NeuroImage 80 (2013) 263–272

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Brainnetome: A new -ome to understand the brain and its disorders

Tianzi Jiang *

Brainnetome Center, Institute of Automation, Chinese Academy of Sciences, Beijing, 100190, China
National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing, 100190, China
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
The Queensland Brain Institute, The University of Queensland, Brisbane, QLD 4072, Australia

ARTICLE INFO

Article history:
Accepted 1 April 2013
Available online 6 April 2013

Keywords:
Brainnetome
Brain network
Connectome
Brain connectivity
Neuroimaging

ABSTRACT

The human brain can be studied as a hierarchy of complex networks on different temporal and spatial scales. On each scale, from gene, protein, synapse, neuron and microcircuit, to area, pathway and the whole brain, many advances have been made with the development of related techniques. Brain network studies on different temporal and spatial scales are booming. However, such studies have focused on single levels, and can only reflect limited aspects of how the brain is formed and how it works. Therefore, it is increasingly urgent to integrate a variety of techniques, methods and models, and to merge fragmented findings into a uniform research framework or platform. To this end, we have proposed the concept of the brainnetome and several related programs/projects have been launched in China. In this paper, we offer a brief review on the methodologies of the brainnetome, which include techniques on different scales, the brainnetome atlas, and methods of brain network analysis. We then take Alzheimer's disease and schizophrenia as examples to show how the brainnetome can be studied in neurological and psychiatric disorders. We also review the studies of how risk genes for brain diseases affect the brain networks. Finally, we summarize the challenges for the brainnetome, and what actions and measures have been taken to address these challenges in China. It is envisioned that the brainnetome will open new avenues and some long-standing issues may be solved by combining the brainnetome with other "omes".

Introduction

The human brain is the most complex network system in the world. It comprises about one hundred billion neurons, with thousands of trillions of connections between them. Its complexity is not only reflected in the numbers of neurons and connections, but also in how the brain is wired on different scales and how such patterns of their connections produce cognitive functions, thoughts, feelings, and behaviors. There have long been efforts to make a connection map of the brain, recently called the "Human Connectome" (Sporns et al., 2005). It is of central significance for understanding how the brain works at a detailed level and what happens when something goes wrong (Insel, 2010). A similar opinion can be traced back to an earlier study (Crick and Jones, 1993). Now, both the academic community and government are aware of its importance. This has been demonstrated by a number of programs and projects launched in different countries. The Human Connectome Project was launched by the National Institutes of Health in the USA. A similar project, CONNECT, was launched by the European Community.

Actually, the complex links within the human brain are presented in the physical (static) architecture as well as dynamic activity. Mathematically, a "network" can be used to model a system that contains multiple components interacting with one other. The neuroscience community refers "brain network" to the brain system that consists of relational units at different tempo-spatial scales. We strongly suggest that the unique features of networks (in the structural and dynamic view) are very important for brain science, so we proposed the brainnetome (Brain-net-ome) as a new "ome" in which the brain network is the basic research unit to investigate the hierarchy in human brain from genetics and neuronal circuits to behaviors. Since the two components of the brainnetome, nodes and their connections, can be defined at different scales with different techniques, the brainnetome is as complex as any other –ome, such as the genome and proteome. It includes at least the following five research themes: (1) Identification of Brain Networks. One goal of the brainnetome is to identify brain networks with multimodal neuroimaging techniques, from the finest scale (such as ultramicrotomy, and staining techniques), to the most macroscopic (such as functional MRI, diffusion MRI and electroencephalography); and to explore the relationships among them. In particular, a new human brain atlas beyond Brodmann's will be established by combining connectivity with cytoarchitecture and other information on the microscale. (2) Dynamics and Characteristics of Brain Networks. The brainnetome will investigate the dynamics and characteristics of brain networks

* National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China. Fax: +86 10 6255 1993.
E-mail address: jiangtz@nlpr.ia.ac.cn.

1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.04.002

during developmental, aging and evolutionary processes and how they are affected by such factors as learning, training, language, culture, diseases, and stimuli. (3) Network Manifestations of Functions and Malfunctions of the Brain. One unique characteristic of the brainnetome is to explore the core brain regions and their connectivity patterns for each cognitive function and to show how they are affected in neurological and psychiatric diseases, and by drugs and other stimuli. A specific goal is to explore how the symptoms of neurological and psychiatric diseases are due to altered brain networks. (4) Genetic Basis of Brain Networks. The brainnetome will investigate the effects of genetic variations on the brain networks associated with behaviors, cognitive functions or cognitive disorders. It will also explore the influence of genetic factors on the developmental processes of specific brain networks through twin and pedigree studies. Moreover, it will investigate the biological mechanisms by which genes modulate the brain networks with gene-modified animal models. (5) Simulating and Modeling for the brainnetome. An essential goal of the brainnetome is to simulate and model brain networks with informatics and simulation technologies to understand the basic organizing principles of the brain. To this end, it is necessary to develop theories and methodologies and to integrate the existing and new supercomputing hardware with software and visualization tools. The concept of the brainnetome has received impetus from a number of programs and projects in China. *In 2010, a project with the same name (that is, the Brainnetome Project) was launched in China. Recently, the European Union has just launched the Human Brain Project and the USA is considering launching the "Brain Activity Mapping" Project. These two projects include the studies of neuronal circuits and brain networks. Table 1 lists some worldwide projects related to the brainnetome.*

In this paper, we present the methodologies and advances of the brainnetome and focus on the studies in our laboratory. We first give a brief review of the methodologies used in the brainnetome, which include techniques on different scales, the brainnetome atlas, and the methods of brain network analysis. Then we take Alzheimer's disease and schizophrenia as examples to show how the brainnetome can be studied in neurology and psychiatry, called the clinical brainnetome. After that, we review studies of how risk genes for brain diseases affect brain networks. Finally, we give a perspective on the brainnetome.

Methodologies for the brainnetome

The human brain is a massively complex system with a hierarchy of different but tightly integrated levels of organisms: from gene, protein, synapse, neurons, and neuronal circuits, to brain areas, pathways and the whole brain. The brain network, in general, should be investigated at each of these levels. Here, we roughly define the macroscale as the level of brain areas and pathway, and the microscale as the level of genes, neurons and neural circuits. The brainnetome is proposed to comprehensively explore brain networks at different spatiotemporal scales, including both human and animal brain networks. Therefore, one of the main goals of the brainnetome is to explore the connections and interactions between neurons, neuronal circuits, brain regions and pathways to reveal how the brain works and what happens when it is faulty. Here, we first review some existing techniques and their roles in the brainnetome. The brainnetome atlas, a new human atlas constructed by combining connectivity patterns and cytoarchitecture, is then discussed. Besides its significance for neuroscience and clinical practice, it plays a central role in guiding the construction of brain networks with neuroimaging techniques on the macroscale. Finally, we review the methods of brain network analysis using neuroimaging data *in vivo*.

Techniques for the brainnetome

Techniques for neuroscience can be roughly divided into two classes based on their functions. One class would be measuring techniques that assess the brain structure and/or function while subjects engage in a particular behavior. Another class would be manipulating techniques that cause the brain structure and/or function to change and consequently influence behavior. We summarize the existing techniques that have played important roles in brain network studies in Table 2. In the following section, we do not review these techniques in detail due to limited space, however, recent reviews are available (Lu et al., 2010; Mei and Zhang, 2012; Michel and Murray, 2012; Palva and Palva, 2012; Reithler et al., 2011; Song and Jiang, 2012; Zuo et al., 2012).

In summary, many techniques have been developed to study brain networks. However, each technique has its own strengths and weaknesses and aims at a specific question. It is important to develop new techniques to study these brain networks. On the other hand, it is still realistic to develop modeling and simulating techniques/methods to integrate the present heterogeneous network features obtained at different scales, which is one of main themes of the brainnetome.

Brainnetome atlas

The brain atlas plays a central role in neuroscience and clinical practice, and is a prerequisite for studying brain networks at the macroscale. The existing human brain atlases segregate human brain into distinct brain areas either by microscopic (e.g., cyto- or myelo-architectonics) or macro-topological (e.g., sulci) methods. Though they have been extensively applied, there are essential limitations for these atlases, for example, their roughness, lacking of correspondence, little subregional information and variable relations between functional boundaries and macroscopic landmarks. Therefore, in order to overcome these limitations, on the one hand, the neuroanatomists have further developed post-mortem brain mapping techniques for atlas construction. On the other hand, the advancing neuroimaging technologies (such as multimodal MRI) have also been extensively used to solve the brain parcellation problem and construct a new brain atlas. The latter is one of the main goals in the brainnetome and the consequent atlas is called the brainnetome atlas.

