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·Review·

A review of functional magnetic resonance imaging for Brainnetome

Ming Song[1], Tianzi Jiang[1,2,3]

[1]*LIAMA Center for Computational Medicine, National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China*
[2]*Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 610054, China*
[3]*The Queensland Brain Institute, the University of Queensland, Brisbane, QLD 4072, Australia*

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Abstract: The functional brain network using blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) has revealed the potentials for probing brain architecture, as well as for identifying clinical biomarkers for brain diseases. In the general context of Brainnetome, this review focuses on the development of approaches for modeling and analyzing functional brain networks with BOLD fMRI. The prospects for these approaches are also discussed.

Keywords: functional magnetic resonance imaging; brain network; functional connectivity; effective connectivity; Brainnetome

1 Introduction

The brain functions by the interactions between neurons within different neural circuits and brain regions. Research in neuroscience is increasingly focused on functional integration in the brain[1], since this may greatly improve our understanding of how the human brain works. Recently, increasing evidence suggests that such functional integration could be helpful for the early diagnosis and prognosis of schizophrenia and other neurological and psychiatric diseases. Therefore, the National Institutes of Health launched the Human Connectome Project[2]. Meanwhile, a similar project entitled "CONNECT" was supported under Framework Program 7 of the European Union. We have also been leading a project called "Brainnetome" in China and elsewhere. The "Brainnetome" consists of networks of the topological structure, performance and dynamics, and manifestation of the functions and malfunctions of the brain at different scales, the genetic basis of brain networks, and simulating and modeling brain networks on supercomputing facilities.

A variety of technologies have been developed to study brain networks. The technologies at the macroscale level at least include resting-state/task functional magnetic resonance imaging (fMRI) and diffusion MRI. Those at the microscale level include brainbow[3], optogenetics[4], and auto-segmentation and three-dimensional (3D) reconstruction of microscopic images[5], all having shown impressive advances. However, each of these technologies aims to answer a different question in a specific domain. It is a major challenge to integrate the multi-level network features obtained using various functional and anatomical imaging technologies on different scales. We therefore have proposed the new concept of "Brainnetome" to represent such an integrative framework. The "Brainnetome" was

Corresponding author: Tianzi Jiang
Tel: +86-10-82614469; Fax: +86-10-62551993
E-mail: jiangtz@nlpr.ia.ac.cn
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conceived to decipher more comprehensive networks from an "–ome" point of view (Brain-net-ome), that embraces not only physical structural connections but also functional connectivities disclosed by various levels of *in vivo* imaging methods and *ex vivo* imaging/staining techniques. More importantly, the Brainnetome emphasizes not only a static description of the network state at a certain time-point, but also dynamic processes throughout the natural maturation, neuropsychiatric evolution, and genetic basis of the networks. More information about the Brainnetome and related projects and resources is available at http://www.brainnetome.org/.

fMRI measures brain activity by detecting the associated changes in blood flow. The primary form of fMRI uses blood-oxygen-level-dependent (BOLD) contrast[6]. In particular, BOLD fMRI uses the change in magnetization between oxygen-rich and oxygen-poor blood as its basic measure. In the general context of Brainnetome, this review focuses on the progress of methods for modeling and analyzing functional integration with BOLD fMRI data. To make it easier to understand each method's strengths and weaknesses, this review first briefly introduces the principles of BOLD fMRI, focusing on its typical spatiotemporal resolution and its actual limitations. Then, centering on how to measure neural connectivity with BOLD fMRI data, we review various methods, including functional connectivity and effective connectivity. Finally, some applications using these methods are presented, and promising directions for future work are discussed.

2 Principles of BOLD fMRI

As a noninvasive means of neuroimaging, BOLD fMRI does not require people to undergo injections or surgery, or to ingest substances, or to be exposed to radiation. Typically, its spatial resolution is 2–5 mm. Although such a volume typically contains a few million neurons and tens of billions of synapses, it is superior to some other neuroimaging techniques, including electroencephalography (EEG) and magnetoencephalography (MEG). Importantly, BOLD fMRI has the capacity to cover the entire brain within a few seconds, which is extremely important for identifying functional networks. On the other hand, the temporal resolution of BOLD fMRI is often 1–3 s. Although this is rather longer than sensory processing (tens of milliseconds), the temporal resolution needed depends on the processing time for various events. For example, neuromodulatory effects, such as those affected by arousal, attention and memory, are slow. Therefore, BOLD fMRI can not only reveal the location of activity (functional segregation), but also probe the interactions between regions (functional integration). In summary, the advantages of BOLD fMRI lie in its noninvasive nature, ever-increasing availability, relatively high spatiotemporal resolution, and its capacity to demonstrate the entire network of areas, which have made BOLD fMRI the mainstay of neuroimaging for functional brain network research[7].

