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Molecular etiologies of Schizophrenia: Are We Almost There Yet?

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Two articles in this issue of the *Journal* represent examples of what research is teaching us and not teaching us about the biological basis of schizophrenia. At best, they illustrate how discoveries in genetics and molecular neurobiology converge at the level of neural systems, and they exemplify progress via integrative approaches. At worst, they underline the very complexity of schizophrenia's nature and the failure of findings to always mesh in a simplistically pleasing way or to map against the disease as it is currently defined clinically. Both studies implicate γ -aminobutyric acid (GABA)/glutamate function, which itself has protean effects on activity of the dorsolateral prefrontal cortex and modulation of neurocircuits that have been implicated in schizophrenia (1).

The study by David Lewis' group (Curley et al. [2]) illustrates the virtues of going where the money is in behavior, and that place is neuronal biology. In a cellular neurobio-logic approach, Curley et al. measured functions of a key molecule, glutamic acid de carboxylase 67 (GAD67, also known as GAD1), the major GABA-synthesizing enzyme. They report more evidence for lower levels of GAD67 protein and RNA in the brains of patients with schizophrenia. Many internal complexities of frontal cortical function remain unknown, but even if we treat the region as the proverbial black box, glutamatergic pyramidal neurons are key to its output to other regions, such as the striatum. Approximately one in four neurons in the frontal cortex use GABA, an inhibitory neurotransmitter. Release of GABA at other GABA interneurons leads to disinhibition. GABA release at dendrites of pyramidal neurons that provide excitatory input to other pyramidal neurons can also modulate that input. Also, many other neurotransmitters, including dopamine, are vital to the function of intrinsic frontal cortical circuitry. GABA interneurons that directly inhibit glutamatergic pyramidal cells appear to be marked by parvalbumin, and expression of GAD67 in these cells is reduced. Therefore, this single finding appears to point directly to an enzyme—and a GABA interneuron that expresses it—whose reduced function partially explains the dysfunction of the dorsolateral prefrontal cortex in schizophrenia.

From a different perspective, Greenwood et al. (3) used a genetic approach to tap the genome, which because of the moderate to high heritability of schizophrenia is a proven reserve of information on the origins of this disease. Taking advantage of the deep neurocognitive phenotyping in the Consortium on the Genetics of Schizophrenia (COGS), this multicenter team detected genetic associations to 12 schizophrenia-related neurocognitive traits, several of which are strongly influenced by frontal function. Among their 96 candidate genes, and taking into account a total of 16,620 tests due to analysis of 1,385 single-nucleotide polymorphisms (SNPs) and 12 endophenotypes, Greenwood et al. found 30 SNPs with p values <0.001 . Of the 96 genes, 23 were implicated at this level, far more than would be expected by chance. Most strongly represented were GABA/glutamate

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genes. Such neurocognitive systems approaches are probably critical for diseases such as schizophrenia, in which there is substantial genetic heterogeneity and where risk alleles may reside in different genes within the same network. Indeed, the schizophrenia genes identified so far as copy number variants have been rare, and there appear to be many genes involved. Because schizophrenia is common and clinically defined, we may perfectly reasonably expect that one day it will be retrospectively viewed as an amalgam of many distinct disorders that are individually much less common. By analogy, schizophrenia is at the state of hereditary deafness or anemia, both of which were syndromes without known causes prior to 20th-century medicine.

The complexity of relating the many neurocognitive features of schizophrenia to the many possible genes that could underlie the responsible changes in nerve cell biology has called for new approaches to data analysis. To statistically evaluate whether there was a global excess of significant genetic findings at multiple genes, the COGS group used a novel bootstrap method. Similarly, false-discovery-rate statistics, as well as the truncated product method, in which p values below a certain threshold are multiplied and compared to random expectation (4), have opened new and mathematically valid ways of evaluating experiment-wide significance. There are several pitfalls, but properly applied, such methods yield an accurate perspective on the experiment-wide level of significance of findings or findings clustered within a molecular network. These methods essentially enable us to answer the question of how likely it was that the lightning struck not just the tree but several trees in the same forest. One might conclude that there was a thunderstorm nearby.

We therefore look once again at the nerve cells whose function is dependent on GABA/glutamate, and while the solution is still elusive, there are encouraging signs. GAD67 is an integral part of a molecular network encompassing GABA and glutamate, and yet GAD67 itself, the enzyme implicated in the Curley et al. analysis, was not among the most significantly associated genes in the Greenwood et al. analysis. As is well known, genetic association findings come and go—and GAD67 has previously been associated with both schizophrenia and decreased expression of GAD67 mRNA in the brains of schizophrenia patients (5). However, genetic and molecular neurobiology findings in GABA/glutamate have established this as a system where some of the answers to the mystery of schizophrenia reside. The Curley et al. and Greenwood et al. studies further strengthen the case that frontal GABA/glutamatergic pathways are targetable in psychosis (6). Also, cognitive symptoms associated to GABA/glutamate genes perhaps best delineate schizophrenia and represent aspects of the disease that remain most treatment resistant.

Why is it that the molecular genetics of schizophrenia has seemingly been forever poised on the brink of great breakthroughs? A variety of partially overlapping theories of schizophrenia have, for good reasons, attracted adherents. Evidence also strongly supports the neurotransmitters dopamine, serotonin, and acetylcholine, as well as neurocircuits they modulate. Too little progress has been made in recent years in the development of new drugs against old targets. However, many of the neurochemical findings converge at the circuit level, and it is at that level—possibly informed by assays of function and genotype—that new interventions can be developed and targeted. Other evidence implicates neurodevelopment, including factors that modulate reaction to stress and immune activation, and in this regard the timing of interventions could be critical. Medical revolutions transform the clinical landscape in ways that make the old medicine look awkward and inadequate—as indeed it was. For example, the tuberculosis sanatorium of which Thomas Mann wrote in *The Magic Mountain* (a place where time seemingly stood still) was shuttered because of the introduction of one drug: isoniazid, for the treatment of tuberculosis in its different manifestations. For schizophrenia, the clinical paradigm has previously

shifted several times. We may look back on this as the era when the groundwork was laid for another sea change in the diagnosis and treatment of this disease.

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