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A cross-disorder connectome landscape of brain dysconnectivity

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Abstract

Many human brain disorders are associated with characteristic alterations in the structural and functional connectivity of the brain. In this article, we explore how commonalities and differences in connectome alterations can reveal relationships across disorders. We survey recent literature on connectivity changes in neurological and psychiatric disorders in the context of key organizational principles of the human connectome and observe that several disturbances to network properties of the human brain have a common role in a wide range of brain disorders and point towards potentially shared network mechanisms underpinning disorders. We hypothesize that the distinct dimensions along which connectome networks are organized (for example, ‘modularity’ and ‘integration’) provide a general coordinate system that allows description and categorization of relationships between seemingly disparate disorders. We outline a cross-disorder ‘connectome landscape of dysconnectivity’ along these principal dimensions of network organization that may place shared connectome alterations between brain disorders in a common framework.

Brain function depends on effective communication between distinct functional brain systems. The anatomical substrate enabling functional neural communication and integration is the ‘connectome’, the complex network of structural connections of a nervous system[1]. The overarching goal of the field of connectomics is to understand how network organization of the connectome relates to the brain’s capacity for neural processing and

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brain function[2]. Conversely, it harbours a powerful toolset to examine how alterations to the connectome may lead to brain dysfunction in disease[3,4].

The human connectome displays multiple features of an efficient communication network, including cost-conserving wiring, a community structure that promotes locally specialized neural processing and long-distance projections that facilitate globally short communication relays[5,6]. The complex architecture of the connectome has an important role in shaping functional communication and connectivity patterns between brain regions[7–10], which ultimately underpin brain function and dysfunction. A key attribute of the human connectome is the large investment of neural resources in macroscale connectivity to keep the brain globally connected, with a considerable proportion of the cerebral volume comprising white matter[11], the anatomical compartment that contains most of the brain's long-range communication pathways[9]. Although high investment in inter-regional connectivity supports integrated brain function, disruption to this connectivity may render brain networks vulnerable to disorders. Adding to a wealth of empirical findings and growing understanding of the biological background of brain disorders at the level of molecular processes, genetics and neuroimaging (for examples, see REFS[12–14]), considerable effort in the past decade has been directed towards identifying connectivity substrates and biomarkers that are associated with specific brain disorders and that predict disease severity, prognosis and outcome.

Promising progress has been made using various 'network neuroscience' tools to search for alterations in structural and functional connectivity underlying brain disorders[15] (see BOX 1 for a brief overview of commonly used network features). A rapidly growing body of literature suggests that many neurological and psychiatric disorders involve changes in the network features of the human connectome (see BOXES 2,3 for examples). This work motivated the early notion that these characteristic network metrics could serve as specific biological markers for these disorders[16,17]. Thus far, the new field of 'disease connectomics' has focused on the characterization of network alterations in one disorder at a time, with many studies reporting disturbances in the same set of network attributes across different disorders. For example, alterations in functional connectivity of the default-mode network have been implicated in Alzheimer disease[18], autism[19], schizophrenia[20], depression[21], amyotrophic lateral sclerosis (ALS)[22] and epilepsy[23], among other disorders. Similarly, disruption of the modular architecture of the connectome has been associated with autism[24], depression[25], epilepsy[26], schizophrenia[27] and 22q11 deletion syndrome[28]. This redundancy naturally has led to a critical discussion of the utility of network metrics as biomarkers for disease[29]. Here, we suggest that it may also point to the existence of shared patterns of dysconnectivity across disorders.

Extending the growing trend for dimensional approaches (as opposed to categorical approaches) in mental health disorders[30–32], transdiagnostic studies have started to emphasize the importance of looking for commonalities and differences in neurobiological changes across brain disorders. In search of common neurobiological substrates[33] and cross-diagnostic convergence[34], studies have started to suggest that alterations in functional systems and anatomical circuits may have a role in cross-disorder dysfunction and symptoms[35,36]. Here, we build on this notion and examine potential common

connectional substrates for brain disorders. Our intent is not to provide a detailed report on all connectome findings in neurological and psychiatric disorders but to focus on commonalities and differences in disease-related changes in connectome organization and leverage these observations into a common cross-disorder framework.

The majority of empirical disease connectome studies have reported alterations in network organization in a single disorder; therefore, little is known about the dimensions along which the connectional substrates of multiple disorders are potentially linked. In other words, we currently lack a ‘common space’ or ‘landscape’ that could link connectome alterations across disorders. Studying patterns of connectivity in multiple disorders and placing them into a cross-disorder landscape may reveal common biological mechanisms of disease and, as such, account for shared symptomology, as well as common developmental and/or genetic mechanisms across disorders. We hypothesize that shared network mechanisms relate to fundamental principles of how human brain networks are organized, shaping brain dysconnectivity effects across disorders in a characteristic fashion. We begin with a brief overview of two of the major principles of network organization of the human connectome: ‘modularity’ and ‘integration’. We consider how these network dimensions define a continuum of all possible human connectome configurations (a ‘space’ of human brain networks). With this framework in mind, we survey empirical findings relating to connectome alterations that are associated with the aetiology of neurological and psychiatric conditions. We then propose a cross-disorder ‘connectome landscape of dysconnectivity’ of brain disorders that is built on the dimensional approach to connectome architecture and hypothesize that common disease-related alterations in the connectome correspond to shifts or displacements of human brain networks among regions in this dimensional landscape. We conclude with an outlook on the future of cross-disorder connectomics and discuss new avenues towards studying common biological substrates of brain disorders.

Principles of connectivity

Network studies across a wide range of species have revealed common ‘principles of connectivity’[5], including network attributes that appear to be widely conserved and represent fundamental features of brain organization and function. Two proposed major driving forces of neural and brain network organization are a tendency to minimize the physical and metabolic cost of wiring (for example, by promoting the use of local circuitry and the formation of local modules) and the need to invest resources in network attributes that promote network efficiency[6].

Cost minimization underpins one of the major themes in connectome organization. It favours the formation of structural connections between geometrically close neural elements, promoting dense local circuitry by forming spatially compact (‘or clustered’) network communities (‘network modules’; BOX 1). Both anatomical and functional network communities support specialized neural processing, a foundation for primary as well as higher-order cognitive brain systems in the non-human[37,38] and human brain[10,39]. Variation in functional modules across individuals has been linked to variation in behaviour, for example, in general intelligence[40], working memory[41] and several personality traits[42,43].

