Brain Imaging and Behavior (2008) 2:249–257
DOI 10.1007/s11682-008-9038-z

# Multimodal Magnetic Resonance Imaging for Brain Disorders: Advances and Perspectives

**Tianzi Jiang · Yong Liu · Feng Shi · Ni Shu · Bing Liu · Jiefeng Jiang · Yuan Zhou**

Received: 8 April 2008 / Accepted: 1 September 2008 / Published online: 5 November 2008


**Abstract** Modern brain imaging technologies play essential roles in our understanding of brain information processing and the mechanisms of brain disorders. Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI) can image the anatomy and structure of the brain. In addition, functional MRI (fMRI) can identify active regions, patterns of functional connectivities and functional networks during either tasks that are specifically related to various aspects of brain function or during the resting state. The merging of such structural and functional information obtained from brain imaging may be able to enhance our understanding of how the brain works and how its diseases can occur. In this paper, we will review advances in both methodologies and clinical applications of multimodal MRI technologies, including MRI, DTI, and fMRI. We will also give our perspectives for the future in these fields. The ultimate goal of our study is to find early biomarkers based on multimodal neuroimages and genome datasets for brain disorders. More importantly, future studies should focus on detecting exactly where and how these brain disorders affect the human brain. It would also be also very interesting to identify the genetic basis of the anatomical and functional abnormalities in the brains of people who have neurological and psychiatric disorders. We believe that we can use brain images to obtain effective biomarkers for various brain disorders with the aid of developing computational methods and models.

T. Jiang (✉) · Y. Liu · F. Shi · N. Shu · B. Liu · J. Jiang · Y. Zhou
LIAMA Center for Computational Medicine, National Laboratory of Pattern Recognition, Institute of Automation,
Chinese Academy of Sciences,
Beijing, 100190, People's Republic of China
e-mail: jiangtz@nlpr.ia.ac.cn

**Keywords** Magnetic resonance imaging · Diffusion tensor imaging · fMRI · Imaging genetics · Brain disorders

## Introduction

The study of brain disorders based on multimodal magnetic resonance imaging technologies has been one of the hottest topics in 21st century science. Traditionally, neuroimaging techniques have been categorized as either structural or functional, depending on the information they provide. In the past two decades, human brain disorders have been studied with various structural and functional neuroimaging techniques. Evidences from a number of studies have demonstrated that multimodal neuroimaging measures have the potential to offer convenient biomarker windows into brain disorders (Chong et al. 2006; Dickerson and Sperling 2005; Fan et al. 2008; Mueller et al. 2005; Shaw et al. 2007a; Supekar et al. 2008). As a result of advances in imaging technologies, noninvasive imaging biomarkers for early prediction and diagnosis of brain disorders have been attracting increasing attention.

In this paper, we will review advances in both methodologies and clinical applications of multimodal magnetic resonance imaging technologies, including structural magnetic resonance imaging (MRI), diffusion tensor imaging (DTI) and functional MRI (fMRI). In "Structural MRI", we review recent advances in studies of brain disorders using MRI. In "Diffusion tensor imaging", we review some advances in DTI and its applications to brain disorders. In "Functional MRI", we provide a brief review of MRI use in the understanding of functional abnormalities in brain disorders. In "Multimodal imaging studies", we review advances in multimodal imaging studies and their applications to brain disorders. In "Imaging genetics", we

touch on advances that combine imaging findings with genetics, a new field called imaging genetics. Finally, future directions are discussed in "Future directions".

## Structural MRI

Structural MRI, also simply called MRI, scans are typically stored in the form of 3D voxels, analogous to 2D pixels in a digital photo. MRI post-processing contains a number of steps, of which two important ones, which have been used in almost all MRI studies, are registration and segmentation. These are also of considerable current interest in medical image analysis. The registration process maps an MRI scan to a pre-defined template. It then matches anatomical landmarks from different MR images and thus makes it possible to explore group differences. The segmentation process classifies the voxels of an MRI scan as gray matter, white matter, cerebrospinal fluid, background, or region of interest (ROI). Thus segmentation serves as the foundation for many analytical tools, such as voxel-based morphology (VBM), cortical surface extraction, and cortical thickness measuring and so on. Automatic processing software, such as SPM (http://www.fil.ion.ucl.ac.uk/spm/) and FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), have been made available and are widely used.

Many measures have been developed to capture the structural features of the brain in MR images, and then to explore structural abnormalities of patients with brain disorders, in comparison with normal controls. Some of the measurements that have often been used include ROI volume, gray/white matter density, cortical surface area, curvature, gyrification index, fractal dimension and so on. Here we will discuss in greater detail the two most commonly used measures, cortical thickness (Fischl and Dale 2000) and VBM (Ashburner and Friston 2000). Cortical thickness reflects the columnar architecture of the cortex and is sensitive to cortical changes caused by development, aging, and diseases. An interesting application of cortical thickness is an investigation into the neurodevelopment trajectory of children with attention-deficit/hyperactivity disorder (Shaw et al. 2007b). In this study, the authors found ADHD patients have later-maturing cognitive controlling regions and earlier-maturing motor areas. Another study investigated cortical thinning in schizophrenia (Kuperberg et al. 2003) and discovered a wide-spread cortical abnormality in schizophrenia patients. VBM measures the concentration and volume of gray matter and white matter at every voxel and is thus able to indicate localized tissue atrophy or expansion. The inventors of VBM applied it to find developmental abnormalities in early blind people (Noppeney et al. 2005). Their results showed a decreased volume in Brodmann area 17/18, the optic radiation and optic chiasm, as well as increased white matter tracts linking the primary sensory cortex with the motor cortex. These findings provide insight into the way that sensory deprivation affects neurodevelopment. Cortical thickness and VBM reflect different morphological profiles of the brain, and they each have their own merits: Cortical thickness is useful in that it is employed in neuroanatomy as well as in neuroimaging, so this measure can easily relate neuroimaging findings with neuroanatomical ones. VBM has the advantage that it can be applied to all kinds of brain tissues, including grey matter, white matter and cerebrospinal fluid, and can thus provide a complete view for detecting potential abnormalities in brain disorders. Furthermore, the morphological correlation of cortical thickness or VBM measurements between different ROIs has received much recent attention (Chen et al. 2008; He et al. 2007a, 2008; Mechelli et al. 2005). This research paradigm may lead to additional interesting findings in neuroscience and psychiatry in the near future.

