J Neural Transm (2017) 124:821–839
DOI 10.1007/s00702-017-1710-2

HIGH IMPACT REVIEW IN NEUROSCIENCE, NEUROLOGY OR PSYCHIATRY - REVIEW ARTICLE

Clinical utility of resting-state functional connectivity magnetic resonance imaging for mood and cognitive disorders

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Received: 15 December 2016 / Accepted: 14 March 2017 / Published online: 23 March 2017
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Abstract Although functional magnetic resonance imaging (fMRI) has long been used to assess task-related brain activity in neuropsychiatric disorders, it has not yet become a widely available clinical tool. Resting-state fMRI (rs-fMRI) has been the subject of recent attention in the fields of basic and clinical neuroimaging research. This method enables investigation of the functional organization of the brain and alterations of resting-state networks (RSNs) in patients with neuropsychiatric disorders. Rs-fMRI does not require participants to perform a demanding task, in contrast to task fMRI, which often requires participants to follow complex instructions. Rs-fMRI has a number of advantages over task fMRI for application with neuropsychiatric patients, for example, although applications of task fMR to participants for healthy are easy. However, it is difficult to apply these applications to patients with psychiatric and neurological disorders, because they may have difficulty in performing demanding cognitive task. Here, we review the basic methodology and analysis techniques relevant to clinical studies, and the clinical applications of the technique for examining neuropsychiatric disorders, focusing on mood disorders (major depressive disorder and bipolar disorder) and dementia (Alzheimer's disease and mild cognitive impairment).

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Keywords Resting-state functional magnetic resonance imaging (rs-fMRI) · Functional connectivity (FC) · Major depressive disorder (MDD) · Bipolar disorder (BD) · Dementia · Alzheimer's disease (AD)

Introduction

Resting-state functional magnetic resonance imaging (rs-fMRI), or resting-state functional connectivity MRI (rs-fcMRI), is an emerging functional brain imaging method (Greicius et al. 2003). This technique investigates the functional integration of neural networks at rest when no particular sensorimotor or cognitive task is imposed. The brain, even at rest, exhibits a highly organized pattern of correlated activity across a set of remote regions, and this phenomenon can be observed through changes in brain hemodynamics, a surrogate marker of summed synaptic and neuronal activities. As with the conventional task fMRI, rs-fMRI typically measures blood oxygenation level-dependent (BOLD) signals reflecting brain hemodynamics. However, one principle of rs-fcMRI contrasts with the conventional task fMRI methods, which measure the modulation of BOLD signals in response to externally controlled tasks or stimuli. Instead, rs-fMRI investigates naturally occurring low-frequency (typically 0.01–0.08 Hz) fluctuations in BOLD signals, considered to reflect physiologically meaningful changes of spontaneous neural activity in the resting-state networks (RSNs). The analysis of RSNs has recently received attention as a clinical tool (Lowe et al. 2000; Lee et al. 2013). Mounting evidence from clinical rs-fMRI studies has indicated that rs-fMRI may be a promising tool for investigating pathophysiological characteristics of RSNs associated with neuropsychiatric disorders (Wu et al. 2011a; Broyd et al. 2009). Rs-fMRI has a number of advantages over task fMRI

for the diagnosis of neuropsychiatric disorders (Grotegerd et al. 2013), which will be discussed in this article.

In this review, we aim to summarize the utility of rs-fMRI studies for examining neuropsychiatric disorders. We will concentrate on two types of neuropsychiatric disorders, namely mood disorders (MD) and cognitive disorders (dementia), because the early diagnosis of these disorders poses important clinical challenges. MD is characterized by disturbances of positive or negative emotional states. MD includes major depressive disorder (MDD), which is characterized by at least 2 weeks of low mood that is present across most situations, and bipolar disorder (BD), which is characterized by abnormally pronounced shifts in mood between "up" and "down" states. Differential diagnosis of MDD and BD is important, because MDD and BD require different therapeutic strategies. However, diagnosis is clinically challenging, because BD often initially presents with several depressive episodes, followed by manic episodes (Bowden 2001). As the diagnosis of BD requires both manic and hypomanic episodes, many patients are initially diagnosed and treated for MDD (Muzina et al. 2007).

Depressive symptoms result not only from MD, but also from stress reactions and a diverse range of neuropsychiatric disorders including dementia, Parkinson's disease, and organic damage to the brain. Differential diagnosis of MDD and early stage dementia is important, particularly in elderly populations. Moreover, MD and cognitive disorders often overlap. Some researchers have proposed that MDD is a prodromal sign, or possibly a prodromal symptom, of dementia (Green et al. 2003; Muliyala and Varghese 2010). Alzheimer's disease (AD) is the most common form of dementia, characterized by memory loss at an early stage of the disease, and then evolving into widespread decline in many cognitive domains. Pathologically, AD is a neurodegenerative disorder involving widespread neuronal cell loss, neurofibrillary tangles, and senile plaques in the brain (Selkoe 1994). Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia (20% of cases at autopsy) after AD (50–60% of cases at autopsy) (McKeith et al. 1996). AD primarily presents with deficits in episodic and working memory (Gold and Budson 2008; Yetkin et al. 2006), while DLB is characterized by decline in attentional and visuoperceptual abilities (Calderon et al. 2001; Collerton et al. 2003). Fronto-temporal lobar degeneration is another type of neurodegenerative dementia (Neary et al. 2005). Mild cognitive impairment (MCI) in many cases represents a transitional, pre-dementia phase preceding all types of dementias including AD. MCI is classified into amnestic and non-amnestic types. Amnestic MCI, once diagnosed, has a conversion rate of 41% to AD after 1 year and 64% after 2 years. The conversion rate of amnestic MCI is higher than that of non-amnestic MCI (Bharath et al. 2016). Differential diagnosis of these several types of dementia at an early stage is challenging because of the heterogeneity of each disease and the overlap of symptoms across dementias.

Rs-fMRI potentially provides a versatile technique for clinicians to determine the neuropathology of patients suffering from mood and cognitive disorders. Moreover, rs-fMRI may become an important technique to provide useful information for the early diagnosis of these disorders in the near future. In addition, rs-fMRI methods are evolving into valuable tools for clinical systems neuroscience (Hanakawa 2015). Here, we overview the basic principles of the technology, the analysis techniques applied to patient populations, and findings from rs-fMRI studies of mood and cognitive disorders.

Introduction to resting-state fMRI

A brief overview of functional MRI methodology

Neural/synaptic activity requires energy in the brain. This energy requirement is primarily fulfilled by adenosine triphosphates generated aerobically from glucose and oxygen supplied via arterial blood flow. Thus, changes in local neural/synaptic activity are accompanied by changes in regional blood flow (Roy and Sherrington 1890), glucose metabolism (Sokoloff et al. 1977), and oxygen consumption (Fox and Raichle 1986). This is the consequence of a complex sequence of cellular, metabolic, and vascular processes, collectively known as "neurovascular coupling". Moreover, changes in the oxygenation, blood flow, and blood volumes are called "hemodynamic changes". These hemodynamic changes induce changes in the relative concentration of diamagnetic oxyhemoglobin and paramagnetic deoxyhemoglobin, which induces inhomogeneity of magnetic fields. This inhomogeneity of magnetic fields can be detected by imaging with a T2*-weighted MRI sequence with a typical spatial resolution of 2–3 mm. These MRI signal changes, using deoxyhemoglobin as an internal contrast medium, are referred to as "BOLD" effects (Ogawa et al. 1990). The technology for detecting changes in BOLD signals associated with cognitive and sensorimotor tasks is now widely known as "task functional magnetic resonance imaging" (task fMRI). BOLD signals peak around several seconds after a stimulus. Brain activity can thus be investigated, albeit indirectly, using fMRI with a spatial resolution of 2–3 mm and the time resolution of seconds.

