

# State of the art

## *The diagnostic concept of schizophrenia: its history, evolution, and future prospects*

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To the best of present knowledge, schizophrenia is a disorder with variable phenotypic expression and poorly understood, complex etiology, involving a major genetic contribution, as well as environmental factors interacting with the genetic susceptibility. Multiple genes and different combinations of their polymorphic variants provide the genetic background, with a proportion of the transmitted genotypes remaining clinically unexpressed. Schizophrenia occurs in diverse populations at comparable rates,<sup>1</sup> which is consistent with an ancient origin

*More than a century since the delineation of dementia praecox by Kraepelin, the etiology, neuropathology, and pathophysiology of schizophrenia remain elusive. Despite the availability of criteria allowing reliable diagnostic identification, schizophrenia essentially remains a broad clinical syndrome defined by reported subjective experiences (symptoms), loss of function (behavioral impairments), and variable patterns of course. Research has identified a number of putative biological markers associated with the disorder, including neurocognitive dysfunction, brain dysmorphology, and neurochemical abnormalities. Yet none of these variables has to date been definitively proven to possess the sensitivity and specificity expected of a diagnostic test. Genetic linkage and association studies have targeted multiple candidate loci and genes, but failed to demonstrate that any specific gene variant, or a combination of genes, is either necessary or sufficient to cause schizophrenia. Thus, the existence of a specific brain disease underlying schizophrenia remains a hypothesis. Against a background of an ever-increasing volume of research data, the inconclusiveness of the search for causes of the disorder fuels doubts about the validity of the schizophrenia construct as presently defined. Given the protean nature of the symptoms of schizophrenia and the poor coherence of the clinical and biological findings, such doubts are not without reason. However, simply dismantling the concept is unlikely to result in an alternative model that would account for the host of clinical phenomena and research data consistent with a disease hypothesis of schizophrenia. For the time being, the clinical concept of schizophrenia is supported by empirical evidence that its multiple facets form a broad syndrome with non-negligible internal cohesion and a characteristic evolution over time. The dissection of the syndrome with the aid of endophenotypes is beginning to be perceived as a promising approach in schizophrenia genetics.*

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and—as far as records go—its incidence has not changed much over the past two centuries.

Diagnostic concepts play a critical role in the management and treatment of schizophrenia patients; in research aiming to identify risk factors and causal mechanisms, as well as in attempts to resolve contentious issues, such as comorbidity and relationships among proximal or partly overlapping disorders. A principal source of difficulty in this endeavor is the complex nature of the disorder itself, and the inherent weakness of the diagnostic concept of schizophrenia, in that it remains based upon assumptions about an underlying but still unknown disease process. Most of the attributes defining schizophrenia are primarily inferential and depend on self-reported subjective experience. The underlying structural and functional pathology is insufficiently understood, and there is no objective diagnostic test or validated biological marker that could provide a secure anchor for either clinical decision-making or biological and epidemiological research. Recurrent controversies in schizophrenia research concern its delimitation from other psychoses, bipolar affective disorder, and neurodevelopmental disorders; the validity of the schizophrenia spectrum concept and the existence of subclinical forms, such as schizotypal disorder; the utility of its categorical classification as compared with descriptive symptom dimensions or subtypes based on quantitative cognitive traits,<sup>2</sup> and the discordances between the *ICD-10* and *DSM-IV* criteria for its diagnosis. The aim of the present paper is to highlight aspects of the origin, evolution, and current state of the diagnostic concept of schizophrenia—ending with a speculation about its future prospects.

## A brief overview of the history of the concept

### Kraepelin and the construction of dementia praecox

The disease concept of schizophrenia is of a relatively recent origin, as compared with disorders such as melancholia, mania, or generic “insanity,” all known since antiquity. By the middle of the 19th century, European psychiatrists began describing disorders of unknown causes, typically affecting the young, and often progressing to chronic deterioration. In France, Morel<sup>3</sup> referred to such cases as *démence précoce*, while in Scotland, Clouston<sup>4</sup> coined the term “adolescent insanity.” In Germany, Kahlbaum<sup>5</sup> delineated the catatonic

syndrome, and his disciple Hecker<sup>6</sup> described hebephrenia. However, it was Emil Kraepelin (1856-1926) who proposed to integrate those varied clinical pictures into a single nosological entity under the name of “dementia praecox,” based on his longitudinal observations of a large number of clinical cases exhibiting a common pattern of course which ultimately resulted in severe cognitive and behavioral decline. Elaborating on the description of the disorder in successive editions of his *Textbook*,<sup>7,8</sup> Kraepelin acknowledged the diversity of the clinical pictures subsumed under dementia praecox and articulated nine different “clinical forms” (*Table I*). Although the core features of the disorder could not always be identified reliably in the cross-section of the clinical presentation, Kraepelin emphasised that “we meet everywhere the *same fundamental disorders* in the different forms of dementia praecox [...] in very varied conjunctions, even though the clinical picture may appear at first sight ever so divergent.”<sup>8</sup> The “fundamental disorders” which supported the concept of the disease entity were cognitive deficit (a “general decay of mental efficiency”) and executive dysfunction (“loss of mastery over volitional action”), most clearly manifested in the residual, “terminal states” of the illness. Kraepelin was reluctant to impute etiological significance to the clinical variants he described, and regarded the issue of a unitary process versus multiple disease states within dementia praecox “an open question.” His approach to the definition and classification of psychiatric disorders was, essentially, based on comprehensive clinical observations and naturalistic descriptions of a large number of individual cases. Kraepelin never issued a definitive list of diagnostic criteria for dementia praecox and was particularly careful to avoid claims about any “pathognomonic” symptoms. The ultimate validation of the disease entity, Kraepelin believed, would come from neuropathology, physiology, and biological chemistry of the brain, whereas the specific contribution of clinical research consisted in identifying replicable patterns of intercorrelations between symptoms, course, and outcome.

Kraepelin’s views on the typology of mental disorders—often quoted, occasionally misquoted, and still debated—continue to frame much of the present-day psychiatric discourse. It looks indeed as if “psychiatry still lives in a Kraepelinian world,”<sup>9</sup> but the exact contours of its map often get blurred. Towards the end of his career Kraepelin experienced doubts about the valid-

ity of his original formulation of the nosology of psychoses and, in a seminal paper published in 1920, he conceded that “our formulation of the problem may be incorrect.”<sup>10</sup> He considered abandoning the categorical disease notions of schizophrenia and manic-depressive disorder, and replacing them with a sort of dimensional model in which schizophrenic and affective syndromes

“do not represent the expression of particular pathological processes, but rather indicate the areas of our personality in which these processes unfold.”<sup>10</sup> The role of “hereditary factors” was to “make certain areas more susceptible and accessible to pathological stimuli.” According to Kraepelin, “the various syndromes of illness may be compared with the different registers of an organ, any of which may be brought into play according to the severity or extent of the pathological changes involved. They impart a characteristic tone to the illness quite irrespective of the mechanism which has brought them into play.” He introduced a notion of phylogenetically preformed templates of brain responses that could be released by a variety of morbid processes—an idea with obvious links to Hughlings Jackson’s theory of the dissolution of higher cortical functions.<sup>11</sup> Kraepelin proposed three hierarchically structured “registers” of psychopathology— affective, schizophrenic, and encephalopathic—which could recombine in different ways to produce the manifold syndromes of the major mental disorders.

