Classification in the 21st Century: Where we are now and where might we be going?

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- Categorical classifications defined descriptively in terms of symptoms which have been observed to covary in individuals
- Supplemented by severity dimensions (e.g., mild, moderate, and severe)
- Largely rooted in Kraepelinian historical tradition
- Authoritative by virtue of “official status”
Current State of Affairs: ICD vs. DSM

ICD
- Product of World Health Organization
- 11th revision (due May 2019)
- Mental and Behavioral Disorders Chapter in overall medical classification
- Used by roughly 70% of psychiatrists in WPA survey

DSM
- Product of American Psychiatric Organization
- 5th revision (published May 2013)
- Freestanding psychiatric classification
- Used by roughly 30% of psychiatrists in WPA survey
Q8 - ‘In your day-to-day clinical work, which classification system for mental disorders do you use most?’

Reed et al, World Psychiatry, 2011
Classification Most Used: Psychiatrists

AFRO
- Kenya
- Nigeria
- South Africa
- Argentina
- Brazil
- Chile
- Colombia
- Costa Rica
- Honduras
- Peru
- USA
- Egypt
- Iraq
- Morocco
- Pakistan
- Armenia
- Austria
- Finland
- France
- Germany
- Italy
- Kyrgyzstan
- Macedonia
- Montenegro
- Poland
- Romania
- Russia
- Serbia
- Slovenia
- Spain
- Sweden
- Switzerland
- Turkey
- UK
- India
- Thailand
- Aus and NZ
- Hong Kong
- Japan
- Korea
- Malaysia
- PR China

AMRO
- China
- Malaysia
- Japan
- Hong Kong
- Aus and H.

EMRO
- Austria
- Armenia
- Pakistan
- Austria
- Bosnia and H.
- Czech Rep.
- Finland
- France
- Germany
- Italy
- Kyrgyzstan
- Macedonia
- Montenegro
- Poland
- Romania
- Russia
- Serbia
- Slovenia
- Spain
- Sweden
- Switzerland
- Turkey
- UK
- India
- Thailand
- Aus and NZ
- Hong Kong
- Japan
- Korea
- Malaysia
- PR China

EURO
- China
- Malaysia
- Japan
- Hong Kong
- Aus and H.

SEARO
- China
- Malaysia
- Japan
- Hong Kong
- Aus and H.

WPRO
- China
- Malaysia
- Japan
- Hong Kong
- Aus and H.

ICD-10
ICD-8/9
Other
DSM-IV
Value of Making a DSM/ICD Diagnosis

- Well defined and reliable terminology facilitates communication among clinicians, administrators, lawyers, patients, and families
  - Provides convenient short-hand when describing psychiatric presentations
- Assigning DSM or ICD diagnosis provides direct access to psychiatric literature about treatment, prognosis, etc.
  - Journal articles, practice guidelines, textbooks) for past 33 years have been geared to DSM or ICD definitions of mental disorders
- Facilitates assignment of diagnostic codes for data collection and/or payment for services
Limitations of DSM/ICD Diagnosis

- Most treatment decisions are geared to symptoms regardless of diagnosis (e.g., psychosis)
- Diagnostic heterogeneity limits predictive power of diagnoses
- Diagnoses are not informative about etiology or pathophysiology
- High rates of NOS limit clinical utility in terms of communication and access to the literature
Methods for Revising Psychiatric Nosology  
(from Kendler and First, BJP 2010, 97(4):263-5)

- **Iterative method:**
  - Assumes each subsequent revision will produce improvements over its predecessor while retaining the fundamental assumptions of the existing model.

- **Paradigm shift:**
  - Underlying paradigm is discarded in favor of a fundamentally new approach.
Iterative Approach

- Incremental changes made while retaining the fundamental assumptions of the existing model

- Over time, rough constructs we now call “disorders” move towards a better and better approximation of the “true” psychiatric diseases as they exist in nature.

- Evolutionary in nature; assumes a continuity of process over time.
Process Followed Since DSM-III

- From introduction to DSM-III-R:
  - “This is the revision of the third edition of the APA’s DSM, better known as DSM-III-R. The last sentence of the introduction to DSM-III, published in 1980, stated ‘DSM-III is only one still frame in the ongoing process of attempting to better understand mental disorders.’ DSM-III-R represents another still frame.” (p. xvii).

- DSM-IV revision strategy called for making changes only if there were sufficient evidence to justify such a change
Iterative Approach

- **Advantages:**
  - Allows each transition, from one iteration of the classification to the next, to be straightforward
  - Minimizes disruption to clinical practice and research.

