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Kraepelin's Crumbling Twin Pillars: Using Biology to Reconstruct Psychiatric Nosology From the Bottom Up

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> *No experienced psychiatrist will deny that there is an alarmingly large number of cases in which it seems impossible, in spite of the most careful observation, to make a firm diagnosis… it is becoming clear that we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation of the problem may be incorrect.*
>
> —Emil Kraepelin (1)

Mia is a 19-year-old girl with brown hair and freckles whose favorite thing in the world is eating ice cream at the beach on Sunday afternoons. She was first admitted to a psychiatric unit 8 months prior, forced to leave school after her college roommates said she was "not acting like herself": she stayed up all night for days in row, was speaking too quickly to be understood, and scared people with her erratic and disinhibited behavior. She seemed improved after discharge from the hospital, sleeping normally and eventually returning to school. Again, though, things went awry: she began staying up all night, pacing her room; she stopped changing her clothes or showering; and, ultimately, she was readmitted to the hospital after smashing a TV with a baseball bat to "purge the demons." On exam, Mia seemed distant, confused, and lost. Sorting through her record—including a family history of both bipolar disorder and schizophrenia—the treatment team also felt lost, wondering which of these diagnoses fit best.

Over a century ago, Emil Kraepelin developed an approach to psychiatric nosology that—remarkably—still stands today, seldom challenged by contemporary clinicians (1). In 1896, trying to make sense of the diagnostic dilemma of psychosis, he hypothesized a fundamental distinction between diseases that were steady and progressive, with poor outcomes, versus those that were cyclical and had relatively better outcomes (1). Specifically, he defined dementia praecox as the "sub-acute development of a peculiar simple condition of mental weakness occurring at a youthful age," placing it alongside degenerative disorders; differentiating it from manic-depressive illness, which he observed to be recurrent and episodic, with between-episode recovery (1,3).

Kraepelin's distinction has fared so well that, as Tim Crow pointed out 100 years later, "no respectable textbook is without separate chapters on the two 'diseases' and much of the

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impetus behind modern diagnostic criteria is directed at distinguishing these supposed entities with maximum reliability" (4). Among the most famous attempts to refine Kraepelin's diagnostic division are Kurt Schneider's efforts to determine psychotic symptoms specific to schizophrenia, like thought broadcasting (2). As such specificities were later disproved, the diagnostic boundaries became blurrier. This is exemplified by the introduction of schizoaffective disorder ("the in-between cases") into DSM-III-R (5), and the emergence of a "continuum" hypothesis—extending all the way through individuals with minor psychotic features and schizotypal or paranoid personality disorders (2,6). Patients like Mia may, after all, be more common than those who fit the molds of Kraepelinian prototypes.

The vast efforts on classification are the byproduct of generations of scientists struggling to interpret an inherently constrained dataset: observable behavior. Researchers have sought to define diseases—specific illnesses with shared pathophysiology. But without having access to relevant biological data (let alone a "gold standard" diagnostic test) what have emerged are syndromes—phenomenological descriptions of similar presentations (4). The history of medicine is replete with similar examples; e.g., fever and heart failure were both once viewed as well-defined diseases before they were shown to be syndromes with a range of underlying causes.

With respect to this particular issue, Kraepelin himself ultimately realized that he was wrong, writing that "we cannot satisfactorily distinguish these two diseases" (1,4). More than a hundred years of continued study have confirmed this conclusion (1,5). And yet, Kraepelin rightfully continues to be regarded as one the most important figures in the history of medicine. Not because of the specific details of the distinction he sought to draw; rather, his greatest contribution was in hypothesizing the existence and scientific accessibility of "natural disease entities" (1). In doing so, Kraepelin established psychiatry as a clinical science to be approached with the same empirical rigor as the rest of medicine (1,3). As is quite fitting for psychiatry, his greatest contribution was one of process, not content.

