

Neurobiology of Schizophrenia and Mood Disorders

This chapter introduces the neurobiology that is thought to underlie the symptoms of schizophrenia. The dopamine hypothesis of schizophrenia has been accepted for a long time, especially as the first antipsychotics were shown to block dopamine D2 receptors. This theory posits that dopamine is overactive in some brain areas, and underactive in other brain areas. This chapter shows that it might be more accurate to say that dopamine is neither "too high" nor "too low" but "out of tune." In addition, ideas about the involvement of glutamate and serotonin have gained momentum in the pathophysiology of schizophrenia, and this chapter aims to give an overview of how these three neurotransmitter systems may come together to induce both the positive and negative symptoms of schizophrenia.

As various antipsychotics have been used in the treatment of mood disorders, this chapter will also go through the hypothetical neurobiology of disorders, such as mania and depression. Beside dopamine and serotonin, norepinephrine is also one of the main players in mood disorders, and will therefore be discussed here.

This brief neurobiological overview of the neurotransmitter systems impacted by antipsychotics will also aid in understanding the occurrence of side effects of different antipsychotics.

Cambridge University Press

978-0-521-14905-1 - Stahl's Illustrated Antipsychotics: Treating Psychosis, Mania and Depression, Second Edition

Stephen M. Stahl and Laurence Mignon

Excerpt

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— SECTION 1 —

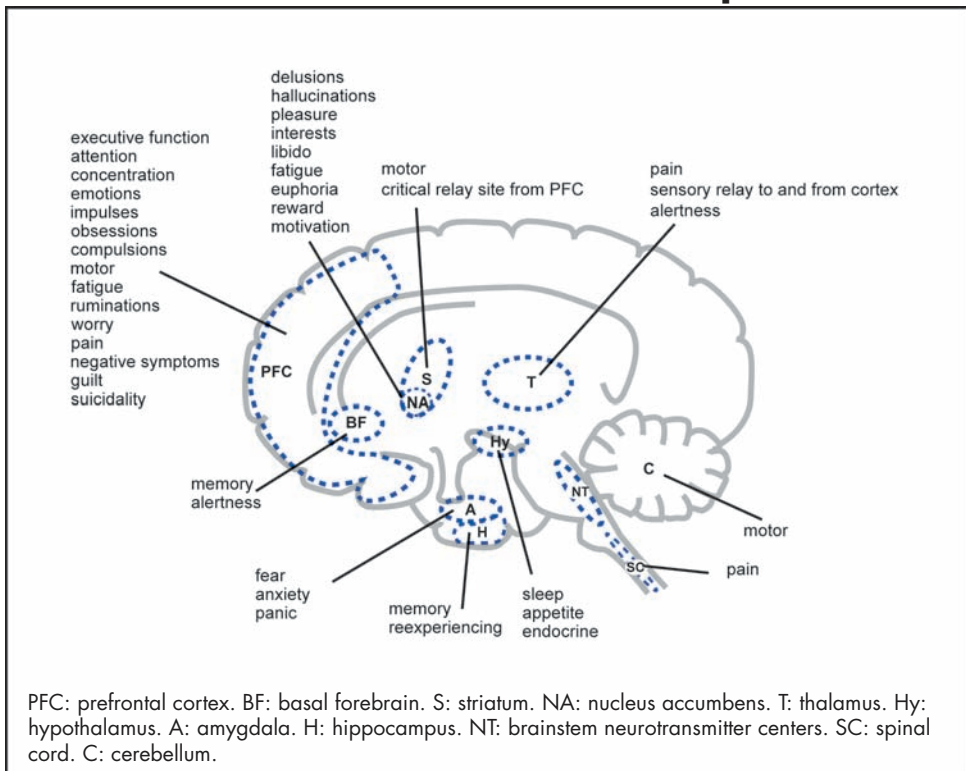
Key Brain Regions and Their Hypothetical Functions: Relevance to Schizophrenia

FIGURE 1.1. Psychiatric disorders hypothetically result from alterations in neurotransmission within different brain regions. A different set of symptoms is unveiled depending on which brain area is functionally impaired.

