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Studying mental health disorders as systems, not syndromes

Eiko I. Fried

Department of Clinical Psychology, Leiden University

www.eiko-fried.com, eikofried@gmail.com

Abstract

Over the last decades, many specialists have worked tirelessly to improve the lives of people affected by mental health problems. Mental health has also received increased political and funding priority. Despite these global efforts, however, progress in understanding, predicting, and treating mental disorders remains disappointing. In this piece, I discuss two roadblocks. The first is diagnostic literalism, the tendency to take mental health diagnoses for more than they are. The second is reductionism, the isolated study of individual elements of mental disorders. Conceptualizing mental disorders as complex systems with inter-dependent hierarchies of biological, psychological, and social elements provides us with new lenses through which we can study mental disorders. It also promises to offer new levers, similar to other disciplines such as biology and ecology. Embracing the complexity of mental disorders successfully will require opening our ivory towers to theories and methods from other fields with long and rich traditions, including network and systems sciences.

"O chestnut tree, great rooted blossomer /

Are you the leaf, the blossom or the bole?"

W. B. Yeats, Among School Children, 1928

Introduction

In this piece, I argue that diagnostic literalism and reductionism have hindered progress in understanding, predicting, and treating mental disorders. Adopting a complex systems perspective offers important ways forward, and allows us to draw on theoretical and methodological tools from disciplines such as network and systems sciences.

Diagnostic literalism

Diagnoses of Generalized Anxiety Disorder, Obsessive Compulsive Disorder, schizophrenia, and Major Depressive Disorder (MDD) can be clinically useful tools to facilitate treatment selection, planning, prognosis, and communication. Psychiatric manuals, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), list mental health diagnoses and criteria by which they are diagnosed. An episode of MDD, for example, can be diagnosed if a person meets at least 5 of 9 symptom criteria, for 2 weeks, along with considerable impairment of functioning. But why these particular 9 symptoms, why 2 weeks, and in particular, why 5 out of 9 symptoms?

The answer to the latter question was provided by Cassidy in an interview in 1980: "It sounded about right" (Kendler et al., 2010). Who was Cassidy? American Psychiatry in the 1950s and 60s was dominated by psychoanalytic theory, where diagnoses were often viewed as an insult to patients. In a concerted effort to introduce a medical model to psychiatry, the Feighner criteria were published in 1972, delineating observable signs and symptoms for common mental disorders, stressing the important of psychiatric diagnoses. The Feighner criteria for depression relied heavily on a phenomenological study by Cassidy, published in 1957. Feighner criteria were influential for DSM-III, and today, over 6 decades later, many of the criteria Cassidy proposed are part of a DSM-5 diagnosis of MDD.

Similar developments can be observed for other mental health diagnoses. Some of these changes, such as the transition from a categorical to a dimensional model of personality disorders in DSM-5, were supported by data. But most diagnostic categories and thresholds have been shaped predominantly by historical forces, not empirical evidence (Lilienfeld, 2014; Lux et al., 2010; Scull, 2021; Zimmerman et al., 2006). If Wernicke, a rival of Kraepelin, had not died prematurely in a bicycle accident, today's DSM may well have looked somewhat (Kendler, 2016).

If absolute thresholds within one construct (water vs steam) or between different constructs (helium vs magnesium) cannot be discovered in nature, they need to be *manufactured*. This does not make them any less important: it is crucial to differentiate between normal and abnormal blood pressure, given that long-term high blood pressure is associated with numerous adverse outcomes. But blood pressure lies on a continuum, and the threshold for abnormal blood pressure remains somewhat arbitrary (Unger et al., 2020). DSM diagnoses and thresholds for common mental disorders work in the same way, as clinically useful tools with heuristic value. But they don't have clear thresholds like water and steam, or can be clearly separated like helium or magnesium.

Seven robust phenomena support this view. (1) Inter-rater reliability for some common mental disorders is low (Regier et al., 2013). (2) For many disorders, diverse measures have been proposed, which differ considerably in content (Fried, 2017; Santor et al., 2006). (3) Many diagnoses feature marked symptom heterogeneity, to the degree that two patients can share the same diagnosis without sharing a single symptom (Fried et al., 2020). (4) There is considerable comorbidity between diagnostic categories (Kessler et al., 2005). (5) There are many transdiagnostic risk factors shared among mental disorders. (6) Disease pathways feature both equifinality (different starting points may lead to the same diagnosis) and multifinality (similar starting points may end up with different diagnoses). And (7) there is overwhelming evidence that many mental health problems lie on a dimension of severity, rather than being best described as categories (Haslam et al., 2012).

None of these issues occur in the nosology of chemistry, where helium and magnesium are clearly defined, not heterogeneous, can be neatly separated, and perfectly diagnosed. In contrast, psychiatric nosology appears to have failed to reach its goal, described over a century ago: “it is the main task of psychiatry to find the natural disease units, which are distinct, in principle and without overlap, from each other and which have the same symptoms, course, cause, and physical abnormalities” (Jaspers 1913, cited in (Heckers et al., 2021). This is not surprising, and similar to many other classification tasks, such as biological species. Beavers and elephants are not like helium and magnesium either. In fact, the notion that species have unchanging, sufficient and necessary properties that clearly define them is inherently pre-Darwinian (Fried, 2015; Wilson et al., 2007).

