Contents

Editorial

Do we need to rethink our current classifications of mental disorders?
Florence Thibaut (France)

State of the art

Changes from ICD-10 to ICD-11 and future directions in psychiatric classification
Wolfgang Gaebel, Johannes Stricker, Ariane Kerst (Germany)

Original articles

Fractures in the framework: limitations of classification systems in psychiatry
Munira Kapadia, Maherra Desai, Rajesh Parikh (India)

Diagnosis as dialogue: historical and current perspectives
Paul Hoff, Anke Maatz, Johannes Simon Vetter (Switzerland)

Wernicke-Kleist-Leonhard phenotypes of endogenous psychoses: a review of their validity
Jack R. Foucher, Micha Gawlik, Julian N. Roth, Clément de Crespin de Billy, Ludovic C. Jeanjean, Alexandre Obrecht, Olivier Mainberger, Julie M. E. Clauss, Julien Elowe, Sébastien Weibel, Benoit Schorr, Marcelo Cetkovich, Carlos Morra, Federico Rebok, Thomas A. Ban, Barbara Bollmann, Mathilde M. Roser, Markus S. Hanke, Burkhard E. Jabs, Ernst J. Franzek, Fabrice Berna, Bruno Pfuhlmann (France, Germany, Switzerland, Argentina, the Netherlands)

Neurobiology and the Hierarchical Taxonomy of Psychopathology: progress toward ontogenetically informed and clinically useful nosology

Neurodevelopmental disorders—the history and future of a diagnostic concept
Deborah J. Morris-Rosendahl, Marc-Antoine Crocq (UK, France)

Do DSM classifications help or hinder drug development?
Michael Davidson, Cristian Gabos-Grecu (Cyprus, Romania)

Brief report

The role of RDoC in future classification of mental disorders
Bruce N. Cuthbert (US)

Issue coordinated by Peter Falkai, with Dieter Naber and Michael Davidson
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Do we need to rethink our current classifications of mental disorders?

Florence Thibaut, MD, PhD - Editor in chief

The traditional categorical classification system and new diagnostic systems will be discussed in this issue.

Keywords: DSM; ICD; classification; mental disorder; behavioral disorder; psychiatric disorder; mental health; international classification; psychiatric classification

In his introduction to the first edition of his book entitled *Medico-philosophical treatise on mental alienation*,1 Pinel, a visionary French psychiatrist, wrote, as early as 1801:

> It is a bad choice to take mental alienation as the specific subject for research, as this opens one up to vague discussions about the seat of the understanding and the nature of its various faults, and nothing is more obscure or more impenetrable than this. But if one confines oneself within sensible limits, keeping to a study of the distinctive varieties of derangement as shown by outward signs, and only adopts the results of enlightened experience as principles of treatment, one then follows the path widely followed in all branches of natural history. Then, by proceeding with reserve in doubtful cases, there is much less fear of going astray.

Then, Esquirol, another French psychiatrist, published in 1838 the results of 40 years of studies and observations of the symptoms of insanity in a book entitled: *Mental maladies: a treatise on insanity.*2 In the aftermath of real attempts to classify mental illnesses by French and German psychiatrists during the 19th century, numerous efforts were made to classify mental disorders in other countries.

Yet, to date, none of these categorical classifications has been the subject of a unanimous consensus among psychiatrists. High rates of comorbidity, nonspecificity of both pharmacological and psychosocial treatments, and lack of support from the current nosology in biomarker research question the specificity of the disorders and their supposed underlying mechanisms. In this issue, Kapadia and colleagues (p 17) have pointed out the inherent Western bias in these classification systems. Methodological flaws have been widely discussed. In particular, the discrepancies between diagnostic systems3 and the weak stability over the long-term course of symptom-based subtyping4 were highlighted in schizophrenia as early as in the 1980s. More recently, for *DSM-5*, field trials yielded low reliability, with nonexpert clinicians diagnosing patient groups based on checklists rather than standard diagnostic interviews.5,6 Notable steps in the direction of dimensionality, at least for some diagnoses, were gradually included in the *DSM-5* and more recently in the *ICD-11* versions. Gaebel et al, in this issue (p 7), have conducted a brief overview of the changes from *ICD-10* to *ICD-11*.

Nonetheless, amidst this chaos, Research Domain Criteria (RDoC) have been considered as an alternative method of classification with a dimensional approach simultaneously defined by observable behavior (including quantitative measures of cognitive or affective behavior) as well as neurobiological measures. Cuthbert, in this issue, (p 81) will discuss the pros and cons of this classification.
Editorial
Do we need to rethink our current classifications of mental disorders? - Thibaut

Concurrently, the Hierarchical Taxonomy of Psychopathology (HiTOP) model, which is derived from factor-analytic studies of symptoms, diagnoses, and maladaptive trait data, describes a hierarchy of continuous dimensions accounting for broader spectra as well as symptom-level manifestations of psychopathology. Perkins et al (including the original author of HiTOP) will introduce this approach in this issue (p 51). However, in clinical practice, scores on higher-order psychopathology dimensions are difficult to interpret.

In fact, the connection between neurobiology and psychopathology is not sufficiently understood to establish a diagnostic system based on it. Yet, the genotype-first approach has led to the identification of specific genetic subtypes for autism spectrum disorders and promising pharmacological treatment targets (Morris Rosendhal and Crocq, in this issue, p 65).

Finally, Davidson and Gabos Grecu (in this issue, p 73) will discuss transdiagnostic approaches and advocate for a drug-centered approach with the example of the potential use of similar pharmacological interventions in the case of cognitive disorders associated with schizophrenia or other mental disorders.

References

State of the art

Changes from *ICD-10* to *ICD-11* and future directions in psychiatric classification

Wolfgang Gaebel, MD, PhD; Johannes Stricker, MSc; Ariane Kerst, MD

This article provides a brief overview of the changes from *ICD-10* to *ICD-11* regarding the classification of mental, behavioral, or neurodevelopmental disorders. These changes include a new chapter structure, new diagnostic categories, changes in diagnostic criteria, and steps towards dimensionality. Additionally, we review evaluative field studies of *ICD-11*, which provide preliminary evidence for higher reliability and clinical utility of *ICD-11* compared with *ICD-10*. Despite the extensive revision process, changes from *ICD-10* to *ICD-11* were relatively modest in that both systems are categorical, classifying mental phenomena based on self-reported or clinically observable symptoms. Other recent approaches to psychiatric nosology and classification (eg, neurobiology-based or hierarchical) are discussed. To meet the needs of different user groups, we propose expanding the stepwise approach to diagnosis introduced for some diagnostic categories in *ICD-11*, which includes categorical and dimensional elements.

**Keywords:** International Classification of Diseases; *ICD-11*; diagnosis; mental; behavioral or neurodevelopmental disorder; diagnostic guideline

**Introduction**

The development of the Mental, Behavioral or Neurodevelopmental Disorders (MBND) chapter of the *ICD-11* was the largest and most participative process in the history of mental health disorder classification. The three major aims for this process were global applicability, scientific validity, and clinical utility.1,2 In 2007, the WHO Department of Mental Health and Substance Abuse assigned the International Advisory Group for the Revision of the *ICD-10* Mental and Behavioural Disorders.3 This advisory group, together with the WHO, established working groups in which experts from all continents reviewed the available evidence and proposed changes to specific parts of the *ICD-10* Mental and Behavioural Disorders chapter. These proposals were discussed in a collaborative process with various stakeholders (eg, mental health professionals and users of mental health services), resulting in a beta-draft of the *ICD-11* MBND chapter. From 2015, the WHO made the *ICD-11* MBND beta draft publicly available on the internet for review and comments.4 Additionally, feedback from mental health practitioners was obtained via formative field studies.5,6 In May 2019, the 72nd World Health Assembly voted to adopt *ICD-11*, which will be implemented by the WHO member states from January 1, 2022.

In this article, we first present a brief summary of changes regarding the classification of mental, behavioral, or neurodevelopmental disorders from *ICD-10* to *ICD-11*. In this summary, we review, with examples, changes in the chapter structure, new diagnostic categories, changes in diagnostic criteria and dimensional approaches in *ICD-11*. Second, we...
review findings from a series of field studies evaluating how well the ICD-11 functions when applied by health professionals. Third, we discuss new approaches in psychiatric nosology and we propose expanding dimensional additions to categorical diagnoses to a broader range of diagnostic categories in ICD-11.

Changes from ICD-10 to ICD-11

Chapter structure

The ICD-11 MBND chapter contains 21 disorder groupings compared with 11 disorder groupings in ICD-10. Table I displays an overview of the disorder groupings in ICD-10 and ICD-11. Sleep-wake disorders and conditions related to sexual health were separated from the ICD-11 MBND chapter and cross-listed from the new sleep-wake disorders and conditions related to sexual health chapters. Principles for ordering disorder groupings in ICD-11 were shared etiology, pathophysiology, and phenomenology. Additionally, the aim of the WHO and American Psychiatric Association to harmonize the structure of ICD-11 and DSM-5 influenced the chapter structure of ICD-11.2 A central difference between ICD-11 and ICD-10 regarding chapter structure is the omission of a separate disorder grouping for mental and behavioral disorders with onset during childhood and adolescence. The disorders previously pooled in this grouping were moved to other disorder groupings in ICD-11, highlighting developmental continuity across the lifespan.1

New diagnostic categories in ICD-11 and changes in diagnostic criteria

Several diagnostic categories were added in ICD-11. Table II displays brief descriptions of these new diagnostic categories. The introduction of some new diagnostic categories in ICD-11 has been controversially discussed.3,8,9 For instance, there were concerns over the pathologization of grief, computer gaming, and compulsive sexual behavior.

In addition to the introduction of new diagnostic categories, there were also changes in the diagnostic criteria for previously existing diagnoses. For example, the diagnostic threshold for Post-Traumatic Stress Disorder (PTSD) was raised in ICD-11 by defining three core symptoms that should be present in all cases: re-experiencing the traumatic event as vivid intrusive memories, flashbacks, or nightmares; avoidance of thoughts and memories of the event, situations or people reminiscent of the event; persistent perceptions of heightened current threat. There is some evidence indicating that the prevalence of ICD-11 PTSD is lower than the prevalence of ICD-10 PTSD.10,11 whereby the ICD-11 criteria seem to identify the more severe cases of PTSD.12 Regarding the prevalence of new diagnostic categories, preliminary evidence suggests that the prevalence of the ICD-11 Prolonged Grief Disorder might be almost three-fold higher than the prevalence of DSM-5 Persistent Complex Bereavement Disorder (18.0% compared with 6.4%).13 In sum, it is unclear how the introduction of ICD-11 will influence the prevalence rate of mental disorders as a whole. To prevent pathologization of normal behavior, the ICD-11 Clinical Descriptions and Diagnostic Guidelines (CDDG), which describe the main clinical features for each disorder, focus on defining the boundary between disorders and variation of normal human functioning.

Dimensional approaches in a categorical system

Current classification systems of mental disorders are based on a polythetic categorical approach. In these classification systems, a list of characteristic symptoms is provided for each diagnosis. The presence of a, usually predefined, number of symptoms from this list is sufficient to assign the respective categorical diagnosis.14 Categorical diagnoses are required to justify treatment in most countries, to communicate efficiently about mental disorders, and to collect epidemiological data. Additionally, a categorical diagnosis may aid in the decision whether to treat or not to treat a patient.15 However, categorical classification of mental disorders is associated with various limitations including large within-category heterogeneity, comorbidity, and difficulties in representing subthreshold symptomatology.16

In a dimensional approach, the severity of a symptom or the degree of disturbance of a specific psychological function is rated on a quantitative dimension. There is a growing under-
### Table I. Disorder groupings in the ICD-11 Mental, Behavioural or Neurodevelopmental Disorders chapter and in the ICD-10 Mental and Behavioural Disorders chapter (and relevant disorder groupings from other ICD-11 chapters).

<table>
<thead>
<tr>
<th>ICD-10 F00-F99 Mental and Behavioural Disorders chapter</th>
<th>ICD-11 06 Mental, Behavioural or Neurodevelopmental Disorders chapter (and relevant disorder groupings from other ICD-11 chapters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F00-F09 Organic, including symptomatic, mental disorders</td>
<td>6D70-6E0Z Neurocognitive disorders (8A20-8A2Z Disorders with neurocognitive impairment as a major feature)</td>
</tr>
<tr>
<td>F10-F19 Mental and Behavioural disorders due to psychoactive substance use</td>
<td>6C40-6C5Z Disorders due to substance use or addictive behaviors</td>
</tr>
<tr>
<td>F20-F29 Schizophrenia, schizotypal and delusional disorders</td>
<td>6A20-6A2Z Schizophrenia or other primary psychotic disorders 6A40-6A4Z Catatonia</td>
</tr>
<tr>
<td>F40-F48 Neurotic, stress-related and somatoform disorders</td>
<td>6B00-6B0Z Anxiety or fear-related disorders 6B20-6B2Z Obsessive-compulsive or related disorders 6B40-6B4Z Disorders specifically associated with stress 6B60-6B6Z Dissociative disorders 6C20-6C2Z Disorders of bodily distress or bodily experience</td>
</tr>
<tr>
<td>F50-F59 Behavioural syndromes associated with physiological disturbances and physical factors</td>
<td>6B80-6B8Z Feeding or eating disorders 6E20-6E2Z Mental or Behavioural disorders associated with pregnancy, childbirth, or the puerperium 6E40-6E40Z Psychological or Behavioural factors affecting disorders or diseases classified elsewhere</td>
</tr>
<tr>
<td>F60-F69 Disorders of adult personality and behaviour</td>
<td>6C70-6C7Z Impulse control disorders 6D10-6D11.5 Personality disorders and related traits 6D30-6D3Z Paraphilic disorders 6D50-6D5Z Factitious disorders (7A00-7A0Z Insomnia disorders) (7A20-7A2Z Hypersomnolence disorders) (7A60-7A6Z Circadian rhythm sleep-wake disorders) (HA60-HA6Z Gender incongruence)</td>
</tr>
<tr>
<td>F70-F79 Mental retardation</td>
<td>6A00-6A00.Z Disorders of intellectual development</td>
</tr>
<tr>
<td>F80-F89 Disorders of psychological development</td>
<td>6A00-6A06.Z Neurodevelopmental disorders</td>
</tr>
<tr>
<td>F90-F98 Behavioural and emotional disorders with onset usually occurring in childhood and adolescence</td>
<td>6C00-6C0Z Elimination disorders 6C90-6C9Z Disruptive behavioural or dissocial disorders</td>
</tr>
<tr>
<td>F99 Unspecified mental disorder</td>
<td>6E60-6E6Z Secondary mental or Behavioural syndromes associated with disorders or diseases classified elsewhere</td>
</tr>
</tbody>
</table>
State of the art
Changes from *ICD-10* to *ICD-11* and future directions - *Gaebel et al*

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catatonia</td>
<td>A syndrome of primarily psychomotor disturbances (no longer regarded as a subtype of Schizophrenia) characterized by the occurrence of several different symptoms including stupor; catalepsy; waxy flexibility; mutism; negativism; posturing; mannerisms; stereotypies; psychomotor agitation; grimacing; echolalia; and echopraxia</td>
</tr>
<tr>
<td>Bipolar Type II Disorder</td>
<td>Defined by the occurrence of at least one hypomanic episode and at least one depressive episode</td>
</tr>
<tr>
<td>Body Dysmorphic Disorder</td>
<td>Characterized by persistent preoccupation with at least one defect or flaw in one’s appearance, unnoticeable or only slightly noticeable to others</td>
</tr>
<tr>
<td>Olfactory Reference Disorder</td>
<td>Characterized by persistent preoccupation with the belief that one is emitting a perceived foul or offensive body odor or breath, unnoticeable or only slightly noticeable to others</td>
</tr>
<tr>
<td>Hoarding Disorder</td>
<td>Characterized by accumulation of possessions due to excessive acquisition of possession or difficulties discarding them, regardless of their actual value</td>
</tr>
<tr>
<td>Excoriation Disorder</td>
<td>Characterized by recurrent picking of one’s skin leading to skin lesions, accompanied by unsuccessful attempts to decrease or stop the behavior.</td>
</tr>
<tr>
<td>Complex PTSD</td>
<td>Develops following exposure to a threatening or horrific event (or series of events) and is characterized by severe and persistent disturbances in affect regulation, a negative self-concept and difficulties in sustaining relationships in addition to the three core features of PTSD (ie, re-experiencing the traumatic event in the present, avoidance of thoughts and memories of the event, persistent perceptions of heightened current threat)</td>
</tr>
<tr>
<td>Prolonged Grief Disorder</td>
<td>Abnormally persistent, pervasive and disabling response to bereavement</td>
</tr>
<tr>
<td>Binge Eating Disorder</td>
<td>Characterized by frequent and recurrent episodes of binge eating</td>
</tr>
<tr>
<td>Avoidant/Restrictive Food Intake Disorder</td>
<td>Characterized by abnormal eating or feeding behaviors resulting in the intake of an insufficient quantity or variety of food to meet adequate energy or nutritional requirements</td>
</tr>
<tr>
<td>Body Integrity Dysphoria</td>
<td>Characterized by an intense and persistent desire to become physically disabled in a significant way with onset in childhood or early adolescence</td>
</tr>
<tr>
<td>Gaming Disorder</td>
<td>A pattern of persistent or recurrent gaming behaviour (“video gaming”)</td>
</tr>
<tr>
<td>Compulsive Sexual Behaviour Disorder</td>
<td>A persistent pattern of failure to control intense, repetitive sexual impulses or urges leading to repetitive sexual behaviour</td>
</tr>
<tr>
<td>Intermittent Explosive Disorder</td>
<td>Characterized by repeated brief episodes of verbal or physical aggression or destruction of property representing a failure to control aggressive impulses</td>
</tr>
<tr>
<td>Premenstrual Dysphoric Disorder</td>
<td>Characterized by a pattern of mood symptoms (eg, depressed mood), somatic symptoms (eg, overeating), or cognitive symptoms (eg, forgetfulness) that begin several days before the onset of menses, start to improve within a few days after the onset of menses, and then become minimal or absent within 1 week following the onset of menses</td>
</tr>
</tbody>
</table>

Table II. Overview of new diagnostic categories in the Mental, Behavioural or Neurodevelopmental Disorders chapter in *ICD-11*. PTSD, post-traumatic stress disorder.
State of the art
Changes from ICD-10 to ICD-11 and future directions - Gaebel et al

Understanding that psychopathology is continuously graded in severity.\textsuperscript{17,18} Dimensional approaches represent the severity of specific symptoms and psychological dysfunctions, including subthreshold symptomatology. A disadvantage of dimensional classification (eg, in the form of diagnostic profiles), however, is its increased complexity and, therefore, reduced clinical utility compared with categorical classification.

For ICD-11, the categorical approach of ICD-10 was largely maintained. Yet, dimensional expansions regarding severity, course, and specific symptoms were added for some diagnoses. These dimensional expansions of categorical diagnoses mirror clinical practice, in which dimensional information (eg, severity of illness) is regularly taken into consideration for selecting treatments.\textsuperscript{19} A large shift towards dimensionality concerned personality disorders.\textsuperscript{20} The division of personality disorders into discrete categories in ICD-10 is not empirically based.\textsuperscript{21} Among other problems, a large proportion of patients simultaneously fulfilled the criteria for multiple personality disorders.\textsuperscript{22,23} Against this background, the different personality disorders in ICD-10 were replaced with a single personality disorder diagnosis in ICD-11 which is characterized by problems in functioning of aspects of the self (eg, identity) and/or interpersonal dysfunction (eg, managing conflict in relationships). The ICD-11 personality disorder diagnosis is further differentiated according to severity into mild, moderate, and severe. The diagnosis may optionally be specified by the presence of one or multiple maladaptive personality traits: Negative affectivity, detachment, disso- ciality, disinhibition, anankastia and Borderline pattern. Whereas a different, more complex, dimensional approach to personality disorders was deemed as not feasible in the development of DSM-5,\textsuperscript{24,25} there was a strong focus on clinical utility and simplicity in the revision of the personality disorders grouping in ICD-11.

Another shift towards dimensionality concerned depressive episodes. In ICD-11, depressive episodes in depressive or bipolar disorders may be described in detail by using qualifiers indicating the presence of specific symptoms: the melancholic features qualifier, the anxiety symptoms qualifier, the panic attacks qualifiers, and the seasonal pattern qualifier. Additionally, depressive episodes can be described according to severity (mild, moderate, or severe) and remission status (in partial or in full remission). For moderate and severe depressive episodes, the presence of psychotic symptoms may also be indicated.

