TITLE:

CONTROVERSIES SURROUNDING THE DIAGNOSIS OF SCHIZOPHRENIA

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ABSTRACT

The diagnosis of schizophrenia and other psychotic disorders in current psychiatric classifications identifies individuals who are severely ill but who have few clinical characteristics in common. The usual picture of psychotic patients is a mixture of mood as well as psychotic symptoms. Fortunately, clinicians do not base their therapeutic strategies exclusively on diagnosis, but also on symptom predominance. Thus, clinicians' treatments have been dimensional in nature for years, though until recently their psychiatric classifications have been mainly categorical.

The main principle in psychosis classification has been the Kraepelinian dichotomy despite its lack of enduring empirical validation. Doubtless, current psychiatric classifications have made great strides in reliability and clinical utility, although these advantages have not been enough to compensate for their shortcomings concerning validity. It has recently been suggested that the Kraepelinian dichotomy may be hindering progress in neurobiological research within psychosis.

Mounting evidence is now fuelling a paradigm shift in the ongoing process of review of psychiatric classifications toward the introduction of complementary dimensional indicators of psychiatric categorical diagnoses. This new approach will allow for understanding psychosis as prototypical extremes of a severity continuum. The gradients of this continuum may begin with subtle expressions in the general population, continue with milder forms in relatives of psychotic patients and subclinical cases, and finally reach the prototypical forms of psychosis at the other extreme.

Future complementary dimensional indicators will require sound instruments capable of reflecting a multidimensional assessment of psychopathological symptoms, poly-diagnostic interviews and the assessment of a wide range of non-symptomatic domains. These new methods of assessment merging created by the shift toward a dimensional paradigm will be applied in the forthcoming new diagnostic criteria and may allow for a phenome-wide scanning for psychosis.

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INTRODUCTION

Schizophrenia (SCH) and other psychotic disorders (OPD) are the most severe and disconcerting of all mental disorders [1]. No other disorder has provoked as much concern in society and in medicine because of its manifold presentations, varied courses and outcomes and because of the lack of awareness about the disorder. While the debate continues in the general public about its role as a true disease, with important social movements against it, clinical knowledge about schizophrenia and other psychoses is growing due to increasing interest in neurobiological research [2-3].

Psychotic disorders usually start in young adulthood and are directly involved in a reduction in life expectancy by approximately 10 years, mostly as a consequence of suicide and loss of physical health. Individuals with psychosis display delusions and hallucinations, thought disorders and negative symptoms (affective flattering, alogia and abulia). Full recovery is not usual, and enduring symptoms and deficient outcomes are the law, not the exception. Affective symptoms are prominent in OPD, such as bipolar disorder (BD), which usually involves dramatic alterations of mood with psychotic phenomena as a frequent accompaniment, and the diagnosis of schizophrenia frequently overlaps.

Recently, cognitive deficits have also been identified as core symptoms of the disorder. Specifically, individuals with the disorder exhibit disturbances in executive, memory. and attentional functioning and alterations in the processing of social information, including processing of emotions, social perception, mentalization and social knowledge [4].

Psychoses cover a wide range of disorders, including not only SCH and BD, but also less common psychotic disorders such as schizophreniform, schizoaffective, brief psychotic, delusional, and shared psychotic disorders; psychotic disorder not otherwise specified (NOS); substance-induced psychotic disorder; psychotic disorder due to a general medical condition (GMC); and atypical psychoses.

There are now highly developed rehabilitation procedures available in addition to effective drugs. Treatment in natural settings is mainly based on prescription of drugs for a variety of psychopathological conditions that are not necessarily related to nosological categories [5]. Heterogeneity of the diagnostic constructs have hampered the advancement of potential drug specificities.

In this essay, the so-called 'clinical problem' of schizophrenia, which is a special case of clinical heterogeneity, will be reviewed in terms of its historical roots, important current issues, and future lines of progress.

RELEVANCE OF SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS

A first approach to the relevance of schizophrenia and other psychoses arose from comparative data on the burdens of brain disorders that have seen widespread use in evidence-based health policy [6]. The epidemiological and economic impact of brain disorders has been relatively little-researched, though there are now consistent studies reporting that brain disorders figure amongst the leading causes of death and disability. Studies on cost estimates for twelve major diseases from European collaborative agencies

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have demonstrated that mental illnesses have among the highest shares of disability-adjusted life-years (DALYs) [7].

