Biological Psychiatry: CNNI

Commentary

Computational Psychiatry Series

Carving Out New Transdiagnostic Dimensions for Research in Mental Health

Claire M. Gillan and Tricia X.F. Seow

Researchers in psychiatry are increasingly moving away from disorder-based distinctions and toward dimensional and transdiagnostic definitions of mental health, citing rising concerns about the validity of categorical definitions and the diminishing utility of case-control designs. These frameworks seek to map normal variation of mental health in the general population that does not obey traditional diagnostic boundaries and prescribes no clear division between individuals with mental illness and healthy individuals. While there is great enthusiasm for this initiative, questions abound. What constitutes a transdiagnostic study? How can we advance knowledge without a standardized rubric for defining clinical phenomena consistently across studies?

A recent article drew an important distinction between soft and hard transdiagnostic approaches (1). Soft methods are those that go beyond simple case-control designs and include case-case comparisons across multiple disorders. These studies have highlighted many examples where disorders lack distinction such as genetic/environmental risk, cognitive/neurobiological profiles, and notably, treatment response. While these studies have been highly influential in diagnosing the problem—that is, underscoring the blurred boundaries between disorder categories—their value has plateaued as we search for new solutions that can capture not just the commonalities across disorders but also the diversity within them.

This is where hard transdiagnostic methods come in. These approaches aim to develop novel definitions of mental illness that are unconstrained by the DSM. In this commentary, we detail one example of a hard approach that aims to identify transdiagnostic dimensions of mental illness that provide a closer mapping to cognitive, neural, environmental, or genetic mechanisms. We summarize recent findings using this method and discuss its limits and the next steps for a somewhat controversial field that is still in its infancy.

Progress to Date. A much-discussed limitation of categorical frameworks is the arbitrary distinction between having mental illness and being healthy. There is little evidence for the existence of categorical boundaries in psychiatry, and various studies have shown that continuous measures of psychopathology have superior reliability. For this reason, it is thought that normal variation in psychopathology in the general population can be used to define new, valid, and psychometrically sound dimensions of mental illness. This approach embraces a necessary shift away from clinical interview to self-assessments, which are much more scalable and, in some cases, more reliable; the interrater reliability of diagnostic interviews is questionable for many common disorders in the DSM-5 (e.g., major depressive disorder).

A method based on these principles (Figure 1A) was developed out of necessity (2)—designed to resolve issues with the (lack of) specificity of a cognitive model of obsessive-compulsive disorder (OCD). Deficits in goal-directed planning, a cognitive capacity that protects against getting stuck in repetitive habits, are characteristic of individuals with OCD when compared with healthy control individuals. However, a host of studies subsequently found similar deficits in other disorders (including addiction, binge-eating disorder, social anxiety disorder, and schizophrenia) when using case-control methods. This suggested that the effect was nonspecific and of limited explanatory potential. Frustrated to have reached this impasse, we designed a study to determine whether this effect was truly nonspecific or whether the spread across diagnostic lines was a consequence of flaws in our classification system. If the latter, are goal-directed deficits best captured in a dimension of mental illness that we have yet to define?

Recruiting a sufficiently large sample of diagnosed patients to test this was not tenable, so data were collected online from >1400 individuals who self-reported on a broad range of mental health issues and performed a task measuring goal-directed control (2). We directly compared the association between goal-directed control and several commonly studied aspects of mental illness. As with the case-control studies, we found the effects to be nonspecific. However, a factor analysis revealed evidence for 3 clinical dimensions that provided a simpler solution, based on the intercorrelation of the symptoms that subjects reported. Participants' scores on one of these dimensions—a compulsive dimension—provided a closer and more specific mapping to goal-directed deficits than any questionnaire total score under study, including one measuring OCD symptom severity. This was an important external validation; not only did the compulsive dimension explain the self-report data best, but it also provided a better explanation of cognition changes. Subsequent work using this framework has shown that the factor structure is robust (3), as is the association with goal-directed deficits (4). Moreover, it has advanced our understanding of other cognitive changes in psychiatry. For example, a dimension representing a complex of anxiety and depression identified in this study was later found to track metacognitive abnormalities. Specifically, individuals high in anxious–depression have abnormally low confidence in perceptual decision-making and reinforcement learning tasks, which is dissociable from compulsivity, which exhibits an opposing pattern of inflated confidence (3,5). In a diagnostic category such as OCD, where subjects have higher

  https://doi.org/10.1016/j.bpsc.2020.04.013
Biological Psychiatry: Cognitive Neuroscience and Neuroimaging October 2020; 5:932–934 www.sobp.org/BPCNNI ISSN: 2451-9022