<ul style="list-style-type: none"> <li>• <b>Dementia praecox simplex</b> (“Impoverishment and devastation of the whole psychic life which is accomplished quite imperceptibly”)</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Hebephrenia</b> (Insidious change of personality with shallow capricious affect, senseless and incoherent behaviour, poverty of thought, occasional hallucinations and fragmentary delusions, progressing to profound dementia)</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Depressive dementia praecox (simple and delusional form)</b> (Initial state of depression followed by slowly progressive cognitive decline and avolition, with or without hypochondriacal or persecutory delusions)</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Circular dementia praecox</b> (Prodromal depression followed by gradual onset of auditory hallucinations, delusions, marked fluctuations of mood and aimless impulsivity)</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Agitated dementia praecox</b> (Acute onset, perplexity or exaltation, multimodal hallucinations, fantastic delusions)</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Periodic dementia praecox</b> (Recurrent acute, brief episodes of confused excitement with remissions)</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Catatonia</b> (“Conjunction of peculiar excitement with catatonic stupor dominates the clinical picture” in this form, but catatonic phenomena frequently occur in otherwise wholly different presentations of dementia praecox)</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Paranoid dementia (mild and severe form)</b> (The essential symptoms are delusions and hallucinations. The severe form results in a “peculiar disintegration of psychic life”, involving especially emotional and volitional disorders. The mild form is a very slowly evolving “paranoid or hallucinatory weak-mindedness” which “makes it possible for the patient for a long time still to live as an apparently healthy individual”)</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Schizophrenia (confusional speech dementia praecox)</b> (Cases meeting the general description of dementia praecox but resulting in an end state of “an unusually striking disorder of expression in speech, with relatively little impairment of the remaining psychic activities”)</li> </ul>

### Bleuler’s “group of schizophrenias”

Eugen Bleuler (1857-1939) significantly modified Kraepelin’s original concept by adding to its scope clinical illnesses which did not evolve into the kind of “terminal state” of deterioration, considered by Kraepelin to be the hallmark of the disease. Having coined the term “schizophrenia” to replace dementia praecox, Bleuler<sup>12</sup> stated that schizophrenia “is not a disease in the strict sense, but appears to be a group of diseases [...] Therefore we should speak of schizophrenias in the plural.” Importantly, Bleuler introduced a fundamental distinction between *basic* (obligatory) and *accessory* (supplementary) symptoms of the disorder. While the accessory symptoms comprised the delusions and hallucinations that today are commonly classified as “positive” symptoms, the basic symptoms included thought and speech derailment (“loosening of associations”), volitional indeterminacy (“ambivalence”), affective incongruence, and withdrawal from reality (“autism”). It was the presence of the basic symptoms that, according to Bleuler, gave schizophrenia its distinctive diagnostic profile. He acknowledged that the clinical subgroups of paranoid schizophrenia, catatonia, hebephrenia, and simple schizophrenia were not “natural” nosological entities and argued that “schizophrenia must be a much broader con-

Table I. Emil Kraepelin’s “clinical forms.”<sup>7,8</sup>

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cept than the overt psychosis of the same name.” Along with the “latent” schizophrenias, which presented attenuated forms of the basic symptoms, manifesting as aberrant personality traits, he also listed within the “broader concept” atypical depressive or manic states, Wernicke’s motility psychoses, reactive psychoses, and other nonorganic, nonaffective psychotic disorders as belonging to the group of schizophrenias, on grounds that “this is important for the studies of heredity,” thus foreshadowing the notion of schizophrenia spectrum disorders.

## Post-Kraepelinian and post-Bleulerian subtypes and dichotomies

During the ensuing decades, a number of European and American clinicians proposed further subnosological distinctions within the widening phenotype of schizophrenia, including schizoaffective disorder,<sup>13</sup> schizophreniform psychoses,<sup>14</sup> process-nonprocess,<sup>15</sup> and paranoid–nonparanoid schizophrenia.<sup>16</sup> Schneider<sup>17</sup> claimed that nine groups of psychotic manifestations, designated as “first-rank symptoms” (FRS), had a “decisive weight” in the diagnosis of schizophrenia: audible thoughts; voices arguing about, or discussing, the patient; voices commenting on the patient’s actions; experiences of influences on the body; thought withdrawal and other interference with thought; thought broadcast (diffusion of thought); delusional perception; and other experiences involving “made” impulses and feelings experienced as caused by an outside agency. Due to the sharpness of their definition and the hope that they could be reliably ascertained,

the FRS were subsequently incorporated in the Research Diagnostic Criteria, *RDC*,<sup>18</sup> *DSM-III*,<sup>19</sup> and *ICD-10*.<sup>20</sup> The Catego algorithm,<sup>21</sup> used in the WHO cross-national studies, defined a “nuclear” schizophrenia (S+) characterized by presence of at least 3 out of 6 FRS. Familiarity and modest to substantial heritability has been reported for the FRS,<sup>22</sup> but a recent study<sup>23</sup> found that these symptoms did not predict severe deterioration and cognitive deficit in schizophrenia patients.

## Leonhard’s alternative classification of the “endogenous” psychoses

In a clinical tradition aiming to group psychotic illnesses on the basis of presumed localized cerebral dysfunction, Karl Leonhard<sup>24</sup> developed an elaborate classification of the “endogenous” psychoses which departed substantially from the Kraepelinian and Bleulerian nosology. Leonhard defined sharply delineated disease entities, described by a detailed psychopathology emphasizing objective signs (eg, psychomotor behavior), course and outcome, and family history. The nonaffective psychoses were split into “systematic” and “unsystematic” groups of schizophrenias, and a third group of “cycloid” psychoses, each containing further subtypes (*Table II*), for which Leonhard claimed distinct categorical disease status. While the “unsystematic” schizophrenias were considered to be primarily genetic, hereditary factors were thought to play a secondary role in the cycloid psychoses and the “systematic” schizophrenias, which were presumed to be exogenously determined, eg, by maternal