A second approach to the true dimension of SCH and OPD is to analyze their prevalence. Traditionally, they have been considered low prevalence disorders. International collaborative research conducted over the past 30 years by the World Health Organization (WHO) [8] indicated that the lifetime prevalence for schizophrenia was assumed to be constant and low (1% of worldwide population), and the same estimates were reported for BD. However, Perala et al. [9] reported the results from one of the most comprehensive general population surveys of psychotic disorders carried out to date. It was achieved in a nationally representative sample in a large data set of Finland inhabitants aged 30 years or older, and the lifetime prevalence of all psychotic disorders was 3.06% and rose to 3.48% when registered diagnoses of the non-responder group were included. In addition, for the first time they examined the prevalence of specific psychotic disorders separately, including SCH and BD disorders and the seven less-common psychosis subtypes. Thus, these results emphasize the role of other subtypes of psychosis apart from schizophrenia and BD.

In addition, a recent systematic review demonstrated that, contrary to previous interpretations, the incidence of schizophrenia shows prominent variation between sites, leaving room for new strategies for interventions in risk populations [10]. If this finding is applied by extension to psychotic disorder (PD), the epidemiological scenarios of PD will change to allow for ascertaining new rich and informative gradients that can guide future research worldwide. In addition, the effect of the individual's experiences will gain new importance through an adequate weighting of environmental risk factors in the etiology of psychoses.

A shortcoming of current research on SCH and OPD is the lack of understanding of their etiology. Research into the mechanism of action of the drugs used to treat psychosis has not provided a clear understanding of the pathogenesis of these diseases. Thus, there is no evidence of clear pathological lesions, and no specific laboratory, neurophysiological, neuroimaging, or any other complementary findings have been reported. However, it is accepted that SCH and OPD can be understood as subtle disorders of brain development 11-14].

SCH and OPD are multifactorial disorders, though their greater risk factor is having a relative with the illness [15]. Their prevalence in the general population increases from 1% to 10% if the subject has a first-degree relative with the illness or to 40% if the proband has a monozygotic twin or two parents with the illness. The heritability score for schizophrenia is approximately 0.8, but the genetics are complex [16]. The interpretation of genetic data has proven difficult, and several interactions (genetic-environment, gen-gen, etc.), copy number variants and other molecular mechanisms are now being studied. Nevertheless, pooled estimated heritability for SCH and BD range from 80% to > 90%, respectively, which are much higher than the rates published for breast cancer (5% to 60%) and Parkinson's disease (13% to 30%), for which several candidate genes are now well established.

Environmental factors also play a role in the etiopathogenesis of PD by disturbing neurodevelopment at early stages (e.g., obstetrical complications, premorbid neurodevelopmental abnormalities); by continuous exposition during childhood and adolescence (e.g., migration, urbanicity, social isolation); and by later insults in late

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childhood and adolescence (e.g., drug abuse). It seems that both premature and later exposition to environment insults may be predisponent factors to developmental abnormalities of the brain as mediating factors that increase the vulnerability to the illness. Within environmental factors, the relationships between trauma and psychosis seem to be complex and multiple [17]. At least for some people, a traumatic experience during early childhood may have later consequences for the individual and may be expressed either as 'posttraumatic stress disorder' [18] or as critical or commanding voices in adulthood [19], which characteristic 'Schneiderian' symptoms of psychosis.

Although gene-environment (GxE) interactions were thought to be rare in psychiatry, empirical findings of measured GxEs are now emerging [20,21]. Preliminary findings of epidemiological gene-environment interaction studies are suggestive of widespread gene-environment interactions in the etiology of schizophrenia [22].

