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The myth of optimality in clinical neuroscience

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Abstract

Clear evidence supports a dimensional view of psychiatric illness. Within this framework, the expression of disorder-relevant phenotypes are often interpreted as a breakdown or departure from normal brain functions. Conversely, health is reified, conceptualized as possessing a single ideal state. We challenge this concept here, arguing that there is no universally optimal profile of brain functioning. The evolutionary forces that shape our species select for a staggering diversity of human behavior. To support our position, we highlight pervasive population-level variability within large-scale functional networks and discrete circuits. We propose that rather than by examining behaviors in isolation, psychiatric illnesses can be best understood through the study of domains of functioning and associated multivariate patterns of variation across distributed brain systems.

Keywords

Psychiatric Illness Risk; Individual Differences; Brain Evolution; Phenomics; Research Domain Criteria (RDoC); Clinical Neuroscience

Healthy variation in the era of dimensional illness

Over the past 30 years, psychiatric research has largely relied on a categorical system of diagnosis through which disorders are often treated as discrete biological entities [1, 2]. Although this approach has clear utility, for example in terms of diagnostic reliability, its validity has been widely challenged [3, 4]. In response, the field has recently begun to embrace a dimensional perspective of illness that incorporates continua of neurobiology and observable behavior [5]. While this theoretical framework facilitates the study of transdiagnostic symptom profiles and biological features that cut across domains of psychopathology, marked inconsistencies exist in how broader variability within the general population is currently interpreted [6–8]. In this regard, a fundamental challenge facing clinical neuroscientists is how to best conceptualize healthy population-level behavioral and

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neurobiological variation when working to understand the **etiology** (see **Glossary**) of dimensional illnesses.

Implicit in modern clinical research is the assumption that deviations from the central tendency within a given **phenotype** by definition reflect an approach to pathology. Said another way, an unintended consequence of the adoption of dimensional models of illness has been the reification of health, a perspective where variability and vulnerability are treated as interchangeable constructs. In this review, we put forth an alternate interpretation of individual differences in the general population, arguing instead that there is no universally optimal profile of brain functioning. Critically, we do not dispute that psychopathologies in their various forms reflect significantly disordered behaviors that warrant treatment and likely possess discoverable brain bases. Rather, we present converging theoretical and empirical evidence demonstrating that pervasive population-level variability, even within clinically relevant phenotypes, should be interpreted in the context of both costs and benefits. Although specific brain functions are often treated as individual causal entities sufficient to generate pathology, they are far from deterministic in isolation. We conclude by proposing that research on the etiological bases of psychiatric illness will benefit from the collection of comprehensive **phenomic**-level datasets necessary to decipher the complex interactions of neurobiological processes, as well as their potential relations to domains of behavior and disease states [9–14].

The evolution of variability

Natural selection is a central organizing principle within the biological sciences. It is the primary mechanism of evolutionary change and provides the theoretical scaffolding that supports diverse fields of study from molecular and cellular biology through genetics, neuroscience, and psychology. Despite the fundamental importance of evolutionary concepts in clinical neuroscience, certain erroneous and unrealistic views have been incorporated, at least implicitly, in modern neurobiological theories of psychiatric illness. In the following sections, we detail core features of human brain evolution, providing selective examples from both cortical and subcortical systems. However, prior to discussing how variation presents in the general population, it is important to first highlight an essential principle of evolution through natural selection that helps to frame our argument.

> “Evolution has no long-term goal. There is no long-distance target, no final perfection to serve as a criterion for selection…”
>
> Richard Dawkins [15, p 50.].

Healthy variation is ubiquitous and adaptive in populations, from the level of genes through expressed behaviors. This variability is a fundamental requirement for evolutionary change, influencing **fitness**-linked traits and providing raw material for the process of natural selection [16]. Historically, intense selection pressures were often theorized to function as a winnowing process, gradually culling all but the most adaptive genetic and behavioral phenotypes [17, 18]. From this viewpoint, **heritable** variation ought to be absent within fitness relevant traits and most of the observable genetic variability in a population should be functionally irrelevant. A property of evolution that is reflected across species, for instance,

in the marked conservation of stereotyped gene regulatory elements that support core aspects of neural development [19]. This theoretical framework provides support for modern classification systems of psychiatric illness where dysfunction has been defined, in part, as deviation from a statistical norm [20], or the disrupted functioning of an evolved process [21]. As initially articulated, these theories of illness were carefully nuanced when defining what might constitute the failure of a biological system, particularly with respect to mental operations [21]. Yet, over time this subtlety has been lost and some persistent misconceptions have emerged across the field. These take two primary forms. First, that within the general population it is possible to identify an optimal value associated with a dimensional trait studied in isolation. Second, that the adaptive value of a trait is immutable or fixed. We briefly address each of these points below.

There are numerous reasons why the process of evolution in a population may not converge on a stable optimal value, or even a narrow range of values within a given trait (Box 1). Reflecting this property of natural selection, there is strong evidence for pervasive variability across species in domains with direct relevance to environmental fitness [22] ranging from morphometric features important to diet (beak depth in finches [23]) and predation (guppy color patterns [24]) through behavior responses linked with reproduction (the propensity to call in male crickets [25] or the mating strategies of large, anadromous male vs. small, mature male parr Atlantic salmon [26]) and temperament (boldness and docility in bighorn sheep ewes [27]). As space does not permit a detailed discussion of each area of possible variability relevant to clinical research, foraging behaviors will be used to illustrate that traits are not universally advantageous but rather reflect a mixture of costs and benefits. Readers should note that a thorough treatment of these arguments within the domain of personality and temperament is available elsewhere [28–32].

Box 1

The evolution of individual differences

Evolution does not obligate an approach toward a single archetypal form for a given trait. Within-population variation is ubiquitous across species in fitness-relevant phenotypes, such as tolerance of natural (abiotic) stressors, dietary preferences, predation risk, parasite resistance/tolerance, dispersal (e.g. partial migration), and temperament (e.g., dominance vs. submissiveness) [for review see, 32]. There are numerous pathways through which fitness-relevant variation is maintained in a population. Due to space limitations, we selectively highlight two interrelated processes that can result in population-level variability. Importantly, although we provide evidence for adaptation in select traits, readers should note that phenotypes may also vary within a population in a neutral manner.