In schizophrenia, the neurotransmitter dopamine (DA) is theoretically dysregulated, and as a result various brain areas are overactive, underactive, or otherwise “out of tune,” resulting in the generation of positive and negative symptoms.

Key DA Pathways

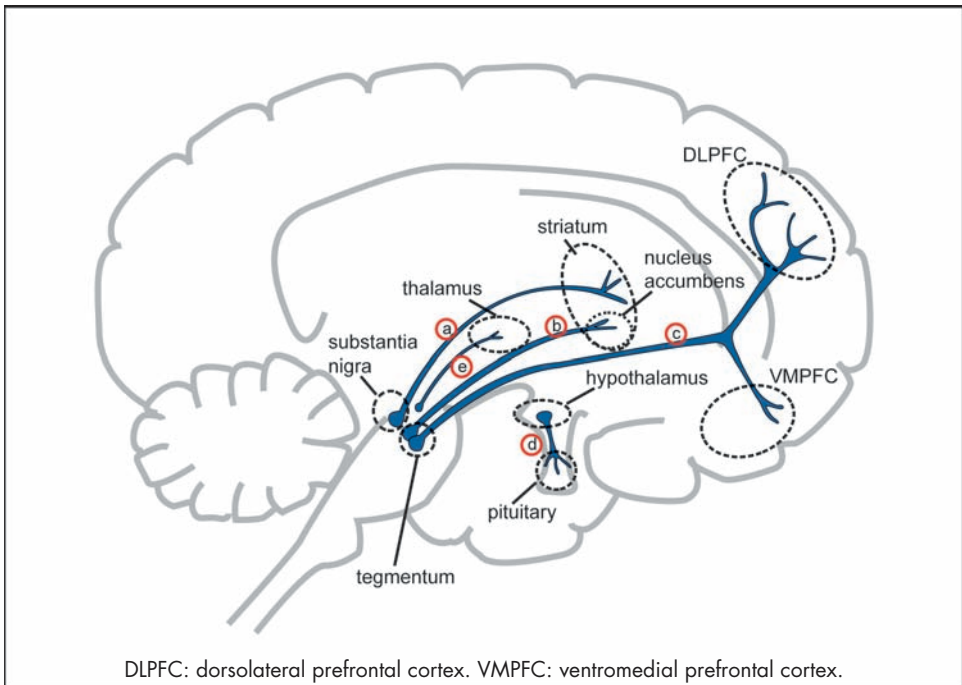


FIGURE 1.2. Five dopamine (DA) pathways are relevant in explaining the symptoms of schizophrenia and the therapeutic and side effects of antipsychotic drugs.

(a) The nigrostriatal DA pathway is part of the extrapyramidal nervous system, which controls motor function and movement.

(b) The mesolimbic DA pathway is part of the brain's limbic system, which regulates behaviors including pleasurable sensations, the powerful euphoria of drugs of abuse, and the delusions and hallucinations seen in psychosis.

(c) The mesocortical DA pathway is implicated in mediating the cognitive symptoms (dorsolateral prefrontal cortex, DLPFC) and affective symptoms (ventromedial prefrontal cortex, VMPFC) of schizophrenia.

(d) The tuberoinfundibular DA pathway projects from the hypothalamus to the anterior pituitary gland and controls prolactin secretion.

(e) The fifth DA pathway arises from multiple sites, including the periaqueductal gray, ventral mesencephalon, hypothalamic nuclei, and lateral parabrachial nucleus and projects to the thalamus. Its function is not well known.

