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Review

Embracing variability in the search for biological mechanisms of psychiatric illness

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Despite decades of research, we lack objective diagnostic or prognostic biomarkers of mental health problems. A key reason for this limited progress is a reliance on the traditional case–control paradigm, which assumes that each disorder has a single cause that can be uncovered by comparing average phenotypic values of patient and control samples. Here, we discuss the problematic assumptions on which this paradigm is based and highlight recent efforts that seek to characterize, rather than minimize, the inherent clinical and biological variability that underpins psychiatric populations. Embracing such variability is necessary to understand pathophysiological mechanisms and develop more targeted and effective treatments.

Highlights

Psychiatric diagnoses do not cleanly map onto specific biological mechanisms or clinical outcomes, limiting progress towards uncovering their biology and developing more effective treatments.

Reliance on classical case–control comparisons of group means is a major reason for limited progress in the field.

Analytic methods for characterizing biological and behavioral variability across individuals are revealing the substantial heterogeneity that characterizes psychiatric illness.

The logjam in biological psychiatry

> The principal requisite in the knowledge of mental diseases is an accurate definition of the separate disease processes. In the solution of this problem one must have, on the one hand, knowledge of the physical changes in the cerebral cortex, and on the other of the mental symptoms associated with them.
>
> [Kraepelin, 1907/1908]

Emil Kraepelin, widely recognized as the founding father of modern psychiatry, believed that accurate diagnoses must ideally be predicated on an understanding of the brain changes that accompany psychopathological symptoms. He investigated postmortem specimens from patients he had diagnosed with **dementia praecox** (see Glossary) in the hope that he would have the same success as his colleague, Alois Alzheimer, in identifying an obvious pathological marker of disease. Kraepelin's search was ultimately less fruitful, and he settled on a diagnostic classification system based on clinical observations of symptoms. Over a century later, we have still not realized Kraepelin's aspirations, with descriptive psychiatric approaches, codified in nosologies such as the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) [1] and the International Classification of Diseases (ICD-11) [2], remaining as the dominant paradigms for clinical diagnosis in psychiatry.

The field is trapped in this morass despite decades of research, thousands of papers, and billions of dollars spent to identify meaningful biological markers of mental illness. Thomas Insel summarized his tenure as Director of the US National Institutes of Mental Health (NIMH) by stating:

> I spent 13 years at NIMH really pushing on the neuroscience and genetics of mental disorders, … while I think 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[i].

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Here, we consider potential reasons for this limited progress, with the hope of identifying new strategies for breaking through the logjam. We focus principally on efforts to uncover the neural mechanisms of psychiatric illness, particularly as revealed through noninvasive neuroimaging, which is the most popular approach for probing brain structure and function in living participants. We draw on examples of structural neuroimaging research, but in most cases our arguments also apply to other imaging and nonimaging contexts. We propose that the current case–control paradigm (Figure 1A) pervading much of the literature is ill-equipped to capture the inherent biological and clinical variability of psychiatric illness, necessarily limiting our ability to uncover associated neural mechanisms. In particular, we focus on four core, yet problematic, assumptions that underpin the application of the conventional paradigm and which limit the progress of the field more generally: namely (i) the group mean is representative of individual patients; (ii) brain regions operate as isolated units; (iii) there is a one-to-one mapping between a given brain region (or network) and a particular psychiatric illness; and (iv) diagnoses are the appropriate level of phenotypic resolution for uncovering pathophysiological mechanisms. We outline the limitations of these assumptions and approaches to circumvent them. We conclude by discussing future directions for embracing variability in the ongoing search for neural mechanisms of psychiatric illness.

Problematic assumption 1: the group mean is representative of individuals within that group

The classical case–control experimental paradigm has been a fundamental cornerstone of biological psychiatric research over the past century (Box 1). In this paradigm, an investigator recruits individuals diagnosed with the psychiatric illness of interest alongside an appropriate 'healthy' control population without a history of psychiatric illness or treatment. Neurobiological phenotypes of interest (e.g., brain volume) are then acquired in each individual, and the averages of each group are compared using some form of statistical inference, such as a *t* test or related quantity.

This paradigm, and the classical inferential procedures on which it is based, largely relies on group-level summaries of the central tendency of brain measures. For instance, most studies in biological psychiatry compare group mean differences between cases and controls using a general linear model or related statistic. This approach will only be useful if the mean offers a representative summary of that group, and the mean will only be representative if the groups define homogenous classes of individuals.

In studies of psychiatric populations, numerous methodological factors and sample characteristics can conspire to increase the interindividual heterogeneity of a group, decrease the representativeness of the group mean, and lead to inconsistent findings across studies (Box 2). However, even if these factors could be perfectly controlled, a more fundamental problem emerges from the fact that diagnostic groups are defined by checklists of self-reported symptoms and clinically observed signs derived from expert consensus rather than an empirically grounded understanding of how clinical phenotypes are tied to biological mechanisms.

The categories that have resulted from such diagnostic procedures yield an extreme diversity of symptom profiles. For instance, there are 636 120 possible symptom combinations that meet criteria for a diagnosis of post-traumatic stress disorder [3], 116 220 possible combinations for attention deficit hyperactivity disorder (ADHD) [4], and 16 400 possible combinations for depression [5]. One empirical study of depression found nearly 50% of people express a symptom profile that is unique to the individual [5]. As such, people can receive the same diagnosis without sharing common symptoms. This interindividual variability is compounded by variations in the age of onset and the frequency, duration, timing, severity, and dynamic transitions between symptoms.