A second key principle is the propensity of connectomes to express network attributes that promote global communication and functional integration[44]. Although costly in terms of neural resources, long-range connections are beneficial for enabling efficient neural communication between brain regions that are not only spatially remote but also functionally distinct. Many of the long-range connections are maintained by highly central hub regions that display diverse connections across a wide range of functional domains[45,46]. These hub regions tend to connect densely to each other, forming a central 'core' or 'rich club' in the network[9,47]. Offsetting its high connection cost[6,48], the central topological embedding of this rich club facilitates global integration of information across different functional domains in the network[49–51]. Empirical observations suggest that inter-individual variation in anatomical and functional hub structure is associated with inter-individual differences in cognition[52,53] and with inter-individual differences in brain dysfunction in disease (for examples, see REFS[44,54,55]).

As is the case with many seemingly distinct attributes of brain networks[56], these two principles of connectome organization ('modularity' and 'integration') should not be considered as mutually independent — instead, they jointly emerge in the course of development and evolution[5,57–59]. However, they are somewhat opposite poles: the drive to conserve wiring cost (for example, promoting modular organization) is generally incompatible with the simultaneous drive to promote efficient system-wide integration (for example, promoting densely connected hubs and global communication). These competing objectives are resolved in a 'compromise' or 'trade-off' in the design of a globally optimal network topology, which maximizes their joint expression in cost-efficient connectome architectures[6,60].

We note that 'modularity' and 'integration' certainly do not describe the entire spectrum of complexity in the brain's network organization and possible connectome alterations in disease. Rather, we adopt them here as candidates for building a parsimonious framework that can capture the rich set of individual variation in the human connectome that is driven by a plethora of specific variations in wiring patterns, myelination, sizes and spatial positions of areas, cortical folding, placement of hubs and the layout of communication paths, among many other factors[5,6,58]. We focus our exploration of disease-related connectome alterations around these two major wiring principles.

Connectome disruptions

Interest is growing in examining the role of alterations in network attributes in the origin, progression and clinical trajectory of brain disorders. For example, studies have reported functional connectivity changes in hub regions in the default-mode network in Alzheimer disease[61,62], alterations in anatomical and functional connectivity in the motor system in ALS[63], altered functional core connectivity in patients with Huntington disease[64] and changes in functional network dynamics in different forms of epilepsy[65]. Similarly, disruptions in connectome organization have been implicated in the aetiology of multiple neurodevelopmental psychiatric conditions, for example, hyperconnectivity in autism spectrum disorder[24,66,67], altered anatomical hub and rich club organization

in schizophrenia[68–70] and impaired inter-hemispheric communication[71] and reduced connectivity in emotion-regulating hub areas in bipolar disorder[72].

As we mentioned, the aim of this article is not so much to provide an in-depth overview of connectome changes in specific psychiatric and neurological disorders (we refer to recent excellent reviews and meta-analyses on this topic[4,73–76]) but to provide a perspective on how different connectome alterations and accompanying variation in brain dysfunction across disorders may relate to each other; we hypothesize that the observed connectome alterations in brain disorders ('connectopathies')[77,78] align along the major dimensions of human connectome organization. BOXES 2 and 3 provide a condensed overview of some of the connectome findings commonly reported for individual neurological and psychiatric brain conditions. Below, we again discuss these empirical findings of connectome alterations in disease but now in light of the 'modularity' and 'integration' dimensions of the human connectome. We hypothesize that these dimensions may together define a proposed connectome landscape of brain dysconnectivity.

Modular organization and disease

Several brain disorders appear to originate from disruptions that are confined to specific local networks. For example, different neurodegenerative syndromes, each characterized by different behavioural symptoms, initially target specific functional subsystems[79]. Evidence suggests that there is spatial overlap between the pattern of atrophy of different neurodegenerative disorders and the layout of specific functional resting-state networks in the healthy brain[79]. From these observations, it has been hypothesized that the existence of different specialized functional connectivity systems in the human brain may underpin the existence of a spectrum of neurodegenerative disorders[73,79]. For example, the pattern of cortical atrophy in Alzheimer disease mirrors the topography of the default-mode network, whereas frontotemporal dementia displays an atrophy pattern that mirrors the layout of the salience network[79] and ALS initially mainly affects the motor network[63,80]. Thus, it appears that each of these neurodegenerative disorders starts from an initial 'epicentre'[81], with progressive atrophy patterns spreading along the epicentre's connectivity pattern and the modular organization of the network at first confining effects to the initially affected subnetwork.

This notion is supported by findings from molecular studies suggesting that multiple neurodegenerative disorders involve a spreading or transmission of misfolded proteins across the brain, as in Creutzfeldt-Jakob disease. In Alzheimer disease, for example, longitudinal changes in imaging tau by positron-emission tomography have indicated a progressive spread of pathology[82], with MRI findings suggesting that the spread of 'disease agents'[83] such as tau may occur along the underlying wiring structure of the connectome[81–83]. These observations suggest that the order and extent to which regions become involved in a disorder are related to whether and how strongly they are connected to other regions in the brain. Similar types of disease spread, and underlying spreading mechanisms have been proposed for Parkinson disease[84] and ALS[63,85], with the pattern of connectome wiring resembling the different stages of disease observed in molecular studies[86,87]. Computational models simulating diffusion of disease particles along inter-regional connections have

generated spreading patterns that are highly similar to those observed by empirical molecular studies in Alzheimer disease[83], ALS[88] and Parkinson disease[89].

This overlap between spatial patterns of neurodegenerative effects and the spatial layout of functional networks leads to the hypothesis that a consequence of the inherent drive towards short wiring and locally connected communities is that disease processes are initially confined by the boundaries of the affected subsystem — the 'ignition' point of the disorder[73,79,81] (FIG. 1). Thus, the existence of modules initially confines spreading processes to specific network communities, which limits global vulnerability. With a large proportion of connectivity concentrated within communities, locally triggered pathophysiological processes — for example, those involved in neurodegeneration — remain initially restricted to a 'target' subsystem, without significant effects on other, topologically more remote parts of the brain[79]. Thus, the modular organization of the connectome not only imposes constraints on healthy brain communication and information flow but also constrains the range of neural perturbations (including pathologies and affected functioning) in the human brain (FIG. 1).

