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REVIEW

Spontaneous brain activity observed with functional magnetic resonance imaging as a potential biomarker in neuropsychiatric disorders

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Abstract As functional magnetic resonance imaging (fMRI) studies have yielded increasing amounts of information about the brain's spontaneous activity, they have revealed fMRI's potential to locate changes in brain hemodynamics that are associated with neuropsychiatric disorders. In this paper, we review studies that support the notion that changes in brain spontaneous activity observed by fMRI can be used as potential biomarkers for diagnosis and treatment evaluation in neuropsychiatric disorders. We first review the methods used to study spontaneous activity from the perspectives of (1) the properties of local spontaneous activity, (2) the spatial pattern of spontaneous activity, and (3) the topological properties of brain networks. We also summarize the major findings associated with major neuropsychiatric disorders obtained using these methods. Then we review the pilot studies that have used spontaneous activity to discriminate patients from normal controls. Finally, we discuss current challenges and potential research directions to further elucidate the clinical use of spontaneous brain activity in neuropsychiatric disorders.

Keywords Resting-state fMRI · Low frequency fluctuation · Functional connectivity · Alzheimer's disease · Schizophrenia

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Introduction

Accurate diagnosis of neuropsychiatric disorders presents a major challenge for psychiatrists and clinicians. The current situation, in which neuropsychiatric disorders are diagnosed mainly based on clinical symptoms and medical history, has spurred the search for objective biomarkers, such as neuroimaging markers.

Spontaneous brain activity, as observed by functional magnetic resonance imaging (fMRI), is termed spontaneous low-frequency fluctuation (SLFF) in blood oxygen level dependence (BOLD) signal and has recently attracted the attention of researchers as a potential biomarker for locating changes in brain hemodynamics associated with diseases because of its clinical advantages. Spontaneous brain activity is usually detected while participants lie quietly in the scanner with their eyes closed or open, i.e. at rest. Compared to positron emission tomography (PET), fMRI is non-invasive and has relatively high resolution and sensitivity (Bandettini and Bullmore 2008). Compared to task-state fMRI studies, at rest studies are easier to perform (no experimental design or subject training is needed) with patients who have neuropsychiatric disorders, especially those who find it difficult to conform to instructions (e.g. children and elderly patients) and those with severely impaired cognition (Fox and Raichle 2007). In addition, findings obtained using resting-state fMRI can be

comparable across different studies. All of these advantages make it possible to obtain large sample sizes and perform repeat scanning, both of which are important for identifying biomarkers for diagnosis, therapy evaluation and prognosis.

Findings of the physiological origin of spontaneous brain activity further strengthen the possibility that detected changes in spontaneous brain activity can be used as potential biomarkers. From the perspective of brain energy metabolism, most of energy (60–80%) that brain consumes is used to support the ongoing neural signaling (Raichle 2010a). It has been proved that signal transmission and neuronal energetic demands are tightly coupled to information coding in the cerebral cortex in fMRI experiments (Wang et al. 2009). A theory of energy coding has been proposed to bridge the gap between functional connections within a biological neural network and energetic consumption (Wang and Zhang 2007; Wang et al. 2008c). Findings have consistently shown that this spontaneous brain activity measured by BOLD is correlated with electrophysiological signal, specially local field potentials in the range of slow cortical potentials, and may be more deeply correlated with functionally important cellular and biochemical processes, such as aerobic glycolysis and spontaneous fluctuations in neurotransmitter release, and thus physiologically meaningful (for reviews, see Fox and Raichle 2007; Kiviniemi 2008; Raichle 2010b). This has inspired more and more researchers to explore whether endogenous fMRI markers can characterize the neurophysiological changes associated with disease or drug treatments. To date many studies have been performed involving nearly all of the major neuropsychiatric disorders. Various methods for detecting spontaneous activity have been used to investigate biomarkers that can be related to specific neuropsychiatric disorders. This review focuses on the methods and their findings. We first review the methods used to study spontaneous activity from the perspectives of (1) the properties of local spontaneous activity, (2) the spatial pattern of spontaneous activity and (3) the topological properties of brain networks. We also summarize the major findings obtained by these methods in two representative neuropsychiatric disorders, i.e., Alzheimer's disease (AD) and schizophrenia, both of which are the most widely investigated. Then we review the pilot studies that have used spontaneous activity to discriminate patients from normal controls. Finally, we provide a discussion of current challenges and future research directions including the development of brain imaging biomarkers and their integration with molecular and clinical signatures for diagnosis, therapy evaluation and prognosis of major neuropsychiatric disorders. Recently, several reviews on this topic have been published. Greicius et al. (2008) emphasized spatial pattern analysis from the perspective of promoting the clinical applications of resting-state fMRI. Kiviniemi (2008) analyzed the physiological origins of endogenous fluctuations but paid less attention to anatomical substructure and topological aspects of these diseases. In our group, Liu et al. (2008a,b) reviewed fMRI findings in AD. However, this review covers fMRI findings related both anatomically and physiologically in major neuropsychiatric disorders with an emphasis on gaining a full picture of the methodologies, the fMRI findings and how the findings relate to each disease and prospects the fMRI findings as biomarkers for neuropsychiatric disorders.

Methods and progress in understanding neuropsychiatric disorders

The brain appears to adhere to two fundamental principles of functional organization, functional specialization and functional integration (Zeki and Shipp 1988; Friston 1994). Connectivity mediates the integration within and among the specialized areas (Friston 1994). Disruptions in these two fundamental principles of functional organization have been implicated in the pathophysiology of neuropsychiatric disorders, such as AD (Delbeuck et al. 2003) and schizophrenia (Friston 1998). Using methods developed to investigate spontaneous activity from the local activity level (properties of local spontaneous activity) to the global activity level (spatial patterns of spontaneous activity and topological properties of brain networks), disrupted functional specialization and integrations have been found in these disorders during rest. In this section, we will separately introduce the methods used to investigate the local spontaneous activity and the global activity as well as the progress of identifying these in neuropsychiatric disorders.

Properties of local spontaneous activity

Due to the lack of specific stimuli, it is difficult to detect localized spontaneous activity during rest using traditional task-related data analyses. Thus data-driven methods have been advanced to study the local spontaneous activity. Using these methods abnormalities in local spontaneous activity have been found in various neuropsychiatric disorders (Table 1). Each of these methods is discussed in the following subsections.

Regional coherence

COSLOF Index: Functional synchrony in a given brain region can be quantified as the mean of the cross-correlation coefficients of spontaneous low frequency (COSLOF) fluctuations between pairs of voxel time courses in the hippocampus, i.e. the COSLOF index (Li et al. 2002).

Table 1 Methods of investigating local spontaneous activity and progress in understanding neuropsychiatric disorders

Authors	Disorders	Patient/Control	Methods
Li et al. (2002)	AD, MCI	10AD/5MCI/9NC	COSLOF index
Xu et al. (2008)	AD, MCI	14AD/8MCI/13NC	phase shift index developed from COSLOF index
He et al. (2007c)	AD, early	15/15	ReHo
Bai et al. (2008)	**aMCI**	**20/20**	**ReHo**
Liu et al. (2006)	schizophrneia	18/18	ReHo
Hoptman et al. (2009)	**Schizophrenia**	**29/26**	**ALFF and fALFF**
Maxim et al. (2005)	AD	9/12	Wavelet-based maximum likelihood of fractional Gaussian noise

AD Alzheimer's disease, *ALFF* amplitude of low-frequency fluctuations, *aMCI* amnestic type mild cognitive impairment, *COSLOF* cross-correlation coefficients of spontaneous low frequency, *fALFF* frational ALFF, *MCI* mild cognitive impairment, *NC* normal controls, *ReHo* Regional homogeneity

Furthermore, in order to cancel the effect of the signal-to-noise ratio on the COSLOF index, the same group developed a phase shift index (PSI) method, which computes the ratio of the cross-correlation coefficient to the maximum-shifted cross-correlation coefficient, and thus provides an accurate measure of the phase shift between SLFF components (Xu et al. 2008). Using these methods, the group separately demonstrated a parametric reduction in the COSLOF index and a parametric increase in the PSI within the hippocampus from controls to patients with mild cognitive impairment (MCI)(a transitional stage between normal aging and AD) to AD patients, suggesting that the synchrony of SLFF components of the hippocampus deteriorates along a continuum from normal synchrony through mild asynchrony in MCI to severe asynchrony in AD (Li et al. 2002; Xu et al. 2008). Additionally, they found that an exponential curve could describe the relationship between the COSLOF index and Mini-Mental Status Examination (MMSE) scores, which indicated a rapid decrease in cognitive capacity in AD (Li et al. 2002). These studies indicate that the cross-correlation coefficients of SLFF could be regarded as quantitative markers for the early diagnosis of AD.