Times have changed. The world we live in today would be unfathomable to Kraepelin. We now have a wide range of tools—including structural and functional neuroimaging, electrophysiology, neurogenetics, and powerful microscopic approaches—that allow us to study the brain with unprecedented resolution. Finally, the interplay between neuroscience and clinical psychiatry gives us the potential to revisit one of our field's most basic questions: how can we define diseases based on their underlying pathophysiology rather than only externally observable behaviors?

One of the most exciting efforts in this regard is the Bipolar-Schizophrenia Network on Intermediate Phenotypes project, which attempts to redefine psychotic disorders from the bottom up (2,7). In this ambitious study, a large cohort of individuals diagnosed with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder type I, in addition to first-degree relatives and healthy control subjects, have been recruited for clinical characterization and phenotyping. The goal is to assess the neurobiological validity of the traditional diagnostic entities and look for alternative ways to understand and categorize psychotic illnesses.

In their first published work, the Bipolar-Schizophrenia Network on Intermediate Phenotypes investigators described a novel approach that was designed to be agnostic to clinical diagnoses (2,7). They began by collecting data on a wide range of potential biomarkers, including tests of cognitive control, electrophysiologic measures of sensorimotor reactivity, and both functional and structural neuroimaging. From this panel, they identified six biomarkers with which they were able to parse the study population into three neurobiologically distinct groups that they named “Biotypes” (2,7). Of note, the defining features of each Biotype were distinct from those used to categorize clinical populations in the past—indeed, most could not be observed during a standard clinical interview. Moreover, not only did the Biotypes show within-group homogeneity, but also they crossed traditional diagnostic boundaries: all three classic diagnoses were represented in each Biotype, therefore challenging the notion of a “continuum” (2,7). These data illustrate how we may now be in a position to reclassify a syndrome into diseases with multiple, distinct underlying causes (Figure 1).

This transformation in diagnostic approaches has unmistakable parallels within other areas of medicine (3,4). For example, advances in molecular biology have helped clinical oncology evolve from characterizing cancers with descriptive TNM staging systems to identifying specific mutations and aberrant biological processes (e.g., disruption of growth factors, angiogenesis, immune evasion). Improved classification has led to more targeted treatments, including gene therapies and immunotherapy, resulting in better outcomes in selected patients. The hope is that our field will be able to emulate the transition from descriptive syndromes to discrete diseases, aligning mental illnesses more closely with the functional operations of the human mind; first for psychoses and ultimately for other conditions.

This issue of *Biological Psychiatry* contains an intriguing study by Nazeri *et al.* (8) that follows this tradition, helping us to move toward biologically based definitions of psychopathology. The authors used a novel diffusion-weighted magnetic resonance imaging acquisition and modeling technique to characterize gray matter microstructure among patients with bipolar disorder type I and schizophrenia as well as healthy control subjects. They also sought to establish the relationship between imaging-driven microstructural measures and neurocognitive performance. As with the Bipolar-Schizophrenia Network on Intermediate Phenotypes, the results of their work suggest that it is possible to capture meaningful biological distinctiveness that traditional diagnoses overlook: in vivo histopathology may provide powerful biomarkers. In conjunction with machine-learning techniques, such biomarkers could be extraordinarily powerful tools (2,8,9).

We are on the cusp of a revolution: more effective diagnostic approaches could transform the clinical practice of psychiatry (9). Today, at least a third of patients do not respond optimally to our standard-of-care treatments. By redefining mental illnesses based on their biology, we can do better. We can refine our practice with more unambiguous and homogeneous diagnoses, early intervention, personalized treatments, and improved outcomes. The recent work by Drysdale *et al.* (10) is an inspiring example (for major depressive disorder) of what such advances might look like, tying biomarkers to specific treatments.