However, BOLD fMRI does have limitations. First, the magnitude of the BOLD fMRI signal cannot be quantified to reflect the strength of neural activity, the behavioral performance, or even dysfunction[8]. Specifically, the signal-to-noise ratio is very low. The noise in the data has an amplitude similar to that of the hemodynamic response, which makes it difficult to quantify the strength of neural activity with the magnitude of the signal. Thus, a higher-amplitude BOLD signal may be seen for stronger neural activity, but it is possible that a peak BOLD signal at the same place represents weaker neural activity. Meanwhile, a complex cognitive task may initially trigger high-amplitude signals associated with good performance, but as the subject gradually adapts to the task, the amplitude may decline with performance staying the same. Second, BOLD fMRI does not directly measure neural activity, but relies on a cascade of physiological events linking neural activity to the generation of the MRI signal[8]. The signal can be contaminated by a number of influences, including heart beat and respiratory rhythm[9]. In addition, effects induced by some diseases (i.e. tumor and stoke) and drugs (i.e. sedatives and vasodilators) strongly modulate the neurovascular coupling[10,11]. These can spoil the analysis of activation and functional networks. Therefore, BOLD fMRI studies, especially those concerned with pathology and pharmacology, cannot fully attribute the discovered

changes to brain activation or functional networks.

3 Methods of brain network analysis using BOLD fMRI

Functional connection is one of the primary topics in studies of functional networks. How to define, quantify and present functional connections remains an active research area in BOLD fMRI studies. A variety of methods have been developed to identify functional connections with BOLD fMRI data. Notably, these methods are not mutually exclusive; in fact, sufficient and increasing interplay exists between them. Meanwhile, the developed analysis methods are in the process of mutual infiltration. The following section will not review these methods in detail due to limited space, and recent excellent reviews are available[12,13].

3.1 Functional connectivity A method widely used to estimate neural connectivity using BOLD fMRI is the temporal correlation of pairs of voxels (or brain regions), referred to as "functional connectivity"[14,15]. It assumes that the more similar the time series are between any given pair of voxels (or brain regions), the more likely it is that a functional connection exists between them. Obviously, such a correlation does not demonstrate either causality, since in itself it tells nothing about the direction of information flow. In addition, the correlation does not tell whether the functional connection is direct or indirect, not to mention differentiating whether there may be a third node between the two voxels, or a third node may be feeding into both, or other connection patterns. Alternatively, another simple method, partial correlation, can estimate direct connections (still not their directionality). Specifically, the partial correlation regresses out the other time series from each of the two series, before estimating the correlation between any two series. However, partial correlation can miss functional connections, since the regression is not selective and may remove too much of the information about the functional connection of the two time series concerned.

3.2 Effective connectivity Correlation and partial correlation cannot estimate the causality of functional connections between brain areas. Fortunately, methods have been developed to handle this. As we know, few connections are unidirectional, with feedback generally running in parallel with feedforward. Nevertheless, in many cases it is interesting to estimate at least the dominant direction of information flow for a given connection[16]. So, the question of directionality is important and has received much attention, despite the fact that in general, estimating the directionality is harder than testing for the existence of a connection[17]. The causality, in other words, the direction of information flow, can be defined from at least two perspectives: (1) the cause precedes the effect (i.e., temporal precedence); and (2) the cause increases the probability of the effect (i.e., conditional independence). So, the methods that attempt to estimate causality may be generally categorized into two classes. One class is temporal lag-based, with the most common example being Granger causality[18]. Here, it is assumed that if one time series looks like a time-shifted version of the other, the one with temporal precedence causes the other, giving an estimate of connection directionality. The second class is based on the idea of conditional independence, typically including Bayes nets[19] and structural equation modeling[20]. For example, if the dominant flow of information is from A to B, then the probability of B given A (P(B|A)) is greater than the probability of A given B (P(A|B)), that is, P(B|A)−P(A|B) >0.