A body of research based on these assumptions has demonstrated that task fMRI can be used to create "activation maps" of signal changes associated with a variety of tasks (movement, perception, attention, emotion, reward, memory, cognitive, and many other tasks). fMRI signals

primarily reflect incoming input to (i.e., synaptic activity), and local processing of, neuronal ensembles in a given area in addition to output neuronal spiking activity (Logothetis et al. 2001). However, task fMRI has several technical caveats. First, it should be noted that low-frequency domains of the BOLD signal time-course include various types of physiological noise caused by respiration and pulsation (Birn et al. 2008). This poses a problem in the interpretation of task fMRI data, since demanding tasks likely evoke changes in respiration and pulsation, which would in turn affect fMRI signals. Another limitation of task fMRI is that the interpretation depends on task performance, which may substantially differ across individuals and study groups. Hence, the interpretation of task fMRI data is often difficult when applied to patients with neuropsychiatric disorders, because those patients typically have difficulty in performing demanding tasks. Thus, methods for examining the resting state may be useful for circumventing these issues.

Basics of resting-state fMRI

Traditionally, fMRI has been used to measure changes of BOLD signals associated with task conditions that are alternated with or inserted into no-task or control conditions. In contrast, resting-state fMRI (rs-fMRI) rests on the acquisition of BOLD fMRI time-series data continuously at rest. As such, participants are not required to perform any motor/cognitive task or to pay attention to any particular stimulus. Participants are typically instructed to clear their minds and not to engage in specific thoughts or visual images. It should be noted that "resting" conditions substantially differ across studies. A resting condition may refer to an eyes-open condition with or without a fixation target, or an eyes-closed condition. The most appropriate method for controlling the "resting state" remains an open question. However, at minimum, it is advised to monitor sleepiness with an adequate questionnaire and other physiological parameters when possible.

The advent of rs-fMRI arose from the observation that correlations could be identified across the nodes of functional networks through the analysis of low-frequency fluctuations extracted from resting-state BOLD fMRI time-series data. Biswal and colleagues (1995) were the first to propose that the analysis of spontaneous BOLD fluctuations revealed distinct neural networks. They reported a high correlation of signal fluctuations, which were most pronounced in the range of 0.08–0.1 Hz, between the bilateral sensorimotor cortices. In addition, they examined the sensorimotor cortex using task fMRI, and found that rs-fMRI identified the same parts of the sensorimotor cortex identified with task MRI. This inter-regional correlation of low-frequency fluctuations is thought to reflect the state of functional connectivity (FC) between remote brain regions constituting the "resting-state networks" (RSNs). The finding that RSN activity can be detected by rs-fMRI has been well replicated, along with the finding that RSNs overlap with task-related networks (Beckmann et al. 2005).

Resting-state networks (RSNs)

The default mode network (DMN) is one of the most commonly examined RSNs. The DMN was originally discovered using positron emission tomography, as a set of brain regions most strongly "deactivated" by demanding cognitive tasks in comparison with a condition without a task (i.e., resting state; Raichle et al. 2001). The finding that DMN can be detected using rs-fMRI triggered the surge of broad interest in rs-fMRI (Barkhof et al. 2014).

The previous studies have used a variety of analysis methods to examine FC in RSNs during rest in healthy participants (Damoiseaux et al. 2006; Beckmann et al. 2005). RSNs include the DMN, medial and lateral visual networks, fronto-parietal network (Yeo et al. 2011; Smith et al. 2009), salience network, executive network (Seeley et al. 2007), attention network (Yeo et al. 2011), sensory-motor network, auditory network, cerebellar network (Smith et al. 2009), basal ganglia network, frontal cortical network, cognitive control network, and affective network. Many previous rs-fMRI studies of neuropsychiatric disorders have focused on the DMN and the salience network in particular.

Advantages of rs-fMRI over task fMRI for clinical applications

Without imposing an external task, rs-fMRI analyzes spontaneous fluctuations of BOLD signals, which reflect intrinsic changes in synaptic/neural activity over time. This task-free protocol has strong advantages over the conventional task fMRI for clinical applications. First, rs-fMRI does not require a complex set-up for stimulus presentation, response recording, or task timing control which are prerequisites for task fMRI studies. Such systems are often expensive, because all equipment must be compatible with strongly magnetic environments. Second, because of the task-free nature, rs-fMRI is less demanding for both participants and investigators in terms of time (no preparation time needed) and effort. Thus, dropouts or exclusion of participants due to poor compliance with instructions (e.g., head motion) or the incidental failure of experimental controls is less likely to affect rs-fMRI studies. Third, the interpretation of rs-fMRI data is simpler than that of task

fMRI, since it is not influenced by task performance. Differences in task performance affect fMRI signals, and thus the results of task fMRI are often confounded by individual differences in task performance. This is particularly problematic in patient studies, since differences in task performance across groups are inherent (e.g., cognitively impaired patients would be expected to show poor cognitive performance, by definition, in comparison with control groups). Fourth, rs-fMRI provides information about functional networks, the level at which many neuropsychiatric disorders involve underlying pathophysiological changes.

Analysis methods of rs-fMRI applied to clinical studies

A variety of methods have been proposed for the processing and analysis of rs-fMRI data. Rs-fMRI methods can be classified into two groups: model-dependent (model-driven) approaches and model-free (data-driven) approaches. For clinical studies, both types of method are applicable to the analysis of rs-fMRI (van den Heuvel and Hulshoff Pol 2010). Popular statistical methods are seed-based analysis, independent component analysis (ICA), and graph analysis.

Model-dependent: seed-based analysis

One traditional approach is a model-based voxel-wise analysis to examine the degree of FC from a seed region to another region, yielding FC (seed-to-seed analysis), or to all the other voxels in the whole brain, yielding an FC map (seed-to-voxel analysis; (Fox and Raichle 2007). This approach is a model-based approach, because a seed region needs to be specified a priori and, to do so, a model of the pattern of FC or FC of interest must be known before the analysis. After setting up a seed region as a volume of interest (VOI), this analysis can inspect FC as a parameter representing temporally coherent fluctuations of BOLD signals between anatomically distinct brain regions. Because the seed-to-voxel analysis is straightforward and provides comprehensible results, it has traditionally been the most popular technique. Since the seed-based comparison of FC can be performed on the basis of the general linear model, it is straightforward to apply for the comparison of FCs between groups. As such, the seed-based analysis may have more diagnostic power than model-free methods such as ICA to differentiate between patients with AD and healthy subjects (Koch et al. 2012).

Model-free: independent component analysis (ICA)

Model-free methods attempt to find a reduced set of temporal basis functions, such that time-course can be well approximated by a linear combination of these temporal bases. ICA is a signal processing technique that separates observed signals into a set of spatiotemporal components mathematically independent of each other. ICA has successfully been used for the investigation of hidden neuronal activation patterns measured with BOLD fMRI (Beckmann and Smith 2004). In an ICA analysis of fMRI data, observable spatially distributed BOLD time-series data are hypothesized to be a linear mixture of spatially independent maps, each of which has particular temporal dynamics. Thus, ICA applied to rs-fcMRI data identifies RSNs as spatially independent components corresponding to RSN maps, accompanied by information about signal variation time-courses attached to each RNS. An advantage of ICA is that it does not require a priori assumptions about the seed regions or neural networks. Furthermore, ICA can separate signals that do not necessarily reflect neural/synaptic activity, so that ICA is widely applied to the removal of noises in rs-fMRI data (Beckmann et al. 2005). However, one of the problems in ICA analysis is that there is not a straightforward way to infer physiological meaning of separated ICA components. The "dual regression" method has been introduced to overcome this limitation of statistical inference for the comparison of ICA components between groups (Filippini et al. 2009). The dual regression method takes both spatial and temporal aspects of RSN information into account to create subject-specific spatiotemporal maps, unlike other back-reconstruction techniques (Filippini et al. 2009). Moreover, not only is the temporally concatenated ICA dual regression approach reliable, it also produces more robust results than template matching ICA performed on an individual level (Zuo et al. 2010). The dual regression approach is performed at three stages. First, using ICA, the concatenated multiple rs-fMRI data sets are decomposed into large-scale patterns of FC in the subject population. Second, subject-specific temporal dynamics and associated spatial maps are identified within each subject's rs-fMRI data set. Finally, the spatial maps are collected across the subjects for each group. The differences between the groups are then tested using voxel-wise non-parametric permutation testing, yielding spatial maps characterizing between-subject/group differences.