Environments are rarely static. Diverse presentations of a given trait may be favored across conditions [145], resulting in population-level variability as fluctuating environments create divergent phenotypic selection. For instance, escape ability among Trinidadian guppies (Poecilia reticulata) evolves as a function of varying predation environments across freshwater streams [146]. Population differences in several antipredator behaviors evolve rapidly following environmental change (15–20 years;

~26–36 generations). Following release from high-predation environments, populations of guppies experience a rapid evolutionary loss of escape ability. This suggests the presence of steep fitness trade-offs associated with the expression of escape traits across contexts, possibly reflecting the increased resource costs associated with vigilance and escape rather than foraging and courting.

The distribution of intra- and inter-species competitors can give rise to distinct, yet equally adaptive, strategies for maximizing fitness in the absence of a universal optimum [134, 147]. As an example, natural selection may favor mechanisms that cause some individuals to seek behavioral and environmental niches with less intense competition [32]. This process of individual niche or strategic specialization can arise through factors including phenotypic variation across sexes [148], differences in size, shape, and behavior [149], and the presence of discrete morphs (forms) within a population [150]. In Atlantic salmon, for example, there is intense competition for mates. As a likely consequence, two alternate male mating strategies have emerged [26]. One phenotype consists of large males who search the spawning grounds courting mates and fighting rivals. In contrast, a second smaller class of males attempt to ‘sneak’ access to mates. Although this behavior carries costs in terms of subsequent growth and survival, it offsets the heavy burden associated with fighting for courtship opportunities. As should be clear in these examples, the expression of a trait is rarely entirely advantageous or disadvantageous; rather, it depends on the environment and relative frequency of phenotypes in a population.

Nearly all early studies of foraging assumed that there is a single ideal strategy with individual differences in behavior reflecting non-adaptive variation surrounding an adaptive mean [33]. In a seminal series of studies on the great tit, *Parus major*, Niels Dingemanse and colleagues elegantly showed the limits of this belief, establishing that the optimal temperamental profile and associated foraging style can vary from year-to-year according to environmental constraints [34–36]. In natural bird populations, as in humans [37], individuals differ in their predisposition to take risks and explore, particularly in novel or challenging situations. Dingemanse’s work revealed that when food was scarce, female birds with a tendency towards exploration were more successful at gathering the limited resources and had an increased probability of survival. Conversely, in years when food was abundant, increased exploration associated with unnecessary, dangerous, and costly aggressive encounters and decreased survival.

The absence of a universally optimal foraging strategy gives rise to the coexistence of a broad range of behavioral responses within populations [38]. Evidence for associated tradeoffs are apparent across evolutionary lineages. In honeybee colonies, for instance, the presence of consistent interindividual differences in behavior are essential to colony survival, enabling flexible responses to environmental variation. Individual bees fall along a continuum from slow-accurate to fast-inaccurate foraging strategies [39, 40]. While quick yet inefficient foraging results in greater total pollen collection within resource-rich environments, this strategy is less effective when resources are limited and accuracy is favored. The benefit of heterogeneous foraging strategies is also apparent in cases of **partial**

migration. As an illustrative example, the likelihood of migration in roach fish is influenced by individual differences in risk taking, with “bold” individuals demonstrating an increased propensity to migrate when temperature change reduces food availability and heightens predation risk [41]. While the act of migration may result in exposure to environmental hazards, it maximizes the availability of scarce resources for this subset of the population.

The presence of fluctuating costs and benefits are apparent over a host of time-scales, environmental contexts, and levels of analyses. In humans, a genetic mutation that reduces height by ~1 centimeter while also increasing osteoarthritis risk by ~80 percent may have helped some populations survive the most recent ice age [42], potentially through selective advantages including energetic control [43] and enhanced thermoregulation [44]. For those of us living within industrialized nations in relatively sterile environments, the *ε*4 allelic variant of the Apoliprotein E (APOE) gene is the strongest genetic risk factor for age-related cognitive decline and Alzheimer’s disease [45]. However, in environments with elevated parasitic loads the *ε*4 ‘risk’ variant of ApoE4 may transform from a liability to an advantage, associating with increased protection from parasitic infection [46–49] and heightened cognitive performance in individuals carrying a high pathogen and parasite load [50].

Why should clinical neuroscientists care about the evolution of the human brain?

A number of important motivations exist for considering the nature of both behavioral and neurobiological variability in the context of human brain evolution. First and foremost, a comprehensive understanding of the brain expansion that separates us from our closest ape cousins allows researchers to identify potential **homologs** and species-specific differences, a process of comparative analyses that serves as the backbone of modern biomedical science. As famously argued by Theodosius Dobzhansky [51], “nothing in biology makes sense except in the light of evolution.” The foundational discoveries that underpin the broad field of human neuroscience were, for the most part, derived on a select set of relatively distant model organisms (including sea slugs, fruit flies, zebrafish, rodents, cats, and macaque monkeys). The utility of this body of work rests on the core assumption that humans share common ancestry with other animals [52]. For clinical neuroscience specifically, the ‘dysfunction’ model of psychiatric illness is anchored in evolutionary biology and predicated on our ability to characterize the naturally selected function/s of disease-relevant biological processes. To accomplish this goal, we must consider the manner in which healthy variation presents throughout the brain, and in turn how that variability relates to suites of behaviors across a host of environmental contexts. In this regard, a striking observation has been that while neurobiological variability is pervasive, it is not distributed in a spatially uniform manner [53–55]. Instead, the observed profile of variability parallels the evolutionary expansion of the human brain (Figure 1A) [55–57].