Nonetheless, because of the numerous brain regions, huge intersubject variations, complex relationships between regional boundaries, and limitations on the spatial resolution of all neuroimaging methods, it is a major challenge to create reliable and accurate parcellation results from *in vivo* data. Recently, mapping the structural and functional connectivity of the human brain *via* non-invasive neuroimaging has offered new insights into functional brain states emerging from their underlying structural substrates. By using diffusion tractography and functional connectivity, researchers can non-invasively explore the connectivity patterns of the brain, and define cortical areas based on distinct connectivity patterns that are well consistent with cytoarchitectonic findings (Johansen-Berg et al., 2005; Mars et al., 2011; Nelson et al., 2010; Wang et al., 2012a). Furthermore, studies with *in vivo* neuroimaging have demonstrated that the finer grained parcellation of large regions of the human brain is possible. For example, the posteromedial cortex is not yet clearly mapped and has always been taken to be a homogeneous structure in most *in vivo* neuroimaging studies. Using probabilistic tractography with diffusion tensor imaging, we parcellated the human posteromedial cortex into five distinct subregions. Furthermore, analyses of anatomical and functional connectivity demonstrated that each subdivision has specific connectivity patterns (Zhang et al., 2012).

However, during the process of brain atlas construction based on connectivity patterns, a number of issues remain to be addressed, for example, how to develop reliable clustering algorithms and effective measures to validate the quality of parcellation, and how to determine the number of subregions in a target brain region. One of the main goals of the brainnetome is to set up and optimize the framework for connectivity-based brain parcellation, and to produce a comparative human brain atlas based on structural and connectivity features. The brainnetome atlases of some important brain regions have been completed and their web-versions will be available at www.brainnetome.org.

Table 1
Projects[#] related to the brainnetome.

Project name	Funding resource	Launched year	Main goals	Data description
Allen Brain Atlas	Allen Institute for Brain Science	2003	• To build tools and freely offer series of atlases and datasets to neuroscience and clinics communities.	• Allen mouse brain atlas, Allen developing mouse brain atlas and Allen human brain atlas. These are mainly based on genomic and anatomic data. • Allen mouse connectivity atlas from virus tracers. http://www.alleninstitute.org
The CONNECT Project	European Union	2009	• To develop tools and protocols to measure brain macro- and micro- structure tissue and connectivity with diffusion MRI. • To produce a connectivity atlas, and micro-structure atlas of axonal density and myelin water fraction and mean axon diameter for normal human and rat brain.	• Some protocols and μatlas are available online. • http://www.brain-connect.eu
The 1000 Functional Connectome Project	Multiple countries	2009	• To share multicenter datasets, especially resting state fMRI. • To investigate reproducibility of functional/anatomic brain networks from multicenter MRI datasets.	• More than 1000 resting state fMRI datasets of normal healthy adult independently collected at more than 30 sites. • Some datasets include multiple modalities data, including task fMRI, diffusion MRI and so on. • Open, public online access. • http://fcon_1000.projects.nitrc.org/
The Brainnetome Project	The Ministry of Science and Technology of China	2010	• To establish human/macaque brain atlas based on brain connectivity. • To develop new protocols and tools to decipher brain networks, especially with MRI and electrophysiology. • To investigate the effect of focal lesions (stroke and glioma) and diffusion lesions (AD and schizophrenia) on structural and functional brain network, and to explore brain network-based biomarkers for these brain diseases. • To understand the mechanism of these diseases by combining the brainnetome with genome.	• sMRI, fMRI, and dMRI datasets and behavioral and blood data of more than 1000 schizophrenia patients, 300 AD/MCI patients, 120 stroke patients, 50 glioma patients and 2000 healthy controls were collected from eleven hospitals and imaging centers in China with a uniform protocol. • The data collection will finish at the end of 2013 and these datasets may be open and available online one day. • http://www.brainnetome.org
The Human Connectome Project	National Institutes of Health, USA	2010	• To characterize brain connectivity and function and their variability in healthy adults. • To share tools and datasets that are collected with the uniform protocol in a single research site.	• A population of 1200 subjects (twins and their non-twin siblings) using multiple imaging modalities along with extensive behavioral and genetic data. • The imaging modalities include diffusion imaging, resting-state fMRI, task-evoked fMRI, T1- and T2-weighted MRI, plus combined MEG and EEG. • Open, public online access or order in a box. • http://humanconnectome.org/
Grand Research Plan for Neural Circuits of Emotion and Memory in China	National Natural Science Foundation of China	2011	• To understand the basic structures and functions of the neural circuitry and brain networks involved in emotion and memory and the related brain diseases. • Developing novel technologies to explore these neural circuitries and brain networks	• The data-sharing is under consideration.
Functional Connectome Project (The Strategic Priority Research Program of Chinese Academy of Sciences)	The Chinese Academy of Sciences	2012	• To develop protocols, tools and imaging and related technologies to characterize structures and functions of the neural circuitry from microscale and macroscale. • To investigate the neural circuitry involved in feeling, memory, emotion, decision-making and the related brain diseases.	–
The Human Brain Project	European Union	2013	• To understand the brain, develop new treatments for brain diseases and build revolutionary new ICT.	• http://www.humanbrainproject.eu/

[#]The projects are listed by the launched year.
Abbreviations: MRI, magnetic resonance imaging; sMRI, structural MRI; fMRI, functional MRI; MEG, magnetoencephalography; EEG, electroencephalography; CONNECT, Consortium Of Neuroimagers for the Non-invasive Exploration of Brain Connectivity and Tracts; ICT, Information and Communications Technologies; AD, Alzheimer's disease; MCI, mild cognitive impairment.

Brain network analysis

Here, we review the methods of brain network analysis using neuroimaging data on the macroscale. These methods can be classified to three types: region of interest based network, specific brain network, and whole brain network.

Region of interest based network

In neuroscience and clinical research, it is useful to investigate a brain network centered on a brain region of interest. The region of interest can be called to the seed region. A region that has been identified as a structural pathological lesion or has been implicated in a specific pathway or function or symptoms of brain disorder can be selected as seed region. *Armed with prior knowledge about the seed region and the investigated disorder, researchers can obtain detailed information on the abnormal brain connectivity pattern of the selected region. To characterize the interactions between the seed region and other brain areas, the common method is either by computing the functional connections between time series of the seed brain region and other voxels using functional MRI data, or by tracking the fiber tracts going through the seed region using diffusion MRI data. This*

Table 2
Important measurement and manipulation techniques for the brainnetome.

Techniques	Role in brainnetome	Summary of features and characteristics
Macro measuring techniques		
Functional MRI	To detect brain activity by measuring BOLD change, and explore functional connections between brain areas	(1) Temporal resolution: seconds (2) Spatial resolution: millimeters (3) Carry on brain functional network analysis based on multiple regions of interest or even each voxels within the whole brain (4) Utilize the synchronization of BOLD signals as functional connectivity or effective connectivity to represent connections
Diffusion MRI	To measure the diffusion of water along axon, and estimate the major fiber tracts between the brain areas	(1) The only noninvasive method for quantifying the white matter connectivity *in vivo* (2) Spatial resolution: millimeters (3) Carry on brain anatomical network analysis based on multiple regions of interest or even each voxels within the whole brain (4) Utilize some characteristics of fiber tracts to represent connections
EEG/MEG	To record electrical/magnetic activity along the scalp, and explore functional connections	(1) Temporal resolution: milliseconds (2) Spatial resolution: centimeters (3) Carry on brain functional network analysis based on either signals of electrodes or inverse mapped signals on the brain (4) Utilize the synchronization of fluctuations of electrical/magnetic fields as functional connectivity or effective connectivity to represent connections
fNIRS	To detect brain activity by measuring changes of attenuation of near infrared through one's cortex, and explore functional connections	(1) Temporal resolution: 1/10 s (2) Spatial resolution: centimeters (3) Carry on brain functional network analysis based on signals of optodes (4) Utilize the synchronization of changes of concentrations of oxyhemoglobin or deoxyhemoglobin as functional connectivity or effective connectivity to represent connections
Micro measuring techniques		
Brainbow	To visualize the intricate architecture of neural circuitry on cellular scale	(1) Label each cells with distinct exogenous fluorescent proteins (2) Genetic engineering required (3) Toolbox available for mouse, drosophila and C. elegans.
MOST	To determine the neuronal connectivity of the whole mouse brain on the neurite level	(1) Golgi staining used (2) An automatic pipeline developed, free of additional image registration and serious deformation (3) The morphology and spatial locations of neurons and traces of neurites clearly distinguished
Macro manipulating techniques		
TMS/tDCS	To establish the causal link between behavior performance and brain activity/connection	Noninvasively stimulate nerve cells in human cortex applying either rapidly changing magnetic field or low direct current to one's scalp
Micro manipulating techniques		
Optogenetics	To achieve precise control specific cells using light	(1) *In vivo* but invasive (2) Exogenous genes encoding light-sensitive proteins expressed in host cells (3) Unveil the causal relationship between the neuronal activity and the animal's behaviors (4) Toolbox available for mouse and primates