Also for the Schizophrenia or Other Primary Psychotic Disorders grouping in ICD-11, dimensional symptom specifiers and course specifiers were added.\textsuperscript{1,26} Symptom specifiers describe the current severity of symptoms in six domains: positive symptoms, negative symptoms, depressive symptoms, manic symptoms, psychomotor symptoms, and cognitive symptoms. The severity of each of these symptoms is rated on a 4-point scale ranging from “not present” to “present and severe.” These symptom qualifiers may be used for any diagnosis from the Schizophrenia or Other Primary Psychotic Disorders grouping. Thus, mental health professionals may compliment categorical diagnoses from this disorder grouping by a profile of specific symptoms that conveys additional information regarding symptomatology. The course qualifiers for the Schizophrenia or Other Primary Psychotic Disorders grouping contain two components, allowing characterization of the longitudinal course. The first component (episodicity) differentiates between first episode, multiple episodes or continuous course. The second component concerns the cross-sectional evaluation of the acuity of the symptoms and allows differentiating the current clinical status: currently symptomatic, partial remission, full remission.

A review of the ICD-11 evaluative field studies

A series of field studies evaluated how well the ICD-11 CDDG function when applied by health professionals. These evaluative field studies were conducted either with real patients (ie, ecological field studies) or online with prototypical patient descriptions (ie, online vignette-based field studies).\textsuperscript{27} A large ecological field study of the ICD-11 MBND chapter examined the reliability and clinical utility of 16 ICD-11 diagnoses in a sample of 339 clinicians from 13 countries.\textsuperscript{28,29} When the ICD-11 diagnostic guidelines were applied to 1806 patients, interrater reliability was excellent for some diagnoses (eg, for social anxiety disorder), but improvable for others (eg, for dysthymic disorder). On average, the reliability of the ICD-11 CDDG was higher compared with previously reported estimates of the ICD-10 CDDG.\textsuperscript{28} Additionally, clinicians’ evaluations of clinical utility were positive: A large majority of clinicians (82.5% to 83.9%) perceived the ICD-11 CDDG as quite or extremely easy to use, accurate, clear, and understandable.
State of the art
Changes from ICD-10 to ICD-11 and future directions - Gaebel et al

However, utility ratings varied between countries. In a different ecological field study with 23 practitioners from Mexico, interrater reliability was high for psychotic disorders, moderate for stress-related and mood disorders, and small for anxiety and fear-related disorders.

A comprehensive online vignette-based field study investigated the diagnostic accuracy and clinical utility of the ICD-11 CDDG compared with the ICD-10 CDDG in a sample of 928 clinicians from all WHO regions. Diagnostic accuracy, time required to come to a diagnosis, and perceived clinical utility (ie, ease of use, goodness of fit, clarity) were more favorable for ICD-11 compared with ICD-10. However, advantages of the ICD-11 over the ICD-10 were largely limited to new diagnostic categories in ICD-11. After excluding all vignettes that pertained to new diagnostic categories in ICD-11, there was no significant difference in diagnostic accuracy, goodness of fit, clarity, or time required for diagnosis, but the perceived ease of use was significantly higher for ICD-11 compared with ICD-10. For feeding and eating disorders, a vignette-based online field study with 2288 practitioners found higher diagnostic accuracy and perceived clinical utility of ICD-11 compared with ICD-10. Also for Schizoaffective Disorder, a vignette-based online field study with 873 practitioners showed small improvements in diagnostic accuracy using ICD-11 compared with ICD-10. A different online vignette-based field study with 1738 practitioners from 76 countries revealed a higher diagnostic accuracy of practitioners diagnosing based on ICD-11 compared with practitioners diagnosing based on ICD-10 for disorders specifically associated with stress. Additionally, in a web-based field study, a sample of 163 mental health professionals rated the ICD-11 classification of personality disorders (including three levels of severity and trait qualifiers) as more useful regarding its utility for treatment planning, communicating with patients, comprehensiveness, and ease of use compared with the ICD-10 classification of personality disorders.

In sum, the results from the evaluative field studies paint a positive picture of the ICD-11 MBND chapter. However, there are different limitations of evaluative field studies that make overly enthusiastic appraisals of ICD-11 premature. First, the samples could be biased in such a way that practitioners who are positive towards ICD-11 are more likely to participate in ICD-11 field studies. This could be particularly the case for online field studies for which participants had to register on their own initiative. Second, individuals’ knowledge that they participate in a field study modifies their behavior. Thus, behavior in ICD-11 evaluative field studies might not adequately reflect diagnostic decision making in routine care. Third, there is some concern over the artificiality of vignette studies. Because vignettes describe prototypic cases, they might not accurately reflect the complexity of real-life situations. In summary, whereas the field studies give first indications regarding diagnostic accuracy and clinical utility, further ecological field studies are needed to reveal how well the ICD-11 works when applied by clinical practitioners under regular conditions.

Critical evaluation and future directions

In the development of the ICD-11 MBND chapter, important steps have been taken to ensure clinical utility, global applicability, and scientific validity. There were also notable steps towards dimensionality regarding symptom severity and time course. Yet, one might argue that changes from ICD-10 to ICD-11 were relatively modest in that both systems are categorical, classifying mental phenomena based on self-reported or clinically observable symptoms. In this paragraph, we discuss different new approaches to psychiatric classification and nosology that might inform future revisions of the ICD.

New approaches in diagnostic classification

Various different approaches to advance psychiatric nosology have been introduced over the last years. Of these approaches, the National Institute of Mental Health’s Research Domain Criteria (RDoC) project has received the most attention. RDoC is a research framework for the investigation of mental disorders that is not intended for immediate practical clinical use. The aim of RDoC is to provide a biologically informed framework for understanding mental disorders. The RDoC matrix distinguishes six domains of functioning (negative valence systems, positive valence systems, cognitive systems, social processes, arousal and regulatory systems, and sensorimotor systems) with various subconstructs and eight units of analysis: genes, molecules, cells, circuits, physiology, behavior, self-report, and paradigms. Varying degrees of functioning and dysfunctions in general psychological and biological systems may be described within this matrix. However, there is one major limitation: The RDoC matrix is too complex to guide diagnosis in clinical practice.
Neither the structure of the ICD-11 MBND chapter nor the structure of DSM-5 are based on neurobiology. Because of the large degree of biological heterogeneity within diagnostic categories of current classification and difficulties distinguishing some diagnostic categories genetically and neurobiologically, different approaches have been proposed to shift diagnostic boundaries in a way that biologically more homogeneous subgroups are formed. One such approach is “reverse nosology,” which suggests redefining diagnostic categories based on their molecular, cellular, and circuit basis. In this approach, patients that display a similar neurobiology (eg, similar brain activation patterns) are grouped in the same diagnostic category, although the self-reported symptoms or observable psychopathology may be fundamentally different. Thus, clinical practitioners would be no longer able to diagnose based on their clinical impression and self-report. Additionally, there would be large difficulties in communicating about a diagnosis because it might contain information regarding neurobiology, but only little information regarding observable psychopathology.

A different group of approaches aims to form biologically more homogeneous subgroups within existing diagnostic categories. For example, the Systems Neuroscience of Psychosis (SyNoPsis) project aims to link clinical manifestations of Schizophrenia onto specific brain systems. SyNoPsis differentiates three behavioral domains of Schizophrenia symptoms that match the function of three higher-order corticobasal brain systems: Language (associative loop), affect (limbic loop), and motor behavior (motor loop). Within the SyNoPsis project, also a psychometric instrument that assesses symptoms from these three behavioral domains has been developed which is used to identify clinically and neurobiologically homogeneous subgroups of schizophrenia patients (Bern Psychopathology Scale). Biologically defining subgroups of patients might then improve care by tailored treatment selection and earlier detection. However, thus far, the connection between neurobiology and psychopathology is not sufficiently understood to establish a diagnostic system on it.

A third approach to psychiatric nosology emphasizes the hierarchical structure of psychopathology. For example, the Hierarchical Taxonomy of Psychopathology (HiTOP) suggests that arbitrary boundaries between diagnostic categories limit the reliability and validity of traditional taxonomies. This taxonomy is based on dimensional assessments of psychopathology and differentiates different levels of psychopathology with specific symptoms (eg, appetite loss) at the bottom and broader spectra or super-spectra as broader constellations of syndromes (eg, internalizing and externalizing spectra) at the top of the hierarchy. Factor analytic evidence also suggests the presence of a general psychopathology factor that explains the co-occurrence of symptoms across various disorders. This general psychopathology factor describes individuals’ propensity to develop any form of psychopathology and is related to increased life impairment. For clinical practice, however, scores on higher order psychopathology dimensions are difficult to interpret leading to a low clinical utility of hierarchical approaches. Yet, dimensional information regarding specific aspects of psychological dysfunctions might aid in guiding interventions.

Reconciling the needs of different user groups: a stepwise approach

A potential problem of current categorical classification systems is that they aim to serve many purposes for various different groups of users. For example, primary care practitioners need well communicable, comprehensible diagnostic categories. Researchers, on the other hand, often prefer detailed dimensional assessments. Whereas complex approaches like RDoC are suitable for research contexts, the categorical approach in ICD-11 provides a higher clinical utility.

To ensure that future versions of the ICD meet the needs of different user groups, a stepwise procedure to diagnosis might be appropriate. In this stepwise approach, each diagnostic step describes a patient’s psychopathology with increasing detail. In the first diagnostic step, a patient’s symptoms may be categorized into broad diagnostic categories. Regarding level of detail, this step might be similar to the ICD-10 Primary Care Version for Recognition and Management of Mental Disorders. On this diagnostic level, patients that experience a level of distress requiring specialized treatment and further diagnostics may be identified. In the second diagnostic step, more specific differential diagnosis might be made. For practitioners in specialized mental health facilities and ambulatory care, the ICD-11 CDDG provide the optimal level of detail. The CDDG contain detailed descriptions regarding the core symptoms of disorders, differential diagnosis, and boundaries with normal human functioning.
In specialized treatment settings and for research, additional dimensional assessments are required to more precisely describe psychopathology. Thus, a third diagnostic step might enrich categorical diagnoses with dimensional assessments, combining the advantages of both approaches (see the ICD-11 Schizophrenia or Other Primary Psychotic Disorders grouping). In this diagnostic step, each categorical diagnosis could be complemented with a symptom profile that provides specific information regarding domains of psychological malfunctioning. Based on this stepwise approach, rapid communication will be possible based on diagnostic categories and dimensional assessments will provide more nuanced profiles for contexts in which detailed dimensional information is needed beyond the overall degree of severity to inform treatment (eg, psychotherapy) and for research. Importantly, the use of nuanced and partly dimensional methodologies, and current status information is needed beyond the overall degree of severity to inform treatment (eg, psychotherapy) and for research.17

In specialized treatment settings and for research, additional dimensional assessments are required to more precisely describe psychopathology. Thus, a third diagnostic step might enrich categorical diagnoses with symptom profiles. Yet, there is large potential for enriching further categorical diagnoses with symptom profiles. For example, it has been suggested to assess all symptoms of substance use disorders in DSM-5 on (at least) a 3-point scale.50

Summary

The development of the ICD-11 MBND chapter was characterized by a focus on clinical utility, global applicability, and scientific validity. Thus far, mental health professionals’ evaluations of the ICD-11 are relatively positive. Changes from ICD-10 to ICD-11 include the introduction of new diagnoses, the refinement of diagnostic criteria of existing diagnoses, and notable steps in the direction of dimensionality for some diagnoses. However, there was no paradigm shift from ICD-10 to ICD-11. There are promising new approaches to psychiatric nosology, which, however, have a low clinical utility. We argue in favor of a stepwise approach to diagnosis that retains categorical classification to ensure clinical utility,51 but allows more detailed dimensional assessments of psychopathology to inform treatment in specialized settings and research. Expanding the stepwise approach to diagnosis introduced for some diagnostic categories in ICD-11 may help to meet the needs of different user groups of the ICD.

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Fractures in the framework: limitations of classification systems in psychiatry

Munira Kapadia, MA; Maherra Desai, MSc, MA; Rajesh Parikh, MD, DPM, DipNBE

This article examines the limitations of existing classification systems from the historical, cultural, political, and legal perspectives. It covers the evolution of classification systems with particular emphasis on the DSM and ICD systems. While pointing out the inherent Western bias in these systems, it highlights the potential of misuse of these systems to subserve other agendas. It raises concerns about the reliability, validity, comorbidity, and heterogeneity within diagnostic categories of contemporary classification systems. Finally, it postulates future directions in alternative methods of diagnosis and classification factoring in advances in artificial intelligence, machine learning, genetic testing, and brain imaging. In conclusion, it emphasizes the need to go beyond the limitations inherent in classifications systems to provide more relevant diagnoses and effective treatments.

Keywords: classification system; psychiatry; culture; comorbidity; alternative classification

Introduction

Classification systems are integral to medical practice. They facilitate diagnosis and thereby impact treatment and prognosis. Further, they enable communication with patients as well as amongst clinicians, researchers, training institutions, judicial systems, and insurance companies. In psychiatry, the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) and the International Classification of Disorders 11 (ICD-11) are the main classification systems in current use. They have evolved over several years and, although not perfect, perform a significant role in psychiatric research and clinical practice.

Psychiatry is probably the only medical specialization to have twice endured a complete discarding of its knowledge, which suggests that the classification of psychiatric disorders is more complex than it seems. This review covers some of the limitations of classification systems in psychiatry, focusing on historical and current fissures in the systems.

Historical perspective

Between 1500 and 1000 BC, ancient Indian scriptures, specifically the Atharva-Veda, provided the earliest descriptions of modern psychiatric illness. Illnesses were classified based on an imbalance of three biological energies or doshas: vata, pita, and kapha. In the 2nd century AD, Galen postulated four categories of temperament: choleric, sanguine, melancholic, and phlegmatic. Excess in one of the temperament humours was linked to an associated pathology.

Emil Kraepelin’s classification in Compendium and Theodor Meynert’s efforts to map mental illness on the brain were important contributions in the development of the current classification systems. However, these classifications often mistook isolated symptoms for illnesses, unduly increased the number of categories of disorders, and were primarily based on patient histories. The European nosological tradition which started in the 18th century was primarily symptom-based.
Within the United States (US), there were four official diagnostic classification systems following World War II. In order to overcome this somewhat chaotic state, the American Psychiatric Association (APA) initiated the creation of a new nosology based on psychoanalytic theory. This effort was influenced by a military manual referred to as Technical Medical Bulletin number 203 of the United States Army, which was issued in 1945. This document, directed by psychoanalyst William Menninger, became the basis of DSM.5,11

**DSM-I** and **DSM-II** were developed for the purpose of gathering statistical information on the prevalence of mental disorders. When the first DSM was published in 1952, psychoanalytic theory dominated American psychiatry. Although an etiological framework was used to classify mental disorders, they were viewed as “reactions” to stressors implying their psychodynamic causality. The second edition attempted a more atheoretical position; however, the nomenclature was still psychodynamic, with replacement of the term “reaction” with the term “neurosis.” 12-14

In the mid-1970s, the lack of empirical research evidence led to the questioning of the legitimacy of psychiatric diagnosis. Thomas Szasz and the antipsychiatry movement considered mental illness a myth.15

In 1970, the US-UK Diagnostic Project found that US clinicians used a broader, more inclusive concept of schizophrenia based on psychoanalytic theory, whereas the British clinicians used more stringent criteria in diagnosis. This led to overdiagnosis of schizophrenia within the US and subsequently greater hospital admissions, resulting in discrepancies in prevalence data amongst the two countries.16,17

In view of these criticisms, **DSM-III**, based on the Feighner criteria, took on an atheoretical approach.18,19 It provided a new hierarchical, multiaxial system for diagnosis utilizing exclusion criteria and introduced the formal operationalization of psychiatric diagnosis with established reliability.20 The new system stimulated empirical research, which showed flaws in the existing diagnostic criteria. It was seen to have low validity, taking on a reductionist and adynamic approach as well as not adequately distinguishing between trait and state.21,22 DSM-III-R was updated to increase the clinical utility of diagnosis based on inputs from practicing clinicians and researchers. It also eliminated the diagnostic hierarchy, which, however, resulted in an increasing number of comorbidities being reported.23 DSM-III-R was criticized for being gender-biased, especially for personality disorders.24,25

**DSM-IV** built on the previous criteria, and added “clinically significant distress or impairment” across diagnostic criteria to improvise on the term “dysfunction” used in its previous version, the concept of which was unclear.26 DSM-IV-TR further detailed the associated features of disorders.27 DSM-5 aimed to bridge these gaps and is currently the most widely used classification system in psychiatry.2,28 With this latest update, the multiaxial system has been discarded, many disorders have been reclassified in a dimensional rather than categorical approach, and increased social sensitivity in terminology (intellectual disability instead of mental retardation) can be observed as striking changes.4,13,29 However, the growing number of disorders outlined in DSM-5 seems to provide little assistance to clinicians in providing optimal treatment.30

The **International Classification of Diseases (ICD)** was first published in 1893 as the International List of Causes of Death. The purpose was to create a comprehensive statistical manual of diseases, including causes of mortality, and to enhance efforts to improve public health.31 In 1948, when the World Health Organisation (WHO) was entrusted with the update of ICD, psychiatric disorders were first included in its 6th edition. However, the classification system was rejected by most countries. A major update was seen in ICD-8.32 With the evolutionary change of DSM-III, the balance was tipped and ICD-9 aimed to match DSM.13 Since ICD-9, both DSM and ICD tend to be aligned with some differences. ICD-11, published in 2019, aimed at improving clinical utility, global application, identify prevalence, and treatment gap to improve public health.34
<table>
<thead>
<tr>
<th>VERSION</th>
<th>YEAR</th>
<th>MAJOR PURPOSE</th>
<th>REVISIONS</th>
<th>CRITICISM RECEIVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-I</td>
<td>1952</td>
<td>Uniformity in clinical diagnosis and gathering prevalence data.</td>
<td>Strong psychoanalytic influence. Terms used deviated significantly from prevailing definitions.</td>
<td></td>
</tr>
<tr>
<td>DSM-III</td>
<td>1980</td>
<td>Atheoretical approach based on the Feighner criteria. To reduce the gap between psychiatry and rest of medicine. Provide valid and reliable diagnosis for empirical research.</td>
<td>It provided a new hierarchical, multiaxial system for diagnosis utilizing exclusion criteria and introduced the formal operationalization of psychiatric diagnosis with established reliability.</td>
<td>The existing criteria had low validity, taking on a reductionist and adynamic approach as well as not adequately distinguishing between trait and state.</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>1994</td>
<td>To increase congruence between DSM and ICD-10. Use empirical data to modify diagnostic criteria.</td>
<td>Modified previous criteria, and replaced the abstract concept of “dysfunction” to “clinically significant distress or impairment.”</td>
<td>Lack of clarity in the definition for threshold resulting in overdiagnosis. High rates of comorbidity in personality disorder diagnosis.</td>
</tr>
<tr>
<td>DSM-IV-TR</td>
<td>2000</td>
<td>Update research literature.</td>
<td>Detailed the associated features of disorders.</td>
<td>Little revision to criteria was made.</td>
</tr>
<tr>
<td>DSM-5</td>
<td>2013</td>
<td>Incorporate neurobiological and etiological research in the criteria of disorders. Improve clinical utility.</td>
<td>Discarded the multiaxial system. Reclassification of some disorders in a dimensional rather than categorical approach. Increased social sensitivity in terminology.</td>
<td>Low reliability across disorders. Poor validity leading to increased comorbidity and lack of specificity in selection of treatment options. Poor correlation between genetic findings and psychiatric diagnosis. Observed syndromes, especially culture-specific, don’t fit any diagnostic criteria. Lowered thresholds and new categories may result in overdiagnosis. Increasing number of disorders provide little assistance to clinicians in providing optimal treatment.</td>
</tr>
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Table I. Developments in various versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM).
ICD uses short text descriptions of each disorder rather than a list of symptoms. Although used in clinical settings, its main focus is on providing a comprehensive list of all diseases with the aim of public health application.3,33