The dynamic causal model (DCM) is a hypothesis-driven method, which can be used to test a specific set of hypotheses, for example, a specific activity pattern of the brain network[21]. In particular, DCM uses an explicit forward or generative model of how the observed fMRI data were caused. Hidden neuronal and biophysical states are invoked in the model, with the assumption that interactions between regions are limited to the neuronal level and each region generates a BOLD fMRI signal depending only on its own activity. Since both the lag-based and the conditional independence-based methods can estimate direct connections at the neuronal level, DCM can, in principle, use each of these methods to infer causality. In addition, DCM is usually combined with model selection methods, such as Bayesian model selection, to test which model provides the most likely explanation of the observed fMRI data.

3.3 Other representative methods Independent com-

ponent analysis (ICA) can decompose the BOLD fMRI data into a set of linearly separable spatial components and their associated time courses[22-24]. In some sense, the spatial component can be viewed as a functional network containing distributed brain regions, with the associated time courses presenting uniform dynamics for the regions within this network. ICA can distinguish between non-task-related signal components, movements and other artifacts, as well as task-related activation. Meanwhile, since ICA is data-driven, many resting-state fMRI studies have widely used it to search for networks[25].

Recently, researchers have started to apply pattern classification algorithms to analyze spatially distributed patterns (voxels or brain regions) of BOLD fMRI, named multivariate analysis or decoding[26,27]. In some sense, decoding distributed patterns from multiple voxels or brain regions may be pertinent to network analysis. Notably, the functional connections between distributed voxels or regions are dynamic and changeable with different trials. The decoding methods constitute a useful new tool that advances our understanding of neural information processing in functional networks, particularly from the perspectives of non-stationarity and non-linearity. In addition, some methods, including psychophysiological interaction[28] and partial least squares[29], have been proposed to detect functional/effective connectivity in relation to the performance of a particular psychological task.

3.4 Model complexity and applicability In summary, with the accumulating studies centered on how to measure neural connectivity with BOLD fMRI data, some methods have been developed and validated, each having its own strengths and weaknesses, and aiming to answer a distinct question. Among these some, such as (temporal) correlation and partial correlation, are simpler than others, such as DCM, in modeling and computation. The simpler methods are just descriptions of the data, and do not relate them to underlying, interpretable physiological parameters for functional brain networks. For example, correlation tells one nothing quantitative about causality or directionality, but just reflects connection strength. As a result, it is more vulnerable to factors such as thermal noise and even head motion during scanning[30]. However, in the more complex methods such as DCM, the model parameters all relate to interpretable and meaningful quantities such as thermal noise, neuronal delay between nodes and the interaction strength between the regions of concern. Estimating quantitative and physiologically meaningful parameters is clearly of great value if one wants to find and interpret changes in functional networks, such as those in a cognitive task or disease state. On the other hand, the simpler methods in general are more robust in fitting the model to the data, and faster to compute, than the complex methods. So, the simpler methods allow the network analysis of large numbers of nodes, including the voxel-wise whole-brain network, while the sophisticated, highly parameterized methods handle fewer nodes, generally less than 20. In addition, the simpler methods do not require the scope of possible network models to be pre-specified or constrained, which makes them computationally practical for network search or discovery. In contrast, the complex methods have much difficulty in fulfilling this purpose, since they have traditionally not been able to search over all possible networks due to the limitations of computational efficiency. These could be the primary reasons for the still wide use of the simpler methods, particularly for resting-state fMRI data. Therefore, for a BOLD fMRI study, one should choose the most suitable method according to the question of concern. Fig. 1 shows a schematic of networks using functional connectivity and effective connectivity.

4 Applications of brain networks based on BOLD fMRI

As mentioned above, distinct methods have been developed for BOLD fMRI analysis, aiming to answer specific questions concerning functional connections. These questions cover many application areas, including resting-state functional connectivity networks, task-induced effective connectivity networks, and parcellation of brain regions. This section mainly presents progress in these areas.