Abbreviations: MRI, magnetic resonance imaging; BOLD, blood-oxygen-level-dependent contrast; EEG, electroencephalography; MEG, magnetoencephalography; fNIRS, functional near-infrared spectroscopy; MOST, micro-optical sectioning tomography; TMS, transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

method is often used in preliminary and tentative exploratory research. It should be noted that this kind of method only provides limited connectivity information about the selected regions, and the result might be led by the selected seed which largely depends on the experience and prior knowledge of the researcher.

Specific brain network

As a prevalent concept, discrete cortical areas have been attributed more or less exclusively to a specific cognitive activity. More and more scientists believe that human cognitive activity and psychological constructs need to be attributed beyond individual areas, and instead, cognitive representation consists of widely distributed networks of areas. Thus, the brain network paradigm is becoming increasingly important for understanding the neural underpinnings of cognition. Recent studies suggest that specific collections of brain areas comparatively prefer to be associated with cognitive behavior, such as attention, memory, language, and emotion. Here, we refer to the "specific brain network" associated with some brain function or brain state.

Using diffusion MRI data, one can track the white matter fibers going through each pair of multiple seed regions within a specific brain network. With functional MRI data, functional connectivity analysis-based multiple seed regions and independent component analyses are the commonly used methods to investigate specific brain networks, for example, the strength of connectivity among seed regions. Functional connectivity analysis based on multiple seed regions and independent component analyses cannot estimate the causality of functional connections between brain areas in a specific network. The functional integration that takes directionality among these regions into consideration can be termed as "effective connectivity". Fortunately, some methods have been developed to investigate effective connectivity, for example, Granger causality (Roebroeck et al., 2005), Bayes nets (Bhattacharya et al., 2006) and structural equation modeling (McIntosh and Gonzalez-Lima, 1994). The dynamic causal model is hypothesis-driven and can be used to test a specific set of hypotheses, for example, a specific activity pattern of the brain network (Friston et al., 2003). *Also, we should remember that the selection of the elements of a special network largely depends on the tasks or the experience of the scientists. And some connectivity measures such as effective connectivity may be greatly affected by the time resolution of fMRI series.*

Whole brain network

Recent developments in the quantitative analysis of complex networks have been applied to studies of human brain networks. Many studies suggest that the structural and functional systems of the human brain have the organizational features of complex networks, such as, small-world topology, highly-connected hubs, and modularity (Bullmore and Sporns, 2009). From the perspective of graph theory, a network includes two components: a set of nodes and a collection of edges that link the nodes. In the most common case, one can extract the subcortical nuclei and cortical regions from a particular brain atlas and define them as the nodes, and then use the neuroimaging data to compute some statistical measures between brain regions, such as the functional connectivity or the fiber tractography, as the edges. Once the whole brain network has been organized in a graphical form, some topological properties can be computed to measure the architecture of the brain network, such as degree, path length, efficiency, and betweenness. For details of the graph theoretical analysis of structural and functional brain networks, recent excellent reviews are available (Bullmore and Sporns, 2009).

However, there is no widely accepted processing protocol for whole brain network (Bullmore and Bassett, 2011; Zalesky et al., 2010). Caution is required when selecting a method. *One of essential issues is which atlas or template is the best for parcellation of the brain. Different brain atlases used to extract brain regions as the nodes may lead to distinct results from brain network analysis. However, unfortunately, so far there is no widely accepted* **in vivo** *brain atlas, which makes the definition of macroscale nodes arbitrary. Actually, as noted above, the existing human brain atlases have parceled human brain either by microscopic (e.g., cyto- or myelo-architectonics) or macro topological (e.g., sulci) methods. Accordingly, many brain regions in these atlases are too general and rough to be a unique functionally meaningful parcel in the brain network analysis. Besides the selection of the brain atlas, how to select an appropriate statistical thresholding for definition and extraction of the brain networks, and how to define the connectivity/edge between the nodes are crucial issues for brain network analysis. Recently, Pearson correlation is a widely accepted method; however, it is really a challenge for neuroscientists to understand negative correlation. And the variability between different image modalities (such as functional networks based on fMRI and anatomical networks based on dMRI) is a big gap to fill.*

Clinical brainnetome

An increasing number of studies have revealed disturbances of the organized architecture of brain structure/function in various brain disorders (Bullmore, 2012). The malfunctioning of connections and brain networks may underlie many brain disorders. These network studies, especially those using modern imaging techniques *in vivo*, have revealed that brain disorders can, for the first time, be studied as abnormalities in the connections between brain areas, or as problems in the coordination of brain areas whose synchronized activity exceeds the normal range. These profiles indicate the potential of such brain network measures as biomarkers or predictors of disease progression. Here, we take Alzheimer's disease (AD) and schizophrenia as examples to demonstrate how we can investigate the patterns of brain networks in neurological and psychiatric disorders in the context of the brainnetome.

Brainnetome for Alzheimer's disease

Alzheimer's disease is a neurodegenerative condition with typically, but not exclusively, memory deficits that affect cognitive function. The emerging evidence demonstrates that AD is not only associated with regional damage but also with abnormal functional integration of different brain regions (Delbeuck et al., 2003). Our studies found that AD patients have reduced regional homogeneity of low-frequency functional MRI oscillations (He et al., 2007). We selected the hippocampus as the seed region to analyze the abnormality of its functional network in AD. We found that the functional connectivity between the hippocampus and a set of brain regions in the default mode network are disrupted in AD patients (Wang et al., 2006b). In addition, we found that the functional connectivity pattern of the default mode network and its anti-correlation network are disrupted, and furthermore that these connections can be used as classification features to distinguish AD patients from healthy subjects (Wang et al., 2006a). Moreover, we divided the whole brain using an anatomically labeled template, and then evaluated the functional connectivity between each pair of brain regions. We found that AD patients show many decreased correlations, nearly half of which are between the prefrontal and parietal lobes (Wang et al., 2007). Particularly, in patients with AD, functional connectivity is attenuated between the regions that are separated by a greater physical distance; and the loss of long-distance connectivity is associated with less efficient global and nodal network topology (Liu et al., 2012c).

In parallel, many studies by other groups have investigated the impaired functional connectivity pattern in AD, such as from regions of interest (e.g. altered functional connectivity of the hippocampus, posterior cingulate cortex, and thalamus) (Allen et al., 2007; Wang et al., 2011, 2012c), and a specific network (such as the default mode network) (Buckner et al., 2009; Greicius et al., 2004; Neufang et al., 2011; Sorg et al., 2007). All together, the brain network architecture disruptions in AD and mild cognitive impairment have been verified using various neuroimaging data, including functional MRI, diffusion MRI, electroencephalography, and magnetoencephalography. Moreover, these studies demonstrated that imaging measures or connectivity patterns can be taken as potential markers to distinguish patients from normal controls.