Regional homogeneity (ReHo): The ReHo method, based on the assumption that the activity of a given voxel is temporally similar to its neighbors (Zang et al. 2004), is now considered to be an useful alternative for measuring regional coherence in spontaneous activity. Basically, it measures regional connectivity by estimating Kendall's coefficient of concordance between neighboring voxels and offers a fast mapping of the regional homogeneity of brain activity across the whole brain (Kiviniemi 2008).

In schizophrenia, a decreased ReHo has been found to be widely distributed over the bilateral frontal, temporal, occipital, cerebellar posterior, right parietal and left limbic regions (Liu et al. 2006), a result which is similar to what has been found in previous resting-state electroencephalograph (Pascual-Marqui et al. 1999), PET (Levy et al. 1992) and single photon emission computed tomography studies (Catafau et al. 1994).

Both in AD and amnestic type mild cognitive impairment (aMCI), significantly decreased regional coherence, along with some compensatorily increased regional coherence, was found in the posterior cingulate cortex/precuneus (PCC/PCu) (He et al. 2007c; Bai et al. 2008), in which a resting hypometabolism has been commonly detected in previous PET studies of early AD. In addition, the decrease in the PCC/PCu coherence was found to be significantly correlated with disease progression, as measured by MMSE scores. More importantly, these findings remained significant even when controlled for regional PCC/PCu atrophy (He et al. 2007c).

The power spectrum analysis

Biswal et al. (1995) and Zang et al. (2007) suggested that the amplitude of low-frequency fluctuations (ALFF) could partially indicate regional spontaneous neuronal activity. Therefore, regional spontaneous activity could also be measured using a power spectrum method based on the ALFF (Zang et al. 2007) and its improved approach, i.e. fractional ALFF (fALFF) (Zou et al. 2008). Yang and colleagues (2007) compared the ALFF during eyes-open and eyes-closed in a resting-state and found an increased ALFF in the visual cortex and a decreased ALFF in the paracentral lobule Yang et al. (2007). A recent study using a multitaper spectral estimation found that the power spectral density of regional signals can identify changes in the oscillatory dynamics across conditions, and could characterize the nature and spatial extent of signal changes underlying changes in functional connectivity (Duff et al. 2008). In disease condition, by measuring the ALFF and fALFF, Hoptman et al. 2010 ave found reduced spontaneous neuronal activity in regions which show deficits in motor and low level sensory processing (the right

precentral gyrus and lingular gyrus etc.) and show deficits in reward sensitivity (the right striatum), and increased activity in regions relevant to internally directed thought such as the medial frontal cortex and the hippocampus/parahippocampus in schizophrenia.

In addition to amplitude, other signatures of the power spectrum distribution, such as the f^{-a} characteristic, have also been used to measure the local spontaneous dynamics. From the power spectral factor f^{-a}, the fractal dimension D_f ($D_f = (3\text{-}a)/2$) and the Hurst exponent (H) ($H = 2\text{-}D_f$) of a given signal can be estimated (Bullmore et al. 2004). The Hurst exponent of the resting-state fMRI has been found to be sensitive to an acute pharmacological challenge (Wink et al. 2006) and to the pathological changes of AD (Maxim et al. 2005). Because spontaneous activity may have too complex a behavior to be adequately described by a single scaling exponent, multifractal formalism, in which the local scaling behavior in the neighborhood of a singularity is characterized by the Hölder exponent, has also been used to measure endogenous spontaneous fluctuations (Wink et al. 2008). Their results also revealed that the latency of response in a fame decision/facial encoding task was negatively correlated with the Hölder exponents of the preceding resting-state signals, indicating that the Hölder exponents are relevant to neurocognitive functions (Wink et al. 2008). The multifractal properties of spontaneous activity may add valuable information for the marker of pathophysiological deterioration in diseases, an area which, of course, needs further studies.

Other methods also could be used to study altered spontaneous activity during the resting-state in neuropsychiatric disease, such as regional temporospatial clustering analysis that is a combined measurement for both the temporal and the spatial patterns of the spontaneous fluctuations (Hunter et al. 2006; Wang et al. 2008b). Using this method, well-organized spontaneous activity that is distinctly clustered both temporally and spatially has be found in the auditory cortex (Hunter et al. 2006) and the visual cortex (Wang et al. 2008b).

Spatial pattern analysis

Correlation or coherence of brain region activity is often thought to reflect functional integration. Resting-state functional connectivity (rsFC) analysis and independent component analysis (ICA) are two main methods of analysis that can be used to investigate the spatial pattern of spontaneous activity on a global level during rest. Both of them process information from time domain. Frequency-specific functional connectivity measures, which allow the patterns of co-variability between brain areas occurring in different time scales to be described, have also been used (Salvador et al. 2007; Salvador et al. 2008).

Conventional rsFC measures correlations between a reference time series and another time series (Friston et al. 1993). Using this method, fMRI studies have demonstrated that spontaneous BOLD fluctuations are coherent within specific neuro-anatomical systems, such as primary motor (Biswal et al. 1995; Lowe et al. 1998; Cordes et al. 2001; Jiang et al. 2004), auditory (Cordes et al. 2001), visual cortices (Lowe et al. 1998; Nir et al. 2006), language (Hampson et al. 2002) and limbic systems (Stein et al. 2000; Greicius et al. 2003; Rombouts et al. 2003; He et al. 2004; Fox et al. 2005; Wink et al. 2006) in healthy subjects. The FC analysis can be divided into three categories: rsFC based on individual regions of interest (ROI), rsFC based on multiple ROIs, and rsFC based on whole brain regions.

The ICA is another commonly used method for identifying spatial patterns in resting-state fMRI data (Calhoun et al. 2001; Greicius et al. 2003; Kiviniemi et al. 2003; van de Ven et al. 2004; Bartels and Zeki 2005). Unlike traditional FC analysis, ICA is a data-driven method that decomposes the data into statistically independent components. Such decompositions are very useful because they allow for separation into different coherent resting networks and separate these networks from other effects such as head motion or other physiological confounds (such as cardiac pulsation or the respiratory cycle). The conventional ICA method can only be used for a single subject. Recently, methods for investigating coherent signals at a group level, such as group ICA (Calhoun et al. 2001) and tensor probabilistic ICA (tensor-PICA) (Beckmann et al. 2005; Beckmann and Smith 2005; De Luca et al. 2006), have been proposed. These methods simultaneously decomposes group fMRI data into modes describing variations across space, time, and subjects. It has been demonstrated that these methods can provide useful representations of group fMRI data in resting-state studies (Damoiseaux et al. 2006; Fransson et al. 2007; Jafri et al. 2008).

Although the two methods each have their pros and cons (Fox et al. 2007), both of them are widely used in resting-state fMRI studies of neuropsychiatric disorders. Additionally, some findings using the two methods have yielded consistent results. But some inconsistent results have been reported. In the following section, we will comprehensively review the progress obtained by using each of the two methods from individual ROI analysis, to local network analysis, to whole brain network analysis (Table 2 and Table 3).