The DA Hypothesis of Schizophrenia: Positive Symptoms

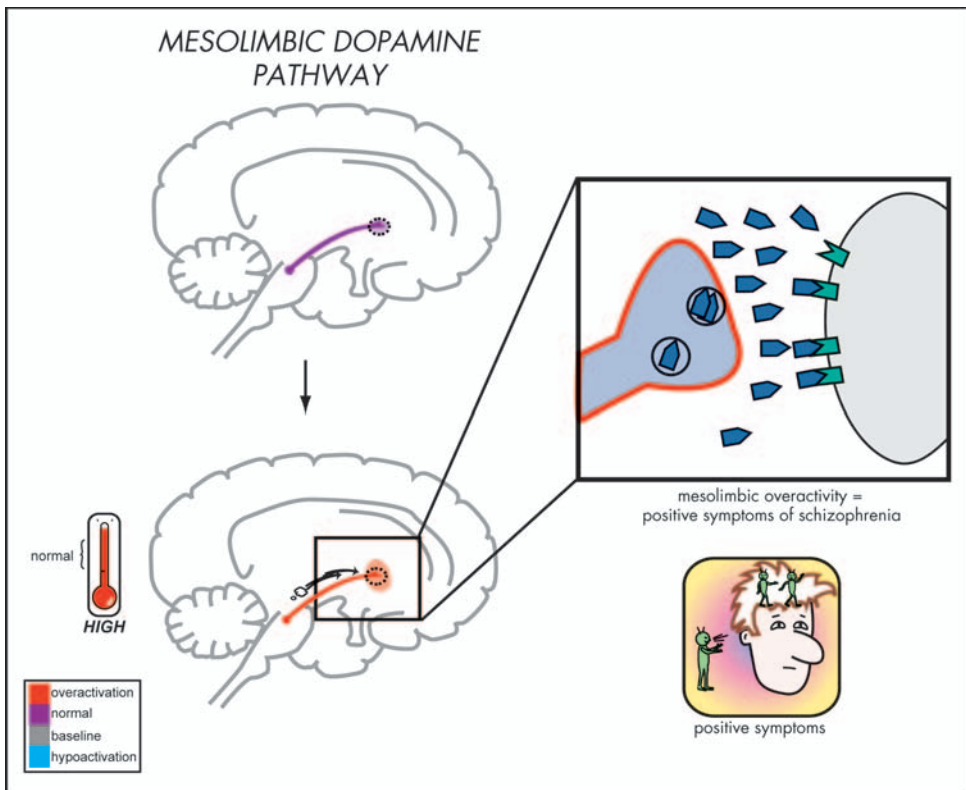


FIGURE 1.3. The mesolimbic DA pathway sends DA projections from cell bodies in the ventral tegmental area to the nucleus accumbens in the ventral striatum. This pathway hypothetically regulates emotional behaviors, pleasure, and reward and is the main candidate thought to regulate the positive symptoms of psychosis.

Specifically, it has been hypothesized that hyperactivity of this pathway accounts for the delusions and hallucinations observed in schizophrenia. This hypothesis is known both as the "DA hypothesis of schizophrenia" and perhaps more precisely as the "mesolimbic DA hyperactivity hypothesis of positive symptoms of schizophrenia."