Brainnetome for schizophrenia

The emerging evidence demonstrates that schizophrenia is characterized by functional disintegration of neuronal systems (Pettersson-Yeo et al., 2011). The symptoms of schizophrenia are thought not to be due to a single, regionally-specific pathophysiology, but rather to result from abnormal interactions between multiple regions. One goal of the Brainnetome Project in China is to understand malfunctions of the brain in schizophrenia from the network perspective. Some important progress has been made and is summarized as follows. Using resting-state functional MRI, we found that the abnormal brain networks in schizophrenia involve the different levels, from the region of interest-based network (i.e., dorsolateral prefrontal cortex (Zhou et al., 2007a) and hippocampus (Zhou et al., 2008)), networks related to a specific cognitive function (i.e., the task-negative network/default mode network and its anti-correlated network (Liu et al., 2012b; Zhou et al., 2007b)) to the whole brain network (Liang et al., 2006; Liu et al., 2008). At the level of region of interest based network, we found that both reduced and excessively enhanced functional integration exist in the resting brains of patients with schizophrenia (Zhou et al., 2007a), and the reduced functional integration may have an anatomical basis (Zhou et al., 2008). At the level of specific brain networks, we found that the increased resting-state functional connectivities within the default mode network existed both in schizophrenic patients (Liu et al., 2012b; Zhou et al., 2007b) and in their unaffected siblings (Liu et al., 2012b), which is consistent with another independent study (Whitfield-Gabrieli et al., 2009). The presence of hyperconnectivity within the default-mode network in the unaffected siblings suggests that this abnormality is a primary process associated with increased susceptibility to schizophrenia rather than a secondary effect of the disease, therefore, this abnormality may be a schizophrenia endophenotypes. At the level of the whole brain network, we found the decreased global and local efficiency in the functional network in schizophrenia compared with normal controls (Liu et al., 2008). And this finding is compatible with that obtained using anatomical network analysis based on graph theory (Wang et al., 2012b). More importantly, these altered

brain network properties are correlated with clinical variables, such as duration of illness (Liu et al., 2008) and severity of clinical symptoms (Wang et al., 2012b).

Many research groups throughout the world are making important contributions to using brain network methods to investigate schizophrenia. Notably, many researchers not only are interested in abnormalities in the resting-state functional networks, but also pay attention to context-dependent abnormalities observed in task-state functional networks in schizophrenia. And they have also developed and used graph-based analysis to investigate the topological properties of functional brain networks in schizophrenia and obtained extraordinary findings. For details of these excellent studies, please refer to a recent review paper (Fornito et al., 2012).

These brain network measures have the potential to serve as imagining biomarkers of schizophrenia. Many efforts have been made to achieve individual classification based on functional MRI data by identifying abnormal brain regional correlations or coupling independent component analyses and classification techniques. In a recent study, we achieved a promising classification performance for distinguishing schizophrenic patients from healthy controls (the classification rate: 87.1%) by taking the combination of the default mode network and temporal lobe network as the classification feature using a novel discriminant analysis algorithm (Fan et al., 2011). In general, the brain network analyses have opened a new window for the leading hypothesis of dysconnection in schizophrenia and improved our understanding of how schizophrenia affects the brain. These findings support the view that the failure to integrate the activity of local and distributed neuronal circuits leads to the cognitive and affective impairments and bizarre behavior often observed in schizophrenic patients. Moreover, the abnormalities in functional integration have the potential to serve as imaging biomarkers for the diagnosis of schizophrenia.

In summary, the studies in AD and schizophrenia have demonstrated that brain disorders result from faulty networks. The human brain can generate/integrate information with high efficiency and maintain a perfect balance between local and global interactions. The disease-related damages may upset the normal balance and make information propagation less organized in the brain. The brain network analysis can help to explain the link between local/long-range damage, and more widespread physiological or clinical dysfunction in patients. Some brain network-based strategies have been used to develop sensitive and specific biomarkers for the prognosis, diagnosis, and monitoring of brain disorders in the individual patient. However, the sensitivity, specificity, and reliability of these measurements await further verification through some initiatives and programs/projects, such as the Brainnetome Project in China, and the Alzheimer's Disease Neuroimaging Initiative in the USA.

Genetic basis for the brainnetome

Convergent evidence from multimodal imaging studies has demonstrated that brain networks are heritable both structurally and functionally (Meyer-Lindenberg, 2009). Specifically, a twin study based on diffusion MRI found that genetic factors may explain 40% to 80% of the observed variability of integrity in the white matter tracts (Chiang et al., 2011). A pedigree study reported that the heritability of functional connectivity within the default mode network can reach 42% (Glahn et al., 2010). Besides, network property analyses based on the functional brain networks of twins demonstrated that the network efficiency is highly genetically influenced both in children and adults (Fornito et al., 2011; van den Heuvel et al., 2012). All of these studies suggest that brain connectivity and networks are under genetic control. Therefore, the mechanisms by which specific genetic variants affect brain networks are attracting more and more attention (Esslinger et al., 2009).

In fact, some pioneering studies have reported that various genetic variants can modulate brain connectivity and brain networks. Here we review some imaging genetic studies that took brain connectivity and brain networks as intermediate phenotypes from functional MRI and diffusion MRI, respectively.

Many studies are investigating the effect of genetic variants on specific task-based and resting state functional connectivity and brain networks based on functional MRI. One of the most interesting findings on functional connectivity concerns the ZNF804A gene, which is strongly supported as a risk gene for schizophrenia. Several studies consistently reported that a ZNF804A polymorphism significantly modulates the functional connectivity between dorsolateral prefrontal cortex and hippocampus during tasks and at rest (Esslinger et al., 2009, 2011; Rasetti et al., 2011). Specifically, the default mode network based on functional MRI is a good example of the genetic aspects of specific brain networks. Very interestingly, distinct resting patterns within the default network in young and older carriers of the APOE-ε4 allele can be detected before any manifestations of cognitive changes (Filippini et al., 2009; Sheline et al., 2010; Trachtenberg et al., 2012). COMT plays a unique role in regulating prefrontal dopamine levels, and our study reported that prefrontal-related functional connectivity within the default mode network in young healthy subjects is modulated by the COMT val158met polymorphism (Liu et al., 2010b).

In parallel, anatomical brain connectivity is also attracting increasing attention in imaging genetics (Marenco and Radulescu, 2010). Some studies have investigated the association between the variations of NRG1 and ErbB4 gene and the white matter integrity of the fronto-thalamic tracts and other white matter tracts (Konrad et al., 2009; McIntosh et al., 2008; Sprooten et al., 2009; Wang et al., 2009; Winterer et al., 2008). Some studies have reported that specific polymorphisms or haplotypes of the COMT gene modulate the integrity of white matter tracts (Li et al., 2009; Liu et al., 2010a; Thomason et al., 2010). Notably, Sprooten et al. (2011) reported a significant association between DISC1Ser704Cys and white matter integrity as measured by diffusion MRI, though this association could not be replicated in the Han Chinese population (Liu et al., 2012a). Further study of the Han Chinese population reported that DISC1 Ser704Cys significantly affects the global information transfer efficiency of the human brain anatomical network (Li et al., 2012).

For gene-based studies with the brainnetome, ethnicity is a pivotal factor to consider since much evidence indicates the heterogeneous genetic effects of ethnicity on the risk for disorders and responses to drug therapy. Here we take 5-HTTLPR as an example. The genotype frequency of 5-HTTLPR differs significantly between Caucasians and Asians. Studies in Caucasian populations have shown that the short allele is the risk allele for mood-related disorders (Caspi et al., 2003; Hoefgen et al., 2005; Kiyohara and Yoshimasu, 2010; Osher et al., 2000; Smeraldi et al., 1998), but it trends to have the opposite association in Asian populations (Kim et al., 2000, 2006; Yoshida et al., 2002; Zhang et al., 2009). In a behavioral and multimodal neuroimaging study of a large group ($n = 233$) of healthy Han Chinese participants, Long et al. found that long-allele carriers have higher anxiety scores, and reduced functional and anatomical connectivity in the prefrontal-amygdala circuit, which correlated with anxiety or depression scores (Long et al., 2013). This finding showed an opposite effect of 5-HTTLRP on the anatomical and functional connectivity between amygdala and prefrontal cortex to that in European populations (Friedel et al., 2009; Heinz et al., 2005; Pezawas et al., 2005). Current studies provide consistent evidences to support the view that the long allele of 5-HTTLPR predisposes to anxiety in a Han Chinese and further indicate that ethnicity is an essential factor in genetic studies of brainnetome.

Although great progress has been made in brain network-based imaging genetic studies, there are still great gaps between the brain networks and specific genetic variants. More solid biological evidence is needed to elucidate the genetic mechanisms of the genetic variations in brain connectivity and networks. For example, brain network

analysis on an animal model combined with some neuroscience techniques, including histological sectioning and dye tracing, may provide further evidence for the effects of genetic variants on neuronal development and brain networks.