- **Disadvantages:**
  - Assumes that the paradigm on which the classification is based is correct.
  - Assumes continuity over time in approach toward validating psychiatric disorders.
Paradigm Shift Model - I
Paradigm Shift Model - II

- Limits of the current paradigm are reached and a consensus arises that the system is broken.
- Rather than fixing the old model, approach is to discard it and start over.
- Kuhn: anomalies and problems in a model accumulate to a point where a scientific revolution is sparked and old paradigm is replaced with a new one.
Paradigm Shift from DSM-II to DSM-III

- DSM-I and DSM-II roundly criticized for being unreliable and tied to unproven psychodynamic etiological theories.

- Introduction of descriptive operationalized diagnostic criteria in the 1970’s (e.g. the Feighner and Research Diagnostic Criteria) transformed psychiatric research by allowing researchers around the world to utilize the same reliable diagnostic definitions.
DSM-III Paradigm Shift

- The revolution embodied by DSM-III involved advocating the adoption for clinical classification of a paradigm that had already been widely embraced by the research community for general clinical and administrative use.
Adoption of Medical Model of Diagnosis

- Articulation of broad syndromes that become divided up into more homogenous entities: diabetes -> type I and type II
- Categorical approach reflects dichotomous nature of clinical medicine: to treat or not to treat, to discharge or hospitalize, to qualify or not for a particular treatment algorithm, to bill or not to bill
- Used in conjunction with quantitative measures (e.g., temperature, fasting blood sugar, WBC, bone densities)
Descriptive Syndromal Approach

- In lieu of defining disorders based on etiology, disorders defined descriptively in terms of symptoms which have been observed to covary in individuals.

- As in medicine, it was assumed that syndromal groupings are indicative of common underlying etiology and pathophysiology.

- Not limited to mental disorders: see International Headache Classification.
Descriptive Approach - II

- Defined according to etiology for those disorders in which etiology is known (e.g., substance-induced disorders)

- Harks back to Kraepelian approach of providing detailed descriptions of disorders: “psychiatrists should avoid postulating etiologies to make a diagnosis and should stick with the course of illness, attend to the final state, and do followup studies where possible.”
“Although there is no guarantee that a reliable system is valid...assuredly an unreliable system must be invalid.”

-- Spitzer and Fleiss, 1974.
Impetus for Development of Diagnostic Criteria

- Discovery in 1960’s of effective medications highlighted need for explicit diagnostic criteria for homogeneous research samples for clinical trials.
- Researchers responded by developing explicit criteria for categories of interest (e.g., New Haven Schizophrenia Index, Feighner criteria, RDC)
Diagnostic Reliability Has Improved

- DSM-III and DSM-5 field trials and ICD-10 and ICD-11 field trials demonstrated improved reliability compared to pre-DSM-III

- However, improved diagnostic reliability does not necessarily lead to improvements in diagnostic validity
Assumption For DSM/ICD Moving Forward

- DSM-III assumed that, as in general medicine, the phenomenon of symptom covariation was an indication that their presentation could be explained by a common underlying etiology and pathophysiology.
- Over time, underlying etiological and pathophysiological factors would be elucidated and incorporated into diagnostic definitions (e.g., biomarkers).
However...

- In the 38 years since the publication of DSM-III, this goal has remained elusive.

- Despite the discovery of many promising candidates over the years, no laboratory marker has been shown to be diagnostically useful for making any DSM or ICD diagnosis.
Other Indicators of Problematic Validity of DSM/ICD Approach

- High rates of diagnostic comorbidity
- Lack of treatment specificity for the diagnostic categories
- Evidence that separate syndromes have shared genetic basis
- High rates of patients requiring the use of the diagnostically unspecific residual Not Otherwise Specified (NOS) category.
Has the time been reached for another paradigm shift?
Three Approaches Moving Forward

- **Iterative:**
  - Syndromal/categorical approaches with dimensional components (severity): DSM-5 and ICD-11

- **Paradigm Shifts:**
  - Empirical Dimensional approaches (HiTOP)
  - Etiological/brain circuitry approaches (RDoC)
DSM-5 Aspired for a Paradigm Shift During Its Development

- Wish to make DSM-5 more “etiological” and connected to underlying neuroscience and genetics
  - Not a single biological test is part the definition of a mental disorder; desperate to include a biomarker
- Wish to make DSM-5 more dimensional
Fate of DSM-5 “Paradigm Shift”

