

Is the Overlap of Neurobiological and Psychopathological Parameters Large Enough to Give up the Dichotomic Classification?

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In the past decade, several neurobiological and clinical findings, especially in the field of genetics, led to the hypothesis that a continuum/spectrum concept of psychotic disorder, ranging from schizophrenia to bipolar disorders, and possibly also to unipolar disorders, might be better supported by data than the traditional dichotomy¹ between schizophrenia and bipolar disorders/affective disorders. The respective data basis was summarized in recent articles.² There were even suggestions about schizophrenia being a psychotic mood disorder, as recently expressed in a review.³ Although

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Dr. Möller has disclosed no relevant financial relationships.

doi: 10.3928/00485713-20100303-07



there is considerable overlap in terms of some epidemiological features, genetic risk factors, and some other neurobiological aspects, which finally lead Craddock and Owen to hypothesize the end of the Kraepelinian dichotomy, the final decision should be made very cautiously.^{4,5} We must take into account structural abnormalities found on magnetic resonance imaging (MRI), which seem to be more pronounced and more progressive in schizophrenia than in bipolar and especially unipolar depressive disorders,⁶⁻⁹ and of differences in long-term outcome, where schizophrenia seems to have the worst outcome compared with affective disorders.^{10,11} Thus, the question is if a revision of our psychiatric classification of schizophrenia and affective disorders is necessary and promises to be fruitful, especially if not only research aspects are considered but also clinical decision-making, cannot be fully answered yet.¹² Also, the consequences for every day clinical treatment care for our patients and the consequences for the licensing of psychotropic drugs have to be carefully considered. In the following article, only some of the respective arguments can be addressed.

At first, it seems meaningful to look back at the history of the systematic of psychiatric disorders. Angst¹³ performed a very comprehensive review of the historical aspects of the dichotomy between schizophrenia and affective disorders. He stated that Guislain and Zeller established a unitarian concept of psychiatric disorder, permutations of which have survived until the present day. Kraepelin's dichotomy¹⁴ between "manic-depressive insanity" and dementia praecox was built mainly on Kahlbaum's classification, which took clinical symptoms, course, and outcome into account. Kraepelin's well-accepted approach sought to provide a basis for diagnosis, prognosis, choice of treatment, and causal research. Kraepelin's

dichotomy came to be questioned on several grounds: 1) doubts about his unification of bipolar disorder with melancholia, and 2) doubts about the significance of Kraepelin's diagnostic groups for causal research (illustrated best by the work of Bonhoeffer), the complex



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psychopathological descriptions and classifications of numerous subgroups of psychoses by Kleist and Leonhard, and descriptions of the psychoses between affective and schizophrenic disorders (intermediate psychoses, mixed psychoses, schizoaffective psychoses), beginning with Kehrner and Kretschmer and persisting up to the modern findings of a continuum between the two major groups of psychiatric disorders.

In the view of Angst, Kraepelin's simplification has so far been more successful than the Kleist-Leonhard approach. However, the modern and more descriptive trend in psychiatric classification apparently favors the syndromal concept already suggested by Hoche at the beginning of the 20th century and the concepts of continua between affective and schizophrenic disorders and between normal and pathological behavior. Traditionally, schizoaffective

disorder is seen as a syndromatological amalgamation of two disorders, not as a comorbidity of two distinct disorders/diagnostic entities. Craddock even suggests a hypothetical genetic model to explain the continuum concept between schizophrenia and bipolar disorder. Besides the historical development of the concept, the current conceptualization of schizoaffective disorders by the *International Classification of Diseases*, 10th edition (ICD-10), and *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria, this model represents a special type of the relevant modern conceptualization of a relationship between schizophrenic and affective symptoms. The affective part occurs either simultaneously with the schizophrenic symptoms or sequentially (without concurrent schizophrenic symptoms), depending on the diagnosis system applied. There is no referral to comorbidity with an affective disorder.