Perspectives

The human brain can be studied as hierarchical complex networks on different temporal and spatial scales. On the microscale level, recent evidence shows that the human brain functions by the interactions between neurons on different temporal and spatial scales. It is becoming increasingly apparent that such a network structure and dynamic interaction produce the physiological activity of the human brain and finally lead to human cognitive behavior. On the macroscale level, more and more neuroimaging studies support the idea that the brain function can be manifested in a network that consists of some brain regions. On each single scale, from gene, protein, synapse, neuron and microcircuit, to areas, pathways and the whole brain, many advances have been made with the development of related techniques. The brain network studies on different temporal and spatial scales are booming. However, findings from such studies on a single scale can only reflect some aspects of how the brain is formed and how it works. Findings on the microscale can only implicate information processing in a local brain network, but it can help us to understand the mechanisms of findings on the macroscale. Therefore, it is increasingly important to integrate a variety of techniques, methods, models, and heterogeneous data, and to merge the fragmented findings to a uniform research framework or platform. To this end, we have proposed the concept of the brainnetome. In future, we believe that brain network studies will play increasing important roles in deciphering the mechanisms of how the brain works, elucidating the causes of brain disorders, and developing new treatments. In what follows, we summarize some of the challenges and opportunities in the brainnetome.

Some large research projects on the brain networks, such as the Human Connectome Project in the USA and the Brainnetome Project in China, are in progress. We believe that they, together with other projects, will generate huge volumes of experimental data and produce a deluge of new findings about the human brain, especially on neuronal circuitry and the connections between brain areas. However, there is no doubt that any single technique cannot address all issues. An urgent need is to integrate the techniques on different spatiotemporal levels and develop new models and methods to fill the gaps between the findings from different techniques. After all, the human brain is a massively complex system with a hierarchy of different yet tightly integrated levels of organisms. Fortunately, some recent techniques show potential, for example, optogenetic functional MRI (Lee, 2012) and the two-photon optogenetic toolbox (Prakash et al., 2012). As a neuro-modulation technique, optogenetics can allow temporally precise, millisecond-scale activity modulation *in vivo*. On the one hand, by combining optogenetics and functional MRI, one can measure the functional MRI signals driven by neurons defined optogenetically by type and wiring across the whole brain. This allows mapping of causal functional connectivity between brain areas. On the other hand, using the two-photon optogenetic toolbox, one can achieve not only spatially but also genetically precise control of targeted cell subpopulations and thereby investigate the activity of the microcircuits, including the synapse. Although optogenetics cannot be directly applied to the human brain at present, optogenetic functional MRI and the two-photon optogenetic toolbox provide good examples of effectively fusing the techniques of measurement and manipulation. It is a great challenge to develop new techniques to integrate the studies of the brainnetome from two different directions at the macro- and micro-scales (Fig. 1).

The brainnetome has opened wide opportunities for both the academic community and government. It has been taken as a strategic priority for the next ten years or longer in China, especially in its applications to psychiatric and neurological diseases. A "1000 Schizophrenia Brainnetome" is under way as one part of the Brainnetome Project supported by the 973 Program in China. A program of two hundred million RMB for eight years was launched by the National Natural Science Foundation of China in 2011. This program focuses on how emotion and memory and their disorders are manifested in brain networks on different scales and what new techniques can meet this need. Moreover, another program of three hundred million RMB for five years in the first stage was launched by the Chinese Academy of Sciences in 2012. The goals of this program are to dissect the functional atlas of brain networks for perception, memory, emotion, and their disorders as well as to develop advanced technologies to achieve these goals. It also aims at collaboration among interdisciplinary researchers through a continuous support for up to 25 top laboratories devoted to brain network studies in China. Though these two programs seem to be devoted to network manifestations of functions and malfunctions of the brain, they will involve all five aspects of the brainnetome. The ultimate goals of these programs are to improve our understanding of the brain and to find new biomarkers for early diagnosis, prognosis, and drug-effect evaluation of psychiatric and neurological diseases, which is a main goal of the brainnetome.

To achieve the ultimate goals of the brainnetome, it needs to be integrated with other "omes", such as the genome. In the future, it will be a central research direction to integrate the brainnetome with the genome, especially for psychiatric research (Akil et al., 2010). It is envisioned that long-standing issues may be solved by combining the brainnetome with other "omes". Understanding the genetic mechanisms of normal and abnormal brain networks is very important in clinical and translational medicine. However, although great progress has been made in the imaging genetic study of brain networks, this question is still understudied. There are great challenges in analytical, statistical, and visualization techniques for big data convergence between the brainnetome and the genome. Furthermore, more biological evidence from different-scale studies is needed to narrow the gap between the brainnetome and the genome. For example, multi-scale brainnetome studies based on transgenic animal models can improve our understanding of the findings of associations between brain networks and specific genetic variants in humans.

The convergence of diverse disciplines, especially biology, medicine and informatics, are dramatically changing brain research. The development of new sequencing and imaging technologies has revolutionized our ability to observe and understand the brain. The advances in sequencing technology have made it feasible to sequence whole genomes, rapidly, at ever-lower cost. New techniques of ultra-microscopy can create detailed 3D pictures of whole animal brains, tracing the circuits involved in specific functions. The advances in imaging technology have made it possible to noninvasively and *in vivo* image the human brain at unprecedented spatiotemporal resolution, including manifesting the shapes and sizes of brain areas, mapping the fibers linking brain areas, and elucidating the networks and pathways responsible for specific functions. The deluge of these complex and heterogeneous biological and medical data poses significant challenges for the informatics community. Novel image data analysis and informatics techniques must be developed to extract, compare, search and manage the biological and medical data. Therefore, how to organize so many researchers with diverse disciplines is another big challenge for the brainnetome.

Acknowledgments

I thank Ming Song, Bing Liu, Yong Liu, Yuan Zhou, Bing Hou, Lingzhong Fan, Xin Zhang, Nianming Zuo, Yue Cui and Yong Fan for their help with manuscript preparation. I also thank Professors Iain Bruce and Sumner MacLean for the proof-reading of the manuscript. This work was partially supported by the National Key Basic Research and Development Program (973) (Grant No. 2011CB707800), the Strategic Priority Research Program of the Chinese Academy of Sciences

