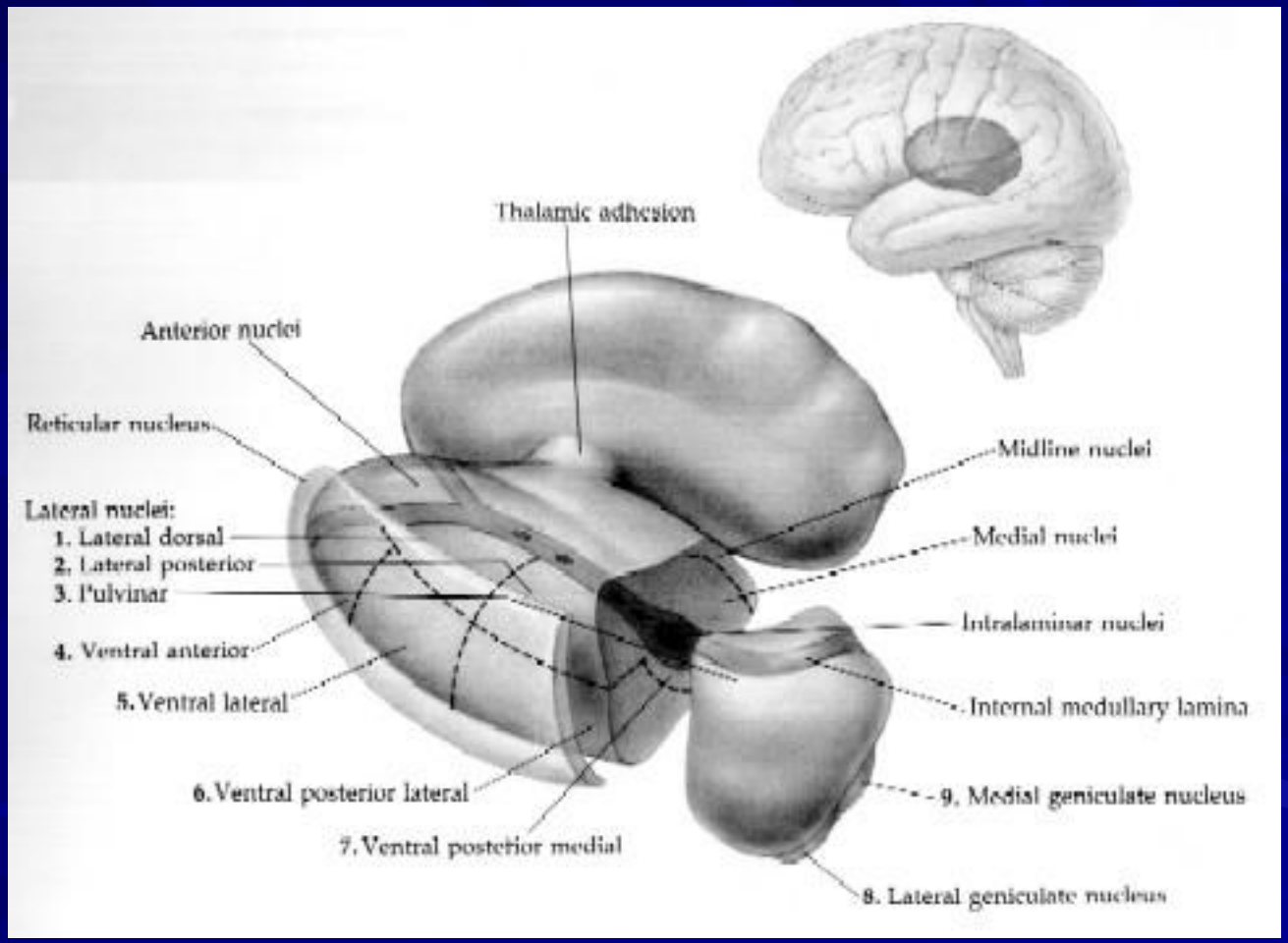
- Problems in defining the phenotype
- No single pathophysiology
- Due to reversible neurochemical processes
- Not accessible using traditional neuropathology tools
- In areas where neuropathologists have not yet looked
- Due to abnormalities in connectivity

Hippocampal Atrophy in Schizophrenia



Patients **Controls**

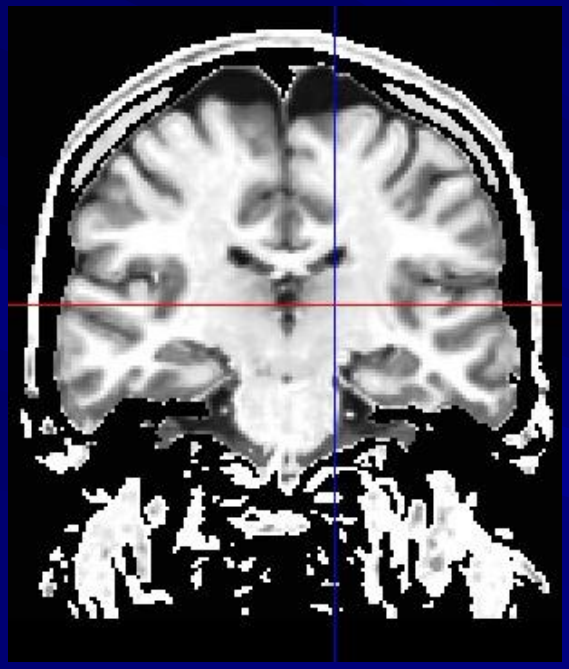
Thalamic Nuclei



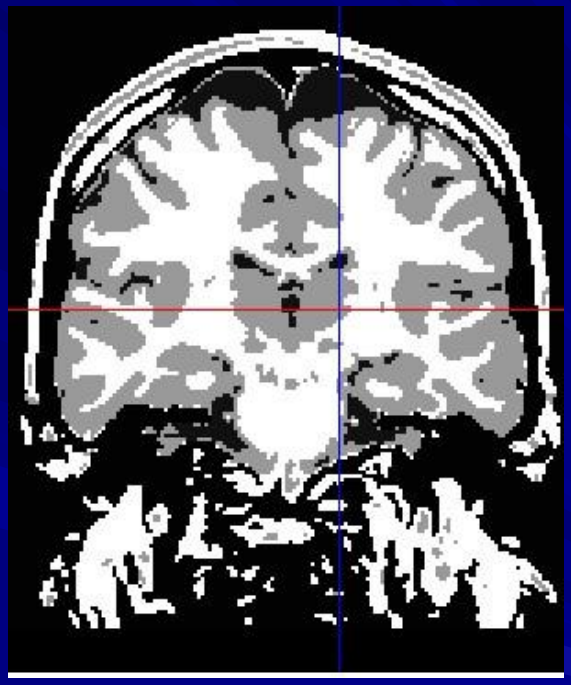
A Neurodevelopmental Disorder: Supporting Evidence from Neuropathology

- Absence of gliosis
- Abnormal cytoarchitecture
- Visible markers of neurodevelopmental abnormalities such as cavum septi pellucidi