Human brain evolution

The oldest known primate fossils are approximately ~55 million years of age, with the earliest primates potentially extending back into the Cretaceous period [58]. As the primate lineage evolved, intense selection pressures shaped and molded the **hominid** brain,

providing our distant ancestors with the capability to create tools, develop language, and form large social groups. As early as the turn of the 20th century, it was recognized that relative to other species, human brains are characterized by increased size, complexity, and circuit structure [59]. In animals, as a broad rule, absolute brain and body sizes share a predictable **allometric** relationship [60]. Yet, when considering body weight, the modern human brain is about 5 times larger than would be expected in a typical mammal [60]. With the exception of tree shrews, as the primate lineage diverged from rodents, rabbits, and flying lemurs, brain sizes increased markedly in proportion to overall body size [61]. This expansion predominantly affected the surface area of the **cerebral cortex** [62]. While all primate brains have disproportionally large neocortices given their absolute brain volume, the human cerebral cortex has vastly expanded since our evolutionary divergence from the last common ancestor shared with macaques ~25 million years ago and the ~6 million years that separate us from chimpanzees and bonobos, our closet living primate relatives [57, 63].

There is a common misconception that the evolutionary enlargement of the human brain is either specific or preferential to prefrontal cortex. Although prefrontal areas are greatly expanded in humans relative to non-human primates, so too are temporal and parietal cortices [64]. Notably, this scaling is not uniform across brain systems [62]. The basic spatial layout of the primary sensory areas that comprise unimodal cortex is largely conserved across mammals. However, as brain sizes increased in primates, a greater percentage of the cortical mantle began to occupy areas between the primary and secondary sensory systems [65], an effect that is amplified in humans [57]. These expanded cortical territories fall within the ‘association centres’ originally hypothesized by Paul Flechsig to serve as the neural substrate for higher cortical functions and complex associative processing [66]. Whereas unimodal sensory areas possess a serial, hierarchical pattern of feedforward/feedback connectivity [67], association cortex is characterized by an intricate non-canonical circuit organization [68]. These evolutionarily expanded aspects of cortex remain structurally immature during gestation [57] and myelinate later in development [69]. This prolonged maturation course exposes association cortex to environmental impacts during periods of high neuroplasticity, a feature of brain development that has clear implications for understanding variability in cognition and behavior [70]. Beyond these shifts in cortical anatomy, other specializations have occurred in the composition of human brain tissue (neurons, glia, axons and dendrites), including increased neuronal diversity and density, altered molecular expression, and different developmental stages and wiring paths [71–73] (Box 2).

Box 2

Human brain evolution beyond the cerebral cortex

The evolution of cerebral cortex should not be viewed as an isolated process, removed from the rest of the brain. Paralleling the increase in cortical surface area, the volume of white matter underlying cortical connections is disproportionately larger in humans than in other primates [151]. A process of ‘neocorticalization’ that provides an anatomical substrate for the increased influence of cerebral cortex on brain functions [61]. While the vast majority of the literature on both brain functioning and evolution is corticocentric, it

is not the case that ‘phylogenetically ancient’ brain regions are identical across species. Indeed, there is evidence for descent with modification across all brain systems throughout our evolutionary lineage, even those often miscast as purely phylogenetically recent (cortical) or evolutionarily old (subcortical). Consistent with the theory that anatomically and functionally coupled brain structures evolve together [152], the relative size and neuron numbers within subcortical regions have been linked to their degree of connectivity with association cortex. The human cerebellum, for example, is ~31% larger than the allometric expectation for a typical mammalian brain [153], a trait that is consistent across humans and great apes relative to other anthropoid primates [153]. While the primary role of the cerebellum was traditionally thought center on the planning and execution of motor movements [154–156], the majority of the human cerebellum is functionally linked with cerebral networks involved in cognition [78, 157]. Consistent with the preferential expansion of association cortex in humans, relative to great apes, the aspects of cerebellum interconnected with the prefrontal cortex are disproportionately larger than regions interconnected with the motor cortex [158]. Similar patterns are also evident across subcortex. For example, while the global volume, primary nuclei, and basic circuit connections and function of the amygdala are conserved across species [159], meaningful differences do exist [160]. Although the proportional volume of the amygdala is not substantially increased, the basolateral nuclei are enlarged in primates relative to rodents [161]. A potential consequence of the substantial increase in the size of the cortical territories that share reciprocal connections concentrated within the basolateral nucleus [104].

Healthy variability is apparent across large-scale networks and circumscribed circuits

Population-level variability is often taken, implicitly and erroneously, to indicate deviation from an archetypal ideal and an associated approach to pathology. Here we detail examples of functional and anatomical variation in healthy populations within both cortical and subcortical brain systems. The selected neurobiological phenotypes are not meant to be exhaustive, rather we hope to illustrate the point that neurobiological ‘markers’ of illness link to broad domains of behavior. In doing so, we highlight the presence of pervasive overlap across healthy and patient populations.

Frontoparietal network function in health and disease

At the turn of the 20th century Aloysius Alzheimer [74] and Elmer Southard [75] proposed a core role for the evolutionarily expanded aspects of human association cortex in neuropathology, suggesting that they underlie forms of dementia and psychotic illness. Rather than reflecting a single functional system, association cortex consists of distinct yet highly interconnected networks, each of which possesses a unique pattern of connectivity. The frontoparietal control network, for instance, which encompasses portions of the dorsolateral prefrontal, dorsomedial prefrontal, lateral parietal, and posterior temporal cortices [76] (Figure 1B) as well as corresponding aspects of the striatum [77] and cerebellum [78], underlies a host of executive functions that play a crucial role in goal-

directed planning [79], the application of complex, nested rules [80], and the dynamic control of motor outputs [81]. Consistent with the central importance of executive functioning deficits in mental health, a growing literature implicates frontoparietal network impairments as transdiagnostic markers of psychopathology [82]. A set of relationships that may emerge through the generation of symptoms that are domain-specific (e.g., impairments in executive function), but cut across a host of pathologies [83]. As one example, our work has demonstrated the presence of disrupted frontoparietal network function in a range of psychotic disorders (including schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis; Figure 1B) [84]. This accumulating body of evidence has prompted speculation that the frontoparietal network, and associated executive functions, may serve as an illness **biomarker** with potential diagnostic or predictive applications.