From the above studies, we can see that MR imaging has provided much important information about the brain. Yet, three fundamental problems remain unsolved. The first relates to understanding and interpreting the biological meanings of the existing measurements, for example, cortical thickness, cortical complexity, and gray/white mater density, which are based on structural MRI. Since we can not see individual neurons with current MRI scans, it is difficult to explain what is occurring at the cellular mechanism level when we find changes in these measurements. The second fundamental problem concerns understanding the relationships among these measurements, especially among cerebral cortical thickness, cortical complexity, and gray/white matter density. The third issue is our ability to detect subtle structural variances from the normal, highly convoluted cerebral cortex. Variability in MRI data, the limitations of our *a priori* knowledge, noise and intensity heterogeneity continue to be major obstacles to accurate MRI findings. To tackle these problems, advanced hardware, such as the 7 T and 9.4 T scanners, has been developed to achieve greater spatial resolution. Further improvements in software, such as adapting up-to-date mathematical tools to achieve better registration and segmentation and inventing new measurements to capture cytoarchitecture, will also be helpful. Future research will be based on the incorporation of both improved hardware and software and will thus be able to reveal more about the nature of the structure of the brain.

## Diffusion tensor imaging

DTI, introduced by Basser and colleagues in 1994 (Basser et al. 1994), is a recently developed MRI technique that can

non-invasively measure macroscopic axonal organization in nervous system tissues. With this technique, white matter integrity and fiber connectivity can be evaluated in vivo.

Two of the major uses of DTI in the central nervous system are in fiber tracing and quantitative white matter analysis. By measuring the direction of the diffusion anisotropy within each voxel, DTI provides an estimate of the neural fiber direction within each voxel. The resulting image represents a three-dimensional vector field image of the neural fiber orientation. The so-called tractography problem entails computationally reconstructing neural pathways from the diffusion tensor vector field. Based on the assumption that the orientation of the largest component of the diagonalized diffusion tensor represents the orientation of the dominant axonal tracts, streamline fiber tracking approaches are widely used to reconstruct white matter connectivity (for a review, see Mori and van Zijl 2002). However, this assumption of only one orientation per voxel in the diffusion tensor model is invalid for the vast majority of the brain at presently achievable voxel resolutions (Tuch et al. 2003). Currently, there is an inevitable mixture of more than one fiber orientation within each voxel, which induces partial volume effects (i.e., crossing, merging and splitting fiber tracts). Also considering the effects of noise, motion and imaging artifacts on the quality of diffusion images, it is important to investigate the uncertainty associated with the estimated fiber bundles. Since 2002, several statistical fiber tracking approaches have been developed to address this problem (Behrens et al. 2003; Friman et al. 2006; Hagmann et al. 2003; Lazar and Alexander 2005). In addition to these statistical fiber tracking methods, advanced imaging and analysis methods have been proposed for solving the "fiber crossing" problem (Tuch et al. 2002, 2003; Wedeen et al. 2005). To improve the imaging, higher *b*-values (i.e. the strength of the diffusion encoding) could be useful for fiber crossing detection. This method will lead to high angular resolution diffusion imaging. The use of diffusion spectrum imaging (DSI) in Q-space could obtain spin propagator and fiber orientation distribution functions by using the Fourier transform (Wedeen et al. 2005). Q-ball imaging has provided an improved version of DSI, as a result of radial projection (Tuch 2004). However, these techniques require large amounts of data and long scanning times, which are not suitable for clinical use. As far as analytical methods are concerned, model-based methods, such as high order tensor (Ozarslan and Mareci 2003), discrete or continuous mixture tensor model (Jian et al. 2007; Tuch et al. 2002), and spherical deconvolution method (Tournier et al. 2004), etc., have been proposed for modeling the diffusion process. However, no perfect method yet exists for solving the fiber crossing problem. In other words, it remains a challenging topic in diffusion MRI studies.

Quantitative white matter analysis is also a major use for DTI. Several diffusion measures, such as mean diffusivity, fractional anisotropy, primary ( $\lambda_1$) and transverse diffusivities ($\lambda_{23}$), are commonly analyzed in clinical studies. Pathologic or plastic changes in these measures may reflect cerebral changes in axonal density, fiber coherence, myelination, extracellular space and so on. Voxel-based analysis (VBA) and ROI based quantitative analysis of diffusion measures are frequently utilized in DTI studies (Foong et al. 2002; Kanaan et al. 2005; Ma et al. 2007; Mori and Zhang 2006; Wang et al. 2003).

Because of the potential of DTI and tractography for investigating white matter integrity and fiber connectivity in vivo, DTI has been widely applied to investigate neurodevelopment and neurodegeneration in recent years (Kubicki et al. 2002; Mori and Zhang 2006). Both normal and pathologic changes in white matter and brain connectivity can be evaluated over the life span through DTI studies of brain development. The white matter abnormalities specific to different brain disorders have been studied for our better understanding of these diseases (Kubicki et al. 2007; Lin et al. 2007; Ma et al. 2007; Medina et al. 2006). It may prove useful to evaluate the correlation between psychiatric symptoms and white matter lesions to determine which specific fiber tracts are affected, as well as the extent of their involvement. In addition, DTI can be used to follow up on the effects of surgical, psychiatric or neurological treatments as well as to monitor the effects of medication.