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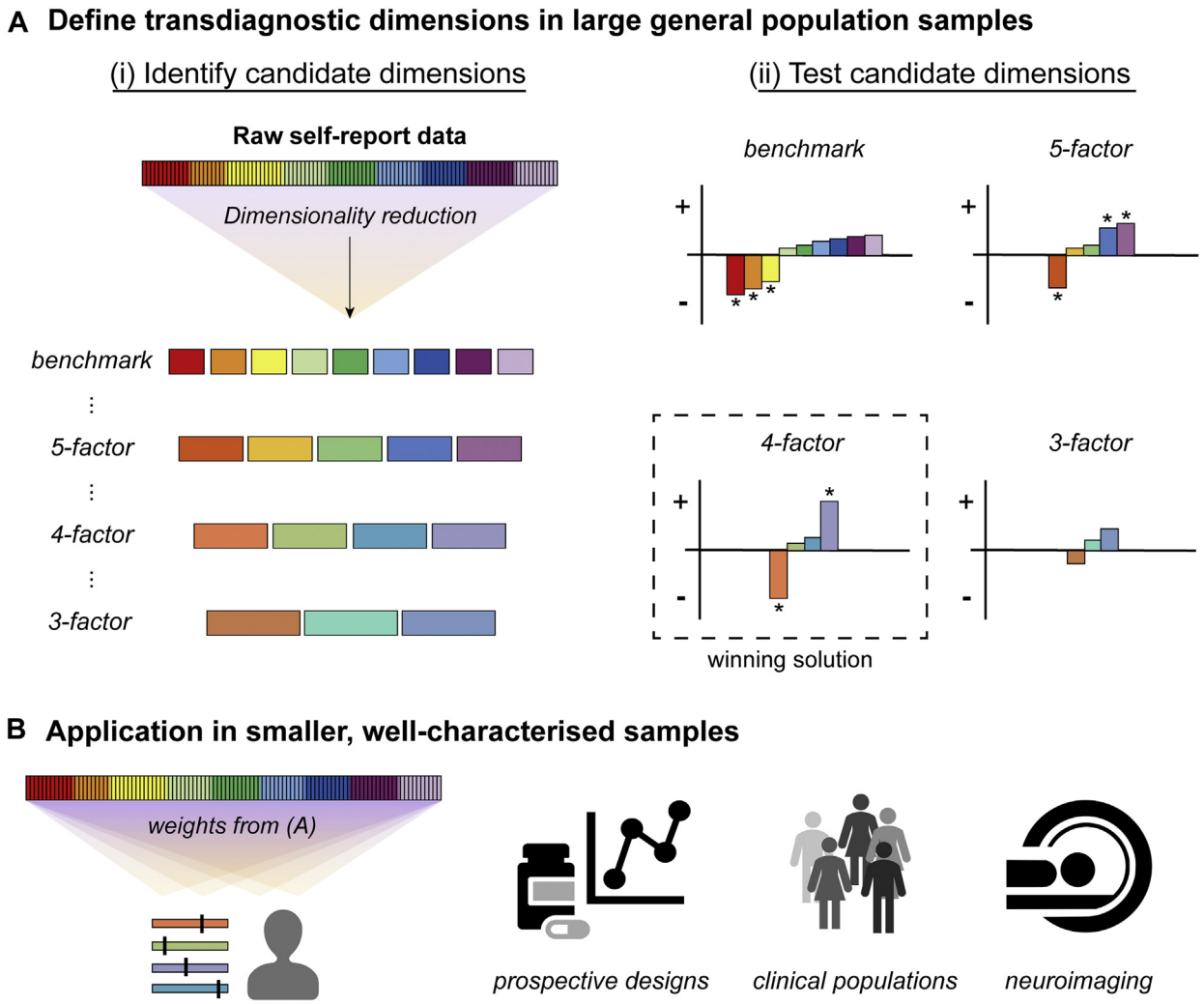

Figure 1. A pipeline for hard transdiagnostic research. **(A)** Define transdiagnostic dimensions in large, general-population samples. Data used to define new dimensions can come from large, open-source datasets or where novel data are required and gathered rapidly and at scale from the general population using online crowdsourcing platforms. Several candidate dimensional structures might be compared with a benchmark (e.g., original questionnaire total scores from which items are derived), including solutions that retain different numbers of factors (pictured), different methods of factor rotation (e.g., orthogonal, oblique), and hierarchical structures. Candidate solutions should then be tested externally—against a measured variable of interest (e.g., cognitive, prognostic, biological)—and a winning solution should be selected depending on key features that one seeks to optimize (e.g., goodness of fit, specificity). **(B)** Apply in smaller, well-characterized samples. The weights defined in **(A)** can be applied to smaller datasets (where exploring factor structure is not possible) to see where a new patient sits on the continuum of each factor. This permits transdiagnostic dimensional analyses in well-characterized patient samples, rich biological data, or longitudinal clinical outcomes.

levels of both anxious–depression and compulsivity than control subjects, important effects such as these may cancel each other out and be rendered "invisible" in a case-control comparison.