Glossary

Biotypes: subtypes of patients with a common diagnosis showing distinct biological phenotypes.
Construct validity: the correspondence between a psychological measure and the psychological attribute or behavior it was designed to measure.
Default mode network: the set of brain regions, including medial prefrontal cortex, posterior cingulate cortex, and lateral parietal and temporal cortices, that show strong functional coupling at rest and decreased activity during tasks requiring attention to external stimuli along with increased activation during introspective processing.
Dementia praecox: a historical term first proposed by Emil Kraepelin, meaning dementia with early onset, that is the precursor of what we now describe as schizophrenia.
Diaschisis: derived from Greek Dia 'in half' or 'across' and schizien 'to split'. Describes the depressed function that can arise in brain regions remote from the area of an initial insult.
Equifinality: a variety of starting points leads to the same diagnosis through different processes.
Idiopathic: a disease or disorder of unknown cause.
Multifinality: similar starting points lead to different diagnoses via multiple pathways.
Pleiotropy: a single brain region may contribute to multiple symptoms/syndromes.
Reliability: the consistency of measurement across items, scales, occasions, or raters. It is inversely related to measurement error and imposes an upper limit on the observed effect size that can be detected between psychiatric and neurobiological phenotypes.
Spectra: Higher-order dimensions, in most cases subsuming one or more related subfactors, that putatively represent liabilities to a broader range of psychopathology, such as the internalizing spectrum, which accounts for covariance between the subfactors of fear and distress.
Subfactors: Constructs combining closely related dimensional syndromes; for instance, the subfactor fear accounts for covariance between social anxiety and phobias.
Superspectra: The highest and broadest level of the hierarchical dimensional structure; for instance, a general psychopathology factor is

proposed to explain covariance between different spectra.
Syndromes: clusters of conceptually and empirically related symptom components and maladaptive traits that are thought to co-occur in some clinically meaningful or statistical way; for instance, depression combines appetite loss and insomnia.

