Temporolimbic or Transcallosal Connections: Where Is the Primary Lesion in Schizophrenia and What Is Its Nature?

by Timothy J. Crow

Abstract

A critique of the article by Bogerts on the temporolimbic system theory is presented. Schizophrenia is conceived as arising as a component of the diversity of interhemispheric (callosal) connectivity associated with the evolution of language, a process that occurred through a genetic change (the speciation event) that allowed the hemispheres to develop with a degree of independence. Language and psychosis thus have a common evolutionary origin. The anatomical changes can be considered as a boundary component of the anatomical variation that is characteristic of the species.


Bogerts (1997, this issue) has made a singular contribution in bringing to light a possible brain change in the case of Ernst Wagner (Gaupp 1974a, 1974b). The clinical history makes fascinating reading and confronts us with the core problem of psychosis: What sort of brain change might we expect to be associated with the protean psychological changes that we see, and what could give rise to it? As he has done so well previously, Bogerts reviews a now-substantial body of literature that he and others have contributed in the past two decades. What firm conclusions can we draw? Is there a key to the nature of the disease process?

The problem is that many changes in many different anatomical structures are reported. Which of these is reliably associated with the disease process? If, as seems likely, there is more than one such change, which is primary and which secondary? Clearly, we need findings that are replicable across series. What firm conclusions can we draw? Is there a key to the nature of the disease process?

The evidence reviewed by Bogerts (1997, this issue) gives us a number of options. But there is an embarrassment of riches. We need a simplifying criterion—a selective filter that narrows the choice.

I want to argue that the problem probably cannot be solved on the basis of postmortem studies alone, valuable though I believe these to be in testing hypotheses. No characteristic histopathological change has yet appeared, although a number of conjectures (e.g., that an inflammatory process is present, or that there is gross disorganization of the hippocampus) have been eliminated. Maybe no such evidence will be obtainable unless we have a very precise idea of what we seek. I suggest that a hypothesis can be generated from what we now know about the population distribution, age of onset, and consequences of the disease, including the brain manifestations. The hypothesis I derive is compatible with some findings, but my conclusion on the identity of the critical anatomical structures differs in emphasis from that reached by Bogerts.

The central problem of etiology arises from two epidemiological findings: First, there is relative constancy of incidence across societies, as demonstrated in the World Health Organization’s (WHO’s) Ten-Country Study (Jablensky et al. 1992, frontispiece): “Schizophrenic illnesses are ubiquitous, appear with similar incidence in different cultures, and have clinical features that are more remarkable by their similarity across cultures than by their difference.”

In this respect, schizophrenia may differ from other common somatic illnesses, such as heart disease and diabetes, and therefore may be more intrinsic (i.e., genetic). Perhaps schizophrenia in this sense is inseparable from human populations—in other words, it is “a disease of humanity.”

Second, onsets occur throughout the reproductive or most healthy phase of life, a fact that acquires particular significance in view of the associated biological disadvantage (decrease in fecundity).

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These facts require an evolutionary theory of etiology, an explanation of why the predisposing genes are not selected out of the population, and a concordant theory of pathogenesis (Crow 1995a).

If, as the WHO study suggests, schizophrenia (more precisely, schizophrenia defined by nuclear symptoms) is a universal characteristic of human populations, it seems that exogenous insult (e.g., viruses, toxins, trauma) is unlikely to feature in its etiology. In any case, the evidence is against such specific agents (Crow and Harrington 1994). One can of course argue that the problem is heterogeneous and that such agents play a role in some (e.g., nonnuclear) forms of psychosis. But in the absence of evidence that psychosis can be reliably subcategorized, I propose that we apply Occam's razor and assume that the solution we require for the core syndrome will also be relevant to the penumbra, an assumption that simplifies the interpretation of neuropathological studies.

With respect to brain changes, the evidence we now have from neuroradiology suggests a degree of homogeneity. For example, ventricular enlargement appears to be characteristic of the group of patients with schizophrenia as a whole, and not of a subgroup (Daniel et al. 1991). Although substantial data are lacking, it seems that the same generalization applies to the other two morphological changes detected in recent radiological and post-mortem studies: (1) a small reduction in total cortical or brain mass, and (2) loss of asymmetry. These three changes must be related. I have suggested (Crow 1990) that the most specific, and certainly the most informative, change is the loss of asymmetry or its failure to develop.

It seems possible that an anomaly of development in asymmetry leads to an arrest of neocortical development, and that ventricular enlargement is secondary to this.

But how are such changes related to what we know about the disease in general? They are compatible with the concept that schizophrenia represents a component of genetic diversity with respect to brain growth—one that persists in the population in spite of being associated with a fertility disadvantage. The reason this genetic variability is not selected out is, I believe, that it is associated with evolution of the speciation characteristic of language. Language evolves by a process of increasing hemispheric specialization. A single polymorphic gene, which Annett (1995) calls the "right-shift factor," acts in conjunction with a random factor to determine which hemisphere will be dominant. According to this concept, language and psychosis have a common evolutionary origin in the genetic mechanism that gave rise to the species (Crow 1996). Genetic diversity is present, and it is still under selective pressure.

This view has implications for the nature of brain changes. It suggests, for example, that the critical changes will be in those anatomical structures that have evolved most recently and are most variable between individuals. If, as seems plausible, schizophrenia is a "misconnection syndrome," the last-evolved fiber pathways (e.g., perisylvian temporal and parietal, and dorsolateral prefrontal cortex) would seem to be the ones at risk of misconnection. Specifically, if this "heteromodal association" cortex has developed with the evolution of the capacity for language, those areas that are asymmetrically distributed between the two hemispheres will be the focus of the disturbance. In particular, we might predict that the critical connections are those that, through the corpus callosum, reciprocally connect regions of the temporal lobe that are homologous but asymmetrically disposed. Such a concept is consistent with a number of the findings reviewed by Bogerts—in particular, the relative selectivity of the changes to "higher" cortical regions and to the temporal lobe, and their lateralization. Indeed, one might ask why, except that the disease process involves the genetic mechanisms underlying lateralization, should there be differential effects on structures in the two hemispheres (Crow 1995b).

The concept of misconnectivity may be difficult to test. One will be looking for quantitative and regionally selective changes in the distribution of fibers and terminal systems within the neocortex. One approach is to examine relative changes in white-matter structures over time. For example, there are reports (Rossi et al. 1994; Bagwell et al. 1996) that the relationship between the corpus callosum cross-sectional area and age differs between groups of patients with schizophrenia and normal controls.

Conclusions

From the known population characteristics of the disease, it is argued that the brain changes in schizophrenia are not secondary to an exogenous insult but arise from genetic variation in the development of those areas of the neocortex that have evolved in relation to the speciation characteristic of language. According to this concept, schizophrenia is a "misconnection syndrome"—the particular fiber pathways in which such misconnections are predicted being those through the corpus callosum that relate homologous but asymmetrically disposed areas of the association cortex. The critical role of asymmetry arises because language evolved under the influence of a gene that allowed the two hemispheres to develop with a degree of independence. Loss of anatomical asymmetry in schizophrenia (from which the other morphological
changes may follow) thus reflects directly on the nature of the genetic predisposition. It is consistent with the proposition that language and psychosis have a common evolutionary origin.

References


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