# Brain Development and Schizophrenia

Recognition of symptoms of schizophrenia is among the staples of any psychiatrist's diagnostic armamentarium. Fewer psychiatrists, however, can give patients or their families anything other than cursory information on how altered brain development and function might contribute to these symptoms. Nevertheless, the slow pace of research does not indicate that substantive work has not been accomplished. Two articles in this issue describe important steps toward developing a more coherent view of how the brain comes to malfunction in schizophrenia.

The effects of chlorpromazine and other antipsychotic drugs were initially discovered through serendipitous clinical observations, but enthusiasm quickly turned to the possibility that their dopamine antagonism might hold the key to the neuronal basis of schizophrenia. Much scientific work was directed toward understanding dopamine and its receptors. This effort led to the development of new classes of antipsychotic drugs, but as every clinician knows, blocking dopamine does not cure schizophrenia. The focus of research therefore expanded to include the fundamental interplay between excitatory and inhibitory neurons in the microcircuitry of the cerebral cortex and thalamus. We presume that as a disorder of thought and language, schizophrenia should somehow involve the most advanced parts of our brains. Research reported in this issue attempts to parse the brain into microcircuits of interacting inhibitory and excitatory nerve cells, much as computers have circuits of interacting on and off transistors.

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## Inhibitory Neurons in Schizophrenia

The article by Volk et al., "Deficits in Transcriptional Regulators of Cortical Parvalbumin Neurons in Schizophrenia," is the product of research by a number of neurobiologists, including its senior author, David Lewis, into cerebral inhibitory neurons (1). Bleuler was among the first to observe schizophrenia as an inhibitory dysfunction, long before the concept had been fully developed by neurobiologists. He was struck that catatonic patients, while seeming to shut out the world around them, actually registered the events in the hospital in excessive detail. As neurobiologists learned that some neurons primarily inhibit other nerve cells, investigators of schizophrenia turned to these neurons for their inquiries. Different types of inhibitory neurons have their unique molecular signatures. The Lewis group has focused on those that contain parvalbumin, a protein that buffers the neuron during the influx of calcium that is part of synaptic transmission from other neurons.

One mystery of interneuron dysfunction in schizophrenia is that the inhibitory neurons are actually present, but they do not make adequate connections with their usual target, the principal excitatory neurons of the cerebral cortex, and they do not adequately synthesize enzymes such as GAD67 that would enable them to make the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Volk and his colleagues investigated why. The different classes of inhibitory neurons have unique types of DNA transcription factors, molecules that tell them to begin transcribing messenger RNA to make GAD67 to enable them to function as inhibitory neurons, rather than just staying alive as cells. The levels of one such factor, Lhx6, were notably decreased, whereas other similar factors, such as Sox6, were not.

The finding introduces a new level of complexity, another set of molecules, but it further unwinds the mystery of why patients with schizophrenia seem to have lost their inhibitory filter. This study was performed in postmortem brain specimens from patients who had been treated during life with antipsychotic drugs. After death, of course, is the only time that human brain tissue is available for detailed molecular study. However, many such activation molecules, including Lhx6, also play a role in brain development, guiding neurons to their proper places in the growing brain. Indeed, inhibitory neurons are also likely to fail to migrate into the cerebral cortex and may be "lost" in the underlying tissue. That fact raises the possibility that what Volk et al. observed in the brains of patients after death is the molecular trace of a much earlier problem in fetal brain development. This developmental abnormality was never normalized, despite a lifetime of drug and other treatments.

## Communication Between Thalamus and Cortex

Although the molecular biology of the brain can be studied only postmortem, the function of the neurons can be studied only in life. Stefan Heckers and his group have been using functional brain imaging techniques to do so. The article by Woodward et al. in this issue, "Thalamocortical Dysconnectivity in Schizophrenia," describes their work using resting-state functional magnetic resonance imaging (fMRI) (2). The thalamus is the principal input from the rest of the brain to the cerebral cortex. Although it thus conveys sensory information to the cortex, it also organizes the cortex's rhythmic activity during various states of sleep and waking. During quiet waking or rest, the thalamic-to-cortical pathway is part of a default network that represents a baseline communication between major brain areas. One way this happens is through the connections of the thalamus to the same inhibitory neurons in the cortex that Lewis et al. studied (3). Defects in this network in schizophrenia were recently described by Garrity et al. (4).

Woodward et al. in a large group of patients and normal individuals measured correlations between blood flow in the thalamus and the cerebral cortex and saw, as was already known from the neuroanatomy, that different areas of the thalamus communicate with unique lobes of the cerebral cortex. They found an initially puzzling finding. In their patients, most areas communicated normally, but the connections with motor and nearby somatosensory areas were abnormally more active and the communications with the more anterior prefrontal cortical areas, concerned with executive function, were abnormally less active. The findings generally correspond to the clinical observation that patients' problems are not with simple responses to stimuli but, rather, with the advanced planning that

normally enables us to stay focused and to develop strategies that take into account our goals and the consequences of our actions. Woodward et al., like Volk et al., interpret their findings in a developmental context. They point out that the regional differences they found in schizophrenia are normally seen in children and adolescents, and they speculate that a developmental failure in late adolescence may contribute to the persistence of this activity in schizophrenia. Like Volk and colleagues, Woodward et al. also studied antipsychotic-treated patients. These deficits were not normalized by their treatment.

## New Possibilities for Intervention

Research in the pathophysiology of schizophrenia thus now extends well beyond dopamine, our current mainstay therapeutic target. This progress does not mean that dopamine's role is being overlooked. Changes in dopaminergic function appear to play a pivotal role in the development of an episode of acute psychosis, when individuals move from the prepsychotic state characterized by attentional difficulties and social problems into a more overtly dysfunctional state (5). Since dopamine cells normally activate inhibitory interneurons (6), the stressful period of adolescence and early adulthood, when dopamine neurotransmission is increased, may present more severe challenges for people who have not adequately developed inhibitory neuronal function.

Current research thus indicates the possibility of a sequence of developmental failures from fetal brain development to late adolescence to the final expression of the psychotic state. This research implies that new interventions to decrease or ameliorate the developmental problems that underlie schizophrenia might need to be designed for much earlier periods in life, during each developmental stage, but long before illness itself is manifested.

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