CONCEPTUALIZATION

The conceptualization of a schizoaffective psychosis covers the range of phenomena, with the term "schizoaffective psychosis" itself. The earlier the prototype of a coexistence with bipolar affective symptoms becomes apparent, the more justified the concept appears. If the depressive symptoms simply coexist with the schizophrenic symptoms, or even only occur during the course of the illness without concurrent schizophrenic symptoms, the less convincing the definition of a schizoaffective psychosis appears. The less restrictive the related definition criteria are, the more diluted the concept becomes, so that in the end, any kind of depressive cosyndromality — simultaneous or sequential — can correspond to the diagnostic concept of a schizoaffective psychosis. It is, therefore, of relevance that DSM-III or DSM-IV defines a much more restrictive concept of schizoaffective psychoses than ICD-10.

In the differentiation between schizophrenia with depressive/manic symptoms, depression or mania with psychotic symptoms and schizoaffective disorders, the psychopathological differentiation between mood-congruent and mood-incongruent psychotic symptoms has traditionally played an important role. Mood-incongruent psychotic symptoms were assumed by classical psychopathologists, such as Karl Jaspers or Kurt Schneider, to be “pathognomonic” for schizophrenia (if an organic or medical condition is excluded), especially the so-called first rank symptoms. The DSM-IV-TR, however, has involved mood-incongruent psychotic symptoms in the concept of mood disorders, as well. This, of course, is a matter of definition and insofar arbitrary or consensus driven to a certain degree. But if mood-incongruent symptoms are defined also to belong to mood disorders, there is an increased risk of confusing diagnostic entities: “pure” mood disorders with schizoaffective disorders and, to some extent, with schizophrenia and schizophrenia disorders. Several findings indicate that especially mood-incongruent psychotic symptoms can be seen as an indicator of a poorer prognosis, a fact that should be better considered in modern classification systems. That questions the approach in DSM-IV-TR,¹⁵ if we hypothesize a chronic and poor course.

Although many experts believe that “schizoaffective disorders,” and possibly even “post-psychotic depression,” are likely mood disorders (“severe with psychotic features”),^{3,16} there are other positions, as well. In his recent paper, Marneros¹⁷ came to the conclusion that the special characteristics of bipolar disorder with mood-incongruent psychotic symptoms can lead to similar conclusions as polymorphism. With the term “polymorphism,” he describes the phenomenon accord-

ing to which episodes, other than mood episodes, can also occur during the long-term course of bipolar I disorders, (eg, schizophreniform and “schizoaffective” episodes, defined as concurrently fulfilling the criteria of schizophreniform and mood episodes). Marneros¹⁷ pointed out that the construct of comorbidity cannot explain that patients with mood incongruent psychotic symptoms (such as bipolar patients with a polymorphic course) differ from patients with prototypic diseases (ie, schizophrenia or mood bipolar disorders without mood incongruent psychotic symptoms, on various relevant levels (age at onset, family history, outcome, etc.). He suggested that perhaps the answer can be found in the “antagonistic influence” of genetically determined or co-determined disorders, the result of which is a position of mood disorders with mood incongruent psychotic symptoms in-between the two prototypes.

DSM-V AND ICD-11

Preparatory work for DSM-V and ICD-11 has begun in the past few years. Both systems will potentially change the traditional classification of psychiatric disorders to a much greater degree than was the case with DSM-IV and ICD-10. For example, they will potentially omit the dichotomy between schizophrenic disorders and affective disorders. It might be that in the end a broad category of “psychotic disorders” may be developed, which can be subdefined by a dimensional/syndromal approach.

The DSM-V Prelude Project considers the following issues as the starting point for the development of a new systematics of psychiatric disorders:¹⁸

- Despite many proposed candidates, not one laboratory marker has been found to be specific in identifying any of the DSM-defined syndromes.
- Epidemiological and clinical studies have shown extremely high rates of

comorbidities among the disorders, undermining the hypothesis that the DSM syndromes represent distinct etiologies.

- The efficacy of many psychotropic medications cuts across the DSM-defined categories. This relates, for example, to selective serotonin reuptake inhibitors (SSRIs) being equally effective for “depression” and “anxiety disorders,” even though they are different DSM entities.
- Reification of DSM-IV-TR entities to the point that they are considered equivalent to diseases is more likely to obscure than to elucidate research findings.
- It can be concluded that the field of psychiatry has, thus far, failed to identify a single neurobiological phenotypic marker or gene that is useful in making a diagnosis of a major psychiatric disorder or for predicting response to psychopharmacologic treatment.