Targeting a specific, well-defined phenotype can provide a mechanistic level of analysis, allowing researchers to investigate the biological underpinnings of associated population-level variability and pathology. Without question, the study of frontoparietal network functions has provided important insights, characterizing aspects of brain biology that link to the presence of illness. Despite this progress, recent work has suggested limited clinical utility for the vast majority of proposed psychosis biomarkers [85, 86]. Potentially contributing to this disconnect, the bulk of case-control analyses report mean differences between groups within single neurobiological phenotypes studied in isolation. While this approach may yield consistent statistical differences, it can also mask the presence of substantial overlap in phenotypic distributions across populations, providing the illusion of group specificity (Figure 1C). This issue is particularly relevant in the evolutionary expanded aspects of association cortex, which are marked by pronounced population-level variability in both anatomy [37] and network topography [87], as well as spatially complex, and non-uniform, patterns of genetic heritability [88]. Across the large-scale cortical networks, frontoparietal exhibits the greatest functional variability, in contrast to the relatively muted intersubject variation within unimodal sensory and motor cortices [56]. This variability may arise, at least in part, though the relaxed genetic control of cortical organization in human association cortex relative to other primate species [89] and a prolonged maturation course. Consistent with this profile, highly overlapping distributions of frontoparietal network function are evident across patient and healthy comparison populations. The neurobiological factors that underlie common psychiatric illnesses do not operate in an isolated manner. Rather, there are numerous interactions that link the collective set of functional connections in the brain (functional connectome [90]) with a given phenotype. Although frontoparietal network disruption may contribute to a variety of psychiatric illnesses, it likely only does so in conjunction with variability in other brain systems [82, 83].

An additional issue that can obscure the relations linking brain functioning with real-world outcomes is a reliance on circumscribed behavioral/clinical endpoints. The frontoparietal network supports a wide-ranging set of executive functions (e.g. motor processing, working memory, and cognitive control) [91]. The perturbation of frontoparietal connectivity would, almost necessarily, influence the expression of a broad set of behaviors. Variation in any one of these processes is not, in and of itself, necessarily pathological. Together, these behaviors

present a complex set of interwoven phenotypes, whose impacts vary across environments. Impulsive sensation seeking provides a potentially useful example relevant to our discussion of foraging behaviors. Impairments in frontoparietal network mediated executive functions are hypothesized to underlie extreme forms of sensation seeking, impulsivity, and substance use in patient populations [92–94]. In healthy young adults, the expression of these behaviors links with subtle variations in brain anatomy, preferentially localized to regions implicated in cognitive control including the anterior cingulate cortex and middle frontal gyrus [37]. These data suggest that normal variation within the brain regions that support inhibitory control and goal-directed action could bias individuals toward substance use and the associated risk of developing abuse and dependence. Yet, this is not the only behavioral consequence. Our tendency to engage in sensation seeking and impulsive behaviors evolved as a function of their influence on survival and reproductive fitness [95]. They are not simply synonymous with adverse outcomes. For instance, increased sensation seeking co-varies with social behavior [96], social support [97], physical activity [98], reproductive opportunities [99], and environmental exploration [100].

Individual variability in amygdala-medial prefrontal cortex circuit anatomy

All creatures from single cells through complex vertebrates have the capacity to detect and respond to environmental threats and opportunities [101]. These behavioral capabilities are fundamental to survival as organisms work to balance potential benefits (e.g. acquiring food or mates) against possible dangers (e.g. predation). In mammals, these survival-relevant processes are supported by the coordinated function of a highly integrated system centered on the amygdala [102]. While there is evidence for a strong conservation of this circuitry across species, throughout primate evolution it has increased in complexity, supporting the development of progressively sophisticated behaviors [103]. In human and non-human primates, the projections that link amygdala with cortex are widespread, but are particularly dense within **medial prefrontal cortex (mPFC)** rostral and ventral to the genu of the corpus callosum [104]. Coordinated amygdala-mPFC circuit function supports a host of behaviors including affective [105, 106] and social processes [107, 108], as well as vigilance and arousal in response to salient environmental stimuli [109, 110].

There is strong evidence for group-level shifts within the structure and function of amygdala-mPFC circuitry across a range of psychiatric disorders marked by heightened threat sensitivity, dysregulated affect, and impaired social cognition. This is perhaps most evident in unipolar and bipolar depression where the disrupted metabolism and function of mPFC is hypothesized to underlie the occurrence of depressive and manic episodes [104, 111, 112], while cortical thinning in mPFC associates with illness chronicity [113]. In healthy populations, the strength of anatomical [114], intrinsic [115] and task-evoked [116] amygdala-mPFC coupling is altered in individuals with high levels of anxiety or related behavioral profiles. Cortical thinning in the mPFC regions associated with negative affect links with decreased social functioning [114] (Figure 2A). However, while affective and social impairments reflect core features of depression, the relations between amygdala-mPFC circuit anatomy and illness are remarkably subtle [117, 118], accounting for a limited amount of the phenotypic variance in case-control analyses (Figure 2B). Although individual differences in affect and social cognition may be neurally embedded within clinically

healthy individuals, and while statistically significant structural abnormalities are evident in large-scale analyses of patient populations, the observed associations are too small to be useful as individual predictors of illness risk or onset.

The relation between psychological health and social functioning is well established [119, 120]. Given the evidence for a broad range of detrimental effects associated with even slight variations in amygdala-mPFC circuit function, much of the research in this area has understandably been focused on maladaptive costs and negative outcomes. While negative affect and reduced sociability may heighten risk for psychiatric [121, 122] and physical illnesses [123, 124], they can also aid in the avoidance of adverse events [125–127]. As noted above, reduced threat sensitivity in animals associates with increased environmental exploration and foraging opportunities, while anxiety and its associated reduction in exploration decreases predation risk [128]. In humans, even moderate levels of anxiety are predictive of reduced accidents and accidental death in early adulthood [129], while the genetic associates of anxiety and worry are linked to affluence, cognitive ability, improved health, and longer life [127]. A similar profile of both beneficial and detrimental impacts is evident when considering social functions. For instance, although social integration might improve access to food, protection, and mating opportunities [130, 131], it also can increase resource competition, role strain, and infection exposure [121, 132, 133].