Individual ROI analysis and progress in understanding neuropsychiatric disorders

RsFC based on a single ROI is the most common method for investigating resting-state functionality in neuropsychiatric disorders. The key point of this method is to select

Table 2 Methods for investigating spatial patterns of SLFFs and topological properties of brain networks and progress in understanding Alzheimer's disease

Authors	Character of disorders	Patient/Control subjects	Methods
Allen et al. (2007)	AD, probable	8/8	Correlation analysis of individual ROI
Bai et al. (2009)	**aMCI**	**30/26**	**Correlation analysis of individual ROI**
Sheline et al. (2010)	**AD, early**	**35/20(PIB+)/48(PIB−)**	**Correlation analysis of individual ROI**
Wang et al. (2006b)	AD, early	13/13	Correlation analysis of individual ROI
Zhang et al. (2009)	AD, mild	16/16	Correlation analysis of individual ROI
Wang et al. (2007)	AD, early	14/14	Correlation analysis of the whole brain and of individual ROI
Sorg et al. (2007)	aMCI	24/16	ICA, correlation analysis of individual ROI, structure
Qi et al. (2009)	aMCI	14/14	ICA
Zhou et al. (2010)	**AD**	**12AD/12 patients with frontotemporal dementia/12NC**	**ICA**
Supekar et al. (2008)	AD	21/18	Complex network analysis

ICA independent component analysis, *ROI* region of interest, *PIB+* healthy controls with brain amyloid deposition, *PIB−* healthy controls without brain amyloid deposition. The others, please see Table 1

an appropriate region as ROI. An ideal ROI should satisfy the following criteria: (1) implicated in a pathological lesion or cognitive dysfunction associated with the brain disorder to be investigated; (2) demonstrated as a local abnormality in anatomy or function in a previous study. Using rsFCs based on an individual ROI has led to some interesting findings for various neuropsychiatric disorders as reviewed below.

AD: Two regions in the default mode network (DMN), the hippocampus and the posterior cingulate cortex (PCC), have attracted the most attention due to their roles in memory and their morphologic and metabolic abnormalities in AD patients (Buckner et al. 2008). As a core region in the DMN (this network is also called the task-negative network, TNN), the PCC showed decreased correlations with other regions in the same network and decreased anti-correlations with regions in the task-positive network (TPN), which is anti-correlated with the TNN, in early AD compared to healthy controls (Wang et al. 2007). In mild AD patients, besides decreased connectivity in the DMN, the increased connectivity between the PCC and prefrontal regions were also found, which suggests the compensatory-recruitment in early stage of AD (Zhang et al. 2009). The recruitment of compensatory mechanisms was further validated in aMCI, a syndrome that carries a high risk for developing AD, with the decreased connectivity between the PCC and the temporal cortex and the increased connectivity between the PCC and the regions in the frontal cortex in these patients (Bai et al. 2009). While the PCu, a region adjacent to the PCC and also located in the DMN, was selected as seed region, the altered FC between the posterior and anterior portions of the DMN was found again (Sheline et al. 2010). More importantly, compared to the cognitively normal elderly without brain amyloid deposition, the cognitively normal elderly with brain amyloid deposition show the same difference pattern (the same regions and the same direction) as that found in the AD group (Sheline et al. 2010).

Additionally, two other recent studies (Wang et al. 2006b; Allen et al. 2007) independently investigated the hippocampal rsFC pattern in AD. Both of the studies found that the hippocampus exhibited disrupted rsFCs with extensive regions, including the PCC/PCu. However, Wang and coworkers (Wang et al. 2006b) also found increased rsFCs between the left hippocampus and the right lateral prefrontal cortex, which was absent in Allen's study (Allen et al. 2007). The differences in results between the two studies likely arose from differences in the ROIs that were selected, from differences in disease severity (Allen et al. 2007) and from differences between the sample subjects (for a review, see Liu et al. 2008b). In a recent study, healthy subjects exhibited differences in rsFC patterns between the anterior hippocampus and the posterior portion, including the body of the hippocampus and the posterior parahippocampus (Kahn et al. 2008). Subtle differences in anterior-posterior hippocampal rsFCs may account for the differences in the two studies, which selected different subregions of the hippocampus as ROIs.

All o f these studies suggest that the rsFC of the DMN region may be an indicator of time course of neuronal function and disease development in AD. Longitudinal studies with large sample would be necessary to validate this speculation. Expecting findings would be revealed with the recruitment of rsFC into the future Alzheimer's Disease

Table 3 Methods for investigating spatial patterns of SLFFs and topological properties of brain networks and progress in understanding schizophrenia

Authors	Character of disorders	Patient/Control subjects	Methods
Bluhm et al. (2007)	Schizophrenia, chronic and medicated	17/17	Correlation analysis of individual ROI
Zhou et al. (2007a)	Schizophrenia, first-episode	17/17	Correlation analysis of individual ROI
Zhou et al. (2008)	Schizophrenia, paranoid	17/14	Correlation analysis of individual ROI, DTI
Bluhm et al. (2009)	**Schizophrenia**	**17/17**	**Correlation analysis of individual ROI**
Hoptman et al. (2009)	**Schizophrenia**	**25/21**	**Correlation analysis of individual ROI**
Whitfield-Gabrieli et al. (2009)	Schizophrenia	13SCH/13 nonpsychotic first-level relatives/13NC	Correlation analysis of individula ROI
Ke et al. (2010)	**Schizophrenia**	**32/16**	**Correlation analysis of individula ROI**
Lui et al. (2009)	**Schizophrenia, antipsychotic-naive first-episode**	**68/68**	**Correlation analysis of individula ROI, structual MRI**
Zhou et al. (2007b)	Schizophrenia, paranoid	18/18	Correlation analysis of multiple ROI
Gavrilescu et al. (2010)	**Schizophrenia, AH**	**27(14 with AH, 13 without AH)/16**	**Correlation analysis of multiple ROI**
Vercammen et al. (2010a)	**Schizophrenia, AH**	**27/27**	**Correlation analysis of multiple ROI**
Vercammen et al. (2010b)	**Schizophrenia, AH**	**18/0**	**Correlation analysis of multiple ROI, rTMS**
Liu (2010)	**Schizophrenia**	**25SCH/25 unaffected siblings/25NC**	**Correlation analysis of multiple ROI**
Skudlarski et al. (2010)	**Schizophrenia,**	**27/27**	**Correlation analysis of multiple ROI, K-means network analysis, DTI**
Garrity et al. (2007)	Schizophrenia	21/22	ICA
Calhoun et al. (2008b)	Schizophrenia, chronic	20/20	ICA
Jafri et al. (2008)	Schizophrenia	29/25	ICA
Camchong et al. (2009)	**Schizophrenia, chronic**	**29/29**	**ICA, DTI**
Ongur et al. (2010)	**Schizophrenia**	**14SCH/17 patients with bipolar disorder/15NC**	**ICA**
Rotarska-Jagiela et al. (2010)	**Schizophrenia, paranoid**	**16/16**	**ICA**
Mannell et al. (2010)	**Schizophrenia**	**15/15**	**ICA and correlation analysis of individual ROI**
Salvador et al. (2007)	Schizophrenia	35/28	Mutual information measures
Liang et al. (2006b)	Schizophrenia	15/15	Correlation analysis of the whole brain (116 regions)
Liang et al. (2006a)	Schizophrenia	15/15	Complex network analysis
Liu et al. (2008a, b)	Schizophrenia	30/30	Correlation analysis of the whole brain (116 regions) and complex network analysis
Lynall et al. (2010)	**Schizophrenia, chronic**	**15/12**	**Correlation analysis of the whole brain (72 regions) and complex network analysis based on wavelet correlation and mutual information**

AH auditory hallucinations, *SCH* schizophrenia. The others, please see Table 1 and 2

Neuroimaging Initiative (ADNI) protocol (Jack et al. 2010).

Schizophrenia: The dorsolateral prefrontal cortex (DLPFC), because of its local abnormalities in anatomy and function (Bunney and Bunney 2000) and its role in various neural circuits relevant to the anatomical and physiological mechanisms of cognitive dysfunction in schizophrenia, has firstly attracted the attention of researchers. By examining the FC pattern of DLPFC in patients with first-episode schizophrenia and matched controls, the researchers from our laboratory found that the DLPFC exhibited decreased rsFC with the PCC, among other regions (Zhou et al. 2007a). In a followed study, the rsFC related to the DLPFC showed different asymmetry

pattern in predominantly positive and predominantly negative schizophrenia (Ke et al. 2010). However, in a relative large sample of antipsychotic-naive first-episode schizophrenia patients, the altered rsFC related to the DLPFC was not found under a strict multiple comparison threshold (Lui et al. 2009). In fact, in this study, no regions of identified gray matter deficits showed differences in the rsFC pattern between the patients and the normal controls. But the functional networks involving the right superior temporal gyrus and middle temporal gyrus were found to be related with clinical symptom severity (Lui et al. 2009).

