Studying mental health problems as systems, not syndromes

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Abstract

Despite decades of clinical, research and sociopolitical efforts, progress in understanding and treating mental health problems remains disappointing. I discuss two barriers that have contributed to a problematic oversimplification of mental illness. The first is diagnostic literalism, mistaking mental health problems (complex within-person processes) for the diagnoses by which they are classified (clinically useful idealizations to facilitate treatment selection and prognosis). The second is reductionism, the isolated study of individual elements of mental disorders. I propose to conceptualize people's mental health states as outcomes emerging from complex systems of biological, psychological, and social elements. I show that this framework explains many robust phenomena in our field, such as variability within diagnoses, comorbidity among diagnoses, and transdiagnostic risk factors. It helps us understand diagnoses and reductionism as useful epistemological tools to describe the world, rather than ontological convictions about how the world is. It provides us with new lenses through which we can study mental illness (e.g., attractor states, phase transitions), and new levers to treat them (e.g., early warning signals, novel treatment targets). Embracing the complexity of mental health problems requires opening our ivory towers to theories and methods from other fields with 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*

Psychiatric classifications systems like the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) categorize mental health problems into diagnoses: schizophrenia, major depressive disorder (MDD), PTSD, and so on. These diagnoses are further described by criteria, often specific symptoms. The history of defining an episode of MDD helps to clarify the crucial distinction between mental health problems and diagnoses by which they are classified.

In DSM-5, an episode of MDD can be diagnosed if a person meets at least 5 of 9 symptoms, for 2 weeks, along with considerable impairment of functioning. What data justify these particular criteria? In an effort to introduce the medical model to psychiatry, the Feighner criteria were published in 1972, delineating observable signs and symptoms for common mental disorders. For determining the symptoms of MDD, Feighner relied on a 1957 paper by Cassidy. The Feighner criteria were highly influential for DSM-III, and today, all MDD symptoms but one (constipation) proposed originally by Cassidy are preserved in DSM-5, with a similar threshold for clinical significance (at least 6 of 10 symptoms). When Cassidy was asked in 1980 about his reasoning behind these criteria, he responded that "it sounded about right" (Kendler et al., 2010).

Similar developments can be observed for other diagnoses. Many of DSM's iterations, such as the transition from a categorical to a dimensional model of personality disorders, were based on data. But psychiatric nosology is "a pragmatic compromise among multiple competing demands and constituencies" (Lilienfeld, 2014, p. 269), and has also been driven by adherence to precedent, patient advocacy, lobbying efforts, and goals to minimize stigma and avoid excessive prevalence rates. These sociopolitical forces have shaped the DSM, as have historical forces and path dependence (Lilienfeld, 2014; Scull, 2021). Feighner, for example, could have relied on one of the many frameworks competing with Cassidy's views, leading to a slightly different DSM-5 today. And if Wernicke (an influential competitor of one

of the founding fathers of psychiatric nosology, Kraepelin) had not died prematurely in a bicycle accident, DSM may look somewhat different, too (Kendler, 2016a).

Diagnostic literalism

Mental health problems are complex, biopsychosocial processes that unfold in individuals over time. Diagnoses, on the other hand, are categorical idealizations designed as clinically useful tools to facilitate treatment selection, planning, prognosis, and communication. Mental disorders can be *described* as diagnoses, and that description can be immensely helpful for research and clinical practice. But they are not the same kind of thing. Conflating mental health problems with rough diagnostic proxies is called *diagnostic literalism* (Kendler, 2016b; Zachar, 2014), taking diagnoses for more than they are. Related concepts are *reification* or *essentialism* (Adriaens & De Block, 2013; Kendler et al., 2011).