Focus on fitness/Focus on the phenome

A core goal of clinical neuroscience is to characterize the biological processes that underlie diseases and disorders of the brain and central nervous system, enabling the development of more effective treatment and prevention strategies. Historically, the vast majority of work in this domain has focused on carefully curated sets of behaviors or symptoms of interest, studied in isolation (Figure 3A). This important work provides a foundational first step in understanding how neurobiological variability relates to clinical pathology, but it can only take us so far. Heritable variation is pervasive across the population and should be expected as the normal outcome of evolutionary processes. With the exception of gross pathology, shifts within a selected neurobiological function or behavior in isolation will neither be necessary nor sufficient to generate psychiatric illness. Within an individual, behavior is not fixed or static, changing in response to available resources, environmental demands, and internally held goals. While there may be fitness disadvantages at the extremes [134], population-level variability must be interpreted in terms of cost-benefit tradeoffs that can dynamically fluctuate across environments [28]. Moreover, the brain functions as an integrated system. Complex demographic, clinical, and behavioral phenotypes arise from coordinated interactions throughout the functional connectome [135]. Functionally flexible brain regions show nonspecific relations to behavior, supporting a wide range of cognitive processes [91, 135] (Figure 3B). Given this level of complexity, it is unlikely that we will achieve a breakthrough in our understanding of how the brain’s intricate functions give rise to psychiatric illness by investigating a handful of candidate biomarkers at a time. Current limits on our ability to understand many important illness-relevant biological phenomena suggest that we are not adequately sampling all the relevant variables and that we must broaden our phenotypic net [9–14].

Understanding how variability in brain functions contributes to the onset of psychiatric illness depends on unraveling the precise and carefully coordinated interactions between networked brain regions and their associated responses to environmental change. Individual differences in behavior are correlated across functional contexts, such as the relationship between foraging and mating [32]. The interactional nature of behavioral phenotypes likely results in complex fitness landscapes [136]. However, most studies of phenotypic variability in health and disease tend to be disconnected from one another, impeding the development of fully dimensional models of brain function and obscuring how neurobiological processes might coalesce to support suites of behaviors within an individual. To characterize the consequences of variability within a given aspect of brain functioning, these relationships need to be fully catalogued, allowing researchers to link phenomena across levels, from genes and molecules through cells, circuits, networks, and behavior (Figure 4, Key figure). Progress in this domain will come through the collection of holistic datasets, or physiomes [9], that encompass brain structure and function as well as diverse clinical, demographic, behavioral, genetic phenotypes.

A call for (multivariate) phenomics in neuroscience and psychiatry

Over the past several decades, geneticists have persuasively argued for the initiation of large-scale phenotyping efforts to link genetic variants and biological outcomes [9–14]. Echoing these debates, clinical neuroscientists must decide between focusing individual efforts on a stable but limited set of measures or expanding our approach to collaboratively purse the collection of phenomic-level data. This is the ideal time to consider such a question. The union of new imaging technologies, methods for online or remote behavioral sampling, and a cultural shift towards open access data have provided the opportunity to rapidly acquire high-dimensional phenotypic data in large populations [137] or in individuals with dense longitudinal sampling [138]. In parallel, the rapid development of computationally sophisticated analytic approaches have allowed us characterize the functional connectome, establishing that large-scale network functions are heritable [88, 139] and serve as a stable and reliable “fingerprint” across individuals [87, 140]. However, despite these important advances, we lack the necessary data to decipher the intricate relations linking the totality of brain functions with complex behavioral phenomena.

Recently, large-scale collaborative efforts have begun to generate broad phenotypic batteries that encompass brain structure and function as well as multiple domains of cognition, behavior and genetics [141–144]. Although challenges remain (Box 3), these herculean efforts have provided a wealth of data for researchers to map links across diverse neural and cognitive states. Unfortunately, these collections have been largely divorced from research on clinical populations (see Outstanding Questions). Understanding how an aspect of brain biology impacts a selected behavior requires the study of how brain processes integrate information across specialized networks to function as a unified whole, how diverse sets of behaviors relate to one another, and how individuals within the population respond to shifting contextual and environmental factors across their lifespan. The map of the relations linking population-level variability with illness risk will be inaccessible without detailed and comprehensive high-dimensional phenotypic data to allow these interactions to be studied.

Box 3

Progress, limitations, and considerations

The unprecedented growth of big data in neuroscience provides opportunities for researchers seeking to understand how brain functions influence suites of behavioral phenotypes and associated illness risk. To date, these efforts have largely focused on cross-sectional samples [141, 142] or longitudinal assessments within select individuals [138]. Initially, open-access datasets within clinical populations were limited in scope and concentrated on the early detection and tracking of age-related pathologies [162, 163]. Recently, collaborative genomic, imaging, and public health initiatives have been formed to improve the diagnosis and treatment of a wide range of serious illnesses across adolescence and adulthood [143, 144, 164–166]. Despite the development of these important resources, several key challenges remain.

Human behavior presents a special challenge for the collection of high-throughput data because of its dynamic nature and dependence on context. As a result, consortia must be somewhat selective when charting out the range of environments, phenotypes, and spatial and temporal scales at which data should be collected. The available data are often limited by our expectations of disease mechanism, potentially obscuring novel discovery. Additionally, these constraints can result in samples that are not fully representative of the general population across a variety of demographic, physical, lifestyle, and health-related characteristics. This is perhaps most relevant in the area of developmental variability. In adult populations, the observed profiles of neurobiological variability may be genetically driven, or could arise in conjunction with developmental and behavioral plasticity or early-life factors such as social status or environment. Clearly, in cases where longitudinal data are unavailable, we must constrain our interpretation to fit the sample characteristics within each dataset.

The scale of open-data consortiums in neuroscience makes it possible to study the relations linking brain functions with rich sets of behaviors, for instance the use of remote collection methods to examine the free movement of individuals interacting with their environment. Yet, as datasets increase in density, it will become more and more difficult to analyze and extract meaningful biological conclusions. For many research groups, a key challenge to overcome in the use of big-data is the substantial compute requirements, and analytic expertise, for the storage and analysis of massive collections of cross-modal digital information that often exceeds tens or even hundreds of terabytes. Here, we need to adopt recent advancements in the analyses of high-dimensional datasets developed in statistics and machine learning [167, 168], collaborating across fields with specialists trained to implement these approaches.