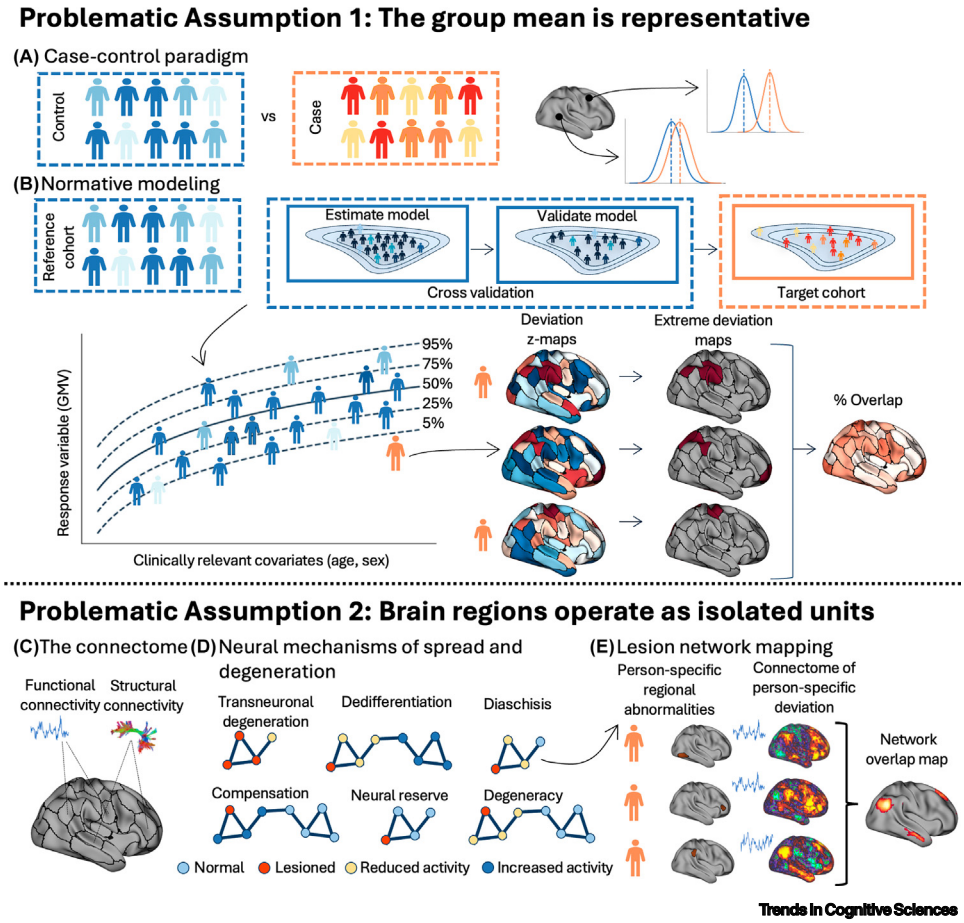

Figure 1. First two problematic assumptions in the search for biological mechanisms of psychiatric illness. Assumption 1: The group mean is representative of most individuals within a group. (A) In the case–control paradigm, cases are enrolled based on a single, specific clinical diagnosis and are compared with controls using some form of statistical inference, such as a *t test* or related statistic, typically at the level of individual brain loci. (B) Normative modeling moves beyond group means to enable statistical inferences at the level of individuals. Normative modeling involves training a model to learn normative expectations for a given brain phenotype, given an individual's age, sex, or other relevant characteristics in a reference cohort (e.g., the controls). The model predictions can then be used to define a normative range of variation, against which new observations can be compared. The model is then validated out-of-sample using crossvalidation and applied to a new target cohort (e.g., the cases). When the model is fitted at many brain regions, it is possible to obtain a deviation map for each individual in the target cohort that identifies regions associated with unusually small or large phenotypic values. From here, a threshold can be applied (e.g., $z < -2.6$) to identify extreme deviations. Figure 1B inspired from [15]. Assumption 2: Brain regions operate as isolated units. Focusing on each area in isolation, without consideration of (C) the broader network within which they are embedded (the connectome) yields an incomplete picture of the pathophysiology, since any local pathology can be accompanied by a broader set of (D) adaptive (compensation, neural reserve, degeneracy) and maladaptive (transneuronal degeneration, dedifferentiation, diaschisis) network-level responses that will influence the clinical phenotype. Transneuronal degeneration occurs when there is structural degeneration of areas connected to affected site. Dedifferentiation occurs when nonspecific brain regions are recruited following the dysfunction of the affected regions. Diaschisis occurs when the affected site depresses the function of connected regions. Compensation occurs when unaffected regions increase their function to preserve behavior. Neural reserve occurs when activity in unaffected regions remains unchanged and behavior is intact. Degeneracy occurs when a second network can support the behavior that is normally mediated by the affected regions, without any substantial changes in function (see [22] for extended discussion). Figure 1D inspired from [22]. (E) Lesion network mapping offers a framework for exploring some of these network-level processes by mapping the areas coupled to putative sites of focal dysfunction in individual patients.

Box 1. The case–control paradigm and the search for a causal brain region

Early investigators such as Kraepelin [104] and Wernicke [105] theorized that psychiatric symptoms could emerge from disruptions of brain function, but methods to probe the biology of mental illness took some time to develop and proliferate, evolving from the rudimentary postmortem investigations of Kraepelin and others to family and twin studies in the early 20th century demonstrating a heritable basis for schizophrenia and other illnesses [106]. This work was followed by the discovery of antipsychotic and antidepressant agents in the 1950s [107,108], and the demonstration of structural and functional brain changes in living patients in the 1970s [109,110]. The advent of MRI in the 1980s, along with ongoing improvements in histological approaches, subsequently triggered an explosion of research into the biological basis of psychiatric disorders.

For much of this history, a major emphasis was placed on identifying the focal, causal brain lesions triggering the onset of each disorder, under the assumption that there is a one-to-one mapping between brain regions and behaviors. Different investigators thus variously emphasized the role of the dorsolateral prefrontal cortex [111], basal ganglia [112], thalamus [113], and temporal lobe [114] in schizophrenia; the hippocampus [115], amygdala [116], and subgenual prefrontal cortex [117] in major depression; and basal ganglia [118] and orbitofrontal cortex [119] in OCD, to name just a few examples.

In line with a growing appreciation that brain regions do not operate as isolated units, and the development of techniques for mapping large-scale brain connectivity [120,121], the focus of the field then shifted from single, focal lesions to mapping dysfunction of large-scale brain circuits. Thus, frontolimbic systems have been emphasized in MDD [122], the **default mode network** in ASD [123], dorsal and ventral frontostriatal systems in schizophrenia [124] and OCD [125], respectively. This work has advanced our understanding of pathophysiological processes [22] and is being leveraged to develop improved stimulation-based therapies targeting dysfunctional circuits [44,99], but progress has nonetheless been slow. We still lack clinically useful biological markers of diagnosis, prognosis, or treatment outcome, and neuroimaging has thus far not informed the development of mechanistically novel pharmacological therapies. The combination of neuroimaging with more causal perturbations (such as lesions and brain stimulation techniques [42,44]), in addition to refined clinical phenotyping (Box 4), will be required to break this impasse.

The problems posed by intradiagnostic heterogeneity are exacerbated by a lack of diagnostic specificity for individual symptoms, leading to high rates of comorbidity. Indeed, comorbidity is the rule rather than the exception, with ~50% of people diagnosed with one condition also meeting criteria for another, 50% of people with two diagnoses meeting criteria for a third, and so on [6]. While the high rates of comorbidity may arise from the coexistence of distinct diseases, a more probable cause is that psychiatric disorders are not discrete entities and, as such, symptoms transcend traditional diagnostic boundaries. For instance, 37% of symptoms within the DSM-5 are not specific to a single illness, and together make up 72% of the symptoms listed in all of the diagnostic criteria, demonstrating a marked lack of symptom specificity [7]. Moreover, when comparing symptom profiles as opposed to individual symptoms, no individual disorder is separable from a randomly selected group of individuals with nominally distinct diagnoses [8]. While this could be driven in part by the extreme heterogeneity within diagnostic groups, it also provides further evidence of the limited specificity and validity of traditional diagnostic boundaries in psychiatry.

These limitations have motivated alternative approaches to characterizing psychiatric phenotypes that do not rely on categorical diagnoses, such as the Research Domain Criteria (RDoC) [9] and Hierarchical Taxonomy of Psychopathology (HiTOP) [10]. These approaches seek to define homogenous groups of individuals through various strategies, such as the use of predefined constructs determined by expert consensus (RDoC) or data-driven quantitative clustering analyses of biological and other measures (HiTOP) to identify putative subtypes or even **biotypes** of illness. However, the results obtained with such approaches can be notoriously susceptible to investigator choices in the analysis pipeline, as well as difficulties in validating the clusters and in determining whether they are really separable. The application of such approaches to psychiatry has therefore met with variable success [11].

An alternative approach is to move away from group mean comparisons and directly characterize the variability within clinical populations. To this end, normative modeling [12–15] (Figure 1B)

Box 2. Potential reasons for inconsistent findings

The lack of consistency and specificity between studies can, at least in part, be attributed to various sources of between-sample/study heterogeneity, which can collectively be referred to as 'site effects'. These differences can vary systematically between patients and controls and between studies. Below, we have separated site effects in terms of methodological considerations and sample characteristics. This is not an exhaustive list and these factors are not mutually exclusive.

