Guide for Health Care Professionals

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Interacting Neurotransmitter Pathways in Schizophrenia

How disruptions across dopamine, serotonin, glutamate, GABA, and acetylcholine pathways may shape schizophrenia circuits

NEUROTRANSMITTER SYSTEMS IN SCHIZOPHRENIA

Schizophrenia is thought to involve disruptions across multiple neurotransmitter systems.[1–3,*]

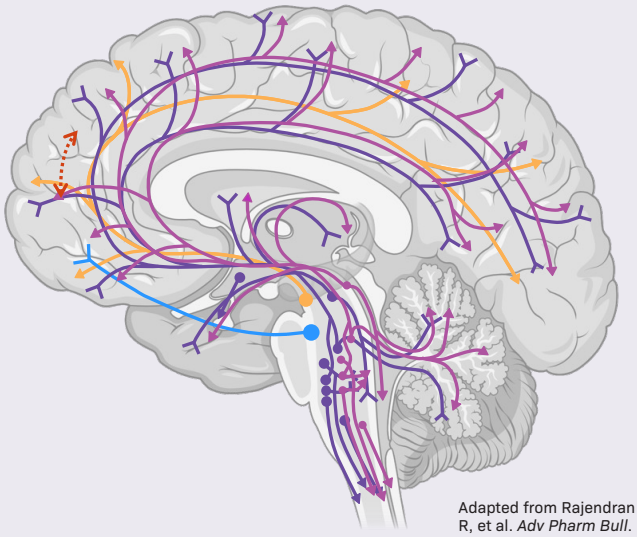
Dopamine[1,2]
Midbrain (striatal) hyperactivity is associated with positive symptoms
Cortical hypoactivity is related to negative and cognitive symptoms

Serotonin[1,3]
5-HT2A (5-hydroxytryptophan 2A) receptor hyperactivation on cortical neurons amplifies glutamate release and modulates striatal dopaminergic signaling

Glutamate[1–3]
NMDA (N-methyl-D-aspartate) receptor hypofunction disrupts cortical excitation-inhibition balance and drives downstream dopamine dysregulation

GABA (gamma aminobutyric acid)[2,3]
Primary inhibitory neurotransmitter
Cortical interneuron deficits impair inhibitory signaling

Acetylcholine[2,3]
Modulates dopamine release and excitation-inhibition dynamics
M1/M4 muscarinic and α7 nicotinic receptor reductions have been observed in schizophrenia



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*Information in this section is hypothesized based on clinical and preclinical studies.

INTERACTING NEUROTRANSMITTER PATHWAYS

Multiple neurotransmitter systems are thought to interact to regulate excitatory and inhibitory signaling across cortical and subcortical circuits.[1–3]

NEUROTRANSMITTER	HYPOTHESIZED PATHWAY INTERACTION(S)	HYPOTHESIZED DYSFUNCTION IN SCHIZOPHRENIA
Dopamine[1–3]	**Glutamate:** upstream modulator of striatal dopamine release **GABA:** inhibitory control of dopaminergic signaling **Acetylcholine:** M4 receptors modulate striatal dopamine release **Serotonin:** upstream modulator of striatal dopamine release	Striatal hyperactivity: elevated dopamine synthesis and release Cortical hypoactivity: reduced dopaminergic signaling
Serotonin[1,3]	**Glutamate:** cortical 5-HT2A receptors modulate downstream glutamate signaling **Dopamine:** striatal release modulated by upstream 5-HT2A signaling	Hyperactivation of 5-HT2A receptors on cortical glutamatergic neurons
Glutamate[1–5]	**GABA:** cortical interneuron activation modulated by NMDA activity **Dopamine:** striatal release modulated by upstream NMDA signaling **Acetylcholine:** M1 receptors modulate cortical neuron excitability **Serotonin:** cortical 5-HT2A receptors modulate downstream glutamate signaling	NMDA receptor hypofunction, particularly on cortical GABAergic interneurons Disrupted synaptic plasticity and cortical excitation-inhibition balance
GABA[1–3,5–7]	**Glutamate:** NMDA activity drives cortical GABA interneuron activation **Dopamine:** inhibitory tone modulates dopaminergic signaling **Acetylcholine:** M1 receptors modulate GABA release in the prefrontal cortex	Reduced cortical interneuron inhibitory tone Decreased GABA synthesis Disrupted cortical excitation-inhibition balance
Acetylcholine[3,5,8,9]	**Dopamine:** M4 receptors modulate striatal dopamine release **Glutamate:** M1 receptors on cortical neurons modulate excitatory activity **GABA:** M1 receptors on cortical interneurons facilitate inhibitory tone	Reduced M1/M4 receptor expression in the striatum and cortex Inconsistent nicotinic receptor changes in the striatum

MULTI-PATHWAY CONTRIBUTIONS THAT MAY IMPACT SCHIZOPHRENIA SYMPTOMATOLOGY

Disruptions across dopamine, serotonin, glutamate, GABA, and acetylcholine pathways are hypothesized to contribute to schizophrenia symptoms.[1,3]

POSITIVE SYMPTOMS

- NMDA receptor hypofunction[1,4]
- GABA-mediated disinhibition of corticostriatal glutamatergic circuits[1,6]
- 5-HT2A receptor amplification of cortical excitability[1,3]
- Reduced M1/M4 receptor modulation of striatal projections[5]
- Striatal dopaminergic hyperactivity[1]
- Positive Symptoms (eg, hallucinations, delusions)*

NMDA receptor hypofunction is thought to reduce cortical GABAergic interneuron activation, potentially disinhibiting downstream glutamatergic circuits and increasing striatal dopamine activity, which may be associated with the emergence of positive symptoms.[1]

NEGATIVE SYMPTOMS

- NMDA receptor hypofunction[1,4]
- GABA-mediated disinhibition of corticostriatal glutamatergic circuits[1,6]
- Cortical dopamine hypoactivity[2]
- Reduced cholinergic modulation of motivational circuits[8]
- Negative Symptoms (eg, avolition, blunted affect)*

Impaired corticostriatal glutamatergic communication, reduced GABAergic inhibitory tone, cortical dopamine hypoactivity, and reduced muscarinic modulation of motivational circuits collectively are thought to contribute to deficits in motivation and affect associated with the negative symptoms of schizophrenia.[1–3,6,8]

COGNITIVE SYMPTOMS

- NMDA receptor hypofunction[1,4]
- Disrupted cortical excitatory-inhibitory balance[1,6]
- Cortical dopamine hypoactivity and impaired prefrontal function[2,3]
- 5-HT2A receptor amplification of cortical excitability[1,3]
- Reduced M1/M4 receptor modulation of attention and memory networks[5,8]
- Cognitive Symptoms (eg, working memory, attention, executive function)*

Cognitive deficits are thought to be associated with a disrupted excitatory-inhibitory balance, which may be driven in part by cortical dopamine hypoactivity, impaired muscarinic modulation of attention and memory networks, and serotonergic amplification of cortical glutamate activity.[1–3,5,6,8]

*Not an all-inclusive list of schizophrenia symptoms.

KEY TAKEAWAY

Schizophrenia is hypothesized to involve disruption across multiple interacting neurotransmitter systems, including dopamine, glutamate, GABA, serotonin, and acetylcholine. No single pathway operates in isolation. Pathway-level disruptions may interact at the circuit and network level to produce the heterogeneity of symptoms observed in schizophrenia.[1–3,6]

References

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