Graph analysis

Graph theory is an advanced network analysis method, and has previously been applied in several clinical rs-fcMRI studies (Sanz-Arigita et al. 2010). A graph theory-

based analysis regards the whole brain as a single interwoven network, which consists of nodes and edges that correspond to brain regions and the pathways between them, respectively. In practice, VOIs are set up as sets of nodes according to a brain atlas or function localizer task (Smith et al. 2011) to create a covariance matrix. However, recent developments have enabled graph analysis at a voxel level (Dai et al. 2015). Graph analysis provides various metrics that describe features of network topology. The metrics include "centrality", "cluster coefficient", "characteristic path length", and "betweenness". In addition, exploratory graph analysis can be performed without any a prior hypothesis about network topology. The metrics estimated at the subject level can be grouped and assessed using the conventional statistical tests to search for group differences. However, it should be noted that graph-derived metrics are sometimes difficult to interpret from behavioral and pathophysiological points of view.

Subsidiary methods: machine learning (ML)

The ML or brain "decoding" technique provides an important complementary method, which may aid the development of effective, reliable rs-fMRI methodology for the early diagnosis of neuropsychiatric conditions. Support vector machine (SVM) methods have widely been used to achieve this objective. SVM is a supervised, multivariate classification method, generating a "hyperplane" that defines the boundary of different data labels (e.g., a patient group and a control group). SVM requires a supervised training phase during which parameters defining a hyperplane are trained based on labeled data, so that distances between the hyperplane and the data points closest to the hyperplane are maximized. In practice, FCs are typically retrieved from pairs of VOIs, forming a covariance matrix (Craddock et al. 2009; Zeng et al. 2012). A classifier is trained by these FCs retrieved from a part of the entire data set. In a test phase, a new data set (not used for training) is fed into the trained classifier for blind separation (Cao et al. 2014). SVM has been applied to neuroimaging data (Lao et al. 2004; Mourao-Miranda et al. 2005) and has already been applied in many clinical rs-fMRI studies (Fan et al. 2005; Kawasaki et al. 2007).

Applications of rs-fMRI to Alzheimer's disease and other dementias

A number of previous studies have demonstrated the potential utility of rs-fMRI for identifying patients with Alzheimer's disease (AD) and other dementias.

Seed-based analysis

Since a seed-based analysis requires an a priori model of the seed regions, the previous rs-fMRI studies have focused on FC involving brain regions already implicated in dementia, including the hippocampus. Wang and colleagues (2006) reported increased FC between the left hippocampus and the right dorsolateral prefrontal cortex (dlPFC) in patients with AD compared with healthy controls. In contrast, the right hippocampus exhibited disrupted FC with the medial prefrontal cortex (mPFC) and ventral anterior cingulate cortex (ACC). Notably, these regions with reduced connectivity are part of the DMN. The right hippocampus also showed reduced FC with other DMN-related brain regions such as the posterior cingulate cortex (PCC) and temporal cortex (Wang et al. 2006) (Fig. 1a). Zarei and colleagues (2013) analyzed FCs associated with three functional sub-regions (head, body, and tail) of the bilateral hippocampi. They showed that patients with AD had stronger connectivity between the PFC and the head of the hippocampus, and weaker connectivity with the PCC in the body of the hippocampus, compared with controls (Zarei et al. 2013).

PCC, a hub of the DMN, has been the subject of substantial attention in AD research. Zhang and colleagues (2009) studied dementia (possible or probable AD) at the early stages and reported lateralized disconnection between the PCC and the left hippocampus. In addition, the results revealed that the PCC exhibited reduced FC with the primary visual cortices, inferior temporal cortex, precuneus, and thalamus. Adjoining the PCC, the retrosplenial cortex is another important seed region (Zhang et al. 2009) (Fig. 1b). Dillen and colleagues (2016) investigated FC patterns of both the PCC and retrosplenial cortex in prodromal-mild AD, subjective cognitive impairment and healthy seniors. The retrosplenial cortex seed revealed higher FC with the mPFC and lateral occipital areas in prodromal AD, whereas the PCC seed exhibited higher FC with the lingual gyrus. This study indicates the distinction of FC between the retrosplenial cortex and the PCC at the early stage of AD (Dillen et al. 2016). Zhang and colleagues (2010) reported that patterns of DMN disconnection were enhanced with the progression of AD, reflecting alterations of FC in AD-affected brains along a continuum. Among the nodes of the DMN, the mPFC and precuneus were found to exhibit the most conspicuous connectivity deficits. Besides the DMN, the amygdala has also been found to be a vulnerable structure in the early stages of AD (Zhang et al. 2010). In a voxel-wise FC analysis using the amygdala as a seed, Yao and colleagues (2013) reported that FC was decreased between the amygdala and the other limbic regions (hippocampus, para-hippocampal gyrus, superior

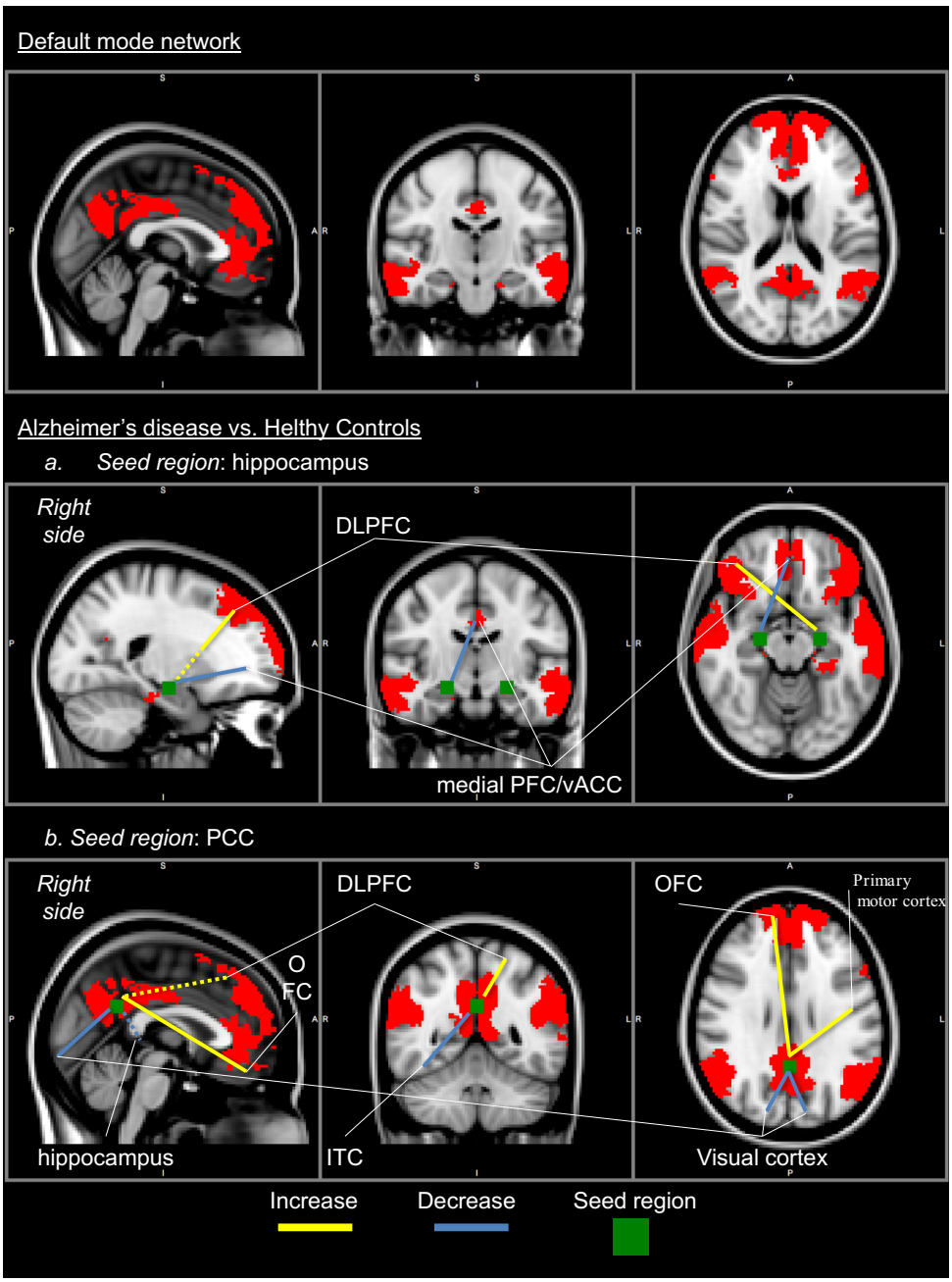

Fig. 1 Functional connectivity in resting-state in Alzheimer's disease (AD). Regions of connectivity loss or increase in AD, **a** case of hippocampus (Wang et al. 2006) and **b** PCC (Zhang et al. 2009) in DMN. The *yellow* is showed increase and *blue* is decrease. *Green* of *square* is showed seed region. *Mask* of DMN is referred to yeo and colleagues (Yeo et al. 2011)