The concept that the modular organization of the human connectome shapes the types of network perturbations that can occur may not only hold for neurodegenerative disorders involving the physical spread or transmission of proteins across the brain. Principles of 'spread', in terms of functional involvement, have also been proposed in the context of neurodevelopmental and/or psychiatric disorders[90–92]. Here, disease processes may initially involve a highly localized (regional) change, which in turn exposes regions in the topological neighbourhood to altered functional input or communication, leading to a sequence of changes across the brain and subsequent reorganization mechanisms to neural circuitry[4,93]. Because they are shaped by the wiring structure of the brain, these changes in connectivity initially remain confined to a restricted subset of functional networks, with matching functional domains that define a distinct spectrum of symptoms.

Neural integration and disease

The drive towards investment of neural resources in network attributes that bring benefits to global neural integration, such as the formation of hubs, rich club structures and global communication paths, also leaves a distinct signature on the spectrum of brain disorders. First, as in Internet, communication and transportation networks, the central placement of brain hubs makes them vulnerable and common sources of global network disruption. Their high centrality further entails differences in neuronal architecture, physiology and metabolism, making them common players in disease processes. Second, the general drive towards keeping high levels of global communication and integration predisposes the human brain to the risk that local changes quickly fan out and initiate a critical cascade of failure across the entire network. Below, we discuss these network attributes and their putative involvement in disease in more detail.

Vulnerable hubs.

The tendency to concentrate connectivity in a set of centrally connected hub regions not only promotes integrative brain function but also has been hypothesized to render the brain

vulnerable to a wide range of brain disorders[44,76]. Their 'rich' character may make these highly connected regions potential 'vulnerability hot spots' for a wide variety of disease processes, and their central position in the network incurs the risk of becoming highly disruptive to the network as a whole. The high participation of hubs in globally short communication pathways predicts disruption of global communication and integration in the case of failure, with damage to hubs and their connections having a disproportional effect on global network organization (FIG. 1).

The general vulnerability of hubs may further owe to the specific biochemistry and metabolism associated with dense connectivity and their role in neural integration. Areas with high structural and functional connectivity have been noted to display a distinct cytoarchitectonic[94,95], chemical[96] and transcriptional fingerprint[97], with characteristic dendritic branching and high synaptic density of pyramidal neurons[98,99], a neuronal infrastructure associated with communication and integrative processing[100]. Hubs are also among the most metabolically active regions of the brain[6,101], with a genetic signature characterized by tightly coupled expression of genes involved in the regulation of energy metabolism[102]. This specific local physiology, high energy utilization and involvement in integrative neural processing suggest that relatively small changes in the functioning of brain network hubs can disproportionately disrupt neural function, making them common players in a wide range of disease conditions.

Cascading network failure.

The drive towards global integration can have consequences for the resilience of a brain network to damage. Recent theories have suggested that neurodegenerative disorders may involve local network disruption (in network terms a failure of one of the 'nodes') that starts a cascade of node failure across the network over time[103–105] (FIG. 1). In analogy to cascade failures in electrical power grids[106], the working load of the initially failing node is redistributed to other nodes by deploying reorganization strategies to maintain network performance. This reorganization, in turn, increases the demand on these other regions, a process eventually leading to the failure of these network nodes as well, starting a cascade across the network. Following this model, the proposed 'cascading network failure' theory of Alzheimer disease[105], for example, suggests that the disorder starts with an initial failure of regions of the posterior default-mode network. In service of maintaining network function, these compromised areas shift their processing load to other systems containing central hub areas, which in turn places stress on these other areas and their connections, thus starting a cascade of failing areas across the entire brain network. Empirical evidence for this type of cascading failure comes from studies of the spatial patterns of tau depositions across individuals at early and late stages of Alzheimer disease, patterns shown to be related to distinct changes in functional connectivity at the different stages of the disorder[105].

The drive towards integration as a risk factor for disease.

Several lines of empirical observations suggest that the drive towards efficient global communication and integration in the brain constitutes a general risk factor for disease. Indeed, meta-analyses of MRI studies reporting on anatomical and functional abnormalities in brain regions in neurological and psychiatric diseases have showed that highest disease

involvement is associated with the most densely connected subcortical and cortical regions of the human brain[76] and their connections[107]. The link between the drive towards neural integration and increased risk of vulnerability is further supported by in silico simulations of brain dynamics emerging from the anatomical wiring structure of the connectome. Computational studies have identified neural hubs as having a central role in creating functional network diversity[51,108] as well as high levels of neural processing and activity, a feature of hub areas that has been suggested to confer vulnerability to, for example, Alzheimer disease[61]. Generative models used to examine the growth patterns of structural and functional brain networks have further indicated an important role of local clustering in the formation of connectivity in the healthy brain and have suggested that slightly detuned model parameters in the growth of brain networks can lead to disturbed network configurations as observed in schizophrenia[109]. These computational findings dovetail with empirical findings suggesting that brain development involves a 'local-to-global' reorganization of connectivity[110], with a growing role of global connectivity in integrative brain processes during adolescence. These developmental changes towards a more integrative brain coincide with the existence of a period of high vulnerability for the development of neuropsychiatric disorders, for example, psychosis, mood disorders and depression[111]. Deviating patterns in the development of brain connectivity may thus represent important risk factors for lasting disruptions of brain structure and function[112].

Connectome landscape

We began with the idea that the tendency towards conserving network cost through modular (segregated) functional systems on the one hand and promoting global (integrated) processing on the other hand represents two major dimensions along which the human connectome exhibits behaviourally and cognitively meaningful individual variation. We then reviewed empirical findings of connectome studies that suggest that different brain disorders appear to be associated with disturbances in connectome organization along these major organizational principles. On the basis of these common dimensions of connectome variation and disturbances in brain organization, we now hypothesize that disparate disorders can be placed in a shared connectome landscape.

As a first step, we suggest that the major wiring principles (dimensions) of connectome organization define a continuous space that describes possible configurations that brain networks can display (FIG. 2). This construct corresponds to a 'network morphospace'[113] that contains all possible network configurations (topologies) arranged along the two dimensions of 'modularity' and 'integration'. Importantly, these two dimensions are somewhat orthogonal, setting up a competitive interaction between modularity and integration that drives a mutual trade-off.

This 2D space of course does not represent the full complexity of the human connectome; there are probably other important factors (that is, other 'dimensions') that similarly have a role in shaping the network organization of the human brain. As indicated above, we focus our discussion here on modularity and integration as they represent commonly examined network features in the context of brain disorders[4,6,44]. Moreover, although a network

space along more dimensions and their potential multidimensional trade-offs would be more realistic, it is also harder to conceptualize.

