Review

Special Issue: The Connectome

Fledgling pathoconnectomics of psychiatric disorders

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Pathoconnectomics, the mapping of abnormal brain networks, is a popular current framework for the study of brain dysfunction in psychiatric disorders. In this review we evaluate the conceptual foundations of this framework, describe the construction and analysis of empirical models of brain networks or connectomes, and summarize recent reports of the large-scale whole-brain connectome organization of two candidate brain-network disorders, schizophrenia and autism. We consider the evidence for the abnormal brain-network nature of psychiatric disorders and find it inconclusive. For instance, although there is some evidence for more random whole-brain network organization in schizophrenia and autism, future studies need to determine if these and other observed brain-network abnormalities represent sufficient phenotypes of psychiatric disorders, in order to validate pathoconnectomics as a scientific and clinical framework.

Promises and challenges of pathoconnectomics

Connectomics, the mapping of brain networks (see Glossary), is a popular current framework for the study of brain function [1]. Connectomics postulates that brain functions, especially higher perceptual and cognitive functions, are contingent on brain-network interactions [2,3] and that an understanding of these higher functions requires an understanding of brain-network organization [4–6].

Abnormalities of higher brain functions are a prominent feature of major psychiatric disorders such as schizophrenia and autism. Pathoconnectomics, the mapping of abnormal brain networks, is a corollary framework of connectomics. Pathoconnectomics postulates that major psychiatric disorders are abnormalities of brain networks [7,8] and that an understanding of these disorders requires an understanding of the corresponding abnormal brain-network organization [9,10]. (We use the term pathoconnectomics for two reasons. First, this usage is consistent with past nomenclature, cf. 'pathophysiology of psychiatric disorders'. Second and more importantly, the mapping of brain dysfunction carries additional challenges to the mapping of healthy brain function and the usage of pathoconnectomics directly emphasizes this differentiation.)

Pathoconnectomics is sometimes termed a new paradigm for the study of psychiatric disorders [11]. But the term paradigm has two distinct relevant meanings [12]. Pathoconnectomics is a paradigm in the sense of being a popular and disruptive framework [13]. But it is not a paradigm in the more important sense of being a significant scientific achievement; the framework is young and faces important challenges, some of which it shares with older branches of biological psychiatry. It remains to be seen whether pathoconnectomics provides anything close to approaching the explanatory power of other successful frameworks such as the neuron doctrine (the fundamental nature of the neuron as a unit of the nervous system [14]).

The main challenges of pathoconnectomics are broadly twofold: a brain-network-based delineation of psychiatric disorders and an accurate definition of empirical models of brain networks. These challenges are notably interdependent: accurate empirical models of brain networks help to delineate psychiatric disorders and delineations of psychiatric disorders help to understand properties of brain networks important for higher brain function and dysfunction.

Fulfillment of these challenges will allow a principled evaluation of the main tenet of pathoconnectomics, namely

Glossary

Autism: a disorder, or spectrum of disorders, characterized by impairment in social interaction and communication and the presence of repetitive, stereotyped behaviors.
Connectome: strictly defined, the complete structural 'wiring diagram' of the brain. More loosely defined, the complete or partial 'wiring diagrams' or networks of structural and functional interactions in the brain.
Diffusion MRI: a method for mapping large-scale structural connectomes based on the inference of uneven (anisotropic) water diffusion, an indirect measure of white-matter tracts.
Endophenotype: a quantifiable and heritable phenotype that aims to identify genetically mediated traits of psychiatric disorders.
Functional MRI: a method for mapping large-scale functional connectomes based on correlations of fluctuations in the blood-oxygen-level dependent (BOLD) signal, an indirect measure of neural activity.
Schizophrenia: a psychiatric syndrome characterized by the presence of hallucinations and delusions, lack of motivation and social withdrawal, and cognitive impairment.
Sufficient phenotype: the simplest-known specific biological phenotype of a disorder and the implicit basis for current biological classification of medical disorders.

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the abnormal brain-network nature of psychiatric disorders. But neglect of these challenges risks leading to a stagnant field of vague searches for unclear targets; similar problems affect other systems-biological investigations of complex disorders [15]. We now discuss these challenges in more detail.

Conceptual challenges of pathoconnectomics

Sufficient phenotypes of psychiatric disorders

Objective delineation of psychiatric disorders is a central and perennial problem of psychiatry. In the current absence of such definitions, psychiatrists define psychiatric disorders using convenient, but not biologically validated, clinical phenotypes or groupings of symptoms and signs [16,17].

