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A Review: Detecting Alterations of Brain Connectivity in Schizophrenia based on Structural MRI

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Abstract

Schizophrenia is a common psychiatric disease with brain connectivity changed. Nowadays brain network has become an effective tool to detect the abnormal brain connectivity in patients. Compared with studies focused on functional and white matter connectivity, the research of grey matter connectivity is relatively less and should be paid more attention. The primary approach of grey matter connectivity analysis is based on brain network constructed from structural MRI (sMRI). There are several morphometric features such as cortical thickness, volume, and curvature etc. Which could be used for sMRI brain network construction? This review briefly introduced sMRI brain network construction and analysis, presenting the most frequently used morphometric features with their effectiveness in schizophrenia, highlighting the application of sMRI brain network in schizophrenia, and finally estimated its potential value.

Keywords: Schizophrenia; Structural MRI; Brain network; Morphometric features

Introduction

Schizophrenia is a complex condition with a wide range of clinical signs [1]. Generally it was defined as a chronic and debilitating mental disorder, which usually has an onset in adolescence or early adulthood [2]. It involves abnormal emotional responses and difficulty with social interactions [3]. In addition, patients with schizophrenia exhibit impairments in both basic sensory processing and higher cognitive functions, such as language, reasoning and planning [4]. Nowadays, there are some brain image systems helping to diagnose of schizophrenia, like structural MRI [5], diffusion MRI [6], functional MRI [7], PET [8], MEG [9] and SPECT [10] etc. However, the etiology and pathophysiology of schizophrenia remain unknown [2], while indeed, schizophrenia has come to be regarded more and more as a disease of disconnectivity [11]. Therefore, it makes brain network play an extremely important role in detection of altered brain connectivity in schizophrenia.

For different diagnosis purpose, various brain networks have been developed. To date, there are mainly three forms of network: functional network derived from BOLD-MRI (**Blood- Oxygen- Level Dependent** (fMRI) [12-14]; structural network derived from diffusion MRI (DTI) focused on white matter [15-17]; and structural network derived from structural MRI (sMRI) focused on gray matter [18-20]. Compared with sMRI-based network, DTI-based and fMRI-based networks are easier to build because it is necessary to extract one or more reasonable morphometric features for construction of sMRI-based network. For this reason, sMRI-based network is relatively less popular used although sMRI has the merit of higher resolution. But with the development of neuroimaging technique, it will be widely used and attach the equal importance with DTI-based and fMRI-based networks.

In this review, we concentrated on application of sMRI-based network in schizophrenia. First, the construction of sMRI-based network was briefly outlined. Second, the frequently used morphometric features were elucidated. Third, analysis of brain connectivity alteration in schizophrenia using sMRI-based network in recently researches were presented. Finally, the problems and future development of sMRI-based brain network were pointed out.

Structural MRI Network

Alexander et al. [11] revealed that networks construction and analyses generally used three steps: seed analysis, principal component analysis (PCA)and graph analysis. These procedures are not exclusive to sMRI network and more details were represented in the following sections.

Seed Analysis

To construct the network, firstly we need to determine the 'nodes' of the network according to brain parcellation. Automated anatomical labeling (AAL) [21] is the most commonly used parcellation template.Besides, there are also Harvard Oxford (H-O) [22], Eickhoff–Zilles (E-Z) [23], Talariach–Tournoux (T-T) [24] and CC200 (or CC400) [25] in use. After parcellation, each node needs to be defined as at least one morphometric feature. Therefore, the morphology in the regions could be compared with each other and then a whole-brain map of structural co-variance could be generated [11].

Principal Component Analysis

PCA uses an **orthogonal transformation** to convert a set of observations of possibly correlated variables into a set of values of **linearly uncorrelated** variables called principal components [26]. This theory was invented in 1901 by **Karl Pearson** [27]. In brain network construction, PCA reduces the inter-regional co-variance

across people to a small number of factors which are easier to visualize and interpret [11].