Surveys on utility of classification systems suggest that, although 57% to 89% of clinicians use classification systems, the most common application is for administrative requirements and assigning a diagnosis for billing and insurance purposes. Communication and teaching were other cited reasons. They found the lowest utility in selection of treatment plans and assessing possible prognosis.30,34,35

Cultural perspective

Psychiatry relies considerably on patient self-report and clinician judgement.36 Cultural influences are integral in determining deviations and threshold for illness. For example, in the Japanese culture, Taijin Kyofusho is an acceptable presentation of anxiety, associated with offending others.37,38 Hikikomori is another Japanese presentation associated with social withdrawal for a period of over 6 months. It parallels chronic schizophrenia or apathetic depression, as sometimes there is a strong immersion in personal interests. However, these individuals report no psychological distress and lifelong financial dependency. This condition is acceptable in Japan.39 However, a Japanese immigrant may find it difficult to convey these concerns to a Western clinician who is unaware of this social context.40–42

Tseng highlights six different ways in which culture can affect psychiatric syndromes—in the formation of the disorder (pathogenic effect), techniques used to cope with stress (psychoselective effect), modification in clinical presentation (psychoplastic effect), behavioral reactions due to cultural reinforcement (pathoelaborating effect), occurrence (psychofacilitating effect), and perceptions and reactions (psychoreactive effect).43

Although culture-specific syndromes by definition can exist in any society, they are typically identified in Eastern cultures as the classification systems are based in Western societies. They were usually observed during colonization and considered as “peculiar” phenomena that did not fit the classification systems developed by Western nations. Even now, most culture bound syndromes parallel disorders seen in Western-based classification systems, eg, Amok, is closely linked to dissociative disorder, Khyl cap, or wind attack, is related to panic disorder.44 On the flipside, some disorders such as anorexia nervosa, paranoid schizophrenia, and drug overdose are seen as culture-bound syndromes of the Western cultures.45 Culture-bound syndromes are identified to be emerging from a particular location or cultural group; however, reports of Dhat syndrome, Amok, Koro, Taijin Kyofusho, and Latah have been found in both Western and Eastern countries.44

Current diagnostic criteria are not culture-sensitive, resulting in a 34-fold variation across countries for social anxiety disorder.46 Prevalence rates for major depression varied between 2% and 19% across countries.47 Variance across 10 countries is seen in the illness course, outcome and incidence of schizophrenia.48 Somatization of anxiety and depression is common in Asian patients.49

Medical institutions and training institutes worldwide focus on teaching the dominant classification systems like DSM and ICD, which are influenced by Western illness presentations.50 This may result in ignorance of local cultural presentations, which may be critical for identification and treatment of mental illness in non-Western cultures.51,52

Political perspective

Classification systems are occasionally driven by the prevalent political agendas. In the 19th century, Cartwright diagnosed the defiance and rebellion of African slaves as signs of mental illness and outlined multiple mental disorders he believed Africans were susceptible to. Acts like avoiding work responsibilities or escaping for freedom were considered mental disorders—Dysesthesiia Aethiopica and Drapetomania respectively. These so called “diseases” were cured by removing both big toes of the “patients” and thereby making running impossible.53,54

In the late 20th century, a classic example of classification systems serving political agendas was seen in the Soviet Union. The Moscow School of Psychiatry expanded on the concept of “sluggish schizophrenia” to classify individuals who had symptoms of “reform delusions,” “struggle for the truth,” and “perseverance.”55
Current debates on the political exploitation of psychiatry are contextual to the People’s Republic of China, where the magnitude of abuse seems to be even more widespread than what took place in the Soviet Union. It involves the psychiatric confinement of the Falun Gong movement followers, trade union activists, human rights campaigners, and those objecting to injustice carried out by local authorities.56,57

**Legal perspective**

Across the world, with a surge in awareness and parental advocacy, there is an increase in provisions made for children with mental illness such as special schools, intervention programs, and concessions in examinations.58,59 A multinational longitudinal study found that over the last 20 years, the prevalence of childhood neuropsychiatric disorders has increased. Further, the age of diagnosis of the disorders was higher than the typical age of onset.60 This may suggest a pattern of misuse by parents and children.61

In recent years, with increasing complexity, public awareness of mental illness as well as laws regarding mental health and disability, there is a surge of psychiatric inputs for resolution of legal conflicts.62

The dependence of psychiatric diagnosis on self-reported symptoms and witness testimony heightens its risk of misuse. In 2011, in Norway, a man was sentenced to 21 years in prison for killing 77 people including children and youth in two separate events. Two separate forensic evaluations, 6 months apart, were conducted, with detailed interviews. The first evaluation posited a psychotic disorder and therefore considered him not accountable for the crime; on the other hand, the second evaluation diagnosed him with a narcissistic personality disorder and therefore accountable.63

Premenstrual Dysphoric Disorder (PMDD) has been the centre of controversy, especially in forensic use. In Britain in 1981, several cases of women—one for threatening a police officer and carrying a knife along with 30 other such crimes, and another of a woman who drove into her lover after an argument—were given reduced charge of the quantum of guilt on account of diminished capacity due to severe Premenstrual Syndrome (PMS).64 Many countries, especially in Europe, accept PMS as a legal defence for diminished capacity or insanity.55,66 This may be misused by woman with milder symptoms and astute attorneys.67

**The potential for misuse**

Lack of affordability results in a significant treatment gap in mental health services. However, with increasing awareness, most government policies have included provisions for mental health services in health insurance coverage.68,69 Classification systems can be misused by insurance companies to deny coverage to those who otherwise may have been eligible.

In DSM-5, Autistic Disorder, Asperger’s Syndrome, and Pervasive Developmental Disorder—Not Otherwise Specified (PDD-NOS) were discarded and reduced to two diagnoses, Autism Spectrum Disorder and Social Communication Disorder. The autism concept was broadened and replaced by only two categories—social communication impairments and restricted and repetitive behaviors, with more stringent criteria for diagnosis to reduce false positives. It was believed that those individuals previously diagnosed as PDD-NOS as per DSM-IV-TR would either meet ASD or SCD criteria. However, this reclassification has resulted in underidentification of children with significant impairments. Three groups—those with a milder form of the disease, higher cognitive functioning (Asperger’s), and older children are underdiagnosed as a result of the new criteria; and therefore, are denied treatment options. These are also the very same groups for who therapy is found to be most beneficial.70

Trends towards increase in disorder categories, lowered threshold, and symptom severity, all result in an increasing number of children and adults being diagnosed, subsequently seeking treatment, and a rise in the sale of pharmaceutical drugs. This, against the backdrop of simultaneous increase in the percentage of individuals on the DSM task force who have ties with pharmaceutical companies from 57% to 72% between DSM-IV and DSM-5, challenges the interests underlying the creation of classification systems.71

Misuse of stimulants among college students without diagnosis of ADHD to improve concentration for cognitive and academic enhancement is a growing dilemma, with prevalence rates between 13% and 43%. Furthermore, many of these disorders are ascertained by patient self-report and
clinician’s judgment—with increasing access to information on the internet and some training, feigning symptoms may not be as difficult after all.72,73

Until the multiaxial system of classification of psychiatric disorders, Axis II diagnoses were often excluded from insurance coverage, being considered as chronic illness. This denied the much-needed treatment that individuals with personality disorders require to cope with their daily issues. Restrictions on therapy to a fixed number of limited sessions may also make it increasingly difficult for patients to work through all their issues and make a full recovery.74

Individuals at subthreshold levels of depression and anxiety often experience impairment as significant as those who meet criteria.75,76 Hence, in an effort to create stringent criteria and reduce false positives, our classification systems may also be serving the interests of insurance companies by excluding individuals from coverage, and denying therapy and treatment to individuals who might benefit from them.

**Issues with the current classification systems**

**Reliability and validity**
An overarching problem with many psychiatric disorders is that validity and reliability research originally carried out for a few groups of disorders in DSM has not been carried out for most of the remaining diagnoses in the manual.31 Even for DSM-5, field trials yielded low reliability, with nonexpert clinicians diagnosing patient groups based on checklists rather than standard diagnostic interviews.77,79

**Multiaxial system**
Introduced in DSM-III, the multiaxial system was created to help clinicians ensure a holistic diagnosis. However, concerns regarding overlap in symptoms between Axis I and II disorders were raised.80 Significant comorbidities have been observed between social anxiety disorder and avoidant personality disorder (PD),81 schizophrenia and schizotypal PD,82 and substance-use disorders and antisocial PD.83 Segregation of medical illnesses on Axis III implied that mental disorders did not have a medical status.84 DSM-5 discarded the multiaxial system in an effort to do away with the above limitations.2 It extensively expanded on possible stressors under Z codes; however without the multiaxial system, they may be dismissed or ignored.85

**Comorbidity**
Comorbidities increased dramatically when the exclusion system was eliminated from DSM-III-TR and disorders were divided into discrete categories.21 Presence of any DSM-III-TR disorder increased the odds of having almost any other disorder.86 Comorbidity affects the specificity with which diagnosis directs treatment. It is also associated with more severe outcomes, impairment, poorer quality of life, higher chronicity rates, resistance to treatment, and a greater suicide risk than any condition alone.87-89 Epidemiological studies revealed high rates of comorbidity—not only within diagnostic groups but also between disorders.90-92

Furthermore, current psychopharmacological treatments are effective for multiple disorders. Selective serotonin reuptake inhibitors are effective in the treatment of depression, eating disorders, and anxiety disorders.93 Likewise, second-generation antipsychotic medications are effective alone or as adjunctive treatments for nonpsychotic mood disorders.94 Psychotherapy has also been successfully generalized to treat multiple disorders.95

Thus, high rates of comorbidity, and nonspecificity of both pharmacological and psychosocial treatments question the specificity of the disorders and their purported underlying mechanisms.4

**Categorization or dimensional approach?**
Several attempts have been made at classifying psychiatric disorders based on various criteria, including etiology, phenomenology, onset age, longitudinal course, and prognosis.96-98 However, these categories are not mutually exclusive and the overlap of symptoms and presentations are common. Currently, DSM adopts both categorical as well as dimensional approaches in classifying disorders. Schizophrenia and autism are two examples of a dimensional approach, and perhaps future shifts in this direction are likely.2,99

**Heterogeneity within diagnoses**
Heterogeneity is seen across persons and across symptoms. Within individuals, for instance, Borderline Personality Disorder (BPD) consists of nine diagnostic criteria of which a minimum of five need to be present for the diagnosis. This results in a staggering 256 distinct presentations of BPD.100 Strikingly, this number is relatively small when compared with other conditions—there are 636 120 ways to have post-traumatic stress disorder.101
Future directions

Alternative methods of diagnosis
Diagnosis in psychiatry relies heavily on clinical interview and clinician judgment. Psychometric tests are used to aid the diagnosis; however there are no internationally standardized tests that are reliable and valid in measuring disorders.102 With advances in artificial intelligence, imaging, and genetic testing, there may be a way forward towards alternative methods of diagnosis which in turn would result in alternative classification systems.103-105

Artificial intelligence has aided the classification of diseases using techniques such as expert systems, artificial neural networks, linear programming, database systems, evolutionary algorithms, and swarm intelligence.106,107 Within psychiatry, machine learning has shown promising results in stratification based on symptom type,108 symptom severity as well as behavior within a single diagnosis,109 in predicting those at risk,110 course and prognosis of illnesses,111 in its ability to differentiate between diagnostic categories,112 understanding correlations between structural and functional alterations through its application in neuroimaging data,113 as well as in transdiagnostic studies clustering symptoms across diagnosis.114

Meta-analysis indicates that structural imaging has 80% sensitivity and specificity in distinguishing between schizophrenic subjects and normal adults.115 Similar results have been found for Major Depressive Disorder.116 Functional magnetic resonance imaging (fMRI) studies have not only be able to accurately distinguish schizophrenia, bipolar disorder, and unipolar disorder, but have also shown evidence for overlapping anatomical changes in schizophrenia and bipolar disorder.117,118

Alternative methods of classification
Current dissatisfaction with the categorical classification systems have emerged predominantly from lack of support for the current nosology in biomarker research. In this chaos, Research Domain Criteria (RDoC) has been seen as a frontrunner for an alternative method of classification.119 Established in 2009, the goal of this research initiative is precision medicine for psychiatric disorders—to facilitate the modification of current diagnosis, improvement of treatment and prevention of mental illness. Its dimensional approach views basic behavior, cognitive domains, and brain circuits on a continuum of functionality from normal to abnormal. It integrates neurobiological data, observable behaviors, and self-reports.120,121

The Hierarchical Taxonomy of Psychopathology (HiTOP) is an alternative classification system suggested by Kotov and colleagues.122 Based on a four-level hierarchical structure, it is composed of broad spectra of internalizing pathology, externalizing pathology, thought disorder, and detachment at the top of the hierarchy. These are divided into factors which are further divided into syndromes or traits. Signs and symptoms form the base of the structure. Using multivariate factor analysis, the goal is to create an empirically based dimensional classification system. It reduces heterogeneity by grouping related symptoms, reduces comorbidity by combining syndromes into spectra, and it has a dimensional approach which eliminates issues regarding categorization.123

Conclusion

While classification systems are essential and do indeed serve important functions in the practice of psychiatry, their inherent limitations result in errors on both sides of the diagnostic spectrum, from overdiagnosis to underdiagnosis. It is important to recognize the fissures in the framework of our contemporary classification systems. Beyond our theoretical constructs, the patient in front of us expects effective treatment. Our goal should be to go beyond the limitations of our classification systems to fulfill the expectations of our patients, as well as those of ourselves as humane and effective psychiatrists.

Acknowledgments/Disclosures: The authors declare no conflict of interest.

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Original article

Limits of psychiatric classification systems - Kapadia et al

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Diagnosis as dialogue: historical and current perspectives

Paul Hoff, MD, PhD; Anke Maatz, MD, PhD; Johannes Simon Vetter, MSc, PhD

Ever since psychiatry emerged as a clinical discipline and field of scientific inquiry in the late 18th century, debates about diagnosis have been at its very heart. Considered by many a requirement for clinical communication as well as for systematic study, others have critiqued psychiatric diagnosis for being modeled on a medical conception of disease that is ill-suited to the specific nature of mental disorders. Based on a review of seminal positions in the conceptual history of psychiatry and an examination of their epistemological underpinnings, we propose to consider diagnosis as dialogue. Such understanding, we argue, can serve as a meta-framework that provides a conceptual and practical umbrella to encourage open-minded conversation across the diverse conceptual and experiential frameworks that are characteristic of psychiatry. In this perspective psychopathology will also reinforce the interpersonal realm as a necessary element of any clinical encounter, be it diagnostic in purpose or otherwise. Current challenges to traditional diagnostic systems like Research Domain Criteria (RDoC) and Hierarchical Taxonomy of Psychopathology (HiTOP) are discussed in light of these considerations.

Keywords: psychiatric diagnosis; dialogue; psychopathology; ICD-11; RDoC; HiTOP; denosologization

Introduction: The entangled nature of psychiatric diagnosis

Ever since psychiatry emerged as an independent clinical discipline and field of scientific inquiry in the late 18th century, debates about the concept (and content) of diagnosis have been at its very heart. Considered by many a requirement for clinical communication as well as for systematic study, others have critiqued psychiatric diagnosis for being modeled on a medical—in the sense of somatic—conception of disease that is ill-suited to the specific nature of mental disorders. Proponents of this latter position argue that psychiatric diagnosis disregards the complex individuality of any given person as well as cultural influences on diagnostic conceptions. Taking this critical perspective further, “anti-psychiatrists” have claimed that psychiatric diagnosis is entirely normative—as opposed to descriptive—and a means of societal oppression. A different, but related, point of critique has been the worry that psychiatric diagnosis rests too much on the assessment of the individual clinician, and that it grossly overrates intuition and personal experience, thereby giving an unacceptably high degree of power to the diagnostician and making diagnosis unreliable.

Whilst some criticisms, especially the lack of reliability, have been addressed by more recent research on and developments of diagnostic systems, the general points of contention remain: The epistemological dichotomy between conceptions of psychiatry as a quantifying nomothetic science searching for general rules behind the individual case on the one hand, and the (much older) “ars medicina-approach” with its focus on qualitative, subjective phenomena to do with the individual person and thus being idiographic in nature on the other hand, results in...
conceptions of psychiatric diagnosis as “carving nature at its joints” as opposed to views according to which psychiatric diagnosis is per se unfounded. Debates about diagnosis can thus not be separated from debates about broader nosological and epistemological frameworks, and diagnosis necessarily mirrors the entangled nature of mental disorders.

What are we to do then if we take up a pragmatic position of minimal epistemological consensus and agree that diagnosis can indeed be helpful to condense information and thereby ensure reliable communication in clinical, research, and teaching contexts?

In this article, we propose to consider diagnosis as dialogue. This implies that we ought to be aware, and teach awareness, that diagnosis cannot be reduced to clear-cut, unequivocally applicable algorithms, but needs to be accompanied by reflection and discussion of its nosological, epistemological, and anthropological underpinnings.

To argue for such a conception, we first give an overview of landmark positions on diagnosis in the conceptual history of Western psychiatry. We then work out the general nosological frameworks underlying these positions, highlighting their implications for the epistemological status of diagnosis. Finally, current approaches to diagnosis are reviewed in light of these considerations. Diagnosis as dialogue, as we understand it, can serve as a meta-framework not to blur the lines where there are ontological or epistemological incommensurabilities between diagnostic systems, but to provide a conceptual and practical umbrella to make underlying theoretical assumptions explicit and to encourage open-minded conversation across diverse conceptual and experiential frameworks, both among clinicians and researchers as well as between clinicians and patients.

Landmark positions on diagnosis in the conceptual history of Western psychiatry

Two markedly different anthropological approaches accompanied and influenced the very beginning of psychiatry as a medical discipline: The era of Enlightenment in the 18th century brought forward a strongly rational understanding of personhood and citizenship as well as an optimistic stance on the scientific comprehensibility, not to say mastery of our world. Autonomous and responsible decision making became one of the hallmarks of being a person. In turn, not being able to make use of one’s own rational powers was increasingly conceptualized not only as a deficit, but as an illness calling for medical diagnosis and treatment. Thus, the conceptual framework for establishing psychiatric diagnosis was rationalism.

Some decades later, at the beginning of the 19th century, romanticism regarded a rationalistic attitude as simplifying and laid emphasis on the affective, not to say the irrational, dimension of human experience and behavior. Mental disorders were now regarded as consequences of excessive or otherwise disturbed affective states: Some authors saw a direct link between such affective instabilities and the person’s attitudes and lifestyle, thus attributing at least a significant part of the responsibility for becoming mentally ill to the patient himself or herself. The scope of psychiatric diagnosis thereby became broader and more value-laden as it conceived of mental illness as an aberration from the proper way of life. Here, the individual biography, personal attitudes, and accepted moral values of a given cultural context shaped the process of generating a psychiatric diagnosis.

Wilhelm Griesinger (1817-1868), a central figure in the conceptual history of psychiatry, pursued the understanding of psychiatry as an integral part of medicine, thus strictly departing from speculative philosophical approaches that had prevailed in the romantic era. Psychiatry should adopt empirical research methods, especially concerning the brain: Griesinger was therefore one of the founders of neuroscience, but he also insisted on the limitations of such an approach and warned not to prematurely accept oversimplifying views. As for nosology, he vouched for the existence of just one all-embracing mental illness, the “unitary psychosis” (“Einheitspsychose”). He argued that there exists only one single mental disorder that in its different stages may exhibit the whole spectrum of psychopathological phenomena. Hence, for Griesinger, diagnosis was centered around the clinical picture, its course in time, and possible correlations with brain dysfunctions, but not around presumably distinct nosological entities.

Based on Karl Ludwig Kahlebaum’s (1828-1899) proposal to direct psychiatric research towards specific patterns in the temporality of defined clinical syndromes (“syndrome-course-entities”, “Syndrom-Verlaufs-Ein-
enheit”), Emil Kraepelin (1856-1926) strongly and sustainably favored the idea of the existence and scientific detectability of “natural disease entities” (“natürliche Krankheitseinheiten”). He saw these entities as objective parts of nature, as given things, although he accepted different scientific ways to detect them: research on etiology, on pathological anatomy, or on clinical course. From this perspective, psychiatric diagnoses were tools to get as close as possible to “real” nosological entities.

