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Reimagining psychoses: An agnostic approach to diagnosis

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ABSTRACT

Objectives: Current approaches to defining and classifying psychotic disorders are compromised by substantive heterogeneity within, blurred boundaries between, as well as overlaps across the various disorders in outcome, treatment response, emerging evidence regarding pathophysiology and presumed etiology.
Methods: We herein review the evolution, current status and the constraints posed by classic symptom-based diagnostic approaches. We compare the continuing constructs that underlie the current classification of psychoses, and contrast those to evolving new thinking in other areas of medicine.
Results: An important limitation in current psychiatric nosology may stem from the fact that symptom-based diagnoses do not "carve nature at its joints"; while symptom-based classifications have improved our reliability, they may lack validity. Next steps in developing a more valid scientific nosology for psychoses include a) agnostic deconstruction of disease dimensions, identifying disease markers and endophenotypes; b) mapping such markers across translational domains from behaviors to molecules, c) reclustering cross-cutting bio-behavioral data using modern phenotypic and biometric approaches, and finally d) validating such entities using etiopathology, outcome and treatment-response measures.
Conclusions: The proposed steps of deconstruction and "bottom-up" disease definition, as elsewhere in medicine, may well provide a better foundation for developing a nosology for psychotic disorders that may have better utility in predicting outcome, treatment response and etiology, and identifying novel treatment approaches.

1. Introduction

The nosology of psychiatric disorders continues to evolve, but remains embroiled in active controversy. Given the overlapping behavioral boundaries of psychiatric disorders, the validity of traditional psychiatric diagnoses remains uncertain. This has limited the establishment of neurobiological models that can guide the development of new and more effective treatment strategies; incorporation of biological/genetic concepts in efforts such as Diagnostic and Statistical Manual (DSM) to refine diagnosis continues to move more slowly than needed.

Perhaps nowhere are these concerns more stark than in the ongoing major dispute, spanning over a century, about how psychotic disorders are optimally defined and classified. This is not merely a theoretical question, but one with immense practical implications for research into the biological basis of psychotic diseases and the development of novel, more effective diagnostic and predictive tests for clinical practice as well as of treatment targets. In this paper, we review the history of this debate, identify the limitations of current approaches, and discuss possible directions for the future in light of emerging new data on the neurobiological substrate of psychotic illnesses as well as evolving approaches to classification of human diseases in the rest of medicine.

2. Classification of psychoses: tracing the past

Psychotic disorders, though not schizophrenia, were recognized at least as far back as ancient Greek (Evans et al., 2003) and Indian descriptions of insanity before the Christian era (Jeste et al., 1985). The identification of these disorders as medical diseases and various attempts at classification of psychoses, however, did not begin until the nineteenth century. One approach, whose proponents were German and French physicians (the "splitters"), was to divide the psychotic disorders into multiple entities based on symptomatology, e.g. catatonia and dementia paranoides (Kahlbaum, 1874), hebephrenia (Hecker, 1871, Cited in Sedler, 1985) and *folie circulaire* characterized by cyclical changes in mood (Falret, 1854). Another approach, by the "lumpers" such as Griesinger (1845), was to view all psychoses as reflecting a single neurobiological entity.

The nosology of psychoses evolved over the first half of the 20th century in three phases (Fig. 1). The first phase was dominated by eminent contemporary theorists; Emil Kraepelin (1899, 1921) (Kraepelin 1921), who kept meticulous longitudinal notes on every patient in his clinic on index cards, observed that patients with catatonia, hebephrenia, and

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paranoid dementia were all characterized by an adolescent or early adult onset, chronic course and a tendency towards functional decline, mental dullness and dementia. He distinguished this "dementia praecox" group from manic depressive insanity, which was episodic with a more favorable outcome. This dichotomy continues to hold sway till today, though Kraepelin himself had doubted this distinction (Berrios and Hauser, 1988). Consistent with the medical models prevalent at his time, Kraepelin argued that dementia praecox, like neurosyphilis, constituted a unique degenerative disease entity whose core feature was a *persistent, declining course* (though he acknowledged in his later writings that recovery could occur in this illness) of unknown etiology. Kraepelin's views were widely influential from the late 19th to the early 20th century when the medical models of psychiatric illness were dominant and the hope was that a neuropathological basis would eventually be discovered. Bleuler (1950) considered the course and outcome to be variable, but defined schizophrenia (a term coined by him) by the core features of *dissociation (or splitting) of the psychic functions occurring in all cases*, leading to the fundamental symptoms of loose association, blunt or incongruous affect, ambivalence, and autism (Bleuler's 4 As); delusions and hallucinations were thought to be "accessory symptoms". In addition to declining course, he noted the interesting combination of avolition and dissociative pathology as defining clinical manifestations. Bleuler viewed this entity as a collection of disorders, the "Gruppe der Schizophrenien", though the field continued to consider this illness as a single disease entity. Jaspers (1946), a psychiatrist and phenomenological philosopher, believed that the core impairment in schizophrenia was one of "*un-understandability*" and an impairment in empathic communication. Kurt Schneider (1959), who focused on the form, rather than on the content of thought processes for defining psychosis, listed 11 first-rank symptoms (which largely refer to *disturbances in ego boundary*) as pathognomonic of this illness. The advent of psychoanalysis (which both raised therapeutic optimism and led to a focus away from categorical diagnosis), coupled with a lack of progress in pathophysiological understanding of psychoses, led to an alternative view, especially in the U.S., that psychoses, like all psychiatric disorders, would be better understood as "reactions" of the individual to one or other stress, i.e. the psychobiological model of the eminent Swiss–American psychiatrist Adolph Meyer (1957). These diverse definitions of schizophrenia were labeled "schizophrenic reaction" in the first edition of the diagnostic and statistical manual (DSMI) of mental disorders, and were variably applied across different countries. A major weakness of this "*eminence-based*" approach was that diagnoses of psychotic disorders lacked reliability, which led to different groups of psychiatrists utilizing differing diagnoses based on what school of thought they endorsed. This was evident in a well-known U.S.–U.K. study which showed a disparity between the U.S./U.K. clinicians in diagnosing psychosis; when presented with the same cases, American psychiatrists diagnosed schizophrenia very frequently while British psychiatrists diagnosed fewer cases as schizophrenia and more as bipolar illness (Kendell et al., 1971).