For psychoses, it is clear that Kraepelin's "twin pillars" have long since fallen—largely due to the overwhelming evidence that they are genetically related (2,11). Whether Mia has bipolar disorder or schizophrenia may be biologically meaningless. By continuing to explore the neurobiology beneath the symptoms we can construct a new biomarker-based classification system brick by brick. There is a long way to go—new approaches will need to be refined and validated. But with the exponential increase in computational power and the example of rapid progress elsewhere in medicine, there are plenty of reasons to be hopeful. As a field, we may be on our way to building sturdier, more reliable, and likely more numerous pillars that will keep the roof from crashing in again and allow clinicians to effectively diagnose and treat patients like Mia.

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References

1. Kraepelin E. Die Erscheinungsformen der Irreseins: Zeitschrift für die gesamte Neurologie und Psychiatrie. 1920. Themes and Variations in European Psychiatry. Edited by Hirsh SR, Sheperd M Bristol, England, J Wright. Cited by Pearlson GD (2015): Etiologic, phenomenologic, and endophenotypic overlap of schizophrenia and bipolar disorder. Annu Rev Clin Psychol. 1974; 11:251–281.
2. Pearlson GD. Etiologic, phenomenologic, and endophenotypic overlap of schizophrenia and bipolar disorder. Annu Rev Clin Psychol. 2015; 11:251–281. [PubMed: 25581236]
3. Kendler K. The transformation of American psychiatric nosology at the dawn of the twentieth century. Mol Psychiatry. 2016; 21:152. [PubMed: 26692416]
4. Crow T. The continuum of psychosis and its genetic origins. The sixty-fifth Maudsley lecture. Br J Psychiatry 156:788–797. Cited by Greene T (2007): The Kraepelinian dichotomy: The twin pillars crumbling? Hist Psychiatry. 1990; 18:361–379.
5. Kendler KS, McGuire M, Gruenberg AM, Walsh D. Examining the validity of DSM-III-R schizoaffective disorder and its putative subtypes in the Roscommon Family Study. Am J Psychiatry. 1995; 152:755–764. [PubMed: 7726316]
6. Craddock N, Owen MJ. The beginning of the end for the Kraepelinian dichotomy. Br J Psychiatry. 2005; 186:364–366. [PubMed: 15863738]
7. Clementz BA, Sweeney JA, Hamm JP, Ivleva EI, Ethridge LE, Pearlson GD, et al. Identification of distinct psychosis biotypes using brain-based biomarkers. Am J Psychiatry. 2015; 173:373–384. [PubMed: 26651391]
8. Nazeri A, Mulsant BH, Rajji TK, Levesque ML, Pipitone J, Stefanik L, et al. Gray matter neuritic microstructure deficits in schizophrenia and bipolar disorder. Biol Psychiatry. 2017; 82:726–736. [PubMed: 28073491]
9. Barch DM. Biotypes: Promise and pitfalls. Biol Psychiatry. 2017; 82:2–3. [PubMed: 28619250]
10. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med. 2017; 23:28–38. [PubMed: 27918562]
11. Cardno AG, Owen MJ. Genetic relationships between schizophrenia, bipolar disorder, and schizoaffective disorder. Schizophr Bull. 2014; 40:504–515. [PubMed: 24567502]