A biological phenotype objectively defines a disorder when it is specific for the disorder, such that its presence implies the presence of the disorder. Modern medicine uses the simplest-known specific biological phenotypes to define disorders [18]. Biological phenotypes that define disorders acquire primacy over clinical phenotypes of these disorders, such that clinical phenotypes are frequently altered to match biological phenotypes more closely. For instance, diabetes mellitus, a metabolic disorder, was initially defined by its clinical phenotype of voluminous urine output, weight loss, and thirst. The detection of elevated blood glucose as a specific phenotype helped to split diabetes mellitus from other disorders which have superficially similar clinical presentations, such as unrelated kidney diseases. Discoveries of more specific phenotypes continue to divide diabetes mellitus into further subgroups [19]. This classification of disorders mirrors similar developments of scientific classification in other fields such as chemistry (of elements), biology (of organisms), and astronomy (of heavenly bodies) [20].

We use the term sufficient phenotype to denote the simplest-known specific biological phenotype of a disorder. We note that the main tenet of pathoconnectomics postulates that abnormal brain-networks are sufficient phenotypes of psychiatric disorders. We consider the available evidence for this tenet below.

Psychiatric disorders associate with many genomic, proteomic, cellular, and systems phenotypes, including abnormalities of gray matter and white matter and functional activation and connectivity [21]. For instance, prominent early examples of abnormal brain structure and function include reduced gray-matter density of schizophrenia [22] and abnormal functional connectivity of autism [23]. However, these associations are in most cases nonspecific.

Psychiatric disorders also associate with abnormalities of brain networks, as we discuss below. But the presence of this association does not imply that psychiatric disorders should be viewed as abnormalities of brain networks, at least until such abnormalities are shown to represent sufficient phenotypes. This simple yet important fact is overlooked in the current discourse of pathoconnectomics. Biological psychiatry has made similar errors in the past, for instance by prematurely viewing schizophrenia and depression as disorders of dopamine and serotonin imbalances, respectively; these approaches have seemingly failed to yield major gains after several decades of research [24,25]. It would be useful for pathoconnectomics to avoid repeating these mistakes [26].

Sufficient phenotypes and endophenotypes

It is difficult to detect sufficient phenotypes of psychiatric disorders. One promising approach is to search for convergent effects of genes associated with these disorders. Major psychiatric disorders show moderate to high heritability and diverse genetic associations [27,28]. Genes associated with these disorders have heterogeneous functions in the nervous system; for instance, autism-associated genes modulate neuronal activity, cell adhesion, and activity-dependent protein synthesis [29].

The concept of an endophenotype is promising for identifying potential convergent effects of heterogeneous gene function. Endophenotypes are measurable and heritable (e.g., present at a higher rate in unaffected relatives) phenotypes of psychiatric disorders [30–32]. Endophenotypes aim to identify genetically mediated traits that are simultaneously simpler than diverse genetic effects and more cohesive than heterogeneous clinical manifestations of disorders.

There are similarities, but also important differences, between the concepts of sufficient phenotypes and endophenotypes. Most sufficient phenotypes are likely to be endophenotypes, but not all endophenotypes are sufficient phenotypes. In contrast to sufficient phenotypes, endophenotypes may include cognitive or behavioral traits and need not be simple or specific. Individual disorders may have many endophenotypes and an endophenotype may associate with many disorders. This lack of specificity makes endophenotypes easier to detect and usefully bypasses the subjective restrictions of psychiatric diagnostic classifications. The lack of specificity, however, also makes endophenotypes non-diagnostic. In the search for definitions of psychiatric disorders, endophenotypes serve as useful precursor traits to sufficient phenotypes.

Methodological challenges of pathoconnectomics

Empirical models of connectomes

The connectome is broadly defined as the complete structural- or functional-network organization of the brain [1,3]. There are multiple microscopy- and neuroimaging-based model realizations of this concept (Table 1). Each of these empirical models has distinct spatial and sometimes temporal resolution, spatial coverage, and susceptibility to noise. The models balance the demands of biological realism and complexity. Neuronal-scale models may be too complex to construct and analyze, whereas regional-scale models may not be biologically realistic. Not all models are necessarily well suited for defining sufficient phenotypes of psychiatric disorders.