<b>I. Group of systematic schizophrenias</b> ( <i>Insidious onset, auditory and somatic hallucinations, delusions, early blunting of affect, continuous unremitting course, personality deterioration</i> )
Paraphrenias ( <i>Auditory hallucinosis, audible thoughts, thought broadcast, passivity experiences, delusional misidentifications, falsifications of memory</i> )
Hebephrenias ( <i>Extreme autistic withdrawal, flat affect, impoverished or disorganized speech and behaviour</i> )
Catatonia ( <i>Excessive parakinesias, mannerisms, verbigeration, posturing, stereotypies, mutism, auditory hallucinations</i> )
<b>II. Group of unsystematic (atypical) schizophrenias</b> ( <i>Rapid onset, relatively preserved affect, remitting course, mild personality deterioration</i> )
Affect-laden paraphrenia ( <i>Paranoid delusions with affective loading</i> )
Cataphasia (schizophrenia) ( <i>Incoherent, pressured speech but well-organised behaviour</i> )
Periodic catatonia ( <i>Episodic hyper- or hypokinesia, mixed excitatory and hallucinatory symptoms</i> )
<b>III. Group of cycloid psychoses</b> ( <i>Sudden onset, pervasive delusional mood, multimodal hallucinations, labile affect, polarity of manifestations, typically complete recovery from episode</i> )
Anxiety-happiness psychosis ( <i>Extreme shifts of affect, polarity intense fear – ecstatic elation</i> )
Motility psychosis ( <i>Impulsive hypermotility – psychomotor inhibition</i> )
Confusion psychosis ( <i>Incoherent pressure of speech – mutism</i> )

**Table II.** Karl Leonhard’s classification of the non-affective endogenous psychoses.<sup>24</sup>



obstetric complications or early failure of social learning. Notably, Leonhard's classification neither expands, nor constricts, the outer boundaries of schizophrenia, but carves up the schizophrenia spectrum in a different way.

### The notion of a schizophrenia spectrum

The concept of a continuum or spectrum of schizophrenia-related phenotypes originates in the observation that several ostensibly different disorders tend to cluster among biological relatives of individuals with clinical schizophrenia.<sup>25</sup> Epidemiological and family studies suggest that the genetic liability to schizophrenia is shared with liability to other related syndromes.<sup>26,27</sup> The term "schizotypy," first introduced by Rado<sup>28</sup> and Meehl,<sup>29</sup> describes a personality characterized by anhedonia, ambivalence, "interpersonal aversiveness," body image distortion, "cognitive slippage," and sensory, kinesthetic, or vestibular aberrations. Chapman et al<sup>30</sup> designed scales to measure perceptual aberrations and "magical ideation" as traits predicting "psychosis proneness." These constructs were later amalgamated with clinical descriptions from the Danish-US adoptive study into the *DSM-III* diagnostic category of schizotypal personality disorder (SPD), which is now central to the spectrum notion.<sup>31</sup> The frequent occurrence of SPD among first-degree relatives of probands with schizophrenia has been replicated in the Roscommon epidemiological study,<sup>32</sup> which added to the schizophrenia spectrum further disorders cosegregating within families. The resulting "continuum of liability" includes: (i) "typical" schizophrenia; (ii) schizotypal and paranoid personality disorders; (iii) schizoaffective disorder, depressed type; (iv) other nonaffective psychotic disorders (schizophreniform, atypical psychosis); and (v) psychotic affective disorders. In all its variations, the spectrum concept remains critically dependent on the validity of the SPD concept. Accumulating evidence from family and twin data indicates that SPD is multidimensional and may be genetically heterogeneous.<sup>33-35</sup> Its manifestations fall into two genetically independent clusters: a "negative" cluster (odd speech and behavior, inappropriate affect, and social withdrawal), more common among relatives of schizophrenic probands, and a "positive" cluster (magical ideation, brief quasipsychotic episodes), associated with increased incidence of affective disorders in relatives. "Negative" schizotypy may indeed represent a subclinical *forme fruste* of schizo-

phrenia, manifesting attenuated cognitive deficits and brain structural abnormalities.

### Positive-negative schizophrenia ("Type I" and "Type II")

A general "weakening" of mental processes resulting in a "defect" was the cornerstone of Kraepelin's *dementia praecox*, who suggested that precursors of "defect" could be detected early in the illness, coexisting with "productive" or "florid" symptoms.<sup>8</sup> Since the 1970s, the terms "defect" and "productive" symptoms have been virtually replaced by "negative" and "positive" symptoms.<sup>36</sup> Crow<sup>37</sup> proposed a simple subclassification of schizophrenia, based on the predominance of either positive or negative symptomatology. "Type I" (positive) schizophrenia was characterized by hallucinations, delusions, and formal thought disorder, with a presumed underlying dopaminergic dysfunction, while patients with "Type II" (negative) schizophrenia displayed social withdrawal, loss of volition, affective flattening, and poverty of speech, presumed to be associated with structural brain abnormalities. Criteria and rating scales for positive (SAPS) and negative (SANS) schizophrenia were proposed by Andreasen and Olsen.<sup>38</sup> The initial typology, implying discrete, mutually exclusive "types," was later replaced by a negative and a positive dimension, allowing the two kinds of symptoms to co-occur in the same individual.<sup>39</sup>

### Deficit–nondeficit schizophrenia

Carpenter and collaborators<sup>40,41</sup> proposed the delineation of a subtype of schizophrenia characterized by enduring "primary" negative symptoms that could not be construed as sequelae of other psychopathology (*Table III*). This clinical construct, evocative of Kraepelin's *dementia praecox*, was termed "deficit schizophrenia" (DS) and hypothesized to be an etiologically distinct "disease" within the schizophrenia spectrum.<sup>42</sup> Studies comparing DS cases with "nondeficit" (NDS) patients and controls, estimated the prevalence of the DS subtype at 16.5% in unselected epidemiological samples of schizophrenia cases and 25% to 30% within samples of chronic schizophrenia. DS and NDS do not differ on age at onset and length of illness, which argues against a progression leading from NDS to DS. Limited support for the DS construct has been provided by neuropsychological studies

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and assessment of soft neurological signs.<sup>43-46</sup> The overall pattern has been interpreted as indicative of a fronto-temporo-parietal dysfunction, against a background of a more global impairment.

