Review

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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