The DA Hypothesis of Schizophrenia: Negative, Cognitive, and Affective Symptoms

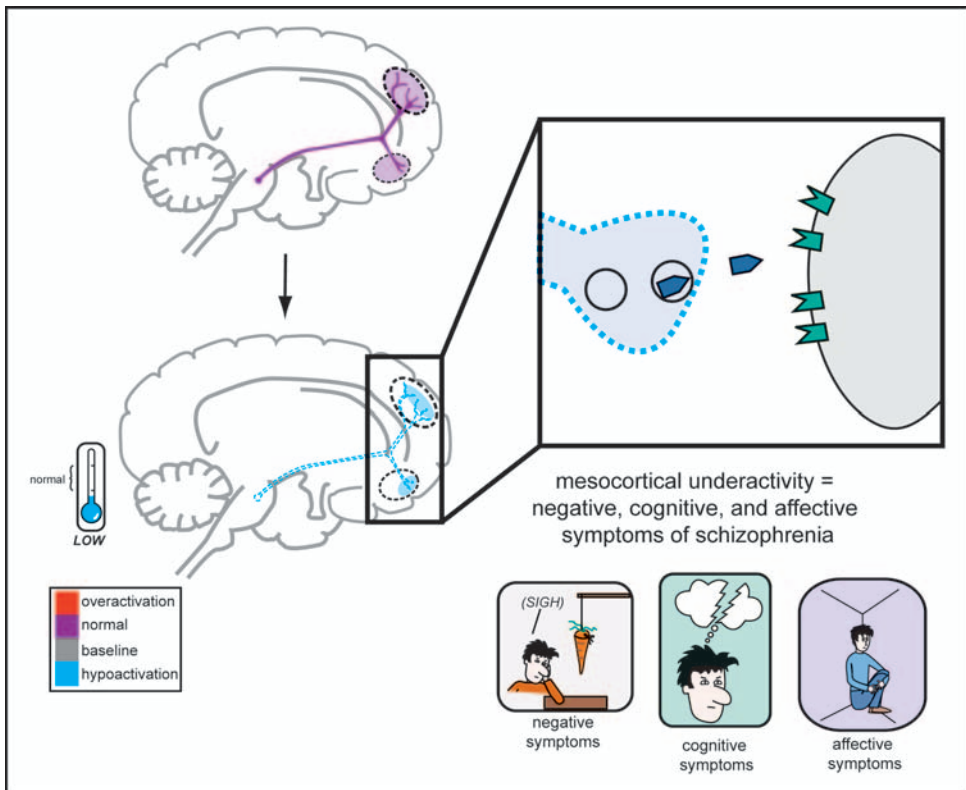


FIGURE 1.4. The mesocortical DA pathway is hypothetically also affected in schizophrenia. Here, DA cell bodies in the ventral tegmental area send projections to the DLPFC to regulate cognition and executive functions, and to the VMPFC to regulate emotions and affect. Hypoactivation of this pathway theoretically results in the negative, cognitive, and affective symptoms seen in schizophrenia. This hypothesis is sometimes called the “mesocortical DA hypothesis of negative, cognitive, and affective symptoms” of schizophrenia.

This DA deficit could result from ongoing degeneration due to glutamate excitotoxicity or from a neurodevelopmental impairment in the glutamatergic system.

Loss of motivation and interest, anhedonia, and lack of pleasure as observed in schizophrenia result not only from a malfunctioning mesocortical DA pathway but also from a deficient mesolimbic DA pathway.

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Additional DA Pathways

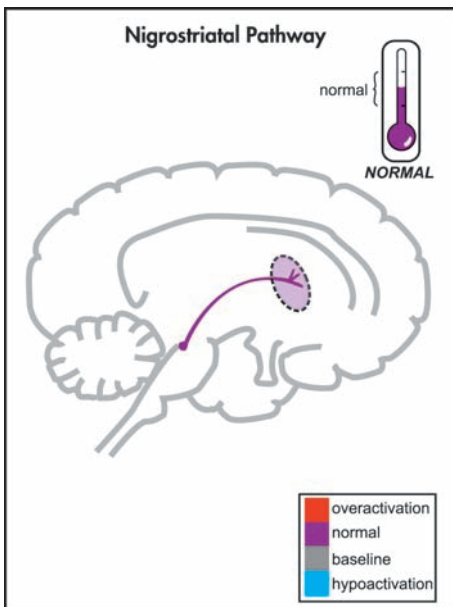


FIGURE 1.5. The nigrostriatal pathway sends DA projections from the substantia nigra to the striatum. This innervation of the basal ganglia regulates motor activity and is part of the extrapyramidal nervous system. A lack of DA here results in symptoms resembling Parkinson's disease, whereas an excess of DA will lead to hyperkinetic movement disorders such as dyskinesias.

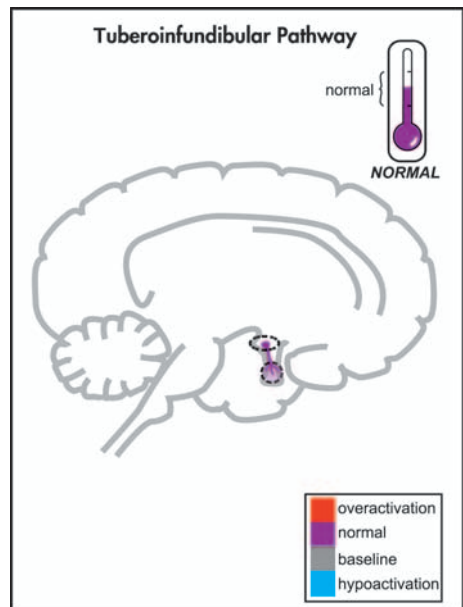


FIGURE 1.6. DA inhibits prolactin secretion via the tuberoinfundibular pathway as DA projections are sent from the hypothalamus to the anterior pituitary.