In summary, DTI has opened up new research possibilities in areas that previously relied largely upon postmortem studies. Future advancements in this technique will, no doubt, provide even more applications in this research field.

## Functional MRI

BOLD fMRI is an important functional brain imaging technique which can be used to measure brain activities that are associated with relative cerebral blood flow rates during tasks (Friston 2005) or in a resting state (for a review, see Fox and Raichle 2007). Since its advent in the early 1990's, the majority of functional neuroscience studies have focused on the brain's response to a task or stimulus.

Using task-based fMRI, we can detect the activity pattern or signal intensity of the brain under various specific tasks. In the past decades, a number of analytic methods have been developed for detecting brain activity patterns and how these patterns change in patients with cognitive disorders. The existing methods can be categorized into two families, the hypothesis-based methods (such as GLM, cross correlation, de-convolution model etc.) and the data-driven methods (such as ICA, PCA, ReHo etc.).

Many excellent toolkits, such as SPM, AFNI, FSL etc., have been released to process this type of data. In addition to its activity during tasks, the brain is very active even in the absence of explicit input. The study of brain spontaneous activity based on resting fMRI has been popular since the first work by Biswal and colleagues (Biswal et al. 1995) and has been well studied, both in animals (Vincent et al. 2007) and humans (Achard et al. 2006; for a review, see Fox and Raichle 2007; K. Wang et al. 2008; L. Wang et al. 2008).

Functional segregation and integration are two major organizational principles of the human brain (Sporns and Zwi 2004). Recently, increasing attention has been focused on a relatively new application of fMRI which involves the measurement of the extent to which different areas of the brain are functionally connected. Functional connectivity has been introduced to measure the coherence between fMRI signals in different brain functional regions. ROI based connectivity analysis and whole brain connectivity are the two most common methods. Using these two methods, researchers can investigate alterations in patients with a brain disorder (He et al. 2007b; Johnston et al. 2008; Liu et al. 2007, 2008b; Supekar et al. 2008; Tian et al. 2008; Wang et al. 2006a, b, 2007; Yu et al. 2008; Zang et al. 2007; Zhou et al. 2008). In recent years, a functional network, the so-called "default mode network (DMN)" of the brain, a set of regions characterized by decreased neural activity during goal-oriented tasks (Raichle et al. 2001), has attracted significant interest as well as controversy (Buckner and Vincent 2007; Morcom and Fletcher 2007a, b; Raichle and Snyder 2007). The functional connectivity pattern in the DMN has been found to be altered in Alzheimer's disease (AD) (Greicius et al. 2004; Supekar et al. 2008), major depression (Greicius et al. 2007), schizophrenia (Garrity et al. 2007; Zhou et al. 2007) and other cognitive disorders (for a review, see Buckner et al. 2008). So some researchers have suggested that the pattern of activity in the DMN maybe an effective biomarker for various brain disorders (for a review see Buckner et al. 2008; Greicius et al. 2004; Wang et al. 2006a).

More interestingly, several groups have also used graph theory to investigate the topological properties of the brain network and have demonstrated that this large, sparse, complex network is characterized by efficient small-world properties (Achard and Bullmore, 2007) as well as that these properties were altered in some cognitive disorders, such as schizophrenia (Liu et al. 2008a), ADHD (K. Wang et al. 2008; L. Wang et al. 2008) and AD (He et al. 2008; Supekar et al. 2008).

In brief, fMRI has provided us with ways to define brain activity under specific tasks state and the resting state. Using task fMRI and resting state fMRI, we can identify some special functional networks, such as an attention network, the DMN, a memory network, and so on (for a review, see Fox and Raichle 2007). In addition, we can investigate alterations in brain activity and functional connectivity patterns in patients with brain disorders. FMRI may eventually be used to assist in the diagnosis and assessment of the impact of treatment of cognitive disorders. Much is known; yet there is more to be discovered. One thing that awaits further investigation is relating disturbances in brain activity (task state or resting state) to underlying differences in anatomy and physiology, determining the sensitivity and specificity of the observed alterations, and treatment monitoring. These areas are likely to become major foci for future research. A second area is whether altered functional connectivity has a foundation in anatomical connectivity. New DTI tractography methods and more advanced hardware need to be developed to investigate this. Finally, the neurophysiological basis for these functional network properties needs further investigation. Meanwhile, the identification of cognitive paradigms appropriate for varying levels of cognitive impairment also poses a practical challenge for future research.

## Multimodal imaging studies

In recent years, increasing numbers of studies have focused on exploring the relationship between resting-state functional MRI and structural connectivity. The goal is to find the anatomical substrates of functional organization in the brain. Diffusion tensor tractography (DTT) can be used to investigate the anatomical connections between different brain regions. From a different perspective, functional connectivity can be reflected by temporal correlations in the BOLD signal of widely separated brain regions. Although these two modalities separately provide both anatomical and functional information about the brain, the relationship between them has attracted increasing attention in recent years (for a review, see Buckner et al. 2008; Greicius et al. 2008; Hagmann et al. 2008; Koch et al. 2002).