## Statistically derived symptom dimensions or clusters

Factor analysis and related methods reduce any correlations present within the data matrix to covariances of a small number of latent factors which account for the interrelationships among the primary variables and explain a proportion of their variance. Based on a relatively small number of input variables (SANS/SAPS scores), a three-factor structure has been proposed<sup>47</sup> and subsequently replicated.<sup>48-50</sup> In this model, negative symptoms load on a single factor of “psychomotor poverty,” while positive symptoms split into a delusions-and-hallucinations factor (“reality distortion”) and a thought-and-speech disorder factor (“disorganization”). The model has been shown to be stable and replicable in non-European populations.<sup>51,52</sup> The output of factor analyses of symptomatology depends strongly on the content of the input - studies using SANS and SAPS result in different solutions from those based on scales such as the Positive and Negative Symptom Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), or Operational Criteria Checklist (OPCRIT). In a large

sample of schizophrenia probands, McGrath et al<sup>53</sup> identified 5 factors (positive, negative, disorganized, affective, and early onset/developmental) associated with risk of psychoses and affective disorders in relatives. In a series of factor analyses based on an expanded list of 64 psychopathological symptoms, Cuesta and Peralta<sup>54</sup> concluded that a hierarchical 10-dimensional model provided the best fit on statistical and clinical grounds. Factor solutions, therefore, are not unique and the question “how many factors parsimoniously describe the symptomatology of schizophrenia?” can only be answered in the context of the particular selection of symptoms and measurement methods. Therefore, factor-analytical studies suggesting “established” dimensions or syndromes of schizophrenia should be viewed with caution, considering the diversity of clinical populations and the limitations of the instruments used to generate the input data.

Whereas factor analysis groups variables, cluster analysis groups individuals on the basis of maximum shared characteristics. Farmer et al<sup>55</sup> identified two clusters into which patients with schizophrenia could be fitted, based on scores of 20 symptom and history items: one characterized by good premorbid adjustment, later onset, and well organized delusions, and another including early onset, poor premorbid functioning, incoherent speech, bizarre behavior, and family history of schizophrenia. Using PANSS, Dollfus et al<sup>56</sup> obtained 4 quite different clusters, corresponding to positive, negative, disorganized, and mixed symptomatology. Thus, cluster analysis is as dependent on the selection of input variables as factor analysis.

Latent class analysis (LCA) assumes the existence of a finite number of mutually exclusive and jointly exhaustive groups of individuals. A latent class typology of schizophrenia, proposed by Sham et al,<sup>57</sup> using data on 447 patients with nonaffective psychoses, suggested three subgroups: a “neurodevelopmental” subtype resembling the hebephrenic form of the disorder (poor premorbid adjustment, early onset, prominent negative and disorganized features); a “paranoid” subtype (less severe, better outcome); and a “schizoaffective” subtype (dysphoric symptoms). In an epidemiological sample of 343 probands with schizophrenia and affective disorders, Kendler et al<sup>58</sup> found 6 latent classes, broadly corresponding to the nosological forms of “Kraepelinian” schizophrenia: major depression, schizophreniform disorder, schizoaffective disorder (manic), schizoaffective

**1. At least 2 of the following 6 negative symptoms must be present:**

- Restricted affect
- Diminished emotional range
- Poverty of speech
- Curbing of interests
- Diminished sense of purpose
- Diminished social drive

**2. Some combination of 2 or more of the above negative symptoms have been present for the preceding 12 months and always present during periods of clinical stability.**

**3. The negative symptoms are primary, ie, not secondary to factors other than the disease process, eg,**

- Anxiety
- Drug effects
- Suspiciousness or other psychotic symptoms
- Mental retardation
- Depression

**4. The patient meets *DSM-III* criteria for schizophrenia**

**Table III.** Diagnostic criteria for the deficit syndrome of schizophrenia.<sup>40,41</sup>

disorder (depressed), and hebephrenia. Similar results, using a combination of principal component analysis and LCA in an epidemiologically ascertained sample of 387 patients with psychoses have been reported by Murray et al.<sup>59</sup> In contrast to conventional LCA, a form of latent structure analysis, known as grade of membership (GoM), allows individuals to be members of more than one disease class and represents the latent groups as “fuzzy sets.”<sup>60,61</sup> The GoM model simultaneously extracts from the data matrix a number of latent “pure types” and assigns to each individual a set of numerical weights quantifying the degree to which that individual resembles each one of the identified pure types. When applied to the symptom profiles of 1065 cases in the WHO International Pilot Study of Schizophrenia,<sup>62</sup> the method identified 8 pure types of which 5 were related to schizophrenia, 2 to affective disorders, and 1 to patients in remission, all showing significant associations with course and outcome variables used as external validators.

### Familial–sporadic schizophrenia

Subtyping schizophrenia by the presence/absence of a positive family history for schizophrenia spectrum disorders was proposed as a strategy expected to be more successful in resolving heterogeneity than symptom-based typologies.<sup>63</sup> Familial (F) cases are usually defined as having  $\geq 1$  affected first-degree relative, while sporadic (S) cases have no affected first- or second-degree relatives. The F/S dichotomy rests on the assumption that familial aggregation is primarily of a genetic origin, while sporadic cases result from environmental insults (eg, maternal obstetric complications) or de novo somatic mutations. In the majority of studies using this classification, the proportion of familial cases was in the range of 8% to 15%. Since the F/S subtypes were hypothesized to differ etiologically, a number of studies, mostly of small to moderate sample size (<100), compared the phenotypic characteristics of the two groups<sup>64,65</sup> but found no significant differences in age at onset, symptom patterns, severity, treatment response and outcome, and the findings regarding obstetric complications are inconclusive.<sup>66</sup> By and large, the F/S classification has not so far identified homogeneous groups for genetic research, possibly due to the likely presence of unexpressed genotypes in schizophrenia families.<sup>67</sup>

### The present diagnostic classifications: DSM-IV and ICD-10

While European psychiatry rarely departed in a significant way from the nosological concepts formulated by Kraepelin and his followers, the practically undisputed dominance of psychodynamic psychiatry in North America over many decades came to an end with the “neo-Kraepelinian revolution” of the 1970s.<sup>68</sup> The development of operational diagnostic criteria,<sup>69,70</sup> which were presumed to reflect the Kraepelinian categorical nosology, and their incorporation in the Third Edition of the *Diagnostic and Statistical Manual of the American Psychiatric Association, DSM-III*,<sup>19</sup> was a turning point in the conceptualization of psychiatric disorders in general and of schizophrenia in particular. The likely gains in the reliability and reproducibility of diagnostic assessment based on explicit rules and criteria led to the adoption of a similar approach in the mental disorders chapter of the 10th revision of the World Health Organization’s *International Classification of Diseases, ICD-10*,<sup>20</sup> which in turn provided a stimulus for the development of *DSM-IV*.<sup>71</sup> The diagnostic criteria of *ICD-10* and *DSM-IV* were originally conceived with a view to achieving three fundamentally different goals: (i) to identify groups of patients with broadly similar clinical presentation and prognosis; (ii) to facilitate early diagnosis and choice of treatment; and (iii) to define a homogeneous heritable diagnostic category for genetic and other aetiological research.<sup>72</sup> While the first two goals have, by and large, been achieved as regards clinical utility of the criteria, attainment of the third goal remains remote.