Eugen Bleuler’s influential innovation in the present context—especially regarding “dementia praecox,” reconceptualized by him as “group of schizophrenias”—was to explicitly acknowledge a hermeneutical—specifically: a psychoanalytical—approach as a scientific element of psychiatric diagnosis, therapy, and research, notably without deemphasizing the role of descriptive and neurobiological factors. Bleuler enriched the scope of diagnosis by the psychodynamic dimension, in this specific respect resembling ideas of “romantic psychiatry” a century before (see above).

The assumption that mental disorders were manifestations of a transgenerational process of “degeneration” (“Entartung”), although lacking a sound scientific basis and conceptual rigor, became highly influential in medicine in the late 19th century. Psychiatry was no exception on the contrary: Most contemporary textbooks introduced chapters on “degenerative psychoses” or similar terms. Psychiatry succumbed to the underlying dogma by focusing on the detection of (somatic or psychopathological) “stigmata degenerationis” (Cesare Lombroso’s (1835-1909) “Criminal Anthropology”12 is a prominent example for this approach, but by far not the only one), thus grossly disregarding the subjective and interpersonal dimensions. This may be a drastic example of neglecting the patient’s individuality, of the very opposite of person-centeredness. However, any diagnostic approach in psychiatry does, in principle, carry this risk.

Considering the conceptual cornerstones of what became known as “psychotherapy” during the 20th century, further frameworks, embedding the diagnostic process, emerged: In the psychoanalytical perspective, diagnosis cannot be neatly separated from therapy since the prominent role of interpretation both of the patient’s narratives and the therapeutic relationship essentially influences any single act within psychotherapy. As opposed to this, behaviorism, at least in its early phase, placed emphasis on the patient’s empirically observable and, therefore, quantifiable behavior, thus keeping its distance from the hermeneutical approach as well as from possible neurobiological underpinnings. Anthropological psychiatry emerged after World War II and, in fact, dominated psychiatric literature for a couple of years. It radically opposed the crude biologism and social Darwinism of psychiatry during the era of national socialism. Authors like Ludwig Binswanger (1881-1966) and Wolfgang Blankenburg (1928-2002) advocated a person- and biography-oriented approach, partly resembling, but not identical with the psychoanalytic one, that searched for a meaningful link between the patient’s mental disorder and his or her individual life. Note that the neurobiological dimension was not neglected in this view. It was credited as necessary, but not sufficient, not as the essential precondition of adequately dealing with the phenomenon of mental illness.

Systemic psychotherapy with its partly eclectic approach enriched the scope of psychotherapy by emphasizing the relevance of the patient’s social context, especially his or her family and occupational situation. Diagnosis had to encompass a much broader range of relevant information than, eg, in descriptive clinical psychopathology. (This outline of major theoretical approaches in psychotherapy focuses on the perspective of conceptual history. Towards the end of the 20th century, eclectic models were developed that explicitly drew on different schools of thought, eg, the Cognitive Behavioral Analysis System of Psychotherapy13).

Concurrent to the discovery of new and effective psycho-pharmacological agents and their subsequent implementation into psychiatric practice starting from about 1950 onwards, the disadvantages of the highly heterogeneous field of psychiatric diagnosis (and nosology) became obvious. Large-scale international clinical studies depended on a common diagnostic language and especially on its reliability in order to quantify therapeutic response, side
effects, and course of illness under treatment. This situation (together with the arrival of modern neuroscientific research methods as biochemistry or brain imaging) prompted the development of operationalized rating scales and, ultimately, diagnostic manuals such as \textit{ICD-10} or \textit{DSM-III}.\textsuperscript{17} They strongly focus on reliability and, in order to achieve it, on precise definitions of psychopathological terms and diagnostic algorithms. This descriptive approach endeavors to avoid implicit theoretical presuppositions, especially regarding etiology and treatment of mental disorders. Not what, eg, schizophrenia “really is” or how it should be optimally treated, but how the term schizophrenia can be defined and used in a reliable way, is the very core of operationalized diagnosis in psychiatry (nominalistic approach, see below). Not leaving these common grounds, but as an amplification of \textit{ICD-10}, additional concepts have been proposed and clinically adapted, for instance, the “Operationalized Psychodynamic Diagnosis.”\textsuperscript{18}

In a remarkable step beyond the “atheoretical” ambition of \textit{ICD-10}, \textit{ICD-11} arranges disorders on the basis of shared putative etiological and pathophysiological features (eg, disorders associated with stress) as well as shared clinical phenomenology (eg, dissociative disorders).\textsuperscript{19} Besides several new diagnoses and alterations to existing criteria of disorders, innovations in \textit{ICD-11} comprise the description of essential features of each disorder and the integration of a lifespan approach as well as culture-related information. Also, as in \textit{DSM-5}, disorder groupings were ordered to be related to developmental psychopathology (eg, neurodevelopmental disorders are enlisted first and neurocognitive disorders at the end). A major innovation is the incorporation of dimensional approaches within the framework of a categorical system with explicit taxonomic restrictions, especially applied in the classification of personality disorders\textsuperscript{20} (and also partially for schizophrenia and other primary psychotic disorders).

Still, and like \textit{DSM-5}, \textit{ICD-11} in many ways offers no strict alternative to the current descriptive-phenomenological approach, and has not introduced fundamental conceptual alterations. One may argue, that \textit{ICD-11}’s main advance is a technological one, ie, the transition to an electronic conceptual infrastructure, to a database that reflects the hierarchical structure of the classification and integrates within a single logical model all categories, conceptions, entities, groups, synonyms, and exclusion criteria as well as their relations (“foundation component”). The coding of diagnoses is altered, offering more precise and differentiated combinations. The documentation, multilingual utilization, and translations as well as linkage to other terminologies are facilitated.

Finally, two distinctively critical lines of thought towards psychiatric diagnosis in general shall be mentioned: Firstly, authors who reproached psychiatry for following a much too narrow medical model of mental disorders and for uncritically accepting the role of a social control agent (“anti-psychiatry”), regarded psychiatric diagnoses as \textit{pars pro toto} for the alleged fundamental shortcomings of psychiatry.\textsuperscript{2} The field of social psychiatry, emerging after 1960, took up, in a more moderate and pragmatic way, some of these arguments, especially concerning the medical model and its implicit risk of fostering rigid, stigmatizing and deindividualized diagnoses.\textsuperscript{22}

Secondly, since about 1980 a profoundly skeptical attitude arose towards nosological entities in psychiatry—and, consequently, towards diagnostic procedures codifying them—in the context of an increasingly neuroscientifically oriented self-understanding of psychiatry, in some respects revitalizing ideas Wilhelm Griesinger (and others) had proposed more than a century ago (see above). This position strongly gained momentum and condensed in a new term, “denosologization.” Van Praag’s plea from 1987\textsuperscript{23} triggered this debate that has been going on up to the present day; in fact, it was markedly boosted by recent concepts such as Research Domain Criteria (RDoC)\textsuperscript{24} or Hierarchical Taxonomy of Psychopathology (HiTOP)\textsuperscript{25,26} and, generally, by the claim of the emerging fields of social neuroscience and computational psychiatry to generate “a new understanding of mental disorders.”\textsuperscript{27} This will be addressed in more detail below.

\textbf{General nosological frameworks and their implications for the epistemological status of psychiatric diagnosis}

From the conceptions of diagnosis sketched above, that have become influential in the history of Western psychiatry, the following three general nosological frameworks can be distilled. They differ markedly in terms of their implications for the epistemological status of diagnosis and entail equally different approaches to the diagnostic process (\textit{Figures 1 and 2}).
Diagnosis as dialogue - Hoff et al

**Framework 1**
Mental illness is a malfunction of certain parts, domains, or networks of the central nervous system that can be detected using neuroscientific methods.

Epistemologically, this approach is close to the classical medical model of somatic disorders. The factual existence of mental illness “within” the patient is regarded as completely independent from the experts’ conceptualization. The clinician just has to “detect” (and then, of course, treat) the illness, and the researcher strives to “carve nature at its joints.” In philosophical terms, this is the naturalistic-realistic view. (“Realism” is here to be understood in an epistemological sense, ie, as the assumption that “natural objects” or “nature” exist completely independently from human beings and their cognitive acts). It typically implies a “reification” of mental illness.

**Framework 2**
Mental illness is an individual reaction to stressful life events or episodes.

The brain’s relevance as a necessary condition for any mental phenomenon is not contested here. However, in contrast to framework 1, the central nervous system is not seen as the essential etiological factor. Rather, these are the patient’s life experiences, personality traits, and social competences. The underlying basis of diagnosis is thus conceptualized as mental phenomena that have to be interpreted or understood. Hence, hermeneutical methods constitute the center of this framework, which may be called the biographical view.

**Framework 3**
Mental illness is a concept based on descriptive psychopathological findings rather than on etiological assumptions. The definitions of symptoms and syndromes as well as diagnostic algorithms are products of an expert consensus, taking epidemiological and other scientific data into account wherever possible.

Diagnoses in this context do not claim to represent “real” entities that independently exist “behind” the clinical picture (as opposed especially to framework 1) but are conceptual conventions on how to use diagnostic terms. Hence, framework 3 can be called the nominalistic view. Such a view was prominently adopted by operationalized diagnostic manuals, eg, ICD-10 and DSM-5. As discussed above, ICD-11 partially moves away from this position.

**Implications for diagnosis**
What are the implications of each of these frameworks for the epistemological status of psychiatric diagnosis and for the clinical process of diagnosing?
In a strictly naturalistic view, that claims to exhaustively explain mental illness as brain disorder, diagnoses represent “natural kinds.” To diagnose accordingly means to depict given facts in a way that is as objective, i.e., researcher- or clinician-independent, as possible. Critics of this viewpoint note the naturalistic fallacy, i.e., the risk of unreflected identification of (neuro-)biological with mental phenomena.²⁹

In the biographical view, diagnoses are patterns of experience and interindividually valid categories of meaning. In the diagnostic process, the clinician thus seeks to understand and interpret the patient’s personal history as well as his or her intra- and interpersonal situation. Emphasizing the explanatory power of these factors bears the risk of a hermeneutic fallacy, i.e., the unreflected identification of a coherent psychological model with the etiology and pathogenesis of a given mental disorder.

Operational diagnostic manuals in psychiatry, like ICD-10 or DSM-5, do not claim to address “real” nosological entities and therefore refrain from “reifying” mental illness. Instead, they construct diagnostic terms by defining rules or algorithms such that these terms can be reliably applied. One of their principal aims is not to make unnecessary theoretical assumptions, e.g., about the etiology or the “nature” of mental disorders, in order to be compatible with different methodological and cultural backgrounds. Taking this approach too far may result in a formalistic fallacy, i.e., the unreflected identification of operationalized psychopathological criteria with the multifaceted mental suffering of the individual person.

As can be seen, there is a considerable link between nosological assumptions, be they explicitly stated or only implicitly influential, and practical diagnostic procedures. Any diagnostic approach comes with theoretical baggage, any one has its blind spots, and none therefore ought to be regarded as or used as a stand-alone-technique.

Why this is relevant for the ongoing debate

Conceptual history of psychiatry is not “l’art pour l’art.” Close readings and thorough reflections on “classical” psychiatric positions as, for example, in the works of Wilhelm Griesinger, Emil Kraepelin, Sigmund Freud, or Eugen Bleuler, facilitate and enrich the present debate on psychiatric diagnosis. This argument becomes even stronger in view of the immense heterogeneity and dynamics of this debate. It is situated (and, in a way, oscillates) between two poles: Emil Kraepelin’s notion of scientifically detectable “natural disease entities” based on philosophical realism on the one hand,³⁰ and the epistemologically more modest nominalistic approach of modern diagnostic manuals on the other hand. In recent years, both poles have been subjected to fierce criticism: From the 1980s onwards, the concept of “denosologization” has increasingly (re-)gained acceptance. More recently, it was integrated into the evolving paradigms of computational and dimensional psychiatry.³⁷ “Denosologization” is spurred by the worry that conventional psychiatric diagnoses—which are still based on Kraepelin’s nosology—³⁴ are neither sufficiently valid nor reliable, but in fact obstruct clinical work as well as scientific research by narrowing down the conceptual horizon. The poor acceptance of diagnoses by patients, relatives, and the general public to do with their stigmatizing potential is another common argument in favor of denosologization.

This complex issue may be condensed in one question: Do we need a “transdiagnostic psychiatry”³⁵ that departs from traditional nosological frameworks? Two recent examples of concepts following such a transdiagnostic path are RDoC²⁴ and HiTOP.²⁵,²⁶

RDoC epistemologically stands closer to Kraepelin’s postulate of the existence and scientific detectability of natural disease entities than to descriptive and hermeneutical concepts. However, its authors claim that nosology has to be data-based rather than, as conventional diagnosis, symptom-based. The substantial heterogeneity of a group of patients diagnosed with, e.g., major depressive disorder according to ICD-10, is sought to be overcome by integrating all available data from the domains genetic risk, brain activity, physiology, behavioral processes and life experiences, aiming to reveal data-based categories or clusters. These are expected to represent more homogeneous groups of patients than, for example, ICD-10 categories. Ultimately, the new systematics is hoped to facilitate specifically targeted research on future pharmacological and psychotherapeutic strategies.

HiTOP shares RDoC’s criticisms of the classical taxonomies as neither sufficiently reliable nor valid. In response,
it offers a data-driven psychometric methodology that attempts to advance consensus dimensional classification and thus enhance conventional diagnostic systems (like ICD and DSM).25 The objective is to define an inner structure of psychopathology. Using a quantitative higher-order dimensional and hierarchical structure of psychopathology, it aims at revealing underlying dimensions of psychopathology and decrease artefactual comorbidity.32 In this way, arbitrary boundaries between disorders as well as insufficient reliability of categorical diagnoses are meant to be overcome.26 Within-disorder heterogeneity is addressed by developing dimensions based on covariations of symptoms thereby detecting coherent constructs. At its core, HiTOP proposes that psychopathological dimensions can be organized in a hierarchical order that ranges from “spectra” (eg, “internalizing” or “thought disorder”), to specific clusters of symptoms.32

The already thriving field of social neuroscience, dimensional and computational psychiatry will presumably be further enlarged and differentiated in the foreseeable future. There is no doubt that this is a scientifically desirable and promising development. However, the following caveat should be considered: The debate on future directions of psychiatric diagnosis critically depends on a sustained and substantial reflection on the epistemological frameworks involved. For example, how shall we integrate the notions of subjectivity, autonomy, and personhood with neuroscientific data? In order to justify the designation of an important realm of current psychiatric research as social neuroscience, this question has to be answered. The proposals of “first-person neuroscience”33 and “two-person neuroscience”34 are attempts to get ahead with this issue.

Generally speaking, any nosological and diagnostic approach developed by psychiatry ever since its beginning carries, more or less, the risk of becoming rigid and dogmatic. Therefore, the essential ambition of the ongoing debate on psychiatric diagnosis should not be to ignore or just to replace previous concepts. This would indefensibly narrow down the scientific scope of our field. Instead, social neuroscience, taken here as pars pro toto for recent conceptual and methodological advances in psychiatric research, should establish a conceptual dialogue, critical and constructive, with “classical” psychopathological concepts. The latter should not be scientifically devaluated only because they are part of a specific intellectual tradition. The ambition to debate diagnosis in the abovementioned sense is supported by many seminal figures in the psychopathological tradition, especially Karl Jaspers (1883-1969). He declared a multidimensional, ie, epistemologically open-minded approach that engages in a critical dialogue between competing positions as necessary requirement of person-centered psychiatry. If we understand psychopathology in this Jaspersian sense, ie, as a comprehensive intellectual framework rather than only a technical guidance for descriptive symptomatology, it might well regain the function of a conceptual bracket for psychiatry.35,36 Given the fragile sense of professional identity within psychiatry we presently witness, such a bracket is very much needed.

**Conclusion: what psychiatric diagnosis in the 21st century is all about**

What is diagnosis in 21st century psychiatry all about, and what ought it to be about? From a conceptual history perspective, in view of the many competing and at least partly incommensurable approaches to diagnosis that psychiatry has seen over the centuries, one cannot help but have the impression that psychiatric diagnosis is essentially about debate: This debate has been ongoing at least since the seminal work of Emil Kraepelin and, after a comparably stable phase of international implementation of the two operationalized diagnostic manuals DSM-III17 and ICD-10,18 the field has become dynamic and substantially controversial again in recent years.

An essential background of this development is to be seen in new perspectives like computational and dimensional psychiatry, social neuroscience, or, generally speaking, in options for mental health issues that have arisen by “big data” and artificial intelligence. At first sight, these recent approaches might be regarded as predominantly methodological in nature; however, they do raise fundamental questions about psychiatric nosology and the epistemological status of diagnosis. This, for sure, is a positive development, since critical evaluation of any given concept is the very core of scientific progress. Therefore, RDoC, HiTOP, and comparable approaches are promising precisely by challenging traditional nosological and diagnostic concepts.

We have to be cautious however that their critique does not become dogmatic but is itself critically debated. As it stands
(November 2019), such critical debate certainly takes place about the scientifically promising and practically relevant ICD-11. Psychiatry, being as complex and entangled with a large variety of “external” factors as it is (and probably always will be), needs a substantial and sustained debate that addresses the foundations, including the conceptual history, of its nosological assumptions and diagnostic procedures. The latter are not only scientifically relevant, but also—explicitly or implicitly—underlie and thus guide everyday clinical work. The question should not be if we need a neurobiological, computational, or a psychopathological approach in psychiatry, but how to establish and foster a critical dialogue between these (and other) different perspectives. 37

For practical diagnostic work, this means that psychiatric diagnosis encompasses more than technical aspects of symptomatology and patient interviewing, and that psychiatric diagnosis is never an end in itself, neither in clinical practice nor in research about diagnostic processes. Of course, it does include technique—e.g., knowing the definitions of psychopathological terms like delusional ideas, hallucinations, stupor etc, and knowing how to establish a therapeutic relationship so that the patient feels comfortable telling the interviewer about personal issues that are typically part of his or her private sphere. 38 But just as diagnostic systems are situated in a historical and cultural context, so is practical diagnosis situated in a cultural and—most importantly—interpersonal context. The act of diagnosis must thus be seen as an interpersonal act. This act too ought to be dialogical.

Understanding diagnosis as dialogue fits well with a Jasperian understanding of what psychopathology basically is about: Psychopathology, we suggest, offers a conceptual bracket that allows keeping together the necessarily different scientific perspectives of psychiatry condensing in manifold debates about diagnosis. It also offers a framework positioning the interpersonal realm at the heart of any clinical encounter, be it diagnostic in purpose or otherwise. Furthermore, it can serve as an epistemological barrier against unreflected or undetected simplifications of psychiatry.

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References


Wernicke-Kleist-Leonhard phenotypes of endogenous psychoses: a review of their validity

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While the ICD-DSM paradigm has been a major advance in clinical psychiatry, its usefulness for biological psychiatry is debated. By defining consensus-based disorders rather than empirically driven phenotypes, consensus classifications were not an implementation of the biomedical paradigm. In the field of endogenous psychoses, the Wernicke-Kleist-Leonhard (WKL) pathway has optimized the descriptions of 35 major phenotypes using common medical heuristics on lifelong diachronic observations. Regarding their construct validity, WKL phenotypes have good reliability and predictive and face validity. WKL phenotypes come with remarkable evidence for differential validity on age of onset, familiality, pregnancy complications, precipitating factors, and treatment response. Most impressive is the replicated separation of high- and low-familiality phenotypes. Created in the purest tradition of the biomedical paradigm, the WKL phenotypes deserve to be contrasted as credible alternatives with other approaches currently under discussion.

Introduction

The field of endogenous psychoses is the one for which the hypothesis of “brain diseases” is the most likely in psychiatry. The past 40 years’ exclusive use of International Classification of Diseases (ICD) – Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnoses, although successful in the field of clinical psychiatry as an applied science, did not allow significant progress in biological psychiatry as a basic science. Two postulates of consensus classifications might have made them unsuitable for this task. First, consensus criteria could not be changed, ruling out any attempt to optimize the descriptions. Second, the atheoretical stance negated any etiological or pathophysiological hypothesis, eg, making no distinction between endogenous and neurotic depressions such as bereavement.

The traditional biomedical paradigm starts from phenotypes rather than consensus-based disorders. Embracing the naturalistic framework, it posits that a disease is a
natural entity defined by an etio-pathophysiological model which accounts for the phenotype. The model is given at the biological level, assuming a single and rare cause of major effect due to selection pressure. The typical correlation-experimental 2-step process is the theory-of-proof of the biomedical paradigm that validates the model, turning it into a disease. The major strength of this approach stems from this model validity or validity per se which translational research converts into the magic triplet of applied medicine: diagnosis, diagnostic test, and treatment.