Because the regions and functions of the DMN have been linked with schizophrenia, the PCC, as a core region in this network, was selected as the ROI to compare the SLFF pattern of chronic, medicated schizophrenic patients with that of control subjects (Bluhm et al. 2007). The PCC was found to show decreased rsFCs in regions associated with the DMN including the PCC, lateral parietal, medial prefrontal cortex (MPFC) and cerebellar regions in chronic, medicated schizophrenic patients (Bluhm et al. 2007). By selecting the retrosplenial cortex as the ROI, the same group replicated the decreased rsFCs within the DMN (Bluhm et al. 2009). Considering that the hippocampus has been implicated as participating in the pathophysiology of schizophrenia, the FC pattern of the anterior hippocampus was also investigated. In patients with schizophrenia, the bilateral hippocampi showed reduced rsFCs to some regions which have been reported to be involved in episodic memory, such as the PCC, the extrastriate cortex, the MPFC, and the parahippocampal gyrus, which may reflect the disconnectivity within a neural network related to the anterior hippocampus in schizophrenia (Zhou et al. 2008).

Except the DLPFC and the DMN regions, the amygdalar/ventral prefrontal cortex (vPFC) circuitry also attract attention of researchers, due to its role in social processing and cognition, which are particularly associated with functional impairments in schizophrenia. The significant reductions in FC between amygdala and vPFC regions supported the speculation of these researchers. And the strength of this connectivity showed a significant inverse relationship with levels of self-rated aggression in patients. This is consistent with the role of amygdalar/vPFC circuitry in the suppression of impulsive/aggressive behaviors and the increased levels of aggression in schizophrenia (Hoptman et al. 2009).

Comments on this method: FC based on an individual ROI can easily be performed and can provide distinct information on specific regions implicated in neuropsychiatric disorders. However, limitations of this method need to be kept in mind. The method strongly depends on prior knowledge about the related disorders. In published studies, the ROI was selected according to the researchers' interest and outlined by hand (Wang et al. 2006b; Allen et al. 2007; Zhou et al. 2008) selected by software (Wang et al. 2007; Zhou et al. 2007a) or identified by known coordinates (Bluhm et al. 2007; Castellanos et al. 2008) This subjectivity in ROI selection has lead to slight differences in the anatomical location of the ROIs, which led to differences in the ROI FC patterns, as we noted in the case of the discrepancy in the hippocampal FC in AD (Wang et al. 2006b; Allen et al. 2007). More deeply, the differences in the anatomical location of the ROIs may be a reflective of the variability in the neuronal composition of the ROIs. For example, the ROI with greater GABAergic tonic firing might show a change in the BOLD signal due to the changed metabolic demand or reduced net spike activity by the inhibitor synaptic activity, than that with less GABAergic tonic firing (Arthurs and Boniface 2002), and thus lead to differences in the ROI FC patterns. In addition, information outside the functional connectivity pattern of a specific ROI cannot be obtained by this method.

Local network analyses and progress in understanding neuropsychiatric disorders

As mentioned above, brain circuits or networks have often been implicated in major neuropsychiatric disorders (Friston 1998; Delbeuck et al. 2003; Just et al. 2004; Sonuga-Barke and Castellanos 2007; Drevets et al. 2008), thus the investigation of rsFC within a specific network may improve our understanding of the neural basis of these disorders. This is supported by findings that have revealed the presence of a number of resting-state brain networks, such as the DMN (e.g. TNN) (Greicius et al. 2003; Fox et al. 2005; Fransson 2005), the TPN (Fox et al. 2005; Fransson 2005), and the dorsal and ventral attention networks (Fox et al. 2006a) in healthy subjects. Additionally, these networks are known to be related to emotion, memory, attention, and other high brain functions, which have often been observed to be impaired in neuropsychiatric disorders.

AD: Using ICA to isolate the DMN during a simple sensory-motor task, Greicius et al. (2004) found decreased connectivity within the DMN in an AD group, which is consistent with findings from rsFC based on individual ROIs (Wang et al. 2006b; Allen et al. 2007; Wang et al. 2007). By applying ICA and ROI-based FC analysis, Sorg et al.2007 further found that the patients with aMCI, demonstrated reduced network-related activity in selected areas of the DMN (left PCC and right MPFC). However, a recent study also found increased activty in the DMN mainly involving the frontal-parietal regions, further supporting the compensatory effect to cognitive deficit which was suggested by the decreased activity in the medial temporal lobes and PCC in aMCI (Qi et al. 2009).

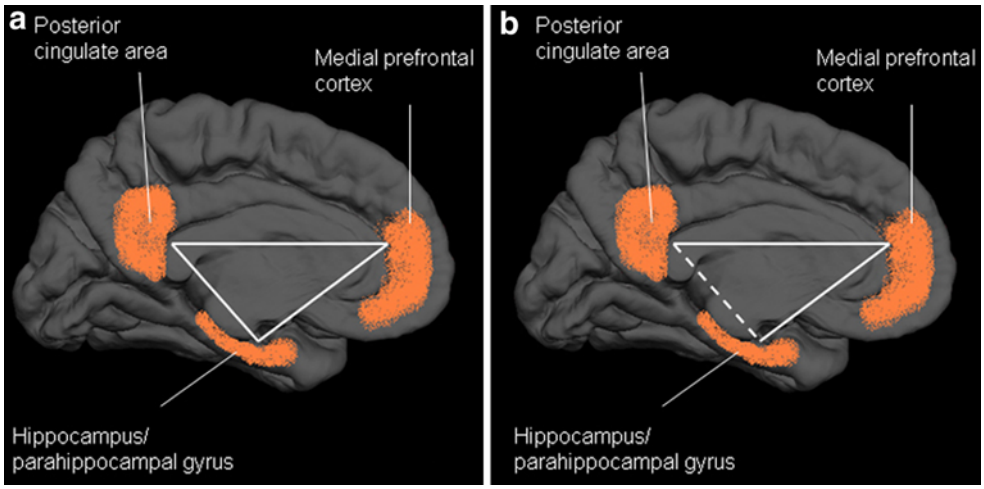

Fig. 1 Altered functional connectivities in the default mode network in Alzheimer's disease. **a** The core brain regions in the default mode network in healthy subjects are illustrated schematically. Prominent components of this network include medial prefrontal regions, posterior regions in the medial and lateral parietal cortex, the lateral temporal cortex and the medial temporal lobe (including the hippocampus and parahippocampal gyrus). Regions within this core brain system are functionally correlated with each other and, prominently, with the hippocampal formation. The solid line represents the correlations between the core regions. **b** The functional connectivity between the hippocampal formation and the medial posterior regions were consistently found to be decreased or absent in patients with Alzheimer's disease (for references, please see the main text). The dashed line represents decreased or absent correlations between the hippocampus/parahippocampal gyrus and the posterior cingulate area

Although the abnormality in the DMN need further to be investigated, these studies strongly indicated that disconnection in the DMN may be a distinctive characteristic of AD (Fig. 1).

In addition to the DMN, Sorg et al. found the executive attention network to be affected, but the remaining resting networks to be intact, in individuals at high risk for AD. The reduced network-related activity in the executive attention network is in line with observed attentional deficits in MCI and AD, indicating impaired interaction between the two anti-correlated networks (TPN and TNN) that prominently organize intrinsic brain activity (Sorg et al. 2007). Additionally, in a recent study, both the increased FC within the salience network, which is anti-correlated with the DMN and a part of the TPN, and the decreased FC within the DMN were found in AD. These alterations were considered as compatible with the symptom-deficit profiles of AD with undermining visuospatial skills and preserving or enhancing social-emotional function, and perfectly differentiated patients with AD from those with frontotemporal dementia, who showed inverse symptom-deficit profiles (Zhou et al. 2010).

