

Beyond the Dopamine Hypothesis to the NMDA Glutamate Receptor Hypofunction Hypothesis of Schizophrenia

By Stephen M. Stahl, MD, PhD

NEW TREND IN PSYCHOPHARMACOLOGY

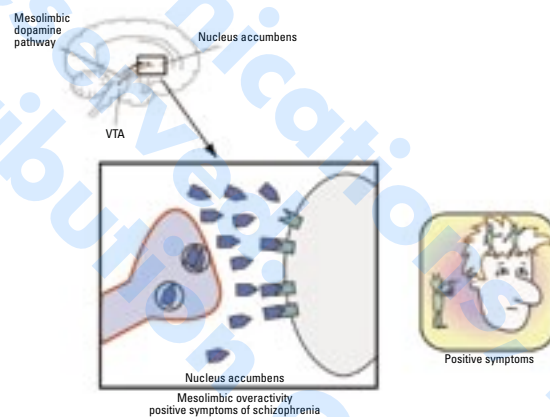
Hypotheses of schizophrenia have progressed beyond the dopamine hypothesis of overactive mesolimbic dopamine neurons, causing the positive symptoms of psychosis and underactive mesocortical dopamine neurons, causing the negative, cognitive and affective symptoms of schizophrenia. A major hypothesis of schizophrenia proposes that numerous genetic risk factors converge on the *N*-methyl-D-aspartate (NMDA) receptor for the neurotransmitter glutamate. Theoretically, neurodevelopmental abnormalities in glutamate synapse formation result in the hypofunction of NMDA receptors. Since NMDA receptors regulate dopamine neurons, the hypofunction of NMDA receptors may be responsible for the abnormal dopamine activity associated with the symptoms of schizophrenia.

For more than 30 years, the dopamine hypothesis has dominated theories of schizophrenia, based initially upon observations that drugs that increase dopamine, such as amphetamine and cocaine, can cause psychosis, whereas antipsychotic drugs that decrease dopamine by blocking dopamine D_2 receptors can treat psychosis.¹ Overactivity in the mesolimbic dopamine pathway is specifically proposed^{1,2} as the mediator of positive symptoms of schizophrenia such as delusions and hallucinations (Figure 1). More recently, underactivity in the mesocortical dopamine pathway is hypothesized^{1,2} to be the mediator of negative, cognitive, and affective symptoms of schizophrenia (Figure 2).

THE NMDA RECEPTOR HYPOFUNCTION HYPOTHESIS OF SCHIZOPHRENIA

A major current hypothesis for schizophrenia arises from observations that phencyclidine (PCP) can produce a psychotic condition very similar to the positive symptoms of schizophrenia, including hallucinations and delusions.²⁻⁴ PCP does this by blocking a type of glutamate receptor known as NMDA,

FIGURE 1.
The mesolimbic dopamine hypothesis of positive symptoms of schizophrenia



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VTA=ventral tegmental area.

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named for the agonist that binds there selectively. This observation has led to the notion that NMDA receptors may be pathologically hypofunctional in untreated schizophrenia, much like the condition produced by the ingestion of PCP.²⁻⁶

An important descending glutamatergic pathway projects from cortical pyramidal neurons to dopamine neurons in the ventral tegmental area (Figure 3A, left panel). This descending cortico-brainstem glutamate pathway normally acts as a brake on the mesolimbic dopamine pathway. It does this by communicating with these dopamine neurons through an inhibitory γ -aminobutyric acid interneuron in the ventral tegmental area (VTA) (Figure 3A, left panel). This normally results in tonic inhibition of dopamine release from the mesolimbic pathway. However, if NMDA receptors in the VTA are hypoactive in untreated schizophrenia, and thus cannot do their job of tonically inhibiting mesolimbic dopamine neurons, this would cause mesolimbic dopamine hyperac-