An analysis that combines multimodal imaging approaches may also be able to provide a unique perspective for understanding abnormalities in connectivity in brain disorders. For example, a study of functional connectivity MRIs of patients with agenesis of the corpus callosum showed little to no functional connectivity between the left and right hemispheric auditory cortices, thus suggesting that structural neural connections are required for functional connectivity (Quigley et al. 2003). Hyperconnectivity in grapheme→color synesthesia was validated by finding increased brain activation and increased anisotropy in the inferior temporal cortex, which also indirectly demonstrated the correlation between functional and structural connectivity (Rouw and Scholte 2007). A concurrence of functional dysconnectivity and damaged anatomical con-

nectivity between the hippocampus and other regions in schizophrenia suggests that the damaged anatomical connectivity may be the neural basis for the altered resting-state functional connectivity (Zhou et al. 2008). Disrupted functional connectivities within the ventral attention network and between the ventral and dorsal attention network have been found to anatomically correspond to the disconnection of white matter tracts connecting the attention relevant regions in patients with spatial neglect following stroke (He et al. 2007).

Multimodal studies using both MRI and fMRI images have recently emerged. For example, one study directly compared an increase in anatomical regions of grey matter with regions of activation (Ilg et al. 2008); another study that investigated the structural–functional basis for dyslexia (Siok et al. 2008) analyzed the correlation between contrast estimations obtained using fMRI images and mean grey matter volume of ROIs calculated using MRI images and found that they were positively correlated. These results link brain dysfunctions to structural abnormalities; yet the underlying interactions between BOLD signals and brain structures need further exploration.

Functional or structural MRI study alone has its own limitations and shortcomings. However, the combined analysis of these could provide a more nearly complete view of the problem. In the future, combination studies of different modalities in both control and patient groups could greatly enhance our understanding of the complex systems of the human brain.

## Imaging genetics

Advances in neuroimaging technology have provided the tools necessary to explore the relationships among genes, brain, and behavior. Imaging genetics, also termed imaging genomics (Hariri and Weinberger 2003), which combines molecular biology and neuroimaging to study genetic effects on brain morphology and function, has become a very interesting and promising research field. Compared with traditional behavioral and clinical phenotypes, imaging endophenotypes (intermediate phenotypes) are objective, heritable, quantitative traits and thus may not require as large a sample size to identify significant genetic effects.

Using an imaging genetics strategy, most studies have focused on specific neurological and psychiatric diseases related to emotional or cognitive functions (Meyer-Lindenberg and Weinberger 2006). Functional genetic variations in several important genes, such as COMT Val158Met, BDNF Val66Met, 5-HTTLPR, etc., have received the most extensive attention. An fMRI study under working memory tasks suggested that the COMT Val allele, by increasing prefrontal dopamine catabolism, could impair prefrontal cognition and physiology and increase the risk for schizophrenia (Egan et al. 2001). Using DTI, our study reported that COMT Val158Met can modulate the association between brain white matter integrity and general intelligence (Li et al. 2008). Studies using high-resolution structural MRI suggested that the Met-BDNF allele may modulate smaller hippocampal volumes and may render people with this allele susceptible to schizophrenia or major depression (Frodl et al. 2007; Szeszko et al. 2005). A recent meta-analysis suggested an association of the 5-HTTLPR polymorphism and amygdala activation (Munafo et al. 2008) with a potential susceptibility to mood disorders.

In the past few years imaging genetics has developed rapidly and great achievements have been obtained. However, some key issues deserve a more thorough study. One of the great challenges is the selection of candidate genetic variations. Previous studies have chosen functional genetic variations which have specific biological significance (Egan et al. 2001; Frodl et al. 2007; Li et al. 2008; Munafo et al. 2008; Szeszko et al. 2005). However, few studies have considered the interactions of other risk alleles, such as haplotypes consisting of multiple individual genetic polymorphisms, which may play an important role in the pathology of brain disorders. Another great challenge is how to measure and understand the genetic impact on brain morphology and function by the integration of multimodal magnetic resonance images. As we have discussed, the brain works as a whole. Thus, investigating the genetic basis of brain connectivity and brain networks should be a pivotal topic in future studies. With advances in genomic and imaging technologies, a more systematic and perfect bridge may be constructed between imaging and genomics for brain disorders, and more effective biomarkers can be obtained by future imaging genomics studies.

## Future directions

Various modern neuroimaging techniques have been applied to combat neurological and psychiatric disorders, especially AD and schizophrenia. The ultimate objectives of our research are to improve our understandings of the pathogenesis of diseases and to find early markers for neurological and psychiatric diseases, based on neuroimages and genome datasets. A long term goal of these studies is to provide objective and quantitative indices for early diagnosis and for evaluating the effect of therapy for cognitive disorders (Fig. 1).

Although much is known, more waits to be discovered, and the following research directions show promise for interesting discoveries in the near future.

The first recommendation is to use a network model to increase our understanding of the organizational architec-