Seven phenomena help to understand the difference between mental health problems and diagnoses (cf Fried et al., 2022 for details). (1) DSM, at least for most diagnoses, ignores causes and etiology. (2) Multiple classification systems for mental disorders exist, and diverse measures for diagnoses have been proposed that differ considerably in content (Fried et al., 2022). (3) Inter-rater reliability for some common mental disorders is low (Regier et al., 2013). (4) On the one hand, people within diagnoses are often somewhat similar. On the other, many diagnoses often show marked heterogeneity (Galatzer-Levy & Bryant, 2013). (5) There is considerable comorbidity between diagnostic categories, and many risk factors are transdiagnostic, i.e., shared among mental disorders (Eaton et al., 2015; Kessler et al., 2005). (6) Most mental health problems lie on a dimension of severity from absent to very severe, rather than being best described as categories—and various thresholds have been proposed where normal functioning turns into mental illness (Haslam et al., 2012; von Glischinski et al., 2021). (7) Disease pathways can feature equifinality (different starting points may lead to the same diagnosis) and multifinality (similar starting points may end up with different diagnoses).

These phenomena are expected results from superimposing clinical idealizations on the complex landscape of mental health problems (Hyman, 2021). Diagnoses do not carve

nature at her joints, but are pragmatic kinds: things constructed (in part based on evidence) to be useful for specific purposes (Kendler et al., 2011). Elements listed in psychiatry's DSM are different than elements listed in chemistry's DSM, the periodic table. Helium and magnesium are natural kinds, unchanging entities with necessary and sufficient properties that clearly define them. Every atom with 2 protons is helium, and helium's internal structure defines kind membership, not expert consensus. Unlike MDD and schizophrenia, there is only one definition of helium; helium can be diagnosed with perfect reliability; and it can be clearly distinguished from magnesium.

That does not mean psychiatric diagnoses have no utility. Like MDD and PTSD, long-term high blood pressure is associated with numerous adverse outcomes. Because blood pressure lies on a continuum, the definition of 'abnormal' blood pressure remains somewhat arbitrary and is, like the criteria for MDD and PTSD, the result of expert consensus taking into account non-scientific factors (Unger et al., 2020). Even the decision of the International Astronomical Union to remove Pluto from the list of planets was based in part on somewhat arbitrary definitions of what a planet ought to be, influenced by non-scientific factors, and heavily opposed by some astronomers (Zachar & Kendler, 2012).

Unfortunately, instead of studying processes between biopsychosocial elements giving rise to psychopathology, our field has devoted most of its resources studying the diagnostic labels that summarize the complex mental health states of people. Case-control studies dominate the literature, in which a healthy control group is compared to a group diagnosed with one specific mental disorder, and have resulted in "risk factors for schizophrenia", "genes for MDD", and "symptoms of PTSD". It is unlikely that such designs are optimally positioned to inform research on psychopathology, and the approach is flawed to the degree that mental health problems are not the diagnostic idealizations they are summarized as (**Figure 1A**).

A

B

Figure 1. (A) 20 hypothetical people diagnosed with PTSD (red) and MDD (blue) on 3 features X, Y, and Z, as a simplification of a much larger, n-dimensional feature space. From a systems perspective, the mental health states of these people are emergent properties arising out of interactions of numerous biopsychosocial features (e.g., risk factors, etiology, thoughts, biological predispositions, social environments). Mental health states cluster to some degree because features stand in probabilistic relations to each other (e.g., severe trauma often leads to intrusion symptoms). Superimposing diagnoses on this complex landscape leads to some people who are more typical of the diagnosis than others (black circles), results in groups that differ in some ways, and may ignore important inter-individual differences. **(B)** Two copies of the same playing card, held between two fingers, as a model for vulnerable and resilient mental health states. The left card is in a vulnerable state (orange dashed line) and can be moved with little energy to an alternative state (grey dashed line). The right card requires considerable energy to force a phase transition from the current attractor (green dashed line) to an alternative state (grey dashed line) and is therefore in a resilient state.