- Genetics, neuroimaging, biological markers, etc. NOT be included in definitions of mental disorders

- Limited adoption of dimensions
  - Dimensional measures (including WHODAS) in appendix
  - Dimensional PD proposal also placed in appendix
  - Autism Spectrum Disorder and Substance Use Disorder “decategorized”: single category with levels of severity
Continuous Iterative Approach

- Rather than updating DSM at arbitrarily set (and increasingly extended) intervals, mechanism set up to allow DSM to be modified on a continuous basis

- Standing DSM Steering Committee will review proposals submitted to DSM-5 website ([www.dsm5.org](http://www.dsm5.org)) according to strict empirical criteria

- ICD-11 will likely allow for changes on an ongoing basis
HiTOP: Dimensional Paradigm Shift
HiTOP: Empirical Dimensional Approach

- HiTOP – Hierarchical Taxonomy of Psychopathology
- Developed by consortium of 75+ quantitative nosologists (international, although primarily US-based)
- Still in early stages of development
- HiTOP rejects DSM approach—aims to be an alternative comprehensive classification
Basic HiTOP Assumptions

- Psychopathology is inherently dimensional (i.e., no natural discontinuities)
- Better reflection of “reality”
- Advantages for etiological research
  advantage: framework for understanding the form and nature of relationships between cumulative risk factors, manifest psychopathology and outcomes
Hierarchical Organization

- Classification organized in hierarchical levels based on empirical data regarding the degree of co-occurrence vs. distinctiveness of the mental phenomena.

- Concepts higher in the hierarchy (spectra and subfactors) are more general and broad and summarize the tendencies for lower concepts to co-occur in specific patterns.

- Concepts lower (symptoms, traits) are more specific and narrow.
“Syndromes” in HiTOP vs. DSM

- Syndromes consist of symptoms that co-vary
- DSM syndromes largely based on clinical observation of co-variation, codified by expert consensus process; categorical constructs
- HiTOP syndromes are constructed empirically;
Example: Depression and Anxiety

- Tendency to experience anxiety is correlated with somatic symptoms and pathological depression and but still distinguishable.
- In a categorical system: results is comorbidity (separate anxiety, depression, and somatic symptom dx).
- In hierarchical system, higher level dimension (distress) that reflects correlations, and lower order dimensions of the “pure” symptoms.
Current Overall HiTOP Hierarchical/ Dimensional Model
Model Differences
Foci of HiTOP Research Consortium

- Continued research into organization of broad spectra of psychopathology
- Connection between personality and psychopathology
- Research utility of constructs
- Translation into clinical practice
- Development of assessment instruments
Weaknesses of HiTOP Approach

- Based on traditional assessment instruments from cross-sectional studies
- Essentially a “snapshot” of symptom distress at time of investigation; no historical information
- Lack of stability of higher order spectra structure over time;
Strengths of HiTOP Approach vs. Categorical Approach

- Addresses arbitrary disorder boundaries by eliminating thresholds
- Addresses excessive comorbidity by identifying higher order dimensions that reflect associations among lower order dimensions
- Aligns better with genetic architecture
RDoC: Etiologically-Focused Paradigm Shift
NIMH Research Domain Criteria (RDoC) Project

- RDoC is a research framework: will use multiple levels of analysis in defining constructs for study (e.g., imaging, physiological activity, behavior, symptom self-report) from which investigators can choose independent variables
- Dimensional system spanning range from normal to abnormal
- Agnostic about current disorder categories; begins with current understandings of brain-behavior relationships and links then to clinical phenomena
- Not intended to replace current diagnostic systems
RDoC Assumptions

- Mental illness is conceptualized as brain disorders
  - in contrast to neurological disorders with identifiable lesions, mental disorders can be addresses as disorders of brain circuits

- Dysfunction in neural circuits can be identified with tools of clinical neuroscience
  - e.g., electrophysiology, functional neuroimaging, and new methods for quantifying connections in vivo

- Data from genetics and clinical neuroscience will yield biosignatures that will augment clinical signs and symptoms
  - e.g., fear extinction, reward, impulse control
**RDoC Matrix**