Failure of neuronal homeostasis was recently devised as an integrative etiopathogenic matrix for common neuropsychiatric disorders [23]. These authors emphasize the role of homeostasis as the main mechanism accounting for disruption of biological processes, which might lead to neuronal dysfunction in a developing brain. As a multitude of processes contribute to the homeostatic regulation of neuronal networks, symptomatic output or expression will depend on the function(s) subserved by the disturbed neuronal networks, such as in the case of mental retardation. Thus, an overlap of neurological and psychiatric phenotypes as is usually observed might result from different causes, such as genetic, environmental or epigenetic, since there are hundreds of known genes whose alteration causes the same psychiatric disturbances (e.g., mental retardation) and, at the same time, one specific gene can cause a myriad of psychiatric disturbances (e.g., Huntington's disease, 22q11.2 deletion or duplication).

DIAGNOSTIC ISSUES IN PSYCHOSIS

Psychiatric diagnosis serves at least three functions, namely communication with others, targeting patients to be treated, and identification of clinical markers of the underlying neurobiological dysfunction since symptoms are the direct expression of the pathological process [24].

Clinical symptoms are still the basis for psychiatric diagnoses because valid biological markers have not been found and because varied patterns of beginnings and courses and many possible final outcomes, which vary in intensity and frequency from normality to severe disability, are possible.

In the epoch of classic psychopathologists, it was assumed that patients suffering from SCH and OPD could be classified into 'essential forms' by the presence of a characteristic set of symptoms. Paradoxically, the three most influential authors argued in favor of three different definitions of patients diagnosed early as either 'dementia praecox' or later as schizophrenia. As an illustration of the above, we have elsewhere examined the concordance between the operationalized definitions of schizophrenia from these three classic authors (Kraepelin, Bleuler and Schneider) in a sample set of 115 inpatients. The mean concordance rate among these three criteria was low, as was the concordance of the three definitions with DSM-III-R criteria [25].

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Traditionally, affective disorders were regarded as having a remitting course and relatively more favorable overall outcome than schizophrenia. However, longitudinal studies addressing long-term outcomes have demonstrated that schizophrenia does not necessarily have a poor outcome [26,27] and that BD results in poorer outcomes than previously reported [28].

Currently available evidence regarding symptomatology has yielded a definitive lack of specificity of any psychopathological symptom [29,30], such as Schneider First Rank symptoms 31], thought disorders [32,33] or negative symptoms [34]. Despite the above considerations, there is some evidence supporting some subtypes for schizophrenia at the syndrome level (the deficit syndrome of schizophrenia) [35] and at the psychopathology level, such as negative symptomatology [36].

Regarding the specificity of symptomatology in affective psychosis, there are no doubts about the great value of euphoric mood [37], but debate continues about the value of depressive symptomatology to helpfully distinguish unipolar and bipolar depression [38]. In addition, the absence of psychotic symptoms in diagnostic criteria for bipolar disorder reinforces the notion that psychosis is a core feature of SCH but not BD [39]. However, mania emerged as the first factor in a factor analysis of a large sample comprising 555 patients with a nonaffective psychosis [40].

Such considerations are not only historical speculations. They still apply in current definitions of both schizophrenia and bipolar disorder since an inspection of possible SCH or BD subtypes in DSM definitions invariably leads to striking findings. As we reported elsewhere, 483 'clinical forms' of schizophrenia can be isolated if all possible combinations and outcomes of criterion A for schizophrenia in the DSM-IV-TR classification [41] are computed [42]. The range is even broader for DSM-IV bipolar disorder since the number of possible combinations of the core episodes ranged from 163 for a manic episode to 37,001 for a mixed episode. When the full collection of specifiers that DSM-IV-TR applies to bipolar disorder was used, the number of possible combinations was over 5 billion [43].

This finding underscores the need for inclusion of non-symptom domains for the diagnosis of SCH and OPD, such as the course. As described above, symptom clusters cannot by themselves define DSM disorders. This led to the paradoxical situation of the inclusion of 'schizophreniform disorder' in the DSM, which is identical to schizophrenia in clinical characteristics but with a brief time course. Thus, a poorer prognosis, such as a diagnosis of schizophrenia and not schizophreniform disorder, is a result not of the symptomatology but of the duration of symptoms.