There are both similarities and differences in the way the two classifications define schizophrenia. In contrast to *DSM-IV*, which provides a single set of “operational” diagnostic criteria for all users, *ICD-10* was designed as a “family” of inter-related versions addressing different users. While the *ICD-10* volume *Clinical Descriptions and Diagnostic Guidelines* is the conceptual “core” of the system, the *ICD-10 Diagnostic Criteria for Research* and the *WHO Guide to Mental Health in Primary Care* are derivatives for use in specific context.<sup>72</sup> A comparison of the two sets of diagnostic criteria (in an abridged format) is provided in *Tables IV and V*.

While the opening of the glossary definition in *ICD-10* is an explicit acknowledgement of Bleuler’s point that “schizophrenia” is in fact a group of disorders, the *DSM-IV*

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criteria implicitly suggest a unitary view of the disorder. Both sets of criteria refer to (i) characteristic symptoms present in the cross-section of the clinical picture, weighted differentially for diagnostic significance (“at least one...” or “two or more...”); (ii) the duration of symptoms required for a reliable ascertainment; and (iii) the longitudinal pattern of course. Both systems require presence of “active phase” diagnostic symptoms for at least 1 month. However, *ICD-10* lays greater emphasis on the Schneiderian first-rank symptoms than does *DSM-IV*. An important difference between the two classifications is the *DSM-IV* requirement of at least 6 months, duration of *any* disturbances (including prodromal and residual symptoms) for a confident diagnosis to be made, which relegates cases of shorter duration to a provisional diagnosis of schizophreniform disorder. This requirement is absent in *ICD-10*, where it was considered that a period of 4 weeks is long enough to eliminate the majority of acute nonschizophrenic psychoses associated with substance use. Another major difference between the two classifications is related to the *DSM-IV* Criterion B requiring the presence of social or occupational dysfunction as part of the definition of schizophrenia. The explicit assumption, applied throughout all diagnoses of *ICD-10*, is that social and occupational functioning is context-dependent and not an invariant attribute of the clinical syndrome. It is widely assumed, though not empirically demonstrated, that in comparison with *ICD-10*, the *DSM-IV* criteria of at least 6 months' duration and social/occupational dysfunction tip the scales towards more severe or chronic illness.

Overall, both *DSM-IV* and *ICD-10* have promoted better diagnostic agreement and improved communication, including statistical reporting on morbidity, services, treatment, and outcomes. The reliability of psychiatrists' diagnosis of schizophrenia and related disorders has been improved, at least in research settings in which structured interviews were used, incorporating explicit definitions, criteria, and decision rules. However, such improvements in reliability have shifted attention to the more fundamental problem of the validity of the diagnostic concepts of schizophrenia incorporated in current classifications.<sup>72</sup>

## The vexing issue of validity versus utility

There is no single agreed meaning of validity in science, although it is generally accepted that the concept

addresses “the nature of reality.”<sup>73</sup> Psychologists generally adopt the distinction between content, criterion-related, and construct validity, and their main concern has been with the validity of psychological tests. Borrowing terminology from psychometric theory, psychiatrists have mainly been concerned with concurrent and predictive validity, partly because of their relevance to the issue of the validity of diagnoses. The ability to predict outcome, both in the absence of treatment and in response to specific therapies, has always been a crucial function both of physicians and of their diagnoses.<sup>72</sup> Robins and Guze<sup>74</sup> proposed several formal criteria for establishing the validity of psychiatric diagnoses: (i) clinical description; (ii) laboratory studies; (iii) delimitation from other disorders; (iv) follow-up studies (including evidence of diagnostic stability); and (v) family studies. This schema was elaborated by Kendler<sup>75</sup> who distinguished between antecedent validators (familial aggregation, premorbid personality and precipitating factors); concurrent validators (including psychological tests); and predictive validators (diagnostic consistency over time, rates of relapse and recovery, and response to treatment). Andreasen<sup>76</sup> has proposed “a second structural program for validating psychiatric diagnosis” and listed several additional validators—molecular genetics and molecular biology, neurochemistry, neuroanatomy, neurophysiology and cognitive neuroscience—all potentially capable of linking symptoms and diagnoses to their neural substrates.

The problem with both Robins and Guze's and Kendler's validity criteria is that they implicitly assumed that psychiatric disorders were discrete entities. The possibility that disorders might merge into one another with no natural boundary (or “point of rarity”)<sup>77</sup> was not considered. Robins and Guze's classical paper was written at a time when it was assumed that schizophrenia and bipolar disorder were transmitted by a single, or at the most by a small number of genes. The present situation is different. It is now almost generally accepted that many different genes and gene networks contribute to the etiology of most of psychiatry's major syndromes, including schizophrenia, and that combinations of such genes are risk factors for what have until now been regarded as unrelated syndromes. For example, the microdeletion in chromosome 22q11 which underlies the velocardiofacial syndrome is associated with a raised incidence of intellectual disability, schizophrenia, and bipolar affective disorder.<sup>78,79</sup> The genetic basis of schiz-



phrenia is likely to encompass a spectrum of other disorders, including schizotypal personality disorder and, possibly, bipolar disorder with psychotic symptoms.<sup>2</sup> It will not be surprising if such findings of overlapping genetic predisposition to seemingly unrelated disorders become soon the rule rather than the exception.

Against this background, a recent review of the evidence for assessing schizophrenia and related psychotic disorders against a range of “validating criteria” proposed by the *DSM-V* Task Force Study Group<sup>80</sup> is worth highlighting. The examined criteria included: (i) shared genetic risk factors and familiarity; (ii) environmental risk factors and gene-environment interactions; (iii) shared neural substrates; (iv) shared biomarkers; (v) shared temperamental antecedents; (vi) shared cognitive and emotional processing abnormalities; (vii) comorbidity among disorders; (viii) course of illness; and (ix) treatment response. The authors concluded that “there is insufficient evidence of the etiology and pathophysiology to base group membership on causality.” Furthermore, they felt that “in-depth phenomenology and pattern of illness are not examined in most studies,” and that “it is not known whether the spectrum criteria would support the *DSM-IV* cluster of schizophrenia and related disorders.”<sup>80</sup>

There are several reasons why the crucial issue here is whether clear boundaries or qualitative differences exist at the level of the defining characteristic of the syndrome, rather than understanding of etiology. In the first place, understanding of etiology is not an all or none issue that can be resolved once and forever—it is a long-term process, with knowledge emerging in stages as a complex network of interacting events is elucidated. The consequence of defining diagnostic validity first in terms of the presence (or absence) of continuities and discontinuities at the level of manifest clinical syndromes is that most contemporary psychiatric disorders, including schizophrenia with a pedigree stretching back to the 19th century, cannot yet be described as valid disease categories. This does not mean, however, that they are not valuable concepts, and it is crucial to maintain a clear distinction between validity and utility. At present, these two terms are often used as if they were synonyms.