Methodological characteristics contributing to inconsistencies between studies include differences in study design, data acquisition, and data processing. For instance, study design characteristics and data acquisition factors such as prescanning instructions, scanner hardware, imaging parameters and protocol, head motion, and physiological noise all affect MRI signal and anatomical measures. These issues are exacerbated when there are systematic differences between samples within a study. For example, patient populations typically exhibit increased head motion in the scanner compared with controls, making it difficult to disentangle the degree to which differences between the groups are due to the underlying neurobiology of a disorder itself or due to motion artifacts. Inconsistencies between data processing and analysis choices have also been reported to influence MRI and anatomical measures. These inconsistencies include, but are not limited to, differences in computer operating system, analysis software packages, specific software versions, data analysis workflows, and parcellation strategies.

Aside from methodological choices, it is well established that sample characteristics such as age, sex, and brain size can confound psychiatric neuroimaging. Other important factors which have been shown to influence MRI signals include demographic variables, such as education and socioeconomic status, lifestyle and behavioral factors, including smoking, substance use and exposure, caffeine, exercise, diet, and hydration, and biological factors including body weight, metabolic variations, time of day, hormonal fluctuations, circadian rhythms and timing. Again, these factors can vary not only between different studies, but they can also vary systematically between patients and controls (e.g., adiposity in schizophrenia). There are also clinical characteristics specific to the patients enrolled in the study including medication use and history, symptom expression including presentation, frequency, direction, severity, and age of onset, mental and physical comorbidities, and current mental state.

All of these factors are compounded by the traditionally small sample sizes studied in biological psychiatry research, which can lead to considerable variability of effect size estimates from study to study and, in some cases, such as in brain-wide association studies (BWASs), require samples in the order of thousands of people to obtain reliable results [126]. Effect sizes in psychiatric disease are generally larger than those in BWAS and can thus be reliably detected with sample sizes numbering hundreds rather than thousands [127], but further work establishing the minimum required effect sizes for different neural and psychiatric phenotypes is required. Improved definitions of clinical phenotypes provide a cost-effective means for mitigating some of this variability and improving effect sizes (Box 4) [93].

offers a promising and statistically rigorous framework for performing inferences at the level of individuals, affording new opportunities for unraveling clinical and biological heterogeneity. In contrast to case–control paradigms, this approach does not assume that individuals share similar patterns of pathology, nor does it assume that the clinical cohort can be neatly partitioned into homogeneous clusters. Instead, normative modeling involves training a statistical model to estimate a normative distribution of a given phenotype, such as brain volume, based on relevant demographic characteristics, such as age and sex. One can then measure the phenotype in a new individual and estimate the extent to which the measured value deviates from model predictions (termed deviations). Extreme deviations (i.e., unusually large or small phenotypic values relative to normative expectations) are theorized to be most likely associated with the presence of pathology as they are the most abnormal [15].

The application of normative models to diverse psychiatric groups has consistently shown that group means derived from case–control group mean comparisons are not representative of most individual patients. Specifically, while individuals with a psychiatric diagnosis typically show a higher frequency of deviations in measures of brain structure and function compared to controls, the location of these deviations varies considerably, regardless of whether robust group-average case–control differences are present. In most cases, less than 10–20% of individuals with a given diagnosis exhibit extreme deviations in the same brain locus [16–18]. For instance, despite widespread reductions of gray matter volume in group-level analyses of schizophrenia, the locations of person-specific extreme deviations from normative estimates fall within the same area in

less than 10% of patients [16,17]. In autism spectrum disorder (ASD), where few case–control cortical thickness differences are reported, patients show highly individualized patterns not only with respect to the locations of brain deviations, but also with respect to the direction of the deviation (i.e., increases or decreases relative to normative estimates), with the maximum overlap never exceeding 20% [18]. Such heterogeneous bidirectional effects will be masked by group-averaged case–control comparisons.

The normative modeling framework has been used to probe individual-level neurobiological variability across diverse clinical cohorts including ADHD [16], ASD [16,19], bipolar disorder [16,17], depression [16,20], obsessive compulsive disorder (OCD) [16,21], and schizophrenia [16,17]. Overwhelmingly, these findings highlight that case–control group-mean differences (or lack thereof) are not representative of most individuals. Continued reliance on group mean comparisons is thus expected to result in a litany of inconsistent findings that may only be characteristic of small subgroups of individuals. We note, however, that the consistency of individual-level inferences drawn from normative modeling studies themselves, particularly with respect to variations in the normative population used as the reference class and/or various other analysis choices, has not been widely explored. Establishing the reliability and robustness of the person-specific inferences drawn from normative models is an important priority of the field.

Problematic assumption 2: brain regions operate as isolated units

A second core assumption of classical inferential procedures is that differences revealed by group mean comparisons represent the core pathophysiological markers of interest. These differences are typically identified by mass univariate analyses comparing mean differences in some neurobiological phenotypic value (e.g., brain volume) across many points in the brain. While these regions are likely to play a role in the expression of psychiatric illness for at least a subset of individuals, focusing on each area in isolation yields an incomplete picture of the pathophysiological process [22,23]. Brain regions do not operate as isolated units but instead form part of an interconnected network, often called the connectome [24,25] (Figure 1C). The connectivity of this network will necessarily shape the spatiotemporal evolution of any dynamical and/or pathophysiological processes that unfold in the brain [22,26] (Figure 1D). This principle is demonstrated by studies showing that gray matter volume changes in psychiatric disorders are associated with the microstructure of adject white matter [27], that they occur in spatial patterns that are constrained by the structural, functional, and genetic architecture of the connectome [28–30], and that their spatial pattern can be predicted by simple models of brain network properties across different stages of illness and diagnostic categories [31–33].