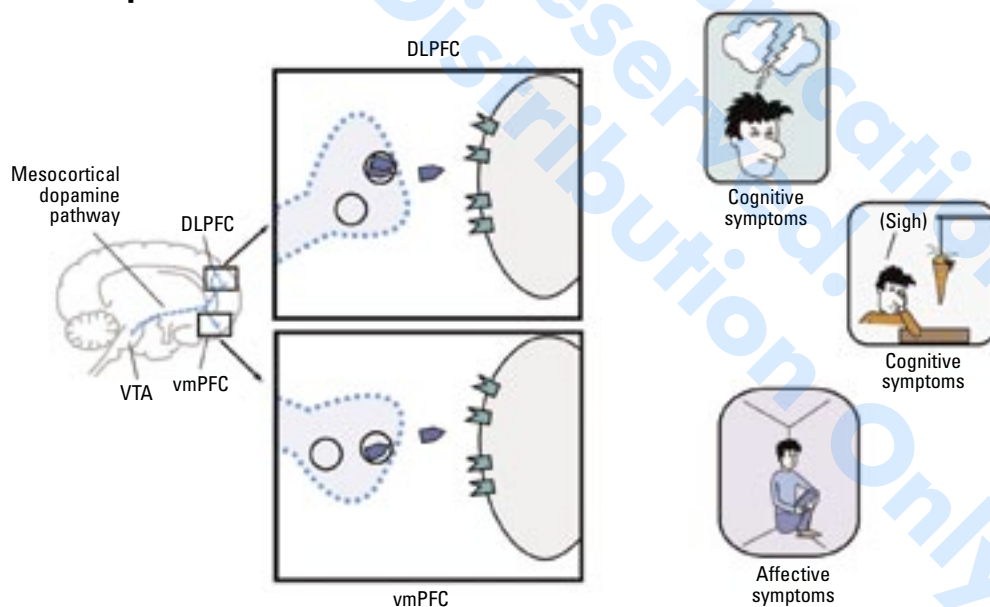
tivity and the positive symptoms of psychosis (Figure 3B, right panel).²⁻⁶

What is so attractive about the NMDA receptor hypofunction hypothesis of schizophrenia is that unlike amphetamine, which activates only positive symptoms, PCP mimics the cognitive, negative and affective symptoms of schizophrenia.²⁻⁴ That is, normal humans who take PCP and render their NMDA receptors hypofunctional not only experience positive symptoms such as delusions and hallucinations but also affective symptoms, such as blunted affect, negative symptoms, such as social withdrawal, and cognitive symptoms, such as executive dysfunction.²⁻⁴ These additional clinical observations have led to the idea that NMDA receptors that regulate mesocortical dopamine pathways may be hypoactive in schizophrenia.²⁻⁶

What would be the clinical consequences of hypofunction of NMDA receptors that regulate mesocortical dopamine neurons? This could possibly explain the negative, cognitive, and

FIGURE 2.

The mesolimbic dopamine hypothesis of cognitive, negative, and affective symptoms of schizophrenia²



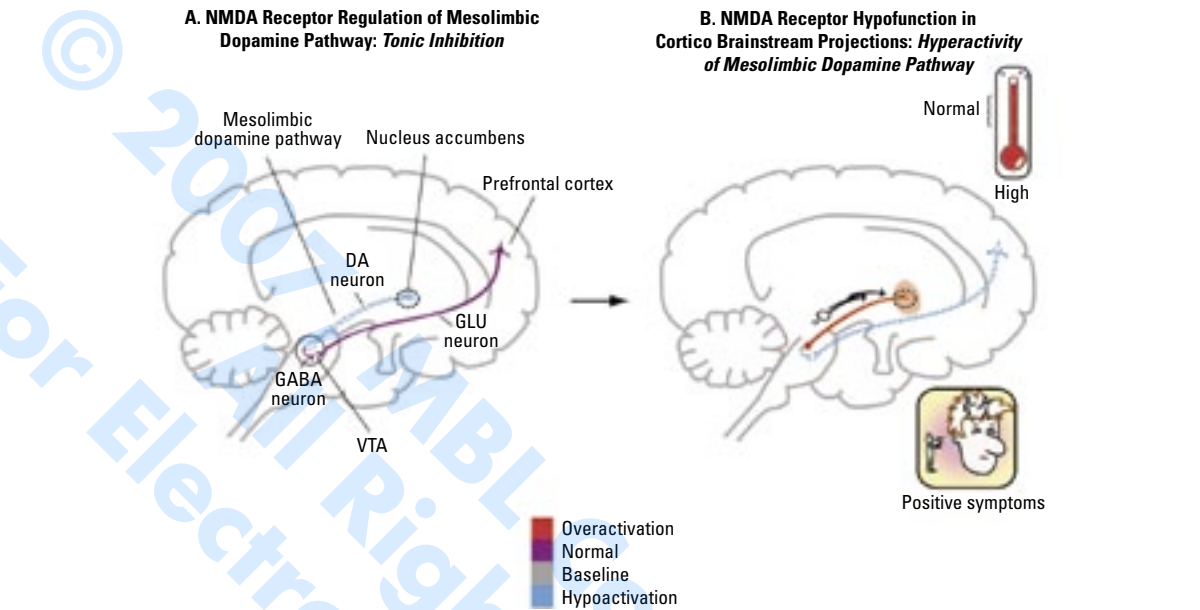
* Mesocortical underactivity: negative, cognitive and affective symptoms of schizophrenia.