The superimposition of categorical diagnoses on the complex landscape of mental health problems explains the robust phenomena I listed above (Hyman, 2021). As Ash put it in 1949: “it is likely that the lack of congruity between the diagnostic label and the complexities of the biodynamics of mental structure is itself at the heart of diagnostic failure” (Ash, 1949). While many clinicians and researchers are aware of these complexities, clinical research is often carried out as if DSM categories cut nature at her joints. Scientific studies often take diagnoses for more than they are, which I refer to as *diagnostic literalism*. Case-control studies dominate the literature, where a healthy control group is compared to a group diagnosed with one specific mental disorder, regarding some variables of interest. Because mental health categories and thresholds are *manufactured* rather than discovered, the question remains whether such designs are optimally positioned to inform research on psychopathology (Cai et al., 2020; Hitchcock et al., 2021). Of note, this position should not be mistaken view the view that mental disorders do not exist, do not involve suffering, or should not be treated. My point is that our *categorization* of mental disorders remains somewhat arbitrary.

Reductionism

A simple mechanical system, such as a bicycle, consists of parts that relate to each other: a pedal moves a cogwheel, which moves a chain, which moves another cogwheel, and so on (A→B→C). To understand how this system functions, we can disaggregate it, analyze its more tractable components, and put it back together. This approach has been remarkable successful, and is known as *reductionism*: figuring out the properties of the whole given the parts. As demonstrated in many sciences throughout the second half the 20th century, however, reductionism has limits when systems become increasingly complex, such as the stock market, the weather, or the internet (Barabási, 2012; Pessoa, 2022). While there is some value studying the biology, psychology, and sociology of mental health in isolation, the integration of these levels is a crucial step too rarely taken.

One of many examples of a lack of integration is biological reductionism, a framework that has dominated our research landscape since the 1980s, and constrained research funds, health-care policy, and clinical service delivery (Borsboom et al., 2019; Miller, 2010; Scull, 2021). While I don't know if individual researchers or organizations hold the view that mental disorders can be *reduced* to biology—reduced in the sense that they are *nothing more* than biology (van Riel & van Gulick, 2019)—research and funding priorities have often progressed as if this position as endorsed. Strategic directives from the National Institute of Mental Health (NIMH), for instance, state that mental disorders are "brain disorders", "brain-circuit disorders", or "dysfunctions of neural circuits" that can be "identified with tools of clinical neuroscience" and treated by "tuning these [neural] circuits", ultimately leading to "neuroscience-based psychiatric classification" (Insel et al., 2010; Insel & Cuthbert, 2015). This moves every aspect of mental health—psychiatric nosology, individual diagnosis, dysfunction, and treatment—to the level of biology. This focus is also reflected in conclusions of large-scale consortia. For example, a cross-sectional mega-analysis comparing ADHD patients and healthy controls identified several group differences in brain structure, with small effect sizes (Hoogman et al., 2017). The authors concluded that "... patients with ADHD have altered brains; therefore ADHD is a disorder of the brain". Although psychological variables such as personality traits are more strongly related to ADHD than these brain structures, one would hardly conclude that "therefore ADHD is a disorder of the personality".

Biological psychiatry has led to considerable insights about how human genes and brains work, but has told us relatively little about the biology of specific mental disorders. The American Psychiatric Association concluded that "neuroimaging has yet to have a significant impact on the diagnosis or treatment of individual patients in clinical settings"

(First et al., 2018). Genome-wide association studies have identified hundreds of hits for common mental disorders, but variants are often related to multiple psychiatric and medical diagnoses, other variables such as personality traits or smoking (Cai et al., 2019), and have little clinical utility given the very small amount of explained variance (Kapur et al., 2012; Kendler, 2012, 2019; Scull, 2021). Celebrated breakthroughs in the field, such as blood tests for depression, have quickly and quietly disappeared (Bilello et al., 2015). And entire literatures, such as the depression candidate-gene literature with considerably over a 1,000 published papers, appear to have been built on false positive results, with not one single effect robustly replicating in large-scale analyses (Border et al., 2019). NIMH director Insel concluded, after "13 years at NIMH really pushing on the neuroscience and genetics of mental disorders [...] I succeeded at getting lots of really cool papers published by cool scientists at fairly large costs—I think $20 billion—I don't think we moved the needle in reducing suicide, reducing hospitalizations, improving recovery for the tens of millions of people who have mental illness" (Rogers, 2017).