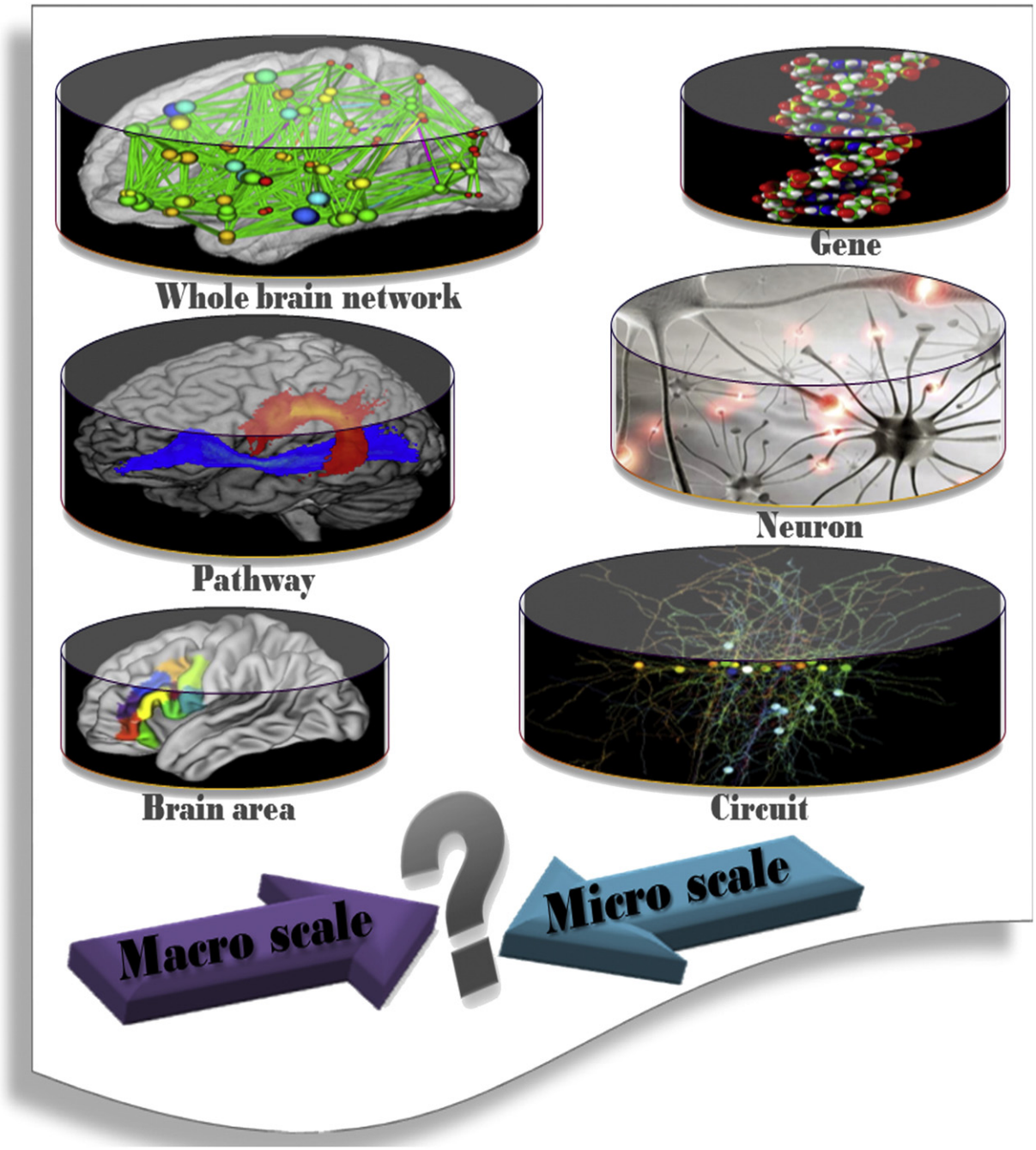

Fig. 1. Challenges for bridging the gap between micro- and macro-scale brain network studies. On each scale, from gene, neuron and neuronal circuit, to brain area, pathway, and the whole brain, many advances have been made. The challenges are to develop new techniques to integrate the studies of the brainnetome from two different directions at the macro- and micro-scales.

(Grant No. XDB02030300), and the National Natural Science Foundation of China (Grant No. 91132301).

References

Akil, H., Brenner, S., Kandel, E., Kendler, K.S., King, M.C., Scolnick, E., Watson, J.D., Zoghbi, H.Y., 2010. Medicine. The future of psychiatric research: genomes and neural circuits. Science 327, 1580–1581.

Allen, G., Barnard, H., McColl, R., Hester, A.L., Fields, J.A., Weiner, M.F., Ringe, W.K., Lipton, A.M., Brooker, M., McDonald, E., Rubin, C.D., Cullum, C.M., 2007. Reduced hippocampal functional connectivity in Alzheimer disease. Arch. Neurol. 64, 1482–1487.

Bhattacharya, S., Ho, M.H.R., Purkayastha, S., 2006. A Bayesian approach to modeling dynamic effective connectivity with fMRI data. Neuroimage 30, 794–812.

Buckner, R.L., Sepulcre, J., Talukdar, T., Krienen, F.M., Liu, H., Hedden, T., Andrews-Hanna, J.R., Sperling, R.A., Johnson, K.A., 2009. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. J. Neurosci. 29, 1860–1873.

Bullmore, E., 2012. Functional network endophenotypes of psychotic disorders. Biol. Psychiatry 71, 844–845.

Bullmore, E.T., Bassett, D.S., 2011. Brain graphs: graphical models of the human brain connectome. Annu. Rev. Clin. Psychol. 7, 113–140.

Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10, 186–198.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301, 386–389.

Chiang, M.C., McMahon, K.L., de Zubicaray, G.I., Martin, N.G., Hickie, I., Toga, A.W., Wright, M.J., Thompson, P.M., 2011. Genetics of white matter development: a DTI study of 705 twins and their siblings aged 12 to 29. Neuroimage 54, 2308–2317.

Crick, F., Jones, E., 1993. Backwardness of human neuroanatomy. Nature 361, 109–110.