Although these two pathways are unaffected in schizophrenia, they do play an intricate part in the development of side effects, as they will not remain untouched by drugs interacting with DA neurons throughout the brain.

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The Integrated DA Hypothesis of Schizophrenia

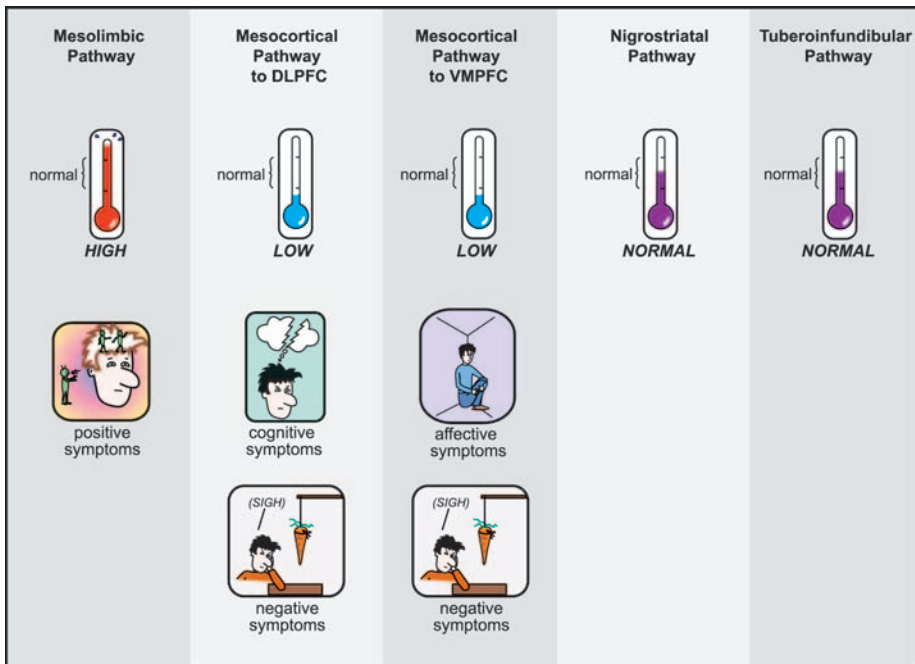


FIGURE 1.7. In schizophrenia, it appears that some DA pathways are overactive, others underactive, and others are functioning normally. Thus the DA system is neither “all too high,” nor “all too low,” but more precisely “out of tune,” and DA needs to be increased in some areas, decreased in others, and left untouched in yet another set of circuits.

Various antipsychotic drugs acting at different receptor subtypes, especially blocking D2 receptors and serotonin 2A (5HT2A) receptors, might lead to that outcome.

Alternatively, regulating DA output by modulating transmitters such as glutamate may prove to be another way to “normalize” or “tune” DA circuits.