Outstanding Questions Box

- How do dynamic changes in brain functions and behavior differentially shape fitness and illness risk across the lifespan? The diversity of human experience, from health to disease, arises through developmental processes that unfold

over the lifespan. The costs and benefits of many behaviors vary over the course of an individual's life, in ways that are largely unexplored.

- To what extent are the adaptive and maladaptive features of clinically relevant behaviors determined by an individual's environment? The detrimental or beneficial impacts of variability in most behaviors remain largely unknown across environments. For many environments, it is not clear if, or even when, experience might influence brain or behavior. Do certain experiences induce shifts in brain function that are transiently adaptive but carry long term costs?
- Are there converging relations across *in vivo* imaging methods that better capture the links between brain and behavior? Most large-scale phenotyping efforts rely on intrinsic connectivity estimates to infer brain function. As an approach, it is not without limitations. If task-evoked manipulations are utilized, which phenotypes should we prioritize?
- To what degree does the unique spatial configuration of an individual's functional connectome relate to inter-subject variation in behavior? Evolutionary expanded aspects of association cortex are characterized by marked variability in both network function and topographic organization. Individualized network parcellations may help disentangle the impact of variability in brain organization from functional integrity when investigating illness risk.
- How should we train future generations of scientists? Traditional statistics emphasize relations between limited sets of predictors and outcome variables. The size and scope of large-scale phenomic datasets will shape future data analysis practices. The study of brain-phenome relations is beyond the expertise of individual labs and will likely require cross-field collaboration and training approaches that extend beyond isolated departments.

Concluding remarks

The ubiquity of healthy variability in behavior and brain functions seems to pose a clear challenge for the study of dimensional illness. While it may not be feasible to identify individual features of brain biology that cleanly separate healthy and disordered populations, multivariate fingerprints of pathology may eventually emerge. To identify such points of demarcation, our data collection and analytic efforts will have to incorporate genetics, neurobiology, and dense phenomic samples of entire individuals and their associated environments. To aggregate, analyze, and interpret such high-dimensional datasets, we will need to reassess our current conceptual framework, extending beyond conventional clinic or laboratory-based behavioral assays. As highlighted in this review, progress in the study of psychiatric illness will require increased collaboration as the field works to piece together the necessary integrative datasets. With a sufficiently dense sample of phenotypes, it may be possible to determine which aspects of brain function underlie differences in behavior and fitness across environments. Such detailed information can then be leveraged to nominate etiological mechanisms underlying vulnerability for illness onset.

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Glossary

Allometric scaling
relation between the size of the body as a whole and the size of a specific structure. Although a given component may differ to a greater degree than another, they must show a predictable relationship. This can differ from isometric scaling, where organisms maintain geometric similarity as they change in size (e.g., the relationship linking surface area and body mass).

Biomarker
a measurable indicator whose presence is an objective sign of a given biological state or condition, including pathogenic processes or pharmacologic responses to a therapeutic intervention.

Cerebral Cortex
the 2–3mm thick multi-layered sheet of gray matter that covers both hemispheres and supports sensory and motor functions as well as the ‘higher’ mental processes that are theorized to distinguish humans from other animals.

Etiology
the study of causation or origination. Etiology is often used to refer to the cause of a pathological or abnormal condition.

Fitness (within the context of evolution)
reproductive success of a genotype or phenotype within a given environment.

Heritable
observed phenotypic variation that is attributable to genetic variation, transmissible from parent to offspring.

Homologs
refers to similar structures, physiological characteristics, or development in related species that have been inherited through their descent from a common ancestor.

Hominids
a taxonomic family of primates that includes humans, the great apes (bonobos, chimpanzees, gorillas, orangutans), and their extinct ancestors.

Medial prefrontal cortex (mPFC)
the medial surface of the frontal lobe encompassing both granular cortical areas (medial aspects of Brodmann areas (BA) 9 and 10) and agranular regions (BA 24, 25, and 32), which

include the peri-/sub-genual anterior cingulate cortex (BA 24), infralimbic cortex (BA 25), and prelimbic cortex (BA 32).

Partial migration
a phenomenon where only a fraction of a population is migratory, some individuals may participate in seasonal migration while others do not.

Phenomics
the area of biology concerned with the measurement of phenomes, or the full set of physical and biological traits belonging to a given organism. Phenomics can also refer to the acquisition of high-dimensional phenotypic data.

Phenotype
the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment.

Phylogenetic
the evolutionary development and history of a species or higher taxonomic grouping of organisms.

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Trends Box

Implicit in modern dimensional theories of psychiatric illness is the assumption that population variability and illness vulnerability are interchangeable constructs.

Mounting evidence suggests that healthy variation is ubiquitous in natural populations and must be interpreted in terms of cost-benefit tradeoffs.

Psychiatric illnesses arise through a web of interactions linking brain function, behavior, and a lifetime of experiences. Research on illness etiology will only progress through the collection of comprehensive phenomic-level datasets.

Large-scale collaborative efforts begun to generate broad phenotypic batteries that encompass environmental and contextual factors, brain structure and function, as well as multiple domains of cognition, behavior and genetics. These datasets hold great potential for clinical researchers seeking to map links across diverse neural and cognitive states.

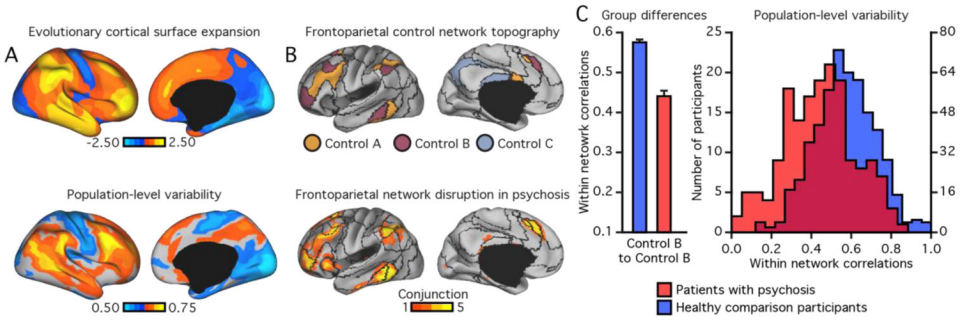

Figure 1. Healthy variability is apparent across neurobiological markers of illness risk