4.1 Resting-state functional connectivity networks Resting-state BOLD fMRI studies have widely used functional connectivity to investigate the organization of

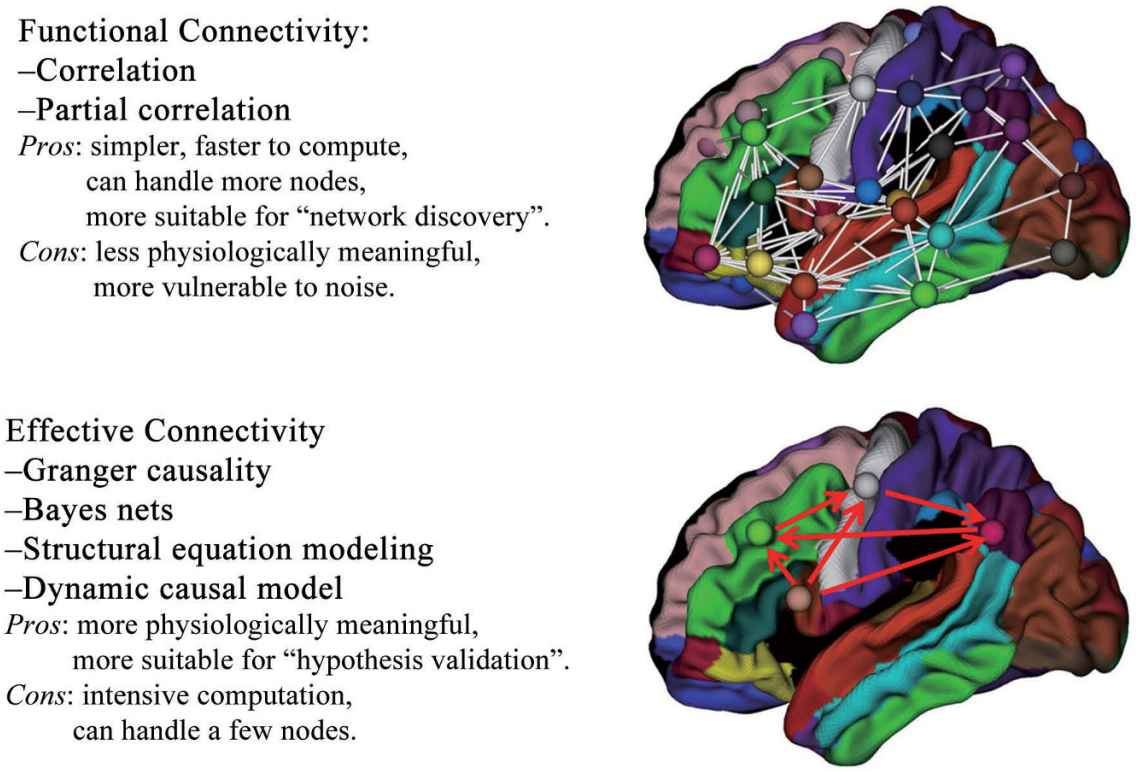

Fig. 1. Schematic of brain functional networks using functional connectivity (upper) and effective connectivity (lower).

functional brain networks[31] and its changes, such as those resulting from disease[11]. The fundamental underpinning of this approach is that correlations in the low-frequency band (0.01–0.1 Hz) of the BOLD signal can provide clues that the two voxels (brain regions) are functionally coupled through direct or indirect anatomical connections[32]. So, it is believed that the resting-state fMRI can make strong, albeit indirect, inferences about the anatomical connections[33]. The spatial patterns of the resting-state networks and their potential relationship with behavior have been intensively investigated.

A brain network consists of two basic components: nodes and edges between a pair of nodes. In fMRI studies, the network node is often referred to as the region of interest (ROI). The ROI can be defined and obtained in varieties of ways, for example, task fMRI activation, ICA components and brain atlases such as the automated anatomical labeling (AAL) atlas. Alternatively, parcellation using the BOLD fMRI data itself or other neuroimaging data can be used to define ROIs. Once defined, each ROI has its own associated time-course (e.g., the average time series from all voxels within the ROI). The correlation between the time-course of a single ROI and that of each voxel in the brain can help to explore the functional connectivity pattern between the ROI and other regions[34]. This can be extended to multiple ROIs covering specific functional networks[35,36], even the entire brain[37,38]. Of course, there are open questions, such as how to determine the location and size of an ROI, and how to present its most representative and meaningful time-course.

Recent developments in the quantitative analysis of complex networks, based largely on graph theory, have been applied to studies of human brain networks[39,40]. Many studies suggest that the human brain's structural and functional systems have features of complex networks, for example, small-world topology, highly-connected hubs, and modularity[41-43]. Some studies have used these methods to explore and interpret changes in resting-state

functional networks, such as those in schizophrenia[44] and dementias[45].