These studies underscore the need to consider the broader network context of any putative pathophysiological marker. This need was well-known to early writers such as von Monakow, who coined the term **diaschisis** to describe how dysfunction in one area can impact the function of other, sometimes physically distant areas [34]. The explanatory power of this concept has recently been demonstrated in lesion network mapping (Figure 1E) studies of overt brain lesions [35,36] that cause neurological or psychiatric symptoms. Such studies have consistently shown that the anatomical location of lesions thought to cause a particular **syndrome** can be highly heterogeneous across individuals, but that these lesioned sites are often structurally or functionally coupled to common systems. These observations indicate that deafferentation of the remote sites, rather than dysfunction of the lesioned area itself, is likely a causal factor shaping the clinical presentation. For instance, only 13% of neurological cases with psychotic symptoms show spatial overlap in the site of the primary lesion, but 84% of the lesioned areas are functionally coupled to the posterior hippocampus [37]. This result aligns with mathematical models implicating the hippocampus as a putative epicentre of gray matter volume change in psychiatric patients with psychosis [31].

The basic logic underlying lesion network mapping has been adapted for the investigation of **idiopathic** psychiatric disorders. In the absence of overt brain lesions, techniques for defining putative foci of pathology using quantitative criteria have been developed. One approach, termed coordinate network mapping, maps heterogeneous neuroimaging coordinates derived from psychiatric meta-analyses onto brain circuits [38]. This method has been applied to a range of disorders, including depression [39] and addiction [40]. One transdiagnostic meta-analysis of gray matter coordinates obtained across six psychiatric disorders from 193 voxel-based morphometry studies found that only 35% of studies contributed to any one anatomically focal cluster. However, 85% of studies were functionally connected to the same network of brain regions, including the insula, anterior cingulate, posterior cingulate, frontal pole, posterior parietal cortex, lateral occipital cortex, brainstem, and cerebellum [41]. In many circumstances, the brain circuitry revealed by this approach aligns with brain circuits implicated by lesion network mapping studies of neurological cases showing psychiatric symptoms as well as brain stimulation targets with therapeutic efficacy, providing an exciting path towards closing the causality gap in the search for biological mechanisms of psychiatric illness [42].

However, while meta-analysis coordinate network mapping captures heterogeneity between studies, it cannot capture neural heterogeneity at an individual level (problematic assumption 1). An alternative framework combines normative modeling with elements of lesion network mapping to characterize the structural and functional network context of individual-specific neuroanatomical deviations [16,21]. Echoing neurological lesion network studies, this work indicates that neuroanatomically heterogeneous deviations in psychiatric disorders aggregate within coupled neural systems, both within and between diagnostic categories. For instance, we characterized disorder-specific gray matter volume heterogeneity across multiple spatial resolution scales in six psychiatric disorders: ADHD, ASD, bipolar disorder, depression, OCD, and schizophrenia. Although gray matter deviations were common in patients, no more than 7% of individuals within a given clinical group showed deviations in the same brain region, supporting prior reports indicating high interindividual heterogeneity. Consistency at the network level was much higher, reaching 50% in some cases. Notably, most of this overlap was attributable to total deviation burden, with the level of network overlap rarely exceeding the expectations of a random spatial distribution of the same number of deviations. This finding suggests that specific neural circuits may be commonly implicated across individuals with the same disorder simply because these areas are more vulnerable to random perturbations. Evidence for selective, disorder-specific targeting of neural systems beyond such expectations was only observed in a few cases, such as the dorsolateral prefrontal cortex in depression and bipolar disorder, the dorsal attention network and medial temporal areas in ADHD, and the salience/ventral attention system in schizophrenia [16]. Collectively, these findings suggest that heterogeneity at the level of regional deviations may be related to intradiagnostic clinical heterogeneity, whereas the aggregation of these regional deviations within common circuits and networks may account for clinical similarities both within and between diagnoses. The findings also suggest that the targeting of different neural systems by distinct disorders may be less specific than previously thought.

These studies demonstrate the need to consider the broader network context of any putative pathophysiological marker [22]. However, these network mapping approaches cannot directly tease apart the cause of pathology from a secondary effect, such as a compensatory neural response or contribution from some comorbid pathology [43]. The use of complimentary evidence drawn from both lesion and brain stimulation research [42,44], or genetics and neuroimaging [45], can be used to more precisely pinpoint aspects of brain dysfunction with

causal influences on psychiatric phenotypes. Future work will also profit from accounting for interindividual variability in network topography, which can influence case–control comparisons of brain activity [46] and may offer a novel set of potential illness biomarkers [47,48].

Problematic assumption 3: there is a one-to-one mapping between disorder and pathophysiological mechanism

A third core assumption of conventional case–control paradigms is that a mean difference in some biological measure can reveal a pathophysiological phenotype that applies to most (if not all) individuals within the patient group. In other words, it assumes a one-to-one mapping between dysfunction in a specific brain region (or network) and a given illness (Figure 2A). As noted in the preceding text, this assumption is contingent on the homogeneity of the patient group itself. However, even if we assume this (unlikely) best-case scenario, strict reliance on group-mean comparisons remains problematic because it ignores mechanistic heterogeneity and pleiotropy, two concepts that have been studied extensively in genetics.