Reductionism

The second roadblock to better understand, predict, and treat mental health problems has been the isolated study of particular parts of mental disorders. A bicycle is a simple mechanical system consisting of parts that relate to each other: A pedal moves a cogwheel, which moves a chain, which moves another cogwheel, and so on ($A \rightarrow B \rightarrow C$). To fully understand how this system functions at the macro-level, it is sufficient to investigate its constituent components at the micro-level. This approach can be understood as *reductionism*: figuring out the properties of the whole given the property of its parts (Pessoa, 2022). It works well here because characteristics of bicycle parts remain unaltered when investigated in isolation. While reductionism has been astonishingly successful in science, its limits became clear in the 20th century when trying to understand increasingly complex systems, such as the stock market, the weather, the internet (Barabási, 2012; von Bertalanffy, 1972), or—as I argue here—mental disorders. This is because complex systems contain inter-dependent elements whose properties depend on each other, calling for the study of system parts *and their relationships* (Fried et al., 2022).

Further, the biopsychosocial nature of mental illness requires investigating parts and relationships *across levels*. A particular barrier to progress has been biological or explanatory reductionism—the idea that lower levels (i.e., biology) offer inherently superior explanatory power than higher levels (i.e., psychology, environment). This framework 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). Highly influential strategic directives from the National Institute of Mental Health (NIMH) are good examples, stating 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 the brain, and is apparent in many of NIMH’s efforts such as early work on the Research Domain Criteria (RDoC) (Insel et al., 2010).

Explanatory reductionism faces a number of challenges (Borsboom et al., 2019; Eronen, 2019). (1) Lower levels are not by definition superior in *explaining* higher-level processes: “No one would seek to understand the origin of hypertension at the level of quarks” (Kendler, 2005). Instead, output from complex systems often requires higher-level explanations. The human heartbeat results from feedback loops among properties such as the joint activity of ion channels and cell potential, not from a central control unit (Eronen, 2019). (2) One may find biomarkers for mental health problems like delusions, but the content of the delusion (e.g., bizarre vs grandiose) drives feelings (e.g., fear vs elation) and behaviors (e.g., fleeing vs approaching), not its biological instantiation. (3) Complex phenotypes such as grandiose delusions are likely multiply realizable, i.e., differ in brain activation across (and perhaps within) individuals.

Biological psychiatry has led to considerable insights into human biology but has told us relatively little about the biology of specific diagnoses. The American Psychiatric Association recently 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, p. 915), and genome-wide association studies have largely resulted in transdiagnostic (rather than diagnosis-specific) hits that explain negligible amounts of variance (Scull, 2021). Even NIMH director (2002-2015) Insel, one of the most influential voices for studying the biology of mental illness, concluded that 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 due to the fact that biology is not crucially involved in mental health states—it is because we have focused on studying the biology of particular DSM labels that are likely the wrong targets, and because we have studied biology in isolation (Cai et al., 2020; Eronen, 2019; Hitchcock et al., 2022).

Diagnostic literalism and explanatory reductionism have formed a vicious cycle of reification. We study the genomes of millions of participants diagnosed via DSM-5 when it is

unclear why these phenotypes would be well-suited for genetic discovery in the first place (Cai et al., 2020; Hitchcock et al., 2022). After identifying weak correlates, we further reify diagnoses by talk about “genes for major depression” or “brain biomarkers for PTSD”. Our natural tendency to essentialize mental disorders (Adriaens & De Block, 2013), as well as flawed inferences from measurement (“we have a commonly used measure for diagnosis X, hence X exists”; cf. McPherson & Armstrong, 2021) and external validation (“diagnosis X correlates with external constructs, hence diagnosis X exists”) provide fertile ground for this vicious cycle of reification.