There is also a significant amount of BOLD fMRI connectivity research not working within the nodes+edges framework. For example, as a data-driven analysis method, ICA does not need to explicitly define the node and the edge, which is good for attempting network search and discovery. So, ICA has been extensively used in resting-state network studies[46-48]. For example, some studies have reported consistent components with potential functional relevance, consisting of regions known to be involved in motor, visual, and auditory processing, memory, executive functioning, and the so-called default-mode network[49]. In addition, some studies have explored the spatially-distributed patterns of connectivity, such as regional homogeneity[50] and the degree/density of local and distant connectivity[51,52]. These investigations have predicted the existence of functional hubs in the human brain, and improved the understanding of brain architecture.

The behavioral significance of the resting-state brain network has been intensively investigated. Many exploratory studies have investigated the relationship between the strength of functional connectivity, or the features of the network from the point of view of graph theory, and varieties of behavioral phenotypes in health and disease, including scale scores[53,54], illness duration[44,55] and genotypic variations[35,56]. Despite this, it remains to be determined which measurements are most appropriate for representing the relationship between functional networks and heterogeneous behavioral phenotype data.

4.2 Task-induced effective connectivity networks As an approach for characterizing neuronal networks based on the effective connectivity between network components, DCM has received much attention[57]. The assessment of effective connectivity measures provides a unique opportunity to determine whether and how activity in different regions within a specific network influences the activity in other regions during a certain task (actually, DCM has been improved for resting-state fMRI data[58]). DCM has already been applied successfully to test competing hypotheses in the sensory fields of neuroscience, such as to investigate the interhemispheric integration of visual processing[59], the suppressive influence of the supplementary motor area on primary motor cortex in motor imagery[60], and somatosensory information processing in primary and secondary somatosensory cortices[61]. In addition, DCM has been successfully applied to more complex cognitive tasks, such as face perception[62] and the cortical interactions related to reading and speech processing[63].

4.3 Parcellation of brain regions It is a major challenge to determine the nodes of brain networks. Although a few studies have investigated networks voxel-wise[64], most analyses have capitalized on atlases that provide a parcellation of the human brain[38,44,65]. It is obviously important to have a complete and functionally meaningful parcellation scheme, so that connectivity patterns can be related to functionally meaningful brain areas. However, none of the current atlases is widely accepted for functionally partitioning the cortex and subcortical structures. For example, the two most popular atlases are Brodmann's cytoarchitectural atlas and the AAL morphological atlas, neither of which provides complete and functionally meaningful parcellations of the human brain. Yet, it is essential to acquire reliable and accurate parcellation not only for network studies, but also for basic neuroscience and clinical research.

Studies have revealed the potential of fMRI (including both resting-state and task fMRI) for brain parcellation. Based on the hypothesis that heterogeneous functional areas have different functional connectivity patterns, some resting-state fMRI studies first computed the functional connectivity matrix, then clustered the voxels with similar connectivity patterns or detected the boundaries between different connectivity patterns, and finally parceled the region[66,67]. With such a parcellation scheme, some cortical regions not previously well-defined have been parceled into functional subdivisions, such as the left lateral parietal cortex[66] and the cingulate cortex[67]. However, validation of the parcellation of human brain regions seems to be a much bigger challenge. So far, there is no uniform framework to manage parcellation. Meta-analysis, task fMRI and other neuroimaging, and comparative biology (for example, comparison of homologous brain areas in human

and macaque) may offer some methods.

5 Future research directions

Functional networks derived from BOLD fMRI have revealed a potential for probing brain architecture, as well as for identifying clinical biomarkers for brain diseases. We think that, over the coming years, the study of functional networks will make increasing progress and achieve more exciting gains. Specific research directions should be given further attention.

5.1 Improving spatiotemporal resolution and signal-to-noise ratio of BOLD fMRI The cerebral cortex is highly convoluted with an average thickness of ~2.4 mm, and the cerebellar cortex is only ~1 mm thick. Subcortical structures include many nuclei, some covering tens of cubic millimeters. However, the spatial resolution of BOLD fMRI to date is typically 2–5 mm, which results in very serious partial volume effects, and the signal-to-noise ratio is very low. Therefore, all of these make fMRI appear like a blurry mosaic, which reduces the accuracy and reliability of functional network studies.

fMRI itself is by no means at the limit of its technical abilities. With higher field strengths, such as 7T, whole-brain high-resolution (1, 1.5 and 2 mm isotropic voxels) resting-state BOLD fMRI can be acquired without sacrificing temporal resolution or coverage. Studies reported that the smaller voxel volumes (1 and 1.5 mm isotropic) result in reduced partial volume effects, permitting the separation of detailed spatial features within functional network patterns as well as a better correspondence between function and anatomy[67]. In addition, several groups are producing new scanning sequences to accelerate BOLD fMRI, with the ability to achieve sub-second whole-brain imaging[68]. Such brief scans can, when combined with new analytical methods, achieve much greater gains in inferring the causality and dynamics of the interactions between brain areas.