In this total space of all possible network configurations, an optimal balance between competing dimensions is achieved at the so-called 'Pareto front'[113], where the two objectives of achieving modularity and integration are jointly optimized. We propose that the area near this front describes the extent of 'normal' variation reflecting the optimal or near-optimal trade-off encountered in the generally healthy population. The trade-off implies a balance between modularity and specialized brain functionality on the one hand and global integration on the other that supports healthy brain function. Network configurations that would afford greater optimality along one or multiple dimensions cannot be realized given the fundamental constraints of geometry and physiology. Network configurations below the front correspond to networks that are physically and biologically possible, but to a network configuration that is 'suboptimal', in the sense that the trade-off between multiple objectives is imperfectly realized.

We propose that this network morphospace may offer a useful representation of network dimensions that characterize dysfunction related to a broad range of brain disorders. As the total network space, by definition, encompasses the full range of individual connectome variation, it naturally also describes the configurations of brain networks that are associated with various disorders. The spectrum of neurological and psychiatric disorders, differing in their behavioural and cognitive manifestations, can thus be mapped to networks that fall within this space. We hypothesize that disease processes move connectomes away from the area of near-optimal trade-off into the domain of 'suboptimal' network configurations. Importantly, we now suggest that network configurations associated with brain disorders are not randomly distributed within the suboptimal space. Instead, we propose that network configurations associated with brain disorders occupy specific regions of the proposed morphospace defined by the suboptimal trade-off between modularity and integration and that disease processes exert effects along these same architectural dimensions. We refer to this area of disease-related connectome configurations as a 'connectome landscape of dysconnectivity' of brain disorders, wherein disorders are positioned according to their effects on the major organizational dimensions of brain networks.

Distinct disease processes exert distinct effects along the two dimensions, leading to disease-specific trajectories from the optimal to the suboptimal network space (FIG. 2). Different classes of disease processes may as such lead to specific categories of suboptimal connectomes, occupying different 'disease zones' in the total landscape. What these disorders share is that their disparate disease processes exert common effects along the principal dimensions of the connectome, thereby sharing aspects of their patterns of dysconnectivity and creating relations among otherwise seemingly discrete and disparate disorders. Depending on the extent to which a disease process affects a specific dimension of the connectome (for example, network efficiency in one and modularity in another), a network will thus move in a characteristic direction away from the optimal trade-off (FIG. 2).

Connectivity reorganization

The alteration of connectome organization in disease with the transition of an individual connectome away from the optimal regime are probably continuous and dynamic processes. Although disease processes may move an individual connectome away from the optimal regime, the existing connectivity could potentially be again reconfigured such that the network moves again closer to the optimal front. Studies have suggested reorganization of functional network connectivity in epilepsy[65] and ALS[114], after stroke[115] and surgery[116] and in general ageing and ageing-related conditions[93]. It remains an open topic of debate to what extent such effects include compensatory mechanisms[65,117] in response to changes to the network, or to what extent these effects are related to, for example, a loss of cortical inhibitory influence and thus are part of the disease mechanism[118,119]. These observations do suggest that changes in the brain's network structure, either locally or globally, and/or either as a direct or indirect effect of disease processes, can result in adaptive reorganization of connectivity across the network[120]. Reorganization processes may include mechanisms that render functional communication and connectivity more resilient to disease-related changes by promoting greater stability in functional connectivity patterns. Proposed examples of such adaptive processes include the upregulation of activity and functional connectivity along existing connections to compensate for loss of other connections[93,121–123] or, for example, the adaptation of alternative connection pathways in reaction to changes in connectome organization during brain development[24,124] (see also REF.[4]).

Cross-disorder connectomics

A central goal of this article is to underscore the need to look for patterns of connectome alterations across multiple disorders and to underscore the importance of moving towards a field of cross-disorder connectomics. We suggest an integrative framework for how connectome alterations and their effect on brain function may relate across disorders, placing disparate disorders into a common 'landscape'. We propose that the principles of wiring of the human connectome that shape healthy variation in connectome architecture also shape a connectome landscape of dysconnectivity that accompanies brain disorders.

The growing use of network neuroscience tools in the investigation of various brain disorders allows the field to start addressing new questions about connectome alterations and their general role in brain function and dysfunction. Following developments in other fields of science[125], we suggest that disease connectome studies should more extensively recognize the examination of the — sometimes blurry — boundaries between brain disorders. Other such attempts to carve out cross-cutting biological substrates of brain disorders include the Research Domain Criteria approach[126] and network-based approaches that emphasize the importance of integrating molecular, genetic and large-scale connectivity disease processes across scales[125,127,128]. By conceptualizing brain disorders as dysfunction of neural circuitry and of biological networks across scales, these approaches go beyond considering disorders within conventional diagnostic boundaries and provide novel angles to the classification or nosology of brain disorders[31,129].

A first step towards experimental testing of the ideas put forward in this article is the application of new multidisorder approaches that go beyond the study of single disorders and focus on the 'connectotyping'[130] of connectivity changes across multiple brain conditions. Such cross-disorder studies need to include the systematic construction of disease connectivity maps of a wide range of brain disorders using uniform acquisition methodology and analysis methods. This should then be followed by a consistent comparison of the resulting 'disease connectivity fingerprints' between disorders[107,131] and examination of where in the proposed landscape disorders can be placed and how they relate to each other in terms of network alterations. The approach to cross-disorder connectomics we propose may define common and distinct connectome fingerprints[132] of disorders and provide a deeper understanding of disease comorbidities and disease-unique behavioural and cognitive changes. Placing disease fingerprints in a common space allows for testing the proposed hypothesis that specific brain network attributes bring general vulnerability to the human brain and are central factors in brain dysfunction. The construction of a cross-disorder connectome landscape also allows for identifying connectome alterations that are potentially unique to brain disorders or subclasses of disorders. Computer-aided approaches for disease classification allow for empirically testing the utility of such connectome fingerprints.

Current multinational initiatives that combine large quantities of neuroimaging data sets across several brain disorders (for examples, see REFS[133,134]) form a crucial step in finding disease-common and disease-specific effects on brain connectivity. These 'big data connectomics' initiatives, which are building detailed databases of multiple conditions, form a vital step in the development of both sensitive and specific disease connectome biomarkers. Connectome information may as such be used to diagnose disorders[135–137], classify distinct patient subgroups[138,139] and/or make predictions on long-term outcome[127,140] and symptom severity[141].