Mental disorders as complex systems

In the Summer of 2019, a scholar I greatly admire was kind enough to lend me his bicycle for a few months, granted I take good care of it. When the bicycle broke down after 3 weeks, I was terribly worried, but reductionism came to the rescue: Bikes can be decomposed into their constituent parts and fixing all parts at the micro-level will restore function at the macro-level. But mental disorders are not like bicycles—they are like many other complex systems in nature (**Figure 1A**). Whether a lake is clean or turbid results from interactions of inter-dependent elements such as oxygen levels, sunlight exposure, fish, pollution, and so on. Whether my mood while working on this manuscript is anxious or cheerful is the outcome of causal relations among elements of my mood system, including my personality and disposition, last night’s sleep, caffeine consumption, and external influences such as the state of my work email inbox. The same applies to mental health states. From a systems perspective depicted in **Figure 1A**, such states result from interactions of numerous biological, psychological, and social features, including specific risk and protective factors, etiology, moods, thoughts, behaviors, biological predispositions, and social environments (Borsboom, 2017; Fried et al., 2022; Kendler et al., 2011; Olthof et al., 2021; Robinaugh et al., 2019).

This framework helps to explain the seven robust phenomena I described above. Some simply follow from acknowledging that diagnoses are superimposed on a complex landscape of mental health states: they may ignore important features like etiology and

summarize dimensional processes as categorical; multiple potentially equally valid summaries and measures as well as thresholds for clinical significance can co-exist; and inter-rater reliability will necessarily be limited for some diagnoses.

This systems perspective also explains why mental health states are somewhat clustered in nature rather than completely randomly distributed: Some states are much more likely than others because features are linked in probabilistic ways. For example, severe traumatic experiences often lead to intrusions, which interfere with daily activities. If trauma is severe enough, most people show some level of impairment, in the same way that very few lakes with severe pollution show healthy fish populations. In other words, feature inter-dependence constrains the states systems can be in. Some people in the feature space will be more typical of the diagnosis than others, marked with a black circle in **Figure 1A**. These people can be thought to be in the most *likely* mental health state, given that they reflect the average result of all probabilistic feature-relations. Probabilistic feature relations allow for considerable inter-individual differences within a given DSM diagnosis, as well as equifinality and multifinality and mental health outcomes.

This framework can accommodate diagnoses to be both similar and different. In **Figure 1A**, PTSD shows much less variability than MDD on feature Z (e.g., the amount of adverse life events experienced in the last year). Diagnoses can also vary in feature differentiation: PTSD and MDD differ strongly on Y (e.g., flashbacks much more common in PTSD), moderately on X (e.g., MDD has somewhat higher comorbidity rates with generalized anxiety disorder), and not at all on Z (e.g., functional impairment). If we were to plot the mental health state of millions of people and superimpose the most prevalent DSM diagnoses, some points clouds would substantially overlap due to shared risk factors, symptoms, or pathophysiology, while others would be somewhat separated. This explains comorbidities and shared risk factors among DSM diagnoses. Splitting or lumping such diagnoses is a pragmatic decision guided by clinical utility, and I understand DSM and ICD as well as recent frameworks like HiTOP (a hierarchical, dimensional taxonomy) as competing attempts to adequately summarize this space.

From this perspective, it is unsurprising that common one-size-fits-all treatments that target diagnoses (e.g., antidepressants for MDD) have shown limited efficacy, and equally unsurprising that biological psychiatry has been largely unsuccessful to identify specific markers for specific diagnoses. Further, symptoms lose their privileged epistemological status as *the* criteria for studying mental disorders, given that many features are associated with diagnoses. In other words, symptoms are not inherently superior features compared to etiology, personality, and other factors.

A systems perspective offers new lenses and levers

A systems perspective provides new lenses through which we can study mental health problems by using theories and methods from other fields with rich traditions, including network and systems sciences (Barabási, 2012; von Bertalanffy, 1972). I introduce a few concepts below that may help to better understand mental health problems.

In complex systems, order can emerge at the macro-level due to local inter-dependence among features at the micro-level. Flocking of birds is an example of an emergent phenomenon arising from self-organization (Olthof et al., 2021). Such emergent properties cannot be fully understood by the study of isolated elements of a system. Bird flocking cannot be identified at level of individual birds, and fluidity is a property of water, not of its constituent elements hydrogen and oxygen. Even systems following very simple rules, such as prey and predator populations that simultaneously depend on each other ($A \leftrightarrow B$), can show emergence (Pessoa, 2022). Ignoring the inter-dependence of such features, like the well-established feedback loop between fear and avoidance relevant to many anxiety disorders, undermines our ability to understand, predict, and treat mental health problems (Robinaugh et al., 2019).