This lack of progress is not because biology is not crucially involved in predisposing or mediating disease trajectory (Cai et al., 2020; Hitchcock et al., 2021)—it arises because we have focused on studying the biology of particular DSM labels that are likely the wrong targets, and because we have studied biology (at least largely) in isolation. Diagnostic literalism and reductionism have formed a vicious cycle of reification, and continue to do so whenever we talk about "risk factors for schizophrenia", "genes for major depression", and "symptoms of PTSD". Measurement (we have a measure for X and commonly use it, hence X exists) (McPherson & Armstrong, 2021), external validation (Y correlates with external constructs, hence Y exists), and our natural tendency of essentialize constructs have provided fertile ground for this vicious cycle (Adriaens & De Block, 2013).

Mental disorders as complex systems

In summer of 2019, my bicycle broke down, on a remote forest road. Methodological reductionism came to the rescue, providing a powerful approach to analyze each part independently, and identify by investigating specific parts why and how the whole did not work. But mental disorders are not like bicycles: they arise within a person over time, and are best understood as phenomena resulting from interactions of biopsychosocial elements organized in hierarchies of inter-dependent levels (Fried & Robinaugh, 2020; Kendler, 2012).

Such complex systems show *emergence*, i.e. macro-behaviors that cannot be explained or understood by the elements from which they arise. We can *reduce* a bicycle to its parts, and fully understand the macrolevel from the microlevel. But even systems following very simple rules can show emergent properties that are not predictable from the microlevel (Pessoa, 2022; Robinaugh et al., 2021). For example, prey and predator populations simultaneously depend on each other (A⟷B). Such vicious cycles, like the well-established feedback loop between fear and avoidance, are common in mental disorders (Robinaugh et al., 2019).

Complex systems have features that are best interrogated from a systems perspective. They can have several stable states, such as a healthy and a psychotic state. They can show phase transitions between states, which can be abrupt or gradual. Transitions between these attractor states are influenced by different kinds of resilience, such as engineering resilience (Robinaugh et al., 2019), describing how long it takes a system to return back to normal after a perturbation. Early warning signals—such as a decline in engineering resilience—may reveal information about upcoming transitions before they occur (van de Leemput et al., 2014).

A systems view highlights the heuristic utility of psychiatric nosology and reductionism. It also provides a powerful antidote against taking these approaches too far, which are best employed as simplifying, useful epistemological tools with the goal to understand the world, rather than ontological convictions about how the world is. As Hoche already stated in 1912, psychiatry is based on the “unassailable belief that even in the field of psychiatry it must be possible to discover clearly defined, pure and uniform forms of illness” (Hoche, 1912). A systems view where disorders emerge out of complex networks challenges this view of clearly separable disease entities, and mono-causal thinking about their etiologies (Kendler, 2012, 2019). Further, it also calls into the question the current privileged epistemological status of symptoms as *the* criteria for diagnoses of mental disorders. Finally, it also aligns closely with how many clinicians think about and treat mental illness (Hayes, 2020; Hayes et al., 2015; Hayes & Strauss, 1998; Schiepek, 2009).

Moving forward: on lenses and levers

If we take the idea of mental disorders as complex systems seriously, what are our next steps?

First, we can continue our study of various microlevels, but should consider to widen our focus on elements that go beyond isolated biological markers or symptoms. Second, we should study systems of elements within respective domains. For example, clinical neuroscience has seen shifts towards studying relations among brain structures, rather than brain structures in isolation (Poldrack & Farah, 2015), and clinical psychology has seen efforts to study relations among affect states and symptoms (Fried et al., 2021). Third, understanding mental disorders as dynamic entities that can no longer be decomposed into simple cause-effect relations highlights the importance of studying mental health *systems* holistically. Doing so successfully will require building more interdisciplinary bridges, and open our ivory towers to theories and methods from network and systems sciences, field with a long and rich tradition (Ahn et al., 2006; Barabási, 2012; von Bertalanffy, 1972). Fourth, complex systems often behave in ways that are not intuitive: Small changes in input can radically change macrobehavior, and understanding the cause of a phase transition will often not provide insight into levers to move the system back to the original state. Building computational models using mathematical language will allow us a more thorough interrogation of our theories, compared to narrative theories that often remain ambiguous (Fried, 2020; Robinaugh et al., 2021).

Many efforts to embrace the complexity of mental health disorders are already on the way. For example, while NIMH's Research Domain Criteria originally defined mental disorders as brain disorders (Insel et al., 2010), recent work highlights the initiatives' integrative nature (Beauchaine & Hinshaw, 2021). Such work brings into sharper focus open questions. How to best define and classify mental disorders if they are not natural kinds? How do systems of mental health and illness interact with other systems such as political, health care, or social systems (Fried & Robinaugh, 2020)? If systems consist of interconnected hierarchies of micro and macrolevels, what are the right levels—and what are the right elements—and are some levels more foundational than others (Eronen, 2019)? While the level of quarks is, in a very literal sense, foundational for the formation of human brains, it is not relevant for studying genes, brains, or clinical phenotypes.

My hope is that a systems view provides us with new lenses through which we can study mental disorders, and has the potential to provide new levers, similar to other disciplines such as biology, medicine, and ecology where understanding systems has resulted in novel tools for intervention.

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