Psychotic symptoms exceed the limits of 'classic' categories of psychotic disorders in current nosotaxias. Many other disorders can include psychotic symptoms, such as some childhood disorders (mental retardation and pervasive developmental disorders), cognitive disorders (delirium and dementia), substance-related disorders, anxiety disorders (post-traumatic stress disorder) and schizotypic disorder, which was previously considered a personality disorder but is now included within the group of Other Psychotic Disorders in both the DSM and ICD systems.

Furthermore, psychotic symptoms are rather ubiquitous, not only in psychiatric patients but also in surveys of normal populations. Milder forms of psychotic symptoms were

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found to be highly prevalent in the general population [44,45], with estimates ranging from 1% [46] to 17% [44]. Differences in either the assessment process and instruments or in the thresholds and definition of psychotic symptoms, as well as differences between the populations surveyed and time periods, may account for the high variability of these estimates.

Reports on the incidence of psychotic symptoms are scarce. Tien et al. [47] found a one-year incidence of 4.6% for hallucinations in the Epidemiologic Catchment Area study. Results from an 18-month follow-up of a national survey to assess self-reported psychotic symptoms in Great Britain reported that 4% of the population reported incident symptoms at follow-up [48].

While the symptom level qualifying for a diagnosis of psychosis is not exempt from significant problems concerning specificity, it is clear that greater problems might exist at higher levels, such as the syndrome level. For example, there are at least 23 operationalized diagnostic criteria for schizophrenia, which identify different subpopulations of patients [49]. An examination of the concordance between classic, country-based and empirically derived definitions yielded rather low concordance [49,50].

IS THE KRAEPELINIAN DICHOTOMY STILL USEFUL?

"We are of course, clearly aware of the fact, which we don't deny even for a second, that the greater part of all genetic work in Psychiatry would immediately collapse like a house of cards if Kraepelin's theory was shown to be altogether mistaken" (R Gaupp, 1939 as quoted by Jablensky, 1999) [51].

The Kraepelinian dichotomy concerning the distinction between 'Demence Precoce' and 'Manic-Depressive Psychosis' has been enthroned as the main classificatory psychiatric paradigm in the last two centuries [52-54] and is the predominant principle in current classificatory systems. Differences in course and different hypothesized aetiologies initially provided the basis for delineation of more pure types by splitting apart the group of psychoses [55]. This distinction has survived in spite of Kraepelin's concerns about the limitation of his dichotomy [56] and despite the lack of evidence of a specific underlying brain disease [57].

Important uncertainties of the Kraepelinian dichotomy for clinical and research use have been the subject of great debate in the past [58], and they have recently been revisited in several psychiatric supplements or monographs [59-62]. With few exceptions, most authors have emphasized the inadequacy of the prevailing taxonomic system for the psychiatry of the 21st century, although conservative postures were recommended in order to ease the transition between the old and new approaches.

The separation of categories in current noxotaxias is very often blurred and imprecise, and there are no objective tests to separate or identify the conditions. However, while the latter is assumed, the descriptions of these disorders indicate that such discrete categories exist.

Several recent studies have addressed concerns about the 'Kraepelinian dichotomy' from clinical and neurobiological perspectives. The success of this dichotomy relies on its success in 'practical' aspects of its application (high clinical utility and reliability) over its

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construct validity (low validity). However, other psychosis subtypes have traditionally been excluded in research studies. Looking at the extremes of a continuum emphasizes dissimilarities over commonalities, leading to 'illusory prototypes'. For example, mixed psychoses, such as schizoaffective disorder and atypical psychosis, or psychosis not otherwise specified are usually missed or excluded in research. Indeed, searching Pubmed (February 2009) for articles that included "psychotic disorder not otherwise specified" or "mood disorder not otherwise specified" within their titles yielded only one study [63] and none, respectively.

Other uncommon subtypes of psychoses encompassing a mixture or succession of psychotic, affective and motor symptoms, such as 'cycloid psychosis' and 'catatonic disorders', have also generated great nosological uncertainty since they are not well accommodated in current SCH or BD definitions [64]. Current evidence supports that cycloid psychoses are closer to affective psychoses than to the schizoaffective or schizophrenia disorders. Cycloid psychosis resembles SCH and BD in symptomatology since psychotic and bipolar symptoms are prominent, but its course and outcome are more similar to affective disorders. However, by considering cycloid psychosis from a comprehensive approach, it can be better understood as a point on a psychotic continuum [65,66].