Complex systems can have two (or more) attractor states in which they can settle (Scheffer et al., 2018; van de Leemput et al., 2014). **Figure 1B** shows playing cards held between two fingers: One system is vulnerable (i.e., prone to a phase transition into an alternative attractor state), the other resilient. Lake states (clean, turbid) and mental health states (healthy, depressed) work in similar ways. These systems experience random

perturbations, depicted as horizontal black arrows in **Figure 1B**, such as a very hot summer or negative life events. As a result of these perturbations, the system state depicted in **Figure 1A** may move around slightly, but as long as it does not leave the safe operating space, which is much smaller for vulnerable systems, the system stays in the current attractor state. If perturbations are severe enough to push the system out of the safe operating space, the system may transition into the alternative state via phase transition. Importantly, removing the force that caused a phase transition does not always return the system to the prior state, known as hysteresis effect (Cramer et al., 2016). For example, pollution can cause a lake to tip into a turbid state, but removing the pollution will not necessarily return the lake to a healthy state.

A systems perspective also offers new levers. When systems become less resilient over time, this can be measured by how long it takes a system to recover from random perturbations. If we pushed against the playing cards in **Figure 1B** and took a slow-motion video, we would see that the card in the vulnerable system would 'snap back' more slowly, because there is less 'grip' on the card to keep it in its current state. This is known as *critical slowing down* of a system, and is one of many early warning signals that may foreshadow transitions into (and out of) mental disorders (Olthof et al., 2019; van de Leemput et al., 2014; Wichers et al., 2016), which may facilitate timely prevention and intervention. A systems view also allows us to utilize frameworks such as control theory to simulate interventions, similar to meteorologists who simulate what would happen to Earth's climate under potential interventions such as reduced CO₂ emissions. Such simulations may reveal more optimal intervention strategies, completely novel intervention targets, or showcase what interventions are most effective in what kind of systems (Henry et al., 2021).

The idea of mental health states as complex systems aligns closely with how many clinicians think about and treat mental illness (Schiepek, 2009). Functional analysis is a commonly employed method in psychotherapy to map out causal relations of a person's system, and clinical psychologists have long made use of the concept of network destabilization. Suppose the resilient system in **Figure 1B** is in a psychopathological attractor state such as PTSD: Destabilizing the attractor state (i.e., softening the 'grip' on the playing

card) will make it much easier to help the system reorganize into a healthy state (Hayes et al., 2015; Olthof et al., 2021). A large-scale consortium in the Netherlands is currently investigating the efficacy of such system-based interventions (Roefs et al., 2022).

Conclusions

A systems view provides a powerful antidote against taking diagnoses and reductionism for anything but useful epistemological tools with the goal to describe the world, rather than ontological convictions about how the world is. It challenges the view of clearly separable disease entities and mono-causal etiologies (Kendler, 2012).

Many promising efforts are on the way to embrace the complexity of mental health problems. For example, while NIMH's RDoC initiative started as a poster child of explanatory reductionism (Insel et al., 2010), it has quickly matured into a truly integrative framework focused on neurobiological, psychological, developmental, and environmental elements of mental health systems. RDoC and other recent initiatives (e.g., Robinaugh et al., 2019; Roefs et al., 2022) bring into sharper focus open questions. What are the right levels to study in mental health systems, what are the right elements of these respective levels, and how do elements of different levels interact with each other (Eronen, 2019)? And if we accept that diagnoses are pragmatic summaries, what should our validators of clinical utility be to evaluate future classification efforts in DSM-6 and beyond? Answering these and other questions will require building interdisciplinary bridges, and opening the ivory towers of clinical psychology and psychiatry to theories and methods from fields with rich traditions such as network and systems sciences (Barabási, 2012; von Bertalanffy, 1972).