The limited construct validity of ICD-DSM disorders, even for schizophrenia, and the recurrent failures to validate any biological model that could account for them, raised doubt about the suitability of the biomedical paradigm in basic psychiatry. The leading proposals now turn towards dimensional approaches, which come with a major paradigmatic framework shift with the adoption of normativistic assumptions. Here a disease is defined as a pathological deviance, ie, a mere deviation from the norm, which makes the implicit hypothesis of multiple and frequent causes of very small effects. These are typically referred to as risk factors or modifiers in medicine rather than diseases, and translate into much less efficient interventions.

Yet, consensus classifications never claimed to be fair implementations of the biomedical paradigm. They were mainly designed for clinical use and not for basic research. Hence, their lack of success in field does not rule out the relevance of the naturalistic framework in psychoses. Indeed, at least one research program, referred to as the Wernicke-Kleist-Leonhard (WKL) pathway, was able to define clear-cut phenotypes. This paper gives an overview of the principles that guided their optimization, and reviews the evidence supporting their construct validity. Validity per se will be only considered for periodic catatonia which currently has the most supported biological model. The terminology has been slightly changed relative to previous publications to adapt to current clinical psychiatry and neuroscience (Appendix I, online version of this article).

Epistemological framework and methods

Major heuristics that guided the empirical elaboration of the phenotypes

The naturalistic assumptions state that, due to selection pressure, disabling phenotypes are accounted for by a single and rare cause of major effect. Hence, they are categorical in nature and liable to the principle of parsimony. A phenotype is a “typical” set of observable characteristics shared by a group of patients which includes the clinical presentation, ie, the set of reported symptoms and clinical signs collected from the patient’s examination, but also the course of the symptoms, ie, how they appear, which ones persist, which ones disappear, or whether they completely change from one clinical picture to its opposite (bipolarity). Finally, typical contextual elements might also enrich the description. The WKL School empirically optimized their phenotype descriptions by sorting patients according to their long-term catamnestic observations following heuristics stemming from the principle of parsimony: symptom-complex, longitudinal and family-aggregation principles (Box 1; Appendix 2, online version of this article).
Box 1.

Principle of parsimony applied to brain, time, and family

**Principle of parsimony:** Among competing hypotheses, the one which needs the fewest assumptions should be favored. Hypothesizing endogenous psychoses being subordinated by a *single cause of major effect* (due to selection pressure), allowed Wernicke, Kleist, and Leonhard to add the following *heuristics* to the *principle of Sydenham*, in order to define *phenotypes* and to test for their construct validity (see Appendix 2 for details).

**Elementary (primary) symptoms principle**

Mental illness affects only a limited part of brain functioning causing specific elementary symptoms in one neuropsychological domain (emotion, thought, or psychomotoricity) which in turn induce secondary symptoms.

**Longitudinal principle**

If an individual presents several clinical pictures over time, he or she is affected by the same pathology, presenting with different manifestations.

**Family aggregation principle**

If several members of the same family present with an endogenous psychosis, they are likely to share the same liability.

*ICD-DSM:* If an individual presents several clinical pictures over time, Sydenham's principle overrules the single liability thesis.
Validity assessment of WKL phenotypes
The construct validity of a phenotype encompasses many different properties. Firstly, to comply with the logical positivist’s call for objectivity, a phenotype must be reliable, and this reliability is assessed by inter-rater reproducibility. Secondly, the fulfillment of the naturalistic assumptions behind the concept of a phenotype could be supported by its predictive, face, differential, and taxonomic validities. Test-retest reproducibility will not only be considered here as a measure of predictive validity but also of face validity, ie, how closely patients match the “typical” definition and to what extent it accounts for all of the patients’ manifestations. Indeed, it shows that phenotype descriptions are either comprehensive enough to include all possible clinical pictures or focus on an unchanging symptom-complex for the diagnosis to remain lifelong stable. Hence it avoids resorting to comorbidities other than behavioral complications, eg, drug abuse. Differential validity looks for the selective associations of a phenotype with external validators through head-to-head comparisons. These can be any clinical, contextual, or biological features that are not part of the original description, eg, age of onset, familiality, gender difference, treatment response, any biological parameter etc. Finally, taxonomic validity appraises the fulfillment of the categorical structure of the phenotypes through taxometric analyses.

Validity per se demands a biological causal model accounting for a phenotype. The model validity is assessed through a two-step process acknowledged as the “theory of proof” in medicine: the demonstration of a strong correlation with the biological cause and the outbreak or the alleviation of the phenotype with the experimental manipulation of the cause. It has mainly been investigated in periodic catatonia.

Overview of WKL classification

The field of endogenous psychoses
The WKL classification is limited to the field of endogenous psychoses. Psychosis does not have the same meaning here as in the DSM or the ICD. It is not restricted to hallucinations or delusions, but stands for a wide range of specific emotional, cognitive, and behavioral disturbances, supposed to be mainly accounted for by some qualitative disturbances of one cerebral process, ie, naturalistic assumption. It is opposed to the old concept of “neuroses” which putatively results from nature-and-nurture-interactions, eg, the maladaptive response of a given personality coping with a specific life event. These are complex diseases mixing trait risk factors (addition of multiple causes of very small effect, ie, normativistic) interacting with other factors, ie, synergistic assumptions.

The WKL phenotypes deserve to be contrasted as credible alternatives with other approaches currently under discussion

While the ICD and the DSM distinguish exogenous disorders, the endogenous - neurotic distinction, which could be rephrased as simple vs complex diseases, has completely disappeared due to the endorsement of the atheoretic principle. Consequently, on the psychotic side, psychotic post-traumatic stress disorder, psychotic body dysmorphic disorder, or stress-related brief psychotic reactions, as observed in borderline personality disorder, are not endogenous psychoses. Yet the largest differences lie on the affective side. Reactive, eg, bereavement, and neurotic depressions, which probably account for most major depressive disorders, are not part of the endogenous psychoses in the WKL perspective. It is worth reminding the endogenous-neurotic distinction has been repetitively supported by taxometric analyses of depressive disorders.

While most WKL phenotypes are within the scope of affective and psychotic ICD or DSM disorders, there are some exceptions, eg, some system schizophrenias might be diagnosed in the autistic spectrum or in cluster A personality disorders.

Basic features and relationship with consensus classifications
The WKL school defines 35 phenotypes, accounting for about 90% of endogenous psychoses (Table I). To achieve this, descriptions do not focus on what phenotypes have in...
### Table I. Overview of the WKL phenotypes (inspired by ref 97). Only the 35 major forms are displayed; the 36 minor forms are two by two combinations of system schizophrenias. See Appendix 2, online for the consensus on the English translation.

<table>
<thead>
<tr>
<th>COURSE</th>
<th>FAMILY</th>
<th>NEUROPSYCHOLOGICAL DOMAINS</th>
<th>POLARITY</th>
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<td>Monopolar</td>
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<td>Pure depressions (D)</td>
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<td>Pure melancholia</td>
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<td>Hyperkinetic-akinet motility psychosis</td>
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common, but rather in what aspects they differ from one another. For instance, positive symptoms might occur in many phenotypes and hence are not helpful per se. Moreover, in contrast to ICD/DSM, symptoms have no meaning by themselves but only as part of a specific symptom-complex organized according to the primary-secondary principle (Box 1, Appendix 2).

Phenotypes are grouped into five families according to their course, mono- or bipolarity, and their primary affected neuropsychological domains: affect, thought, and psychomotoricity (Table I). There are one monopolar, three bipolar, and one monomorphic families, gathering not 1 but 12 monopolar affective phenotypes and not 1 but 7 bipolar phenotypes. According to the WKL perspective, the term “schizophrenia” only applies to phenotypes with residual symptoms which encompasses one bipolar and the monomorphic families.

The WKL classification is strikingly different from consensus ones. While ICD-10 and DSM-IV have a concordance of λ=0.86 with one another, WKL clearly gathers patients differently since its concordance is only of λ=0.4 with ICD-10 and of 0.56 with DSM-IV.24

Reliability of WKL phenotypes

On average, WKL phenotypes are highly reliable with 97% of inter-rater diagnostic consistency when performed by expert raters, giving an average kappa value of 0.82 to 0.93.25,26 In comparison, consensus disorders have kappa values of 0.84 for schizophrenia, 0.71 to 0.83 for bipolar disorder, and 0.22 for schizoaffective disorder.27

Test-retest reproducibility, prognostic and face validity

In prospective studies, the test-retest reproducibility at 15 years, follow-up was 93% and ranged from 76% to 93% at 33 years follow-up.28,29 This stands well even in comparison to the much broader ICD diagnosis of schizophrenia which remains consistent in 90% of the patients in retrospective chart review after a follow-up of 25 years.30

Differential validity of the main phenotypes

Monopolar affective phenotypes with purely relapsing-remitting course

Pure melancholia and pure mania

Pure melancholia and pure mania are monopolar affective phenotypes.31 The term “monopolar” is used here rather than “unipolar” to emphasize the differences between the original WKL concept and consensus classifications. Monopolarity implies symptomatic stability both within and between the episodes, ie, monomorphy, as well as the absence of mixed or incomplete states (see manic-depressive illness). Hence, monopolarity applies also to the manic pole. The independence of the pure mania phenotype has been replicated in the Zurich cohort.32 While grounded in the affect, pure mania and pure melancholia characteristically also affect the other domains, eg, drive, speed of thought, and psychomotoricity.

The prevalence of pure melancholia is many times higher, accounting for up to 10% of endogenous psychoses, whereas pure mania is below 1%. The course is purely relapsing-remitting with an average of 12 months for an episode of melancholia.33 Symptoms typically respond to usual antidepressant or antimanic therapeutics. Both phenotypes have little inheritance with 3% of affected first-degree relatives which significantly differs from manic-depressive illness (22% to 36%).34,35

Pure depressions and pure euphorias

These are also relapsing-remitting monopolar phenotypes, ie, monomorphic without mixed or incomplete states (see manic-depressive illness, MDI).31 The five pure depressions and the five rare pure euphorias are characterized by specific disturbances of distinct emotional systems within the affective domain sparing thought, drive, and psychomotoricity. They often go along with characteristic delusions or hallucinations: delusional guilt in self-torturing depression, persecutory ideas in suspicious depression and unpleasant bodily sensations in hypochondriacal depression. These may be ICD-diagnosed as depression with psychotic features or schizoaffective disorders. These phenotypes only account for 4% of inpatients with endogenous psychoses.33 In contrast to pure melancholia, their episodes typically last years with progressive beginnings and endings16 and they are less responsive to therapeutics.36,37 They also have a low familiality when compared with MDI (3% vs 22% to 36%).34,35

Bipolar phenotypes with purely relapsing-remitting course

In the WKL sense, bipolarity is not limited to affective disorders but extends to schizophrenia-like psychoses as
well. Only manic-depressive illness belongs to the affective disorders in the narrower sense.

**Manic-depressive illness**

MDI is the most frequent bipolar phenotype, accounting for 19% of patients with endogenous psychoses. Even though the ICD/DSM’s concept of bipolar disorder stems from the WKL-MDI one, there are major differences. Episodes have distinctive clinical features allowing MDI to be diagnosed even in patients having depressive recurrences only, in most cases from the first episode. Affective episodes are characterized by their polymorphic manifestations and the mixed or incomplete features, both being currently rediscovered under the emerging concept of bipolar depression. Clinical manifestations are qualified as polymorphic because they change within and between episodes. The span of MDI’s clinical presentations is so large that it can mimic any monopolar or cycloid picture, yet generally not in a stable way. The trigger for these phenotypical changes can be endogenous, but these patients are also highly reactive to external events. For instance, patients can be talkative and lively during the interview, showing no outer manifestation of depression, while apathy and suffering can come back as soon as they walk out of the office. Such mood reactivity can also be observed in neurotic forms, but then of lesser magnitude. Mixed states are defined as the co-occurrence of both the manic and depressive pole among the different domains: affect, thought, and psychomotoricity. This can be seen for instance in the combination of inhibited affect (sadness), excited thinking process (racing thoughts), and excited psychomotoricity (agitation). Incomplete states are an extension of the former concept, meaning that aside from being excited and inhibited, a single domain can also be completely unaffected. For instance, affect and psychomotoricity might be inhibited while the speed of thought might be normal.

On average, MDI episodes are of shorter duration than monopolar ones, ie, 6 months on average for depressive episodes. Acute onset, sudden cessation; or rapid switches are common. This phenotype shows more frequent relapses than monopolar phenotypes and this tendency tend to increase with aging.

The hereditary burden of MDI is significantly higher than for monopolar affective phenotypes and cycloid psychoses, with 22% to 36% of affected first-degree relatives. There are two reasons for the familiality of MDI to exceed the one of ICD/DSM bipolar affective disorder (9%). Firstly, as the MDI diagnosis can be made early, even if the clinical presentation is purely depressive, most intra-familial incongruencies vanish as nearly all of the (pseudo-) unipolar patients are diagnosed as MDI. Secondly, ICD/DSM bipolar disorder subsumes some cycloid psychoses which have low familiality.

**Cycloid psychoses**

Cycloid psychoses are bipolar phenotypes of purely relapsing-remitting course. They have more intense psychotic manifestations, and are hence routinely diagnosed by ICD/DSM as schizoaffective or schizophrenic disorders. There are three different cycloid psychoses corresponding to the predominantly affected domain within which they quantitatively oscillate between opposite extremes. These are referred to as “poles,” organized into three axes:

- Hyperkinetic-akinetiform motility psychosis in the psychomotor domain
- Anxiety-happiness psychosis in the emotional domain
- Excited-inhibited confusion psychosis in the thought domain.

Cycloid psychoses represent 20% of all endogenous psychoses. Their clinical manifestations are highly polymorphic, due to rapid changes in the intensity and even in the polarity of the manifestations within the same episode. Importantly however, the opposite poles always manifest successively and never at the same time.

The ICD-10 diagnosis of “acute and transient psychotic disorders” or ATPD (F23), was designed to embody these phenotypes together with the “bouffées délirantes aiguës des dégénérés” or BDA (acute delusional outburst of the degenerates). Yet, studies have found that ATPD only overlaps with the BDA and cycloid diagnoses in half of the cases. Furthermore, cycloid psychoses are defined as lifelong phenotypes, while BDA and ATPD are only defined as episodes. Hence the latter diagnoses are instable on follow-up: a third of initial BDA switches to schizophrenia or schizoaffective disorder after 10 years, while it happens in half of initial ATPD after 5 years. Cycloid episodes usually last between 1 to 3 months, and have acute onset and ending in up to two thirds of the cases.
Yet, these two features are neither sensitive nor specific enough to be used as diagnostic criteria.\(^{38}\) The relapsing-remitting course means that, in the interepisode interval, patients develop full insight about their illness and do not present significant residual symptoms whatever the number of recurrences.\(^{48,49}\) Cycloid psychoses might be related to minimal brain damage. Unspecific MRI abnormalities are more frequent relative to non-system schizophrenias, eg, enlarged ventricles, white matter hyperintensity, or small cortical defects.\(^{50,52}\) These might be acquired early: mothers of cycloid patients report significantly more infections of the upper airway during the first trimester of pregnancy, childbirth complications are more frequent and seasonality of birth is larger in cycloid phenotypes relative to controls and non-system schizophrenias.\(^{52-54}\) Conversely, the heritability of these phenotypes is low, with only 5% of affected first-degree relatives, indistinguishable from controls and significantly lower than in MDI, cataphasia, and periodic catatonia.\(^{34,35,40,55}\)

Patients affected by cycloid psychoses are more vulnerable to precipitating factors: stress, sleep disorders, cannabis, etc. Women are especially sensitive to estrogen drop: 88% of episodes start in the luteal phase, which is significantly higher than for any other phenotype.\(^{56}\) Accordingly, cycloid phenotypes account for 60% of postpartum psychoses, with motility psychosis accounting for 36% on its own.\(^{57}\)

Antipsychotics shorten the episodes but should be used with caution in motility psychosis, which is especially at risk for neuroleptic malignant syndrome.\(^{58}\) They are also effective in relapse prevention, bearing in mind that these patients are especially sensitive to their side effects. The maintenance of too-high doses of first-generation antipsychotics after remission favors post-psychotic depression and abulia, so that otherwise fully remitted cycloid patients might appear to suffer from residual schizophrenia.\(^{59}\) Yet, once maintained for more than a month, the rapid discontinuation of antipsychotics increases the risk of relapse to a point that was unknown in the pre-neuroleptic era,\(^{59,60}\) raising the hypothesis that most these relapses might be induced dopamine supersensitivity psychosis.\(^{59,60}\) Mood stabilizers not only help as an add-on treatment in the acute phase, but might also be considered as viable alternatives to antipsychotics in the maintenance phase considering their decent relapse prevention.\(^{48}\)

### Phenotypes with build-up of residual symptoms: the schizophrenias

In the WKL perspective, the term “schizophrenia” carries a prognostic value as these phenotypes progress toward a persistent residual state of which abulia is a frequent, though not characteristic, feature. WKL schizophrenias have phenotype-specific residual symptoms.

“System” and “nonsystem” schizophrenias have nothing to do with the concept of “delusion systematization,” ie, the logical organization of delusional ideas. Here, “system” must be understood analogously to the involvement of a specific biological function as in organic medicine, ie, system diseases. Regarding brain diseases, these systems are functional networks, eg, the pyramidal system is the one that degenerates in amyotrophic lateral sclerosis. Multiple systems can be affected, as in multiple-system atrophy, which combines the degeneration of extrapyramidal, cerebellar, and vegetative systems. Due to their clear-cut and life-long monomorphic residual symptoms, system schizophrenia are qualified as such because they are supposed to be accounted for by the impairment of such specific functional networks, whereas non-system schizophrenias are polymorphic, bipolar, and putatively involve many “systems.”

#### Non-system schizophrenias

There are three non-system schizophrenias characterized by a predominantly affected domain within which they can express both poles. In contrast to cycloid psychoses, changes are not purely quantitative, but also qualitative, with symptoms from both poles occurring together. Because of their bipolarity, they show a broad, yet specific, clinical spectrum. They mostly run a progressive-relapsing course and develop a characteristic set of residual symptoms of increasing severity. All have a specific heredity burden, without crossed liability. Interestingly, domain-specific attenuated symptoms have been reported in nonpsychotic relatives, especially in obligate carriers.\(^{61}\) As a whole, nonsystem schizophrenias respond much better to antipsychotics\(^{62,63}\) and to the addition of mood stabilizers\(^{37}\) compared with system schizophrenias. However, treatments mostly improve acute manifestations but have virtually no effect on residual symptoms.

**Affect-laden paraphrenia** is a schizophrenic bipolar phenotype of the affective domain. It only accounts for 5% of...
Cautious and grandiosity often accompanied by multimodal state leads to more or less systematized delusions of self-importance of the other pole. This specific affective of responders.62,63 The median age of onset is 36 years, but patients to fully distance themselves from their ideas (84% of responding). A feature that repeatedly impressed many authors was the contrast between the judgment errors, up to the acceptance of fantastic ideas, with a generally well-organized thought process which is constant out of the episode.64,66,69 The course is mostly progressive-relapsing. Over 10 to 30 years, patients develop increasingly pervasive reference ideas of more and more fantastic coloring. Yet they remain able to adapt to the interviewer in superficially denying their delusions.

Antipsychotics help in blunting the affective pressure that ensues, but also fuels the delusions, yet never allowing the patients to fully distance themselves from their ideas (84% of responders).62,63 The median age of onset is 36 years, but is highly variable explaining late-onset cases. The phenotype has an autosomal recessive inheritance pattern with 12% of affected siblings vs only 2% of affected parents.34,35 There is also a significantly larger number of patients born from consanguineous weddings relative to other schizophrenias and cycloid psychoses (3.3% vs 1%).56,61

Cataphasia (schizophasia) is a bipolar phenotype mainly affecting thoughts and language. It accounts for about 8% of endogenous psychoses and its estimated prevalence is about 0.1 to 0.2% in Germany.72 Its excited pole was first described by Kraepelin under the label “schizophasia.” The observation of multiplex families allowed to relate this clinical picture to its counter-pole dominated by thought inhibition.73 The core of the phenotype is a specific thought and language disorganization with incoherence and logical derailment coming with syntactic and semantic errors, eg, paragrammatism, paraphasias, and neologisms. These core symptoms need to be specifically investigated, especially in the residual phase. As everyday concrete thinking is less affected, they frequently remain discreet in ordinary conversations and behavior. The thought and language test, a standardized WKL examination procedure that challenges abstract thinking, greatly sensitizes the detection of catapathic features.72,74,75 Language errors must be appraised in the context of patients’ skills, so are hence harder to ascertain in non-native speakers; in such cases they may be secured by long-term follow-up re-examination. As the disease progresses, nonspecific fluctuating persecutory ideas might remain but are secondary to the core residuum which impairs patients’ understanding, leading to misinterpretations in close similarity with residual Wernicke’s aphasias.76 During episodes, patients exhibit a variety of affective and psychotic symptoms, that are frequently in the foreground.