The Kraepelinian dichotomy does not cover the whole psychosis spectrum, and more categories are needed. Diagnosis does not assure differences in functionality either among psychoses or among psychiatric disorders. Symptom overlap is the rule and not the exception. Affective symptoms are rather common among non-affective psychoses [64,67], and psychotic symptoms, both mood congruent and incongruent, are prevalent in BD [68,69].

The DSM system is based on a hierarchical structure that ranks subtypes on the basis of exclusion due to the fulfillment of criteria for a hypothetically superior disorder. While this hierarchical rule is a way to reduce comorbidity and is a useful and practical convention for achieving parsimony of diagnosis, it introduces constraints into the clinical presentation of patients. Few studies have addressed this problem. Zimmerman et al. [70] reported that between 20 and 34% of depressed outpatients also fulfilled criteria for generalized anxiety disorder when the hierarchical principle was removed. In addition, comorbidity is the rule, not the exception, and it should be accepted as an integral part of the disorder [71]; it has been reported that schizophrenia patients display many other psychiatric disorders throughout the course of their illness. A recent study reviewed the literature to examine disorders frequently associated with schizophrenia, such as anxiety, depression and substance abuse, and considered four possible kinds of relationships: random association, secondary manifestations of schizophrenia, truly comorbid disorders, or direct consequences of the disorder [72]. They found that schizophrenia patients also have a lifetime diagnosis of depression and substance abuse in 50% and 47% of cases, respectively. Moreover, 29%, 23% and 15% of schizophrenia patients displayed lifetime diagnoses of post-traumatic stress disorder, panic disorder and obsessive-compulsive disorder. All of these disorders occurred at rates exceeding those in the general population. The evidence from this review suggests that depression, substance abuse and obsessive compulsive disorder are comorbidities that occur more as part of the illness, probably related to its underlying pathogenesis, than as random or choice associated phenomena. This panorama could also be notably augmented if the exclusion criteria indicating the impossibility of co-occurrence of SCH and OPD were ignored.

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Since diagnosis is an essential step in research as well as psychiatric practice, evaluations of both short- and long-term diagnosis stability were needed to increase knowledge about the causation of psychoses. A common finding to these studies is that rates of consistency of some diagnoses decreased as the follow-up period increased [73-75]; short-term studies demonstrated relatively good stability in diagnoses of SCH and BD [76]. This finding is in full agreement with a recent report based upon an analysis of a register from a catchment area comprising a large number of patients (n=10.025) with at least ten consultations over a period of ten years, which found a low temporal consistency of diagnoses for schizophrenia and mood disorders in usual practice [77].

CURRENT STATE OF THE EVIDENCE FOR THE KRAEPELINIAN DICHOTOMY

Psychiatric disorders are, by their nature, complex multilevel phenomena [21,78]. Thus, one way to address the current status of the Kraepelinian dichotomy is, in addition to examining its historical roots and conceptual basis and its current limitations [79], to review results from potential validators. In this part of the article, we will review to what extent studies examining external validators, from the genetic level to studies addressing potential biological markers, support the Kraepelinian dichotomy.

Schizophrenia and mood disorders run in families, and it is assumed from **genetic studies** that they are highly heritable. Over the past several years, mounting evidence from genetic association and linkage studies has reported increasing evidence that there is a large array of candidate genes accounting for each disorder and its predominant clinical presentation [81]. In addition, new strategies for studying neuropsychiatric disorders, such as molecular cytogenetics and copy number variants, will uncover new candidate genes [81].

Although many candidate risk genes were originally implicated in SCH, a recent review of genetic findings in psychosis provided evidence for an expanded set of shared genetic associations of these 'schizophrenia genes' with many psychosis dimensions, paving the way to a psychosis continuum [82].