Structural connectomes are maps of anatomical interactions between neural elements. Individual models differ on the spatial resolution and spatial extent of these maps. At the microscale, maps of synaptic connections between neurons represent the most intuitive representation of the structural connectome. High-resolution electron-microscopic and neuronal reconstruction techniques provide detailed neuronal and synaptic maps of these spatially dense neuronal circuits [33]. These techniques were used

Table 1. Methods of structural connectomics

Imaging method	Approximate spatial scale	Environment and example organisms	Advantages	Disadvantages
Electron microscopy	~Nanometer	*Ex vivo*, roundworm, fruit fly	Accurate characterization of dense neuronal and synaptic connectivity	Small volume of brain coverage, high computational cost
Light microscopy	~Micrometer	*Ex vivo*, mouse	Large volume coverage of neuronal projections	Inability to differentiate synapses and characterize dense connectivity
MRI	~Millimeter	*In vivo*, monkey, human	Whole-brain coverage of large brains	Inability to differentiate directionality, high susceptibility to noise

to reconstruct the only currently-known complete synaptic wiring diagram of an organism, the roundworm *Caenorhabditis elegans* [34]. The high computational cost and limited spatial extent of these techniques restrict their current use to mapping connectomes of small organisms. At the mesoscale, intermediate-resolution intermediate-extent light-microscopic and neural staining techniques provide whole-brain neuronal connection maps of larger organisms [35,36] and are currently used to derive connectome models of the mouse [37]. The increase in volume of these models comes at the expense of sparser neuronal maps and reduced ability to infer the presence of neuronal connections. At the macroscale, low-resolution high-extent MRI techniques allow *in vivo* reconstruction of whole-brain connection maps of larger organisms, including humans [38], and are presently used to construct a macroscale model of the connectome of humans [39]. These imaging techniques, however, produce relatively coarse grained and noisy maps.

In contrast to the structural connectome, the functional connectome is inherently less precise and more difficult to define [40]. Functional interactions most meaningfully reflect directed causal relationships, but most present methods are only able to infer these relationships indirectly, through observation of undirected correlations. Furthermore, the possibility of such interactions to occur on multiple temporal scales places an additional challenge on the detection of frequency-specific interactions [3]. Models of functional connectomes may differ on the spatial resolution, temporal resolution, and spatial extent of these maps. At the microscale, models of the functional connectome are based on extracellular recordings and optical calcium-imaging techniques, which allow the mapping of dynamical interactions between small groups of individual neurons of animals [41,42] and between cultured neurons developed from stem cells or fibroblasts of patients with psychiatric disorders [43]. At the macroscale, functional MRI allows the study of interactions between brain regions in living animals [44] or humans [45] and neurophysiological recordings allow the study of high-frequency interactions between broader (less well resolved) areas of brain tissue [46].

Analysis of empirical models of connectomes

Analyses of empirical models of the connectome aim to describe the organization of these models by characterizing local and global network topology patterns. Simple connectome models are networks of nodes (neurons, neuronal ensembles, or brain regions) and edges or links (synapses, projections, tracts, correlational, or causal interactions) [47]; more sophisticated models may additionally include types of nodes and links [48,49] as well as directionality and weight of links [50,51].

Models of the connectome have many nodes and links and are difficult to characterize qualitatively. Investigators seek general rules for the global organization of these models. Early rules for brain-network organization postulated simple principles of this organization. For instance, Ramón y Cajal's principle of wiring economy proposes that anatomical connections are primarily governed by minimization of neuronal wiring [52,53], whereas Peters' rule proposes that anatomical connections nonspecifically form in proportion to synaptic density [54,55]. Together, these rules propose a random organization of synaptic connections within spatially constrained clusters.

More recently, complex-network analysis tools [56] have allowed to probe the whole-brain organization of connectome models. One of the main insights of these analyses is the finding of simultaneous and partial reconciliation of the principles of economical and nonspecific (random) wiring [8,53]. These analyses collectively demonstrate a clustered network organization with a substantial number of long-range connections and the presence of prominent central neural elements or hubs.

We focus on whole-brain principles of connectome organization, but note that the description of specific nodes or connections [57] or specific network clusters [58] of connectome models represent important complementary analysis approaches. Although the focus on whole-brain organization reflects our research interests, we note that psychiatric disorders manifest abnormalities in other models of the connectome [43] or with other analyses, such as regional-connectivity mapping methods [59]. These models and analyses are equally associated with all the above-described conceptual and methodological limitations of pathoconnectomics.