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Bibliography

- Adriaens, P. R., & De Block, A. (2013). Why we essentialize mental disorders. *The Journal of Medicine and Philosophy*, 38(2), 107–127. <https://doi.org/10.1093/jmp/jht008>
- Barabási, A. (2012). The network takeover. *Nature Publishing Group*, 8(1), 14–16. <https://doi.org/10.1038/nphys2188>
- Borsboom, D. (2017). A network theory of mental disorders. *World Psychiatry*, 16, 5–13. <https://doi.org/10.1002/wps.20375>
- Borsboom, D., Cramer, A. O. J. J., & Kalis, A. (2019). Brain disorders? Not really: Why network structures block reductionism in psychopathology research. *Behavioral and Brain Sciences*, 42, 1–63. <https://doi.org/10.1017/S0140525X17002266>
- Cai, N., Choi, K. W., & Fried, E. (2020). Reviewing the genetics of heterogeneity in depression: Operationalizations, manifestations, and etiologies. *Human Molecular Genetics*, 00(00), 1–9. <https://doi.org/10.1093/hmg/ddaa115>
- Cramer, A. O. J., van Borkulo, C. D., Giltay, E. J., van der Maas, H. L. J., Kendler, K., Scheffer, M., & Borsboom, D. (2016). Major Depression as a Complex Dynamic System. *Plos One*, 11(12), e0167490. <https://doi.org/10.1371/journal.pone.0167490>

- Eaton, N. R., Rodriguez-Seijas, C., Carragher, N., & Krueger, R. F. (2015). Transdiagnostic factors of psychopathology and substance use disorders: A review. *Social Psychiatry and Psychiatric Epidemiology*, 50(2), 171–182. <https://doi.org/10.1007/s00127-014-1001-2>
- Eronen, M. I. (2019). The levels problem in psychopathology. *Psychological Medicine*, 1–7. <https://doi.org/10.1017/s0033291719002514>
- First, M. B., Drevets, W. C., Carter, C., Dickstein, D. P., Kasoff, L., Kim, K. L., McConathy, J., Rauch, S., Saad, Z. S., Savitz, J., Seymour, K. E., Sheline, Y. I., & Zubieta, J. K. (2018). Clinical applications of neuroimaging in psychiatric disorders. *American Journal of Psychiatry*, 175(9), 915–916. <https://doi.org/10.1176/appi.ajp.2018.1750701>
- Fried, E., Flake, J. K., & Robinaugh, D. (2022). Revisiting the theoretical and methodological foundations of depression measurement. *Nature Reviews Psychology*. <https://doi.org/10.1038/s44159-022-00050-2>
- Galatzer-Levy, I. R., & Bryant, R. a. (2013). 636,120 Ways to Have Posttraumatic Stress Disorder. *Perspectives on Psychological Science*, 8(6), 651–662. <https://doi.org/10.1177/1745691613504115>
- Haslam, N., Holland, E., & Kuppens, P. (2012). Categories versus dimensions in personality and psychopathology: A quantitative review of taxometric research. *Psychological Medicine*, 42(5), 903–920. <https://doi.org/10.1017/S0033291711001966>
- Hayes, A., Yasinski, C., Ben Barnes, J., & Bockting, C. L. H. (2015). Network destabilization and transition in depression: New methods for studying the dynamics of therapeutic change. *Clinical Psychology Review*. <https://doi.org/10.1016/j.cpr.2015.06.007>

