Symptoms and Circuits, Part 3
Schizophrenia

Stephen M. Stahl, M.D., Ph.D.

Issue: *Schizophrenia is composed of not only positive symptoms, but also cognitive and affective symptoms that contribute significantly to morbidity. Each of these symptoms may be mediated by a separate and distinct neuronal circuit.*

This feature is the third in a 3-part series discussing the paradigm shift that is occurring in conceptualizing the biological basis of psychiatric disorders, namely the notion of "symptoms and circuits." Psychiatric syndromes are deconstructed into their various symptoms, and then each symptom is matched to hypothetically malfunctioning neuronal circuits that can potentially not only explain the genesis of these symptoms but also provide a target for therapeutic agents to relieve these symptoms.[1,2] We have already discussed this idea in relationship to major depressive disorder[3] and anxiety disorders.[4] Here we discuss how symptoms and circuits are relevant to a modern formulation of schizophrenia.

Beyond Positive Symptoms in Schizophrenia

It is well known that schizophrenia is defined by its prominent positive symptoms such as delusions, hallucinations, and thought disorder.[5] Recently, other symptoms of schizophrenia have been emphasized, such as cognitive dysfunction and affective symptoms, because they may be more closely linked to the ultimate outcome of patients with this disorder than are positive symptoms.[5,6]

Table 1. Hypothetical Topography of Symptoms in Schizophrenia

Symptom	Circuit
Positive symptoms (delusions, hallucinations, thought disorder)	Mesolimbic dopamine pathway
Cognitive symptoms (executive dysfunction)	Dorsolateral prefrontal cortex
Mood symptoms (depression, sadness, mood instability)	Medial prefrontal cortex, anterior cingulate cortex, orbitofrontal cortex

The classical theory to explain schizophrenia is the "dopamine hypothesis," which proposes that the positive symptoms of schizophrenia are related to hyperactivity of dopamine neurons in the mesolimbic dopamine pathway.[5] However, this theory fails to account for cognitive and affective symptoms. Recent neuroimaging studies suggest that other pathways malfunction and cause cognitive symptoms (i.e., in dorsolateral prefrontal cortex) and affective symptoms (i.e., in medial prefrontal cortex) (Table 1).[2,5,6] Neurotransmitters interact with receptors and enzymes within neuronal circuits to regulate various functions of the brain. Theoretically, dysfunction in different circuits results in the various symptoms of schizophrenia (Table 1).[2–6] Whereas excessive dopamine may be an important dimension in the circuit mediating positive symptoms, deficient dopamine may be an important dimension in the cognitive and affective circuits.[5,6]

It is interesting to note that the cognitive symptoms of schizophrenia may involve dysregulation of neurons within the very same circuit hypothesized to mediate the cognitive symptoms associated with major depression[3] and anxiety disorders,[4] namely the dorsolateral prefrontal cortex. Likewise, the affective symptoms of schizophrenia may involve dysregulation of neurons within the very same circuit hypothesized to

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From the Neuroscience Education Institute in Carlsbad, Calif., and the Department of Psychiatry at the University of California San Diego.

Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, Neuroscience Education Institute, 5857 Owens Street, Ste. 102, Carlsbad, CA 92009.

mediate the sadness associated with major depression[3] and the fear and worry associated with anxiety disorders,[4] namely the medial prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex. Thus, it appears that there are a limited number of neuronal highways over which similar symptoms may be mediated across various psychiatric disorders. It would not be surprising if treatments able to improve symptoms by correcting dysfunction in a given circuit would work for similar symptoms across different psychiatric disorders.

Take-Home Points

- Neuroimaging studies are demonstrating that distinct symptom domains in schizophrenia can be topographically mapped to distinct malfunctioning neuronal circuits.
- Positive symptoms have long been hypothesized to be mediated by a hyperactive dopaminergic limbic neuronal circuit.
- More recently, cognitive symptoms in schizophrenia have been hypothetically linked to dysfunctional neuronal circuits in dorsolateral prefrontal cortex where dopamine activity may be too low.
- Affective symptoms in schizophrenia may be linked to the same abnormal circuit implicated in sadness of major depressive disorder, namely dysfunctional neurons in orbitofrontal and medial prefrontal cortex.
- Since outcomes in schizophrenia are linked not just to reducing positive symptoms but also to reducing affective symptoms and especially cognitive symptoms, neurobiologically informed treatment strategies for patients with schizophrenia call for targeting all of these symptoms by selecting treatments capable of modulating specific neurotransmitters in the hypothetically malfunctioning circuits.

Neurotransmitters, Circuits, and Novel Treatment Strategies

Constructing a diagnosis of schizophrenia by noting all its symptoms is important; however, the traditional hierarchy of positive symptoms over the other symptoms of schizophrenia such as cognitive and affective dysfunction can distract clinicians from observing, monitoring, and targeting these symptoms too, particularly if positive symptoms improve but other symptoms remain following treatment.[2] A novel strategy to potentially improve outcomes in schizophrenia is to attempt to reduce the residual cognitive and affective symptoms that may persist after positive symptoms improve. To do this, the clinician can deconstruct the syndrome of schizophrenia in each patient into its specific symptoms, especially after short-term treatment with an antipsychotic, and then choose further psychopharmacologic interventions to target whatever malfunctioning neuronal circuits are still hypothetically mediating any residual symptoms, especially cognitive and affective symptoms.[2–4]

Although it is well known that antipsychotics reduce positive symptoms of schizophrenia, recent evidence is now beginning to suggest that the atypical antipsychotics—but not conventional antipsychotics—may also improve the cognitive and affective symptoms of schizophrenia. This improvement may be due in part to the actions of most atypical antipsychotics on 5-HT_{2A} receptors, which cause increased dopamine release in cortex at the same time that dopamine receptors are being blocked in the mesolimbic dopamine pathway.[5] Additional pharmacologic properties of some atypical antipsychotics differ one from another, including differential 5-HT_{2C}, 5-HT_{1D}, and 5-HT_{1A} activities, among others.[5,7] Research is now attempting to clarify if these properties can account for differences in various patients' responses between one atypical antipsychotic and another in terms of improving cognitive and affective symptoms. Such an approach gives rise to a rational, hypothesis-driven and testable action plan for selecting the best treatment by targeting symptoms in circuits. The goal is to reduce whatever residual symptoms are unique to an individual patient and thus attain a better outcome.[2–4]

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