temporal gyrus, and middle cingulate cortex) in AD and MCI. They also found decreased FC between the amygdala and several non-limbic regions (inferior frontal cortex, putamen, and sensory-motor network). The involvement of the non-limbic/non-DMN network in pathophysiology of AD was also suggested by another seed-based rs-fMRI study (Yao et al. 2013). Brier and colleagues (2012) employed five RSNs (DMN, dorsal attention network, control network, salience network, and sensory-motor network) as seeds, revealing that all RSNs were affected, in association with the severity of AD (Brier et al. 2012).

Seed-based analysis of rs-fMRI has been applied for examining DLB. Kenny and colleagues (2012) used the hippocampi, PCC, precuneus, and primary visual cortices as seeds, and compared FC across DLB, AD, and healthy controls. DLB patients exhibited greater connectivity involving the PCC, while AD patients exhibited greater FC of the left hippocampus in comparison with controls, as reported previously (e.g., Wang et al. 2006). Specifically, in DLB, the right PCC showed significantly greater connectivity with the cerebellum, ACC, and globus pallidus, compared with controls. However, the results from the precuneus and primary visual cortex seeds did not show

significant differences in FC between the groups. This finding may seem surprising, considering that visual symptoms, such as hallucination, are a hallmark of DLB (Kenny et al. 2012). However, using the precuneus as a seed region, Galvin and colleagues (2011) showed that DLB patients exhibited decreased connectivity between the precuneus and primary visual cortex, compared with AD patients or controls. Furthermore, DLB patients showed reduced precuneus connectivity with the mPFC and hippocampus compared with controls. In addition, DLB patients showed positive correlations between the precuneus and putamen where AD patients and controls showed anti-correlations. Thus, connectivity with PCC/precuneus may help differentiate between DLB, AD, and healthy older people (Galvin et al. 2011).

ICA

Greicius and colleagues (2004) were the first to apply ICA analysis of rs-fMRI to dementia. Using the ICA-based analyses, several other studies replicated the results from seed-based rs-fMRI studies, which indicated reduced DMN-hippocampus FC in AD (Wu et al. 2011b; Schwindt et al. 2013; Binnewijzend et al. 2012). Pasquini and colleagues (2015) investigated FC related to the DMN using both local (limited search volume) and global (whole-brain exploratory) methods. The analysis of global connectivity replicated reduced DMN/hippocampus FC in AD. However, the analysis of local connectivity suggested a fine-graded abnormality in DMN-hippocampus FC in AD and related disorders. Local connectivity in the hippocampus was increased in AD and MCI compared with controls, while local connectivity in PCC was reduced in AD compared with MCI and controls. Importantly, increased hippocampal connectivity was negatively correlated with performance in a delayed memory task in patients with dementia (Pasquini et al. 2015). Damoiseaux and colleagues (2012) used ICA and separated the DMN into three sub-networks (anterior, posterior, and ventral DMN). They reported decreased connectivity in the posterior DMN and increased connectivity in the anterior and ventral DMN in a baseline investigation. At the follow-up stage, FC was reduced in all three sub-networks of DMN. This result suggests that FC may show differential changes over time across the sub-networks of DMN as AD progresses (Damoiseaux et al. 2012).

An advantage of ICA-based analyses over seed-based analyses is that multiple RSNs can be systematically examined. Castellazzi and colleagues (2014) developed a strategy for selecting RSNs of interest and applied the technology with AD, MCI, and control groups. The ICA analysis first identified 15 RSNs. Although all 15 RSNs showed some differences across the groups, the RSNs were ranked according to the magnitude and extension of FC alterations. This procedure yielded six significant RSNs: the DMN, frontal cortical network, lateral visual network, cerebellar network, and basal ganglia network. Notably, the prefrontal cortex and mesial temporal cortex (hippocampus) exhibited common alterations across different RSNs, suggesting a hub-like role of those two regions in dementia (Castellazzi et al. 2014). Adriaanse and colleagues (2014) examined FC in the early onset AD patients (<65 years old), late-onset AD patients (≥65 years old), and young and older control participants. Compared to late-onset AD patients, the early onset AD patients exhibited reduced FC in five RSNs: the auditory network, sensory-motor network, dorsal visual network, and DMN. Thus, RSNs may be more widely disrupted in early onset AD than late-onset AD (Adriaanse et al. 2014).

ICA analysis has been applied to the comparison of AD with other types of dementia. Franciotti and colleagues (2013) assessed whether typical DLB patients exhibit different FC patterns compared with AD patients. Direct comparison between AD and DLB patients failed to reveal significant group differences. In AD, however, FC in the DMN was found to be lower than that of controls, and this reduction was mainly ascribed to a decrease in FC involving the PCC. In DLB patients, the engagement of the PCC was no different from that of controls. In DLB patients, compared with controls, FC was reduced for the interhemispheric network and for the right fronto-parietal networks, and this reduction was correlated with the level of cognitive fluctuation in DLB (Franciotti et al. 2013). In a study by Lowther and colleagues (2014), DLB patients showed reduced FC in the DMN, salience network and executive network compared with AD patients and controls, whereas DLB patients showed increased FC in the basal ganglia network. Overall, several network features retrieved with ICA can provide valuable information for differentiating between AD and DLB (Lowther et al. 2014).

Graph analysis

Sanz-Arigita and colleagues (2010) compared AD patients and healthy controls using several metrics obtained using graph analysis. They found abnormalities in global (characteristic path length) rather than local (cluster coefficient) metrics in AD patients, suggesting a conversion from a small world network to less optimal network topologies in AD. These abnormalities in global graph metrics were particularly evident for the connections between the frontal lobe and parietal/occipital lobes, in accord with suggested anterior–posterior disconnections in AD (Sanz-Arigita et al. 2010). Toussaint et al. (2014) combined ICA and graph analysis for rs-fMRI data derived from young and

older healthy subjects and patients with AD. ICA was first used to identify sub-systems of the DMN. Network features were retrieved using graph analysis. For the comparison between the young and older subjects, long-range fronto-parietal interactions were decreased (lower global efficiency) with age, but local coupling within each lobe was increased (higher local clustering) with age (Toussaint et al. 2014). The decreases in fronto-parietal interactions, particularly in the precuneus–PCC, were more pronounced in patients with AD compared with the older control patients, consistent with the findings of Sanz-Arigita and colleagues (2010). This study highlights the value of the complementary use of ICA and graph analysis for examining rs-fMRI. Kim and colleagues (2015) investigated changes in topological measures of the brain network among a diverse sample of participants, ranging from healthy subjects to patients with prodromal and intermediate stages of AD. They compared seven graph analysis-derived parameters: the characteristic path length, clustering coefficient, global efficiency, local efficiency, betweenness centrality, assortativity, and modularity. The results indicated non-monotonic changes (higher in MCI and the prodromal stage of AD compared with the other groups) as AD progressed in several network properties (global efficiency, local efficiency, and betweenness centrality; (Kim et al. 2015). Graph analysis conventionally uses a set of VOIs to construct a connectivity matrix; however, recent developments have enabled graph analysis at a voxel level. Dai and colleagues (2015) investigated intrinsic FC patterns of whole-brain networks, using voxel-based graph theory analysis. It was suggested that pathophysiology of AD selectively affects highly connected hub regions of brain networks, involving the medial and lateral prefrontal and parietal cortices, insula, and thalamus. AD patients also showed disrupted connectivity within the DMN, saliency network, and executive network. Moreover, the nodal connectivity strength in the PCC-precuneus was highly relevant for distinguishing individuals with AD from healthy subjects. This study highlights the value and feasibility of voxel-level graph analysis (Dai et al. 2015).