Classified Images



Continuous



Discrete

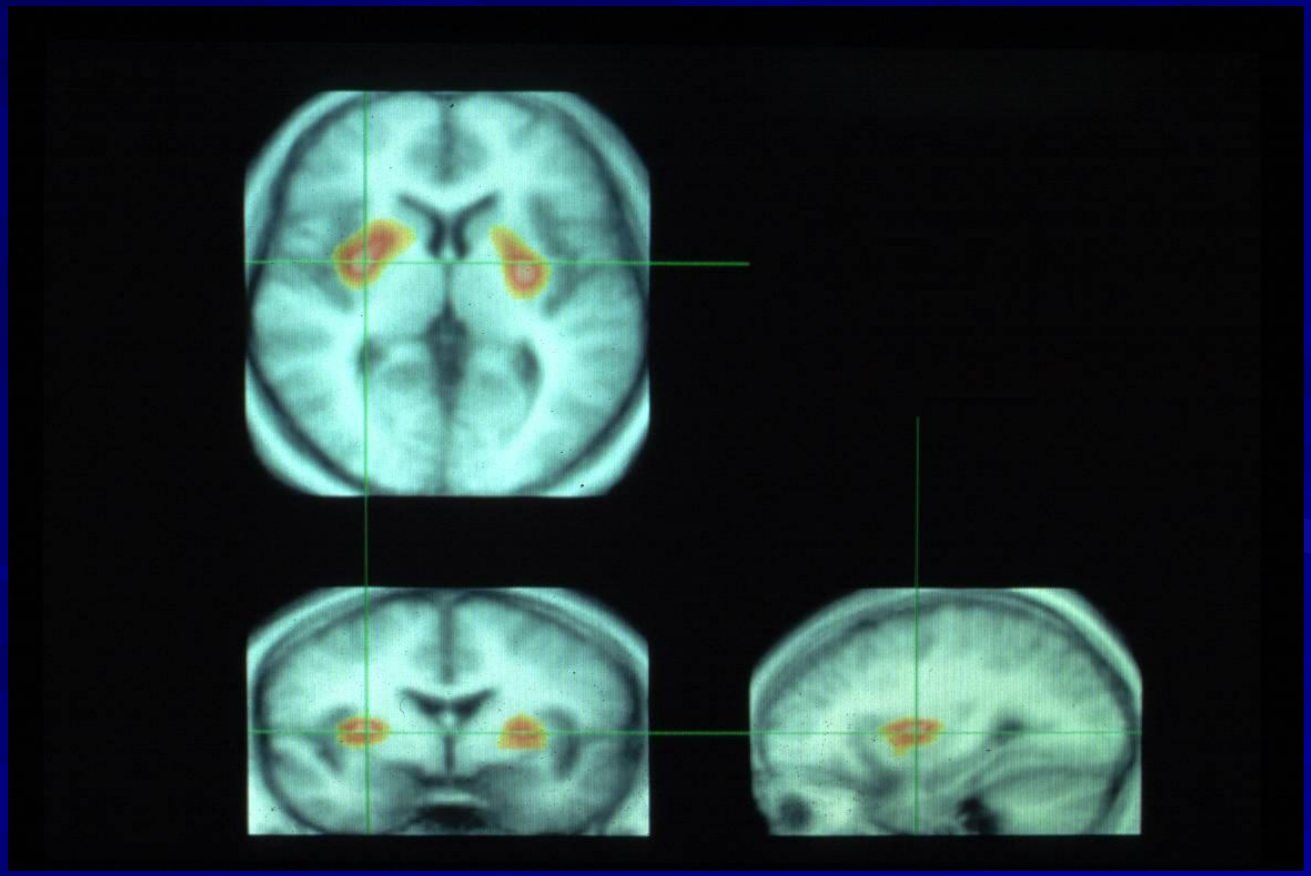
MR Studies: Brain Abnormalities

- Decreased temporal lobe size
- Decreased frontal lobe size
- Decreased hippocampal size
- Decreased thalamic size
- Gyral decreases (superior temporal gyrus, ventral frontal gyri)
- General and regional decreases in gray matter volume

A Neurodevelopmental Brain Disease

- Most brain abnormalities are present at onset: e.g., decrease in total brain tissue
- Occasional evidence of defects in neuronal migration: gray matter heterotopias
- Midline abnormalities: cavum septi pellucidi, dysgenesis of the corpus callosum, ventricular enlargement

Increased Blood Flow in Striatum due to Chronic Dopamine Blockade by Haloperidol



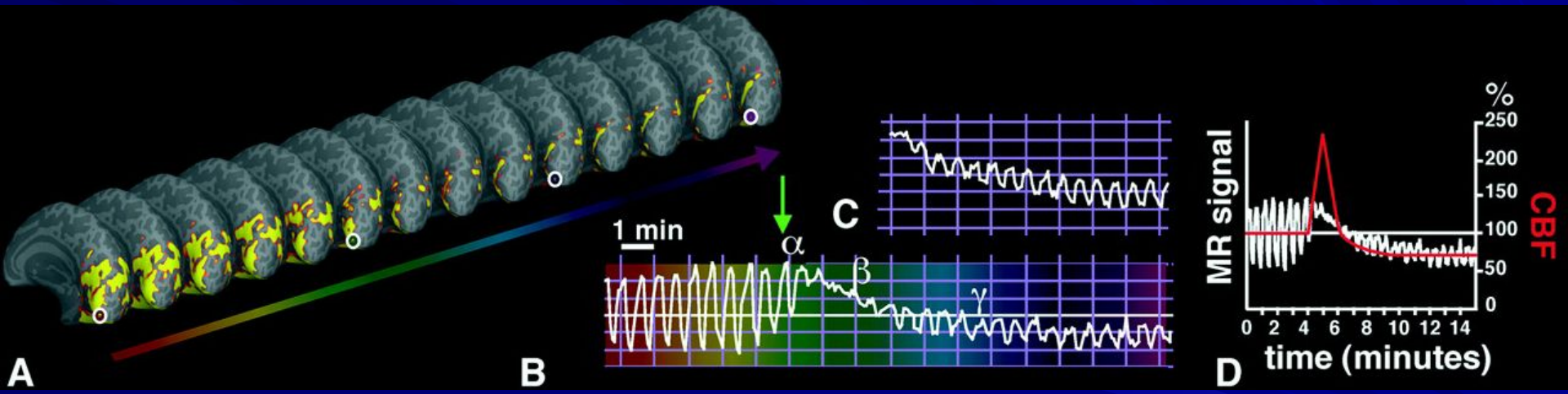
Functional Imaging Tools

- Single Photon Emission Computed Tomography (SPECT)
- Positron Emission Tomography (PET)
- Functional Magnetic Resonance (fMR)