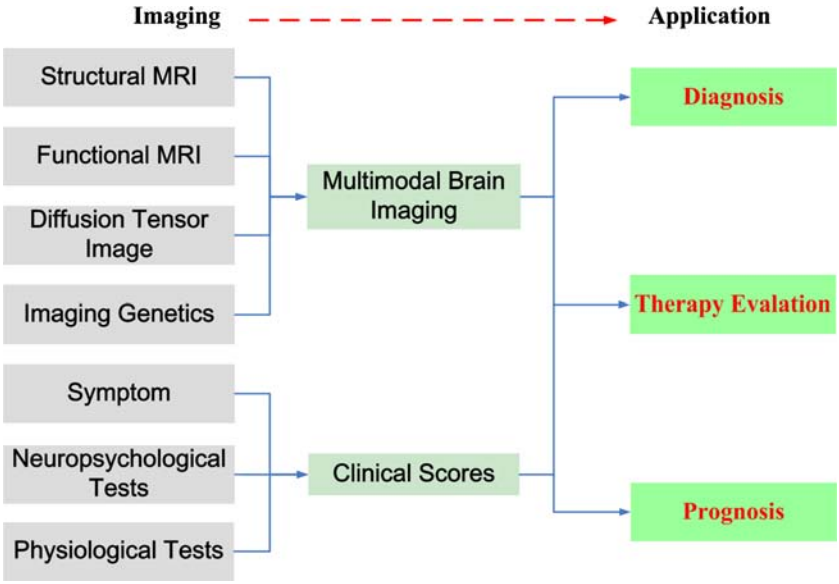


**Fig. 1** Sketch map for future studies

ture of the brain. Recent studies using EEG, MEG, fMRI, structural MRI and DTI have demonstrated that the human brain network has efficient small world properties and a highly modular structure. More interestingly, these network properties are altered in some disorders. Hence, network measures may be useful as an imaging-based biomarker to distinguish patients with brain disorders from normal controls.

A further recommendation would be to combine multimodal imaging studies with genetic studies to predict the progress of brain disorders. It would be very interesting to identify the genetic basis of anatomical and functional abnormalities of human brain and show how this is connected with neurological and psychiatric disorders. A remarkable trend is to use imaging findings of brain disorders to reveal the endophenotypes for various gene mutations. Another important trend for the future will be to decode global gene expression programs in brain disorders and other diseases, such as various cancers, using multimodal noninvasive imaging.

Another recommendation for future research would be to carry out longitudinal studies to attempt to find effective biomarkers for cognitive disorders.

Given the small sample size of the patients in most studies, statistical power is of potential concern. Larger sample sizes would reduce individual effects on the results and allow us to develop effective and applicable biomarkers for psychiatric diseases.

In the near future, convenient, noninvasive imaging biomarkers for early prediction and diagnosis of brain disorders will be available as a result of increasing collaboration among multiple centers/institutions as well as datasets that are shared all over the world. Such collaborative networks will play an essential role in combating human brain disorders. Specifically, Pacific Rim collaboration in this field is not only possible, but should also be particularly fruitful for the following reasons. One major advantage is that modern imaging scanners from 1.5 to 3.0 T are available in middle-sized and large cities in China, which has the largest population and thus the widest disease spectrum. Within China formal collaborative networks have been established by various projects, such as the collaboration of our group with many hospitals throughout our country. These may also be informal, regionalized or national ones that come about as a result of the natural collaboration within a unified country. The other major advantage to Pacific Rim collaboration is that the governments of the USA, Australia, Japan, and Korea have invested in this field for a number of years, leading to important advances. It is time to establish a more extensive Pacific Rim collaboration network to push the development of this field by combining the expertise of different groups. This network could easily become the hub for a collaborative network in this field throughout the whole world. Moreover, we envision that a new field, named Computational Medicine, will emerge soon. Its fundamental goal will be to couple biological models with medical data and practices by applying modern computational techniques to medicine. In fact, a new research center for computational medicine, which consists of five laboratories: computational anatomy, medical imaging, systems biomedicine, biomarker analysis, and brain-machine inter-

face, has been established at our institute (www.brain spans.org). Its goal is to provide a platform for collaboration between our institute and hospitals throughout China.

**Acknowledgements** The authors appreciate the English language assistance of Drs. Rhoda and Edmund Perozzi. This work was partially supported by the Natural Science Foundation of China, Grant Nos. 30425004 and 30730035, and the National Key Basic Research and Development Program (973), Grant No. 2004CB318107.

## References

Achard, S., & Bullmore, E. (2007). Efficiency and cost of economical brain functional networks. *PLoS Computational Biology*, *3*(2), e17. doi:10.1371/journal.pcbi.0030017.

Achard, S., Salvador, R., Whitcher, B., Suckling, J., & Bullmore, E. (2006). A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *The Journal of Neuroscience*, *26*(1), 63–72. doi:10.1523/JNEUROSCI.3874-05.2006.

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—the methods. *NeuroImage*, *11*, 805–821. doi:10.1006/nimg.2000.0582.

Basser, P. J., Mattiello, J., & LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, *66*(1), 259–267.

Behrens, T. E., Woolrich, M. W., Jenkinson, M., Johansen-Berg, H., Nunes, R. G., Clare, S., et al. (2003). Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magnetic Resonance in Medicine*, *50*(5), 1077–1088. doi:10.1002/mrm.10609.

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, *34*(4), 537–541. doi:10.1002/mrm.1910340409.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, *1124*, 1–38. doi:10.1196/annals.1440.011.

Buckner, R. L., & Vincent, J. L. (2007). Unrest at rest: default activity and spontaneous network correlations. *NeuroImage*, *37*(4), 1091–1096. doi:10.1016/j.neuroimage.2007.01.010.

Chen, Z. J., He, Y., Rosa-Neto, P., Germann, J., & Evans, A. C.(2008). Revealing modular architecture of human brain structural networks by using cortical thickness from MRI. *Cereb Cortex*.

Chong, M. S., Lim, W. S., & Sahadevan, S. (2006). Biomarkers in preclinical Alzheimer's disease. *Current Opinion in Investigational Drugs (London, England)*, *7*(7), 600–607.

Dickerson, B. C., & Sperling, R. A. (2005). Neuroimaging biomarkers for clinical trials of disease-modifying therapies in Alzheimer's disease. *Neurorx*, *2*(2), 348–360. doi:10.1602/neurorx.2.2.348.

Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., et al. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(12), 6917–6922. doi:10.1073/pnas.111134598.

Fan, Y., Resnick, S. M., Wu, X., & Davatzikos, C. (2008). Structural and functional biomarkers of prodromal Alzheimer's disease: a high-dimensional pattern classification study. *NeuroImage*, *41*(2), 277–285. doi:10.1016/j.neuroimage.2008.02.043.