This motivated the next phase of nosology: of the development of *expert consensus-based* operational criteria such as the research diagnostic criteria (RDC) (Spitzer et al., 1975) and DSM-III (1980), not only for psychoses, but also for other psychiatric diagnoses. While the operational criteria inherent to the DSM-III and then DSM-IV significantly addressed the challenge of diagnostic reliability, there remained the problem of validity, i.e. whether the syndromes as defined actually represent truly distinct and independent disorders (whether they were capturing "pure types" as envisioned by ancient Greek thinkers such as Plato) or clinically similar but etiopathologically distinct entities such as "dropsy". Unfortunately, unlike many other branches of medicine, psychiatry lacked clinico-pathological confirmation of symptom-based diagnoses.

The need for an *evidence-based* approach to classification of psychoses led Robins and Guze (1970) at the Washington University to identify four sets of external "validators" of a distinct and singular psychiatric category, a) phenomenology of cross-sectional symptoms; b) course of illness, (e.g. a chronic, persistent course defined schizophrenia while a recurrent course more likely accompanied an affective psychosis); c) family history, (with the provision that patients with a particular

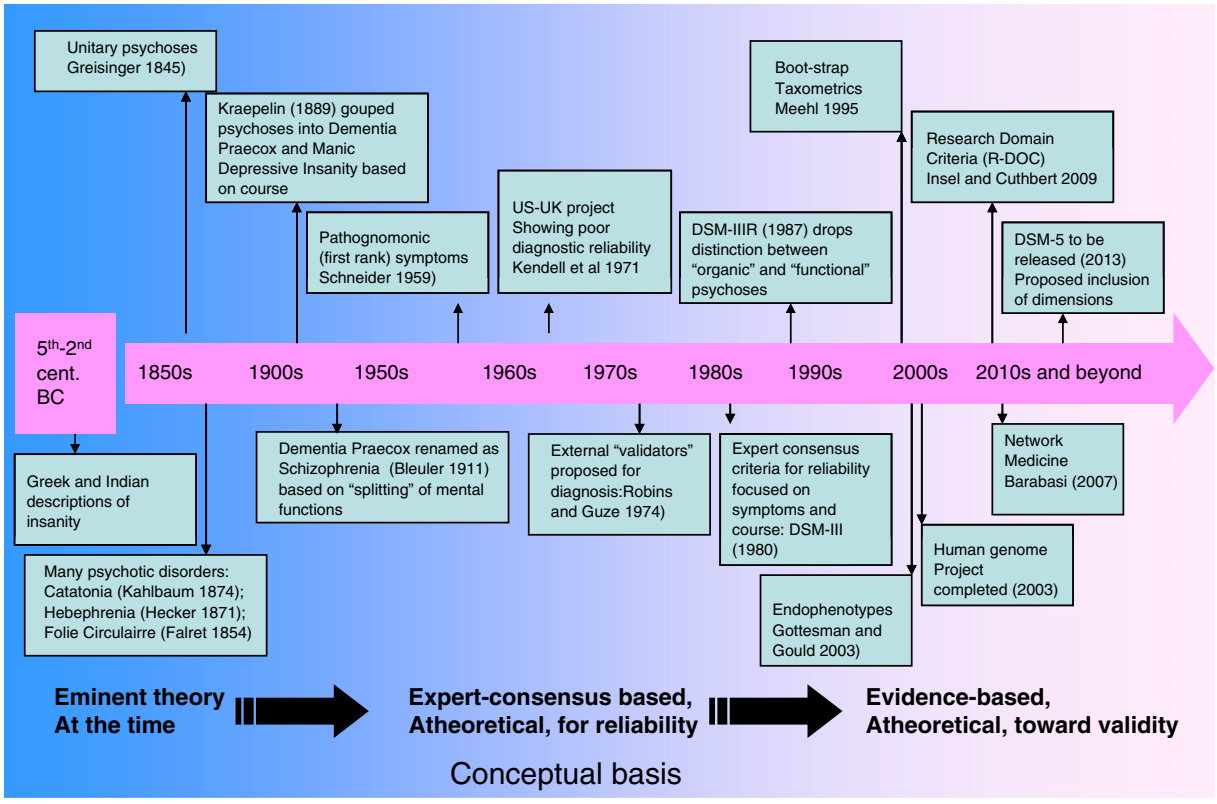

Fig. 1. The history of nosology of schizophrenia.