Although these general-population studies are highly suggestive, the findings might not extend to diagnosed patients. A recent study tested this, comparing the association between goal-directed deficits and dimensions versus disorder classification in patients who met criteria for OCD, generalized anxiety disorder, or a combination of both (6). While diagnostic categories did not differ from one another in terms of their goal-directed learning ability, the self-reported dimension of compulsivity was specifically associated with deficits in this cognitive capacity. Similar findings have recently emerged for neuroimaging. One study first defined transdiagnostic dimensions of interest (here, impulsivity vs. compulsivity) in a large general-population sample (7). These data were subsequently used to score a smaller sample of diagnosed patient groups along these dimensions. Distinct patterns of effective connectivity were found to map onto impulsivity and compulsivity dimensions, whereas distinctions between the diagnosis of OCD and that of pathological gambling were not apparent in the same sample. This hybrid approach strikes a balance of using large-scale general-population samples (which can be

rapidly and cheaply acquired online) to first define dimensions of interest and then apply them to well-characterized and more severely disabled clinical cohorts (Figure 1B).

The Next Challenge. A great strength of existing disorder-based frameworks is that they facilitate comparison across studies—providing a coherent literature that enables incremental advances. Hard transdiagnostic approaches will find this difficult at first. For instance, dimensionality reduction methods seek to explain the data provided to them, which means that the resultant factor structure depends substantially on the set of questions provided. Not wishing to prematurely lock in an imperfect dimensional framework, studies applying these methods will likely each describe a new (and partially overlapping) dimensional structure as they probe different aspects of mental illness. The unfortunate consequence is that integration of knowledge across studies will be compromised.

We posit that this is a necessary, albeit undesirable, phase.

In the original study using this method (2), the self-report items we studied were selected to promote the quantification of compulsivity and juxtapose it with other noncompulsive dimensions of symptomatology that bear OCD relevance. Theory-driven approaches like this should be at the heart of all studies employing this hard transdiagnostic method, but the dimensions that emerge cannot be perceived as fixed or final. A balance must be struck between studying the same (imperfect) dimensions ad nauseam to enable comparison across studies and the desire to iteratively refine these dimensions to systemically improve the correspondence between clinical symptoms and brain mechanisms.

Two recently published studies hit this note. In the first study, the authors examined negative affective biases in a large general-population sample, asking whether the tendency to treat ambiguous stimuli as more negative is characteristic of variation in depression, anxiety, or other correlated aspects of mental illness (8). Importantly, rather than examining just one dimensional solution, a variety of methods were used to define a range of candidate dimensions. When the candidate dimensions' fits to cognition were compared, two of the dimensional solutions mapped onto negative cognitive bias—a depression dimension and a complex of anxiety and depression, with some evidence that depression might capture the lion's share of variance. A second study took a different approach to iterative refinement. The authors sought to reduce subject burden by identifying the smallest number of items needed (from ~200 originally) to estimate individual scores on previously defined transdiagnostic dimensions (9). This kind of optimization, if taken forward, will be essential; future work may entail data-driven comparisons of fit between dimensions estimated from alternative reduced item sets.

The Future. Individuals with mental illness seek help for symptoms. Hence, research must continue to focus on understanding these subjective experiences. However, we must recognize that the path to clinical translation, the holy grail of research in biological psychiatry, may then be longer and more indirect than we would like. At a time of unprecedented access to large datasets, we have the opportunity not just to redraw the lines of mental illness but also to reframe the question entirely. The ground truth for research must ultimately move away from the symptoms that a patient reports and toward more practical clinical outcomes such as clinical course, relapse, and treatment response (10). This is the most exciting opportunity for the next wave of transdiagnostic research.

Acknowledgments and Disclosures

CMG is supported by a fellowship from MQ: Transforming Mental Health (No. MQ16IP13). TXFS is funded by a Postgraduate Ussher fellowship from Trinity College Dublin.

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

From the School of Psychology (CMG, TXFS), Trinity College Institute of Neuroscience (CMG, TXFS), and Global Brain Health Institute (CMG), Trinity College Dublin, Dublin, Ireland.

Address correspondence to Claire M. Gillan, Ph.D., at gillancl@tcd.ie.

Received Apr 12, 2020; accepted Apr 27, 2020.

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