A recent work published in the January 17 issue of the Lancet reported the largest and most definitive study to date challenging the Kraepelinian dichotomy by showing a shared genetic risk for SCH and BD [83]. The authors of the study followed more than nine million Swedish people over 30 years. Children and siblings of schizophrenic patients showed relative risks of 5.2 (95% CI 4.4 to 6.2) and 3.7 (95% CI 3.2 to 4.2), respectively, for having bipolar disorder themselves, and for patients with bipolar disorder, their children and siblings had relative risks of 2.4 (95% CI 2.1 to 2.6) and 3.9 (95% CI 3.4 to 4.4), respectively, for developing schizophrenia. Two additional findings from this study were highly relevant. First, a lower estimation of heritability was found than in previous investigations, 64 percent for schizophrenia and 59 percent for bipolar disorders. Second, the correlation of genetic risk for the two disorders was 0.60, a number that indicates that a large part, but not all, of the genetic risk for the disorders is shared.

Owen and Craddock [84], in the accompanying editorial, emphasized the importance of the results and wrote: "We now must ask whether clinical practice and research can continue to be best served by persistence in basing our diagnoses on the binary concept".

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Few studies have been carried out relaxing the hierarchical rules or exclusionary principle. Depressive disorder and generalized anxiety disorder have demonstrated shared genetic factors, with or without using the diagnosis hierarchy ([85,86]. Moreover, bipolar, schizoaffective and schizophrenia disorders demonstrated significant genetic associations when they were nonhierarchically defined [87].

As the identification of heritable quantitative traits may increase the power of genetic studies substantially, to what extent the symptom dimensions may have a heritable genetic basis is the subject of great interest. This has recently been accounted for in a study [88] that evaluated the clinical and demographic features and symptom dimensions of schizophrenia in 137 families. They found significant evidence supporting the heritability of schizophrenia dimensions and clinical characteristics, and those psychopathological dimensions explained more of the disease characteristics than did the diagnosis [89].

Certain genetic studies addressing particular associations with a quantitative approach to symptomatology (i.e.: positive, negative and disorganization dimensions) are in the beginning stages. Individuals with severe negative symptoms are more likely to inherit the high-risk haplotype of DTNBP1 ([90,91]; new data also suggest that DTNBP1 influences the severity of intellectual decline in schizophrenia [92]; and positive and disorganization symptoms have been associated with functional variants from a region of chromosome 6q [93].

Relatively little is known about the **familial history of psychosis subtypes** and their dimensional counterparts. Familiarity is not heritability. Traits are familial if members of the same family share them, for whatever reason. Traits are heritable only if the similarity arises from shared genotypes. The distinction between familiarity and heredity is not always so obvious.

A number of studies with conflicting results have examined the familiarity of schizophrenia and its syndromes. While some authors have favored the use of the familial risk approach for delineating subtypes of psychotic disorders [94], others have discouraged their use due to the relative lack of specificity of familial risk across subtypes of psychotic disorders [95]. Previous studies examining the relationship between psychopathological dimensions and a family history of schizophrenia or mood disorders in psychosis have rendered a myriad of non-converging results.

A recent study by our group on a large sample of psychotic probands and their first-degree relatives aimed to further scrutinize the relationship between psychopathological syndromes of the psychotic illness and familial liability to schizophrenia and mood disorders [96]. In this study, familial morbid risk of schizophrenia was predicted by the negative syndrome in probands, but a relative independence of clinical syndromes and diagnostic categories from familial liability to schizophrenia, bipolar disorder, or both was found. Familial loading for schizophrenia and mood disorders cut across the DSM-IV categories of psychotic disorders in probands, suggesting some continuity in the causes of the psychotic illness.

One of the most fruitful lines of research in the past decade has been the study of psychiatric disorders from a life-course perspective by examining their **neurodevelopmental precursors** since it is now evident that SCH and OPD can be

conceived as the adult outcomes of processes that have their origins at young ages [97]. Indeed, genetic and environmental risk factors have been seen to operate across diagnostic categories [98-100]. Moreover, quantitative but not qualitative differences in risk factors between schizophrenia and affective psychosis and preferential associations with predominant symptoms are consistently reported [101]. The preponderance of negative features within the psychopathological spectrum was associated with "developmental" factors, such as childhood dysfunction, increased cerebral ventricle size, and familial morbid risk of schizophrenia. Affective features were modulated preferentially, though not specifically, by "social" factors, such as ethnic group, adverse life events and familial morbid risk of affective disorder.