Brief summary of rs-fMRI studies in dementia

Studies using seed-based analysis have supported the association between AD pathophysiology and previously identified anatomical structural abnormalities in particular brain areas, including the hippocampus and PCC. In particular, alteration of FC involving the hippocampus and PCC/retrosplenial cortex has been found to be related to disease severity. Seed-based analysis of rs-fMRI applied to DLB revealed that connectivity with PCC/precuneus may help distinguish among DLB patients, AD patients and healthy older people. Studies using ICA analysis have revealed similar results to seed-based investigations. However, ICA allows for semi-automatic and objective identification of different RSNs, including sub-systems of the DMN. ICA-based studies also revealed that the PFC and mesial temporal cortex constitute a functional hub, the abnormality of which affects multiple RSNs in AD patients. Graph analysis has provided a new perspective in the analysis of rs-fMRI, and its clinical relevance should be tested and replicated in studies with large samples.

Applications of rs-fMRI to mood disorders

Major depressive disorder (MDD)

Seed-based analysis Several rs-fMRI studies have highlighted dysfunctional DMN activity in MDD. Peng and colleagues (2015) measured FC in first-episode, medication-naive patients with MDD and healthy controls, using a node of DMN (precuneus) as a seed region. The results revealed that MDD patients exhibited stronger anti-correlation between the precuneus and the sensory processing/premotor regions than controls. In other words, the inherently inverse relationship of spontaneous activity between DMN and non-DMN areas was exaggerated in MDD (Peng et al. 2015). Chen and colleagues (2015a, b) performed a seed-based FC analysis in the first-episode, treatment-naïve MDD patients. The researchers used a seed in the PCC and identified 12 DMN nodes (PCC, dorsal/ventral mPFC, medial temporal cortex, inferior parietal cortex, superior frontal cortex, thalamus, and cerebellum). Region-to-region connectivity of MDD, compared with healthy controls, exhibited lower FC between the PCC and dorsal mPFC, between the PCC and right inferior parietal cortex/angular gyrus, and between the left thalamus and cerebellum (Chen et al. 2015b). In a study by Liu and colleagues (2012), patients with MDD were found to exhibit decreased FC between the cerebellum and the DMN/executive network as well as increased FC between the cerebellum and the temporal pole/middle frontal cortex (Liu et al. 2012).

Prefrontal regions have long been implicated in the pathophysiology of MDD. Sheline and colleagues (2010) used the DMN, cognitive control network, and affective network as seed regions. Despite starting from these separate seeds, increased FC in MDD converged onto the bilateral dorsal prefrontal areas, leading the authors to term these prefrontal areas the "dorsal nexus". In MDD, this "dorsal nexus" exhibited extremely strong connectivity with large parts of PFC (dorsolateral, dorsomedial, and ventromedial areas), ACC (dorsal, pregenual, and subgenual areas), and PCC/precuneus (Sheline et al. 2010). Other rs-fMRI studies have also reported alterations of FC involving the PFC in MDD. In a comparison of the first-episode MDD patients and healthy controls, Ye and

colleagues (2012) used the right dorsolateral PFC as a seed and investigated resting-state FC alterations in MDD. The results revealed that MDD patients exhibited increased FC between the right dorsolateral PFC and the left dorsal ACC, left para-hippocampal gyrus, thalamus, and pre-central gyrus compared with healthy controls, along with decreased FC with the right parietal lobe (Ye et al. 2012). A study using the left and right dorsolateral PFC as seeds reported that the left dorsolateral PFC exhibited increased FC with the middle frontal gyrus, parietal lobe, post- and pre-central gyrus, precuneus, superior temporal gyrus, inferior parietal lobule, and cingulate regions (Shen et al. 2015). The basal ganglia have also been implicated in MDD by several seed-based rs-fMRI studies. Kerestes and colleagues (2015) used subdivisions of the striatum (ventral striatum/nucleus accumbens, dorsal caudate, dorsocaudal putamen, and ventrorostral putamen) as seed regions. A comparison between moderate-to-severe medication-free patients with MDD and healthy controls revealed a diffuse pattern of increased FC between the dorsal caudate and ventrolateral PFC bilaterally (Kerestes et al. 2015).

Several rs-fMRI studies have investigated the underlying mechanisms of inter-individual differences in response to treatment in MDD. Lui and colleagues (2011) evaluated FC in patients with treatment-resistant MDD (TRD) and treatment-responsive MDD (TSD) and healthy controls, using 13 seeds (hippocampi, insula, dorsolateral PFC, amygdala, putamen and thalami bilaterally, and ACC). Both groups of MDD patients exhibited reduced FC in the bilateral prefrontal-limbic-thalamic areas compared with healthy controls. In a comparison between TSD and TRD, TSD patients revealed more distributed decreases in FC especially in the ACC and in the amygdala, hippocampus, and insula. In contrast, TRD patients showed disrupted FC mainly in the PFC and thalami. These results suggest that distinct functional deficits in distributed brain networks may characterize TRD and TSD (Lui et al. 2011). In an rs-fMRI study using cerebellar seeds (Guo et al. 2013), both TRD and TSD patients exhibited a similar pattern of abnormal cerebellar–cerebral FC involving the PFC, DMN, visual recognition network, and para-hippocampal gyrus. However, TRD patients exhibited more decreased cerebellar–DMN FC than TSD patients. Ma and colleagues (2012) combined structural and functional MR to examine whether abnormalities in gray matter volume might relate to alterations of FC in TRD and TSD. First, a structural MRI analysis revealed gray matter abnormalities in the right middle temporal cortex (MTG) and bilateral caudate among TSD patients, compared with TRD patients and healthy controls. Reduced MTG volume was shown in both TSD and TRD patients, while that of the caudate was only seen in TRD patients. Second, a seed-based analysis was applied to rs-fMRI to examine the effect of gray matter abnormalities on FC. An rs-fMRI analysis using a right MTG seed showed altered FC, particularly with the DMN. Analysis using a caudate seed was performed in the frontal areas in both groups, but some differences in FC were only found between TRD and TSD patients. Altered FC with the right middle orbitofrontal cortex was shown in TRD, while altered FC was found in the right inferior frontal gyrus, middle frontal cortex, superior frontal cortex and dlPFC in TSD. The two subtypes of MDD had some common and some differential abnormalities in FC and gray matter volume, which may reflect depressive "traits" and "states", respectively (Ma et al. 2012).

ICA Greicius and colleagues (2007) applied ICA analysis to MDD patients and healthy controls. After ICA was used to isolate the DMN, the results revealed increased DMN-related FC in the orbitofrontal cortex, subgenual cingulate cortex, thalamus, and precuneus in MDD. This study was the first to demonstrate DMN abnormalities in MDD (Greicius et al. 2007). Zhu and colleagues (2012) showed increased FC in the mPFC and ACC, and decreased FC in the PCC/precuneus in the first-episode, medication-naïve young adults with MDD compared with healthy controls. This result suggests dissociation of FC between the anterior and posterior regions of DMN in MDD (Zhu et al. 2012). Likewise, Li and colleagues (2013) reported dissociation of the anterior and the posterior sub-networks of DMN in MDD. Although MDD patients exhibited increased FC in both anterior and posterior DMN sub-networks, antidepressant medication normalized FC in the posterior sub-network, but not the anterior sub-network (Li et al. 2013).

Graph analysis Peng and colleagues (2014) applied graph analysis to patients with first-episode, medication-naive MDD. For global brain modularity (i.e., "small-worldness"), no difference was observed between MDD patients and controls. For local modularity, however, abnormalities were found in eight regions, including the orbitofrontal cortex and amygdala. These findings suggest altered modular architecture in MDD (Peng et al. 2014).

Brief summary Seed- and ICA-based rs-fMRI studies of MDD have suggested the involvement of the DMN and prefrontal areas in addition to cognitive and affective RSNs. Importantly, some studies have discovered differential involvement of DMN sub-networks between TRD and TSD, casting new light on pharmaceutical rs-fMRI studies in MDD. ICA studies have also consistently indicated that RSNs, especially the DMN, are poorly regulated in patients with MDD (Zhu et al. 2012; Lemogne et al. 2012). However, the direction of changes has not been consistent across rs-fMRI studies (as seen in dementia). Early studies using graph analysis of rs-fMRI have begun

to reveal abnormal network architecture in MDD patients compared with controls.