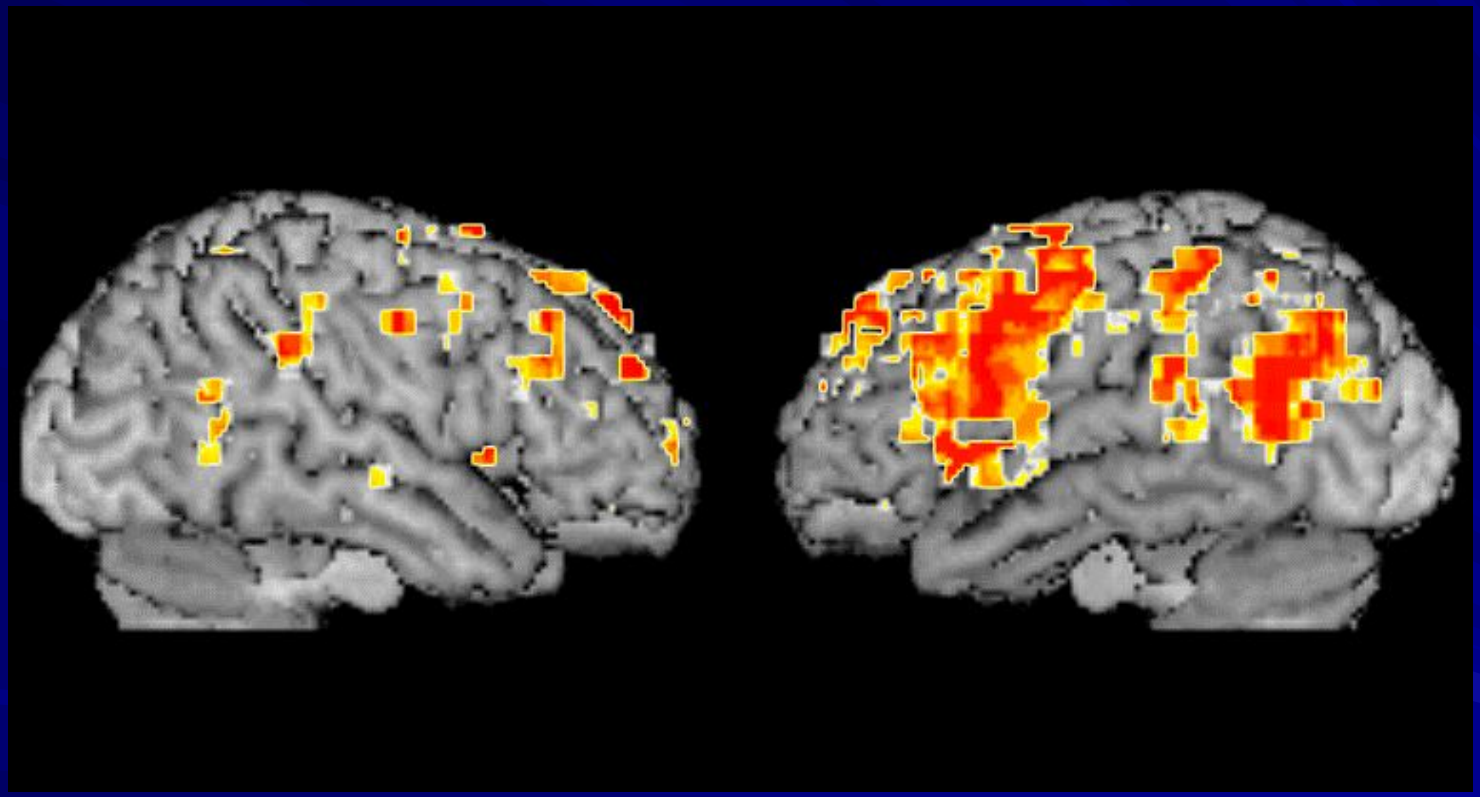
Conclusions from PET Studies

- Schizophrenia is not a disease of a single brain region
- Areas of abnormality vary depending on the task and the nature of current symptoms
- Schizophrenia affects distributed circuitry throughout the brain