Schizophrenia: Given the relevance of the functions of DMN and its anti-correlated TPN to schizophrenia, there has been increasing interest in the role that altered connectivity of these networks may play in the disease (Williamson 2007; Broyd et al. 2009). The DMN are relevant to internally generated stimulus-independent thoughts, self-monitoring, and baseline monitoring of the external world, while the TPN supports active exploration of the external world. The proper communication and coordination between these two intrinsic anti-correlated networks is thought to be crucial for optimal information integration and cognitive functioning (Buckner et al. 2008). In schizophrenia, some symptoms may stem from the failure to differentiating between internal and external sources of information, such as hallucinations (Williamson 2007). And one of the core symptoms of schizophrenia, cognitive deficits (such as impaired working memory, attention allocation, and central executive function), may be the reflection of impaired functions ascribed to the TPN (Corbetta and Shulman 2002). Thus, examining the connectivity and coordination of both the anti-correlated intrinsic networks may improve our understanding of their roles in schizophrenia susceptibility and pathophysiology.

Aberrant FC within the DMN has been observed in schizophrenia using ICA, demonstrating increased activity in the ACC/MPFC, the parahippocampus and the PCC in patients, and the aberrant FC was correlated with severity of positive symptoms (Garrity et al. 2007). These researchers also found that patients with schizophrenia showed significantly more high-frequency fluctuations and controls showed significantly more low-frequency fluctuations in the DMN (Garrity et al. 2007). This pattern was validated and extended to the rest of the resting-state networks in a later study (Calhoun et al. 2008b). But, the DMN abnormalities in patients with schizophrenia was different form those in the patients with bipolar disorder (Ongur et al. 2010). By

directly investigating the interregional rsFCs among the regions constituting the DMN, increased rsFCs within this network were also observed in schizophrenia (Zhou et al. 2007b). The FCs, that primarily increased within the TPN, as well as increased anti-correlations between the two networks were also found in this disease (Zhou et al. 2007b). Another study that has examined the mean correlation strength between the DMN and TPN found increased connectivites between these anti-correlated network in schizophrenia during rest (Jafri et al. 2008). Combined these findings with those obtained from individual ROI FC analysis, the connectivity pattern within the DMN seems complex. That is, both increased and decreased connectivity were observed in schizophrenia. A more complex connectivity pattern of both decreased frontal connectivity and increased posterior connectivity in the DMN was recently found in the same group of schizophrenia both by ICA and ROI-based FC analysis (Mannell et al. 2010).

The inconsistency and complexity to date of DMN findings in schizophrenia urge investigators to include the unaffected relatives of patients in order to elucidate the connectivity changes that are primary to schizophrenia and those associated with illness risk. The hyperconnectivity within the TNN were further supported by a recent study in which schizophrenic patients and their unaffected first-degree relatives demonstrated both hyperactivity and hyperconnectivity of the default network, and these abnormalities were correlated with psychopathology and working memory deficits (Whitfield-Gabrieli et al. 2009). Furthermore, although the unaffected siblings shared increased resting-state functional connectivity within the DMN with their matched schizophrenic patients, the anti-correlation between the DMN and TPN was unchanged in the siblings (Liu et al. 2010).

Although there is inconsistency in the abnormal pattern of the DMN and its anti-correlated network, all these findings point to the direction that these altered connectivities may contribute to the pathophysiology of schizophrenia and may serve as a marker of the development of the illness. Further studies require to recruit the unmedicated patients with homogenous clinical profile to reduce the confounding factors and differentiate the differences of connectivity pattern within the the DMN and its anti-correlated network in different patient population.

In addition to the TPN and DMN, the frontostriatal circuit is another candidate network worthy to be investigate using rs-fMRI in schizophrenia. This circuit not only is the anatomical basis of executive, social and motive behavior in human (Masterman and Cummings 1997; Bonelli and Cummings 2007), but also has been implicated in schizophrenia (Tekin and Cummings 2002; Bonelli and Cummings 2007). Up to data, there is one study focusing on the resting-state connectivities among three main components of the frontostriatal circuit (DLPFC, the basal ganglia, and the thalami) in schizophrenia (Salvador et al. 2007). In this study, using a method measuring mutual information, the increased connectivity between the DLPFC and the basal ganglia in schizophrenia were consistently found across low, medium and high frequency bands (Salvador et al. 2007). The finding provides new evidence to the dysfunctions in the frontostriatal loop in patients with schizophrenia, and suggests a need to validate this finding using different methods in future.

Additionally, some investigators begin to investigate the relationship between the specific symptom or psychopathology and rsFC. By ICA to isolate the networks involving in neuropsychological models of psychosis, Rotarska-Jagiela et al. comprehensively investigated the the neural correlates of individual psychopathology in patients with paranoid schizophrenia. In the patients, they found that the aberrant functional connectivity in the DMN was correlated with severity of hallucinations and delusions, decreased hemispheric separation of fronto-parietal activity was correlated with disorganization symptoms, and the rsFCs of fronto-temporal and auditory networks were correlated with, the severity of positive symptoms. Finally, the DMN and auditory networks showed increased spectral power of low frequency oscillations, which correlated with positive symptom severity (Rotarska-Jagiela et al. 2010). These results suggest that psychopathology is associated with aberrant intrinsic organization of functional brain networks in schizophrenia. Moreover, auditory hallucinations (AH), as a hallmark symptom in psychosis, become a hot topic in this field and attract investigators to study its neural basis using rs-fMRI. Gavrilescu et al., found that interhemispheric connectivity of both primary (A1) and secondary (A2) auditory cortices were decreased in schizophrenic patients with AH when compared with non-AH patients and healthy controls, whilst the latter two groups did not show any differences in functional connectivity. These findings suggest a disruption of the integration of multiple auditory functions (basic and higher order) in AH patients (Gavrilescu et al. 2010). Another study group focused on a network which is composed of regions known to be involved in (inner) speech processing and verbal thought, encompassing the temporo-parietal junction (TPJ), inferior frontal gyrus (IFG) (consisting of Broca's area and the right hemisphere homotope), anterior cingulate cortex (ACC), amygdala, and insula. By investigating the rsFC between the TPJ, a critical node, and the other regions in this network, they found that the rsFC between the left TPJ and the right homotope of Broca was decreased in schizophrenic patients with chronic hallucinations, and the severity of AH was negatively correlated with the rsFC between the left TPJ and bilateral anterior cingulate and amygdala in these patients (Vercammen et al.

2010a). Furthermore, after a 6-day treatment with repetitive transcranial magnetic stimulation (rTMS) to the left TPJ, both symptom improvement and an increase in connectivity between the left TPJ and the right insula were observed in the group although no corresponding changes were observed in the rsFC previously found to be associated with AH severity (Vercammen et al. 2010b). Together, both of these studies suggest a phenomenon of disconnectivity of the TPJ from brain activity in areas involved in the attribution of agency, self-referent processing, and attentional control, and indicate a modulation effect of rTMS on the rsFC. The endeavorment to unreveal the neural basis of the specific symptom or psychopathology, which is helpful to improve our understanding both to the clinicla profiles of schizophrneia and to the physiology of resting-state networks, will be an important facet in future studies.

Comments on this method: Identification of the affected regions is the primary prerequisite for investigations into the rsFC within a disease-related network. However, determining which regions should be recruited for this purpose is limited by the prior knowledge of the researchers. Although some methods, such as ICA, can greatly reduce the researcher's subjectivity, some key steps, such as deciding on the number of components and determining how to classify each component into noise or physiologically meaningful signals, still depends on the subjective opinions of researchers. This subjectivity leads to differences in the regions that are determined to constitute a network and thus leads to difficulty in comparing results across studies. Furthermore, the functionality and physiological meaning of these resting-state networks need to be further clarified. With this in mind, caution must be exercised in interpreting the findings obtained by comparing the rsFC in the resting-state networks of patients with that of controls.

Whole brain network analyses and progress in understanding neuropsychiatric disorders

In contrast to local network-based interregional FC, which focuses on the FCs associated with a few preselected seed regions within a specific network or circuit while ignoring other potentially interesting patterns of connectivity, whole brain network-based FC analysis can objectively and comprehensively detect altered FCs throughout an entire brain level by automatically dividing the entire brain into multiple regions and performing correlation or partial correlation analysis on each pair of these regions. This method was first used in a single patient who was minimally conscious following a brainstem lesion (Salvador et al. 2005) and then was developed and used in schizophrenia and AD (Liang et al. 2006b; Wang et al. 2007) (Fig. 2).

