Advances in neuroimaging, cell biology, and post mortem analysis are starting to explain what happens in the brain of a person who develops schizophrenia. Schizophrenia appears to be a developmental disorder of disrupted neural connection within and between regions of the brain. These disruptions seem to result from genetic predispositions interacting with negative environmental events.

A matter of gray and white

Individuals with schizophrenia have deficits in gray matter and white matter, as illustrated by studies linking auditory hallucinations with brain regions associated with normal hearing (Box).

Gray matter. Magnetic resonance imaging (MRI) indicates that gray matter volume peaks in early adolescence and declines with age. The normal adolescent brain shrinks as inefficient neural connections are pruned away, a process that refines and matures gray matter. In individuals with schizophrenia, this reduction is more aggressive—perhaps because of excessive pruning—and occurs in the time frame when schizophrenia symptoms typically emerge.

Rapoport et al1 documented this process through sequential MRI scans in children with early-onset schizophrenia (mean age 14.5). Compared with age-matched healthy controls, youths with schizophrenia show greater and more rapid gray matter loss during late adolescence (Figure 1).2

Increased density. Reduced neuronal branching and spine formation also likely causes subtle reductions in gray matter volume (Figure 2, page 92). The resulting lack of dendritic connectivity may produce cognitive impairments and negative symptoms seen in schizophrenia.

Postmortem studies of gray matter cells show increased neuron density in patients with schizophrenia when compared with controls.3 Patients with schizophrenia have the same number of neurons as controls, but the neurons are more tightly packed because of reduced cell size, branching, and synapse formation.4

Research over the past decade has revealed schizophrenia to be a neurodegenerative disorder characterized by substantial brain tissue loss during first and subsequent psychotic episodes.5 Neuroimaging studies show that clinical and functional deterioration...
accompanies progressive loss of cortical gray matter volume and enlargement of cerebral ventricles. Thus, preventing relapses has come to be regarded as critical to long-term schizophrenia management.

White matter. Recent research suggests that white matter deficits also may be involved in schizophrenia’s pathophysiology. Studies using diffusion tensor imaging (DTI)—which measures the sum of vectors of water diffusion along axons—have documented white matter impairments in patients with schizophrenia.6

White matter tracks—myelinated axons that transport electrical signals among neurons—connect regions within the cortex and between the cortex and deeper brain structures. Disruption of white matter tracks may degrade signals and confuse neuronal communication.

Myelination. Genetic studies in patients with schizophrenia also have suggested that decreased neuron myelination may play a role in white matter deficits. Hakak et al8 examined more than 6,000 genes using microarray analysis and found only 17 genes were significantly down-regulated in patients with schizophrenia. Of those 17 genes, 6 were related to myelin and 11 showed no pattern.

Oligodendrocytes are glial cells that insulate axons with myelin and allow faster transmission of electrical impulses in the brain. In a postmortem study, Hof et al7...
found 7 patients schizophrenia had 28% fewer oligodendrocytes per section of the superior frontal gyrus and 27% less white matter compared with 7 age-matched controls (Figure 3, page 96).

### Genes and the environment

Schizophrenia’s heritability is among the most repeated research findings in psychiatry. Other mechanisms besides genetics must be involved, however, as studies consistently show that monozygotic twins have a concordance rate of approximately 50% for the development of schizophrenia.

### Environmental factors

Adverse environmental events may act in conjunction with genetic predisposition to trigger schizophrenia development. Ischemia or an impoverished diet, for example, have the potential to change DNA methylation.

Environmental factors associated with increased risk for schizophrenia include:
- maternal starvation during pregnancy
- prenatal exposure to influenza
- obstetrical complications with hypoxia
- being born and raised in an urban environment
- using marijuana during adolescence

### Gene expression

Important genes may be silenced in individuals with increased DNA methylation and a susceptible genetic profile. Alterations in gene expression are the fundamental mechanism of behavioral change. Research shows that environmental events can alter gene expression without changing the genetic code, such as by adding methyl groups to DNA. The silencing of important developmental genes in this way can have devastating effects on development.

One explanation for the development of schizophrenia is that environmental events in susceptible individuals silence the production of proteins essential for maintaining neuronal connections through methylation of DNA. Postmortem analysis of brains of patients with schizophrenia show reduced mRNA of reelin, a protein produced in gamma-aminobutyric acid neurons involved in neuronal migration, axon branching, and synapse formation during brain development. Lowered production of proteins such as reelin may reduce connections between neurons and cause schizophrenia symptoms. Two research groups also have reported increased methylation of reelin DNA in postmortem studies of the brains of patients with schizophrenia.

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**Clinical Point**

Lowered production of proteins such as reelin may reduce connections between neurons and cause schizophrenia symptoms.

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**Figure 2**

**Structural differences between neurons in patients with schizophrenia and controls**

<table>
<thead>
<tr>
<th>PYRAMIDAL NEURONS</th>
<th>DENDRITES AND SPINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy neuron</td>
<td>Schizophrenic neuron</td>
</tr>
<tr>
<td>Control</td>
<td>Schizophrenic</td>
</tr>
</tbody>
</table>

Schizophrenic neurons show reduced soma size, spine formation, and dendritic branching.

Source: Adapted from reference 2

*continued on page 96*
Clinical Point
Auditory hallucinations originate from altered connectivity in the same regions that process normal hearing and speech.

In a postmortem analysis, stained white matter sections taken from schizophrenia patients had fewer oligodendrocytes, cells that insulate axons with myelin and facilitate electrical transmission.


References
4. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Arch Gen Psychiatry 2008;57(1):65-73.