- Henry, T. R., Robinaugh, D., & Fried, E. (2021). On the control of psychological networks. *Psychometrika*, 1–30. <https://doi.org/10.1007/s11336-021-09796-9>
- Hitchcock, P. F., Fried, E. I., & Frank, M. J. (2022). Computational Psychiatry Needs Time and Context. *Annual Review of Psychology*, 73(1), 243–270. <https://doi.org/10.1146/annurev-psych-021621-124910>
- Hyman, S. E. (2021). Psychiatric Disorders: Grounded in Human Biology but Not Natural Kinds. In *Perspectives in Biology and Medicine* (pp. 6–28).
- Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *The American Journal of Psychiatry*, 167(July), 748–751. <https://doi.org/10.1176/appi.ajp.2010.09091379>
- Insel, T., & Cuthbert, B. N. (2015). Brain disorders? Precisely. *Science*, 348(6234), 2015–2017.
- Kendler, K. (2005). “A gene for...”: The nature of gene action in psychiatric disorders. *The American Journal of Psychiatry*, 162(7), 1243–1252. <https://doi.org/10.1176/appi.ajp.162.7.1243>
- Kendler, K. (2012). The dappled nature of causes of psychiatric illness: Replacing the organic-functional/hardware-software dichotomy with empirically based pluralism. *Molecular Psychiatry*, 17(4), 377–388. <https://doi.org/10.1038/mp.2011.182>
- Kendler, K. (2016a). The nature of psychiatric disorders. *World Psychiatry*, 15(1), 5–12.
- Kendler, K. (2016b). The Phenomenology of Major Depression and the Representativeness and Nature of DSM Criteria. *American Journal of Psychiatry*, 173(8), 771–780. <https://doi.org/10.1176/appi.ajp.2016.15121509>

- Kendler, K., Munõz, R., & Murphy, G. (2010). The development of the Feighner criteria: A historical perspective. *American Journal of Psychiatry, February*, 134–142.
<https://doi.org/10.1176/appi.ajp.2009.09081155>
- Kendler, K., Zachar, P., & Craver, C. (2011). What kinds of things are psychiatric disorders? *Psychological Medicine, 41*(06), 1143–1150.
<https://doi.org/10.1017/S0033291710001844>
- Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 617–627.
<https://doi.org/10.1001/archpsyc.62.6.617>
- Lilienfeld, S. O. (2014). DSM-5: Centripetal Scientific and Centrifugal. *Clinical Psychology: Science and Practice, 21*(3), 269–279.
- McPherson, S., & Armstrong, D. (2021). Psychometric origins of depression. *History of the Human Sciences, 1*–17. <https://doi.org/10.1177/09526951211009085>
- Miller, G. A. (2010). Mistreating Psychology in the Decades of the Brain. *Perspectives on Psychological Science, 5*(6), 716–743. <https://doi.org/10.1177/1745691610388774>
- Olthof, M., Hasselman, F., Maatman, F. O., & Bosman, A. M. T. (2021). Complexity theory of psychopathology. *PsyArxiv*, 1–35.
- Olthof, M., Hasselman, F., Strunk, G., van Rooij, M., Aas, B., Helmich, M., Lichtwarck-Aschoff, A., & Shiepek, G. (2019). Critical Fluctuations as an Early-Warning Signal for Sudden Gains and Losses in Patients receiving Psychotherapy for Mood Disorders. *Clinical Psychological Science*. <https://doi.org/10.1177/2167702619865969>

