Structural brain networks and neuropsychiatric disorders

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Purpose of review

Graph theoretical analysis of neuroimaging data has emerged in the last few years as a powerful yet accessible tool to examine brain connectivity in a quantitative framework. In this review, we summarize recent advances in structural brain network research pertaining to neuropsychiatric disorders.

Recent findings

Although many neuropsychiatric disorder studies have used brain network approaches, the majority are of functional brain networks. However, seven recent studies, three on Alzheimer's disease, three on schizophrenia, and one on epilepsy, have used a structural brain network approach using either inter-regional cortical thickness, gray matter volume correlations, or diffusion tensor imaging tractography. The findings of these studies demonstrate that the structural brain network approach can be effectively used in the neuropsychiatric disorder studies to capture the abnormalities of regional and whole-brain network organizations.

Summary

By modeling the brain as a complex network, we can use graph theoretical analysis to study neuropsychiatric disorders by exploring its topological attributes. The interesting findings of the limited number of previous studies from the perspective of brain connectivity should attract more researchers to apply this method. This emerging quantitative framework may lead us to better understanding of neuropsychiatric disorders.

Keywords

graph theory, human brain connectivity, neuropsychiatric disorders, structural brain network

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Introduction

Traditionally, the relationships between brain structure and neuropsychiatric disorders have been studied by examining circumscribed atrophy or other abnormalities of various gray or white matter regions of interest using three-dimensional T1-weighted structural MRI scans. However, there are limitations of this approach. Firstly, in disorders such as schizophrenia and Alzheimer's disease, a large number of structures show abnormality and the significance of any one structural change is difficult to establish. Secondly, this approach disregards the fact that the brain functions as a network of interconnected regions, and it is the abnormality in the network that is more proximate to the functional impairment. The emerging and rapidly moving network approach based on graph theory has the important advantage of a rich structural description, which allows efficient computation and comparison of different connection topologies within a common theoretical framework [1••].

In this review, we summarize recent advances in structural brain network research pertaining to neuropsychiatric disorders. Brain networks can be described at different organizational levels such as single neurons (microscale), a group of neurons (mesoscale), or anatomically distinct brain regions (macroscale or large-scale) [2]. We will focus on the alterations of topological organization in structural brain networks based on graph theory at the macroscale.

Method

We carried out a literature search in Medline using the following keywords: structural brain network and neuropsychiatric disorders, dementia, Alzheimer's disease, schizophrenia, depression, attention deficit hyperactivity disorder, obsessive compulsive disorder, and epilepsy. This search was limited to the last 3 years. The majority of the studies were of functional brain networks that were not within our scope of review. We selected papers that

conducted some form of analysis on the structural brain data using the graph theory approach.

Basic concepts of structural brain network

In graph theory, a network is defined as a set of nodes and the edges between them [3]. In order to explore the associations between different brain regions in macroscale, one can represent the human brain as a graph with brain regions, arguably, a cortical parcellation, a group of spatially connected voxels or a single voxel as its nodes, and structural connectivity between each pair of nodes as its edges [1••]. A graph can be undirected or directed and unweighted or weighted. So far, only the undirected graph has been implemented in the brain network research, whereas both unweighted and weighted graphs have been used in the recent structural brain network studies. One can use a connectivity matrix to summarize an undirected graph, and graph or network metrics can then be calculated. The clustering coefficient and characteristic path length are two basic measurements of a network [4]. The former is the average of the clustering coefficients over all nodes in the network, which is a measure of local cliquishness or local efficiency of information flow of the networks. The latter is the average minimum number of connections that link any two nodes of the network, which serves as a measure of global efficiency or the capacity for parallel information propagation of the network. These two metrics can be used to distinguish different classes of network such as regular, small-world, or random networks. A small-world network has a shorter characteristic path length than a regular network but a greater local interconnectivity than a random network [4]. Other important metrics include modularity and nodal properties such as the degree, efficiency and betweenness centrality. See the study by Boccaletti *et al.* [3] for a comprehensive description of these network metrics and [1••] for how they are used in the context of brain networks.

Structural brain network studies have generally been constructed using two types of neuroimaging data approaches. The first type uses brain regions as a set of nodes and the inter-regional correlations of regional cortical thickness or cortical and subcortical gray matter volumes across individual brains as edges between the nodes. This type of structural brain network is constructed using three-dimensional T1-weighted structural MRI (sMRI) scans, and, because it uses inter-regional correlations of gray matter thickness or volume of brain regions, only one graph can be constructed for a group of patients. The notion of morphological correlations has been widely used to study correlated evolution in mammalian brain structure [5] or to infer structural connectivity between human brain regions [6]. The work by He *et al.* [7••] that formulated the method and constructed the first such structural brain networks was published in 2007. The modular architecture of such structural brain network revealed the correspondence to six known brain functional neuroanatomy modules [8•].