Although the episodes respond to antipsychotics (up to 78% using first-generation drugs),62,63 the specific symptoms are treatment-resistant. The association of thought disorganization with emotional turmoil make cataphasic patients particularly at risk for suicidal behavior (52% of patients) and deaths by suicide (18% of patients).72 The phenotype shows familial aggregation, with 15% to 25% of affected first-degree relatives, on top of which 12% of non-psychotic first-degree relatives also show milder forms of the typical thought and language disorganization.34,35,72 A genetic locus has recently been found for cataphasia on Chr11p, the strongest association being found with a gene coding for cathepsin-D, a lysosomal protease which mutations can cause neurodegenerative storage disorder (Roth et al, unpublished material).

In accordance with their residual thought and language impairments, cataphasic patients have a specific dysfunc-

tion of their temporoparietal junctions bilaterally; these are hypoactive and functionally disconnected.77 This fits with multimodal imaging results showing that the same cortices, together with their underlying white matter, were hypo-myelinated and had an increased iron content (Foucher et al, unpublished material). Considering that the latter could likely result from microglial activation, these findings are in line with those reported in cathepsin-D deficits,78 suggesting a neurodegenerative model for cataphasia.
**Periodic catatonia** is roughly as common as cataplexy, accounting for about 7% of patients suffering from endogenous psychoses. Despite its name, WKL’s periodic catatonia should not be viewed as the mere recurrence of IDC/DSM catatonic episodes. Beyond mere global bipolar quantitative motility changes, the core of this phenotype is a specific disorganization of psychomotor functions, ie, mostly affecting expressive and reactive movements. The qualitative changes manifest as the mixing of both akinesia and hyperkinesia but to different body parts, eg, rigid hypokinesia of the upper limb together with facial restlessness. Other qualitative anomalies are parakinesias that alter simple movements, making them appear stiff and/or jerky, or distort expressive movements, especially the mimics, going as far as grimacing. These are currently rediscovered under the name of spontaneous dyskinesias. However, parakinesias have a wider spectrum and distinctive features that allow them to be differentiated from tardive dyskinesias. The residual state includes the persistence of these characteristic psychomotor anomalies together with abulia, while residual psychotic symptoms are rare. The social or occupational impairment is highly variable (GAF = 57±19 after an average of 13 years of progression).

This phenotype is responsive to antipsychotics (60% of responders with first-generation drugs), but also sensitive to their extrapyramidal side effects, hence its large response increment after switching to clozapine. Further benefits from benzodiazepines and electroconvulsive therapy which are inefficient in system catatonias. Yet all therapeutic efforts can only help coping with exacerbations but fail to improve the specific residual symptoms.

At the **etiological level**, several studies have confirmed the high heritability of periodic catatonia, with 21% to 26% of affected first-degree relatives, which is significantly larger than for system catatonias (4%). Considering the extended phenotype, ie, including nonpsychotic relatives with only psychomotor signs, the percentage raises to 32% to 41% of affected first-degree relatives. Transmission is autosomal dominant with incomplete penetrance and anticipation. Two genome-wide linkage studies found a major susceptibility locus on Chr15q accounting for about two thirds of the pedigrees (OMIM 605419). This has recently been supported by an association peaking in an intergenic region between CGNL1 and GCOM1 (Gawlik et al, unpublished material), the latter being implicated in an NMDA-dependent neuroprotection pathway that might be especially important for GABAergic interneurons. Yet periodic catatonia is likely to be genetically heterogeneous: other pedigrees matched on other loci, eg, Chr21q13-ter. The unity of the phenotype might be better explained at the *pathophysiological level*. Based on previous literature, especially on the independent replication of its specific left premotor hyperactivity when compared with other psychoses, periodic catatonia is currently modeled as an acquired deficit of intra-cortical inhibition possibly ensuing the degeneration of GABA interneurons. As a first validation step, the strength of the correlation between left premotor hyperactivity and the phenotype was prospectively tested in individual patients by comparing a new group of periodic catatonias to other psychoses, including system catatonias. The association was found to be both sensitive (98%) and specific (88%), making the case for this functional imaging measure to be a viable biomarker. As interventional validation step, personalized rTMS was used to correct left premotor inhibition deficit. Not only did the improvement of residual symptoms resulted in substantial functional gains, but was also specific for premotor targets (vs prefrontal and parietal ones) and for periodic catatonia (vs system catatonias).

**System schizophrenias**

System schizophrenias account for 21% of inpatients with endogenous psychoses. They have an insidiously progressive course resembling that of slow encephalitis. They begin with a *process phase* of 1 to 5 years, in which unspecified dysthymic and psychotic manifestations can accompany the growth of a distinct symptom-complex, presumably due to the deterioration of a specific system. After processual symptoms vanish, the residual clinical picture will remain unchanged up to the end of the patient’s life, ie, monomorphic. Phenotypes are ordered according to the domain to which belongs the affected system:

- The four phenotypes of hebephrenias share a specific disturbance of judgement emotions which leads to affective flattening and loss of initiative. Judgement emotions are the one needed to evaluate non-concrete and non-present issues such as the course of life
- There are six major phenotypes of system paraphrenias having specific combinations of hallucinatory and delusional features
- System catatonias consist of six varieties of definite qualitative psychomotor impairment.
The three subfamilies have different age of onset: 24 for system catatonias and 23 for hebephrenias, but 36 for system paraphrenias.33 No significant hereditary burden has been reported. The percentage of 2% to 4% of affected first-degree relatives is not significantly different from what is seen in controls but significantly different from periodic catatonia.25,34,35,83 In system catatonias, 34% of the mothers report an infection of the upper airways during the second trimester of pregnancy which significantly differs from periodic catatonia (8%).25 Neuroimaging reveals significantly more cortical atrophy in system schizophrenias than in non-system schizophrenias.36,37,38 Finally, contrary to other phenotypes, interventions have little or no effectiveness: antipsychotics (1% to 40% of responders to first-generation antipsychotics),62,63 no advantage for clozapine, 37,83 mood stabilizers, or antidepressants.37

Conclusion

In accordance with the biomedical paradigm, the WKL School has empirically optimized the descriptions of putatively natural phenotypes inspired by neuroscience and based on common medical heuristics. They are reliable, they have good predictive validity and differential validity regarding gender ratio, age of onset, familiality (without crossed-heritability), pregnancy complications, and response to treatment. Only their taxonomic validity deserves to be further evaluated. While the biological model for cataphasia remain to be tested, the one for periodic catatonia has already been supported by correlational and interventional evidence.

Despite their elaboration in the purest tradition of the biomedical paradigm, yet diverging from dominant paradigms, these phenotypes received poor attention from basic researchers (see also Appendix 2). On the other hand, clinicians value them for their long-term stability and their prognostic and therapeutic relevance. We hope that this review will contribute to revive the interest of the psychosis research community for this research program which deserves to be confronted with others in an adversarial collaborative way.4

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Original article

Validity of Wernicke-Kleist-Leonhard phenotypes - Foucher et al

Neurobiology and the Hierarchical Taxonomy of Psychopathology: progress toward ontogenetically informed and clinically useful nosology

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The Hierarchical Taxonomy of Psychopathology (HiTOP) is an empirical structural model of psychological symptoms formulated to improve the reliability and validity of clinical assessment. Neurobiology can inform assessments of early risk and intervention strategies, and the HiTOP model has greater potential to interface with neurobiological measures than traditional categorical diagnoses given its enhanced reliability. However, one complication is that observed biological correlates of clinical symptoms can reflect various factors, ranging from dispositional risk to consequences of psychopathology. In this paper, we argue that the HiTOP model provides an optimized framework for conducting research on the biological correlates of psychopathology from an ontogenetic perspective that distinguishes among indicators of liability, current symptoms, and consequences of illness. Through this approach, neurobiological research can contribute more effectively to identifying individuals at high dispositional risk, indexing treatment-related gains, and monitoring the consequences of mental illness, consistent with the aims of the HiTOP framework.

Keywords: Hierarchical Taxonomy of Psychopathology; dimensional; ontogenetic; neurobiology; liability; psychopathology; RDoC

Introduction

The Hierarchical Taxonomy of Psychopathology (HiTOP) was advanced to characterize the empirical structure of psychopathology and overcome the myriad problems inherent in consensus-based nosologies such as the Diagnostic and Statistical Manual of Mental Disorders (DSM). The HiTOP model, which is derived from factor-analytic studies of symptoms, diagnoses, and maladaptive trait data, describes a hierarchy of continuous dimensions accounting for broader spectra and super-spectra as well as narrower, symptom-level manifestations of psychopathology (Figure 1). For example, the Internalizing spectrum encompasses narrower subfactors including Fear and Distress, which, in turn, encompass even more specific clinical phenotypes (eg, social anxiety, insomnia). One particular strength of
HiTOP provides a framework for more systematically investigating common and specific etiological processes in psychopathology using neurobiological methods and measures.6

Improved measurement of manifest symptomatology, as represented in the HiTOP framework, provides an unprecedented opportunity to elucidate the ontogeny of mental illness—the developmental-experiential processes that, over time, give rise to psychopathology and its consequences.10

A deeper, developmentally informed understanding of the mechanisms and processes that contribute to the range of known psychological problems would contribute directly and importantly to prevention and intervention efforts,11 consistent with calls by psychiatrists for transdiagnostic "staging models" of psychopathology.12 The goal of the present paper is to describe an ontogenetic framework for continuing research on the emergence, progression, and persistence of psychopathology in the context of the HiTOP framework. In doing so, we argue for the utility of neural systems variables alongside experiential and behavioral descriptions in characterizing these pathways.6,13,14

Importantly, however, we also highlight distinctions in the role neurobiology is expected to play at different points in the ontogeny of psychopathology. For example, neural indicators of latent liability for psychopathology need to be distinguished from those reflecting symptoms and consequences of clinical illness. The ANA and similar initiatives do not specifically address this critical point, and it remains unclear what aspects of substance addiction are indexed by variables they identify as relevant neural indicators. This muddled picture is likely to impede the development of

the HiTOP framework is that continuous symptom dimensions exhibit higher reliabilities than categorical diagnoses,4 laying the foundation for more valid measurement of psychopathology.1,5 Other strengths include the capacity of a dimensional approach to accommodate the heterogeneity of diagnostic conditions and their systematic co-occurrence. For example, high rates of comorbidity between DSM-defined generalized anxiety disorder and major depressive disorder—themselves highly heterogeneous syndromes—are likely to reflect cognitive, behavioral, and neurobiological commonalities between the two. Within HiTOP, these shared features are reflected in the Distress subfactor, with traits and symptoms specific to one or the other syndrome represented at lower levels of the hierarchy. Each level is conceptualized as a continuous dimension from minimal to extreme severity, rather than coded as absence versus presence of that feature. This structure facilitates the linkage of both broader and more specific HiTOP dimensions, identified through self-, peer, and clinician report, to variation observed in other measurement modalities (eg, functional neuroimaging) as a way to better understand psychobiological systems contributing to both transdiagnostic and condition-specific aspects of psychopathology.6 In this respect, the HiTOP approach is consistent with the National Institute of Mental Health’s Research Domain Criteria (RDoC) initiative.7

HiTOP’s emphasis on transdiagnostic common factors contrasts with the recent Addictions Neuroclinical Assessment (ANA) framework, which attempts to use neurobiology to address heterogeneity within a single phenomenon (ie, addiction), failing to consider that many neural indicators may operate transdiagnostically. The hierarchical structure of HiTOP provides a framework for more systematically investigating common and specific etiological processes in psychopathology using neurobiological methods and measures.6

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effective interventions. Differences among latent liability, current symptomatology, and consequences of psychopathology warrant strong consideration in the search for biological indicators of mental illness.

The HiTOP framework, too, can benefit from a formalized ontogenetic model of psychopathology. The current focus of HiTOP is on the most clinically salient point of this progression—i.e., current manifest symptomatology. However, it cannot be assumed—indeed, it seems unlikely—that biological correlates of manifest symptom dimensions represented at various levels of the HiTOP hierarchy will necessarily reflect etiological mechanisms contributing to these dimensions. The HiTOP model is descriptive, providing important information about the empirical structure of psychopathology and points of observed occurrence versus distinctiveness of symptoms, with major implications for nosological refinement. Building upon the model as it stands, the ontogenetic synthesis presented here is intended to more clearly explicate the temporal and etiological aspects of psychopathology. From this perspective, a systematic, developmentally oriented program of research is needed to characterize the nature of biological processes that are relevant to various stages in the progression from latent liability to active psychopathology and its consequences.

The basic form of the proposed ontogenetic framework for psychopathology is depicted in Figure 2. Each element of the framework is discussed in further detail below with reference to the running example of substance problems, as well as other syndromes where space allows. Briefly,
The model defines liability factors as premorbid, transdiagnostic individual-difference characteristics conducive to psychopathology. These risk factors are presumed to reflect genetically influenced neural and cognitive processes, as well as early childhood experiences such as maltreatment or fetal alcohol exposure, that create a context for the operation of experiential influences on psychological processes and behavior. The delineation of dispositional characteristics that prospectively predict psychopathology can help to identify individuals in greatest need of preventive efforts and those likely to be most amenable to particular treatments.

The second part of the model depicted in Figure 2 consists of current symptomatology—that is, the presence of thoughts, feelings, and behaviors that are associated with some degree of distress and/or impairment, and the neural indicators that covary with them over time. (While distress and impairment criteria are ubiquitous in current nosological frameworks of mental illness, discussion is ongoing about the exact manner in which distress and impairment are modeled within HiTOP.) Within the ontogenetic model, current symptoms are conceptualized as products of the complex interplay of liabilities and experience in promoting a particular manifestation of psychopathology. This stage of the ontogenetic progression corresponds to the symptom dimensions represented in HiTOP, which vary continuously in severity—rather than dichotomously as presence versus absence of particular features. In contrast with the relative stability of liability factors, current symptomatology and its associated neural indicators are expected to fluctuate over time, and thus can be used to monitor therapy-related improvements.

Finally, consequences of psychopathology encompass the lasting psychological and neurobiological alterations that are caused by mental illness and persist despite fluctuations in symptom expression. Of particular interest in this ontogenetic model are the structural and functional neural abnormalities caused by episodes of mental illness, consistent with a “scar model.” “Scarring” differs from current symptomatology in that it is maintained regardless of improve-
ment in symptoms. Consequences of psychopathology play an important role in the ontogenetic pathway because they can be used to monitor the progression of a syndrome in terms of persisting effects on the brain and behavior.

**Liability and its neural indicators**

Within the ontogenetic framework, liability factors can be defined as genetically influenced dispositions, susceptible to early environmental modulation, that are associated with risk for psychopathology prior to the onset of illness. The identification of liability factors is a crucial research priority, as they serve as the basis for investigating how distal, heritable dispositions intersect with and contribute to more proximal pathogenic processes to give rise to manifest psychopathology. Further, research on latent liability factors and their manifestations across particular measurement modalities (eg, specific patterns of neural response; Figure 3) can allow for the identification of individuals most likely to exhibit later psychopathology, so they can be prioritized for prevention programs. Knowledge of an individual’s constellation of liability factors could also be used to predict the efficacy of particular intervention approaches and thereby guide treatment planning.

Different strategies can be used to identify indicators of liability and establish their prognostic efficacy (Figure 4). The first and most crucial is to conduct longitudinal studies of young people exhibiting a candidate liability indicator to determine whether it prospectively predicts the emergence of the expected form of psychopathology. For example, longitudinal studies have identified indicators that are informative about the future likelihood of developing substance problems (SPs) and the probable course of such problems. Of note, although initially aimed at specific SPs such as alcohol or cocaine use disorder, numerous studies over the past several decades suggest that the most robust indicators of SP liability reflect risk for externalizing problems more broadly. The implication is that these indicators operate at higher levels of the HiTOP system (ie, the Disinhibited Externalizing spectrum or Externalizing super-spectrum.) (Although not visually depicted in the original HiTOP model [Figure 1], the Externalizing super-spectrum is conceptualized as encompassing the Disinhibited Externalizing and Antagonistic Externalizing spectra). HiTOP-aligned research can facilitate efficient discovery of such principles by attending to multiple levels of the hierarchy simultaneously, rather than requiring decades of research on clinical groups segregated by diagnosis to reach the same conclusion.

![Figure 3. Depiction of the relation of liability to its indicators](image)

Here, liability is conceptualized as a latent (unobservable) predisposition to some form of psychopathology (eg, externalizing problems). This latent factor can be operationalized and measured through observable indicators from different modalities, including neural (eg, blunted target-P3 response), behavioral (eg, lower accuracy on an executive function task), and report-based indicators (eg, higher scores on a questionnaire assessing disinhibition). See ref 37 for further discussion of the relations between latent constructs and observable indicators.
One example of a well-established neural indicator of liability for SPs and other externalizing conditions is the target-P3 event-related potential (ERP), a brain response elicited by infrequently occurring task stimuli requiring a response. The P3 is thought to reflect cognitive processing following stimulus events, and it covaries positively with task measures of executive function. Research beginning in the 1980s found blunted amplitude of the target-P3 ERP response to be consistently linked to SPs, with later research extending this finding to individuals with externalizing problems of other types. Blunted target-P3 was also observed in clinically unaffected relatives of individuals with externalizing problems, such as children of parents with SPs, and twin studies revealed a substantial contribution of genetic influences to target-P3 amplitude. Building on these findings, Iacono and colleagues demonstrated that blunted target-P3 in adolescence predicted subsequent development of SPs and other externalizing problems in adulthood. The prospective nature of this association, together with evidence for familial aggregation, suggests that blunted target-P3 response, as a reflection of diminished cognitive processing of task-relevant stimuli, may constitute an indicator of liability for externalizing psychopathology.

Another key approach to evaluating candidate liability indicators is to quantify genetic influences on an indicator variable’s association with psychopathology using multivariate causal modeling in twin studies. A substantial genetic contribution to the observed covariance between a putative liability indicator and an outcome measure of psychopathology implicates the presence of a common genetic predisposition in both. In conjunction with longitudinal research showing that the indicator predates and prospectively predicts symptomatology, twin study analyses demonstrating common genetic influences provide compelling evidence that the variable in question operates as an indicator of liability to that form of psychopathology.

As an example, Hicks and colleagues used twin modeling to demonstrate that the association between blunted target-P3 amplitude and externalizing symptomatology was attributable entirely to genetic influences in common between the two. In sum, blunted target-P3 amplitude appears to be evident prior to the onset of externalizing psychopathology and shares heritable variance with externalizing problems. (Of note, target-P3 and other executive function-related liability indicators are unlikely to be innately determined, but rather represent a product of genetic and environmental influences that give rise to a characteristically disinhibited cognitive-motivational style.) These features suggest that blunted target-P3 response can be considered an indicator of liability for externalizing psychopathology.