AD: Wang et al. (2007) found that AD patients show many decreased rsFCs, which are mainly between the prefrontal and parietal lobes, but these patients also show increased rsFCs mainly between regions within lobes, such as within the prefrontal lobe, within the parietal lobe, or within the occipital lobe. These findings are compatible with the anterior–posterior disconnection phenomenon and compensatory effect within lobes observed previously in AD patients (for review, see Liu et al. 2008b). More interestingly, by using whole brain network analysis, the authors also found decreased anti-correlations between the two abovementioned intrinsically anti-correlated networks (TPN and TNN), again suggesting that disturbance of the balance between the intrinsically anti-correlated networks may be associated with attention deficits in AD patients.

Schizophrenia: Liang et al. (2006a) found that in patients with schizophrenia the decreased FCs were widely distributed throughout the entire brain, although most of

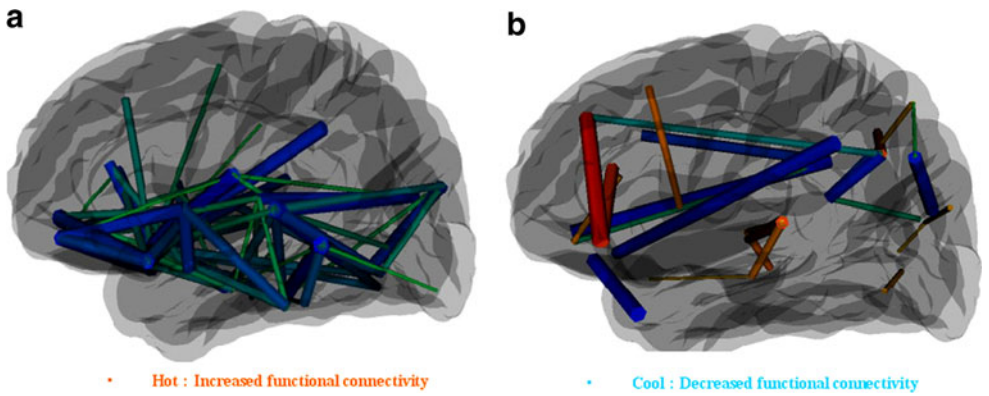

Fig. 2 Altered resting-state functional connectivity in schizophrenia and Alzheimer's disease. **a** Schizophrenia patients mainly showed decreased functional connectivities and such abnormalities were widely distributed throughout the entire brain rather than restricted to a few specific brain regions. **b** Alzheimer's disease mainly showed decreased functional connectivities between the prefrontal and parietal lobes, but increased functional connectivities within the prefrontal lobe, parietal lobe and occipital lobe

them were related to the insula, the temporal lobe (including the medial temporal structures), the prefrontal lobe and the corpus striatum. Increased FCs were mainly related to the cerebellum in patients. Although in this preliminary study, interregional anti-correlation was not considered, which made it difficult to directly compare the distribution of these altered FCs with that in other disorders, this study provides further support for the hypothesis that schizophrenia may arise from the disrupted functional integration of widespread brain areas (Liang et al. 2006b).

Comments on this method: By comparing the global distribution of these altered FCs in different disorders, it is possible to find various disease-related characteristics and thus to differentiate different disorders. However, some issues need to be addressed. First, the findings obtained by this method are affected by anatomical parcellation. Therefore, it is necessary to pay attention to the fact that mapping the resulting whole brain network using different templates may induce different findings (Wang et al. 2008a). Secondly, current automatic registration techniques make it difficult to guarantee the exact match of some small gyri/sulci, especially in the cerebellar lobes, across subjects. Finally, inter-subject variability in the anatomical regions must also be considered carefully in future studies.

In brief, by analyzing the spatial pattern of spontaneous BOLD activity, some disease-related abnormalities can be obtained. Disrupted rsFCs within the DMN, especially those associated with the hippocampus and the PCC, may be a distinctive characteristic of AD (Fig. 2). The regions showing disrupted rsFCs are highly similar to those that show pathology in the early stages of the disease, as measured by molecular imaging of amyloid plaques using PET, and those that are affected by structural atrophy, as measured by longitudinal MRI (Buckner et al. 2008). Decreased rsFCs within the attention related-networks is another consistent finding in AD and is consistent with observed attention deficits in MCI and AD. In schizophrenia, aberrant rsFCs within the DMN are found, but the main difference is that the strength of the rsFCs are abnormally increased in patients. By analyzing the clinical correlates of the strength of the rsFC, the rsFCs associated with the component regions of the DMN are found to vary with positive symptoms measured by different clinical scales (Bluhm et al. 2007; Garrity et al. 2007; Zhou et al. 2008). The positive symptom-dependent correlation of the component region in the DMN suggests that functional dysconnectivity in the DMN may be a reflection of an impaired self-monitoring function in schizophrenia, which could lead to positive symptoms such as hallucinations and delusions (Williamson 2007).

It is noteworthy that not all of these abovementioned findings were obtained in the resting-state. These differences in the studies increase the complexity of interpreting the ways the altered SLFF is manifest in neuropsychiatric disorders. Most of the findings of altered SLFF in neuropsychiatric disorders were obtained during rest, in which the participants were instructed to do and think nothing with their eyes either open or closed; however, some findings are from studies performed during different tasks. In these studies, in order to extract the so-called spontaneous BOLD activity from the task-state time series, some processes can be performed, such as band-filtering data during a simple perceptual task (Greicius et al. 2004), cutting and pasting blocks of rest from within a longer cognitive task (Cherkassky et al. 2006), regressing task-related activation out of a time series and using the residual signal (Andrews-Hanna et al. 2007; He et al. 2007a), or just extracting the resting-state network components from a task time series (Calhoun et al. 2008b). In these studies, the SLFF may be affected by the task, including such activities as rumination on what has been done or anticipation on what to do during the task. Thus inter-group differences may not be attributable to differences in the SLFF but in how the SLFF is altered by task performance (Fair et al. 2007). Thus caution should be taking in comparing these findings with those from studies with rest conditions.

Topological properties of the brain network

Functional segregation and integration are two major organizational principles of the human brain. In other words, an optimally functioning brain requires a suitable balance between local specialization and global integration of brain functional activity (Tononi et al. 1998). Since the seminal research of (Watts and Strogatz 1998) introduced graph theory to the neuroscientific field, investigation of brain activity has put significant emphasis on large-scale functional interactions among different functional brain areas. In a brain network, brain regions are nodes, and connectivities between regions are edges. Eguiluz et al. (2005) were the first to study topological properties of brain networks, including clustering coefficients, path lengths, and degree distributions in relation to fMRI data. Clustering coefficients show the likelihood that neighbors of a vertex will also be connected, and thus reflect functional segregation. Path length is the average of the shortest distance between pairs of vertices counted in number of edges, and thus reflects functional integration. Higher clustering coefficients and shorter absolute path length are characteristic of small-world networks which offer a structural substrate for functional segregation and integration of the brain (Sporns and Zwi 2004). Efficiency provides a vital measure of how well information is transferred over the entire network (Achard and Bullmore 2007). The combination of these factors makes efficient small-world topology an attractive model for understanding the brain functional network.

In the past few years, studies of the patterns of FC (coherence or correlation) among cortical regions using different modern brain imaging techniques, including magnetocencephalography (Stam 2004), electroencelography (Micheloyannis et al. 2006b) and fMRI (Eguiluz et al. 2005; Salvador et al. 2005; Achard et al. 2006), have demonstrated that large-scale human brain networks exhibit efficient small-world architecture. These findings support the presence of a rapid real-time integration of information across segregated sensory brain regions (Sporns and Zwi 2004), conferring resilience against pathological attack (Achard et al. 2006) and maximizing efficiency at a minimal cost for effective information processing between different brain regions (Achard and Bullmore 2007). In addition, this pattern has been found to have a large degree of topological similarity with the organization of large-scale structural networks of the human brain and some animal brains (Sporns and Zwi 2004; Sporns et al. 2005; Sporns 2006; Sporns and Honey 2006; He et al. 2007b), possibly reflecting the underlying structural organization of functional connections. More importantly, these topological properties have also been used to characterize the pathophysiological changes in normal aging (Achard and Bullmore 2007) and in neuropsychiatric disorders, such as schizophrenia (Liang et al. 2006b; Micheloyannis et al. 2006a; Rubinov et al. 2007; Bassett et al. 2008; Liu et al. 2008a) and AD (Stam et al. 2007; Supekar et al. 2008). These findings from different brain imaging techniques reveal disease-related deviations in functional network topological properties from the optimal small-world architecture.

