MORPHOLOGIC MARKERS OF NEURODEVELOPMENTAL PATHS: REVISITED

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INTRODUCTION

"Morphology... is the largest single basis of behavior."

Recent decades have seen a transformation in attitudes, both lay and scientific, about the causes of schizophrenia. There is no longer much debate that schizophrenia reflects brain dysfunction, but there remain many questions about the nature of this dysfunction and its basic causes. Gerald Edelman (1988) presented compelling arguments that all function (or dysfunction) is ultimately rooted in structure (or dysmorphology). Functioning of the brain may be altered by structural abnormalities at the level of individual molecules (i.e., those comprising receptors and membrane elements), at the level of molecular aggregates comprising cells and their interactions, or at the level of interconnected networks of cells, comprising functional anatomic systems. To understand the causes of schizophrenia it is important to determine what structural anomalies exist at the molecular, cellular, and gross anatomic levels, and how these structural abnormalities are related to physiologic abnormalities. Although ultimately even gross anatomic features are explicable in terms of more microscopic processes, it is striking that in schizophrenia, we have clues to pathophysiology that are so obvious -- on a scale that they may be observed by the unaided eye. Characterizing the gross anatomic abnormalities in schizophrenia therefore offers a useful starting point in our attempts to appreciate the fundamental causes of schizophrenia. Once abnormalities on the macroscopic level are more clearly understood, in terms of their population distributions, antecedents, and associated features, organized searches for the more molecular changes underlying these abnormalities may be conducted.

In a chapter contributed to this volume's predecessor three years ago, we speculated that the most widely studied morphologic abnormalities in schizophrenia reflect independent pathologic processes (Bilder and Deguef, 1991). Further, we hypothesized that morphologic "markers" may help define syndromes with unique developmental trajectories or "paths," with distinctive courses and modes of symptom...
expression, neuropsychological deficit patterns, and a range of other features. This
speculation was designed to help constrain the range of hypotheses to be tested in a
research program that often risks suffering from "data toxicity"; we typically study such
a large number of morphologic, neuropsychologic, physiologic, symptomatic, and
historical variables that there are far too many opportunities to detect chance
associations in exploratory analyses.

We offered a set of hypotheses, suggesting that at least three independent
neurodevelopmental paths to schizophrenia could be identified. These were: 1. a
medial fronto-limbic path; 2. a periventricular path; and 3. a cerebral specialization
path. Some further development of these hypotheses has been published elsewhere
(Bilder, 1992; Bilder and Szeszko, in press). The goal of this chapter is to review the
status of the hypotheses given data collected in our laboratory and elsewhere. Given
that the key advantage of any specific hypothesis is its falsifiability, it is unfortunate to
report that most of the key elements of these hypotheses have not been disconfirmed.
This could, of course, suggest that the hypotheses are ill framed and untestable.
Alternatives include the probability that critical data needed to disconfirm the
hypotheses are not available, and the possibility that the hypotheses have elements of
truth. In the meantime, some additional supporting evidence has come to light.

MEDIAL FRONTO-LIMBIC PATH

This "path" was hypothesized to reflect a neurodevelopmental abnormality in the
growth or migration of cellular elements within the dorsal or medial cytoarchitectonic
trend (also know as the archicortex, following the nomenclature of Sanides, 1969, and
elaborated by Pandya and Barnes, 1987; Yeterian and Pandya, 1988). This archicortical
trend includes the hippocampus, cingulate gyrus, and the medial and dorsal aspects of
the neocortex, including both posterior and frontal cortices. We had hypothesized that
this trend may be marked by two types of abnormality: (a) volume reductions in the
mesiotemporal (MT) lobe (specifically in the anterior hippocampal formation); and (b)
prominence of cortical sulci, especially on the dorsal aspects of the frontal and parietal
lobes. The hypothesis that they may be linked was based on the possibility that a basic
neuromigratory defect affecting the core element of this cytoarchitectonic trend
(namely, the hippocampal formation), might also disturb the organization of other
dorsomedial structures (i.e., cingulate gyrus, the dorsal interhemispheric fissure, the
dorsal and medial frontal and parietal sulci).

The simplest element of this hypothesis to test is that a unitary process might
lead to both volume reductions in the anterior hippocampal formation, and to multi-site
cortical abnormalities (in the sense used by Cannon and his colleagues, 1989; 1993),
and that both of these features should be independent of other morphologic
abnormalities, such as ventricular enlargement, or abnormal hemispheric asymmetries.
Thus these morphologic abnormalities should be correlated. We are not aware of any
published data either supporting or disconfirming the association of mesiotemporal
volume reductions with multisite cortical abnormalities. In our studies using Magnetic
Resonance (MR), preliminary analyses have failed to detect significant correlations of
anterior hippocampal volume with either the volume of the CSF or ratings of sulcal
prominence on a single slice at the level of the anterior commissure in sample of
patients with first-episode schizophrenia (Bilder et al., 1994b). If this observation is
supported through further research, then it could suggest either that there is not a
unitary process affecting both hippocampal volume and cortical sulcal prominence, or
that the features we are measuring are not adequate indices of this process.

There has been some partial and indirect support for other elements of this