Bipolar disorders (BD)

Seed-based analysis Torrisi and colleagues (2013) studied euthymic patients with BD, focusing on the bilateral amygdalae and ventrolateral PFC, which are implicated in emotion regulation. Compared with healthy controls, euthymic patients with BD exhibited higher FC between the right ventrolateral PFC and amygdala. The results suggested that the ACC mediated this abnormal FC, since the ACC exhibited positive connectivity with both the right amygdala and right ventrolateral PFC (Torrisi et al. 2013). Favre and colleagues (2014) used a seed-based correlation method to explore FC with the ventromedial PFC (a DMN seed) in the whole brain. Euthymic patients with BD exhibited a loss of anti-correlation between the mPFC and the right dlPFC, and abnormal hyper-connectivity between the mPFC and right amygdala (Favre et al. 2014).

A notable feature of BD is that the same patients exhibit different states of mood. These states may be accompanied by different states of RSNs, which could be assessed using rs-fMRI. Rey and colleagues (2016) investigated FC in euthymic and non-euthymic patients with BD, focusing on brain regions implicated in emotion regulation and self-referential processing. Compared with controls, BD patients exhibited increased FC between the left amygdala and left subgenual ACC/PCC overall. However, non-euthymic BD patients exhibited decreased FC between the right amygdala and subgenual ACC, whereas euthymic BD patients exhibited decreased FC between PCC and subgenual ACC. This study also indicated that subgenual ACC–PCC and subgenual ACC–amygdala connections were related to rumination tendency in non-euthymic BD (Rey et al. 2016). In the comparison between manic and euthymic states in BD patients, Brady and colleagues (2016) revealed that manic BD patients exhibited decreased FC between the amygdala and ACC compared to euthymic BD patients. Another study with seeds in bilateral amygdala reported that both manic and non-manic BD patients exhibited reduced FC between the bilateral amygdala and orbitofrontal cortex, striatum, lingual gyrus, and PCC, compared with controls (Li et al. 2015). However, right amygdala–hippocampal connectivity was decreased in manic states but increased in non-manic states. Overall, BD in different mood states most likely exhibits a contrasting pattern of FC involving the amygdala and DMN, including the hippocampus (Brady et al. 2016).

Using the whole hippocampus as a seed, Samudra and colleagues (2015), demonstrated broadly distributed reduction of FC in psychosis, including BD patients, compared with healthy controls. Patients with psychosis showed reduced hippocampal FC with the PCC, superior temporal gyrus, thalamus, and cerebellum, with a tendency for more left-sided disconnection. When separate seeds were placed in the anterior and posterior sectors of the hippocampus, reductions in FC with the anterior hippocampal seed were found in the ACC, superior temporal gyrus, and thalamus (Samudra et al. 2015).

ICA ICA has been applied for comparing BD with related psychiatric disorders. Ongur and colleagues (2010) examined DMN alterations in manic BD patients and acute schizophrenia (SZ) patients. The results indicated that BD might be characterized by a reduction of coherence in several nodes within the DMN, including the hippocampus, as well as involving abnormal recruitment of the pontine, lateral parietal, and occipital regions in the DMN (Ongur et al. 2010). In another study of SZ and BD patients, Khadka and colleagues (2013) identified abnormal activity in seven RSNs: fronto-occipital, midbrain/cerebellum, frontal/thalamic/basal ganglia, meso/para-limbic, posterior DMN, fronto-temporal/para-limbic and sensory-motor networks. In particular, abnormal FC in the meso/para-limbic and posterior DMN was common among SZ and BD patients. This result is consistent with the notion that SZ and psychotic BD share pathophysiological mechanisms (Khadka et al. 2013). Recently, Goya-Maldonado and colleagues (2016) demonstrated that characteristic changes in large-scale networks could distinguish between bipolar MD (BD) and unipolar MD (MDD). BD and MDD patients, despite similar depressive symptoms, were found to exhibit clear differences in the fronto-parietal network, cingulo-opercular network, and DMN (Goya-Maldonado et al. 2016).

In a comparison between euthymic BD patients and healthy controls, Lois and colleagues (2014) performed an ICA inter-network connectivity analysis that revealed increased FC between the meso/para-limbic and the right fronto-parietal network. However, this finding remains inconclusive, because the abnormal connectivity pattern did not correlate with variables related to the clinical course of BD (Lois et al. 2014). In contrast, Ford and colleagues (2013) used ICA analysis to examine FC correlated with the bipolarity index in a group of MDD and BD patients. The scores of trait bipolarity were positively correlated with FC involving the DMN, the right putamen/claustrum extending into the insula as well as a negative correlation with FC in the left postcentral gyrus, extending into the PCC. Furthermore, increased FC between the putamen and DMN represented a marker distinguishing between BD and MDD (Ford et al. 2013).

Brief summary Rs-fMRI studies in BD have thus far identified abnormal functional connectivity between

several brain regions. Seed-based studies have concentrated on the DMN, hippocampus ,and amygdala, implicating the DMN and affective networks in the pathophysiology of BD. Research using ICA has identified more extensive RSNs, not limited to the DMN, as underlying mechanisms of BD. These RSNs include fronto-parietal and meso/para-limbic networks, possibly explaining cognitive abnormalities in BD.

Application of machine learning (ML) to neuropsychiatric disorders

ML has typically been applied to neuroimaging for the "decoding" of brain signals. After an ML-based classifier is trained with a data set (learning), the classifier then attempts to classify a new data set (prediction). If this technology becomes established as part of routine clinical practice, rs-fMRI may become an immensely valuable tool for clinical practice. ML has recently been used to examine rs-fMRI data obtained from patients with MDD, BD, and neurodegenerative disorders such as AD. Below, we describe the findings of clinical studies using SVM, which is currently the most widely used ML technology.

In two previous ML studies of MDD, Craddock and colleagues (2009) and Zeng and colleagues (2012) applied SVMs to the classification of healthy controls and patients with MDD. Craddock and colleagues (2009) defined feature vectors for a linear kernel SVM as the correlation scores between pairs from 15 selected regions, and then examined the performance of two different feature selection methods: reliability filter (RF) and reliability reverse feature elimination (RRFE). While RF determines a threshold for multivariate patterns using partial least squares, RRFE minimizes prediction error. The results indicated that SVM successfully classified whether patients belonged to the healthy group or the MDD group. Classification accuracy was 95% when RF was used for feature selection, and 85% when RRFE was used. These findings suggest that the performance of SVM classification depends in part on the method of feature selection (Craddock et al. 2009). Zeng and colleagues (2012) reported that a multivariate pattern analysis of FC with linear SVM had an accuracy of 94.3% for distinguishing MDD patients from healthy controls. The Kendall tau rank correlation coefficient was used as a feature extraction method to preserve the best discriminating FC, and exclude the rest. The majority of FC alterations with high discriminative power were located in the DMN, affective networks, visual areas, and cerebellum. In particular, FC between the amygdala, ACC, para-hippocampal gyrus, and hippocampus exhibited high discriminative power in classification. These results demonstrated that multivariate pattern analysis of whole-brain rs-fMRI allowed researchers to distinguish MDD patients from healthy controls (Zeng et al. 2012).

Several clinical studies proposed that the combination of different MRI modalities might improve imaging-based classification of AD (Zhang et al. 2011; Sui et al. 2013). However, several recent studies found better classification performance with a single MRI modality (Dyrba et al. 2015; Dai et al. 2012). Zhang and colleagues (2011) performed a multi-modal group comparison, by combining structural MRI, functional PET and CSF protein level to differentiate healthy controls, MCI patients, and AD patients. The classification accuracy was 93% for healthy versus AD and 76% for healthy versus MCI (Zhang et al. 2011). To distinguish patients with AD from healthy controls, Dai and colleagues (2012) applied graph analysis to a single MRI modality and proposed a methodological framework (multi-modal imaging) and multi-level characteristics with a multi-classifier. The application of this technology to an rs-fMRI data set consisting of AD and controls led to a classification accuracy of 89% with a sensitivity of 88% and a specificity of 91% (Dai et al. 2012). Dyrba and colleagues (2015) reported a similar result. The authors developed a multiple-kernel SVM classifier based on diffusion MRI, gray matter volume, and derivatives of graph-theoretical analysis of rs-fMRI data (local clustering coefficient and shortest path length). Classification based on a single modality revealed area-under-the-curve (AUC) values of the receiver-operating characteristic (ROC) curve of approximately 80% for rs-fMRI, 87% for diffusion MRI, and 86% for gray matter volume (Dyrba et al. 2015). The combination of all three modalities did not improve the classification accuracy (82%).