- Rows correspond to specified functional dimensions of behavior (and implementing genes and circuits) called *Constructs*.
- Related constructs are grouped into five major *Domains of Functioning*: negative affect, positive affect, cognition, social behavior, and arousal/regulatory systems.
- Columns represent *units of analysis* used to study the constructs (e.g., genes, circuits, behavior).
- Circuits represent the core variables and constrain the number of constructs.
<table>
<thead>
<tr>
<th>RDoC Domain</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Negative Valence Systems</td>
<td>Responses to aversive situations or contexts, such as fear, anxiety, and loss.</td>
</tr>
<tr>
<td>Positive Valence Systems</td>
<td>Responses to positive motivational situations or contexts, such as reward seeking, consummatory behavior, and reward/habit learning.</td>
</tr>
<tr>
<td>Cognitive Systems</td>
<td>Responsible for various cognitive processes (attention, perception, declarative memory, language, cognitive control, working memory)</td>
</tr>
<tr>
<td>Systems for Social Processes</td>
<td>Mediates responses to interpersonal settings, including perception and interpretation of others’ actions.</td>
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<tr>
<td>Arousal/Regulatory Systems</td>
<td>Responsible for generating activation of neural systems and providing appropriate homeostatic regulation of such systems as energy balance and sleep.</td>
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</tbody>
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Constructs/Subconstructs of Positive Valence Domain

- **Reward Responsiveness**
  - Reward anticipation
  - Initial response to reward
  - Reward satiation

- **Reward Learning**
  - Probabilistic and reinforcement learning
  - Reward prediction error
  - Habit

- **Reward Valuation**
  - Reward (probability)
  - Delay
  - Effort
# Negative Valence Domain

<table>
<thead>
<tr>
<th>Constructs</th>
<th>Genes</th>
<th>Molecules</th>
<th>Cells</th>
<th>Circuits</th>
<th>Physiology</th>
<th>Behavior</th>
<th>Self-Report</th>
<th>Paradigms</th>
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<tbody>
<tr>
<td>Acute threat (fear)</td>
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<td>Potential Threat (anxiety)</td>
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<tr>
<td>Sustained Threat</td>
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<tr>
<td>Loss</td>
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<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>LEDS (life events and difficulties schedule)</td>
<td>STRAIN</td>
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<tr>
<td>Frustrated Non-reward</td>
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<td>Sadness eliciting film clips</td>
</tr>
</tbody>
</table>
Circuits in “Loss” Construct in Negative Valence Systems

- Amygdala
- Default mode network
- Dorsolateral prefrontal cortex
- Habit systems (striatum/caudate/accumbens)
- Hippocampus
- Insula
- Orbitofrontal cortex
- Parietal cortex
- Posterior cingulate
- Paraventricular nucleus
- Reward circuitry
- Ventromedial prefrontal cortex
Behaviors in “Loss” Construct in Negative Valence Systems

- Amotivation
- Anhedonia
- Attentional bias to negative valence information
- Crying
- Executive function
- Guilt
- Increased self-focus
- Loss of drive
- Loss-relevant recall bias
- Morbid thoughts
- Psychomotor retardation
- Rumination
- Sadness
- Shame
- Withdrawal
- Worry
Selection of candidate constructs

- Constrained by whether particular brain circuit could be specified that implements the behavioral dimension (e.g., inattention not included because it is spread diffusely over many brain areas)

- Attempts made to constrain “grain size” to keep list tractable: sub-constructs for different types of aggression not included

- Based on current neurobehavioral research base
Example of a Study

- Study of fear circuitry might include all patients presenting to an anxiety clinic (as opposed to subjects with particular DSM/ICD diagnoses)
- Independent variable: defense system reactivity (e.g. Fear-potentiated startle)
- Dependent variables: scores on fear, distress, and symptom measures
Caveats re: Impact on Practice

- Whether RDoC will alter clinical practice (and impact future clinical classifications) will depend on how well RDoC performs for research, i.e., how well the new molecular and neurobiological parameters predict prognosis and treatment response
  - e.g., if a BDNF polymorphism identifies people with anxiety disorders who do not respond to CBT
  - If a copy number variant defines a form of psychosis with high remission rates
  - If neuroimaging yields a subtype of mood disorders that consistently respond to lithium
DSM/ICD vs. HiTOP vs. RDoC

Three competing classification systems

- Only DSM/ICD function as a classification system;
- HiTOP is a hierarchical model under development that aspires to replace DSM/ICD
- RDoC is a research framework for understanding etiology
Prognostications for the Future of Classification

- DSM/ICD approaches will be used less and less for research on etiology/pathophysiology/genetics
- DSM and ICD will continue to be separate classifications
- Dimensions will play an increasingly important role in DSM/ICD approaches
- Research findings guided by RDoC and HiTOP approaches will improve validity of DSM/ICD categories by reducing heterogeneity