The second type of structural brain network is based on the diffusion tensor imaging (DTI) fiber tract-derived connectivity between gray matter regions, presenting anatomical connections between brain regions. Recent advances in DTI and tractography have facilitated the noninvasive mapping of structural networks in the human brain at an individual level, that is, a graph can be constructed for each brain. In DTI-based tractography, what is reconstructed does not represent actual axonal fibers, which have diameters of a few microns, whereas the voxel size of DTI scans is usually more than 2 mm^3. Nevertheless, the DTI scan does reflect the macroscopic configuration of 'axonal bundles', which are large enough to be visually appreciated. Using DTI data of two healthy human brains, Hagmann *et al.* [9] demonstrated small-world topology in the structural brain networks of fiber tractography type. In a subsequent study, the modular and core structure of the cortical networks of five healthy volunteers were investigated [10•] using diffusion spectrum imaging (DSI).

The two main organizing principles found in the brain, that is, segregation and integration of information process [2,11], suggest that, although particular brain regions are important for specific functions, the capacity of information flow within and among specialized regions and the information about the tightly correlated vulnerability of certain gray matter regions and white matter tracts are also crucial. The importance of structural brain network based on the DTI (and/or DSI) tractography is easy to see and understand, as these axonal bundles provide physical connections between brain regions. On the contrary, the idea of establishing a network based on the inter-regional correlations can be difficult to appreciate. If cortical thickness is used as the measure, then two cortical regions are considered anatomically connected if their thickness is significantly correlated. The meaning of such coupling between cortical regions is not well understood [12], but this coupling can be explored at two levels. At the first level, one can directly use such concurrent brain region volume changes to examine atrophy rates and patterns or distributions of different populations. For example, if a region has shown neurodegenerative-related atrophy and this particular region is positively correlated to another region, then this coupling demonstrates that the two regions (for instance, the posterior cingulate/precuneus and medial temporal atrophy as found in Alzheimer's disease) are undergoing similar atrophy. Correlation slope can be used to investigate the rate of atrophy between different brain regions among different population groups. At the second level, one could use the quantitative

analyses of structural brain networks to make sense of these concurrent brain region volume changes and relate these to functional changes. However, true structural connectivity should be supported by white matter fiber-tracking, for example using DTI, to demonstrate a physical connection between two brain regions that are correlated with each other. However, one should be careful in interpreting such findings. It is possible that correlations between brain regions may emerge even if they are not directly connected, either by their connectivity to a third region, or because of shared mechanisms in development or degeneration.

Neuropsychiatric disorders and structural brain networks

Although there are many neuropsychiatric disorder studies using brain network approaches, they are nearly all functional brain networks. Examples of functional brain network studies include functional magnetic resonance imaging studies of Alzheimer's disease [13•], schizophrenia [14•], and attention deficit hyperactivity disorder (ADHD) [15•], electroencephalography (EEG) study of schizophrenia [16•], epilepsy [17,18], Alzheimer's disease [19•] and depression [20], and magnetoencephalography study of Alzheimer's disease [21]. Our literature search has resulted in seven structural brain network publications, three on Alzheimer's disease, three on schizophrenia, and one on epilepsy.

Alzheimer's disease and mild cognitive impairment

Structural imaging reveals that atrophy of medial temporal structures is now considered to be a valid and effective diagnostic marker of Alzheimer's disease [22]. Alzheimer dementia is associated with prominent medial temporal, posterior cingulate/precuneus and lateral temporo-parietal atrophy. Because specific neurodegenerative diseases target differently patterned brain systems, the network topological attributes of Alzheimer's disease patients are likely to be different from other neurodegenerative diseases as well as cognitively normal controls. The examination of Alzheimer's disease using structural brain networks has shown some interesting and promising results. The first such study, by He *et al.* [23••], which used sMRI-based inter-regional correlations network, compared the patterns of structural connectivity between Alzheimer's disease patients and healthy controls. This study [23••] constructed regional cortical thickness correlation matrices for both the Alzheimer's disease group (92 early-stage Alzheimer's disease patients) and the cognitively normal group (97 normal controls) and found some significant alterations in the connection strength between brain regions in the Alzheimer's disease group. One of the observations they made was the disruption of the structural correlations between the bilateral parietal regions in Alzheimer's disease patients, which is in accordance with many electrophysiological and neuroimaging studies in Alzheimer's disease. The study also reported that Alzheimer's disease patients showed regional cortical thinning and increased inter-regional thickness correlations in the 'default mode' network (including the lateral temporal and parietal cortex, as well as the cingulate and medial frontal cortex regions), which has been known to exhibit Alzheimer's disease-related breakdown of brain activities, such as amyloid deposition and metabolic and spontaneous activity disruption [24–28]. Also using inter-regional gray matter volume correlations, a recent study [29••] of 98 normal controls, 113 mild cognitive impairment (MCI) patients and 91 Alzheimer's disease patients found that the Alzheimer's disease network had the longest path length, followed by MCI. The abnormality of structural correlations may be attributed to the Alzheimer's disease-related ultrastructural changes such as the local cell death/shrinkage, reduced dendritic extent, and synaptic loss.