Disease connectomics would also benefit from new ways to more directly test causal mechanisms. Thus far, most disease connectome studies have been descriptive and reported differences in connectome organization between individuals with a disorder and healthy controls. One way to provide more insight into the causal effects of connectome alterations is to examine longitudinal changes in connectome structure in patients and individuals from high-risk populations (for examples, see REFS[142–144]) and examine how connectome alterations may precede behavioural changes.

A complementary way to empirically test the hypothesized involvement of connectome principles in brain dysfunction is the use of perturbation models. Such perturbations may involve the use of animal models as well as advanced computer models that simulate neural dynamics and brain connectivity in silico on the basis of anatomical connectome information[145,146]. Although there is growing availability of data on the normative wiring structure of various animals[5], animal models that describe the effects of wiring alterations in relation to brain dysfunction are limited. This type of study would provide an important source of information on how alterations to the connectome can cause brain dysfunction. It would also be an important resource to examine how disruptions in brain connectivity may be at the basis of — as we hypothesize in this article — multiple psychiatric

and neurological conditions[147,148]. Computational models — for example, simulating the functional effects of damage to the anatomical structure of the connectome[149,150] — further represent an important step in elucidating mechanistic principles of how changes to the connectome may lead to brain dysfunction[145].

Such models — animal and computational alike — are important tools to empirically test hypotheses on connectome involvement in brain dysfunction as they allow for inducing distinct changes to the system and to systematically test whether disruptions in brain function associated with distinct disorders may better relate to disruptions of local processes due to focal damage to brain regions and/or relate to changes to integrative brain connections and network attributes. In addition, animal models allow deep-rooted questions of how genetic[151,152] and environmental risk factors[153] for brain disorders may causally relate to network alterations to be addressed. Knockout mouse models, for example, are a powerful tool for systematic testing of whether, and if so how, specific genetic variants associated with a risk of developing a disorder relate to alterations to brain connectivity that underlie brain dysfunction[151,152].

Cross-disorder connectotyping has the potential to generate detailed high-dimensional maps of a person's connectivity profile, which may prove useful in determining an individual's vulnerability and/or resilience to the development of specific brain disorders (BOX 4). Following in the footsteps of precision medicine, we believe that 'precision connectomics', by incorporating data on an individual's connectome may become a useful component for strategies that customize medical interventions at the level of the individual patient[154]. Combined with the use of complex computer simulations of brain dynamics (for example, the 'virtual brain')[146], they could potentially be used in 'virtual trials' to test the effectiveness of novel treatment strategies[121]. Although many steps have yet to be taken, precision connectomics may develop into a promising avenue for understanding the effects of changes to macroscale connectivity in the human brain and the role they play in common and specific disease effects in individual patients.

We hope that insight into how the inherent structure of the human connectome may shape the landscape of brain connectivity dysconnectivity opens a useful new chapter in our understanding of how a large set of biological mechanisms cause a variety of brain disorders, by disclosing common dimensions of network failure and informing a framework for discovering potential cross-disorder relationships.

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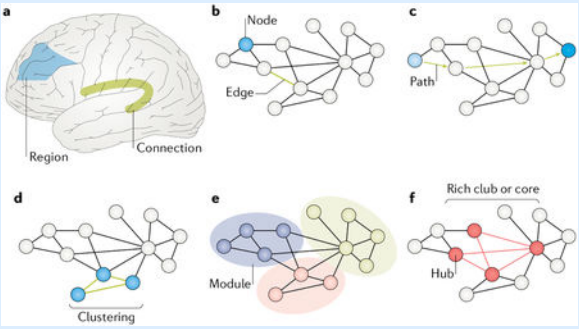
Box 1|

Connectomics and network theory

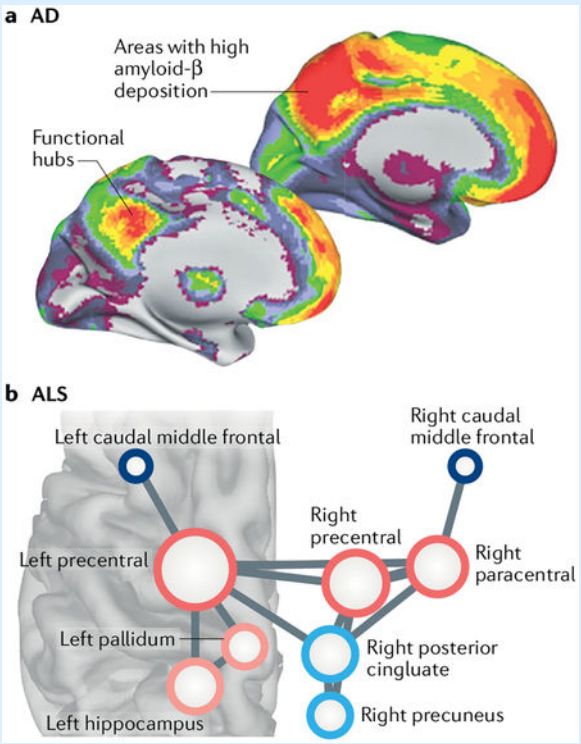
Advances in neuroimaging techniques have made it increasingly feasible to reconstruct anatomical connectivity and to record functional interactions across regions of the human brain. Once acquired, connectivity maps can be represented as a mathematical graph (also called a network) consisting of a collection of ‘nodes’ and ‘edges’, describing, respectively, the different regions of the brain and their reconstructed structural and/or functional connections (see the figure, parts **a** and **b**). These graphs can be examined using analytical and modelling tools of graph theory and network science. Graph metrics that are commonly used in the field of disease connectomics are the network’s ‘clustering coefficient’ and ‘modularity’, the ‘characteristic path length’ and various measures of ‘centrality’ that allow the identification of central ‘hub nodes’[155] (see the figure, parts **c**–**f**). First, brain networks have a strong tendency to form locally dense clusters or modules, reflected by an abundance of connectivity within such a module and relatively sparse connectivity between modules. These features are captured by a high network clustering coefficient, a metric that measures the tendency of network nodes to form locally connected triangles, and by a high level of network modularity, a metric that captures the formation of densely connected network communities. Combined, the presence of these network attributes reflects the brain’s tendency towards information segregation, forming the anatomical basis for specialized neural processing and distinct functional systems[58]. A second common feature of connectome maps are network attributes that support network-wide integration. These features can be examined by computing the characteristic path length of the graph, a metric that measures the average number of network edges that are minimally traversed when travelling from one node to another node in the network. The presence of highly central nodes can be measured by the metric of ‘degree’, which expresses the number of connections per node. High-degree nodes, often interpreted as candidates for brain hubs, can form a densely connected ‘core’ or ‘rich club’[47] by showing a dense level of connectivity between them (see the figure, part **f**).