Key Glutamate Pathways

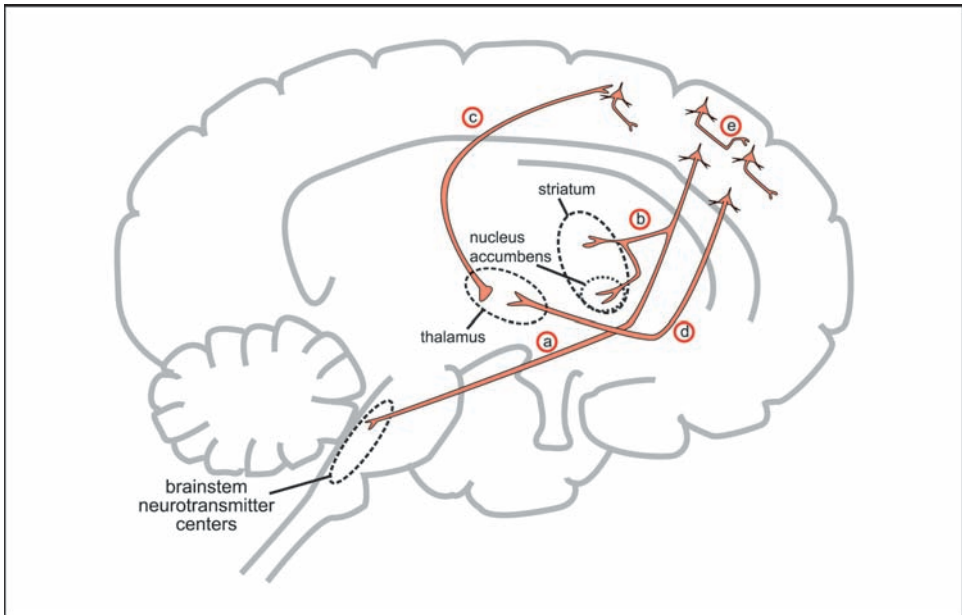


FIGURE 1.8. Similarly to DA, there are five glutamate pathways in the brain that are of particular relevance to schizophrenia.

(a) The cortical brainstem glutamate projection descends from layer 5 pyramidal neurons in the prefrontal cortex (PFC) to brainstem neurotransmitter centers, including the raphe (5HT), the locus coeruleus (norepinephrine), and the ventral tegmental area and substantia nigra (DA). This projection mainly regulates neurotransmitter release in the brainstem.

(b) The cortico-striatal glutamate pathway descends from the PFC to the striatum and the cortico-accumbens glutamate pathway sends projections to the nucleus accumbens. These pathways make up the “cortico-striatal” portion of cortico-striatal-thalamic loops.

(c) Thalamo-cortical glutamate pathways encompass pathways ascending from the thalamus and innervating pyramidal neurons in the cortex.

(d) Cortico-thalamic glutamate pathways descend from the PFC to the thalamus.

(e) The cortico-cortical glutamatergic pathways allow intracortical pyramidal neurons to communicate with each other.