Many Alzheimer's disease-related diffusion MRI studies have shown compromised white matter integrity, such as reduced fractional anisotropy or increased mean diffusivity of some major white matter tracts. Large-scale functional network studies also indicated that Alzheimer's disease patients had aberrant connectivity patterns [13•,19•,21]. Lo *et al.* [30••] in their recent work found that Alzheimer's disease patients had reduced nodal efficiency predominantly in the frontal regions. Our literature search, however, failed to find any studies on MCI by the whole-brain structural network approach using DTI tractography. DTI studies which used conventional regions of interest and voxel-based morphometry analyses have reported white matter alterations in MCI individuals in the frontal, parietal and temporal lobes [31,32], posterior cingulum [33–36], splenium of corpus callosum [34,37,38], long association fascicles [39], and internal capsule [32,34]. A recent study found that amnestic MCI (aMCI) could be best identified from cognitively normal by combining fractional anisotropy measures of the splenium of corpus callosum and crus of fornix [40]. In comparison with aMCI, the white matter abnormality of nonamnestic MCI (naMCI) patients was more anatomically widespread, but the temporal lobe white matter was relatively spared [40]. These findings provide direct evidence for structural abnormalities in the neuronal networks of MCI and suggest that the characteristics of DTI tractography-based brain networks of aMCI and naMCI are likely to vary because aMCI is characterized by early Alzheimer's disease pathology, whereas underlying pathology in naMCI is more heterogeneous.

Schizophrenia

Schizophrenia is a heterogeneous disorder with variations in expression and pathophysiology [41]. A review of longitudinal MRI studies [42] of first-episode patients,

prodromal patients, and high-risk individuals suggests an acceleration of gray matter reduction early in the course of illness. Specifically, there is gray matter reduction in prefrontal regions, which these investigators believe leads to further progressive changes in medial temporal and orbitofrontal brain regions.

Using anatomical networks derived from analysis of interregional covariation of gray matter volume in MRI data on a sample of 203 people with schizophrenia and 259 healthy volunteers, Bassett *et al.* [43••] found that the multimodal network organization of the people with schizophrenia was abnormal, as indicated by reduced hierarchy and the loss of frontal and the emergence of nonfrontal hubs. Furthermore, the mean connection distance was significantly greater for the multimodal network in people with schizophrenia than in healthy volunteers.

There have been nearly 200 DTI studies of white matter pathology in schizophrenia [41] since the first such study in 1998 [44]. A main focus of DTI studies in schizophrenia has been fronto-temporal connections in the brain [45]. One of the two DTI tractography-based schizophrenia studies we located was by van den Heuvel *et al.* [46••], which reported an aberrant topology of the structural infrastructure of the schizophrenia brain network. Their study included 40 schizophrenia patients and 40 healthy controls and the strength of the connections was defined as the level of myelination of the tracts measured by magnetization transfer ratio. Patients displayed a preserved overall small-world network organization, but, when focusing on specific brain regions and their capacity to communicate with other regions of the brain, significantly longer node-specific path lengths of frontal and temporal regions were revealed, especially of bilateral inferior or superior frontal cortex and temporal pole regions. The other study was by Zalesky *et al.* [47••], which reported that impaired connectivity in the patient group was found to involve a distributed network medial frontal, parietal/occipital, and the left temporal lobe. The cortex was interconnected more sparsely and up to 20% less efficiently in patients. Given the large number of DTI findings of reduced fractional anisotropy in large amounts of fiber tracks, DTI tractography-based structural brain network is thus a promising framework to further explore how the compromised integrity of white matter tracts negatively impacts on the information flow between the brain structures and results in aberrant topological patterns of the networks.

Epilepsy

A recent temporal lobe epilepsy (TLE) study of 14 patients with TLE with mesial temporal lobe sclerosis (TLE–MTS), 14 patients with TLE with normal MRI (TLE-no), and 30 controls [48] has derived whole-brain networks from volumetric data and obtained network measures. The network measures captured cortical thinning characteristic of TLE. The network measures were then used to classify a given MRI scan into TLE or normal, and obtain additional summary statistics, which related to the extent and spread of the disease. The nodes of the graph were still brain regions, but the edges represented disease progression paths. Furthermore, this study's approach created a network for each patient instead of one network for a group of patients. The proposed network approach improved classification accuracy (control and TLE) from 78% for non-network classifiers to 93%.