Heterogeneity occurs when multiple genetic variants contribute to the same phenotype, yielding a many-to-one mapping (also referred to as polygenicity) (Figure 2B). Conversely, pleiotropy occurs

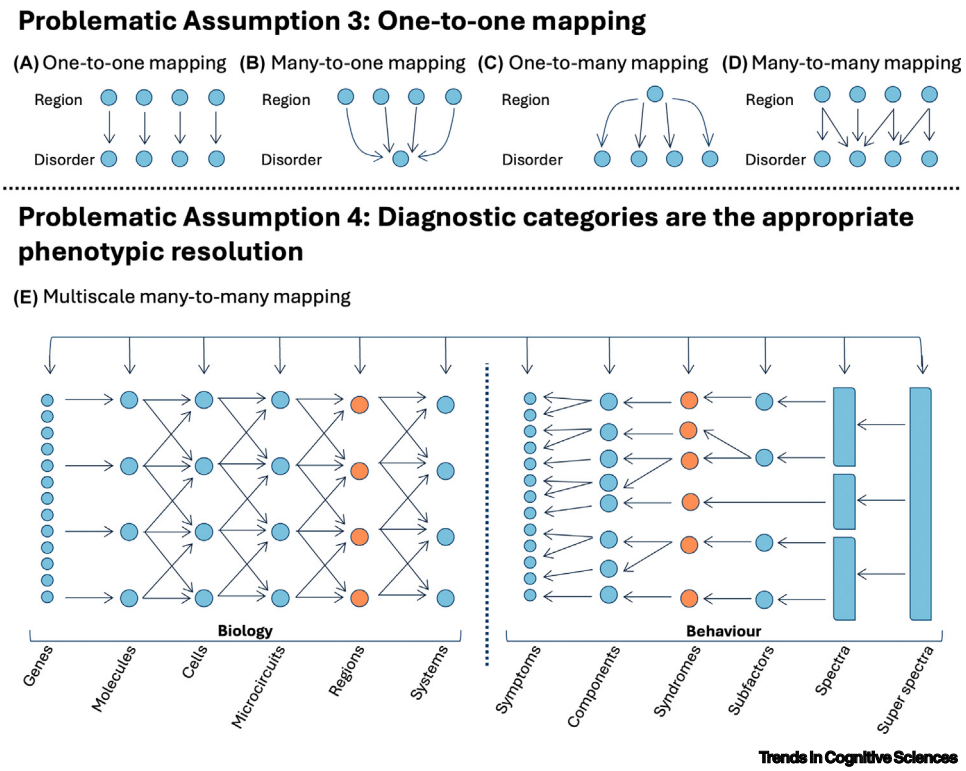

Figure 2. Second two problematic assumptions in the search for biological mechanisms of psychiatric illness. Assumption 3: There is a one-to-one between brain dysfunction and a given diagnosis. (A) A one-to-one mapping assumes that dysfunction of a specific brain region maps onto a specific disorder. Many other scenarios are possible including (B) a many-to-one mapping (i.e., heterogeneity), in which multiple brain regions contribute to the same disorder; (C) a one-to-many mapping (i.e., pleiotropy), in which a single brain region is involved in multiple disorders; and (D) a many-to-many mapping, in which multiple brain regions are involved in multiple disorders. Assumption 4: Diagnostic categories are the appropriate phenotypic resolution. Both biological and behavioral phenotypes can be described at different resolution scales, from genes and molecules through to higher-order behavioral dimensions such as 'p-factor'. As such, brain and behavior can be related at different levels of resolution (E). Orange shows the levels typically considered in neuroimaging, but there are possible links between every pair of levels.

when a single variant contributes to multiple phenotypes, yielding a one-to-many mapping (Figure 2c). In psychology, these two concepts are respectively referred to as **equifinality** (different starting points leading to the same diagnosis) and **multifinality** (similar starting points leading to different diagnoses).

In neurobiological investigations, mechanistic heterogeneity means that dysfunction across multiple brain regions or systems may contribute to a given diagnosis. For example, schizophrenia is widely regarded as a disorder of abnormal connectivity between spatially distributed interconnected neural systems [49], with widespread structural and functional cortical and subcortical alterations [50]. Likewise, ASD is associated with widespread cortical and subcortical morphometric [51] and functional connectivity differences [52]. The Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium has aggregated neuroimaging data across thousands of individuals and found widespread neuroanatomical disruptions in many psychiatric disorders, including depression [53], bipolar disorder [54] , and schizophrenia [55].

Neurobiological **pleiotropy** means that a single brain region may contribute to multiple symptoms/syndromes. For example, consistent reports of reduced prefrontal cortex (PFC) volume across diverse disorders, including ADHD [56], depression [57], OCD [58], and schizophrenia [59], are consistent with a one-to-many mapping. When studies adopt cross-disorder and transdiagnostic approaches to directly tease apart disorder-specific from disorder-general effects, general effects across diagnostic categories are frequently reported. A meta-analysis of voxel-based morphometry case–control studies across six psychiatric diagnoses (addiction, anxiety, bipolar disorder, depression, OCD, and schizophrenia) reported bilateral, disorder-general, gray matter volume reductions in the anterior insula and in the dorsal anterior cingulate cortex [60]. Patient-specific gray matter volume deviations identified through normative modeling provide converging evidence within this network across different diagnoses [16]. Transdiagnostic functional dysconnectivity of frontoparietal networks has also been established in depression, bipolar, schizoaffective disorder, and schizophrenia [61]. Such findings may either reflect mechanistic pleiotropy or the contribution of a more general factor related to one's overall burden of psychopathology (i.e., p-factor) [62] [63].

Considering this literature, a one-to-one mapping between diagnoses and pathophysiological mechanism seems unlikely. Rather, the available evidence suggests that dysfunction of any single brain region (or network) is neither necessary nor sufficient for symptom expression (consistent with a many-to-one mapping), and dysfunction of any given brain region (or network) is not unique to any disorder (consistent with a one-to-many mapping). A reasonable response following such observations would be to assume a many-to-many mapping, in which multiple brain regions or systems contribute to either common or divergent psychiatric phenotypes (Figure 2D). While this assumption may be more realistic based on current evidence, it does not offer a parsimonious explanation.