Given that known liability factors tend to operate in a multifinal manner—increasing risk for a variety of psychopathologies—future research should establish whether liability factors as described here relate mainly to higher-order HiTOP dimensions, or in some cases relate selectively to a more specific form of psychopathology. For example, neuroimaging studies suggest that differentiable structural and functional correlates are observed at general versus more specific levels of the hierarchy, but it is not yet known whether these correlates function as liability indicators. Similar to Barlow’s triple vulnerability model, which posits that increasingly specific liabilities guide the expression of anxiety, transdiagnostic liabilities operating at higher levels of HiTOP (eg, the Externalizing spectrum) could be supplemented by more specific risk factors to produce particular signs and symptoms at the lower levels (eg, SPs).
One promising approach to improving the quantification of liability factors is to combine measures of a liability construct from different response modalities (e.g., self- or other report, neural reactivity, task performance; Figure 3) into a multi-method “psychoneurometric” composite.6,37,38 For example, liability for externalizing problems can be operationalized by combining scores on one or more questionnaire measures of disinhibition (i.e., dispositional proneness to impulsive, irresponsible behavior) and increased number of externalizing symptoms appears to reflect both genetic and non-genetic influences.39 C) The observed association (r~.2) between higher scores on a scale measure of trait disinhibition and blunted target-P3 response appears to reflect mostly shared genetic influences.39 D) The observed association between a “psychoneurometric” (PNM) factor—computed by aggregating disinhibition-scale scores with P3-response measures6,32—and number of externalizing symptoms (r~.5) appears to reflect mostly shared genetic influences.32 The latter finding suggests that combining indicators of externalizing proneness from different measurement modalities (e.g., questionnaire and brain response) may provide a purer index of liability than a questionnaire measure alone, and—as indicated by the greater overlap between ovals in D)—capture a larger portion of heritable variance in externalizing symptomatology than electrocortical responses alone.32,33

**Figure 5. Visual representation of findings from twin studies of liability for externalizing.** A) The observed association (r~.2) between blunted target-P3 response and increased number of externalizing symptoms appears to reflect mostly shared genetic influences.33 B) The observed association (r~.6) between higher scores on a scale measure of trait disinhibition (i.e., dispositional proneness to impulsive, irresponsible behavior) and increased number of externalizing symptoms appears to reflect both genetic and non-genetic influences.39 C) The observed association (r~.2) between higher scores on a scale measure of trait disinhibition and blunted target-P3 response appears to reflect mostly shared genetic influences.39 D) The observed association between a “psychoneurometric” (PNM) factor—computed by aggregating disinhibition-scale scores with P3-response measures6,32—and number of externalizing symptoms (r~.5) appears to reflect mostly shared genetic influences.32 The latter finding suggests that combining indicators of externalizing proneness from different measurement modalities (e.g., questionnaire and brain response) may provide a purer index of liability than a questionnaire measure alone, and—as indicated by the greater overlap between ovals in D)—capture a larger portion of heritable variance in externalizing symptomatology than electrocortical responses alone.32,33

**Indexing liability using measures from different modalities: the psychoneurometric approach**

One promising approach to improving the quantification of liability factors is to combine measures of a liability construct from different response modalities (e.g., self- or other report, neural reactivity, task performance; Figure 3) into a multi-method “psychoneurometric” composite.6,37,38 For example, liability for externalizing problems can be operationalized by combining scores on one or more questionnaire measures of disinhibition (i.e., assessing tendencies to act in impulsive-irresponsible ways) with one or more variants of P3 brain response.38 This approach to quantifying externalizing liability is advantageous compared with a purely questionnaire-based measure because twin research demonstrates that a larger portion of the composite’s predictive association with externalizing problems can be attributed to shared genetic variance.32 The reason is that the variance in common between scale-assessed disinhibition and externalizing problems reflects overlap in terms of environmental as well as genetic influences, whereas the variance in common between P3 brain response and externalizing problems reflects mainly overlapping genetic influences35,39 (Figure 5). Prospective-longitudinal research could be undertaken to confirm that dispositional characteristics quantified in this manner predate manifest symptomatology and persist.
through remission and relapse, as would be expected of liability factors (Figure 4).

**The role of the environment**

The progression from latent liability to manifest psychopathology depends importantly on environmental influences. For example, genetic predispositions appear to exert greater influence on SPs among adolescents who associate with alcohol-using peer groups, an example of gene x environment interaction. In other words, the contribution of liability tends to be amplified in a developmental context that is conducive to psychopathological expression. Moreover, an individual’s level of exposure to adverse environments can be predicted by genetic liability factors, a phenomenon known as gene-environment correlation. For example, individuals exhibiting weak inhibitory control—a heritable liability factor—appear more likely to self-select environments that lead to easier drug access, such as deviant peer groups. Moreover, upon initiating substance use, an individual’s overestimation of their peers’ drug use predicts cognitive and physiological changes associated with a worse trajectory. Overall, the cascading associations between liability and environment promote the emergence of psychopathology.

**Current symptomatology and concomitant neural indicators**

Neural indicators of liability, as described above, predate the emergence of clinical symptoms and are likely to remain stable over the course of the illness. In contrast, as psychopathology first arises and fluctuates in severity over time, other neurological indicators are likely to follow a temporal course that parallels symptom changes. Such concomitant indicators are part and parcel of the psychopathology itself (ie, disease-related dysfunction), as they accompany the presence of and changes in subjective experience and observed behavior patterns. Importantly, HiTOP-aligned symptom dimensions allow for the precise delineation of longitudinal relations between self- or other-rated symptoms and neural features, in ways that traditional diagnostic categories cannot. Small changes in expression of HiTOP dimensions over time, regardless of their proximity to arbitrary DSM diagnostic thresholds, could be linked to modest within-person changes in neural response, whereas studies using diagnostic categories would offer far less precision in identifying such associations. An example of a concomitant process pertaining to SPs is incentive sensitization, wherein stimuli that become associated with substance-related reward over time (eg, a hypodermic needle) acquire potency as motivational cues (ie, become objects of “wanting”) separate from the hedonic impact of the substance itself (“liking,” eg, high of heroin). This process is thought to contribute to the maintenance of SPs and proneness to relapse following cessation of use.

HiTOP provides an ideal platform for ontogenetic research, given its reliable, clearly organized, and structurally valid symptom dimensions

Incentive sensitization to psychoactive substances can be considered a concomitant indicator of SPs because it appears to (i) develop alongside SPs; and (ii) vary longitudinally with SP symptom severity. Evidence for these points comes from ERP research demonstrating variability in the neural responses to substance-related cues among individuals with varying severity of SPs, as well as longitudinal changes in these responses within SP-diagnosed individuals who experience recovery. One robust electrocortical indicator of incentive sensitization is the alcohol cue reactivity P3 response (ACR-P3), which is evoked by alcohol-related cues in the context of a larger visual categorization task. The ACR-P3 appears to capture incentive valuation (ie, degree of “wanting”) of alcohol and is greater in heavier-drinking individuals. Other ERP indicators of incentive sensitization appear to covary with the longitudinal course of SPs. For example, in one study of individuals treated for cocaine use disorder, increases from pre- to post-treatment in the late positive potential response to pleasant non-drug-related images were found to be associated with decreased craving of cocaine following treatment.

Taken together, these findings suggest that neural indicators of incentive sensitization may covary with the severity of SPs, both across individuals and within the same subjects over time. Importantly, unlike a liability factor, incentive sensitization cannot occur in substance-naïve individuals, instead developing concomitantly with the emergence
of SPs. One benefit of identifying such indicators is that they can then be utilized as measures of within-subject change in psychopathology, including treatment-related improvements. Incorporating regular assessment of these indicators into treatment could be particularly helpful for syndromes characterized by low insight into one’s own symptoms, such as SPs, as a supplement to report-based measures and behavioral tasks (eg, the drug-choice paradigm, in which subjects decide between viewing substance-related and -unrelated images). Knowledge of concomitant neural indicators could also facilitate the development of novel interventions, such as neurofeedback training, that hold promise for ameliorating certain forms of psychopathology.

Neural indicators that change concomitantly with symptomatology can also shed light on the prospective course of psychopathology, perhaps because of their presumed proximity to an underlying neural mechanism. (Note that it is critical not to conflate observed differences between patient and healthy control groups on some neural measure with discovery of a mechanism underlying that form of psychopathology, given: [i] the abovementioned limitations of diagnostic-group research that HiTOP was designed to address, as well as [ii] the impossibility of making mechanistic inferences from cross-sectional, ontogeny-agnostic studies, particularly when relevant experimental work has not been performed.) For example, once an individual has accumulated experience with alcohol, ACR-P3 amplitude appears to prospectively predict increased engagement in heavy drinking; this association may reflect the mechanistic role of incentive sensitization in the transition from repeated alcohol use to alcohol dependence. Whereas neural indicators of liability are clinically useful for identifying individuals at increased risk for psychopathology prior to symptom onset, concomitant neural indicators may have distinct utility for predicting future course among those already experiencing psychopathology.

Complicating matters further, liability and concomitant processes likely interact, such that mechanisms promoting symptom maintenance and exacerbation are enhanced by dispositional risk factors. One example from the neuroimaging literature is that, as incentive sensitization increases, a growing imbalance between incentive reward and executive control brain networks seems to lead to increasingly compulsive drug-related urges. Although executive control network activation in part reflects externalizing-related liability, its interaction with other brain systems in the context of emerging incentive sensitization promotes further development of substance-related psychopathology. This type of interplay is important to consider in studies seeking to identify neurobiological indicators of psychopathology risk and expression.

Consequences of psychopathology

The final component of this ontogenetic framework consists of the lasting consequences of psychopathology, including neurobiological measures indicative of dysfunction caused by illness. In contrast to the concomitant indicators described above, neural indicators that do not abate with the remission of psychological symptoms are consistent with a “scar” resulting from the experience of mental illness. Some of the most apparent consequences of psychopathology are medical, such as liver failure resulting from chronic alcohol overuse, or esophageal damage following frequent purging behaviors in eating pathology. However, psychopathology can also have lasting impacts on many psychological domains, from cognitive ability and personality to sensorimotor adaptations, and these effects are likely mediated by biological changes. Neural consequences of psychopathology play an important role in the ontogenetic pathway because they can be used to monitor the progression of an illness in terms of lasting effects on the brain, in the same way that medical tests can be used to quantify the progression of liver failure.

As discussed for liability factors, one critical tool for establishing a given neural indicator as a consequence of psychopathology is longitudinal research. In contrast to liability indicators, which must be present prior to the onset of psychopathology and persist over the course of illness, and concomitant neural indicators, which must be present alongside clinical symptoms, scarring becomes apparent only following symptom onset and must persist in the face of changes in clinical presentation. Studies examining such a progression are exceedingly rare, and none to our knowledge have used HiTOP-aligned symptom-dimension designs. In the psychosis field, research has suggested that individuals diagnosed with schizophrenia may experience greater brain tissue loss per year (-0.5%) than healthy controls (-0.2%), with inconsistent links between symptom fluctuations and the rate of neural degeneration. However, these
gray matter alterations may also be present in high-risk premorbid individuals, suggesting they are not solely a consequence of the experience of psychosis. The advent of large-scale longitudinal studies that include functional and/or structural neural data will be of enormous utility in the search for indicators of neural scarring, as premorbid brain data will be available for those who go on to develop psychopathology.

In addition to longitudinal studies, co-twin control analyses provide another means for evaluating whether an individual difference characteristic reflects liability for versus consequences of psychopathology. This approach involves comparing twins with differing levels of symptomatology on a characteristic of interest, controlling for genetic and shared environmental influences. Evidence from co-twin control studies suggests that central nervous system hyperarousal and resultant negative affectivity—as well as alterations in electrocortical dynamics related to response inhibition—occur as consequences of alcohol use, and that alcohol, cannabis, and tobacco use contribute causally to reduced ventral striatum functional connectivity. Each of these indicators is strongly linked to externalizing psychopathology, but they are also implicated in other syndromes; in contrast, as described above, gray matter decrements appear relatively unique to psychosis. It remains to be seen which neural indicators reflect scarring effects at differing levels of specificity within the HiTOP hierarchy.

Research on other spectra and future directions

Various report-, performance-, and physiology-based measures have been shown to relate to diverse forms of psychopathology, but it remains unclear whether the constructs assessed by such measures represent stable preexisting liability factors, correlates of current psychopathology, or lasting consequences of illness. Ongoing work on the ontogeny of mental illness will require comprehensive, multimodal assessment as well as longitudinal studies with genetically informative samples (eg, twins and/or individuals providing genomic data).

The topics discussed here are not unique to SPs, nor to the Externalizing super-spectrum. Neural indicators of liability have been described in relation to numerous other forms of psychopathology. For example, the reward positivity (“RewP”) brain-ERP response shows a consistent negative association with major depression and prospectively predicts increases in depressive symptomatology. Importantly, this brain-response measure appears to index proneness to depression rather than neural dysfunction associated with current depressive symptomatology. Bolstering the case for liability status, reduced RewP response is present in unaffected family members of depressed individuals and is observed even in preschool-aged depressed children. The RewP is also beginning to be examined in relation to other forms of psychopathology involving reward system dysfunction, including SPs. Beyond the RewP, numerous studies demonstrate that neurobiological indicators, including other ERP measures, can be used to index liability for a range of psychopathology, including—but not limited to—SPs. A limitation of work to date is that relatively few studies have utilized dimensional symptom measures, and none to our knowledge have explicitly examined higher-order spectra of psychopathology in relation to ERPs, apart from the externalizing-P3 literature described above. HiTOP provides an optimal platform for testing research questions of this kind. For example, the notion that neural indicators of liability might operate primarily at higher-order levels of the HiTOP model represents an important topic for future investigation.

In contrast to the growing literature on neural indicators of liability, relatively little dimensional work has been undertaken to distinguish these from neurobiological indicators of current symptoms or lasting consequences for any of the HiTOP dimensions. Much more extensive longitudinal and dimensional work is needed to better understand the latter two elements of the ontogenetic pathway, with the goal of predicting the future course of clinical problems and monitoring disease- and treatment-related change using neural measures.

Beyond the individual model elements we have emphasized (liability, current symptomatology, consequences) and our specific focus on neurobiological indicators, the ontogenetic framework proposed here is not unique to the SP literature, nor to explicitly HiTOP-aligned research: It complements and extends existing ontogenetic models of externalizing, bipolar, and thought disorders. For example, McGorry et al proposed a “clinical staging” model of psychosis, mania, and depression wherein signs and symptoms largely overlapped at the earliest stages but became increasingly
distinct during the progression to acute, severe symptomatology. In parallel, our model posits that factors driving symptom expression at early stages should not be studied in isolation (e.g., mania versus control group), but rather in line with a hierarchical understanding of mental illness at the HiTOP spectrum or super-spectrum level. For purposes of early identification and intervention, time is better spent understanding liability processes contributing to the generation of disordered cognitive and behavioral patterns shared across syndromes (i.e., at higher levels of HiTOP), rather than in any subgroup alone. Conversely, symptom expression at the last stage of McGorry’s model is highly differentiated and would likely operate at the symptoms/components level of HiTOP, potentially driving consequences specific to psychotic symptom expression and not mania, or vice versa. Here, neural indicators of current symptomatology and, perhaps, lasting consequences would be expected to show specificity to a particular syndrome. As illustrated by the parallels with McGorry’s model, as well as with models of other forms of psychopathology, the HiTOP framework and this ontogenetic perspective can be applied to myriad psychopathological conditions.

Conclusion

The ontogenetic model we have described provides a framework for organizing existing knowledge and guiding continued research on the etiology, mechanisms, and consequences of mental illness as represented in the HiTOP model. In particular, we have emphasized how neurobiological measures can aid in this endeavor and the ways in which HiTOP provides an ideal platform for ontogenetic research, given its reliable, clearly organized, and structurally valid symptom dimensions. With a greater knowledge of the distinct liability factors, concomitant indicators, and lasting consequences associated with particular symptom dimensions, mental health professionals will be better equipped to identify and intervene with at-risk individuals and monitor the progressive remediation and lasting consequences of their psychopathology.

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Original article
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Do *DSM* classifications help or hinder drug development?

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Development and regulatory approval of psychotropic drugs targets individuals with syndromes described in the current *Diagnostic and Statistical Manual of Mental Disorders (DSM)*. This helps drug developers and regulators to communicate with prescribers, and prescribers to match a specific psychotropic with the individual patient(s) most likely to benefit from it. However, this practice has been criticized on the grounds that *DSM* syndromes are too heterogenous biologically, and the effects of psychotropics are too nonspecific to allow for an effective match. This review considers the advantages and disadvantages of the current practice and the possible alternatives. It concludes that efforts should be made to explore psychotropic development transdiagnostically, free of the *DSM* boundaries. However, currently there exists no alternative diagnostic system that is clearly superior to the *DSM* in terms of communications between the stakeholders in drug development.

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**Key words:** *DSM*; classification; psychotropic; drug development

**Introduction**

After a flurry of novel psychotropics in the 1980s and 1990s, which had a moderately superior tolerability profile compared with existing drugs, the 2000s have been characterized by a stagnation of productivity in drug development. The presumed stagnation has been lamented in editorials and attributed to a lack of pathophysiological understanding of the brain’s normal and abnormal functioning, difficulties in identifying targets, poor translation from animal models to human ones, the absence of biological markers, and the high financial risks associated with CNS drug development. Adherence to diagnostic systems which were not specifically designed for drug development, such as the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, has also been suggested as a major reason for the paucity of novel psychotropics.

The use of diagnostic systems including the *DSM* is the medical profession’s attempt to classify and circumscribe clinical presentations in the belief that such classification will facilitate matching a specific disease and treatment for an individual patient and optimize the clinical benefits. Diagnosis is based on the similarity of the symptoms and test results of the individual patient to a known pathophysiological process, and on known interactions between the process and the therapeutic intervention.

As health care provision has evolved beyond the traditional doctor-patient interaction, diagnostic systems have also been employed to communicate between the various stakeholders of health care provision: patients, their families, clinicians, academic researchers, insurers, the pharmaceutical industry, and government agencies. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) employ the *DSM* classification to support...
DSM will remain a useful tool for drug development, yet all stakeholders should be aware of its limitations and maintain the necessary flexibility.
The most frequent and probably valid criticism is that heterogeneity within diagnostic groups dance of criticism. Based on the descriptive umbrellas of schizophrenia, depression, or anxiety—a continuum between normality and disease—there probably exists many heterogenous biological processes. Are two schizophrenic individuals, one with an IQ of 105, persistent auditory hallucinations, and mildly declining social functioning, and another with an IQ of 85, severe thought disorder, mild paranoid ideation, and severely declining vocational functioning affected by the same pathophysiological process? Are two individuals with MDD, one suffering from severely depressed mood, hypersomnia, hyperphagia, motor retardation, poor concentration, and nihilistic ideas, and another with moderately dysphoric mood, insomnia, motor agitation, poor concentration, and very severe anxiety affected by the same pathophysiological process?

Overlap between diagnostic groups
To further complicate matters, symptomatic manifestations of syndromes with a distinct DSM diagnosis tend to overlap. Most MDD patients are anxious, and most patients who meet the criteria for GAD are unhappy. Patients who meet criteria for schizophrenia are often depressed, and patients who meet criteria for depression are occasionally psychotic. If indeed several pathophysiological processes are contained within the same diagnostic class, it explains why only a minority of the target population included in randomized controlled trials (RCTs) or treated in clinical practice, responds to the treatment. Were all or the majority of the patients who meet DSM criteria for MDD affected by the same pathophysiological process, it could be expected that all or most would respond to the same treatment and not only <30% as indicated by RCTs. This is not surprising if one considers that phenomenological description in the DSM is attempting to reflect the end result of close to 1 trillion neural connections, their interactions with genetic programming, functionally and dynamically changing proteins, and environmental effects.

Disconnect between psychotropics and DSM diagnosis
Further evidence of the disconnect between DSM diagnosis and specific pathophysiological process is the fact that in daily clinical practice, psychotropics are prescribed regardless of the specific DSM diagnosis. Drugs which block dopamine (DA) and serotonin (5HT) receptors, originally developed and approved for marketing in schizophrenia, are prescribed for almost all DSM syndromes. Similarly, selective serotonin reuptake inhibitors (SSRIs) were first developed and indicated in MDD, and later in anxiety disorders and post-traumatic stress disorder (PTSD). For example, quetiapine is prescribed as a hypnotic at approximately 50 mg/day, as an antidepressant at 150 to 300 mg/day, as a mood stabilizer at 400 mg/day, and as an antipsychotic at >600 mg/day.