Emerging evidence from a thorough review of biological markers, life course, and cross-cultural findings led Dutta et al. to conclude that psychotic illness is merely the final common pathway of a cascade of risk factors, which can deviate an individual's developmental trajectory into psychosis [102]. Moreover, **premorbid risk factors for psychosis** were not able to discriminate between dimensional groupings of symptoms or categorical diagnoses [103], suggesting a non-specificity across antecedents of psychosis.

A variety of potential abnormalities in neurodevelopment, such as **neurological soft signs** and neuropsychological performance, are known antecedents of psychosis. Indeed, they are consistently found in individuals who later develop psychosis, and most studies have found that they are much more abnormal in schizophrenia than bipolar disorder [104]. In fact, children who later develop bipolar disorder do not share the excess of subtle neuromotor and cognitive impairments of their pre-schizophrenic counterparts and often appear superior to the normal population in motor development and school examinations [105].

From **neuroimaging studies,** we know that very early-onset schizophrenia patients show striking anatomical profiles of accelerated gray matter loss, with a specific shifting pattern of brain tissue loss in schizophrenia in the follow-up [106]. These deficits evolve dynamically and increase throughout adolescence. These emerging patterns seem to be related to patients' psychotic symptom severity and cognitive impairments.

What is relevant here is whether there are differential neuroimaging profiles for SCH and OPD. This question was further examined by McDonald et al. [107], who reported white matter volume reductions in the left frontal and temporo-parietal regions for both schizophrenia and bipolar disorders, but different locations of gray matter reductions for each of the disorders in a magnetic resonance imaging study. This study showed both similarities and dissimilarities in the brain structural abnormalities related to variable genetic risk for SCH and BD.

Another level of analysis to challenge the Kraepelinian dichotomy is the endophenotypic level. **Endophenotypes** were introduced by Gottesman and Shields [108] into the schizophrenia literature to denote quantitative measures from functional markers in the pathways between genetic variation and clinical manifestation of the disorder. Later developments of the concept [109] resulted in the establishment of criteria for potential candidate markers, emphasizing their genetic properties. Originally, endophenotypes were proposed specifically for either SCHZ or BD, but as true intermediate markers, they now form a vast group in a shared pool emphasizing more commonalities than differences

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[110,111] and showing a gradient of quantitative measures across psychosis, as was reported for cognitive deficits [112].

Cognitive deficits have become an important focus for psychiatric research in major psychiatric disorders, especially schizophrenia [113,114], and they are endorsed as a 'core' deficit of schizophrenia patients as well as patients with other psychotic disorders. Cognitive impairments better predict functioning in daily life than symptoms in SCH and BD [115].

As cognitive dysfunction is now a recognized, relevant and nearly ubiquitous aspect of schizophrenia that will undoubtedly be important for understanding the disease and for treatment success, it has been proposed that it be included within the diagnostic criteria of schizophrenia in the future DSM-V [116]. However, though this proposal was accepted without much criticism, there are at least three lines of evidence against this proposal. First, it is often forgotten that any group of psychiatrically disordered patients may be found to have cognitive impairments in comparison to a control population. Cognitive dysfunction is widely distributed across many other psychiatric disorders, such as depression, anxiety, obsessive-compulsive disorder or personality disorders. A recent study carried out on a Swedish conscript cohort, which included an IQ assessment and full psychiatric evaluation at conscription of all 18- to 19-year-old males, found that reduced intellectual functioning was found in association with psychosis and neurotic disorders including depression, personality disorders, alcoholism, and drug dependence [117]. This follow-up study consistently demonstrated that the strong association between premorbid cognitive performance and follow-up assessment might represent a combination of antecedents (as demonstrated in those who developed schizophrenia some years later) plus coincidence [117].

Second, there is now strong evidence against qualitative differences in cognitive performance between schizophrenia and mood disorders. Most studies report that any differences are mainly quantitative, not qualitative, in nature [118-120].