Many, though not all, of the diagnostic concepts represented by the categories of disorder listed in contemporary classifications like *DSM-IV* and *ICD-10* are extremely useful to practising clinicians, and most would

be hard put to cope without them. Diagnostic categories provide invaluable information about the likelihood of future recovery, relapse, deterioration, and social handicap; they guide decisions about treatment; and they provide a wealth of information about similar patients encountered in clinical populations or community surveys throughout the world—their frequency and demographic characteristics, their family backgrounds and premorbid personalities, their symptomatology and its evolution over time; the results of clinical trials of several alternative therapies; and research into the etiology of the syndrome.<sup>72</sup>

### Categories and/or dimensions?

There are many different ways in which classifications can be constructed. The fundamental choice is between a categorical and a dimensional structure, and it is worth recalling the observation by the philosopher Carl Hempel<sup>81</sup> that, although most sciences start with a categorical classification of their subject matter, they often replace this with dimensions as more accurate measurement becomes possible. The requirement that the categories of a typology should be mutually exclusive and jointly exhaustive has never been fully met by any psychiatric classification. Medical, including psychiatric, classifications are eclectic in the sense that they are organized according to several different classes of criteria (eg, causes, presenting symptoms or traits, age at onset, course), without a clear hierarchical arrangement. One or the other among them may gain prominence as knowledge progresses or conditions change. However, despite their apparent logical inconsistency, medical classifications survive and evolve because of their essentially pragmatic nature. Their utility is tested almost daily in clinical or public health decision-making, and this ensures a natural selection of useful concepts by weeding out impracticable or obsolete ideas.

Categorical typologies are the traditional, firmly entrenched form of representation for medical diagnoses. As such, they have many practical and conceptual advantages. They are thoroughly familiar, and most knowledge of the causes, presentation, treatment and prognosis of mental disorder was obtained, and is stored, in relation to these categories. They are easy to use under conditions of incomplete information; and they have a capacity to “restore the unity of the patient’s pathology by integrating seemingly diverse ele-

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ments into a single, coordinated configuration.”<sup>82</sup> The principal disadvantage of the categorical model is its propensity to encourage a “discrete entity” view of the nature of psychiatric disorders, ignoring the evidence that diagnostic categories do not necessarily represent discrete entities. Dimensional models, on the other hand, have the conceptual advantage of introducing explicitly quantitative variation and graded transition between forms of disorder, as well as between “normality” and pathology. This is important for classifying patients who fulfill the criteria for two or more categories of disorder simultaneously, or who straddle the boundary between two adjacent syndromes. Whether schizophrenia can be better described dimensionally or categorically remains an open, researchable question.<sup>83</sup> The difficulties with dimensional models stem from their novelty; lack of agreement on the number and nature of the dimensions required to account adequately for clinically relevant variation; the absence of an established, empirically grounded metric for evaluating severity or change; and, perhaps most importantly, the complexity and cumbersomeness of dimensional models in everyday clinical practice. In the instance of schizophrenia, the majority of dimensional models that have been proposed to date build upon well-known factor-analysis models grouping into factorial dimension symptoms, typically assessed using rating scales with predetermined sections assessing “positive” “negative,” “disorganization,” and “affective” disorders. The proposed dimensions usually involve the assignment of some sort of a rank scale with arbitrarily assigned scores of presence/absence and severity (“more” or “less”). Clearly, such crude measures fail to do justice to the descriptive psychopathology and phenomenology of psychotic experience which aims to discern meaningful *qualitative* distinctions within symptom domains—eg, the differences between primary and secondary explanatory delusions, or between common second-person auditory hallucinations and voices experienced as coming from one’s own body. These considerations seem to preclude, at least for the time being, a radical restructuring of psychiatric classification from a predominantly categorical to a predominantly dimensional model. Moreover, categorical and dimensional models need not be mutually exclusive, as demonstrated by so-called mixed or class-quantitative models<sup>84</sup> which combine qualitative categories with quantitative trait measurements. For example, there is

increasing empirical evidence that should make it attractive to supplement a retained (and refined) categorical clinical description of the syndrome of schizophrenia with selected quantitative traits such as attention or memory dysfunction and volumetric deviance of cerebral structures.

## Endophenotypes in schizophrenia

Amidst growing doubts in the capacity of the broad diagnostic category to serve as a reliable phenotype for gene discovery,<sup>85</sup> the concept of endophenotypes (intermediate, elementary, alternative, or correlated phenotypes) offered a novel perspective on subtyping schizophrenia that could be either an alternative or a complement to symptom-based phenotypes. The term was introduced into schizophrenia genetics by Gottesman and Shields.<sup>86</sup> As “measurable components unseen by the unaided eye along the pathway between disease and distal genotype,”<sup>87</sup> endophenotypes are expected to be: (i) associated with the clinical disorder but not part of its diagnosis; (ii) heritable; (iii) state-independent (ie, present before the onset of active illness or during remissions); (iv) cosegregating with illness in families; and (v) found in unaffected family members at a higher rate than in the general population.<sup>88</sup> Earlier expectations, eg, that endophenotypes would have a simpler genetic architecture, now appear as unrealistic. An important requirement, however, is that an endophenotype should be represented by a quantitatively measurable trait. In schizophrenia research, an increasing number of endophenotypes, mainly related to psychophysiological, brain imaging, and cognitive measures, are being explored (*Table VI*).

## Cognitive dysfunction as an endophenotype

Cognitive deficits are now widely accepted as a core feature of schizophrenia, rather than an epiphenomenon of the illness state.<sup>89,90</sup> Deficits in multiple cognitive domains predate the onset of clinical symptoms<sup>91-93</sup>; are not attributable to antipsychotic medications<sup>94</sup>; persist over the course of the illness and are unrelated to its duration<sup>95,96</sup>; and represent a stable trait.<sup>97</sup> Pervasive cognitive dysfunction has been reported in >50% of schizophrenia patients,<sup>98</sup> and there is compelling evidence that cognitive deficits are significantly correlated with impairments in activities of daily living (ADL),<sup>99,100</sup> but

only weakly associated with psychotic symptoms.<sup>101</sup> Population-based cohort studies<sup>102,103</sup> have found that compromised general cognitive ability in late adolescence is a strong predictor of subsequent schizophrenia risk. Family studies indicate that a proportion of the unaffected first-degree relatives of index cases of schizophrenia display similar patterns of deficit in an attenuated form.<sup>104-106</sup> The balance of evidence suggests that cognitive dysfunction meets most of the criteria of an endophenotype in schizophrenia. This is underscored by the meta-analysis by Heinrichs and Zakzanis<sup>107</sup> of 204