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(20), 11050–11055. doi:10.1073/pnas.200033797.

Foong, J., Symms, M. R., Barker, G. J., Maier, M., Miller, D. H., & Ron, M. A. (2002). Investigating regional white matter in schizophrenia using diffusion tensor imaging. *Neuroreport*, *13*(3), 333–336. doi:10.1097/00001756-200203040-00017.

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews. Neuroscience*, *8*(9), 700–711. doi:10.1038/nrn2201.

Friman, O., Farneback, G., & Westin, C. F. (2006). A Bayesian approach for stochastic white matter tractography. *IEEE Transactions on Medical Imaging*, *25*(8), 965–978. doi:10.1109/TMI.2006.877093.

Friston, K. J. (2005). Models of brain function in neuroimaging. *Annual Review of Psychology*, *56*, 57–87. doi:10.1146/annurev.psych.56.091103.070311.

Frodl, T., Schule, C., Schmitt, G., Born, C., Baghai, T., Zill, P., et al. (2007). Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. *Archives of General Psychiatry*, *64*(4), 410–416. doi:10.1001/archpsyc.64.4.410.

Garrity, A. G., Pearlson, G. D., McKiernan, K., Lloyd, D., Kiehl, K. A., & Calhoun, V. D. (2007). Aberrant "default mode" functional connectivity in schizophrenia. *The American Journal of Psychiatry*, *164*(3), 450–457. doi:10.1176/appi.ajp.164.3.450.

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., et al. (2007). Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biological Psychiatry*, *62*(5), 429–437. doi:10.1016/j.biopsych.2006.09.020.

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. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(13), 4637–4642. doi:10.1073/pnas.0308627101.

Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F.(2008). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cereb Cortex*.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., et al. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biology*, *6*(7), e159. doi:10.1371/journal.pbio.0060159.

Hagmann, P., Thiran, J. P., Jonasson, L., Vandergheynst, P., Clarke, S., Maeder, P., et al. (2003). DTI mapping of human brain connectivity: statistical fiber tracking and virtual dissection. *NeuroImage*, *19*(3), 545–554. doi:10.1016/S1053-8119(03)00142-3.

Hariri, A. R., & Weinberger, D. R. (2003). Imaging genomics. *British Medical Bulletin*, *65*, 259–270. doi:10.1093/bmb/65.1.259.

He, B. J., Snyder, A. Z., Vincent, J. L., Epstein, A., Shulman, G. L., & Corbetta, M. (2007). Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. *Neuron*, *53*(6), 905–918. doi:10.1016/j.neuron.2007.02.013.

He, Y., Chen, Z., & Evans, A. (2008). Structural insights into aberrant topological patterns of large-scale cortical networks in Alzheimer's disease. *The Journal of Neuroscience*, *28*(18), 4756–4766. doi:10.1523/JNEUROSCI.0141-08.2008.

He, Y., Chen, Z. J., & Evans, A. C. (2007a). Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cerebral Cortex (New York, N.Y.)*, *17*(10), 2407–2419. doi:10.1093/cercor/bhl149.

He, Y., Wang, L., Zang, Y., Tian, L., Zhang, X., Li, K., et al. (2007b). Regional coherence changes in the early stages of Alzheimer's

disease: a combined structural and resting-state functional MRI study. *NeuroImage*, *35*(2), 488–500. doi:10.1016/j.neuroimage.2006.11.042.

Ilg, R., Wohlschlager, A. M., Gaser, C., Liebau, Y., Dauner, R., Woller, A., et al. (2008). Gray matter increase induced by practice correlates with task-specific activation: a combined functional and morphometric magnetic resonance imaging study. *The Journal of Neuroscience*, *28*(16), 4210–4215. doi:10.1523/JNEUROSCI.5722-07.2008.

Jian, B., Vemuri, B. C., Ozarslan, E., Carney, P. R., & Mareci, T. H. (2007). A novel tensor distribution model for the diffusion-weighted MR signal. *NeuroImage*, *37*(1), 164–176. doi:10.1016/j.neuroimage.2007.03.074.

Johnston, J. M., Vaishnavi, S. N., Smyth, M. D., Zhang, D., He, B. J., Zempel, J. M., et al. (2008). Loss of resting interhemispheric functional connectivity after complete section of the corpus callosum. *The Journal of Neuroscience*, *28*(25), 6453–6458. doi:10.1523/JNEUROSCI.0573-08.2008.

Kanaan, R. A., Kim, J. S., Kaufmann, W. E., Pearlson, G. D., Barker, G. J., & McGuire, P. K. (2005). Diffusion tensor imaging in schizophrenia. *Biological Psychiatry*, *58*(12), 921–929. doi:10.1016/j.biopsych.2005.05.015.

Koch, M. A., Norris, D. G., & Hund-Georgiadis, M. (2002). An investigation of functional and anatomical connectivity using magnetic resonance imaging. *NeuroImage*, *16*(1), 241–250. doi:10.1006/nimg.2001.1052.

Kubicki, M., McCarley, R., Westin, C. F., Park, H. J., Maier, S., Kikinis, R., et al. (2007). A review of diffusion tensor imaging studies in schizophrenia. *Journal of Psychiatric Research*, *41*(1–2), 15–30. doi:10.1016/j.jpsychires.2005.05.005.

Kubicki, M., Westin, C. F., Maier, S. E., Mamata, H., Frumin, M., Ersner-Hershfield, H., et al. (2002). Diffusion tensor imaging and its application to neuropsychiatric disorders. *Harvard Review of Psychiatry*, *10*(6), 324–336. doi:10.1080/10673220216231.