The fMR Blood Flow Signal



Verbal Fluency

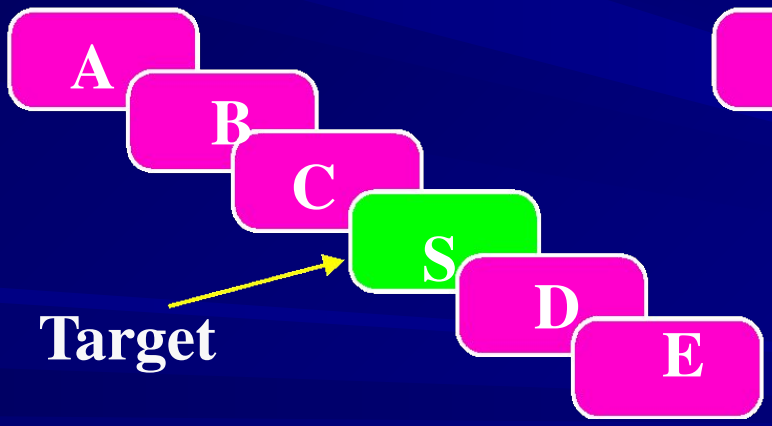


Patients **Controls**

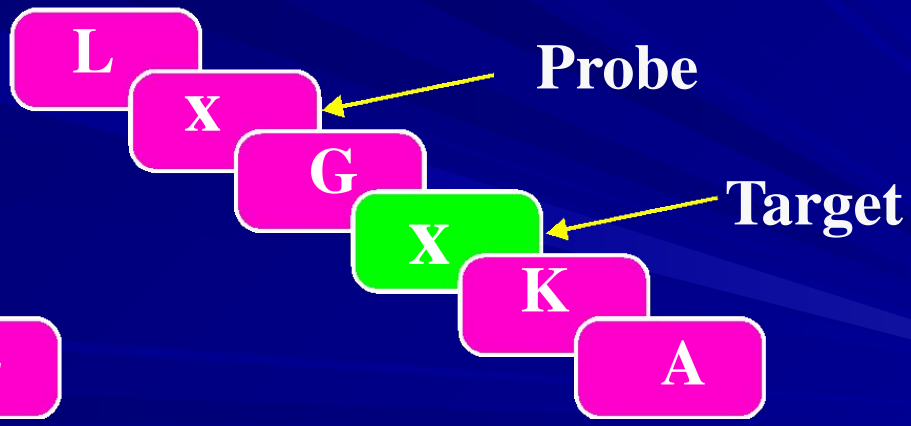
The N-Back Task for fMR

Experimental Task (2-Back): Remember the Probe and Monitor for It

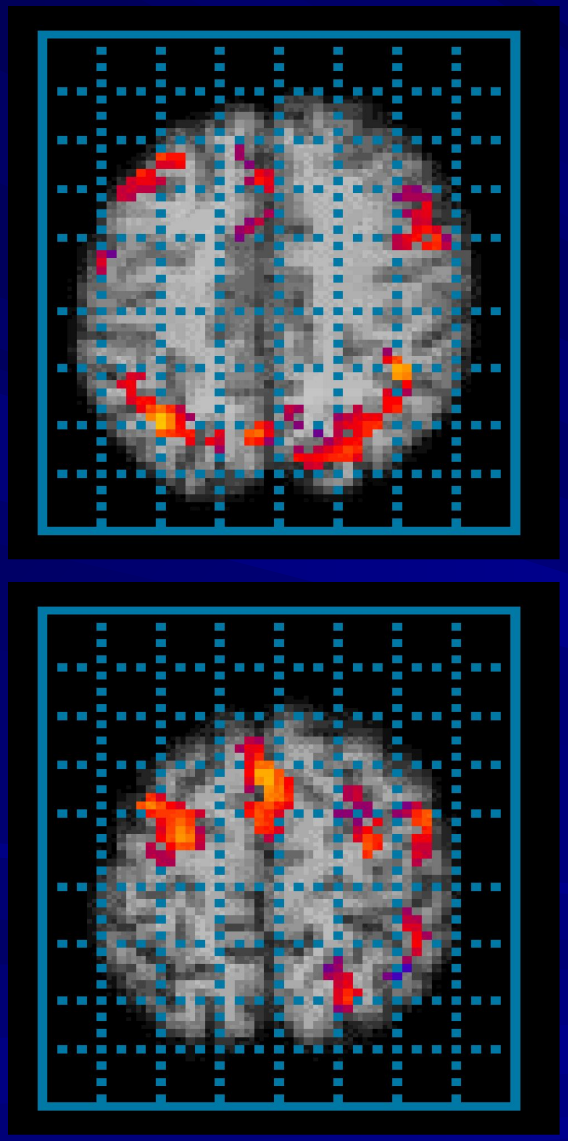
Look for the S



2-Back Task

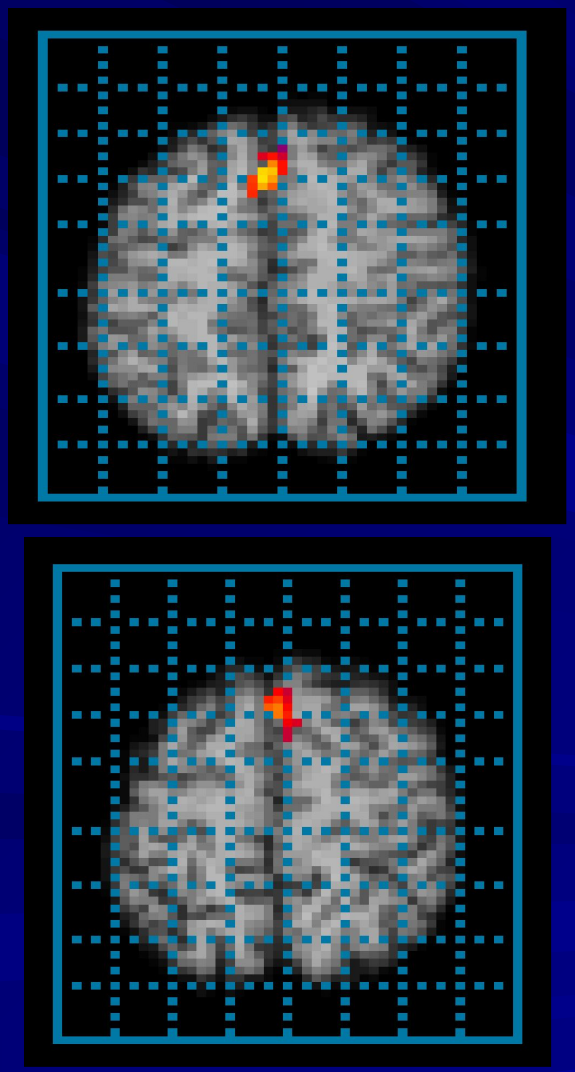


2-Back Task in Normals



- Bilateral dorsolateral frontal
- Bilateral parietal
- Anterior cingulate

2-Back Task in Schizophrenia (unmedicated)



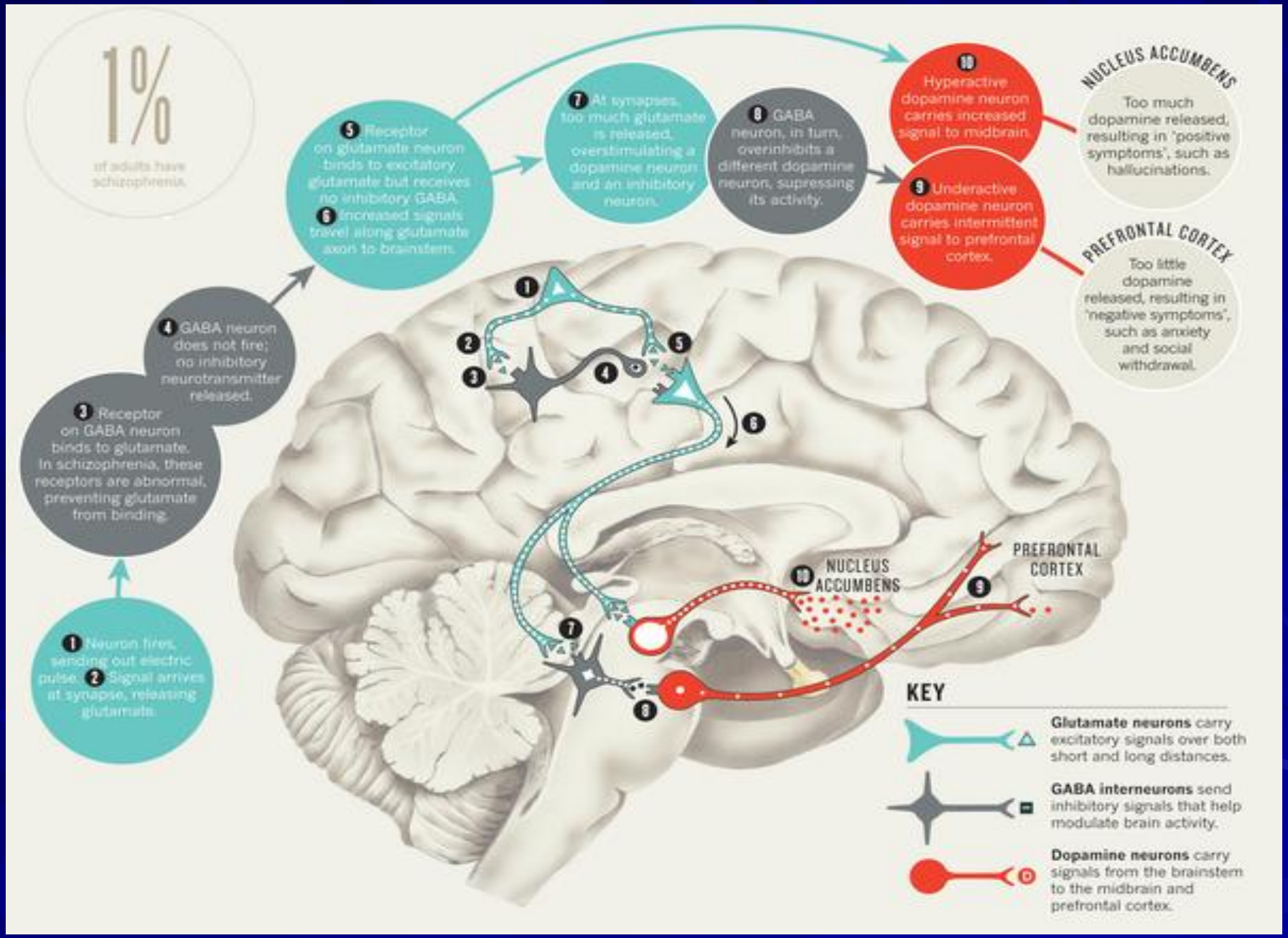
- Blood flow markedly decreased or absent in regions used by normals
- Main activation is anterior cingulate

Sensory Gating

- A problem in filtering or gating information
- Leads to the subject experience of being bombarded by stimuli
- Explains most symptoms—e.g., confusion of internal and external stimuli would cause delusions and hallucinations
- Supported by neurophysiological studies of prepulse inhibition

Cognitive Dysmetria

- A defect in coordinating mental activity
- Due to disturbed functional connectivity between the cortex and subcortical regions (thalamus and cerebellum)
- Leads to functional and cognitive misconnections
- Explains diversity of symptoms (e.g., misconnecting a perception and its meaning might lead to delusions and hallucinations)
- Supported by functional imaging studies


1%
of adults have schizophrenia.
1 Neuron fires, sending out electric pulse. 2 Signal arrives at synapse, releasing glutamate.
3 Receptor on GABA neuron binds to glutamate. In schizophrenia, these receptors are abnormal, preventing glutamate from binding.
4 GABA neuron does not fire; no inhibitory neurotransmitter released.
5 Receptor on glutamate neuron binds to excitatory glutamate but receives no inhibitory GABA.
6 Increased signals travel along glutamate axon to brainstem.
7 At synapses, too much glutamate is released, overstimulating a dopamine neuron and an inhibitory neuron.
8 GABA neuron, in turn, overinhibits a different dopamine neuron, supressing its activity.
10 Hyperactive dopamine neuron carries increased signal to midbrain.
9 Underactive dopamine neuron carries intermittent signal to prefrontal cortex.
NUCLEUS ACCUMBENS
Too much dopamine released, resulting in 'positive symptoms', such as hallucinations.
PREFRONTAL CORTEX
Too little dopamine released, resulting in 'negative symptoms', such as anxiety and social withdrawal.
NUCLEUS ACCUMBENS
PREFRONTAL CORTEX
KEY
Glutamate neurons carry excitatory signals over both short and long distances.
GABA interneurons send inhibitory signals that help modulate brain activity.
Dopamine neurons carry signals from the brainstem to the midbrain and prefrontal cortex.