Some other structural brain network studies

Several studies that are not usually categorized clinically as neuropsychiatric disorders are also worth discussion. Small-world efficiency of structural brain networks in multiple sclerosis (MS) was disrupted, and the severity of disruption was in proportion to the extent of total white matter lesions [49•]. In a study of normal aging with two large cross-sectional samples, it was found that the brain structural networks of the younger cohort ($N = 428$; mean age = 46.7, range 44–48) and older cohort ($N = 374$; mean age = 66.6 years, range 64–68) had small-world architecture, and the older cohort had lower global efficiency but higher local clustering in the brain structural networks compared with the younger cohort [50]. The older cohort had reduced hemispheric asymmetry and lower centrality of certain brain regions such as the bilateral hippocampus, bilateral insula, left posterior cingulate and right Heschl gyrus, but that of the prefrontal cortex was not different [50]. Summarizing these brain network studies which used regional gray matter correlations, we found that the studies of Alzheimer's disease [23••], schizophrenia [43••], MS [49•] and normal aging [50] had one thing in common, that is, all the populations in the studies had considerable gray matter changes due either to disease [23••,43••,49•] or to normal aging process [50]. The earliest sites of MRI-based atrophic changes in Alzheimer's disease typically lie along the perforant (poly synaptic) hippocampal pathway (entorhinal cortex, hippocampus and posterior cingulate cortex), consistent with early memory deficits. Later, atrophy in temporal, parietal and frontal neocortices is associated with neuronal loss, as well as language, praxic, visuospatial, and behavioral impairments [22]. MS structural MRI studies have consistently shown the loss of gray matter in thalamus, hypothalamus, putamen, caudate nucleus, and cortex [51]. The list of brain regions reported as abnormal in schizophrenia is also extensive [41]. Age-related rates of change in many structural measures are well documented [52]. It is therefore not surprising that positive findings have been reported in the gray matter correlation-related brain network studies. It is yet to be seen whether this type of

network approach will produce insightful results in the neuropsychiatric disorders that have less consensus on the location and extent of structural changes, such as ADHD [53]. A major shortcoming of this type of structural brain network is perhaps that usually only one graph (network) can be established for a group of patients. An encouraging and important exception is the recent epilepsy study [48], in which each brain was modelled with its own unique network and which thus might be more sensitive to the subtle alterations of network organizations.

Several DTI tractography-based network studies have explored brain structural connectivity patterns from different perspectives with different populations. Crofts *et al.* [54•] found that changes in brain structure occurred in remote regions following focal damage. Reduced communicability was found in patients in regions surrounding the lesions in the affected hemisphere [54•]. In addition, communicability was reduced in homologous locations in the contralesional hemisphere for a subset of these regions [54•]. Li *et al.* [55•] showed that higher intelligence quotient scores were associated with greater brain network global efficiency. Shu *et al.* [56] showed that early-blind patients were associated with decreased connectivity degree and global efficiency in the structural brain networks, particularly in the visual cortex. However, increased connections were detected in the motor or somatosensory areas. These results imply a topological re-organization of structural brain connectivity. Gong *et al.* [57•] demonstrated that the local efficiency of brain networks decreased with age (from 19 to 85 years) and that there was a shift of regional efficiency from the parietal and occipital to the frontal and temporal neocortex in older brains. Interestingly, they also showed that female brains have greater overall connectivity and higher efficiency than male brains. Wen *et al.* [58•] reported the association of cognitive assessments and the connectivity of the whole-brain network and individual cortical regions (342 healthy individuals aged 72–92 years). Correlations between connectivity of specific regions and cognitive assessments were also observed; for example, stronger connectivity in the regions such as superior frontal gyrus and posterior cingulate cortex were associated with better executive function. Similarly to the relationship between regional connectivity efficiency and age, greater processing speed was significantly correlated with better connectivity of nearly all the cortical regions.

Conclusion

Despite promising findings, we are far from understanding how various neuropsychiatric disorders alter the neuronal organization of the brain differently. The following are some of the outstanding questions that remain to be addressed: is there a causative relationship between gray matter abnormalities observed with the network using inter-regional correlations of sMRI data and white matter abnormalities observed with DTI tractography-based network in the neuropsychiatric disorder studies? When do structural brain network abnormalities first occur and how they progress in these disorders, etc.? We believe that more research is needed to explore and establish comprehensive and specific descriptions for patterns of structural brain connectivity. The efforts reported in this review have shown a new and promising research framework to address these questions.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 259).

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