(A) The evolutionary expansion of human cerebral cortex is highly correlated with inter-subject variability in functional connectivity. The top image reflects a comparison of evolutionary cortical expansion between an adult macaque and the average human adult. Values indicate the absolute expansion ratio, normalized by taking the logarithm subtracted with a constant. Data are displayed on the lateral and medial cortical surfaces. Bottom image displays the intersubject variability in functional connectivity across the cerebral cortex. Cool colors reflect values below the global mean, while values above the global mean are shown in warm colors. Figures adapted from data provided by van Essen [55], Mueller [56] and colleagues. (B) Top image reflects frontoparietal control network topography revealed through intrinsic functional connectivity. Colors reflect regions estimated to be within the same frontoparietal sub-network (control A, B, and C). Bottom image displays the functional connectivity differences between patients with psychotic illness and healthy comparison participants across regions in the control B network, shown using a conventional seed-based approach. Values reflect conjunction of significant differences across control B regions displayed on the left hemisphere. (C) Analytic approaches that focus on group differences may mask the presence of substantial overlap in phenotypic distributions across populations, providing the illusion of diagnostic specificity. Bar graph and histograms show the correlations between components of the frontoparietal control network in patients with psychotic illness and healthy comparison participants. Error bars denote SE. Adapted with permission from [84, 142].

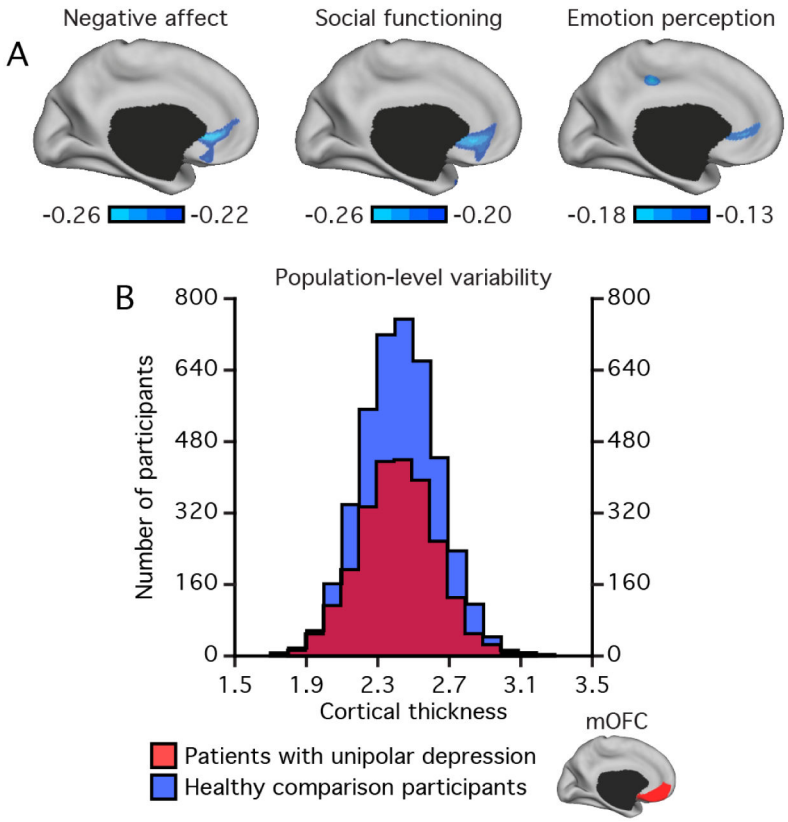

Figure 2. Healthy variability is apparent across circumscribed brain circuits

(A) In healthy young adults, subtle shifts in the gray matter thickness of medial prefrontal cortex links negative affect, impaired social functioning, and errors in emotion perception. These data suggest that variability in multiple domains of function are reflected in the normal anatomical variability of a shared mPFC network. Color bars reflects Pearson correlations. Adapted with permission from [114]. (B) Although statically significant structural abnormalities are evident in large-scale analyses of psychiatric illness, pervasive overlap exists across healthy and patient populations. The observed associations are likely too small to be useful as predictors for individuals and a limited amount of the phenotypic variance is accounted for in case-control analyses. Histogram shows the mean cortical thickness of the left medial orbitofrontal cortex (mOFC) for adult patients with major depressive disorder and healthy comparison participants. Figure adapted from data provided by Schmaal and colleagues [117] (http://enigma.ini.usc.edu/ongoing/enigma-mdd-working-group/).