Box 2 |

Connectome alterations in neurological disorders

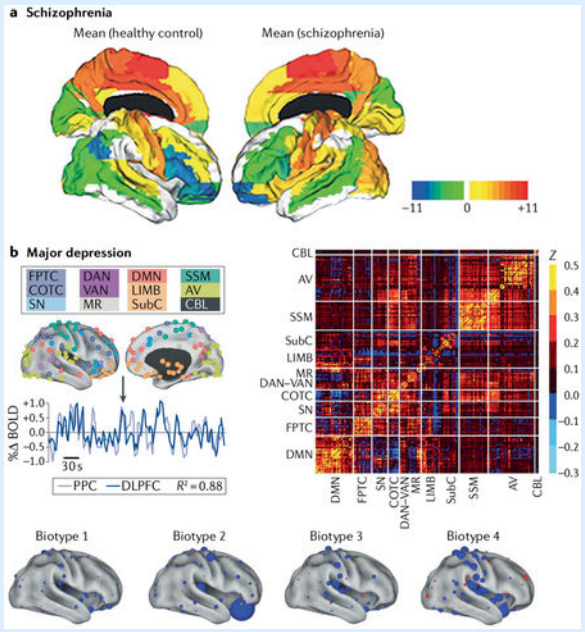
Connectome alterations have been described in several neurological disorders. Alzheimer disease (AD) appears to involve widespread changes to the structural and functional connectome, including the loss of small-world organization[156,157], a diminished anatomical core[54], changes to functional hubs[61] and modular reorganization of resting-state networks[158]. Cross-modal studies suggest that areas that show high levels of amyloid-β deposition overlap with those areas of the brain network that display high levels of functional connectivity[18,62] (see the figure, part **a**; red regions show overlapping areas with high amyloid-β deposition levels (upper image) and high functional connectivity (lower image)). Mild cognitive impairment (MCI), which can develop into AD, is reported to involve disorganization of functional hubs and the modular structure of the default-mode network[159–161]. Indeed, alterations in functional connectivity have been proposed as a marker for identifying MCI[162] and other individuals at risk of AD[163]. In Huntington disease, network studies have indicated reduced regional communication[164] and affected hub and rich club connectivity[64,165], and Parkinson disease has been associated with frontoparietal-striatal dysconnectivity and a breakdown in the modular structure of cognitive brain networks[166]. Amyotrophic lateral sclerosis (ALS) appears to involve changes to the anatomical[63] and functional[114] connectivity of the motor network; these seem to be apparent in patients with the disorder and presymptomatic genetic carriers at risk of ALS[167] (see the figure, part **b**, showing affected brain network regions and connections in individuals with ALS, with red regions indicating primary motor network regions and dark-blue, pink and light-blue regions indicating secondary motor, subcortical and associative brain regions, respectively), with the extent of the changes related to individual disease severity and progression[168]. Multiple sclerosis (MS) is an inflammatory demyelinating disease reported to affect the structural and functional connectome[169], including by reducing functional network efficiency[170]. In MS, variation in network structure has been linked to disease stage[170], duration[170] and clinical subtypes of the disorder[171]. In epilepsy, studies have suggested a dynamic reconfiguration towards a strongly clustered network during epileptic seizures[172,173], with individual variation in network structure linked to type of seizure propagation and clinical outcome after surgery[173,174]. Part **a** is adapted from REF.[62], CC-BY-4.0. Part **b** is adapted from REF.[80], CC-BY-4.0.



Box 3 |

Connectome alterations in psychiatric disorders

Brain network studies have similarly indicated connectome involvement in a wide range of psychiatric disorders. For example, studies have reported early developmental connectome changes in autism spectrum disorder (ASD)[66], including lower white matter integrity, larger fibre count and increased network path length[24]. Network studies have further reported under-functioning of the brain's integrative circuitry[175,176], combined with functional over-connectivity of local circuitry in ASD[67], as well as inter-individual variation in levels of functional connectivity that potentially relates to traits associated with the disorder[19]. For schizophrenia, brain connectivity studies have reported widespread changes in anatomical connectivity[177–179], including alterations in rich club and core architecture in people with the disorder[68,70,179] and their siblings[180] and in individuals at clinically high risk of developing psychosis[143,144]. Functional studies have further suggested reduced levels of connectivity as well as more random patterns of functional connectivity in patients with schizophrenia[181–184] (see figure, part **a**; the figure shows differences in brain functional connectivity between individuals with schizophrenia and controls for the left and right hemispheres, with red regions indicating the areas with the largest decreases in connectivity), with the extent to which connectivity is perturbed potentially relating to symptom dimensions and severity[183,185]. Bipolar disorder in turn has been linked to alterations in anatomical inter-hemispheric connectivity[71,186–188], loss of connectivity around hub areas involved in emotional processing[72] and disrupted functional connectivity of associative networks[188–190]. Major depression may involve changes in anatomical connectivity between regions that are key for emotional processing[191]. Different patterns in functional connectivity have been linked to the type and severity of symptoms in depression[192] and distinct clinical subtypes[193] (see the figure, part **b**). The upper left panel of the figure shows the derivation of functional connectivity between brain regions of 12 functional networks (for example, red regions indicate areas of the default-mode network (DMN)) in individuals with major depression, with the panel to the right showing the connectivity matrix depicting the level of functional connectivity (blue indicates low functional connectivity and yellow indicates high functional connectivity) between areas of each of the 12 brain networks. The lower panel shows the different patterns of functional connectivity (named 'biotypes') as observed between four different subtypes of depression in the total examined population, supporting the notion that distinct patterns of dysconnectivity relate to different types of depression. AV, auditory-visual network; BOLD, blood oxygen level-dependent; CBL, cerebellum; COTC, cingulo-opercular task-control network; DAN, dorsal attention network; DLPFC, dorsolateral prefrontal cortex; FPTC, frontoparietal task-control network; LIMB, limbic; MR, memory retrieval network; PPC, posterior parietal cortex; SN, salience network; SSM, somatosensory-motor network; SubC, subcentral; VAN, ventral attention network. Part **a** republished with permission of the Society for Neuroscience, Lynall, M. E. et al. Functional connectivity and brain networks in schizophrenia. *J. Neurosci.* **30**, 9477–9487 (2010); permission conveyed through Copyright Clearance Center, Inc. (REF.[69]). Part **b** is adapted from REF.[193], Springer Nature Limited.