<b>Neurophysiological markers and endophenotypes</b>
Electrodermal deviance
Prepulse inhibition of the startle reflex (PPI)
Deficient gating of the auditory evoked response (P50)
P300 amplitude reduction and latency delay
N400 amplitude reduction (semantic context underutilization)
Mismatch negativity (MMN)
Smooth pursuit eye movement dysfunction (SPEM)
Antisaccade error rate (AS)
Multivariate electrophysiological endophenotype (MMN, P50, P300, AS)
<b>Neuroimaging markers and endophenotypes</b>
Fronto-thalamic-cerebellar gray matter deficit
Fronto-striato-thalamic gray matter deficit
MRI whole-brain non-linear pattern classification
Frontal hypoactivation in response to cognitive tasks (hypofrontality)
Atrophic and static (neurodevelopmental) schizophrenia endophenotypes
<b>Cognitive markers and endophenotypes</b>
Continuous performance tests (CPT, signal/noise ratio)
Attention and vigilance-based cognitive subtype
Verbal dysmnesic cognitive subtype
Verbal memory deficit, cortical or subcortical cognitive type
Dysexecutive cognitive subtype
Prefrontal executive/working memory phenotype
Frontal/abstraction deficit profile
Spatial working memory
Generalised (diffuse, pervasive) cognitive deficit, CD
<b>Other markers and endophenotypes</b>
Neurological soft signs
Composite laterality phenotype
Nailfold plexus visibility
Minor physical anomalies

**Table IV.** 'Candidate' endophenotype markers in schizophrenia research (reviewed in ref 72).

<b>Schizophrenia (F20): diagnostic criteria for research</b>
<b>At least one...</b>
(a) thought echo, insertion, withdrawal or broadcasting
(b) delusions of control, influence or passivity
(c) hallucinatory voices – running commentary or discussing the patient
(d) persistent delusions - culturally inappropriate and completely impossible
<b>Or at least two...</b>
(a) persistent hallucinations in any modality, when accompanied by delusions
(b) neologisms, breaks or interpolations in the train of thought, incoherence
(c) catatonic behaviour
(d) 'negative' symptoms: apathy, paucity of speech, emotional blunting or incongruity
<b>...should be present for most of the time during an episode of psychotic illness lasting for at least 1 month</b>
<b>Pattern of course</b> (period of observation at least 1 year)
Continuous (no remission of psychotic symptoms)
Episodic with progressive deficit ('negative' symptoms in the intervals)
Episodic with stable deficit (persistent but non-progressive 'negative' symptoms)
Episodic remittent (complete remissions between psychotic episodes)
Incomplete remission
Complete remission
Other
Course uncertain, period of observation too short
<b>Clinical subtypes</b>
Paranoid
Hebephrenic
Catatonic
Undifferentiated
Post-schizophrenic depression
Residual
Simple
Other
Unspecified
<b>Other F2 disorders</b>
Schizotypal disorder (F21)
Persistent delusional disorders (F22)
Acute and transient psychotic disorders (F23)
Induced delusional disorder (F24)
Schizoaffective disorders (F25)
Other non-organic psychotic disorders (F28)
Unspecified non-organic psychosis (F29)

**Table V.** ICD-10 / F2 group of disorders.<sup>72</sup>

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studies published between 1980 and 1994 (a total of 7420 schizophrenia patients and 5865 controls), in which effect sizes (Cohen's *d*) and the U statistic (degree of non-overlap) were calculated for 22 neurocognitive test variables ranging from IQ, verbal memory, and attention to executive function and language. Although no single test or cognitive construct was capable of separating perfectly schizophrenia patients from normal controls, 7 measures achieved effect sizes greater than 1.0 (60-70% non-overlap between the cases and controls): verbal memory (1.41), bilateral motor skills (1.30), perfor-

mance IQ (1.26), the continuous performance task (1.16), word fluency (1.15), the Stroop task (1.11), and WAIS-R IQ (1.10). Although a subset of ~50% of patients had nearly normal performance, significant cognitive impairment was common in schizophrenia and exceeded the deficits found in some neurological disorders, justifying the view that "schizophrenia is a neurological disorder that manifests itself in behavior."<sup>107</sup> There is, at least, a preliminary evidence that composite cognitive endophenotypes have the capacity to identify genetically distinct subtypes of schizophrenia.<sup>108</sup>

<b>A.</b> Two (or more) <i>characteristic symptoms</i> , each present for a significant portion of time during a 1-month period (or less if successfully treated): (1) delusions; (2) hallucinations; (3) disorganized speech (derailment or incoherence); (4) grossly disorganized or catatonic behavior; (5) negative symptoms (affective flattening, alogia, or avolition). ( <i>Only one symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary...or two or more voices conversing with each other.</i> )
<b>B.</b> Social/occupational dysfunction
<b>C.</b> Duration: Continuous signs of the disturbance persist for at least 6 months, including at least 1 month of active-phase symptoms and may include periods of prodromal or residual symptoms. During prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or 2 or more <i>Criterion A</i> symptoms in an attenuated form (eg, odd beliefs, unusual perceptual experiences).
<b>D.</b> Schizoaffective and mood disorder exclusion
<b>E.</b> Substance/general medical condition exclusion
<b>F.</b> Relationship to a pervasive developmental disorder: If there is a history of Autistic Disorder or another pervasive developmental disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month.
<b>Subtypes:</b>
Paranoid (295.30)
Disorganized (295.10)
Catatonic (295.20)
Undifferentiated (295.90)
Residual (295.60)
<b>Longitudinal course:</b>
Episodic with interepisode residual symptoms (prominent negative symptoms may be added)
Episodic with no interepisode residual symptoms
Continuous (prominent negative symptoms may be added)
Single episode in partial remission (prominent negative symptoms may be added)
Single episode in full remission
Other of unspecified pattern
<b>Other disorders within the same group:</b>
Schizophreniform disorder (with / without good prognostic features) (295.40)
Schizoaffective disorder (bipolar or depressive type) (295.70)
Delusional disorder (297.1)
Brief psychotic disorder (with / without stressor, or with postpartum onset) (298.8)
Shared psychotic disorder (297.3)
Psychotic disorder due to a general medical condition (293.xx)
Substance-induced psychotic disorder (291.xx or 292.xx)
Psychotic disorder not otherwise specified (298.9)

**Table VI.** DSM-IV-TR Schizophrenia and other psychotic disorders.<sup>72</sup>



## Conclusion: the way forward

More than a century since the delineation of dementia praecox by Kraepelin, the etiology, neuropathology, and pathophysiology of schizophrenia remain elusive. Despite the availability of criteria allowing reliable diagnostic identification, schizophrenia essentially remains a broad clinical syndrome defined by reported subjective experiences (symptoms), loss of function (behavioral impairments) and variable patterns of course. Research has identified a number of putative biological markers associated with the disorder, including neurocognitive dysfunction, brain dysmorphology, and neurochemical abnormalities. Yet none of these variables has to date been definitively proven to possess the sensitivity and specificity expected of a diagnostic test. Genetic linkage and association studies have targeted multiple candidate loci and genes, but failed to demonstrate that any specific gene variant, or a combination of genes, is either necessary or sufficient to cause schizophrenia. Thus, the existence of a specific brain disease underlying schizophrenia remains a hypothesis.

