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Viewing the Elephant from 200 feet: Reconstructing the Schizophrenia Syndrome

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It was a field-changing clinical insight when German-speaking psychiatrists, most notably Kraepelin, described the clinical syndrome of schizophrenia. Kraepelin, Bleuler and their contemporaries worked in an era before the era of molecular biology and brain imaging. They did the best with the tools of their time, and made many crucial contributions. The series of papers by Keshavan and colleagues provide a valuable introduction to important biological findings about schizophrenia for students and those working in other disciplines, and a trajectory for planning future research and conceptual developments for clinicians and researchers working within the field. The lays out the argument that it is time to move on from the ideas of our “fathers”, and boldly deconstruct and reconfigure our understanding of the causes and boundaries of the schizophrenia syndrome.

The paper by Keshavan and colleagues points out, as have others (Hyman, 2010), that conceptual thinking and research in the field of schizophrenia has been trapped by a reification of traditional ideas about schizophrenia nosology. They highlight the multiple risks that extend from a circularity of studying and treating an outmoded disease concept. These risks extend beyond the intellectual constraints associated with prematurely defining a conceptual starting point for viewing the disorder. Traditional ideas also determine patient selection for clinical studies, targets for drug development, and the perceived validity of preclinical models. Given the limited success from attempting to deconstruct schizophrenia on the basis of clinical manifestations, the biological approaches proposed by Keshavan and colleagues, and others (Hyman, 2007), seem to offer the greatest leverage for identifying discrete diseases within the schizophrenia syndrome based on distinct etiological and pathophysiological mechanisms.

From a historical perspective, the field of schizophrenia research in the late 1970's and early 1980's was faced with decades of limited progress. There was a growing disenchantment from the failures of broad theorizing about concepts as diverse as ego dysfunction to the etiological significance of negative family interactions. At the same time, there was growing recognition of the potential opportunities from new ideas and methods of neuroscience for invigorating and integrating the field. These two factors contributed to the field turning abruptly from an interest in broad comprehensive psychological and psychosocial theories, to bottom-up inductive efforts to establish the neurobiological underpinnings of schizophrenia. In the USA, a strong commitment from the NIMH for schizophrenia research from the mid-1980's contributed greatly to the accumulation of facts and models chronicled in the series of papers by Keshavan and colleagues. Since then, the field has been

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assimilating a cascade of new discoveries about alterations in genes, neurotransmitter systems and brain circuitry, with the effect that consideration of their broader implications for diagnostic nosology has been put on hold as ever more refined strategies were employed to understand their biological mechanisms. In this process, questions about what is abnormal in schizophrenia took precedence over questions about what unique alterations defined the syndrome and distinguished it from other conditions. Concern about environmental risk factors also lost some sway in this process, but that has been corrected to a considerable degree in recent years (van Os, 2010).

Still, findings from studies of the neurobiology of schizophrenia could be compared to those from independent studies of other disorders. These comparisons have shown a surprising if not disturbing degree of overlap across common disorders in psychiatry including autism, schizophrenia and bipolar disorder. This was seen initially in neuropsychological and neuroimaging studies, but these similarities often were viewed as final common pathway effects of different etiologies in different disorders. More recently, overlaps in risk genes have challenged models of a fundamental distinctiveness across these disorders (Berrettini, 2003; Owen et al, 2007). Keshavan and colleagues propose that the field needs to deconstruct the schizophrenia syndrome, using biological strategies for determining what is fundamental and unique to the syndrome. The promise of this effort is not only in improving clinical diagnosis, but in speeding gene and drug discovery and more individualized effective patient care.

Following this path may prove to be field changing, redefining in one step nosological frameworks, etiological models and patient care. As we make progress, it now seems unlikely that currently defined psychotic disorders (essentially schizophrenia, and bipolar and unipolar affective disorders with psychotic features) will be revealed to comprise only three etiologically distinct conditions. In other areas of medicine, a greater number of delineated diseases generally have been identified within initially-identified clinical syndromes.

