Current Psychopathological Issues in Psychosis: Towards a Phenome-wide Scanning Approach

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Introduction

Two main pillars are essential for advancement in the understanding of complex illnesses such as schizophrenia and bipolar disorders. While the main advances in medicine and neuroscience currently come from progress in discovering new causal pathways or pathophysiological mechanisms, what is also needed, but often neglected, is parallel progress in refining the clinical paradigm.

In this respect, the original clinically based Kraepelinian distinction between dementia praecox and manic-depressive illness endures in the current classification systems of psychosis. Also, despite the fact that it continues to be the focus of much criticism,1 it still persists as the prevailing clinical model for neurobiological research.

Three main changes have notably modified the corresponding modern terms of the Kraepelinian dichotomy. First, Kraepelin’s earlier unitary concept of manic depression, which included manic, circular, as well as recurrent depressive conditions, was changed to clearly differentiate bipolar from unipolar major depressive disorders.2 Second, Jaspers’ hierarchical principle stating that “schizophrenic” symptoms have diagnostic prominence over “mood” symptoms for diagnostic and prognostic purposes was inverted.3 Third, avolitional and dissociative symptoms, which were described as distinctive manifestations of dementia praecox, as well as further nuclear manifestations of schizophrenia, were de-emphasized in favor of Schneiderian first-rank symptoms, which greatly influenced current consensus classifications, such as International Classification of Diseases (ICD)-10 and the third and subsequent Diagnostic and Statistical Manual (DSM) editions.4 It is not unfeasible that these changes might result in an unexpected reduction of “points of rarity” among psychosis subtypes by emphasizing common instead of distinguishing features.

Little is known about why some illness concepts survive longer than others, but 2 main factors seem to be involved. First, sociopolitical factors might support an “authority” bias in the existence of particular models.5 Second, there may be a lack of new scientific models that are needed for a paradigm shift that could overturn the previous models. Moreover, although current diagnoses are useful concepts,6 mounting evidence confirms that psychiatric disorders still cannot be conceptualized as definitively valid.

Heterogeneity and pleiotropy are hallmarks of the complex nature of psychoses at the clinical level7 and have further confounded neurobiological research on psychosis. Elsewhere, we emphasized that “... as long as we are not able to disentangle the heterogeneity question at the clinical level, it is unlikely that heterogeneity at the etiologic and pathophysiologic levels may be resolved.”8

General scepticism among new professionals about the value of careful clinical descriptions led some authors to question whether the DSM system might, paradoxically, lead to “the death of psychopathology.”9 DSM diagnoses emphasized reliability over validity and narrowed the scope of psychopathological symptoms and signs to those included in the manuals. Nonetheless, lack of interest in the clinical domain, such as psychopathology, is not an isolated phenomenon for psychiatry; one can find great similarities within other branches of medicine. For example, clinical history, signs and symptoms, and physical examinations are losing ground due to the development of complementary or instrumental exams. In fact, there is not only a psychopathological crisis but also a clinical crisis extending to the entire field of medicine.

Empirical Data Support Multidimensional and Polydiagnostic Models of Psychopathology in Psychosis

Two basic tenets of nosology in medicine hold that (1) symptoms, signs, and disease course conform to syndromes or entities clearly distinct from normality and (2) symptoms and signs are the direct expression of underlying biological dysfunction.

Extensive searches for clinical similarities and differences among psychosis subtypes (eg, between schizophrenia...
Schizophrenia is a complex disorder characterized by hallucinations, delusions, disorganized speech, and abnormal behavior. It is not a disease with clear boundaries or a distinct set of symptoms, which makes it difficult to diagnose and treat. The concept of schizophrenia as a distinct entity has been challenged by the notion of a clinical continuum among psychoses.

Over the past decades, there has been a shift in the understanding of schizophrenia from a categorical approach to a dimensional one. In the categorical approach, schizophrenia is seen as a distinct disorder with a clear set of symptoms. However, this approach has several limitations, including the lack of pathognomonic symptoms, the difficulty in identifying clear boundaries among psychotic disorders, and the lack of stability over time.

Dimensional models in psychiatry are not intended to substitute for categorical ones but instead to complement them in clinical practice and to challenge the exclusivity of the categorical approach. A promising line of research for assessing the validity of competing definitions or continuum models in psychotic disorders is to establish a strategy that combines multidimensional and polydiagnostic approaches to define clinical markers or phenotypes.