Brief summary and comments

The application of ML to rs-fMRI allows for the semi-automatic labeling of data sets (e.g., distinguishing a patient group and a healthy group). The distinguishing features are typically related to FC between VOIs, but other features such as graph-derived parameters have already been reported to be useful. Although application of ML to rs-fMRI is a promising technique, it should be noted that high discrimination accuracy might result from overfitting to the data when the training data is not sufficiently large.

Discussion

This review provides that an overview of the ways rs-fMRI technology has been applied to the study of neuropsychiatric disorders. For clinical applications, rs-fMRI methods

have a number of advantages over other functional imaging methods. Importantly, rs-fMRI does not rely on active participation by patients. Thus, rs-fMRI may be the sole form of fMRI suitable for uncooperative populations for which an adequate level of performance may be difficult to attain. Similar to other functional imaging methods, patient immobility is essential for rs-fMRI, since movement-related artifacts can significantly impair the detection of spontaneous brain activity. However, since rs-fMRI can be performed (and RSN activity can still be detected) in patients under sedation, patients (e.g., pediatric patients) may be sedated if necessary to attain an acceptable level of immobility (Greicius et al. 2008; Kiviniemi et al. 2003). Moreover, rs-fMRI is free from the potentially confounding effects of differences in the level of task performance.

Early studies using these methods have uncovered a wide array of brain regions that exhibit group-wise differences between neuropsychiatric disorders and control subjects. Many RSNs have been implicated in the pathophysiology of neuropsychiatric disorders, particularly the DMN, which is particularly active during rest and is deactivated during a variety of tasks. Moreover, the DMN is likely to be involved in the pathophysiology of dementia. One of the first clinical studies of rs-fMRI revealed that AD patients exhibited disrupted FC in the PCC, a hub of the DMN, and in the hippocampi (Greicius et al. 2004). Second, in patients with MDD, all nodes of DMN have been found to exhibit abnormal resting FC. These findings strongly suggest pervasive involvement of DMN in the pathophysiology of MD. To better understand how the DMN interacts with the pathophysiology of MD, continuous cross-referencing with task fMRI studies is needed. In a study of MDD, for example, the "dorsal nexus" including the dorsal PFC shows increased connectivity with three important cognitive-affective networks: the cognitive control network, DMN, and affective network (Sheline et al. 2010). In future studies, the function of the "dorsal nexus" should be explored with task fMRI, since its function is not well understood.

However, the results of many previous rs-fMRI studies should be interpreted with caution because of small sample sizes, heterogeneity of patients, and differences in methodological approach. In most rs-fMRI studies discussed in this review, sample sizes have been relatively small (Table 1). Theoretically, studies with larger samples should provide more reliable results. Laird and colleagues (2011) investigated intrinsic connectivity networks using a large data set derived from the Brain Map database (Laird et al. 2011, 2013). The spatial topographies derived from the Brain Map networks matched the set of RSNs derived from a 306-subject data set (Biswal et al. 2010) more closely than the set of RSNs derived from a 36-subject data set (Smith et al. 2009). Thus, it is likely that with an increased sample size, delineation of RSNs will become more stable. It has been suggested that rs-fMRI studies with small samples (<50 subjects) have a substantial risk of producing false negative results (Lieberman and Cunningham 2009), and the currently recommended sample size is over 100 participants. Although clinical applications of rs-fMRI appear to be promising, more work is needed before rs-fMRI will be routinely useful in clinical settings. Developments in MRI acquisition and preprocessing techniques have enabled the effective removal of problematic motion artifacts (Satterthwaite et al. 2013; Feis et al. 2015). However, one of the most important limitations of rs-fMRI studies is the need of vigorous correction for physiological artifacts resulting from respiration and cardiac activity. With current fMRI technology, low-frequency noise from the cardiac and respiratory cycle still affects the results of rs-fMRI. The ICA method is often applied to extract the physiological noise, and Griffanti and colleagues (2015) used ICA-based artifact removal in a clinical population, highlighting the importance of sensitive analysis of fMRI data for detecting FC alterations (Griffanti et al. 2015).

It should be borne in mind that intrinsic fluctuations as detected by rs-fMRI are small and variable, resulting in a large inter-individual variability in the RNS. Moreover, the degree of inter-individual variability may differ across brain regions/networks. In fact, a study on the inter-individual variability of rs-fMRI has shown that unimodal brain region has a low individual variability and polymodal association cortices have high individual variability (Mueller et al. 2013). The inter-individual variability seems to pose an issue against the clinical utility of rs-fMRI. Importantly, Finn and colleagues (2015) have demonstrated that individual variability in functional connectivity is reproducible across different rs-fMRI sessions (Finn et al. 2015). Consistently, a few other studies showed that functional connectivity was reproducible within a participant over a month (Chen et al. 2015a) or even over a period of 3.5 years (Choe et al. 2015). Using this 'stable' inter-individual variability, Finn and colleagues (2015) have even shown that inter-individual variability in rs-fMRI can be used as a "fingerprint" of a person (Finn et al. 2015). Hence, evidence is available in support for the robustness and stability of rs-fMRI measurement over time. To argue for the clinical utility, the issue is the degree of inter-individual variability induced by a disease process in comparison with that of in non-pathological conditions. This is an important open question, which should be answered in the future studies, and answers to this question might differ depending on what kind of neuropsychiatric pathology is questioned. However, a very recent rs-fMRI study of depression has shown that, when properly analyzed, rs-fMRI can provide information to help differentiate subtle

Table 1 Studies examining rs-fMRI for mood and cognitive disorders or healthy controls