NMDA Receptor Hypofunction Hypothesis of Schizophrenia

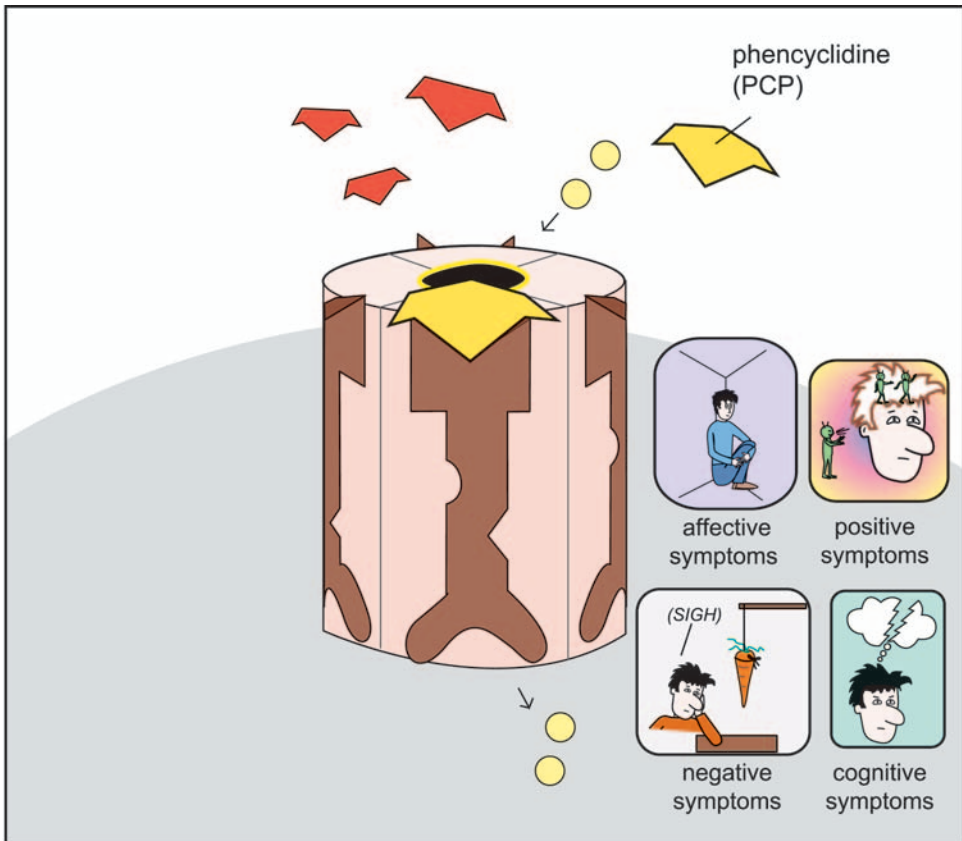


FIGURE 1.9. The NMDA (N-methyl-*D*-aspartate) receptor hypofunction hypothesis has been put forth in an attempt to explain mesolimbic DA hyperactivity. This hypothesis relies on the observation that when normal humans ingest phencyclidine (PCP), an NMDA receptor antagonist, they experience positive symptoms very similar to those observed in schizophrenia such as hallucinations and delusions.

Thus hypoactive glutamate NMDA receptors could theoretically explain the biological basis for the mesolimbic DA hyperactivity. PCP also induces affective symptoms such as blunted affect, negative symptoms such as social withdrawal, and cognitive symptoms such as executive dysfunction in normal humans. Hypofunctional NMDA receptors might therefore be involved in all symptoms of schizophrenia.

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Role of Glutamate in the Mesolimbic System

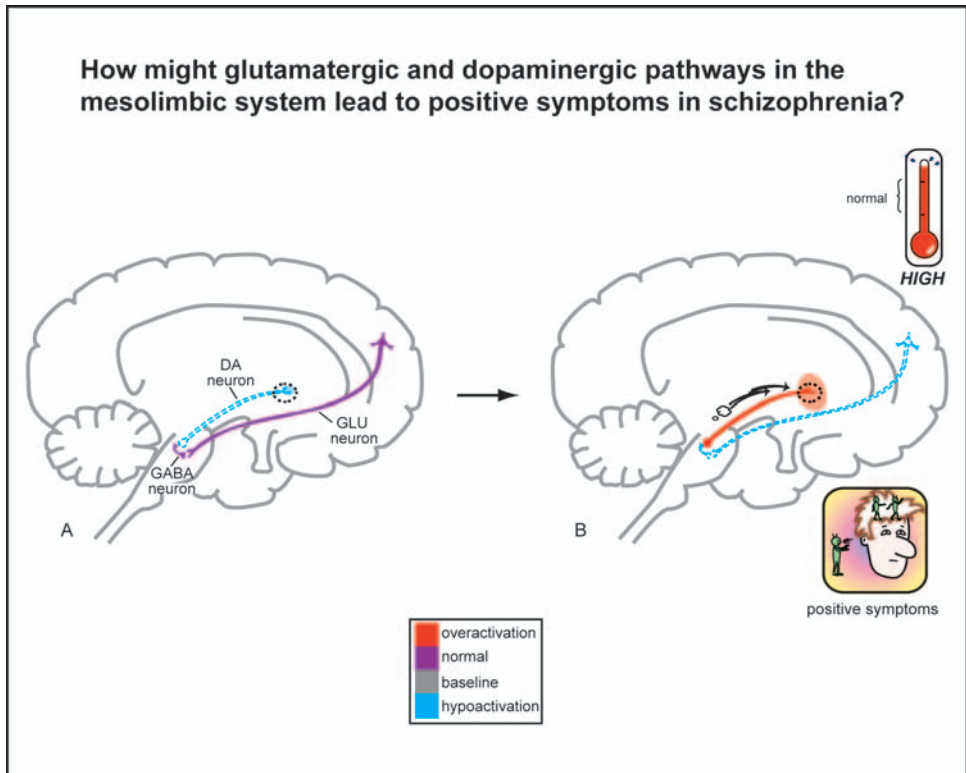


FIGURE 1.10. Various theories have been put forth trying to explain the overactivity of the DA pathway in the mesolimbic system in schizophrenia. The descending cortico-brainstem glutamate pathway normally acts as a brake for the mesolimbic DA pathway, via gamma-aminobutyric acid (GABA) interneurons in the ventral tegmental area, leading to a tonic inhibition of the mesolimbic DA pathway (A). If glutamate projections become hypoactive, this tonic inhibition of the mesolimbic DA pathway will not occur, leading to hyperactivity in the mesolimbic DA pathway (B).