Abnormalities of connectomes in psychiatric disorders

In this section we provide an overview of recently reported whole-brain abnormalities of anatomical and functional MRI-based connectome models of schizophrenia and autism. The focus on schizophrenia and autism reflects the weight of the current literature; there are considerably fewer and less conclusive results of whole-brain connectome organization for other psychiatric disorders, such as major depression, bipolar disorder, and attention-deficit/hyperactivity disorder.

MRI-based structural models of the connectome infer the presence of white-matter fibers from patterns of uneven (anisotropic) water diffusion, whereas MRI-based functional models of the connectome infer the presence of functional interactions from correlations of fluctuations

in the blood-oxygen-level dependent signal, an indirect measure of neuronal activity. Important issues for construction of MRI-based connectome models include the adequate removal of noise such as head-motion artifact, spatial normalization of images to a common template for between-group comparisons, accurate definitions of brain regions as nodes, and robust and reproducible inference of structural or functional links [38]. The lack of a standardized analysis pipeline is an important additional problem which makes it difficult to compare results between different studies [107].

Network analyses of whole-brain organization often make inferences about brain activity, such as the propensity or presence of segregation and integration of brain dynamics, from properties of whole-brain organization. Such inferences are based on measures of network topology such as the 'small-world' property, the simultaneous presence of clustered and distributed network topology [60]. In structural networks, such analyses reflect the potential for properties of brain dynamics to emerge on a structural substrate, but are based on generic assumptions such as the propagation of information along shortest paths. In functional networks, the situation is even less straightforward because links represent the presence of functional interactions and hence cannot measure the potential for dynamics to emerge on these interactions [49]. The relevance of such interpretations is hence unclear and we omit these interpretations below.

Total connectivity

The total number or total 'weight' of links is a simple whole-brain analysis of the connectome. This analysis describes the potential, presence, or extent of whole-brain network interactions and is relatively easy to interpret. The total number and weight of links additionally influences higher-order measures of network organization, such as clustered and distributed topology [61].

Early studies of regional connectivity in schizophrenia show reduced structural and functional connectivity, predominantly in frontal regions [62,63]. More recent studies of whole-brain connectivity [64] find, with some exceptions [65,66], broad evidence for reduced whole-brain structural [67–72] and functional [73–77] connectivity. For instance, an interesting comparison of whole-brain functional connectivity between schizophrenia, bipolar disorder, and healthy control subjects reports a lowest-to-highest schizophrenia/bipolar disorder/healthy subject spectrum of total connectivity [77]. Meanwhile, a direct comparison of structural and functional connectivity finds reduced whole-brain structural, but not functional, connectivity in schizophrenia and a reduced correlation between structural and functional network topologies [72], suggesting potential decoupling of functional brain networks from their structural substrates.

Early studies of regional connectivity in autism find strong evidence of abnormal and typically reduced functional connectivity [78,79], although a recent detailed survey notes that studies report less evidence of underconnectivity when comparisons are made between target regions and the rest of the brain, an observation suggesting that underconnectivity may not be present in whole-brain analyses [80]. Two recent studies of the whole-brain functional connectivity of high-functioning autism have lent support to these findings by reporting areas of regional but not global underconnectivity [81,82]. Conversely a recent report in children and adolescents finds reduced whole-brain functional connectivity, but increased whole-brain structural connectivity (albeit with reduced white-matter integrity) [83]. An additional recent multisite analysis of more than 1000 autism and control subjects, likewise shows whole-brain underconnectivity, with pockets of regional overconnectivity involving connections to subcortical regions [84]. Hence the total-connectivity findings in autism are equivocal; the biological basis of this heterogeneity may be partly attributable to the distinct clinical profiles and ages of participating subjects, as recently discussed [85].

Clustered and distributed topology

Whole-brain network measures of clustered topology, such as the clustering coefficient (the fraction of all possible triangles in the network), show the extent to which brain networks are clustered, without necessarily delineating individual clusters. Measures of distributed topology, such as the global efficiency (the inverse mean length of shortest paths between all pairs of nodes in the network), show the extent to which brain regions are connected by short paths or sequences of links [47]. Brain networks typically have the simultaneous presence of clustered and distributed topology, compared with random networks (which have distributed but not clustered topology) and ordered networks (which have clustered but not distributed topology).

Most [73,74,76,86–90] but not all [66,91] whole-brain functional studies of schizophrenia find less clustered topology and equally distributed [66,73,87–91] or more distributed [74,76,86] topology. Together these changes have led to a speculation of a 'subtle randomization' of whole-brain functional network organization in schizophrenia [92]. By contrast, structural studies of schizophrenia report globally unaltered clustered and distributed topology [65,67–70,93]. A general picture may thus emerge of randomized large-scale functional topology occurring on a broadly intact large-scale structural topology, in keeping with the posited decoupling between structural and functional connectivity of the disorder [72]. A recent study finds evidence for proportionally greater length (Euclidean distance) of functional connections in schizophrenia [86], potentially providing a simpler and more biologically grounded explanation of these effects.