A major impediment to achieving such parsimony is that we do not currently understand how different scales of resolution in our biological measures should be aligned. Here, a resolution scale refers to our capacity to map the brain at the level of individual cells, regions, circuits, or broader macroscopic regions (Figure 2E). Noninvasive neuroimaging is limited in this respect, with most current techniques only able to probe brain structure and function at a spatial resolution of 1mm^3. Over the past decade, progress has been made in combining coarse-scale measures with complementary information that allows various annotations of the brain across different scales [64], such as data provided by transcriptomics [65–68], histology [69], and chemoarchitectonic

mapping [70], among others [71,72]. The combination of these techniques has already helped to characterize the molecular correlates of various clinical imaging phenotypes [65], but a major challenge will involve integrating information across different spatial scales [73,74] to understand precisely how microscale processes may drive the macroscale morphological and functional changes observed in patient populations. Indeed, dysfunction within a single brain region may emerge from multiple cellular or molecular causes.

Problematic assumption 4: diagnostic categories are appropriate phenotypic constructs for uncovering pathophysiological mechanisms

The fourth core assumption of the case–control paradigm is that diagnoses are the appropriate phenotypic resolution for uncovering pathophysiological mechanisms. It remains to be determined whether investigation of individual signs, symptoms, traits, behaviors, syndromes, or broader dimensions/constructs would be more fruitful (Figure 2E). The limited progress encountered after decades of work focusing on diagnoses should cause us to question whether this is the most appropriate level of phenotypic resolution or granularity, particularly given the issues considered in relation to problematic assumption 1.

A parallel approach, with its origins in cognitive neuropsychiatry [75] and lesion studies [76], focuses on specific symptoms and/or symptom components, such as delusions [77], hallucinations [78], and anhedonia [79]. This work has shed light on the neurocognitive mechanisms of specific clinical features, but it has not yet explained how different symptoms relate to each other and why some covary with each other more than others [80–82].

Alternative approaches leverage quantitative methods, predominantly factor analysis, to identify an empirically derived model of psychopathology. Such analyses of a large number of psychopathology signs, symptoms, and behaviors suggest that illness can be explained by a small set of hierarchically-organized and continuously distributed phenotypic dimensions, as exemplified by the HiTOP [10,83] (Box 3). A strength of these approaches is that they can facilitate our ability to map brain alterations occurring at different spatial and temporal scales to clinical phenomena with varying degrees of specificity in a way that circumvents many of the problems associated with reliance on diagnostic categories.

Box 3. HiTOP maximizes phenotypic variability in the measurement of psychopathology

The HiTOP model [10] comprises conceptually and empirically homogeneous psychopathology dimensions hierarchically organized from broad generality to high specificity (https://www.hitop-system.org/the-framework). At the top of the HiTOP model is the *p*-factor, conceptualized as a broad liability to many forms of psychopathology [62]. Empirically related but subordinate to the *p*-factor are conceptually and empirically narrower dimensions consisting of **superspectra** and **spectra**, such as Internalizing, describing syndromes focused on the self, and embedded below more specific **subfactors**, such as Distress, incorporating components related to depression and anxiety. At the bottom of the hierarchy are individual signs, symptoms, and maladaptive behaviors [10]. The HiTOP approach seeks to maximize phenotypic variability within and between individuals in the measurement of psychopathology, to facilitate the likelihood of identifying the neural mechanisms of psychiatric illness. First, individuals are not arbitrarily grouped together in heterogenous clusters because of the assignment of a common diagnostic label, and each are measured separately. Second, psychopathology is measured dimensionally, such that individual differences along the full continua of frequency, intensity, and/or severity are captured. Third, each individual is comprehensively profiled across the full spectrum of psychopathology, such that differences in all hierarchical dimensional components are measured. Fourth, psychopathology is assessed at a high level of granularity, including homogenous symptom components and maladaptive traits and individual signs, symptoms, and behaviors, maximizing individual differences. An omnibus measure of the HiTOP model is currently in development [128]. In the meantime, researchers can use existing measures to assess HiTOP constructs (https://hitop.unt.edu/clinical-tools/hitop-friendly-measures). Ideally, multiple HiTOP constructs at any level of generality or specificity can be chosen as targets for researchers conducting psychiatric neuroimaging studies. HiTOP is an empirically-grounded, comprehensive characterization of psychopathology that provides for the study of phenotypic variability. However, at present, this framework is largely theoretical and requires further biological validation [129].

Such efforts will be enhanced by a greater appreciation for the need for precision phenotyping. This need has been recognized in neuroimaging research for some time, with efforts directed towards improving scan acquisitions [84], data processing and denoising pipelines [85–87], and the acquisition of more extensive data in individuals [88,89]. More accurate and consistent terminology surrounding biological phenotypes, such as the definitions of brain regions and networks, will also be pivotal for future work [90].

By comparison, improving the measurement precision of psychiatric behavioral phenotypes (that is, observable characteristics or traits) is a cost-effective means for more accurately mapping the neural correlates of psychiatric illness, but it has received less attention (Box 4) [91–94]. This is a critical omission since phenotypic imprecision (a collection of factors that compromise the **construct validity** and **reliability** of behavior phenotypic measures) affects all subsequent inferences [93].