Third, we carried out a poly-diagnostic study assessing the empirical validity of 23 diagnostic criteria of schizophrenia through neuropsychological performance in a large set of patients suffering from psychosis [121]. While an association of schizophrenia definitions with predominant residual symptoms with cognitive impairment was found, the functional outcomes of the patients achieved superiority over all schizophrenia diagnostic criteria, suggesting a lack of diagnostic effectiveness of cognitive dysfunction over schizophrenia diagnosis [121].

Taken together, the Kraepelinian dichotomy continues to lack the enduring empirical validation to be maintained as the main paradigm for diagnosis in psychiatry. Great advantages in reliability and clinical utility are no longer enough to continue overlooking the lack of validity.

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EXPERT COMMENTARY

While a change in the diagnostic paradigm from the exclusive Kraepelinian dichotomy to a combination of current categorical contentions and new dimensional scorings is a nosological revolution, it will not dramatically affect practice. Three arguments support this statement. First, as described above in the Introduction, psychiatrists are now and have long been mainly "dimensional" in their prescribing practices since drugs are not necessarily prescribed for nosological categories, but according to the intensity of behavioral syndromes. Second, advances from other branches of medicine allow us an understanding of the common usage of both dimensional and categorical constructs, such as in other complex diseases (hypertension and diabetes). And third, psychiatric nosology is a 'moving target' and has been changed many times in the last centuries. We have experienced numerous changes of the names and amplitudes of many disorders in the successive editions of current classifications.

Though the combination of categorical and dimensional diagnosis notably increases the validity of psychiatric syndromes, the future mixed DSM-V classification will have to account for many of the problems that current categorical models now face. Validity is not assured only for the paradigm shift, and empirical guided studies should be aimed to challenge it.

FIVE-YEAR VIEW

In the next several years, we will have available new, sound instruments both for research and practice that will allow better characterization of multiple domains of symptomatology of psychotic patients. At least three types of instruments should be developed. First, multidimensional assessment instruments seem to be one of the most promising approaches since they can capture and quantify a wide range of psychopathological symptoms in each patient. Quantification of symptoms will be useful to better characterize patients' course and response to treatment, and it will allow for new and fine-grained phenotypes to be used in research.

Moreover, in order to examine in depth the nosological status within psychosis, poly-diagnostic instruments will be needed to empirically re-test all available clinical constructs for any hypothetical subtype proposal.

And third, non-symptomatic manifestations, such as antecedent, concurrent, and predictive clinical markers, should be investigated as alternative phenotypes.

Ideally, by analogy to a genome-wide scanning approach, a complete clinical phenome scan should be available for each patient for clinical purposes and for groups of patients for neurobiological research. This approach will include dimensional and categorical and clinical and non-clinical phenotypes, in a strategy that is being called a 'phenome-wide scanning of psychosis' [122].

Endophenotype research from the cognitive, neurophysiological and neuroimaging disciplines may eventually help to refine new targets or avenues to increase our knowledge of underlying pathophysiological processes. It might also establish bridges between outcome and response to treatment parameters and these neurobiological underpinnings, not only in psychosis, but also in other psychiatric disorders.

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Finally a pending question is whether to rename psychosis within the paradigm shift. In this respect, the replacement of current terms, such as SCH and BD, should be guided by two aims: first, reducing stigma in patients and families since most of our terms are now used as negative metaphors, both in popular usage and the media. This stigma discourages individuals from awareness and from seeking treatment for their illness. Second, a relabeling of these disorders should increase the labels' descriptive contents based on current clinical and neurobiological findings.

Several new names have now been proposed, such as integration disorder in Japan [123], which encompass good clinical and neurocognitive explanations; dopamine dysregulation disorder, although this name has been used recently to describe the iatrogenic disturbance that may complicate long-term symptomatic therapy of Parkinson's disease [124]; sensitization disorder to account for the diversity of environmental influences associated with schizophrenia [125]; and recently, salience dysregulation syndrome [126].

The logic behind the paradigm shift and its associated label change, which are now in progress, is to more precisely describe phenotypes to allow for new advances in neurobiological research and therapeutic management of psychotic patients. Nonetheless, we have to be aware that the new paradigm is a tool that must itself be analyzed based on its coherence, logic and empirical consistency, since no paradigm can stand without supporting evidence.

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