Two possibilities for the future seem likely. First, the field may come to accept that major mental illnesses comprise a continuum of pathology with only modestly distinct clinical syndromes that have highly overlapping and heterogeneous clinical features and etiology (van Os, 2010). This outcome is suggested by the increasing number of studies showing genetic overlap between schizophrenia and disorders as apparently diverse as autism and bipolar disorder, the overlap in a number of clinical and intermediate heritable phenotypes (endophenotypes) across these disorders, and the apparent etiological impact of diverse sites of copy number variation (CNVs) and allelic variation. In this case, diagnostic reformulation may be modest, but understanding of the pathophysiological processes underlying these disorders may change appreciably.

Second, as in neurology and many other fields of medicine, multiple discrete disease entities may be progressively pulled from the clinical syndrome of schizophrenia to vastly change diagnostic and treatment practice. Subgroups identified with a biological rationale may ultimately differ in clinical characteristics such as in poor premorbid adjustment, cognitive deficit, persistent negative symptoms, prominent affective features, etc., but these features would not be the starting points for nosological classification. An important reason for identifying even relatively rare discrete conditions within clinical syndromes such as schizophrenia is that treatments targeting their specific pathophysiological processes for relevant patients have the potential for significantly better clinical outcomes than standard treatment for the syndrome.

Rather than considering these “lumping” and “splitting” outcomes as alternate possibilities, it may be most likely that currently defined global clinical syndromes such as schizophrenia will gradually have homogeneous subgroups pulled out based on newly emerging evidence about distinct and treatment-relevant etiological and pathophysiological mechanisms. This is a pathway forward for diagnostic nosology that has been described as a process of cumulative epistemic iteration (Kendler, 2009). It is hard to estimate the rate of progress or eventual success of parsing schizophrenia into separate diseases, and whether categorical approaches ultimately will hold sway over dimensional approaches. It may yet be the case that there are widely divergent etiologies that impact a small number of pathophysiological mechanisms to justify maintaining a diagnostic nosology with a small number of syndromes. Schizophrenia research is moving forward in multiple directions to provide the data needed answer these questions. They will not guide DSM-V, but hopefully will make significant contributions to DSM-VI.

To succeed in this effort of reconsidering the syndrome of schizophrenia, the field needs to more aggressively merge molecular genetic research with dense intermediate phenotyping strategies (Owen et al, 2007; Kempf et al, 2005) in large multisite studies with more than one disorder studied in parallel. Single-site studies examining single or few phenotypes are progressively adding less knowledge to the field. Studies like the ongoing NIH-funded Bipolar-Schizophrenia Network for Intermediate Phenotypes (BSNIP) protocol, pursuing this tact with schizophrenia and psychotic bipolar disorder, are an important beginning along those lines. Importantly, this study may help resolve longstanding and vexing questions about the concept of schizoaffective disorder (Malhi et al, 2008; Kempf et al, 2005). Large scale studies of this nature offer the potential benefits of establishing etiologically and pathophysiologically distinct subgroups within the schizophrenia syndrome based on genotype-phenotype associations, and to simultaneously examine genotype-phenotype relationships across disorders to delineate both illness-specific and illness-shared aspects of psychiatric syndromes.

The proposed nosological reorganization based on biological discoveries converges with the urgent need for biomarkers of pathophysiological processes to guide future drug development. Such biomarkers can be used to treat patients with a defined neurobiological alteration in new targeted ways, and provide translational targets and “a priori” rationale for drug development across preclinical and clinical platforms to speed drug discovery (Gerretsen et al, 2009; Laughren 2010; Gobburu, 2009). Biomarkers can greatly reduce the risk profile of drug development for schizophrenia. Thus, reconsideration of the schizophrenia syndrome can not only break the logjam in psychiatric nosology, but also the logjam in developing individualized treatment strategies for patients presenting with various manifestations of the schizophrenia syndrome. Such progress in improving patient care is the ultimate promise of the nosological reconsideration proposed by Keshavan and colleagues.

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