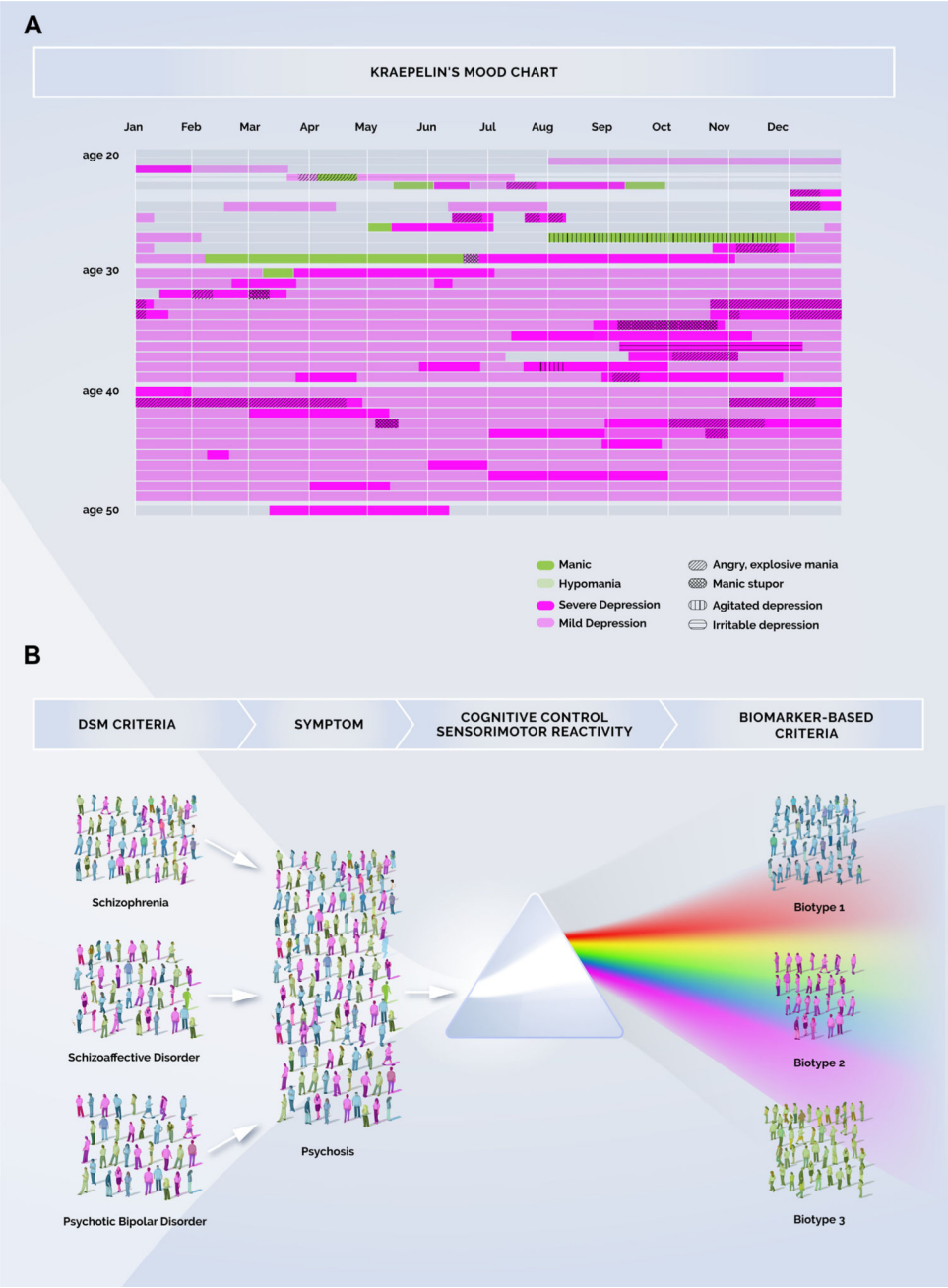

Figure 1.

This figure contrasts the research armamentarium available to Kraepelin in the early 20th century and the biomarker panel used by the Bipolar-Schizophrenia Network on Intermediate Phenotypes investigators 100 years later. **(A)** Kraepelin's depiction of a patient's illness course—across over 30 years—from intermittent episodes to continuous cycling. The occurrence of mania, hypomania, and depression were meticulously recorded in a diagrammatic form, on a monthly basis. Kraepelin noted the age of the patient on the left side of the diagram, and the months of the year across the top row, with shades of different colors indicating the severity of each episode. Additionally, he further characterized each

presentation by crosshatching in the color of the opposite affective pole, distinguishing a variety of types of mania, manic stupor, and mixed states. **(B)** The Bipolar-Schizophrenia Network on Intermediate Phenotypes consortium's approach of pooling individuals across three diagnostic categories and then categorizing them into "Biotypes" on the basis of biomarkers. Such approaches may have greater biological validity and better clinical predictability than diagnostic categories that are rooted only in observable behavior.