Craddock and Owen recently published an article⁴ with the critical title, “Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages.” This article, published in the *Journal of World Psychiatry* was published in a forum with the provocative title: “Do the disadvantages of the Kraepelinian dichotomy now outweigh the advantages?” Several international experts, such as Carpenter, Murray, Angst, Brockington, Marneros, and others, commented in this forum on the paper by Craddock and Owen.

A CONTINUUM

The arguments based on genetic findings, indeed, hint at a psychiatric continuum. However, the magnitude of relative risk mediated by sequence variants in each specific susceptibility gene is very modest.¹⁹ Some experts claimed that altogether the percentage of explained variance is lower than 10%. Although some MRI studies do not find differences in kind and severity of brain alterations between schizophrenic and bipolar patients,²⁰ the studies point

at a more severe neuropathology in schizophrenic patients all in all.⁹ Also the reference to the findings on endophenotypes, serving as an argument for the differentiation between “psychotic mood disorders” and “non-psychotic mood disorders,”^{3,20} cannot sufficiently solve this issue.²¹⁻²⁵

It seems to be premature to base a new classification of psychoses in the sense of a continuum hypothesis on these findings. “Continuum,” in this sense, relates to type and severity of symptoms, as well as chronicity of course. In his comment on the article by Craddock and Owen, Murray²⁶ warns against being too radical and suggests that the traditional categorical system should be combined with a dimensional approach. This combined approach should be further validated with neuroimaging, neuropsychology, molecular genetics, etc. From a clinical point of view, it can be questioned why the arguments focus primarily on a spectrum of schizophrenic and bipolar disorders while unipolar depression, which was included in Crow’s continuum concept, with its special feature of a psychotic depression, is not included. Thus, the discussion on the psychotic continuum seems incomplete, especially considering the fact that diagnostic differentiation between bipolar and unipolar disorder is associated with several diagnostic problems.

The inclusion of cognitive impairment in the diagnostic criteria for schizophrenia, as suggested by Keefe,²⁷ would enrich the diagnostic concept and, hopefully, contribute toward a better definition of a “point of rarity” between schizophrenia and affective psychosis. Indeed, the exclusion of this very relevant core syndrome in research on the differences between schizophrenia and affective psychosis (unipolar and bipolar) might be one explanation why past research on this subject was not so fruitful.

CONCLUSIONS AND FUTURE CONSIDERATIONS

Because most psychiatric disorders still lack clear biological correlates, follow-up studies on their course, outcome, and prognosis are traditionally viewed as playing an important role in psychiatric research, especially in terms of validation of psychiatric diagnoses and other psychiatric concepts;



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for example, negative symptoms. Only a few studies have addressed the differences between the course of schizophrenia and that of other psychiatric illnesses. These studies basically come to the same conclusion that the course and outcome of schizophrenia is less favorable than that of affective and schizoaffective disorders.^{28,29} However, this dichotomic view was criticized. A small subgroup of patients with affective disorders has recurrent episodes and does not have such favorable courses of illness as was once believed. Also, about one-third of schizophrenic patients have a relatively favorable outcome without

a deficit syndrome.^{17,30} Although patients with unipolar or bipolar depression do not always achieve full remission, an outcome defined by chronic symptoms or a subsyndromal residual state is frequent. However, this cannot be compared with the persistent and severe deficit syndrome, which is typical for most patients with schizophrenia. The heterogeneity in outcome may depend on a variety of factors, such as the severity of symptoms at onset, comorbidity, expressed emotions of relatives, social support, working conditions, stressful life events, and the sociocultural environment.

Besides those differentiations that the long-term course of schizophrenia seems to be more devastating than the long-term course of affective disorders, some research groups have even hypothesized that there might be progressive brain alterations in at least a subgroup of schizophrenic patients. In addition, other neurobiological hypotheses might be good justifications for continuing with the Kraepelinian dichotomy. The vision for the future would be to construct a psychiatric classification with related brain dysfunctions on a neuro-anatomical or neuropathological basis, which might even be of greater importance in this context than genetic findings.³¹ However, a mixture of both approaches, if possible, may have an even greater effect. At the moment, the idea of constructing a new classification, only based on neurobiological parameters and not including the clinical features, does not seem promising.

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