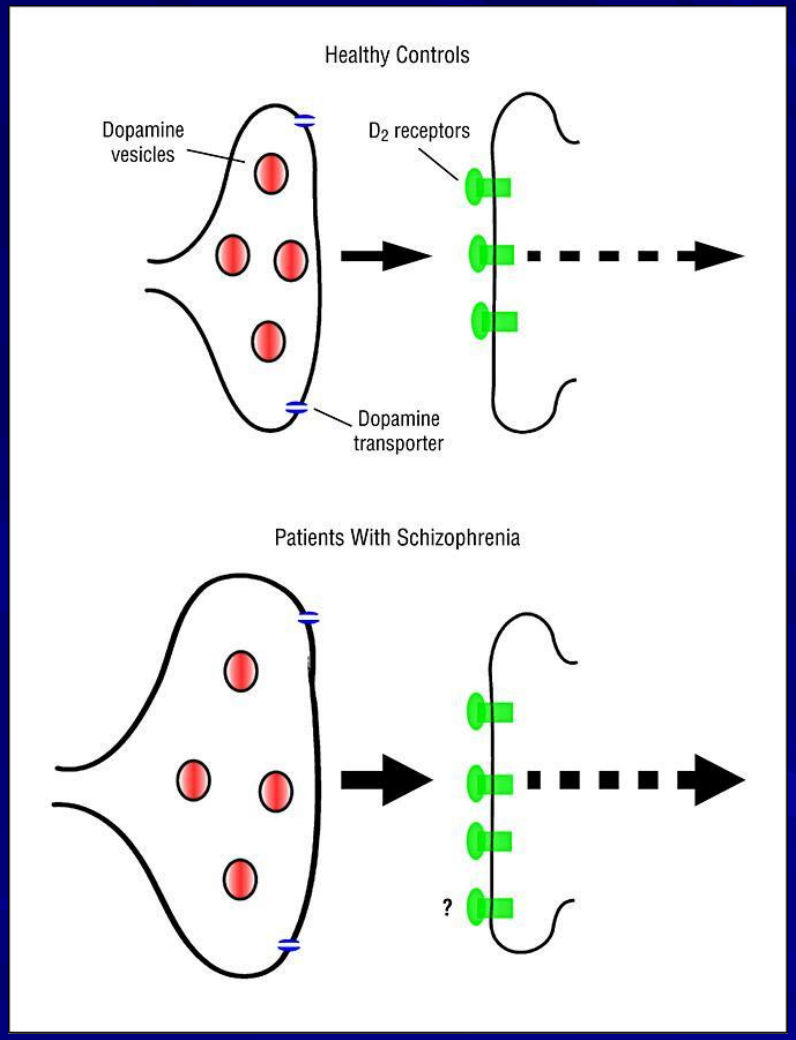
Simplified Summary of Various Anatomical Refinements of the Dopamine Hypotheses of Schizophrenia

Region	DLPFC	VST	AST
Classical Hypothesis (1960–1990)	–	Increased DA (associated with psychosis)	Normal DA
First Revision (1990–2010)	Decreased DA (associated with cognitive impairment)	Increased DA (associated with psychosis)	Normal DA
Second Revision (2010–?)	Decreased DA (associated with cognitive impairment)	Normal to Decreased (associated with negative symptoms)	Increased DA (associated with psychosis)

AST, associative striatum; DA, dopamine; DLPFC, dorsolateral prefrontal cortex; VST, ventral striatum

Laruelle, Biol psychiatry 2013;74:80–81

Schematic diagram summarizing the findings from our meta-analyses of dopamine function in schizophrenia



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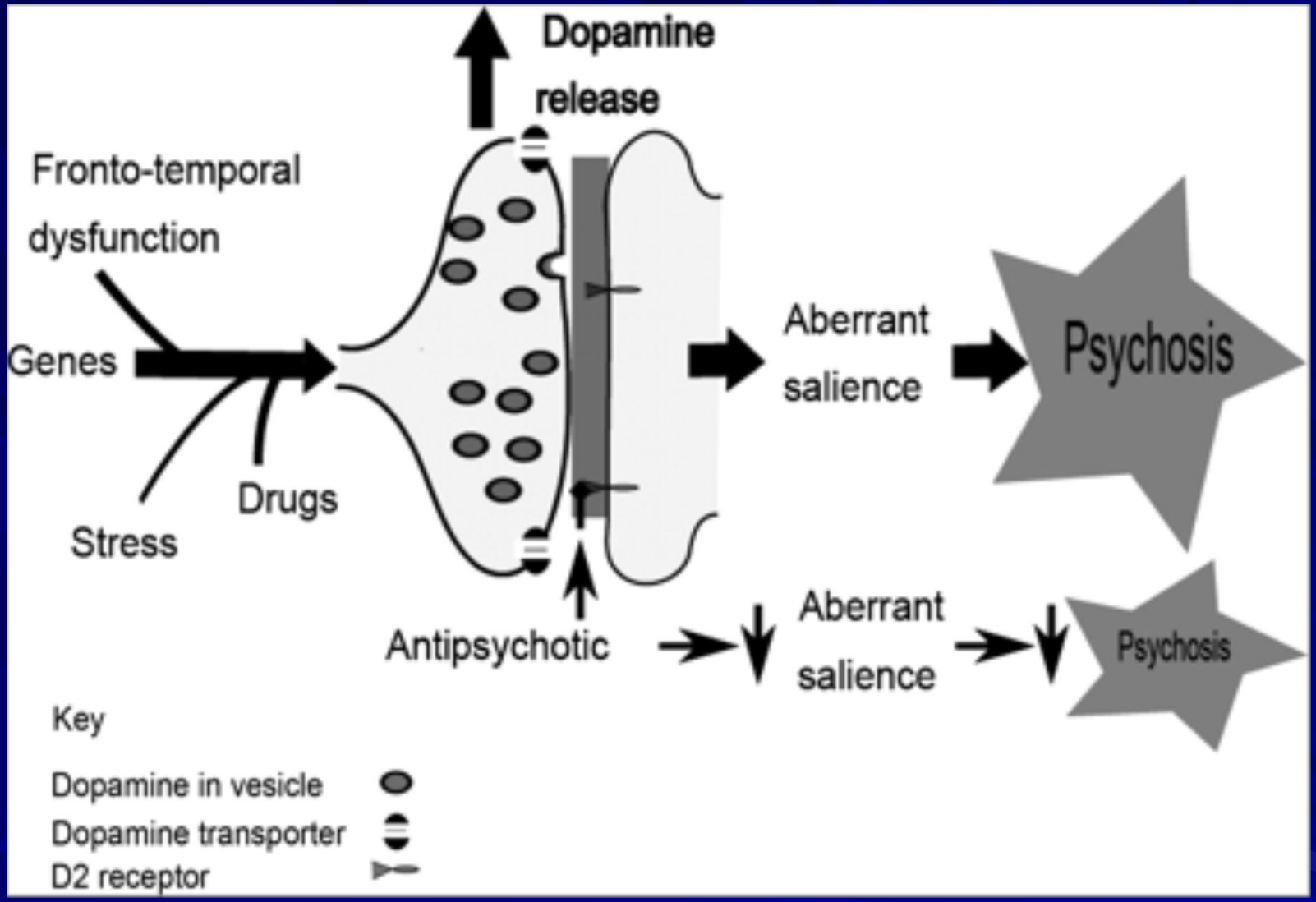


Multiple hits interact to result in (1) striatal dopamine dysregulation to alter (2) the appraisal of stimuli and resulting in psychosis, whilst current antipsychotic drugs (3) act downstream of the primary dopaminergic dysregulation.

