The Final Common Pathway of Schizophrenia

Peter Williamson

The last 2 decades have been marked by concerted search for the gene or genes which would account for schizophrenia. It has become increasingly obvious to many investigators in the field that these genes are not going to be found. Schizophrenia is not likely a simple genetic disorder nor is it likely accounted for by a few major genes. Where does this leave us? Some have suggested that a more productive approach would be to try to look at how a few genes may contribute to a vulnerability or endophenotype in certain individuals. There is some useful work along these lines, particularly those efforts which try to link a physiological or neurocognitive marker to a particular gene. van der Stelt and Belger review electrophysiological endophenotypes which deserve further examination in this theme issue. Other endophenotypes have been considered recently by Braff et al in a Schizophrenia Bulletin theme issue.

Another approach to understanding schizophrenia has been to model features of schizophrenia in animals. This has led to the development of several models which provide at least a partial explanation for features of schizophrenia such as the therapeutic effects of dopamine antagonists and the tendency of N-methyl-D-aspartate antagonists to exacerbate symptoms in schizophrenic patients. However, many models fail to examine the role of structures which integrate affect in the brain such as the amygdala. Laviolette (in this theme issue) discusses some of these shortcomings and proposes that more attention should be given to amygdala-prefrontal interactions.

Most animal models are based on basal gangliothalamocortical neuronal circuits or structures such as the amygdala which project to them. However, there may be other brain networks relevant to the pathophysiology of schizophrenia. The recent characterization of networks in the human brain associated with self-monitoring and stimulus-independent thought, referred to as the default network, and networks associated with attention-demanding tasks, referred to as the task-related network, could have some implications for understanding schizophrenia.

The default network and task-related network include structures that are part of the basal gangliothalamocortical neuronal circuits and may provide a way of translating dopaminergic abnormalities in these circuits to a more experiential level. It is curious that the medial prefrontal cortex, which is part of the default network, may be involved with encoding. Neufeld (this theme issue) proposes that encoding deficits are central to the cognitive abnormalities found in schizophrenia.

More direct evidence of the involvement of the default and task-related networks comes from Bluhm et al (this theme issue) and Garrity et al. Both show deficiencies in the default network which may be linked to positive symptoms. Of particular note in the Bluhm et al article is the use of a new imaging technique to define functional brain networks based on spontaneous low-frequency fluctuations of the blood oxygenation level–dependent signal. These fluctuations may reflect coherent electrophysiological activity in functional brain networks. Although findings are preliminary, both the brain imaging technique and the networks that it defines show considerable promise for the understanding of the pathophysiology of schizophrenia.

A miracle is certainly possible but it appears to this observer that we are not likely to discover the cause of schizophrenia anytime soon. Schizophrenia almost certainly is a heterogeneous disorder, much like heart failure, caused by a number of neurodevelopmental, genetic, and environmental factors which are likely to differ between patients. However, like heart failure, it may have a final common pathway no matter what the cause. Maybe it is time to set aside the search for the cause of schizophrenia and make a concerted effort to understand the final common pathway.

References

4. Braff DL, Freedman R, Schork NJ, Gottesman II. Deconstructing schizophrenia: an overview of the use of...
endophenotypes in order to understand a complex disorder. *Schizophr Bull.* 2007;33:21–32.