Graphic Theory

Graphic theory provides a powerful tool to quantitatively describe the topological organization of brain network connectivity [28,29]. Clustering coefficient [30], shortest path length [31], small-worldness [32], degree [33], nodal efficiency [34] and betweenness centrality [35] are the most frequently used parameters to describe the topological properties of brain network. Moreover, the abnormal regions could be identified using brain network.

Morphometric Features

Various forms of brain network have been established based on the corresponding brain features. For DTI-based brain network, the tensor of water molecules in fiber bundles of white matter is the feature which represents how seed regions connect to each other. And in fMRI-based brain network, the correlation between BOLD signals is the feature to present whether the seed regions have the connectivity. While for sMRI-based brain network, the feature is extracted from grey matter based on morphometry.

Levitt et al. proposed that schizophrenia is believed to be a disorder which many regions of the brain affected [36]. There have been large amount of imaging studies assessing brain morphometry to detect abnormalities in multiple regions in this devastating disorder. Therefore, morphometry, and specifically, morphometric feature is the basis of the sMRI-based brain network construction and analysis. There are diverse morphometric features because brain morphometry can be measured through multiple ways, which turns out to be an advantage of sMRI that can tell us more than one aspect of brain condition. We will elaborate the common morphometric features with references as following.

Cortical Thickness

Cortical thickness was estimated as the shortest distance between the gray and **white matter** border and the **pial** surface at numerous points across the entire cortical mantle [37]. Its variation across the **human brain** follows **small-world** principles [38]. Kuperberg et al. have found significant thinning in distributed areas of the cortex, most prominently in frontal and temporal region sinchronic schizophrenia patients [39]. Nesvåg et al. found thinner cortex located in prefrontal and temporal regions of both hemispheres in schizophrenia patients, while parietal and occipital regions were relatively spared [37]. But Wieg and et al. did not detect cortical thinning averaged across the entire prefrontal lobe in first episode schizophrenia patients [40].

Volume

Brain size is measured by **volume** via **MRI** scans. Van Haren et al. suggested that brain maturation occurring in the third and fourth decade of life is abnormal in schizophrenia, based on the longitudinal study that different age-related trajectories of brain tissue loss are present in patients compared to healthy subjects [41]. Scheewe et al. found significantly smaller baseline cerebral (grey) matter, and larger **third ventricle** volumes, and thinner cortex in most areas of the brain in patients with schizophrenia [42]. Abbs et al. [43] found that in **schizophrenia**, **anterior cingulate gyrus** (ACG) volume was reduced in females, but not in men, relative to controls.

Curvature

Curvature of the brain surface provides an effective method for assessing the character of convolutions on the brain's surface, thereby serving as an index of normal versus abnormal brain development [44]. Ronan et al. found that millimeter-scale intrinsic curvature measures were more robust and consistent in identifying reduced gyrification in patients with schizophrenia [45].

Complexity

Cortical complexity is a measurement which could quantify the spatial frequency of gyrification and fissuration of the brain surface [46]. Wiegand et al. found prefrontal cortical complexity was not significantly different among the groups including both subtypes of patients and healthy controls [47]. However, the schizophrenia patients differed significantly from the healthy subjects in asymmetry, showing less left-greater-than-right asymmetry in cortical complexity than the controlled subjects.

Density

After the individual images were segmented and **registered**, each voxel then achieved a measure of the probability, according to which it belongs to a certain tissue class. For gray matter, this quantitative measurement is usually represented as gray matter density (GMD) or gray matter concentration (GMC), or gray matter probability (GMP) [48]. Stegmayer et al. had the main finding which suggests severe emotional disturbance in schizophrenia be particularly associated with reduced GMD in a large cluster including the ventral striatum [49].