	Schizophrenia	Bipolar disorder
Family studies	Shared inheritance	Shared inheritance
Genetics	Shared common variants (SNPs); more CNVs	Shared common variants (SNPs
Age-at-onset	Adolescence/early adulthood	Adolescence/early adulthood
Male/Female	Age-at-onset 2.5y earlier in men	Earlier in men
Social-economic status	Low	High
IQ	Low	High
Obstetric complications	Yes	No
Excess of winter/spring birth	Yes	No
Early childhood trauma	Yes	No

	Schizophrenia	Bipolar disorder
Urban upbringing	Yes	No
Migration	Yes	No
Cannabis	More	Less
Advanced parental age	Yes	No
Reproductive output	Low	Normal
Brain structural abnormalities	More severe; present in premorbid/prodro-mal phases	Less prominent
Cognitive dysfunction	Generalized deficit; presents in prodrome	Less severe

The Essence of Schizophrenia

- Originally called “dementia praecox”
- Produces severe incapacity – “dementia”
- Typically begins in adolescence – “praecox”

Kraepelin: Course and Outcome

- Split “dementia praecox” from manic-depressive illness
- Early onset
- Marked deterioration
- Chronic course
- Diversity of signs and symptoms
- Importance of volition and affect

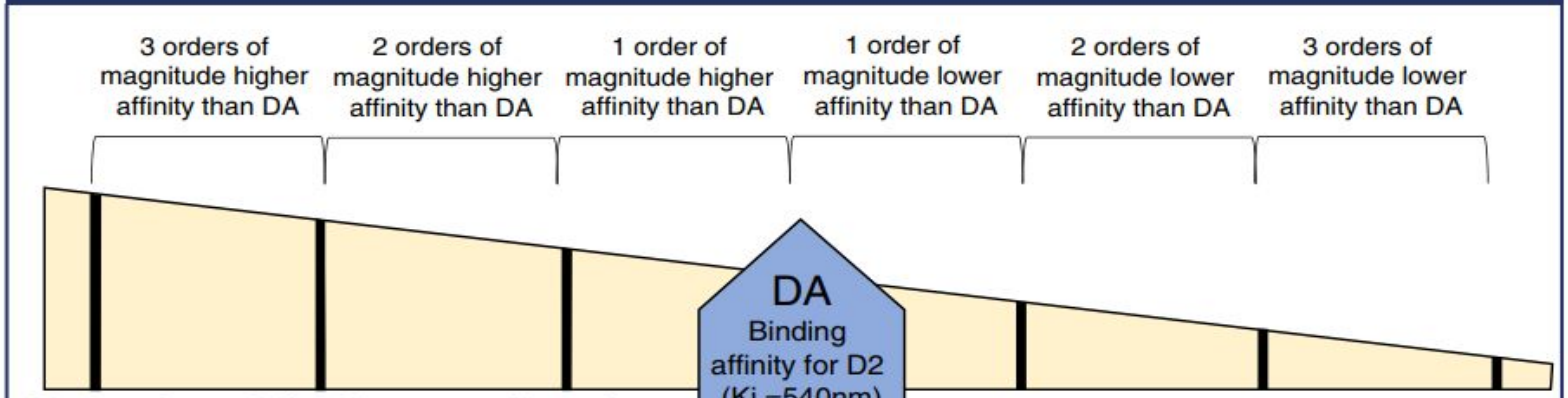
Fundamental Questions about Schizophrenia

- What are the characteristic symptoms?
- What are the boundaries of the concept?
- Is the disorder a single illness or multiple disorders?
- If multiple, what are the subtypes?

Lifetime Prevalence

- What proportion of the population will develop the disorder at some time during their lifetime?
- Perhaps the most important statistic for schizophrenia because of its inherent chronicity
- Prevalence **0.30-0.66%** - narrow diagnostic category of schizophrenia
- Prevalence **2.3%** - schizophrenia and related psychoses (e.g., delusional, catch-all category of NOS)
- Prevalence **3.5%** - broader category of psychotic disorders including schizophrenia and related disorders, substance-induced psychotic disorders and bipolar disorder

Figure 4. This figure shows the relative affinities of drugs for psychosis and mood for D2 receptors compared to the affinity of dopamine itself for D2 receptors. All agents have equal or higher affinity for the D2 receptor than does dopamine itself. Many agents have higher or much higher affinities for D2 compared to dopamine.



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Clozapine binding affinity for D2 (147nM)

Quetiapine binding affinity for D2 (437nM)

Figure 5. This figure shows the relative affinities of drugs for psychosis and mood for D3 receptors compared to the affinity of dopamine itself for D3 receptors. All but 2 agents have affinities for D3 within 1 order of magnitude higher or lower than does dopamine itself. One agent has very much higher affinity for D3 than does dopamine, namely cariprazine; 1 agent has somewhat higher affinity, namely blonanserin.

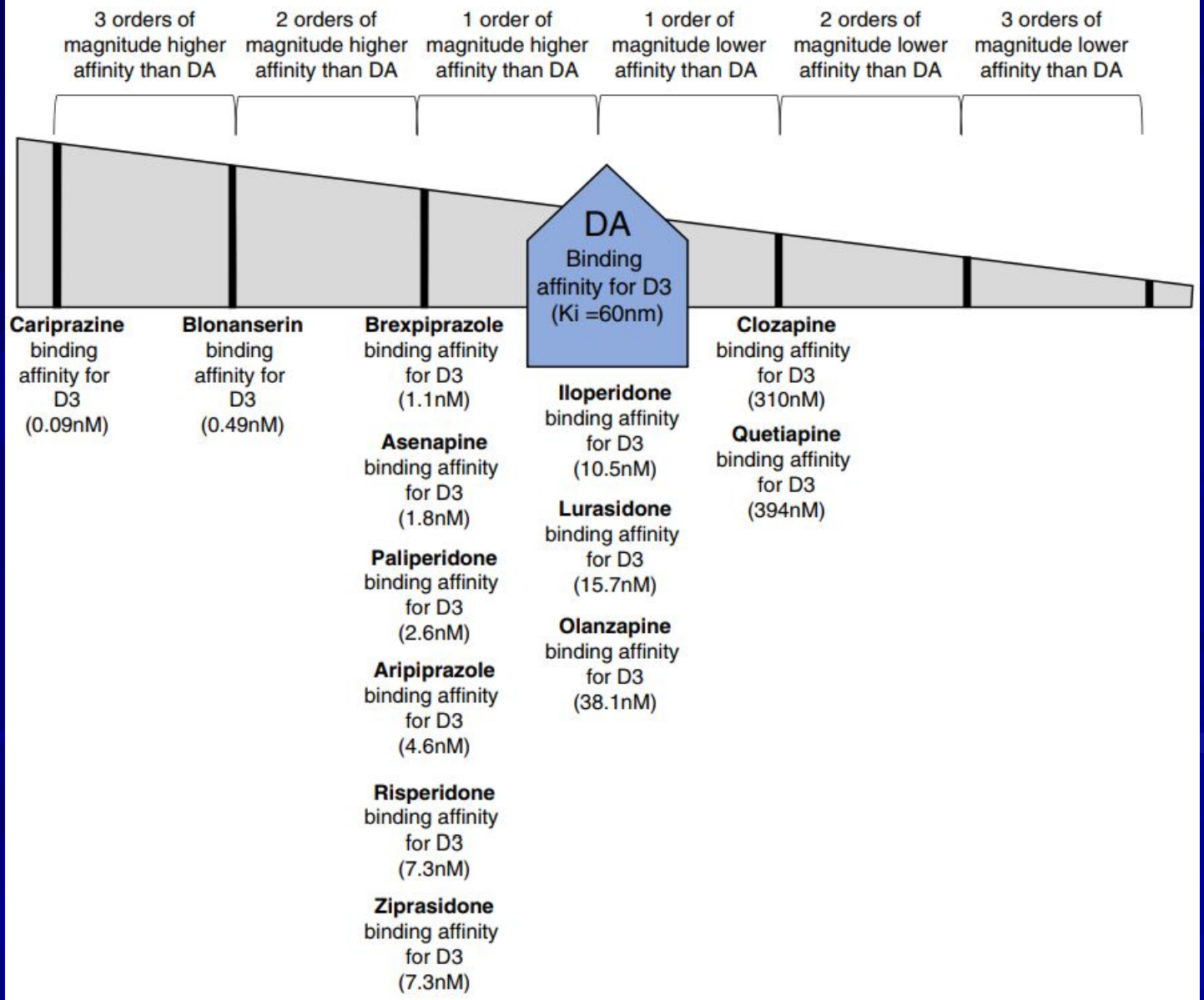


Figure 3. This figure shows the relative affinities of drugs for psychosis and mood for D1 receptors compared to the affinity of dopamine itself for D1 receptors. All agents have equal or higher affinity for the D1 receptor than does dopamine itself.