Alzheimers disease and other dementia		
References	Subjects	Method
Wang et al. (2006)	13 AD (8 F) 70.1 years, 13 HCs (8 F) 69.5 years	Seed-based
Zarei et al. (2013)	16 AD (8 F) 69.5 years, 22 HCs (13 F) 70.7 years	Seed-based
Zhang et al. (2009)	16 Mild AD (10 F) 71.6 years, 16 HCs (9 F) 71.3 years	Seed-based
Dillen et al. (2016)	24 Prodromal AD (10 F) 71 years (55–78 years), 27 SCI (15 F) 65.7 years (51–79 years), 25 HCs (10 F) 62.4 years (50–73 years)	Seed-based
Zhang et al. (2010)	39 AD (21 F) 74.3 years (62–84 years): 16 mild AD (10 F) 71.6 years, 11 moderate AD (5 F) 76.6 years, 12 severe AD (6 F) 72.0 years, 16 HCs (9 F) 71.3 years	Seed-based
Yao et al. (2013)	35 AD (23 F) 72.4 years, 27 MCI (14 F) 73.8 years, 27 NC (11 F) 69.2 years	Seed-based
Brier et al. (2012)	510 (270 F) 77 years: 386 CDR 0, 91 CDR 0.5, 33 CDR 1	Seed-based
Kenny et al. (2012)	16 AD 77.3 years, 15 DLB 80.6 years, 16 HCs 76.3 years	Seed-based
Galvin et al. (2011)	35 AD (22 F) 75.3 years, 15 DLB (4 F) 71.7 years, 38 HCs (26 F) 73.9 years	Seed-based
Binnewijzend et al. (2012)	39 AD (16 F) 67 years, 23 MCI (8 F) 71 years, 43 HCs (20 F) 69 years	ICA
Schwindt et al. (2013)	16 AD (4 F) 72.2 years, 18 HCs (6 F) 71.0	ICA
Wu et al. (2011b)	15 AD (9 F) 64.0 years (53–79 years), 16 HCs (9 F) 65.1 years (47–79 years)	ICA
Pasquini et al. (2015)	21 AD (13 F) 72.3 years, 22 MCI (11 F) 65.3 years, 22 HCs (16 F) 66.3 years	ICA
Damoiseaux et al. (2012)	21 AD (12 F) 64.2 years, 18 HCs (6 F) 62.7 years	ICA
Castellazzi et al. (2014)	14 AD (10 F) 70.34 years, 12 MCI (8 F) 73.6 years, 16 HCs (12 F) 69.0 years	ICA
Adriaanse et al. (2014)	48 AD: 20 early onset (6 F) 59 years, 28 late-onset (11 F) 72 years, 46 HCs: 15 young (6 F) 61 years, 31 Old (14 F) 72 years	ICA
Franciotti et al. (2013)	18 AD (7 F) 76 years, 18 DLB (9 F) 75 years, 15 HCs (5 F) 74 years	ICA
Lowther et al. (2014)	13 AD (6 F) 75.5 years, 15 DLB (6 F) 80.6 years, 40 HCs (20 F) 77.8 years	ICA
Sanz-Arigita et al. (2010)	18 Mild AD (9 F) 70.7 years (59–79 years), 21 HCs (13 F) 70.7 years (60–81 years)	Graph analysis
Toussaint et al. (2014)	20 AD (9 F) 62 years, 38 HCs: 19 young (7 F) 20 years, 19 elderly (4 F) 61 years	Graph analysis
Kim et al. (2015)	71 AD (41 F): 25 CDR 0.5 (15 F) 70.0 years, 36 CDR 1 (20 F) 72.6 years, 10 CDR 2 (6 F) 70.9 years, 50 aMCI (28 F) 70.4, 31 HCs (26 F) 67.6 years	Graph analysis
Dai et al. (2015)	32 AD (18 F) 71.3 years (52–86 years), 38 HCs (25 F) 68.4 years (50–86 years)	Graph analysis
Major depressive disorder		
Peng et al. (2015)	16 MDD (9 F) 34.4 years, 16 HCs (9 F) 33.8 years	Seed-based
Chen et al. (2015a, b)	36 MDD (24 F) 32.1 years, 38 HCs (23 F) 30.8 years	Seed-based
Liu et al. (2012)	20 MDD (14 F) 28.4 years, 20 HCs (16 F) 29.0 years	Seed-based
Sheline et al. (2010)	18 MDD (7 F) 35.9 years, 17 HCs (12 F) 30.9 years	Seed-based
Ye et al. (2012)	22 MDD (14 F) 46.7 years, 30 HCs (19 F) 45.9 years	Seed-based

Table 1 continued

Alzheimers disease and other dementia		
References	Subjects	Method
Shen et al. (2015)	16 MDD 25–50 years, 16 HCs 25–50 years	Seed-based
Kerestes et al. (2015)	21 MDD (11 F) 19.3 years, 21 HCs (11 F) 19.2 years	Seed-based
Lui et al. (2011)	21 MDD: 32 non-refractory (11 F) 32 years, 28 Refractory (10 F) 33 years, 48 HCs (17 F) 35 years	Seed-based
Guo et al. (2013)	23 TRD (12 F) 27.4 years, 19 TSD (9 F) 28.1 years, 19 HCs (9 F) 24.4 years	Seed-based
Ma et al. (2012)	18 TRD (7 F) 27.4 years, 17 TSD (7 F) 26.7 years, 17 HCs (7 F) 24.2 years	Seed-based
Greicius et al. (2007)	28 MDD (16 F) 38.5 years, 20 HCs (11 F) 35.4 years	ICA
Zhu et al. (2012)	32 MDD (14 F) 20.5 years, 33 HCs (14 F) 20.3 years	ICA
Li et al. (2013)	24 Pretreatment MDD (16 F) 31.8 years, 16 posttreatment MDD (13 F) 32.6 years, 29 HCs (20 F) 33.6 years	ICA
Peng et al. (2014)	16 MDD (9 F) 34.4 years, 16 HCs (9 F) 33.8 years	Graph theory
Bipolar disorder		
Torrisi et al. (2013)	20 BD (10 F) 42.1 years, 20 HCs (10 F) 39.8 years	Seed-based
Favre et al. 2014)	20 BD-euthymic (11 F) 42.0 years, 20 HCs (10 F) 43.7 years	Seed-based
Rey et al. (2016)	15 BD-euthymic (6 F) 41.4 years, 12 BD-non-euthymic (9 F) 42.6 years, 15 HCs-EU (6 F) 40.8 years, 12 HCs-NE (9 F) 40.8 years	Seed-based
Brady et al. (2016)	28 BD-manic (8 F) 27.5 years, 24 BD-euthymic (8 F) 30.9 years, 23 HCs (7 F) 29.7 years	Seed-based
Samudra et al. (2015)	21 SZ (7 F) 38.1 years, 40 SAD (22 F) 39.0 years, 27 BD (8 F) 39.7 years, 65 HCs (36 F) 40.0 years	Seed-based
Ongur et al. (2010)	17 BD (8 F) 34.4 years, 14 SZ (6 F) 42.3 years, 15 HCs (6F) 37.9 years	ICA
Khadka et al. (2013)	64 BD (29 F) 35.1 years, 70 SZ (27 F) 37.4, 118 HCs (63 F) 36.4	ICA
Goya-Maldonado et al. (2016)	20 BD (13 F) 35.8 years, 20 unipolar (14 F) 35.6 years, 20 HCs (13 F) 36.2 years	ICA
Lois et al. (2014)	30 BD (17 F) 40.8 years, 35 HCs (20 F) 41.9 years	ICA
Ford et al. (2013)	15 MDD (5 F) 20.6 years, 15 BD-Type1 (11 F) 19.8 years	ICA

differences in symptoms belonging to a single disease entity at an individual level. Furthermore, using each subtype diagnosis and features in functional connectivity, they were able to predict patients' responses to transcranial magnetic stimulation at individual levels (Drysdale et al. 2017). This new evidence promises the utility of rs-fMRI in clinical settings at an individual level.

Conclusion

Rs-fMRI has many advantages over task fMRI for clinical applications. Many early studies have already suggested that cognitive, affective, sensorimotor RSNs can be retrieved with rs-fMRI in the resting-state brain. Clinical rs-fMRI studies have shown that differences in intrinsic activity in resting-state brain reflect the pathophysiology of neuropsychiatric diseases, not limited to MD and dementia. Moreover, RSN activity provides information with value for distinguishing clinical populations into groups, such as healthy and patient groups.

Despite several limitations in the current body of clinical rs-fMRI studies, improvement of acquisition and analysis methods is currently under intensive investigation. In this regard, it should be noted that MRI is not the only way to capture spontaneous fluctuation of brain activity. Since Berger, it has been well known that electric signals recorded from the brain shows fluctuation of brain rhythms, while subjects are at rest. The combination of fMRI and other neurophysiological measurements to examine resting-state fluctuations of brain status would become a powerful tool to hunt for biomarkers of neuropsychiatric

disorders. For example, simultaneous electroencephalogram (EEG)-fMRI can observe neurophysiological states in high temporal and spatial resolution, despite technical challenges (Omata et al. 2013). The establishment of clinical biomarker with rs-fMRI may refine the staging and classification of the patients and may help predict the effects of treatment (Drysdale et al. 2017). Such technique can be further sophisticated by combining possibly with other measurements such as EEG, given the development of easy-to-use, next-generation EEG-fMRI technique. Therefore, we conclude that clinical rs-fMRI, possibly in combination with other measurement for spontaneous fluctuation of brain activity, will likely become a clinically important tool in the near future.

Acknowledgements This study was in part supported by the Strategic Research Program for Brain Science of BMI Technologies for Clinical Application carried out under the Strategic Research Program for Brain Sciences and Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS), Health Labor Science Research Grants from Japan Agency for Medical Research and development (AMED) and KAKENHI (26120008 and 16H03306) from MEXT, the Research Grant for Janssen Pharmaceutical K.K. and the Intramural Research Grant for Neurological and Psychiatric Disorders of National Center of Neurology and Psychiatry, Japan.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest in relation to this article.

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