The Future of Psychopathology in “Genetic Times”

The strategy of using clinical data to resolve the underlying neurobiological heterogeneity of complex disorders has been used in the past with remarkable success, such as with breast cancer or Alzheimer’s disease. This fruitful approach is essential for developing new psychopathological instruments that enable multidimensional and polydiagnostic assessments with a special emphasis on the hierarchical structure of symptoms. Furthermore, validation studies with normal populations should be undertaken in order to set appropriate cutoff points for these instruments because there is increasing evidence that psychotic symptoms may be present in the general population.

More research is needed to disentangle the underlying constructs of psychopathological symptoms, which continue to be inbred by conceptual and semiological links with “Gestalt Psychology” and outdated localizationist theories. A new psychopathology based upon current models of brain functioning, which focuses mainly on modular functioning, large-scale neurocognitive networks, and schizophrenia can be deconstructed into 3 latent constructs or “domains of psychopathology” with different etiopathogenetic mechanisms and treatments. This line of thinking led recently to the development of a consensus statement on the domain of negative symptoms within the National Institute of Mental Health-Measurement and Treatment Research to Improve Cognition in schizophrenia (NIMH-MATRICS) initiative, which clearly attempts to delineate between negative symptoms and other features of the illness and which advocates a distinct therapeutic indication area.

Setting the boundaries for psychosis is not a limiting problem in dimensional models as it does in categorical models, but whether there is a continuum from normality to psychosis is controversial. This field has made remarkable empirical progress in the last few years, identifying milder forms of expression of the core symptoms of psychosis in the general population. These milder forms are associated with the same demographic and environmental risk factors as the clinical disorder.

Converging evidence from critical studies comparing categorical and dimensional models of psychosis demonstrated that symptoms and disease course, risk factors, endophenotypes, and putative neurobiological underpinnings are better explained in terms of continuous distributions. From a clinical perspective, studies from our own group failed to identify clear boundaries among psychoses in a large data set of psychotic patients. In fact, on the contrary, a monotonic dose-response relationship was found among the main schizophrenia-defining symptoms, main defining-associated features, and features not included in the definition for an empirically derived schizophrenia general factor. Moreover, psychotic symptoms did not possess a taxonic structure, which strengthens the concept of a clinical continuum among psychoses.

Given its theoretical groundwork, great efforts have been made to address the problem of intermediate conditions in psychosis, such as schizoaffective disorder. By examining the heterogeneity underlying schizoaffective disorder in detail, we recently demonstrated that these “zones of rarity” can be distilled into a clear continuum of clinical manifestations, ranging from “nonaffective psychoses” at one extreme to “psychotic mood disorders” at the other.

Regarding the number of putative dimensions underlying psychosis, there is some consensus that there are at least 6 symptom dimensions underlying the latent structure of psychosis: reality distortion, disorganization, negative, catatonia, mania, and depression. We also reported a hierarchical multidimensional model of psychosis comprising 10 dimensions and integrating the majority of psychopathological symptoms already present in psychosis. An insightful alternative paradigm currently under growing study holds the assumption that...
parallel processing, will be welcome. Deconstructing current complex psychopathological symptoms into a set of interacting sub-symptoms and neurobiological signals by means of neuroimaging techniques would help in the development of these new fine-grained instruments. Furthermore, the scope of clinical information gathered should be widened to include not only psychopathological symptoms but also other domains of psychosis and its risk factors. There are many candidates for clinical markers (ie, alternative phenotypes), such as antecedent markers (eg, familial aggregation, obstetric abnormalities, neurodevelopmental abnormalities, premorbid functioning/personality, and precipitating factors), demographic markers (eg, age at onset, gender, ethnicity, and urbanicity), concurrent markers (eg, IQ, cognitive functioning, neurological soft signs, minor physical abnormalities, substance abuse, and community functioning), and predictive markers (eg, diagnostic consistency over time, rates of relapse and recovery, and response to treatment).

Reaching a consensus among experts about the clinical markers to be assessed would lead to delineation of the "psychosis phenome," which has been advocated by the Human Phenome Project as an ideal strategy to deal with complex illnesses.27 This strategy would be capable of generating a clinical phenome scan, which would be included in a database,28 for each patient. This would be appropriate for large-scale phenotypic analysis, such as has recently been reported for bipolar disorder,29 and for the advancing knowledge of the transdiscipline of phenomenics in psychosis.30

Analogous to the genome-wide scanning approach (a top-down hypothesis-driven approach), phenome-wide scanning of psychosis (a bottom-up hypothesis-driven approach) would allow investigators to address whether a given gene, group of genes or genes variants, or a gene-environment interaction is associated with all known psychosis phenotypes, either dimensional or categorical. It would also allow investigators to empirically validate these phenotypes with regard to any pathophysiological mechanism.

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References