Delbeuck, X., Van der Linden, M., Collette, F., 2003. Alzheimer's disease as a disconnection syndrome? Neuropsychol. Rev. 13, 79–92.
Esslinger, C., Walter, H., Kirsch, P., Erk, S., Schnell, K., Arnold, C., Haddad, L., Mier, D., Opitz von Boberfeld, C., Raab, K., Witt, S.H., Rietschel, M., Cichon, S., Meyer-Lindenberg, A., 2009. Neural mechanisms of a genome-wide supported psychosis variant. Science 324, 605.
Esslinger, C., Kirsch, P., Haddad, L., Mier, D., Sauer, C., Erk, S., Schnell, K., Arnold, C., Witt, S.H., Rietschel, M., Cichon, S., Walter, H., Meyer-Lindenberg, A., 2011. Cognitive state and connectivity effects of the genome-wide significant psychosis variant in ZNF804A. Neuroimage 54, 2514–2523.
Fan, Y., Liu, Y., Wu, H., Hao, Y., Liu, H., Liu, Z., Jiang, T., 2011. Discriminant analysis of functional connectivity patterns on Grassmann manifold. Neuroimage 56, 2058–2067.
Filippini, N., MacIntosh, B.J., Hough, M.G., Goodwin, G.M., Frisoni, G.B., Smith, S.M., Matthews, P.M., Beckmann, C.F., Mackay, C.E., 2009. Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. Proc. Natl. Acad. Sci. U. S. A. 106, 7209–7214.
Fornito, A., Zalesky, A., Bassett, D.S., Meunier, D., Ellison-Wright, I., Yucel, M., Wood, S.J., Shaw, K., O'Connor, J., Nertney, D., Mowry, B.J., Pantelis, C., Bullmore, E.T., 2011. Genetic influences on cost-efficient organization of human cortical functional networks. J. Neurosci. 31, 3261–3270.
Fornito, A., Zalesky, A., Pantelis, C., Bullmore, E.T., 2012. Schizophrenia, neuroimaging and connectomics. Neuroimage 62, 2296–2314.
Friedel, E., Schlagenhauf, F., Sterzer, P., Park, S.Q., Bermpohl, F., Strohle, A., Stoy, M., Puls, I., Hagele, C., Wrase, J., Buchel, C., Heinz, A., 2009. 5-HTT genotype effect on prefrontal-amygdala coupling differs between major depression and controls. Psychopharmacology (Berl) 205, 261–271.
Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. Neuroimage 19, 1273–1302.
Glahn, D.C., Winkler, A.M., Kochunov, P., Almasy, L., Duggirala, R., Carless, M.A., Curran, J.C., Olvera, R.L., Laird, A.R., Smith, S.M., Beckmann, C.F., Fox, P.T., Blangero, J., 2010. Genetic control over the resting brain. Proc. Natl. Acad. Sci. U. S. A. 107, 1223–1228.
Greicius, M.D., Srivastava, G., Reiss, A.L., Menon, V., 2004. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc. Natl. Acad. Sci. U. S. A. 101, 4637–4642.
He, Y., Wang, L., Zang, Y., Tian, L., Zhang, X., Li, K., Jiang, T., 2007. Regional coherence changes in the early stages of Alzheimer's disease: a combined structural and resting-state functional MRI study. Neuroimage 35, 488–500.
Heinz, A., Braus, D.F., Smolka, M.N., Wrase, J., Puls, I., Hermann, D., Klein, S., Grusser, S.M., Flor, H., Schumann, G., Mann, K., Buchel, C., 2005. Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. Nat. Neurosci. 8, 20–21.
Hoefgen, B., Schulze, T.G., Ohlraun, S., von Widdern, O., Hofels, S., Gross, M., Heidmann, V., Kovalenko, S., Eckermann, A., Kolsch, H., Metten, M., Zobel, A., Becker, T., Nothen, M.M., Propping, P., Heun, R., Maier, W., Rietschel, M., 2005. The power of sample size and homogenous sampling: association between the 5-HTTLPR serotonin transporter polymorphism and major depressive disorder. Biol. Psychiatry 57, 247–251.
Insel, T.R., 2010. Rethinking schizophrenia. Nature 468, 187–193.
Johansen-Berg, H., Behrens, T.E., Sillery, E., Ciccarelli, O., Thompson, A.J., Smith, S.M., Matthews, P.M., 2005. Functional–anatomical validation and individual variation of diffusion tractography-based segmentation of the human thalamus. Cereb. Cortex 15, 31–39.
Kim, D.K., Lim, S.W., Lee, S., Sohn, S.E., Kim, S., Hahn, C.G., Carroll, B.J., 2000. Serotonin transporter gene polymorphism and antidepressant response. Neuroreport 11, 215–219.
Kim, H., Lim, S.W., Kim, S., Kim, J.W., Chang, Y.H., Carroll, B.J., Kim, D.K., 2006. Monoamine transporter gene polymorphisms and antidepressant response in Koreans with late-life depression. JAMA 296, 1609–1618.
Kiyohara, C., Yoshimasu, K., 2010. Association between major depressive disorder and a functional polymorphism of the 5-hydroxytryptamine (serotonin) transporter gene: a meta-analysis. Psychiatr. Genet. 20, 49–58.
Konrad, A., Vucurevic, G., Musso, F., Stoeter, P., Dahmen, N., Winterer, G., 2009. ErbB4 genotype predicts left frontotemporal structural connectivity in human brain. Neuropsychopharmacology 34, 641–650.
Lee, J.H., 2012. Informing brain connectivity with optogenetic functional magnetic resonance imaging. Neuroimage 62, 2244–2249.
Li, J., Yu, C., Li, Y., Liu, B., Liu, Y., Shu, N., Song, M., Zhou, Y., Zhu, W., Li, K., Jiang, T., 2009. COMT val158met modulates association between brain white matter architecture and IQ. Am. J. Med. Genet. B Neuropsychiatr. Genet. 150B, 375–380.
Li, Y., Liu, B., Hou, B., Qin, W., Wang, D., Yu, C., Jiang, T., 2012. Less Efficient Information Transfer in Cys-Allele Carriers of DISC1: A Brain Network Study Based on Diffusion MRI. Cereb. Cortex.
Liang, M., Zhou, Y., Jiang, T., Liu, Z., Tian, L., Liu, H., Hao, Y., 2006. Widespread functional disconnectivity in schizophrenia with resting-state functional magnetic resonance imaging. Neuroreport 17, 209–213.
Liu, Y., Liang, M., Zhou, Y., He, Y., Hao, Y., Song, M., Yu, C., Liu, H., Liu, Z., Jiang, T., 2008. Disrupted small-world networks in schizophrenia. Brain 131, 945–961.
Liu, B., Li, J., Yu, C., Li, Y., Liu, Y., Song, M., Fan, M., Li, K., Jiang, T., 2010a. Haplotypes of catechol-O-methyltransferase modulate intelligence-related brain white matter integrity. Neuroimage 50, 243–249.
Liu, B., Song, M., Li, J., Liu, Y., Li, K.C., Yu, C.S., Jiang, T.Z., 2010b. Prefrontal-related functional connectivities within the default network are modulated by COMT val(158) met in healthy young adults. J. Neurosci. 30, 64–69.
Liu, B., Li, Y., Hou, B., Yu, C., Jiang, T., 2012a. Lack of association between white matter integrity and DISC1 Ser704Cys in a large sample of healthy Han Chinese individuals. Trans Med Res 2, 77–80.
Liu, H., Kaneko, Y., Ouyang, X., Li, L., Hao, Y., Chen, E.Y., Jiang, T., Zhou, Y., Liu, Z., 2012b. Schizophrenic patients and their unaffected siblings share increased resting-state connectivity in the task-negative network but not its anticorrelated task-positive network. Schizophr. Bull. 38, 285–294.
Liu, Y., Yu, C., Zhang, X., Liu, J., Duan, Y., Alexander-Bloch, A., Liu, B., Jiang, T., Bullmore, E., 2012c. Impaired long distance functional connectivity and weighted network architecture in Alzheimer's disease. Cereb. Cortex.
Long, H., Liu, B., Hou, B., Wang, C., Li, J., Qin, W., Wang, D., Zhou, Y., Kendrick, K., Yu, C., Jiang, T., 2013. The long rather than the short allele of 5-HTTLPR predisposes Han Chinese to anxiety and reduced connectivity between prefrontal cortex and amygdala. Neurosci. Bull. 29, 4–15.
Lu, C.M., Zhang, Y.J., Biswal, B.B., Zang, Y.F., Peng, D.L., Zhu, C.Z., 2010. Use of fNIRS to assess resting state functional connectivity. J. Neurosci. Methods 186, 242–249.
Marenco, S., Radulescu, E., 2010. Imaging genetics of structural brain connectivity and neural integrity markers. Neuroimage 53, 848–856.
Mars, R.B., Jbabdi, S., Sallet, J., O'Reilly, J.X., Croxson, P.L., Olivier, E., Noonan, M.P., Bergmann, C., Mitchell, A.S., Baxter, M.G., Behrens, T.E., Johansen-Berg, H., Tomassini, V., Miller, K.L., Rushworth, M.F., 2011. Diffusion-weighted imaging tractography-based parcellation of the human parietal cortex and comparison with human and macaque resting-state functional connectivity. J. Neurosci. 31, 4087–4100.
McIntosh, A.R., Gonzalez-Lima, F., 1994. Structural equation modeling and its application to network analysis in functional brain imaging. Hum. Brain Mapp. 2, 2–22.
McIntosh, A.M., Moorhead, T.W., Job, D., Lymer, G.K., Munoz Maniega, S., McKirdy, J., Sussmann, J.E., Baig, B.J., Bastin, M.E., Porteous, D., Evans, K.L., Johnstone, E.C., Lawrie, S.M., Hall, J., 2008. The effects of a neuregulin 1 variant on white matter density and integrity. Mol. Psychiatry 13, 1054–1059.
Mei, Y., Zhang, F., 2012. Molecular tools and approaches for optogenetics. Biol. Psychiatry 71, 1033–1038.
Meyer-Lindenberg, A., 2009. Neural connectivity as an intermediate phenotype: brain networks under genetic control. Hum. Brain Mapp. 30, 1938–1946.
Michel, C.M., Murray, M.M., 2012. Towards the utilization of EEG as a brain imaging tool. Neuroimage 61, 371–385.
Nelson, S.M., Cohen, A.L., Power, J.D., Wig, G.S., Miezin, F.M., Wheeler, M.E., Velanova, K., Donaldson, D.I., Phillips, J.S., Schlaggar, B.L., Petersen, S.E., 2010. A parcellation scheme for human left lateral parietal cortex. Neuron 67, 156–170.
Neufang, S., Akhrif, A., Riedl, V., Forstl, H., Kurz, A., Zimmer, C., Sorg, C., Wohlschlager, A.M., 2011. Disconnection of frontal and parietal areas contributes to impaired attention in very early Alzheimer's disease. J. Alzheimers Dis. 25, 309–321.
Osher, Y., Hamer, D., Benjamin, J., 2000. Association and linkage of anxiety-related traits with a functional polymorphism of the serotonin transporter gene regulatory region in Israeli sibling pairs. Mol. Psychiatry 5, 216–219.
Palva, S., Palva, J.M., 2012. Discovering oscillatory interaction networks with M/EEG: challenges and breakthroughs. Trends Cogn. Sci. 16, 219–230.
Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., Mechelli, A., 2011. Dysconnectivity in schizophrenia: where are we now? Neurosci. Biobehav. Rev. 35, 1110–1124.
Pezawas, L., Meyer-Lindenberg, A., Drabant, E.M., Verchinski, B.A., Munoz, K.E., Kolachana, B.S., Egan, M.F., Mattay, V.S., Hariri, A.R., Weinberger, D.R., 2005. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat. Neurosci. 8, 828–834.
Prakash, R., Yizhar, O., Grewe, B., Ramakrishnan, C., Wang, N., Goshen, I., Packer, A.M., Peterka, D.S., Yuste, R., Schnitzer, M.J., Deisseroth, K., 2012. Two-photon optogenetic toolbox for fast inhibition, excitation and bistable modulation. Nat. Methods.
Rasetti, R., Sambataro, F., Chen, Q., Callicott, J.H., Mattay, V.S., Weinberger, D.R., 2011. Altered cortical network dynamics: a potential intermediate phenotype for schizophrenia and association with ZNF804A. Arch. Gen. Psychiatry 68, 1207–1217.
Reithler, J., Peters, J.C., Sack, A.T., 2011. Multimodal transcranial magnetic stimulation: using concurrent neuroimaging to reveal the neural network dynamics of noninvasive brain stimulation. Prog. Neurobiol. 94, 149–165.
Roebroeck, A., Formisano, E., Goebel, R., 2005. Mapping directed influence over the brain using Granger causality and fMRI. Neuroimage 25, 230–242.
Sheline, Y.I., Morris, J.C., Snyder, A.Z., Price, J.L., Yan, Z., D'Angelo, G., Liu, C., Dixit, S., Benzinger, T., Fagan, A., Goate, A., Mintun, M.A., 2010. APOE4 allele disrupts resting state fMRI connectivity in the absence of amyloid plaques or decreased CSF Abeta42. J. Neurosci. 30, 17035–17040.
Smeraldi, E., Zanardi, R., Benedetti, F., Di Bella, D., Perez, J., Catalano, M., 1998. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. Mol. Psychiatry 3, 508–511.
Song, M., Jiang, T., 2012. A review of functional magnetic resonance imaging for Brainnetome. Neurosci. Bull. 28, 10.
Sorg, C., Riedl, V., Muhlau, M., Calhoun, V.D., Eichele, T., Laer, L., Drzezga, A., Forstl, H., Kurz, A., Zimmer, C., Wohlschlager, A.M., 2007. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 104, 18760–18765.
Sporns, O., Tononi, G., Kotter, R., 2005. The human connectome: a structural description of the human brain. PLoS Comput. Biol. 1, e42.
Sprooten, E., Lymer, G.K., Munoz Maniega, S., McKirdy, J., Clayden, J.D., Bastin, M.E., Porteous, D., Johnstone, E.C., Lawrie, S.M., Hall, J., McIntosh, A.M., 2009. The relationship of anterior thalamic radiation integrity to psychosis risk associated neuregulin-1 variants. Mol. Psychiatry 14, 237–238 (233).
Sprooten, E., Sussmann, J.E., Moorhead, T.W., Whalley, H.C., Ffrench-Constant, C., Blumberg, H.P., Bastin, M.E., Hall, J., Lawrie, S.M., McIntosh, A.M., 2011. Association of white matter integrity with genetic variation in an exonic DISC1 SNP. Mol. Psychiatry 16 (685), 688–689.
Thomason, M.E., Dougherty, R.F., Colich, N.L., Perry, L.M., Rykhlevskaia, E.I., Louro, H.M., Hallmayer, J.F., Waugh, C.E., Bammer, R., Glover, G.H., Gotlib, I.H., 2010. COMT