- Pessoa, L. (2022). Chapter 8. Complex systems: The science of interacting parts. In *The Networked Brain*. MIT Press.
- Regier, D. A., Narrow, W. E., Clarke, D. E., Kraemer, H. C., Kuramoto, S. J., Kuhl, E. A., & Kupfer, D. J. (2013). DSM-5 Field Trials in the United States and Canada, Part II: Test-Retest Reliability of Selected Categorical Diagnoses. *The American Journal of Psychiatry*, 170(1), 59–70. <https://doi.org/10.1176/appi.ajp.2012.12070999>
- Robinaugh, D., Haslbeck, J. M. B., Waldorp, L. J., Kossakowski, J. J., Fried, E., Millner, A. J., McNally, R. J., Nes, E. H. V., Scheffer, M., Kendler, K. S., & Borsboom, D. (2019). Advancing the Network Theory of Mental Disorders: A Computational Model of Panic Disorder. *Preprint, PsyArXiv*, 647209, 1–76.
- Roefs, A., Fried, E. I., Kindt, M., Martijn, C., Elzinga, B., Evers, A. W. M., Wiers, R. W., Borsboom, D., & Jansen, A. (2022). A new science of mental disorders: Using personalised, transdiagnostic, dynamical systems to understand, model, diagnose and treat psychopathology. *Behaviour Research and Therapy*, 153, 104096. <https://doi.org/10.1016/j.brat.2022.104096>
- Rogers, A. (2017). Star Neuroscientist Tom Insel Leaves the Google-Spawnd Verily for ... A Startup? *WIRED*.
- Scheffer, M., Bolhuis, J. E., Borsboom, D., Buchman, T. G., Gijzel, S. M. W. W., Goulson, D., Kammenga, J. E., Kemp, B., van de Leemput, I. A., Levin, S., Martin, C. M., Melis, R. J. F., van Nes, E. H., Romero, L. M., Olde Rikkert, M. G. M. M., Elizabeth Bolhuis, J., Borsboom, D., Buchman, T. G., Gijzel, S. M. W. W., ... Olde Rikkert, M. G. M. M. (2018). Quantifying resilience of humans and other animals. *Proceedings of the National*

- Academy of Sciences of the United States of America*, 115(47), 11883–11890.
<https://doi.org/10.1073/pnas.1810630115>
- Schiepek, G. (2009). Complexity and nonlinear dynamics in psychotherapy. *European Review*, 17(2), 331–356. <https://doi.org/10.1017/S1062798709000763>
- Scull, A. (2021). American psychiatry in the new millennium: A critical appraisal. *Psychological Medicine*. <https://doi.org/10.1017/S0033291721001975>
- Unger, T., Borghi, C., Charchar, F., Khan, N. A., Poulter, N. R., Prabhakaran, D., Ramirez, A., Schlaich, M., Stergiou, G. S., Tomaszewski, M., Wainford, R. D., Williams, B., & Schutte, A. E. (2020). 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*, 75(6), 1334–1357.
<https://doi.org/10.1161/HYPERTENSIONAHA.120.15026>
- van de Leemput, I. A., Wichers, M., Cramer, A. O. J., Borsboom, D., Tuerlinckx, F., Kuppens, P., van Nes, E. H., Viechtbauer, W., Giltay, E. J., Aggen, S. H., Derom, C., Jacobs, N., Kendler, K., van der Maas, H. L. J., Neale, M. C., Peeters, F., Thiery, E., Zachar, P., & Scheffer, M. (2014). Critical slowing down as early warning for the onset and termination of depression. *Proceedings of the National Academy of Sciences of the United States of America*, 111(1), 87–92. <https://doi.org/10.1073/pnas.1312114110>
- von Bertalanffy, L. (1972). The history and status of general systems theory. *The Academy of Management Journal*, 15(4), 407–426.
- von Glischinski, M., von Brachel, R., Thiele, C., & Hirschfeld, G. (2021). Not sad enough for a depression trial? A systematic review of depression measures and cut points in clinical trial registrations: Systematic review of depression measures and cut points.

Journal of Affective Disorders, 292(March), 36–44.

<https://doi.org/10.1016/j.jad.2021.05.041>

Wichers, M., Groot, P. C., Psychosystems, ESM Group, & EWS Group. (2016). Critical Slowing Down as a Personalized Early Warning Signal for Depression. *Psychotherapy and Psychosomatics*, 85, 114–116. <https://doi.org/10.1159/000441458>

Zachar, P. (2014). *A Metaphysics of Psychopathology*. MIT press.

Zachar, P., & Kendler, K. S. (2012). The removal of pluto from the class of planets and homosexuality from the class of psychiatric disorders: A comparison. *Philosophy, Ethics, and Humanities in Medicine*, 7(1), 4. <https://doi.org/10.1186/1747-5341-7-4>