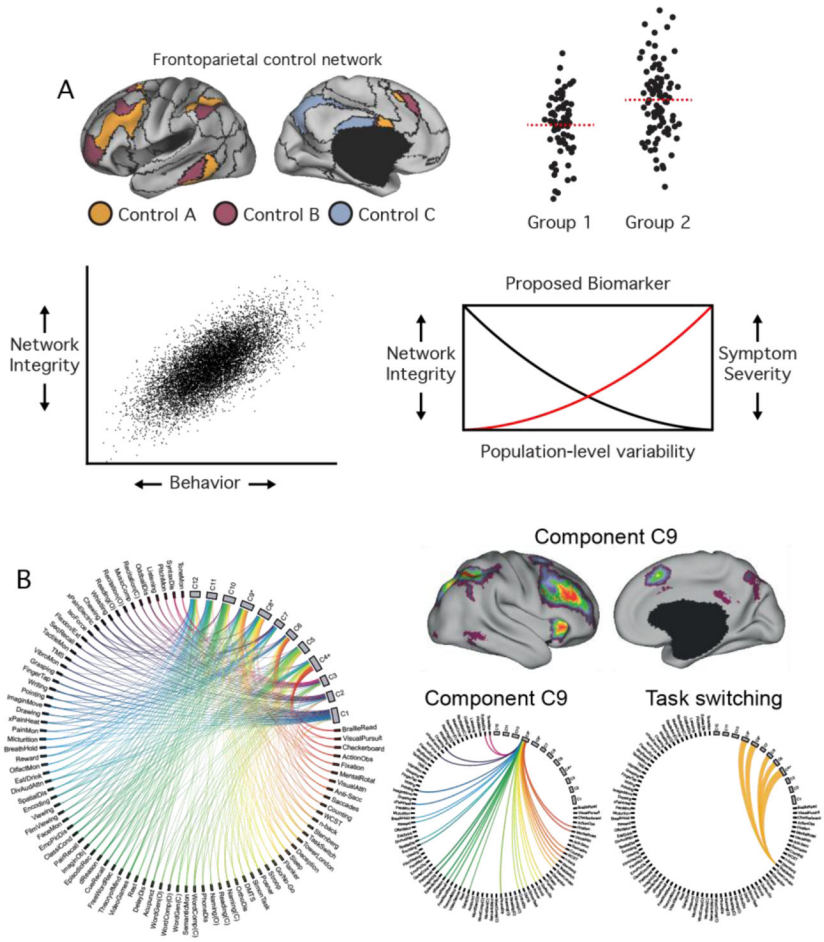

Figure 3. Complex phenotypes arise from coordinated interactions across the functional connectome

(A) Research on psychiatric illness etiology often focuses on isolated aspects of brain function and limited sets of behaviors. Here, toy data provides an example where case/control differences in frontoparietal network connectivity, and evidence that network variability links with a circumscribed behavior, may be taken to suggest the presence of an illness biomarker. (B) However, attempts to nominate biomarkers with a few curated phenotypes are unlikely to be successful. The brain functions as an integrated system. Complex behaviors emerge from coordinated interactions throughout the functional connectome (many-to-one). A given neurobiological process can support suites of behaviors (one-to-many). The circle plot on the left reflects a nested cognitive ontology estimated from 10,449 fMRI experiments across 83 task categories. Adapted from data provided by Yeo and colleagues [91]. Each line connects 1 task with 1 cognitive component. Tasks grouped with similar components are more closely positioned and their lines were assigned similar colors. Component C9, which largely overlaps the frontoparietal network, and task switching are highlighted to demonstrate that a given component can support multiple behaviors while a select behavioral task can engage numerous cognitive components, which are in turn supported by multiple overlapping brain regions. To characterize the consequences of

variability within a given aspect of brain functioning, we should work to catalogue how the brain functions as a unified whole to influence diverse sets of interrelated behaviors.

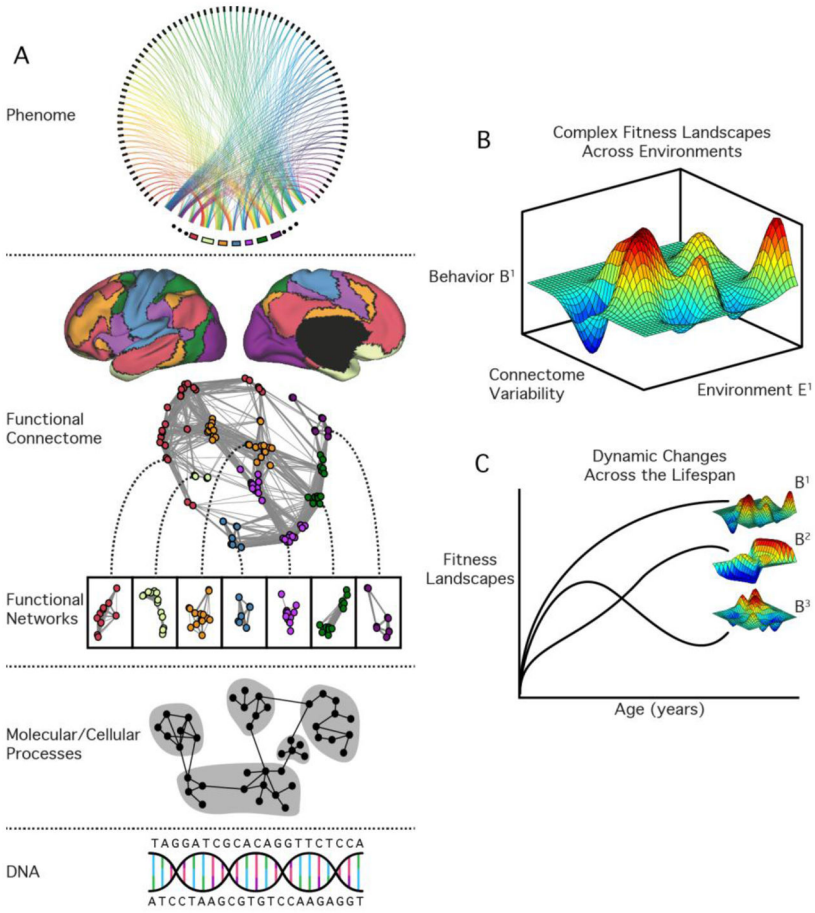

Figure 4. Focus on the phenome

The collection of detailed and comprehensive high-dimensional phenotypic data will facilitate the study of relationships that link individual variability with illness risk across the lifespan. (A) Schematic representation of the complex interactions linking genetic and neurobiological variation with the full set of phenotypes expressed by an individual. At the base of the figure, heritable genetic variation (DNA) biases molecular and cellular processes. A network view of interacting molecular and cellular process is depicted as a graph, where individual processes are shown as nodes and process–process interactions as edges connecting the nodes. From there cellular and circuit functions emerge, up through the formation and maintenance of large-scale networks. Integrated functioning across the connectome influences the expression of complex demographic, clinical, and behavioral phenotypes. Readers should note that feedforward/feedback relations also link across the levels. Connectome and phenome data provided by [91, 142]. (B) The phenome is not static. The varying costs and benefits of behavior across environments results in complex fitness landscapes. Graph reflects a schematic example of the potential impact of behavior B^1 in environment E^1. (C) Fitness landscapes shift across the lifespan. Both brain functions and environments change across time. Behaviors demonstrate dissociable cost/benefit trajectories over the lifespan. Identical behaviors may have opposing effects fitness at early and late ages. These relationships need to be fully catalogued, allowing researchers to link

phenomena across levels, from genes and molecules through cells, circuits, networks, and behavior.