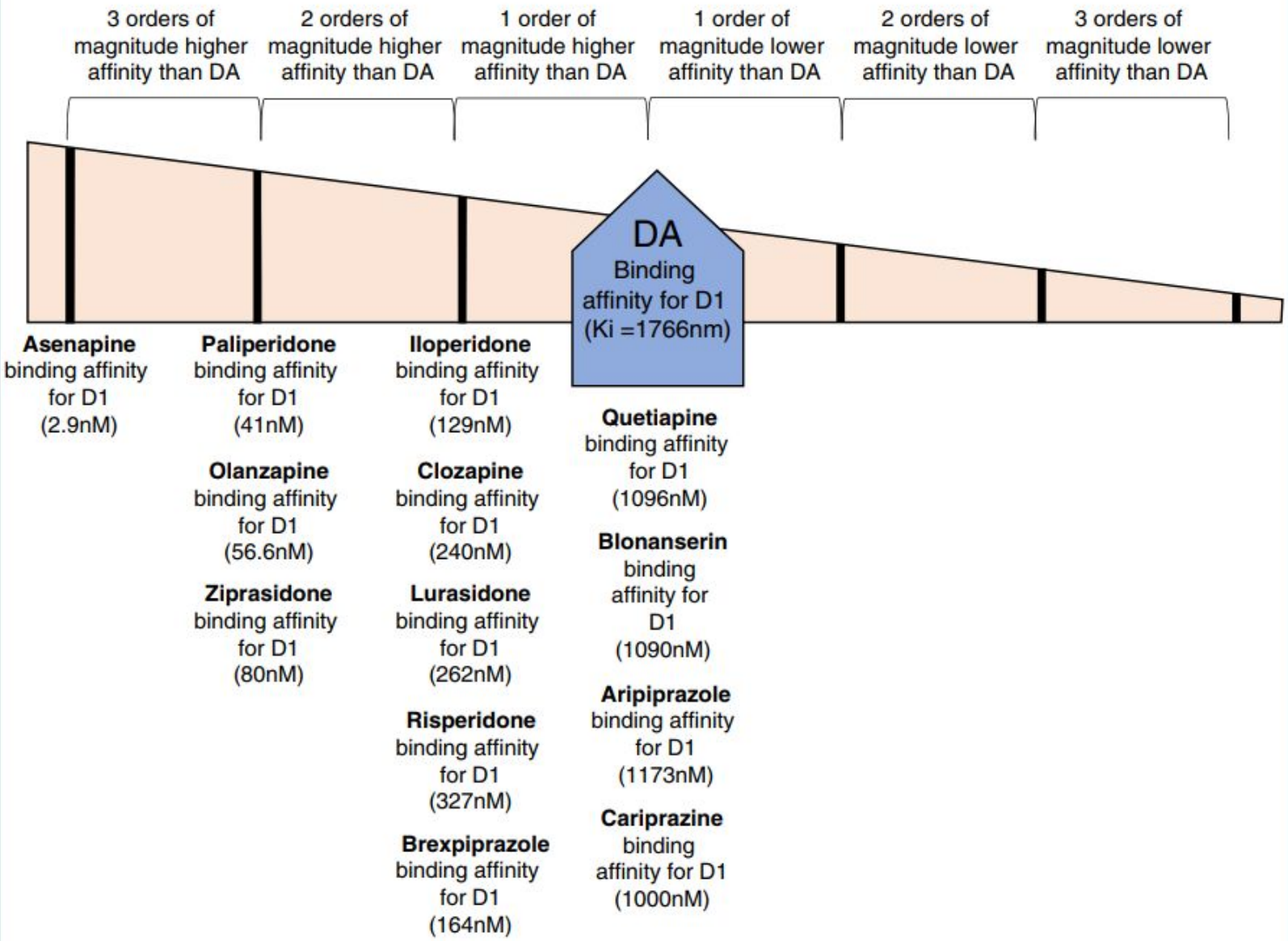


Figure 7. Antagonist/partial agonist effects at D2 dopamine receptors are illustrated here. These are well-known antipsychotic actions at D2 receptors in the nucleus accumbens, and also motor side effects at D2 receptors in the motor striatum.

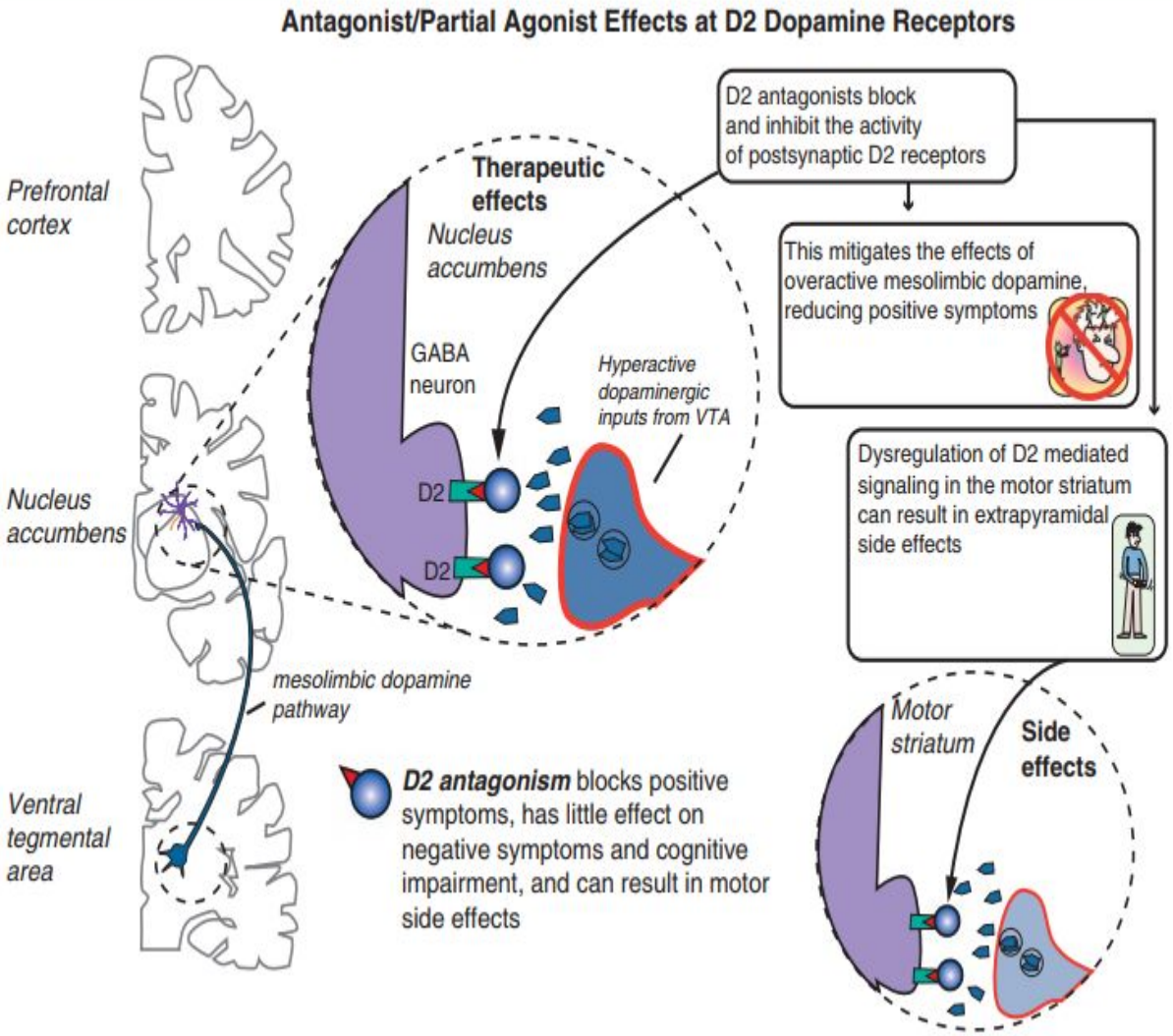


Figure 8. Antagonist/partial agonist effects at D3 receptors are illustrated here. Theoretically, D3 actions disinhibit dopamine release in the prefrontal cortex, which could improve negative symptoms, cognition, and mood.