The advent of modern psychopharmacology and of phenomenologically-based diagnostic system(s), starting with DSM-III, has inadvertently created mutual validation between diagnosis and psychotropic drugs (see ref 12, p 241). Along these lines, DA receptor-blocking antipsychotics are indicated for schizophrenic psychosis, and individuals whose psychosis ameliorated in the course of antipsychotic administration are likely to be diagnosed with schizophrenia. A similar relationship has been postulated between MDD and tricyclics (TCAs) or selective serotonin reuptake inhibitors (SSRIs). At the time, the simplistic explanation that specific psychotropics reverse a putative monoaminergic neurotransmitter disturbance, which is central in the mental illness for which the drug has been indicated, was hardly disputed. DA hyperactivity, later to be replaced by DA dysregulation, was at the basis of the DA-blocking drugs’ beneficial effect in schizophrenia. A similar dysregulation of noradrenergic-serotonergic neurotransmission was invoked to account for SSRI and TCA benefits in MDD. Although hundreds of nonreplicable and negative studies have been published since, and the field has moved into genetic markers such as single nucleotide polymorphisms and copy number variations, the simplistic monoaminergic hypotheses, which emerged in the 1970s, have not yet been fully dislodged.

Splitting and lumping
The most vociferous critics of drug development and of regulatory approval based on DSM syndromes have raised the possibility that stakeholders in the treatment of mental illnesses unnecessarily split and repackage syndromes to
justifies psychotropic overprescribing. According to this view, for example, the definition of MDD in DSM-III and subsequent revisions is overinclusive, comprising individuals with transient sadness. Furthermore, by lumping melancholic depression with mild-to-moderate anxious depression into MDD, DSM-5 has created a widely heterogeneous syndrome devoid of biological common ground.15 This on the one hand, accounts for the large proportion of MDD patients treated with antidepressants who do not respond to treatment.16 On the other hand, a considerable number of individuals who are clearly in need of treatment will not get it because they will never meet any DSM criteria for a mental illness. For example, almost 80% of youngsters frequenting Schizophrenia Prodromal Clinics and considered at high risk for schizophrenia will never progress to schizophrenia and many will never suffer from a classifiable mental illness. Yet, they manifest apathy, avolition, dysthymia, and negative symptoms, to name a few.17 A departure from the DSM-driven drug development or a more flexible approach would be an incentive to develop drugs for such populations.

Disease-centered approached vs drug-centered approach

A few scientists have called into question the disease-centered approach, by which psychotropics are indicated for specific psychotic disorders or for MDD or GAD, and propose a drug-centered approach. The claim is that substances with psychotropic properties do not reverse an imbalance or an abnormality, which is responsible for the aberrant behaviors or emotions, but rather create a de novo mental status in both ill and healthy individuals. For example, amphetamine-like compounds improve temporary concentration and sociability in healthy individuals and in Alzheimer’s disease or post-stroke apathy/social withdrawal.18 Likewise, DA-blocking psychotropics reduce reactivity to environment stimuli or internal emotions in healthy individuals and in almost all disorders classified by DSM. Also, effective psychotropic drugs such as benzodiazepines have been developed much before the modern diagnostic systems existed, and were prescribed, transdiagnostically, to individuals who do not qualify for any DSM diagnosis, individuals suffering from insomnia, anxiety, depressed mood or psychotic agitation.19 To fully understand and take advantage of the effects of psychotropics, a drug-centered approach is suggested. Accordingly, trials involving normal controls (Phase 1 of development) should be much more extensive than the current practice and only when all the effects and adverse effects on normal behavior are well understood should psychiatric patients be involved in trials.

The monoaminergic hypothesis and DSM

It is reasonable to assume that the link between DSM diagnosis and indicated psychotropics has gained popularity because in the late 1970s the field was trying to make the best of the available scientific knowledge and to replace the scientifically ambiguous psychoanalytic explanations to the etiology of major mental disorders. While it was clear that the monoaminergic hypotheses explaining the link between psychotropics and major mental disorders would not replicate the link between spirochete, penicillin, and the mental manifestation of syphilis,20 it still reflected plausible, incremental scientific progress. This in turn allowed the providers of mental health care the comfort of leaning on what appeared to be solid scientific foundations which also fitted the medical model.

In daily clinical practice, patients approach physicians with the expectation that they may get relief from their pain and anguish. The providers of mental health care, and in particular psychiatrists, are aware that on one hand they operate in an environment of high diagnostic and therapeutic uncertainty, and on the other hand, that the therapeutic response to any psychotropic drug represents the sum of both the drugs’ pharmacological effect and the placebo effect. Clearly, acknowledgement of the poor link between the psychotropic mechanism of action and the assigned DSM diagnosis would deprive patients of the full power of the placebo effect.21

The weak relationship between DSM psychiatric syndromes and psychotropics indicated for them, has not been ignored by regulators. Paul Leber, MD, who headed the relevant division of the FDA between the early 1980s and late 1990s, fully acknowledged that the DSM syndromes were poor reflections of true biological processes, if at all. In his view, the DSM was an expedient, available way in which the FDA could communicate to practicing prescribers about the general characteristics of the patient populations most likely to benefit from a particular psychotropic (see ref 15, pp 22). Along the same lines, the EMA is continuously updating its development recommendations to address transdiagnostic development.22
Potential solutions

The general idea for revising the relationship between psychiatric syndromes and drug development is to (a) identify basic symptoms that manifest trans-diagnostically across DSM syndromes, (b) identify biological circuits or genetic-molecular processes and markers common to these manifestations, and (c) devise therapeutic interventions that engage targets common to these circuits and/or genetic-molecular processes.

Research Domain Criteria (RDoC)

Research Domain Criteria (RDoC) is an initiative of the US National Institute of Mental Health (NIMH), and is such an approach. It proposes to divide current DSM syndromes into simpler, more basic, observable manifestations, for which measurable physiological correlates can be devised (see article by Cuthbert in this issue, p 81). The assumption is that observable behaviors and emotions, and their respective neurobiological measurable correlates, span across multiple DSM disorders.

The RDoC includes five domains: Negative Valence or response to threats, Positive Valence or response to expected rewards, Cognitive Systems, Social Processes, and Arousal/Regulatory Systems. The Negative Valence construct, or potential threat/anxieties, is present in phobia, panic, social anxiety, PTSD, and GAD, as well as in schizophrenia, autism spectrum disorders, MDD, and substance use disorders. Genetic, neurochemical, imaging, electrophysiological, observational, and self-reported data all converge upon commonalities in the abovementioned DSM syndromes. Benzodiazepines, which bring partial relief in all syndromes related to Negative Valence, are widely prescribed in clinical practice.

Impairment in Cognitive Systems, from very mild to severe, manifest in almost all DSM syndromes. It is unclear whether manifestation of cognitive impairments such as for example, these manifested in schizophrenia, reflects the coincidental occurrence of two abnormalities in the same individual—psychosis and cognitive impairment—or derives from the same biological abnormality. Assuming the former, it is likely that the same pharmacological intervention could improve cognition in individuals at the lower level of normality without a DSM disorder, as well as in cognitively impaired individuals with schizophrenia, MDD, or any other mental disorder along the lines of a drug-centered approach.

Psychiatric Ratings using Intermediate Stratified Markers

Psychiatric Ratings using Intermediate Stratified Markers (PRISM) is a European Union-funded initiative, similar to the RDoC, intended to investigate the common and the distinct biological background of social withdrawal in schizophrenia, MDD, and Alzheimer disease (AD), and to design the regulatory path to develop drugs for social withdrawal across syndromes. Social withdrawal is among the earlier, often persistent and disabling manifestations of schizophrenia, MDD, and progressive brain degenerative disorders such as AD; hence the need to investigate treatment for this condition.

However, social withdrawal is a complex behavior which can be modulated by aging, concomitant medical diseases, and social, vocational, and economic circumstances. A more basic component of social withdrawal is disturbance in motivation which, like social withdrawal, is manifested in stroke, traumatic brain injury, schizophrenia, and MDD. Disturbance in motivation has created a nomenclature conundrum for both researchers and clinicians such as apathy, avolition, anhedonia, negative symptoms. While each label reflects a slightly different clinical manifestation, there is a large phenomenological and biological overlap in particular between apathy, avolition, and anhedonia.

Apathy, avolition, and anhedonia reflect an abnormality in which reward is processed in order to motivate behavior. To motivate behavior, it is necessary to be able to anticipate reward, generate options for behavior, evaluate the options in terms of effort/risks and other costs all versus the potential rewards. Any disruption along this chain might generate apathy and/or anhedonia and therefore can be a target of putative treatment. DA, noradrenaline (NE) and serotonin neurotransmission was shown to play a role along this chain suggesting that pharmacological manipulation of the neurotransmission might have a beneficial effect. Apathy and anhedonia manifests in >19 DSM-5 syndromes. Looking beyond the restrictions of the DSM system, it might be possible to develop a drug to treat these conditions trans-diagnostically. L-dopa, methylphenidate, bupropion, and modafinil are examples of drugs which affect monoaminergic neurotransmission and have been
used in single case series as well as in some RCTs in an attempt to treat apathy/avolition. Although a large number of reports of individual patients benefiting from such interventions exist, and a large RCT with methylphenidate is ongoing, for the moment, none of these drugs has produced consistent benefits. A sigma/5HT antagonist compound currently in development has shown superiority over placebo in negative symptoms in schizophrenia, including apathy, which translated into improvements in social performances. If indeed this type of compound can affect a specific component of apathy it is reasonable that future studies investigate its effect in apathy associated with brain degenerative disorders, MDD, and other developmental disorders.

Conclusions

The current trend to identify basic symptoms that manifest transdiagnostically, investigate biological circuits or genetic-molecular processes and markers common to these manifestations, and develop drugs that engage targets common to these transdiagnostic circuits and/or genetic-molecular processes should be encouraged. DSM and similar classifications should be mainly used for communication as they were initially intended.

However, several notes of caution are pertinent before reliance on DSM classification as a guide to drug development is abandoned. First, decomposing complex behaviors and emotions like the ones reflected by DSM into basic functions such as working memory and then relating it to a biological marker such as reactivity as measured during a functional magnetic resonance imaging (fMRI) as suggested by the RDoC initiative is not the end of the road. Individuals with similar fMRI reactivity can manifest distinctly diverse phenomenology.

The attractive hypothesis of one cause for one disease pioneered by Koch and Pasteur has been disappointing in explaining the causes of mental illnesses. Genetic and genetic environmental interaction studies have demonstrated that the same phenomenological manifestation can result from almost infinite numbers of combinations of single-nucleotide polymorphisms (SNPs), frequently reacting to ever-changing environmental circumstances. A much better understanding of the normal and abnormal brain functioning is necessary before diagnostic classifications can truly reflect pathophysiology. Second, for any novel classification to be helpful it has to be first adopted by the community of prescribers. Currently, terms like RDoC Negative or Positive Valence do not define a patient population for whom the average prescriber can prescribe a specific psychotropic. It is likely that for the foreseeable future DSM will remain a useful tool for drug development, yet all stakeholders should be aware of its limitations and maintain the necessary flexibility to develop, approve, and use in clinical practice psychotropics which might be effective transdiagnostically.

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**Original article**

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Brief report

The role of RDoC in future classification of mental disorders

Bruce N. Cuthbert, PhD

The Research Domain Criteria (RDoC) project constitutes a translational framework for psychopathology research, initiated by the National Institute of Mental Health in an attempt to provide new avenues for research to circumvent problems emerging from the use of symptom-based diagnostic categories in diagnosing disorders. The RDoC alternative is a focus on psychopathology based on dimensions simultaneously defined by observable behavior (including quantitative measures of cognitive or affective behavior) and neurobiological measures. Key features of the RDoC framework include an emphasis on functional dimensions that range from normal to abnormal, integration of multiple measures in study designs (which can foster computational approaches), and high priority on studies of neurodevelopment and environmental influences (and their interaction) that can contribute to advances in understanding the etiology of disorders throughout the lifespan. The paper highlights key implications for ways in which RDoC can contribute to future ideas about classification, as well as some of the considerations involved in translating basic behavioral and neuroscience data to psychopathology.

Keywords: psychiatric diagnosis; psychiatric nosology; Research Domain Criteria; RDoC

Introduction

The role of this essay is to provide a brief speculation regarding the role of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) project in future psychiatric classification systems. Initiated by NIMH in 2009, RDoC constitutes a framework for translational research that shifts the focus away from traditional DSM / ICD disorder categories and toward research on functional dimensions of behavior or cognitive/affective processes (eg, reward learning or working memory) as studied across the entire range of functioning from normal to abnormal.1,3

The paradigm emphasizes the inclusion in study designs of multiple measures (eg, behavioral/cognitive, phenomenological, physiological) for examining such psychological constructs, thus promoting an integrative rather than reductionistic approach.4 High priority is placed upon the examination of neurodevelopmental processes and environmental influences (and their interaction) in research designs.5 Figure 1 depicts the way in which the various components of the RDoC framework are organized to stimulate transdiagnostic research that can examine the joint influences of biological and external risk factors. Neurodevelopment and environmental effects represent important considerations in research designs, and various domains of function (Negative Valence, etc) are studied across multiple Units of Analysis from Genes to Self-Reports. (Both the Domains and Units of Analysis are considered as heuristic exemplars rather than fixed components.)

A discussion of RDoC’s future role in classification necessarily depends upon one’s long-term vision of what future nosologies might comprise and what assessment problems they try to address. It is important to emphasize the phrase “long-term vision” since the aim of current diagnostic manuals centers explicitly upon clinical utility6; this
seems to reflect a tacit assumption that current diagnoses and treatments will change only modestly and incrementally over time, and that the symptom-based architecture of disorder categories will remain static. In contrast, a major role of funding agencies is to generate new concepts and research, pursuing breakthroughs that could lead eventually to substantive reductions in the burden of mental illness through enhanced treatment and prevention. As RDoC is a research framework intended to inform future diagnostic systems, the long-term goal envisions a precision-medicine concept that fosters empirically based approaches to assessment, treatment, and prevention which can be updated rapidly on the basis of ongoing data—much like current practices in other areas of medicine such as cancer.7

How can the RDoC framework contribute to this future vision? It is useful to note that NIMH did not initiate the RDoC project as the pilot test for a new classification system as such (much as the Research Diagnostic Criteria of the 1970s represented a stalking horse for the DSM-III). Rather, the initiative was a nascent idea that resulted from the increasing realization that traditional disorders were
broad and heterogeneous syndromes that did not correspond to specific biological or behavioral systems and thus were hampering efforts to develop new clinical tests or treatments; the problem was compounded by a de facto practice in grant review committees stipulating that clinical research should only be conducted in terms of DSM/ICD disorder categories. The RDoC alternative was to adopt a translational approach: The framework consists of a set of flexible guidelines for approaching psychopathology in terms of departures from normal-range functions rather than starting with a priori disease definitions based upon sets of presenting symptoms.

Key RDoC features

This shift directly connects the accelerating body of basic research on behavioral and neural functioning with psychopathology, enabling several novel approaches. First, functional dimensions are explicitly conceived as psychophysiological constructs that are jointly defined by data for a particular functional aspect of behavior or cognition and data for an implementing neural circuit or system—thus addressing head-on the mind-body challenges that have long stymied attempts to understand biological aspects of mental disorders (and the attendant eliminative reductionism that has proved controversial in so many quarters). Second, such a perspective encourages the study of dysregulated functioning (eg, cognitive problems, disrupted motivational processes), in addition to symptom reports, as significant problems in and of themselves rather than as one of several indices of an “underlying” syndrome.

Relatedly, enhanced assessment of behavioral/cognitive functions enables the use of quantitative measurements that bring to bear modern psychometric and computational techniques as opposed to qualitative symptom reports. The functional domain approach also fosters the exploration of similar mechanisms that are disrupted in multiple disorders (as implied by the extensive comorbidity of current diagnostic classes), and the last decade has seen a notable increase in various types of transdiagnostic studies that can help untangle questions about whether or not similar kinds of impairment or symptoms across disorders can be more efficiently regarded (and treated) as involving similar (or identical) mechanisms.

An apt example is provided by a large program of anxiety disorders research in which patients’ imagery of fearful and control situations were assessed with psychophysiological measures. Five quintiles of patients were defined transdiagnostically on the basis of highest-to-lowest psychophysiological reactivity during aversive (as compared with neutral) images. Independent of primary diagnosis, greater functional impairment and self-reported symptomatology were associated with blunted physiological reactivity rather than the higher reactivity that might have been expected. These data demonstrate the utility of examining relationships among multiple measures, and suggest the potential of physiological reactivity as a prognostic biomarker for differential treatment (eg, exposure therapy versus medications or cognitive therapy).

Finally, RDoC’s role as a flexible research framework serves as a model for further major revisions to conceptions of mental illness—in the near term, in such growing research areas as connectomics and the genomics of functional systems; and in the longer term, potentially radical change stemming from computational modeling and machine learning.

Early detection and prevention

A more extended, but critically important, aspect of classification systems in upcoming decades regards the capability for very early detection of future risk for psychopathology. Such a consideration may not seem tethered to a classification system at all with respect to current nosologies; however, a significant weaknss of symptom-based diagnostic systems is that, by definition, some pathological process is already established by the time that a diagnosis can be made. The full-range dimensional approach that RDoC embodies is well-positioned in order to reach toward future prevention and pre-emption of disorders, in that growth patterns—whether assessed in behavioral/cognitive, brain-based measures, or both—could be monitored across neurodevelopment in order to detect early aberrations before any overt symptoms are present. For instance, data from the Pennsylvania Neurodevelopmental Cohort have shown that the onset of psychotic symptoms in adolescence is associated with relatively lower cognitive test scores across development (compared with typically developing participants) in an unselected sample of children. These results imply that norms for cognitive and emotional growth across childhood, similar to familiar height and weight charts for children, could be useful tools in standard practice for
early detection. At least one such effort is already under way: A developmental battery that assesses six cognitive domains—employing “gamified” tasks on a mobile e-platform to engage participants’ interest—has been piloted for 3-year-old children in rural India, with the goal of developing normative curves across development as the project grows. These projects demonstrate that quantitatively based efforts at prevention, assessed relative to continuous population (or large-sample) distributions, are not simply a promissory note but are already being implemented.

Computational approaches

Finally, the newly emerging field of computational psychiatry and the RDoC framework have mutually influenced each other. Given the indeterminate nature of traditional disorder categories, RDoC has provided a more tractable basis for efforts to apply computational procedures to psychopathology. Computational methods have been applied to two broad aspects of research. The first aspect comprises computational modeling to validate model-based predictions about relationships between brain activity and various aspects of behavior in parametrically designed experiments, which typically involve functional operations similar (often identical) to RDoC constructs. The second aspect encompasses the use of computational techniques to identify data-driven phenotypes not dependent upon traditional diagnoses, inspired in no small part by the RDoC framework. This has proven to be a promising area for study: Although the subgenre is only a few years old, several results suggesting actionable outcomes for treatment or assessment have already appeared in the literature. For instance, a recent study employed a wide variety of measures to analyze the heterogeneity in a large sample of patients diagnosed with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder; a multistep analysis revealed three transdiagnostic clusters (“biotypes”) of patients defined primarily by cognitive test scores and electrophysiological responses to various stimuli. Other measures indicated that the biotypes comprised more biologically valid groupings than the diagnostic categories, and the data suggested significant implications for more precise clinical treatment. Machine learning and artificial intelligence (AI) appear poised to produce yet more generative findings, given the power of these techniques to find relationships in high-dimensional data sets that integrate behavioral, symptomatic, and biological measures. While such developments may seem far off, regulatory agencies are already actively considering the process for approving use of AI and machine learning as medical devices.

Conclusion

In conclusion, the RDoC framework has catalyzed activities in multiple areas of mental disorders research that can contribute to future classification systems aligned with precision medicine avenues to diagnosis, treatment, and prevention. A number of caveats are in order. First, a common criticism of RDoC from clinical researchers and service providers holds that RDoC diverges too much from current practice to be used by clinicians—a not unreasonable concern. However, there will inevitably be a transition period as precision medicine procedures are introduced, and the majority of current RDoC-themed research projects involve subgroups of one (or two) current disorder categories. So, it is likely that service settings will experience gradual shifts in assessment and treatment as new “biotypes” are validated and enter the clinic. Second, some observers seem to infer that the introduction of biological and quantified behavioral measures are threats to the use of traditional assessments and individualized treatment plans. However, individual assessments will remain essential for the vast majority of patients, as life histories and symptom reports will be even more important to precision medicine than current syndromal approaches. Finally, some researchers regard the current RDoC framework as a finite set of components and constructs that are insufficient to address the totality of mental illness. However, RDoC is better understood as a set of dynamic principles with which the field can build a cumulating knowledge base about psychopathology and how it emerges from perturbations in normal functioning. Rapidly emerging data, technologies, and concepts consistent with the RDoC approach demonstrate its capability to inform future versions of psychiatric nosologies.

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