Schizophrenia and Disordered Neural Circuitry
by David A. Lewis

Abstract

The knowledge of how alterations in neural circuitry relate to the symptoms of schizophrenia may depend on our ability to disentangle a complex cascade of pathological events that affect multiple brain regions. Recent progress in Alzheimer's disease research may provide several useful guiding principles in this pursuit. Schizophrenia Bulletin, 23(3):529-531, 1997.

Schizophrenia and Alzheimer’s disease (AD) were both recognized as discrete disease entities around the turn of the century, but our understanding of the pathogenesis of AD has far outdistanced that of schizophrenia. Although many other factors are certainly important, the identification of reliable and distinctive neuropathological features in the brains of individuals with AD has clearly contributed to the differential rate of progress in understanding these disorders. Indeed, the recognition of the potential pathophysiological significance of neuritic plaques, a histological hallmark of AD, led to the discovery of the beta-amyloid protein, a pivotal finding underlying recent advances in our understanding of the genetic precipitants and pathophysiological mechanisms of AD.

Until recently, opportunities to forge similar advances in schizophrenia research were hindered by a lack of information about the possible locations within the brain that might exhibit pathological changes specific to schizophrenia and about the types of abnormalities to expect in these brain regions. The articles in this issue by Goldman-Rakic and Selemon (1997), Graybiel (1997), and Haber and Fudge (1997) examine the evidence suggesting that the prefrontal cortex, basal ganglia, and amygdala, respectively, are sites of dysfunction in schizophrenia and are thus likely sites of pathology. Although each article focuses on a particular brain region, the authors all emphasize that each region must be considered as part of a distributed neural system involving multiple areas of the brain. That is, each region does not operate in isolation, but its functional attributes emerge as a consequence of the flow of information processing through its connections with other brain regions. Thus, a disturbance in one region may be due to an abnormality in a region from which it receives afferent input; these changes in turn can produce additional disruptions in the functional architecture of regions further downstream.

Furthermore, many of the brain regions implicated in the pathophysiology of schizophrenia share direct reciprocal connections. (The unidirectional projections from the cerebral cortex to the striatum are the most prominent exception, but even this connection is reciprocated through an indirect pathway.) Thus, a primary abnormality in one region is likely to produce secondary changes in an interconnected brain region, which may in turn produce additional changes in the region with the primary pathology. Even if these secondary changes are in some way compensatory, they will certainly alter the functional circuitry of the affected region. Clearly, disentangling such a potentially complex pathological cascade, one that affects multiple neural circuits, is a formidable task. However, the history of AD research may provide several useful guiding principles in this pursuit.

First, although a number of brain regions have been reported to exhibit abnormalities of different types in schizophrenia, few studies have attempted to examine the distribution of alterations across regions in the same cases. In AD, characterization of the regional distribution of the pathological changes was a critical step in gaining insight into the affected neural circuits. For example, the discovery that neurofibrillary tangles and neuritic plaques had distinctive patterns of distribution in the cerebral cortex within AD cases, and that the patterns were consistently seen across cases (Pearson et al. 1985; Lewis et al. 1987; Arnold et al. 1991), made it possible to identify...
the most vulnerable regions and layers in this disorder. More importantly, these observations demonstrated that the patterns of pathology closely reflected the organization of the connectivity across affected cortical regions, making it possible to formulate testable hypotheses about both the origins of these changes and their pathophysiological significance (Pearson et al. 1985; Lewis et al. 1987; Morrison et al. 1988).

By analogy, the examination of multiple brain regions in the same cases of schizophrenia may prove to be an extremely rich field of endeavor. Indeed, as summarized in the articles in this issue, abnormalities in a variety of brain regions—including the prefrontal, anterior cingulate, superior temporal, and entorhinal cortices, amygdala, hippocampus, thalamus, basal ganglia, and brainstem structures—have been described in schizophrenia but, for the most part, each region has been studied by a different group of investigators using different cohorts of brain specimens. Only by examining these regions in the same cases will it be possible to determine whether pathological changes coexist in different regions, and whether these changes can be understood in the context of the circuitry that connects these areas. Although similar suggestions have been pursued in neuroimaging studies that are likely to yield very valuable information, as indicated by Goldman-Rakic and Selemon, only postmortem approaches currently provide the level of resolution required to detect alterations in specific elements of neural circuitry.

Second, these types of multiregion studies may make it possible to determine how interindividual differences in the phenotypic features of schizophrenia are associated with specific patterns of pathological changes. For example, in AD the evaluation of multiple cortical regions in the same cases clearly revealed distinctly different patterns of pathology in patients with or without a prominent deficit in visuospatial skills (Hof et al. 1989). In contrast, a study confined to a single brain region would have been much less likely to detect this robust clinicopathological correlation.

Third, these types of studies not only promise new information on the brain regions and circuits that are disturbed in schizophrenia, but may also reveal whether the components of neural circuitry that are disturbed in each region share certain features that may underlie their vulnerability. For example, the regional and laminar distribution of neurons containing neurofibrillary tangles in AD closely matches that of neurons in nonhuman primates that have a common profile of axonal projection and biochemical features (Pearson et al. 1985; Lewis et al. 1987; Morrison et al. 1987; Hof et al. 1990; Hof and Morrison 1995). In schizophrenia, a similar knowledge base would both substantially advance our understanding of the pathophysiology of the disorder and create new avenues for therapeutic interventions.

The importance of studying schizophrenia as a disorder of neural circuitry may be illustrated by a consideration of the following findings from postmortem studies of schizophrenia: (1) the number of neurons in the dorsal medial thalamus is reduced by 40 percent (Pakkenberg 1990); (2) the density of basilar dendritic spines, sites of excitatory synapses, are decreased on layer 3 pyramidal neurons in the prefrontal cortex (Garey et al. 1995; Glantz and Lewis 1995), and these neurons exhibit dystrophic morphological changes (Rajkowski et al. 1994); (3) the expression of the messenger ribonucleic acid (mRNA) for glutamic acid decarboxylase (GAD), the synthetic enzyme for gamma-aminobutyric acid, is significantly diminished in the prefrontal cortex (Akbarian et al. 1995); (4) markers of synaptic number or activity are decreased in the prefrontal cortex (Sower et al. 1993; Glantz and Lewis, in press).

Based on these findings, it is possible to speculate that an abnormality in thalamic neuron number leads to diminished afferent drive to the middle layers of the prefrontal cortex, producing a decrease in spine density on the pyramidal neurons that are among the likely recipients of this input, a consequent activity-dependent down-regulation of GAD mRNA expression (Jones 1993), and a reduction in markers of synaptic transmission. The resulting altered activity in prefrontal cortex output neurons would be predicted to produce similar types of changes in brain regions, such as the striatum and certain posterior cortical association regions, that normally receive a prominent input from the prefrontal cortex. However, it is possible to construct other plausible scenarios from these same data, and only by the coordinated examination of these and related components of neural circuitry in the same brain specimens will it be possible to determine which is likely to be the case and how these disruptions in circuitry differ across individuals with schizophrenia.

**References**


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