In the case of resting-state fMRI studies), Liu and colleagues (Liu et al. 2008a) demonstrated that the efficient small-world topological properties were significantly disrupted, especially in the prefrontal, parietal and temporal cortex regions in patients with schizophrenia, a finding consistent with a preliminary study (Liang et al. 2006a). This disruption may partially account for the reduced global/local efficiency of information processing within the brain, which may lead to the deficits of cognition and behavior of patients with schizophrenia. Additionally, these altered topological measurements negatively correlate with illness duration in schizophrenia, suggesting that these topological measurement will be further disrupted as the condition deterioates These findings are validated in a recent study with chronic schizophrenic patients, in which the disrupted and diverse functional network as well as the correlation between the behavior performance of a verbal fluence tasck and the functiona connectivities and topological measurements were found in these chronic patients (Lynall et al. 2010). These studies provide supporting evidence that schizophrenia is a disconnection syndrome from the perspecyive of brain network. Using the same method as Achard and colleagues (Achard et al. 2006), Supekar and colleagues (Supekar et al. 2008) have demonstrated that resting-state fMRI-derived functional brain networks in AD show a loss of small-world properties. In contrast to a previous EEG study (Stam et al. 2007) and a structural MRI study (He et al. 2008), Supekar and colleagues (2008) found that the loss of small-world properties in AD were characterized by a significantly lower clustering coefficient. This may indicate a disrupted local connectivity, not a significantly longer path length as the earlier two studies reported.

As a new study hotspot, these detected changes in the topological properties of the brain network in neuropsychiatric disorders need to be validated in future studies.

Functional connectivity and structural connectivity

Because of the similarity between the functional organization, revealed by spontaneous BOLD activity, and anatomical organization, structural–functional connectivity has become a hot topic in this field. In preliminary studies, interhemispheric FC has been found to be reduced in patients with agenesis of the corpus callosum (Quigley et al. 2003) or multiple sclerosis (Lowe et al. 2002), findings which suggest that reduced structural connectivity is related to a reduction in spontaneous BOLD activity. Recently, advances in diffusion tensor imaging (DTI) techniques have provided an opportunity to measure structural connectivity by analyzing local white matter attributes or by more directly tracking the fiber tracts linking cortical regions of interest. From the perspective of network, the shared "small-world" topologies and hub nodes between the functional network and anatomical network derived from diffusion MRI further suggest the close coupling between functional connectivity and structural connectivity (Achard et al. 2006; Hagmann et al. 2008; Iturria-Medina et al. 2008; Gong et al. 2009). By combining diffusion MRI and fMRI, it is promising to provide an attractive perspective for interpreting the spontaneous BOLD activity. Along this line, correspondence between structural connectivity and functional connectivity in healthy subjects has been observed in regions linked by white matter fibers, such as adjacent gyri (Koch et al. 2002), the DMN (Greicius et al. 2008), and the cerebral cortex (Hagmann et al. 2008; Honey et al. 2009). However, the relationship between structural and functional connectivity seems complicated. By investigating macaque neocortex and healthy human cortex, investigators found that the strength, persistence, and spatial statistics of rsFC are constrained by the large-scale anatomical structure of the cerebral cortex, although the rsFC is variable and is frequently present between regions without direct structural linkage (Honey et al. 2007, 2009).

Researchers have also begun to seek to understand the neurobiological infrastructure of aberrant functional connectivities in neuropsychiatric disorders by combining diffusion MRI and fMRI. In patients with schizophrenia, a reduced hippocampal rsFC and a reduced integrity of the fornix (the major fiber bundle linking the hippocampus and other brain regions) was found in the same patients (Zhou et al. 2008). And both the decreased rsFCs within the DMN, especially altered conenctivities in the MPFC, and reduced integrity of the anterior cingulate bundle were found in chronic schizophrenia patients (Camchong et al. 2009). The convergent fMRI and DTI findings support the internal consistency between the anatomical and functional connectivity, but direct correlations between fMRI and DTI measures were not found (Zhou et al. 2008) or not investigated (Camchong et al. 2009). In order to directly measure the spatial correlation between the structural connectivity and functional connectivity, Skudlarski et al. (2010) used the similarities in the connectivity matrices obtained from the DTI and rs-fMRI to investigate the spatial coherence from the global, regional, voxel and network level. The global tests of mean connectivity showed that, compared to healthy controls, schizophrenia patients exhibit decreased anatomical connectivity and decoupling between anatomical and functional connectivities due to the coexistence of decreased and increased functional connectivities. These findings were confirmed by inter-regional connectivity analysis and regional maps, localizing the decoupling to networks originating in the PCC. Further network analysis showed that schizophrenia-related alterations affected the frontoparietal portions of the DMN (Skudlarski et al. 2010). Taken together, these studies suggest a complex relationship between the structural connectivity and functional connectivity. That is, the damaged structural connectivity is not necessarily companied with the decreased functional connectivity.

One of the reasons that the structural dysconnectivity cannot completely predict functional dysconnectivity may be due to the existence of polysynaptic pathways, which makes it difficult to measure the direct anatomical connections but not affect to the detection of BOLD correlations between regions, and thus explains the phenomenon that there is BOLD correlations between regions that have no direct anatomical connections, as observed in the visual system of anaesthetized macaque monkeys (Vincent et al. 2007). On the other hand, the technique issues, such as resolving crossing fibers (particularly in DTI), the detection of relatively small fiber bundles running perpendicular to major fasciculi, and the reliable detection of very long fiber bundles in diffusion MRI (Honey et al. 2009), as well as susceptibility artifacts and the confounding factors from vascular, respiratory, and preprocessing artifacts on the BOLD signal in fMRI (Honey et al. 2009), enhance the difficulty and complexity to link the structural conenctivity and functional connectivity.

Pilot studies of SLFF as a brain imaging biomarker

Possibility of SLFF as a brain imaging biomarker

A biomarker is a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention (Shaw et al. 2007). Based on the criteria of an ideal biomarker (Growdon et al. 1998), we think that an ideal brain imaging biomarker should be: (1) linked to fundamental features of neuropathology of neuropsychiatric disorders, (2) validated in neuropathologically confirmed cases, (3) able to detect the brain disorder early in its course and distinguish it from other disorders, (4) non-invasive, simple to use and inexpensive. Good biomarkers also need to be sensitive and specific. Some pilot studies have made advances in this direction.

Pilot studies of SLFF as a brain imaging biomarker on neuropsychiatric disorders

As mentioned above, much work has been carried out to evaluate the altered activity pattern of SLFF in patients with neurological or psychiatric disease. Essentially, these are individual voxel-based or individual ROI-based studies which use measurements of the voxel or region as independent variables and compare differences in these independent variables between groups. These studies have provided some preliminary evidence for activity patterns of SLFF as potential neuroimaging biomarkers for neurological and psychiatric diseases.