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DLPFC=dorsolateral prefrontal cortex; vmPFC=ventromedial prefrontal cortex; VTA=ventral tegmental area.

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FIGURE 3.
NMDA receptor hypofunction hypothesis and positive symptoms of schizophrenia²

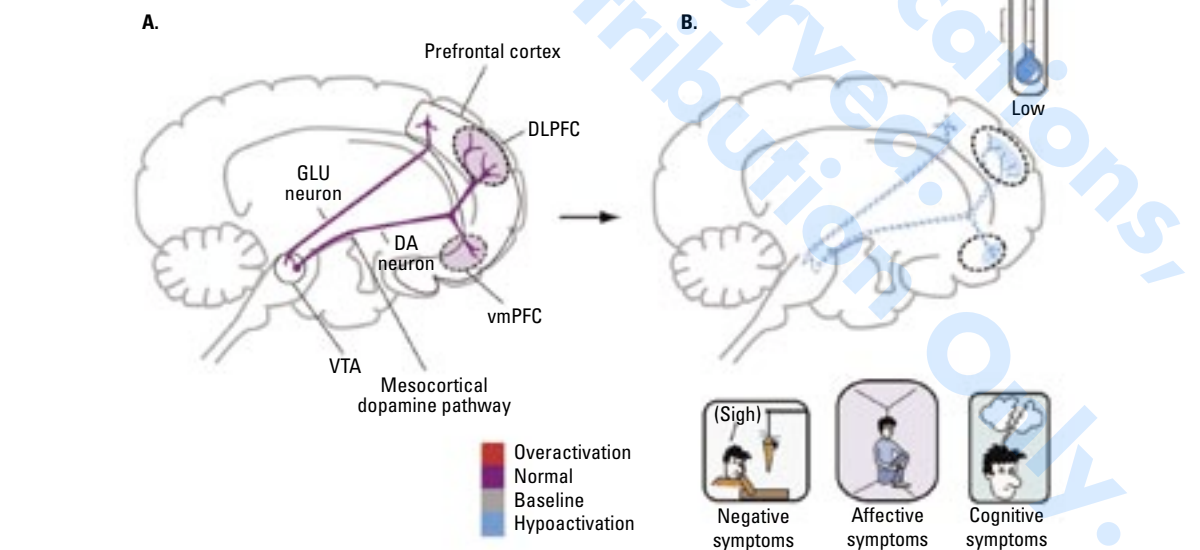


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NMDA=*N*-methyl-D-aspartate; DA=dopamine; GLU=glutamate; GABA= γ -aminobutyric acid; VTA=ventral tegmental area.

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FIGURE 4.
NMDA receptor hypofunction hypothesis and negative, cognitive, and affective symptoms of schizophrenia²



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affective symptoms of schizophrenia. That is, normally, descending cortico-brainstem glutamate neurons act as accelerators to mesocortical dopamine neurons. Unlike the actions of cortico-brainstem glutamate neurons on mesolimbic dopamine neurons shown in Figure 3A (left panel) where they act via an intermediary γ -aminobutyric acid interneuron, cortico-brainstem glutamate neurons synapse directly upon those dopamine neurons in the VTA that project to the cortex, those so-called mesocortical dopamine neurons (Figure 4A, left panel). This means that cortico-brainstem glutamate neurons normally function as accelerators of these mesocortical dopamine neurons and, therefore, they tonically excite them (Figure 4A, left panel).

The consequence of this neuronal circuitry is that when cortico-brainstem projections to mesocortical dopamine neurons have NMDA receptor hypoactivity, they lose their excitatory drive and become hypoactive, as shown in Figure 4B (right panel). This could hypothetically explain why mesocortical dopamine neurons are hypoactive. Thus, their link to the cognitive, negative, and affective symptoms of schizophrenia shown in Figure 4B (right panel). Supporting this hypothesis are observations that several of the known susceptibility genes for schizophrenia impact the NMDA receptor.^{2,7}

CONCLUSION

The bottom line is that a powerful convergence of evidence suggests NMDA receptors are hypofunctional in schizophrenia, and this may lead to abnormal dopamine activity in critical brain pathways in order to mediate the symptoms of this illness.²⁻⁷ Genes coding for connectivity, synaptogenesis, and neurotransmission at glutamate synapses and specifically at NMDA receptors may produce dysregulation at these synapses that results in hypofunctionality at NMDA receptors and thus the symptoms of schizophrenia (Figures 3 and 4).^{2,7} Several new drugs that target NMDA receptors are being tested as novel therapeutic agents for the treatment of schizophrenia.^{2,5,6} **CNS**

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