Precision phenotyping approaches that leverage quantitative methods (e.g., Box 4) will shed light on how different signs, symptoms, traits, behaviors, syndromes, or broader dimensions/constructs relate to each other and map onto biological measures at different resolution scales. Such efforts may be complemented by a focus on clinically meaningful outcome measures, such as treatment response or longitudinal prognosis. This effort could be facilitated by linking

Box 4. Precision behavioral phenotyping as a strategy for uncovering the neural mechanisms of psychiatric illness

The measurement precision of psychiatric phenotypes is often neglected in biological studies. Phenotypic imprecision can be defined as a collection of factors that compromise the construct validity and reliability of behavioral phenotypic measurement. Phenotypic imprecision affects all levels of inference as any analyses that rely on the psychological measure will be inaccurate [93]. Precision behavioral phenotyping offers a cost-effective way of enhancing effect sizes in such research and can involve several strategies:

(i) Sampling participants along the full dimensional continuum of severity increases phenotypic variability and statistical power while mitigating sampling biases.

(ii) Comprehensive assessment of psychological attributes using multiple measures (i.e., deep phenotyping) allows modeling of comorbidity and heterogeneity and facilitates data pooling.

(iii) Splitting psychopathology constructs into finer-grained elements ensures that variance in a measure reflects a single target psychiatric behavioral phenotype enabling reliable and valid inference.

(iv) Increasing phenotypic resolution by adding items from a scale that measures a construct representing the opposite, adaptive end of the continuum (e.g., assessing a spectrum of behavior ranging from attention problems to attention control) extends the proportion of the phenotypic latent trait continuum that quantifies meaningful individual differences.

(v) Establishing measurement invariance (i.e., equivalence of measurement properties of psychopathology scales between subgroups or subsamples, such as females and males) allows meaningful comparison between a greater number of groups and individuals.

(vi) Mixture modeling is an analytic approach that is used to address non-invariance and identify clusters or homogeneous subtypes/subgroups embedded within participant samples.

(vii) Multimethod assessment (i.e., pooling results from different types of measures of the same construct, such as questionnaire-based and cognitive measures) can overcome method bias, which results from error due to a reliance on one single type of measurement.

One or more of these techniques may be implemented in psychiatric neuroimaging studies to improve construct validity and reliability and to capture increased variability of the target behavioral phenotype (for discussion and worked examples, see [93]). For instance, the Extended Strengths and Weaknesses Assessment of Normal Behavior (E-SWAN) is an example of a collaborative effort focused on improving the measurement of psychiatric phenotypes through development of questionnaires that capture the full spectrum of the phenotypic distributions (http://www.eswan.org/; [130])

neuroimaging studies with the comprehensive longitudinal data captured by electronic health records.

Concluding remarks

Traditional one-size-fits-all approaches, as embodied by classical case–control paradigms, are unlikely to significantly advance our understanding of the biology of mental illness. Here, we have outlined the problematic assumptions on which this approach is based and have considered some potential solutions that can be used to move the field forward.

A common thread linking these possible solutions is that they embrace, rather than seek to mitigate, variability. Normative modeling offers a way to move beyond group mean comparisons to characterize neural variability across individuals by generating personalized brain maps [15], while precision phenotyping of symptomatology is perhaps the quickest and most cost-effective way to improve robust and reliable brain–behavior associations [93]. As these techniques evolve, incorporating the time and context within which biological and behavioral changes emerge at an individual level [95–97], and the inclusion of clinically meaningful outcome measures, will be essential for developing personalized and effective interventions [98,99] that address the diverse and interconnected factors influencing mental health. This effort should include, but should not be limited to, improving our understanding of how brain and behavior are related across sociodemographically diverse groups in different environmental and cultural contexts [100–102] (see Outstanding questions).

Such investigations will need to be viewed from a network-based perspective of brain function and pathology. Numerous adaptive and maladaptive changes can occur in the brain following pathology or insult (see [22,26,103] for discussion). Analytical frameworks that directly test competing hypotheses regarding the neural processes that mediate and constrain network changes will help to localize pathological vulnerabilities earlier in development, track and predict patterns of disease spread, and provide insight into which networks to target for treatment (see Outstanding questions).

Finally, as the field strives to uncover more parsimonious explanations of the biological mechanisms underlying psychiatric illness, future research should focus on two challenges/directions. First, most approaches within biological psychiatric research, and neuroimaging in particular, cannot tease apart cause (i.e., an upstream factor related to pathogenesis) from consequence (a downstream effect). It is also often unclear whether a particular brain change represents a primary effect of pathology, a compensation for pathology, confound (a methodological artifact), or comorbid effect [43]. Methods for disentangling these processes at the individual level are required (see Outstanding questions). Second, precision phenotyping across spatial and temporal scales, in terms of biology and behavior remains a challenge for the field (see Outstanding questions). Embracing frameworks that account for biological, behavioral, and environmental variability across scales will enhance our understanding of the biological mechanisms underlying psychiatric illness.

Outstanding questions

What is the time and context within which neural alterations emerge and change for a given individual?

In the absence of objective diagnostic measures for psychiatry, how can we make the most of clinically useful outcome measures (such as those derived from electronic health records) to understand the biological mechanisms of psychiatric illness?

How representative are our clinical samples compared to those encountered in real-world clinical settings?

What are the underlying neural mechanisms that mediate and constrain the phenotypic expression of psychiatric illness?

How do we disentangle the cause from consequence, compensation, confound, comorbidity and confound for disorder-related findings?

How can we integrate biological and behavioral information across spatial and temporal scales?

How can we optimize the measurement of clinical and biological phenotypes?

How can large-scale population studies be balanced with deep phenotyping to provide unique and complementary insights in biological psychiatry?

Declaration of interests

The authors declare no completing interests.

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Resources

[i]www.wired.com/2017/05/star-neuroscientist-tom-insel-leaves-google-spawned-verily-startup/?mbid=social_fb_onsiteshare

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