There is another type of study, i.e. multi-variant analysis, which analyzes patterns of spatial distribution of multiple measurements over multiple voxels or regions, and integrates them into a single score that can be used to discriminate patients from normal controls. In contrast to the individual voxel-based or individual ROI-based studies, the multi-variant analysis focuses on multiple voxels or regions at once and can provide a perspective for investigating patterns of brain activity across multiple brain regions. Therefore, multi-variant analysis can provide greater specificity and sensitivity for detecting differences between normal controls and patients. The most important step in this type of study is extraction of the classification features. Different types of properties, such as local spontaneous activity (ReHo), local network (DMN and/or its anti-correlated network), and whole brain network, derived from SLFF have been taken as features to discriminate

Table 4 Multi-variance analysis and progress in neuropsychiatric disorders

Authors	Disorders	Patient/Control subjects	Feature	Sensitivity(%)	Specificity(%)
Greicius et al. (2004)	AD, mild	14/14	Goodness of fit to the default mode template	85	77
Wang et al. (2006a)	AD, early	14/14	Correlation/anti-correlation coefficients of two intrinsically anti-correlated networks	93	72
Zhou et al. (2010)	**AD**	**12AD/12 patients with frontotemporal dementia/12NC**	**A combined index of Salience Network and Default Mode Network connectivity**	**91.7**	**95.8**
Calhoun et al. (2008a)	Schizophrenia	26/21	Euclidean distance between an individual's map of temporal lobe and the default mode component and group average map	90	95
Shi et al. (2007)	Schizophrneia	48/35	Mean and stand deviation of ReHo value of each region (in total 116 regions)	83	78
Song et al. (2006)	Schizophrenia	17/17	Correlation coefficients between each pair of brain regions (in total 116 regions)	82.3	82.3
Shen et al. (2010)	**Schizophrenia**	**32/20**	**150 featured rsFCs derived from the correlation coefficients between each pair of brain regions (in total 116 regions)**	**75**	**93.75**

Abbreviations: please see Table 1

patients from normal controls (Table 4). In general, both the sensitivity and specificity of these studies has been above 80% (Greicius et al. 2004; Song et al. 2006; Wang et al. 2006a; Calhoun et al. 2008a; Shi et al. 2007; Shen et al. 2010; Zhou et al. 2010), suggesting that the activity patterns of SLFF have the potential to become brain imaging biomarkers to improve the sensitivity and specificity of the current clinical diagnosis of neuropsychiatric disorders. And compared to task-related fMRI, the SLFF within the resting-state network may be more effective at identifying functional pathology associated with AD risk (Fleisher et al. 2009).

However, the complexity of the results as well as limitations in the number of samples is issues in the current multi-variant analyses. Additional clinical parameters that affect the sensitivity and specificity of imaging results in neuropsychiatric disorders, including age at illness-onset, family history, symptom features, and response to biological interventions, also need to be considered. In addition, future work should be done to assess the effect of different MRI scanners and different image acquiring parameters on the discriminant analysis. A practical neuroimaging biomarker should be stable, sensitive and easily detectable, so more effort is required.

Conclusions and future research directions

In conclusion, altered activity patterns of SLFFs have been found in numerous neuropsychiatric disorders, whether at a local level or a global level. These studies highlight the usefulness of resting-state fMRI for studying the brain in neuropsychiatric disorders. More importantly, these studies suggest the possibility that the altered SLFFs in neuropsychiatric disorders could be valuable brain imaging biomarkers for diagnosis, therapy evaluation and prognosis. But various challenges need to be overcome in order to realize this potential. Finally, some future directions are proposed at the end of this paper.

Current challenge

One of the current challenges is that our poor understanding of the physiological correlates of the brain's SLFF limits clinical application. Although SLFFs observed by BOLD-fMRI have been suggested as related to fluctuations in the power of higher frequency electrical activity, or slow (<0.1 Hz) electronic fluctuations, or slow (<1 Hz) fluctuations in electrical membrane potential (Fox and Raichle 2007), the exact physiological correlates of the SLFF are yet to be discovered. This poor understanding makes it more challenging to interpret the clinical correlates of altered SLFFs in neuropsychiatric disorders and thus definitely hampers the clinical application of SLFF to these disorders.

Another challenge is the limited availability of clinical samples and data. Although studies of SLFF are more easily performed in neuropsychiatric disorders than are task-state fMRI or PET/SPECT ones, the available samples and data are still limited (Table 1, 2 and 3). The limited sample size makes statistical power of particular concern. Obtaining a large sample size by using multiple centers

may be a solution, but practical problems, such as how to ensure high quality scanning at multiple hospitals, how to efficiently manage the database, how to effectively use the database, etc., would still remain to be solved.

A third challenge is how to translate the basic researches into clinical application. Differences in professional backgrounds and complexity of the computational theory and methods of neuroimaging may be the major issues that hamper communication between basic researchers and physicians. User-friendly data analysis software and toolkits may be helpful for razing the barriers in the way of physicians to conduct or be involved with translation researches.

Finally, the effects of cardiac and/or respiratory cycle-related pulsations, instrumental and thermal sources of noise on BOLD signals need to be considered.

Future research directions

One potential direction would to be to validate the altered SLFFs found in different pathological conditions. Clinical or behavioral correlates of the altered SLFFs in neuropsychiatric disorders have improved our understanding of the pathophysiological basis of these disorders. However, these findings, which have been obtained by small sample sizes, need to be validated using many more samples.

Additionally, longitudinal studies, which are helpful for tracking the trajectory of disorders; studies on treatment effect, which can enrich our understandings of both pharmacology and pathophysiology; and studies recruiting relatives who are at higher than normal risk of developing disorders, which can provide useful information on "trait" characteristic of disorders, will be important for further enriching our understanding of these diseases and for identifying brain imaging biomarkers for future clinical applications.

Another recommendation involves investigating the association between brain spontaneous activity and task-related activity in pathological conditions. In healthy subjects, coherent spontaneous activity can account for inter-subject variability in event-related BOLD responses and even for inter-trial variability in behavior (Fox et al. 2006b, 2007). A greater amount of variability in behavior has commonly been observed in patients. Thus whether altered spontaneous activity contributes to abnormal performance during tasks in various neuropsychiatric disorders should be examined.

Finally, biomarkers should be integrated. It is likely that a combination of biomarkers will provide greater diagnostic accuracy than any single analysis. Thus, brain imaging biomarkers that are identified should be compared and integrated with other biomarkers (e.g. molecular biomarkers) and clinical signatures to develop a biomarker-based predictive model for diagnosis, therapy evaluation and prognosis of various neurological and psychiatric diseases. In Fig. 3, we show our vision of how these biomarkers could be integrated to develop a predictive model for clinical applications (Fig. 3).

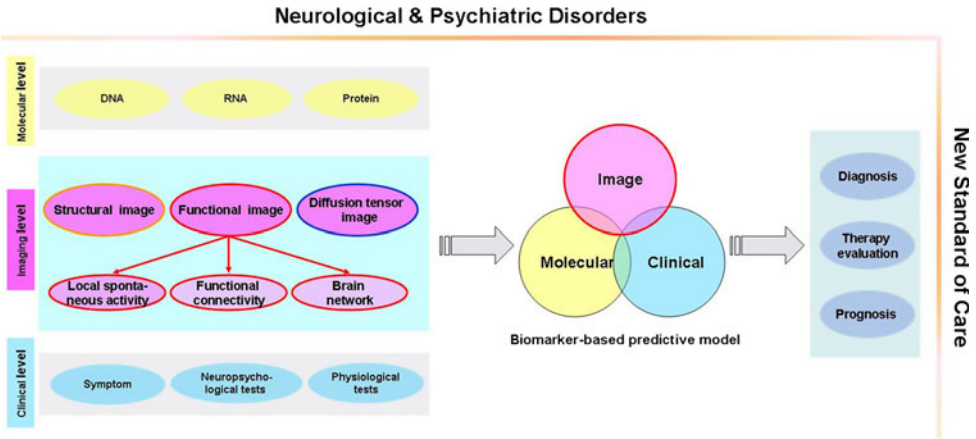

Fig. 3 Biomarker-based predictive model for diagnosis, therapy evaluation and prognosis of neuropsychiatric disorders. Neuropsychiatric disorders are studied from three aspects: molecular, imaging and clinical. Molecular changes in the disorders are found at the DNA, RNA and protein levels and could be used as molecular biomarker for the diseases. Alterations in brain imaging characteristics are identified in structural, functional and diffusion tensor images, in which the functional image (the focus of this article) is examined from the perspectives of local spontaneous activity, functional connectivity and brain networks and can be integrated with the structural and diffusion tensor images. Altered brain imaging features could be used as brain imaging biomarkers; Clinical characteristics obtained from symptoms and neuropsychological and physiological examination of the diseases could be considered as clinical biomarkers. Taken together, the combination of the three types of biomarkers can be compared and integrated to form a predictive model for diagnosis, therapy evaluation and prognosis of the diseases and can thus provide a new standard for clinical care

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