Kuperberg, G. R., Broome, M. R., McGuire, P. K., David, A. S., Eddy, M., Ozawa, F., et al. (2003). Regionally localized thinning of the cerebral cortex in schizophrenia. *Archives of General Psychiatry*, *60*(9), 878–888. doi:10.1001/archpsyc.60.9.878.

Lazar, M., & Alexander, A. L. (2005). Bootstrap white matter tractography (BOOT-TRAC). *NeuroImage*, *24*(2), 524–532. doi:10.1016/j.neuroimage.2004.08.050.

Li, J., Yu, C., Li, Y., Liu, B., Liu, Y., Shu, N., et al. (2008). COMT Val158Met modulates association between brain white matter architecture and IQ. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, in press.

Lin, F., Yu, C., Jiang, T., Li, K., & Chan, P. (2007). Diffusion tensor tractography-based group mapping of the pyramidal tract in relapsing–remitting multiple sclerosis patients. *AJNR. American Journal of Neuroradiology*, *28*(2), 278–282.

Liu, Y., Liang, M., Zhou, Y., He, Y., Hao, Y., Song, M., et al. (2008a). Disrupted small-world networks in schizophrenia. *Brain*, *131*(Pt 4), 945–961. doi:10.1093/brain/awn018.

Liu, Y., Wang, K., Yu, C., He, Y., Zhou, Y., Liang, M., et al. (2008b). Regional homogeneity, functional connectivity and imaging markers of Alzheimer's disease: a review of resting-state fMRI studies. *Neuropsychologia*, *46*(6), 1648–1656. doi:10.1016/j.neuropsychologia.2008.01.027.

Liu, Y., Yu, C., Liang, M., Li, J., Tian, L., Zhou, Y., et al. (2007). Whole brain functional connectivity in the early blind. *Brain*, *130*(Pt 8), 2085–2096. doi:10.1093/brain/awm121.

Ma, N., Li, L., Shu, N., Liu, J., Gong, G., He, Z., et al. (2007). White matter abnormalities in first-episode, treatment-naive young adults with major depressive disorder. *The American Journal of Psychiatry*, *164*(5), 823–826. doi:10.1176/appi.ajp.164.5.823.

Mechelli, A., Friston, K. J., Frackowiak, R. S., & Price, C. J. (2005). Structural covariance in the human cortex. *The Journal of Neuroscience*, *25*(36), 8303–8310. doi:10.1523/JNEUROSCI.0357-05.2005.

Medina, D., DeToledo-Morrell, L., Urresta, F., Gabrieli, J. D., Moseley, M., Fleischman, D., et al. (2006). White matter changes in mild cognitive impairment and AD: a diffusion tensor imaging study. *Neurobiology of Aging*, *27*(5), 663–672. doi:10.1016/j.neurobiolaging.2005.03.026.

Meyer-Lindenberg, A., & Weinberger, D. R. (2006). Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nature Reviews. Neuroscience*, *7*(10), 818–827. doi:10.1038/nrn1993.

Morcom, A. M., & Fletcher, P. C. (2007a). Cognitive neuroscience: the case for design rather than default. *NeuroImage*, *37*(4), 1097–1099. doi:10.1016/j.neuroimage.2007.07.018.

Morcom, A. M., & Fletcher, P. C. (2007b). Does the brain have a baseline? Why we should be resisting a rest. *NeuroImage*, *37*(4), 1073–1082. doi:10.1016/j.neuroimage.2006.09.013.

Mori, S., & van Zijl, P. C. (2002). Fiber tracking: principles and strategies—a technical review. *NMR in Biomedicine*, *15*(7–8), 468–480. doi:10.1002/nbm.781.

Mori, S., & Zhang, J. (2006). Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron*, *51*(5), 527–539. doi:10.1016/j.neuron.2006.08.012.

Mueller, S. G., Weiner, M. W., Thal, L. J., Petersen, R. C., Jack, C., Jagust, W., et al. (2005). The Alzheimer's disease neuroimaging initiative. *Neuroimaging Clinics of North America*, *15*(4), 869–877 xi–xii. doi:10.1016/j.nic.2005.09.008.

Munafo, M. R., Brown, S. M., & Hariri, A. R. (2008). Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biological Psychiatry*, *63*(9), 852–857. doi:10.1016/j.biopsych.2007.08.016.

Noppeney, U., Friston, K. J., Ashburner, J., Frackowiak, R., & Price, C. J. (2005). Early visual deprivation induces structural plasticity in gray and white matter. *Current Biology*, *15*(13), 488–50. doi:10.1016/j.cub.2005.06.053.

Ozarslan, E., & Mareci, T. H. (2003). Generalized diffusion tensor imaging and analytical relationships between diffusion tensor imaging and high angular resolution diffusion imaging. *Magnetic Resonance in Medicine*, *50*(5), 955–965. doi:10.1002/mrm.10596.

Quigley, M., Cordes, D., Turski, P., Moritz, C., Haughton, V., Seth, R., et al. (2003). Role of the corpus callosum in functional connectivity. *AJNR. American Journal of Neuroradiology*, *24*(2), 208–212.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(2), 676–682. doi:10.1073/pnas.98.2.676.

Raichle, M. E., & Snyder, A. Z. (2007). A default mode of brain function: a brief history of an evolving idea. *NeuroImage*, *37*(4), 1083–1090 discussion 97–99. doi:10.1016/j.neuroimage.2007.02.041.

Rouw, R., & Scholte, H. S. (2007). Increased structural connectivity in grapheme-color synesthesia. *Nature Neuroscience*, *10*(6), 792–797. doi:10.1038/nn1906.