Against a background of an ever-increasing volume of research data, the inconclusiveness of the search for causes of the disorder fuels doubts about the validity of the schizophrenia construct as presently defined, some leading to proposals to discard the category,<sup>109</sup> or to replace it with a continuum of “psychosis.”<sup>110</sup> Given the protean nature of the symptoms of schizophrenia and the poor coherence of the clinical and biological findings, such doubts are not without reason. However, simply dismantling the concept is unlikely to result in an alternative model that would account for the host of clinical

phenomena and research data consistent with a disease hypothesis of schizophrenia. Although there are grounds for the suspicion that schizophrenia is not a homogeneous entity, this has never been directly demonstrated, mainly because few studies of the appropriate kind have ever been undertaken. For the time being, the clinical concept of schizophrenia is supported by empirical evidence that its multiple facets form a broad syndrome with non-negligible internal cohesion and a characteristic evolution over time. The dissection of the syndrome with the aid of endophenotypes is beginning to be perceived as a promising approach in schizophrenia genetics. As new concepts and data emerge from molecular genetics, cognitive science, or brain imaging, new perspectives on disease causation and brain function are likely to be on stage in the next decade.

A recent strategic proposal about a future typology of psychiatric disorders, linking genomics and neural circuits functioning as “hubs” for a range of phenotypes—cutting across the present categories and joining schizophrenia, autism, bipolar disorder, as well as forms of epilepsy and intellectual disability—may be a signpost of future developments.<sup>111</sup> Such research must be supported by a refined, reliable, and valid phenotyping—not only at the level of symptoms, but increasingly involving correlated neurobiological features. The study of endophenotypes transcending the conventional diagnostic boundaries may reveal unexpected patterns of associations with symptoms, personality traits, or behavior. The mapping of clinical phenomenology on specific brain dysfunction is now becoming feasible and the resulting functional psychopathology may in the future substantially recast the present nosology. □

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# State of the art

## ***El concepto diagnóstico de la esquizofrenia: su historia, evolución y perspectivas futuras.***

*Aunque hace más de un siglo que Kraepelin delimitó la demencia precoz, la etiología, la neuropatología y la fisiopatología de la esquizofrenia persisten escurridizas. A pesar de la disponibilidad de criterios que permiten identificaciones diagnósticas confiables, la esquizofrenia sigue siendo esencialmente un amplio síndrome clínico definido por el relato de experiencias subjetivas (síntomas), la pérdida del funcionamiento (deterioros conductuales) y patrones variables de evolución. La investigación ha identificado un número de reputados marcadores biológicos asociados con el trastorno, incluyendo disfunción neurocognitiva, alteraciones de la morfología cerebral y anomalías neuroquímicas. A la fecha todavía ninguna de estas variables ha demostrado que posea definitivamente la sensibilidad y especificidad esperadas para una prueba diagnóstica. Los estudios genéticos de ligamiento y de asociación han apuntado a múltiples loci y genes candidato, pero no se ha podido demostrar que alguna variante específica de un gen, o de una combinación de genes, sea necesaria o suficiente para causar la esquizofrenia. Por lo tanto, la exis-*

*tencia de una enfermedad cerebral específica a la base de la esquizofrenia sigue constituyendo una hipótesis. En oposición a los antecedentes de un volumen siempre creciente de información proveniente de la investigación, la falta de conclusiones en la búsqueda de causas para este trastorno genera dudas acerca de la validez del constructo esquizofrenia como está actualmente definido. Considerando la naturaleza versátil de los síntomas de la esquizofrenia y la pobre coherencia de los hallazgos clínicos y biológicos, tales dudas son razonables. Sin embargo, el dismantelar simplemente el concepto es poco probable que se traduzca en un modelo alternativo que pudiera dar cuenta de la presentación de los fenómenos clínicos y de los datos de la investigación que sean consistentes con la hipótesis de enfermedad de la esquizofrenia. Por ahora, el concepto clínico de la esquizofrenia está sustentado por la evidencia empírica en que sus múltiples presentaciones forman un amplio síndrome con una coherencia interna no insignificante y una evolución característica a lo largo del tiempo. La disección del síndrome con la ayuda de endofenotipos está comenzando a ser percibida como una prometedora aproximación en la genética de la esquizofrenia.*

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### **Le concept diagnostique de la schizophrénie: histoire, évolution et perspectives futures**

Plus d'un siècle après la description de la démence précoce par Kraepelin, l'étiologie, la neuropathologie et la physiopathologie de la schizophrénie demeurent difficiles à appréhender. Malgré la disponibilité de critères permettant une identification diagnostique fiable, la schizophrénie reste surtout un vaste syndrome clinique défini par le rapport d'expériences subjectives (symptômes), la perte d'une fonction (déficits comportementaux) et des modalités évolutives variables. La recherche a trouvé plusieurs marqueurs biologiques possibles associés à la maladie comme des dysfonctions neurocognitives, des anomalies morphologiques cérébrales et des désordres neurochimiques. Aucune de ces variables n'a encore montré à ce jour la sensibilité et la spécificité attendues d'un test diagnostique. Les études d'association et de liaison génétiques ont ciblé de nombreux gènes et locus candidats sans mettre en évidence un variant de gène spécifique ou une combinaison de gènes

nécessaire ou suffisant pour provoquer la schizophrénie. L'existence d'une maladie cérébrale spécifique sous-tendant la schizophrénie reste donc une hypothèse. Les données de la recherche sont en augmentation constante mais leur incapacité à conclure sur les causes de la schizophrénie fait douter de la validité de sa définition actuelle. Et ces doutes trouvent leur source dans la nature inconsistante des symptômes de la schizophrénie et la faible cohérence des résultats cliniques et biologiques. Cependant, un simple démantèlement du concept ne suffira pas à produire un modèle alternatif capable d'expliquer la série de symptômes cliniques et des données de recherche concordant avec une hypothèse de maladie pour la schizophrénie. Pour l'instant, le concept clinique de la schizophrénie est fondé sur des preuves empiriques, ses multiples facettes formant un vaste syndrome avec une certaine cohésion interne et une évolution caractéristique dans le temps. L'analyse fine de ce syndrome à l'aide d'endophénotypes commence à être perçue comme une approche prometteuse dans la génétique de la schizophrénie.

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