genotype affects prefrontal white matter pathways in children and adolescents. Neuroimage 53, 926–934.
Trachtenberg, A.J., Filippini, N., Ebmeier, K.P., Smith, S.M., Karpe, F., Mackay, C.E., 2012. The effects of APOE on the functional architecture of the resting brain. Neuroimage 59, 565–572.
van den Heuvel, M.P., van Soelen, I.L., Stam, C.J., Kahn, R.S., Boomsma, D.I., Hulshoff Pol, H.E., 2012. Genetic control of functional brain network efficiency in children. Eur. Neuropsychopharmacol.
Wang, K., Jiang, T.Z., Liang, M., Wang, L., Tian, L.X., Zhang, X.Q., Li, K.C., Liu, Z.N., 2006a. Discriminative analysis of early Alzheimer's disease based on two intrinsically anti-correlated networks with resting-state fMRI. In: Larsen, R.N.M.S.J. (Ed.), 9th International Conference on Computing and Computer-Assisted Intervention, Copenhagen, DENMARK, pp. 340–347.
Wang, L., Zang, Y., He, Y., Liang, M., Zhang, X., Tian, L., Wu, T., Jiang, T., Li, K., 2006b. Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. Neuroimage 31, 496–504.
Wang, K., Liang, M., Wang, L., Tian, L., Zhang, X., Li, K., Jiang, T., 2007. Altered functional connectivity in early Alzheimer's disease: a resting-state fMRI study. Hum. Brain Mapp. 28, 967–978.
Wang, F., Jiang, T., Sun, Z., Teng, S.L., Luo, X., Zhu, Z., Zang, Y., Zhang, H., Yue, W., Qu, M., Lu, T., Hong, N., Huang, H., Blumberg, H.P., Zhang, D., 2009. Neuregulin 1 genetic variation and anterior cingulum integrity in patients with schizophrenia and healthy controls. J. Psychiatry Neurosci. 34, 181–186.
Wang, Z., Liang, P., Jia, X., Qi, Z., Yu, L., Yang, Y., Zhou, W., Lu, J., Li, K., 2011. Baseline and longitudinal patterns of hippocampal connectivity in mild cognitive impairment: evidence from resting state fMRI. J. Neurol. Sci. 309, 79–85.
Wang, J., Fan, L., Zhang, Y., Liu, Y., Jiang, D., Yu, C., Jiang, T., 2012a. Tractography-based parcellation of the human left inferior parietal lobule. Neuroimage 63, 641–652.
Wang, Q., Su, T.P., Zhou, Y., Chou, K.H., Chen, I.Y., Jiang, T., Lin, C.P., 2012b. Anatomical insights into disrupted small-world networks in schizophrenia. Neuroimage 59, 1085–1093.
Wang, Z., Jia, X., Liang, P., Qi, Z., Yang, Y., Zhou, W., Li, K., 2012c. Changes in thalamus connectivity in mild cognitive impairment: evidence from resting state fMRI. Eur. J. Radiol. 81, 277–285.
Whitfield-Gabrieli, S., Thermenos, H.W., Milanovic, S., Tsuang, M.T., Faraone, S.V., McCarley, R.W., Shenton, M.E., Green, A.I., Nieto-Castanon, A., LaViolette, P., Wojcik, J., Gabrieli, J.D., Seidman, L.J., 2009. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 106, 1279–1284.
Winterer, G., Konrad, A., Vucurevic, G., Musso, F., Stoeter, P., Dahmen, N., 2008. Association of 5' end neuregulin-1 (NRG1) gene variation with subcortical medial frontal microstructure in humans. Neuroimage 40, 712–718.
Yoshida, K., Ito, K., Sato, K., Takahashi, H., Kamata, M., Higuchi, H., Shimizu, T., Itoh, K., Inoue, K., Tezuka, T., Suzuki, T., Ohkubo, T., Sugawara, K., Otani, K., 2002. Influence of the serotonin transporter gene-linked polymorphic region on the antidepressant response to fluvoxamine in Japanese depressed patients. Prog. Neuropsychopharmacol. Biol. Psychiatry 26, 383–386.
Zalesky, A., Fornito, A., Harding, I.H., Cocchi, L., Yucel, M., Pantelis, C., Bullmore, E.T., 2010. Whole-brain anatomical networks: does the choice of nodes matter? Neuroimage 50, 970–983.
Zhang, K., Xu, Q., Xu, Y., Yang, H., Luo, J., Sun, Y., Sun, N., Wang, S., Shen, Y., 2009. The combined effects of the 5-HTTLPR and 5-HTR1A genes modulates the relationship between negative life events and major depressive disorder in a Chinese population. J. Affect. Disord. 114, 224–231.
Zhang, Y., Fan, L., Wang, J., Zhu, M., Yu, C., Jiang, T., 2012. Connectivity-based parcellation of the human posteromedial cortex. Cereb. Cortex.
Zhou, Y., Liang, M., Jiang, T., Tian, L., Liu, Y., Liu, Z., Liu, H., Kuang, F., 2007a. Functional dysconnectivity of the dorsolateral prefrontal cortex in first-episode schizophrenia using resting-state fMRI. Neurosci. Lett. 417, 297–302.
Zhou, Y., Liang, M., Tian, L., Wang, K., Hao, Y., Liu, H., Liu, Z., Jiang, T., 2007b. Functional disintegration in paranoid schizophrenia using resting-state fMRI. Schizophr. Res. 97, 194–205.
Zhou, Y., Shu, N., Liu, Y., Song, M., Hao, Y., Liu, H., Yu, C., Liu, Z., Jiang, T., 2008. Altered resting-state functional connectivity and anatomical connectivity of hippocampus in schizophrenia. Schizophr. Res. 100, 120–132.
Zuo, N., Cheng, J., Jiang, T., 2012. Diffusion magnetic resonance imaging for Brainnetome: a critical review. Neurosci. Bull. 28, 10.