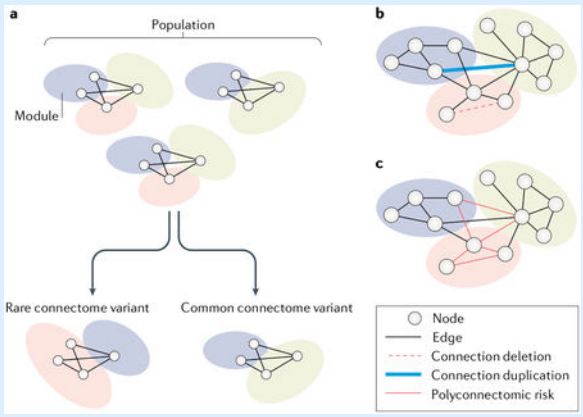
Box 4 |

Connectome vulnerability and resilience

The connectome landscape may offer a framework for hypothesizing about how individual variation in connectome layout may define personal vulnerability and/or resilience to brain disorders. Network studies have demonstrated associations between inter-individual differences in connectome organization and inter-individual differences in healthy human behaviour, including individual differences in personality traits[43], arousal[194], memory[41] and cognitive functioning[52,195]. Conversely, individual variation in connectome structure may also relate to a person's risk or vulnerability to develop brain disorders. Variations in functional brain network organization have, for example, been associated with dimensions of psychopathology, including variation in mood, psychotic behaviour and feelings of fear[196]. Other variations of functional brain network organization have been argued to relate to the development of mental illness[197] and to confer risk of the development of neurodegenerative disorders such as Alzheimer disease[163]. Other such examples of inter-individual variation in connectome organization to relate to elevated risk of the development of brain disorders include reports of alterations in intra-modular connectivity[198] and hub connectivity[144,199] to confer risk of the development of, for example, psychosis.

Within this framework, certain types of brain networks may thus be more vulnerable to the development of mental health problems than others[200], with variability in connectivity architecture between individuals potentially linked to disease susceptibility[201]. We propose that these connectome 'variants' could manifest in several forms. In analogy to similar frameworks in genetics, they may constitute a 'common variant' and thus occur in a large part of the population or be considered a 'rare variant' and only be found in a small part of the population (see the figure, part **a**). Moreover, they may comprise missing or enhanced connections ('deletions and duplications'; see the figure, part **b**) and/or include complex combinations of multiple connections and features of connectome organization ('polyconnectomic risk'; see the figure, part **c**).

Aspects of connectome architecture may also act as protective factors against the clinical manifestation of psychiatric and neurological disorders. Such connectome-based protective factors could similarly manifest in several forms; for example, network configurations that are more resilient to initial forms of attack to the network in disease conditions or network configurations that can better compensate for disease-related changes. For example, elevated functional communication among higher-order functional networks may serve as a protective factor for the development of bipolar disorder[142], certain patterns of individual connectome organization have been linked to cognitive reserve[202] and resilience against mental retardation[203,204] and types of brain connectivity configurations may be protective against the development of psychosis[205]. These observations suggest that individual connectome organization predicts not only potential risk of developing psychiatric and neurological conditions but also strategies for coping with these alterations by conferring resilience against network dysfunction.