Cortical folding

The degree of folding relative to brain size remains relatively stable from early childhood [50,51], and is thus a suitable subject for investigation of brain disorder. Abnormalities like schizophrenia might denote abnormal cortical folding development, which can now be investigated using **gyrification** measures [52]. Nesvåg et al. [53] found the reduced degree of folding in large regions of the cerebral cortex across two independent samples indicates that reduced gyrification is an inherent feature of the brain pathology in schizophrenia.

sMRI-based Brain Network Application in Schizophrenia

With the development of morphometric feature studies, brain network helps us get more information about the whole brain connection. Besides, discoveries of structural MRI-based network in schizophrenia can complement studies which show disrupted white matter tracts [3] and functional connectivity [54] between brain regions in the disease [11]. Then, we will present the results of recent researches of sMRI-based network applied in the schizophrenia.

Salgado et al. compared grey matter volumes using voxel-based morphometry (VBM) and discovered volume reductions in medial cortical regions which overlapped with the same parts of the functional network in the patients [19,55]. Bassett et al. [56] constructed the anatomical networks derived from analysis of inter-regional co variation of gray matter volume. They proposed that the topological differences between divisions of normal cortex may represent the different growth processes. What's more, neuro developmental abnormalities in schizophrenia specifically impact multimodal cortical organization. Shi et al. [57] indicated that the

brain structural associations of the high-risk neonates tended to have globally lower efficiency, longer connection distance, and less number of hub nodes and edges with relatively higher betweenness by the morphological network analysis. Zhang et al. constructed the brain networks by thresholding cortical thickness correlation matrices and they found both characteristic path length and clustering coefficient increased in the structural cortical networks of patients [18]. Moreover, in two years later, Zhang et al. also found that less distributed cortical regions were identified in the thalamo-cortical network in patients with schizophrenia, but vertex-wise comparison revealed decreased thalamo-cortical connectivity in bilateral **inferior frontal gyrus**, the left **superior temporal gyrus** and the right parieto-occipital region, by constructing a thalamo-cortical network to assess the correlation between the thalamic volume and cortical thickness at each vertex on the cortical surface [58]. Rüsch et al. did a research on regional gray **matter** volumes [59] and analyzed by VBM within SPM5 (statistical parametric mapping) [60], the results show that patients with schizophrenia have reduced gray matter volume in dorso lateral prefrontal and **anterior cingulate**. Jagannathan et al. found gray matter deficited in patients with schizophrenia consistently with previous reports, including frontal and temporal lobes and **thalamus** [61]. Bagary et al. found that smooth pursuit abnormalities were associated with reduced magnetization transfer ratio in several regions, predominantly in the right **prefrontal cortex** [62]. Collin et al. discovered schizophrenia patients showing both decreased (e.g. between left frontal and bilateral subcortical, $p \leq 0.005$) and increased (e.g. between left temporal and bilateral subcortical, $p \leq 0.001$) coupling between lobar grey matter volumes [63]. Glahn et al. found patients had reduced gray matter density in a distributed network of regions (including bilateral **insular cortex**, **anterior cingulate**, left **parahi ppocampal gyrus**, left **middle frontal gyrus**, **postcentral gyrus**, and **thalamus**) and increased gray matter density in striatal regions [64].

Conclusions

Brain network construction and analyses is becoming an essential tool recently, to help diagnosing the nerve system disorder and orientating the foci, such as schizophrenia which might not has apparent brain damages presented on MRI or other images. For sMRI-based brain network, according to the recent researches, the detected localization of foci, like **frontal lobes**, thalamus, **hippocampus** and **temporal lobes**, is generally same with the result by fMRI-based network. Altered morphometric features such as grey matter reduction and density change were discovered, and the network topology analysis of patients showed lower globally efficiency, longer connection distance, less number of hub nodes and edges with relatively higher betweenness, increased characteristic path length and clustering coefficient.

Compared with the other two forms of brain network, the development of sMRI-based brain network is a little bit lagged behind. On the other way, it still has so many interesting and amazing properties remained to explore. At present, sMRI-based network is constructed on inter-regional correlations estimated from a group of individual images [11], which means it's not feasible for individual. Although there are some studies proposed methods [65,66] to solve this problem, they still have limitations and needs to be improved for application. Another problem is that, morphometric features used in network construction were generally focused on cortical thickness and volume, which more sensitive morphotric features able to describe the disease should be considered.

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