There has been only one case-control study of clustered and distributed topology in children and adolescents with autism [83]. This study also found a less-clustered topology in functional networks but unaltered network topology in structural networks. Interestingly, three additional correlation studies described below corroborate this result by similar findings of more random network organization in autism.

Regional centrality

Measures of regional centrality detect important brain regions; these brain hubs may be especially vulnerable to pathological attack and are likely to disrupt higher brain

function when attacked [53]. Most studies identify hubs in prefrontal, temporal, and parietal heteromodal association cortical regions, as well as in limbic regions [50,94].

Structural studies of schizophrenia report decreased centrality in hubs in frontal association [65,67,69], parietal [69], and limbic and paralimbic [65,67] regions. Functional studies of schizophrenia report similar results, with abnormalities in frontal, temporal, parietal, limbic, and occipital areas [75,86,87,95]. In general these studies converge on a set of a heteromodal association regions previously implicated in gray matter, white matter, and activation studies of schizophrenia [22,96–98]. By contrast, to our knowledge there has been only one autism study of abnormal brain hubs (rather than brain regions more generally). This study compared hubs between autism and attention-deficit/hyperactivity disorder and detected autism-specific abnormalities of temporolimbic areas [99]. A general challenge for future studies of abnormal brain hubs is to show that hubs are differentially affected in distinct psychiatric disorders.

Clinical and genetic correlations

Clinical correlations and heritability are potentially important clues in the search for sufficient phenotypes of psychiatric disorders. Unfortunately such correlations are not frequently reported and are often not significant when reported [65,69,88,91,100].

Schizophrenia studies show some evidence for correlations between structural [68] and functional [74,77] whole-brain connectivity and cognitive ability, consistent with previous work in healthy populations [101,102]. Cognition is increasingly recognized to be a key component of schizophrenia and indeed some call the disease a cognitive illness [103]. However, cognitive dysfunction is unlikely to be a specific phenotype of schizophrenia. Other studies have focused on the positive and negative symptom scale, a potentially more specific symptom-rating scale of schizophrenia. There is some evidence that whole-brain connectivity negatively correlates with severity of symptoms on this scale [66,67,72], although most studies have not examined these correlations and there is at least one study that reports no such effects [74].

Three autism studies examine and show correlations between whole-brain network organization and traits relevant to autism [104–106]. A structural study reports a negative correlation between clustered topology and the presence of autistic traits, assessed on the autistic-spectrum screening questionnaire [104], whereas another structural study reports a complementary positive correlation between distributed topology and the expression of a higher-risk variant of CNTNAP2, a gene associated with cell adhesion and implicated in the development of autism [105]. A third functional study measured changes in network topology in children with autism asked to perform a sustained-attention task. The study finds a positive correlation between distributed topology and inattention scores in children with autism, measured on the attention-deficit/hyperactivity disorder rating scale [106]. Interestingly all three studies find convergent effects of a more random-like network organization in autism, despite their use of different empirical models of the connectome (structural and functional), different network measures (of clustered and distributed topology), and different measures of autistic traits (clinical and genetic), providing strong evidence for converging effects.

Box 1. Outstanding questions

- Do psychiatric disorders represent coherent biological entities?
- Do abnormalities of the connectome represent sufficient phenotypes of psychiatric disorders?
- Which spatial and temporal scales (or combinations of scales), and which analyses of the connectome, are most valuable in elucidating the basis of normal and abnormal brain function?

Concluding remarks

We examined the conceptual and methodological foundations of the emerging framework of pathoconnectomics and reviewed recent studies of large-scale whole-brain network abnormalities in schizophrenia and autism. These studies find some evidence for more random-like brain-network organization in schizophrenia and autism. The challenge for future studies is to show that such a biological marker represents a sufficient – specific and simplest-known – phenotype of these psychiatric disorders (Box 1). An additional important challenge is the delineation of the optimal combination of spatial and temporal scales at which such putative phenotypes may be detected. We hope that increasingly accurate empirical models of the connectome will help to elucidate these answers and hence allow investigators to test the main tenet of pathoconnectomics—the brain-network nature of psychiatric disorders—in a principled way.

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