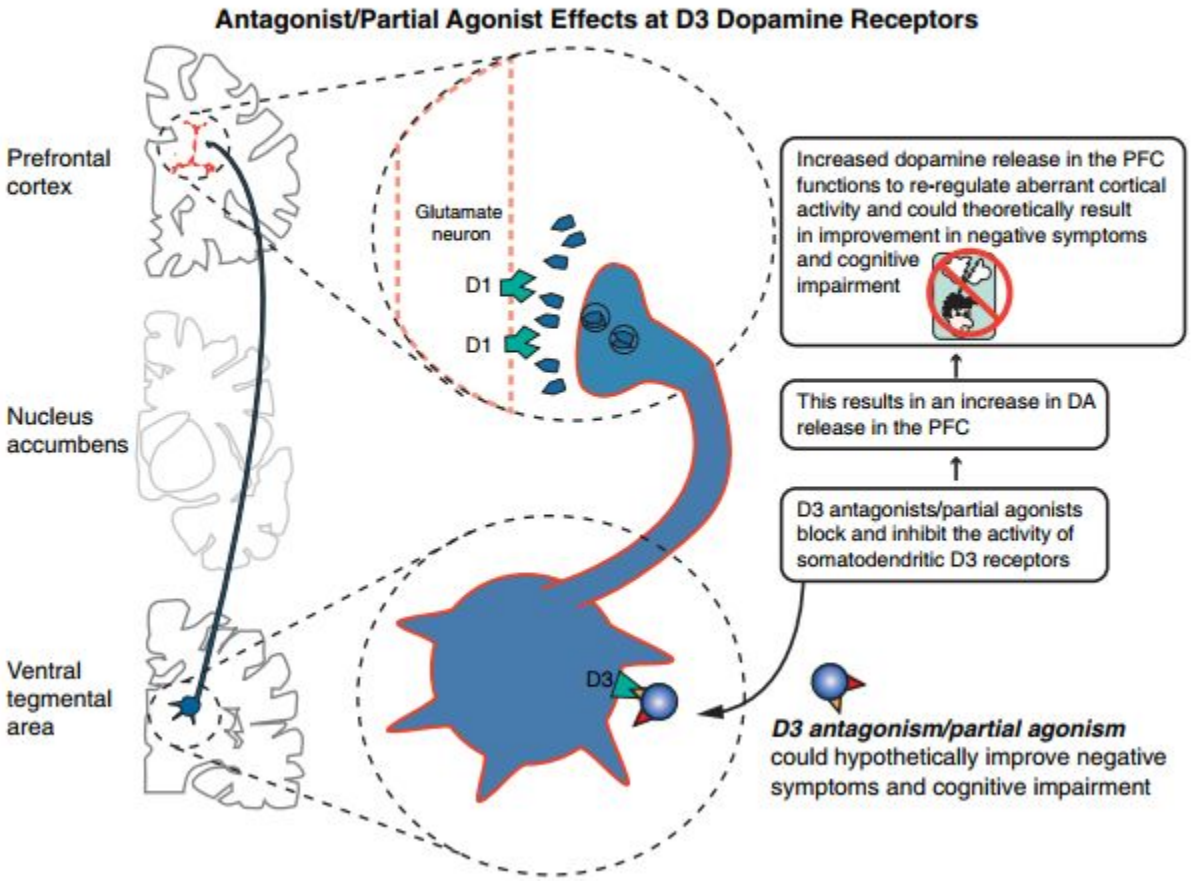
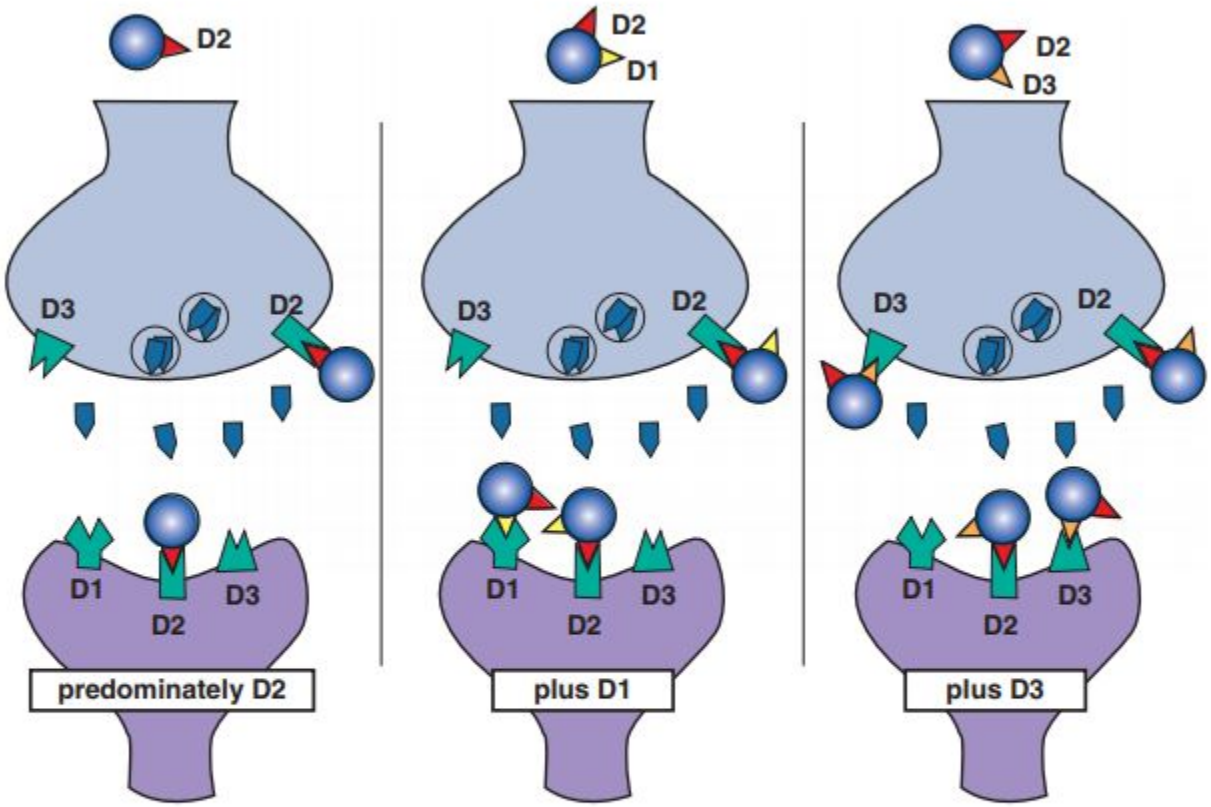


Figure 9. Three classes of drugs that bind to dopamine receptors. Eight agents bind predominantly to D2 receptors alone, 3 agents bind as well to D1 receptors, and 2 agents bind D3 receptors as well as D2 receptors.



brexpiprazole
paliperidone
aripiprazole
risperidone
ziprasidone
iloperidone
lurasidone
quetiapine

asenapine
olanzapine
clozapine

cariprazine
blonanserin

Figure 6. Antagonist effects at D1 dopamine receptors are illustrated here. These include reducing dopamine neurotransmission in the prefrontal cortex, and theoretically causing cognitive dysfunction by "de-tuning" D1 receptor activity.