5.2 Reducing the confounds of BOLD fMRI with multiple complementary technologies BOLD fMRI does not measure neural activity directly, but relies on a cascade of physiological events linking neural activity to the generation of an MRI signal. Many potential confounds can contaminate BOLD fMRI, including disease, sedation, anxiety, medications that dilate blood vessels, and attention neuromodulation[69]. Therefore, combination of BOLD fMRI with complementary functional neuroimaging, such as perfusion, positron emission tomography and EEG, can be helpful. In addition, diffusion MRI can estimate the orientations and trajectories of fiber bundles that connect different voxels, and thus explore the anatomical connectivity. Studies find that although resting-state functional connectivity is variable and is frequently present between regions without direct structural links, its strength, persistence, and spatial statistics are nevertheless constrained by the large-scale anatomical structure of the human cerebral cortex. Therefore, the anatomical connectivity from diffusion MRI will provide good complements or constraints for modeling functional networks, with not only functional connectivity[10] but also effective connectivity[33]. Finally, there is also a wide range of interventional techniques, some that can be applied to the human brain (e.g., transcranial magnetic stimulation[70]), and others that can be used only in animals (e.g., optogenetic fMRI[71]). These technologies can help ameliorate the limitations of pure BOLD fMRI data, and as a result improve functional brain network research.

5.3 Developing new methods for modeling and measuring brain networks No one disputes that each brain is different. These differences include size and shape, cortical convolutions, areal position and size, and connection patterns. Although spatial normalization to a standard atlas is usually used to compensate for individual variability, it is notable that both volume-based and surface-based registration algorithms are constrained by anatomical rather than functional features. Approaches that capitalize on measures more closely related to connection patterns than folding patterns, for example, resting-state functional connectivity and anatomical connectivity, should in principle be able to achieve much better intersubject alignment. In addition, advanced analytical methods, including novel approaches to parcellation, will enable mapping of functionally distinct parcels in individual subjects, which provide the promise of investigating networks in individuals.

Most BOLD fMRI network research to date has explicitly or implicitly assumed that the functional connection is stationary and/or linear. For example, correlations often take the time-courses of two regions to obtain a single value as the measurement of a functional connection. Obviously, as the scanning time changes, the connection is changing, possibly hugely and even heteropolarly. Actually, studies showed that there are distinct periods when two regions are positively correlated, and others when they are anticorrelated, a simple example of non-stationarity[72]. In addition, evidence has shown that the brain functions in a non-linear fashion. As a result, some researchers are starting to develop non-stationary and non-linear methods to measure the functional connections between brain regions, which will require more attention in the future.

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Appendix. Software packages freely available for brain network analysis with BOLD fMRI

Package	Features for functional network analysis	Website
SPM	Preprocessing, psychophysiological interaction, dynamic causal model, statistical comparison	www.fil.ion.ucl.ac.uk/spm
FSL	Preprocessing, independent component analysis, statistical comparison	www.fmrib.ox.ac.uk/fsl
GIFT	Independent component analysis	mialab.mrn.org/software/gift/index.html
PLS	Partial least squares	www.rotman-baycrest.on.ca/index.php?section=84
Princeton Multi-Voxel Pattern Analysis Toolbox	Multivariate analysis	code.google.com/p/princeton-mvpa-toolbox/
Brain Connectivity Toolbox	Network construction with connections matrix, network measures computation, reference network generation	sites.google.com/a/brain-connectivity-toolbox.net/bct
REST	Functional connectivity analysis, regional homogeneity, Granger causality analysis	www.restfmri.net
Brainnetome Toolkit*	Functional connectivity analysis, regional homogeneity, network construction with connections matrix, network measures computation	www.brainnetome.org/software.html

*For more suggestions about data processing, network construction and visualization, visit the website: http://www.brainnetome.org/wiki.

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