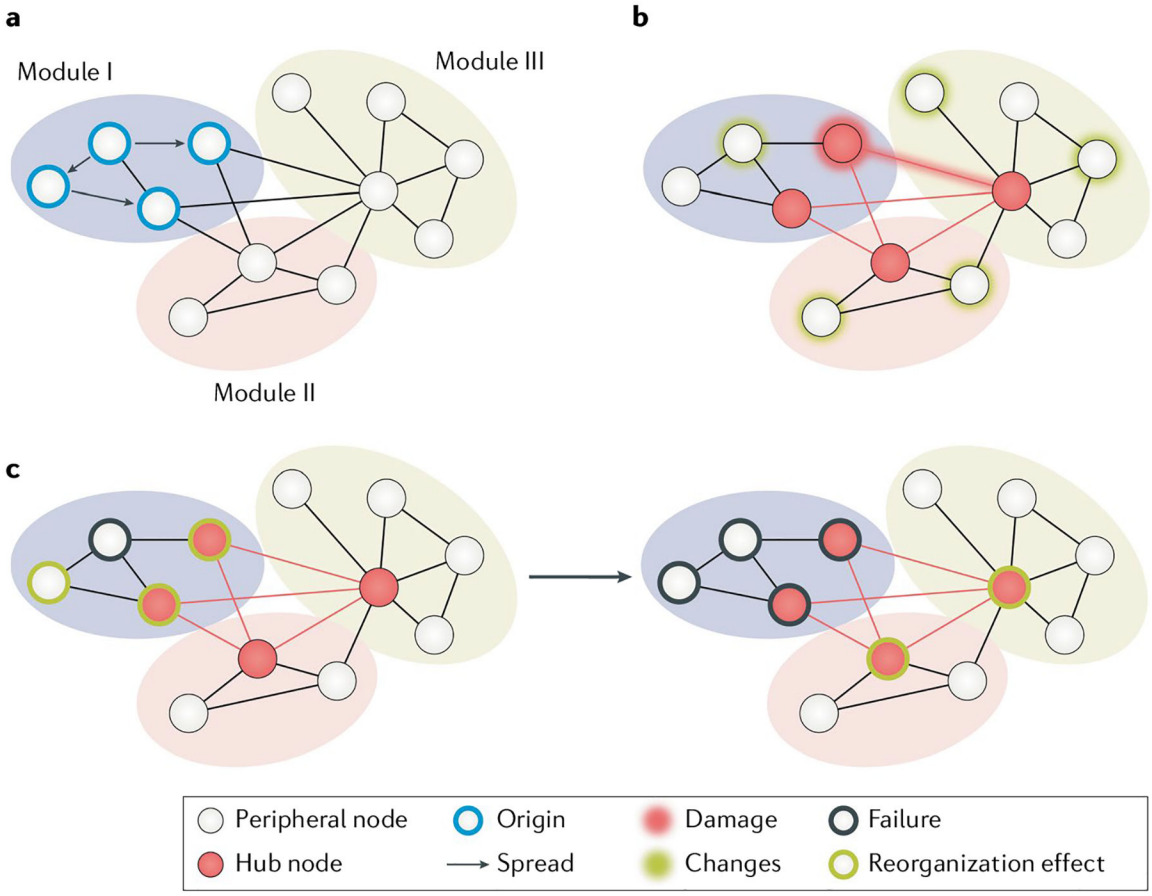


Fig. 1 |. Modular and hub organization of the human connectome-shaping disease processes.
a | The modular character of the connectome can shape the pattern of the disease-spreading process, with early effects of the disease remaining mostly concentrated in one specific network module. **b** | Damage to hub nodes (red nodes) and their connections (red connections) can lead to structural and functional changes across many places in the connectome. **c** | This part illustrates the 'cascading network failure' theory, which states that the initial, local changes to the connectome are cascaded across the network. Failure in one of the network nodes triggers compensatory effects in topologically adjacent nodes (for example, increased activity), aiming to take over the role of the failed nodes and to maintain optimal brain function. The increased burden on these nodes will in turn lead to an increased probability of their failure, triggering a cascade of failure of nodes across the entire network. The global connectivity character of hub nodes makes them more likely to be involved in such compensatory processes.

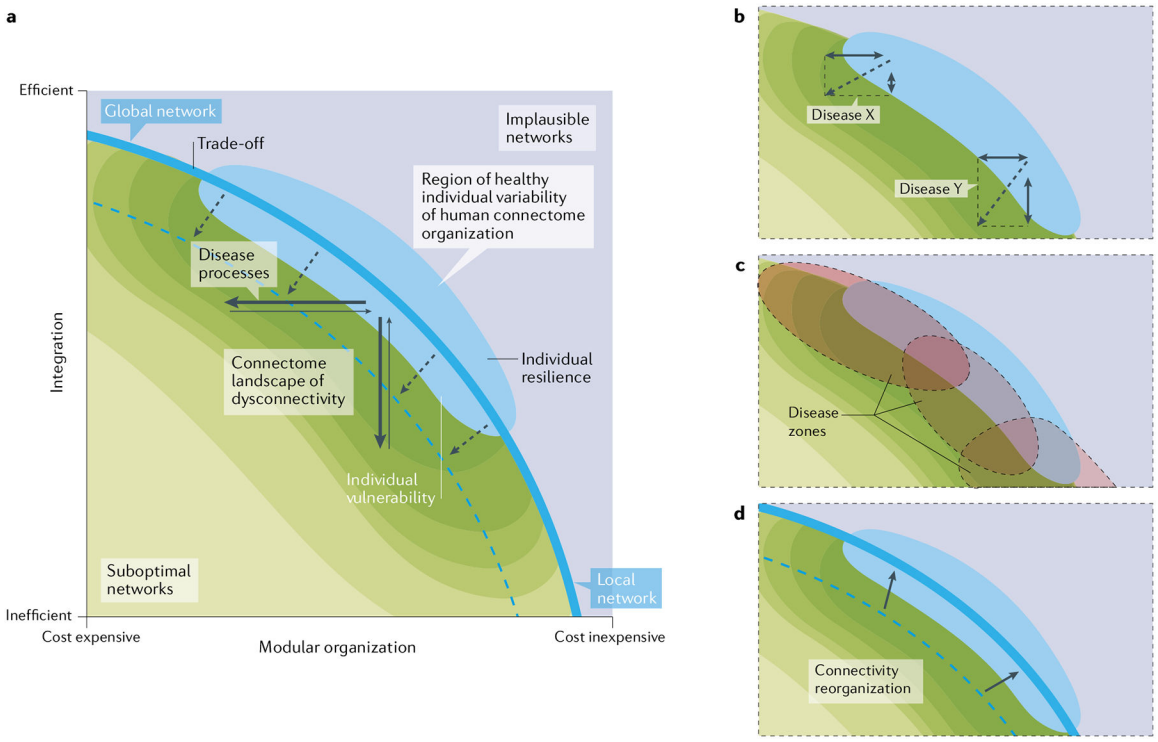


Fig. 2 |. Connectome landscape of dysconnectivity.

a | Two of the major principles of wiring the human connectome are the tendency to minimize the overall cost of wiring (*x*-axis), favouring the formation of local circuitry and local subsystems, and the drive to invest in resources that allow efficient global communication and integration (*y*-axis).Together, they describe a 2D space (referred to as 'network morphospace')[113] of all possible network configurations. Within this space, the two principles compete and their trade-off (blue line) defines an efficient organization of the network, where both objectives are together optimized. The region beyond this front[113], relating to 'greater optimization' (grey area), cannot easily be realized given the constraints of geometry and physiology. In turn, networks in the region below the front could be considered as 'suboptimal' (green area, with shades of green indicating less and less optimal network configurations) in the sense that the trade-off between multiple objectives is inefficiently realized: with the subregion furthest away from the trade-off optimum (lower left corner space, lightest green) comprising networks that would be biologically unworkable and thus too maladaptive to support human behaviour. The area around the trade-off optimum and in between the regions of 'impossible' and 'suboptimal' networks describes the extent of normal variation of efficient cost integration in the general healthy human population (light-blue zone). Within the area of healthy human variation, certain individual variants in connectome organization may represent configurations of the connectome showing resilience or vulnerability to disease. In this framework, disease processes can be theorized to move an individual connectome away from the optimal balance (blue line) into the suboptimal regime (blue dotted line); the disease processes may exert effects along the architectural dimensions (arrows parallel to the *x*-axis and *y*-axis). Together, they form a characteristic 'connectome landscape of dysconnectivity' (shades of

green). **b** | Distinct disease processes may involve different trajectories away from the area of healthy human variation and efficient network performance (blue) depending on how they affect the network (for example, disease X has a stronger effect on modular organization, whereas disease Y has a stronger effect on network integration). **c** | This may, in turn, lead to disorganized connectomes displaying specific types of connectional variation that occupy different subspaces (‘disease zones’) in the total landscape. Through this approach, relationships may be observed among otherwise seemingly discrete and disparate disorders. **d** | In some disorders, reorganization mechanisms (arrows) may work to refind a position for the shifted trade-off (dotted blue line) that is closer to the optimal trade-off in the human connectome (blue area) in order to maintain brain function.