Shaw, L. M., Korecka, M., Clark, C. M., Lee, V. M.-Y., & Trojanowski, J. Q. (2007). Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. *Nature Reviews. Neuroscience*, *6*, 295–303. doi:10.1038/nrd2176.

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D., et al. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(49), 19649–19654. doi:10.1073/pnas.0707741104.

Siok, W. T., Niu, Z., Jin, Z., Perfetti, C. A., & Tan, L. H. (2008). A structural–functional basis for dyslexia in the cortex of Chinese readers. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(14), 5561–5566. doi:10.1073/pnas.0801750105.

Sporns, O., & Zwi, J. D. (2004). The small world of the cerebral cortex. *Neuroinformatics*, *2*(2), 145–162. doi:10.1385/NI:2:2:145.

Supekar, K., Menon, V., Rubin, D., Musen, M., & Greicius, M. D. (2008). Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Computational Biology*, *4*(6), e1000100. doi:10.1371/journal.pcbi.1000100.

Szeszko, P. R., Lipsky, R., Mentschel, C., Robinson, D., Gunduz-Bruce, H., Sevy, S., et al. (2005). Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. *Molecular Psychiatry*, *10*(7), 631–636. doi:10.1038/sj.mp.4001656.

Tian, L., Jiang, T., Liang, M., Zang, Y., He, Y., Sui, M., et al. (2008). Enhanced resting-state brain activities in ADHD patients: a fMRI study. *Brain & Development*, *30*(5), 342–348. doi:10.1016/j.braindev.2007.10.005.

Tournier, J. D., Calamante, F., Gadian, D. G., & Connelly, A. (2004). Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. *NeuroImage*, *23*(3), 1176–1185. doi:10.1016/j.neuroimage.2004.07.037.

Tuch, D. S. (2004). Q-ball imaging. *Magnetic Resonance in Medicine*, *52*(6), 1358–1372. doi:10.1002/mrm.20279.

Tuch, D. S., Reese, T. G., Wiegell, M. R., Makris, N., Belliveau, J. W., & Wedeen, V. J. (2002). High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. *Magnetic Resonance in Medicine*, *48*(4), 577–582. doi:10.1002/mrm.10268.

Tuch, D. S., Reese, T. G., Wiegell, M. R., & Wedeen, V. J. (2003). Diffusion MRI of complex neural architecture. *Neuron*, *40*(5), 885–895. doi:10.1016/S0896-6273(03)00758-X.

Vincent, J. L., Patel, G. H., Fox, M. D., Snyder, A. Z., Baker, J. T., Van Essen, D. C., et al. (2007). Intrinsic functional architecture in the anaesthetized monkey brain. *Nature*, *447*(7140), 83–86. doi:10.1038/nature05758.

Wang, F., Sun, Z., Du, X., Wang, X., Cong, Z., Zhang, H., et al. (2003). A diffusion tensor imaging study of middle and superior cerebellar peduncle in male patients with schizophrenia. *Neuroscience Letters*, *348*(3), 135–138. doi:10.1016/S0304-3940(03)00589-5.

Wang, K., Jiang, T., Liang, M., Wang, L., Tian, L., Zhang, X., et al. (2006a). Discriminative analysis of early Alzheimer's disease based on two intrinsically anti-correlated networks with resting-state fMRI. *Med Image Comput Comput Assist Interv Int Conf Med Image Comput Comput Assist Interv*, *9*(Pt 2), 340–347.

Wang, L., Zang, Y., He, Y., Liang, M., Zhang, X., Tian, L., et al. (2006b). Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. *NeuroImage*, *31*(2), 496–504. doi:10.1016/j.neuroimage.2005.12.033.

Wang, K., Liang, M., Wang, L., Tian, L., Zhang, X., Li, K., et al. (2007). Altered functional connectivity in early Alzheimer's disease: a resting-state fMRI study. *Human Brain Mapping*, *28*(10), 967–978. doi:10.1002/hbm.20324.

Wang, K., Jiang, T., Yu, C., Tian, L., Li, J., Liu, Y., et al. (2008). Spontaneous activity associated with primary visual cortex: a resting-state FMRI study. *Cerebral Cortex (New York, N.Y.)*, *18*(3), 697–704. doi:10.1093/cercor/bhm105.

Wang, L., Zhu, C., He, Y., Zang, Y., Cao, Q., Zhang, H., et al.(2008). Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. *Hum Brain Mapp*.

Wedeen, V. J., Hagmann, P., Tseng, W. Y., Reese, T. G., & Weisskoff, R. M. (2005). Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. *Magnetic Resonance in Medicine*, *54*(6), 1377–1386. doi:10.1002/mrm.20642.

Yu, C., Liu, Y., Li, J., Zhou, Y., Wang, K., Tian, L., et al. (2008). Altered functional connectivity of primary visual cortex in early blindness. *Human Brain Mapping*, *29*(5), 533–543. doi:10.1002/hbm.20420.

Zang, Y. F., He, Y., Zhu, C. Z., Cao, Q. J., Sui, M. Q., Liang, M., et al. (2007). Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain & Development*, *29*(2), 83–91. doi:10.1016/j.braindev.2006.07.002.

Zhou, Y., Liang, M., Tian, L., Wang, K., Hao, Y., Liu, H., et al. (2007). Functional disintegration in paranoid schizophrenia using resting-state fMRI. *Schizophrenia Research*, *97*(1–3), 194–205. doi:10.1016/j.schres.2007.05.029.

Zhou, Y., Shu, N., Liu, Y., Song, M., Hao, Y., Liu, H., et al. (2008). Altered resting-state functional connectivity and anatomical connectivity of hippocampus in schizophrenia. *Schizophrenia Research*, *100*(1–3), 120–132. doi:10.1016/j.schres.2007.11.039.