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Regional homogeneity, functional connectivity and imaging markers of Alzheimer's disease: A review of resting-state fMRI studies

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Abstract

Resting-state functional magnetic resonance imaging (fMRI), a promising technique for measuring brain activities during rest, has attracted much attention in the past few years. In this paper, we review recent progress on the study of Alzheimer's disease (AD) based on resting-state fMRI. First, we briefly introduce some AD-related studies from other groups. Then we describe our AD-related work in detail from three aspects: (1) alterations in regional homogeneity (ReHo) of the fMRI signal in the resting state, (2) altered patterns of functional connectivity from regions of interest and whole brain analyses, and (3) discriminative analyses based on classification features from resting-state fMRI data for differentiating AD patients from healthy elders. Finally, we summarize the main results and some prospects for future work.

Keywords: Alzheimer's disease; Resting-state fMRI; ReHo; Functional connectivity; Biomarkers

1. Introduction

Alzheimer's disease (AD) is a major neurodegenerative disorder characterized by cognitive and intellectual deficits and behavioral disturbances without a definitive cause or an effective treatment. It gradually destroys a patient's memory and ability to reason, make judgments, communicate and carry out daily activities (Jeong, 2004). With the aging of the population worldwide, this disorder has attracted much attention, especially by neurologists, neuroscientists and neuroradiologists.

In the past two decades, several imaging techniques have been used to investigate changes in brain functions in patients with AD. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are effective methods for investigating brain activity through observing changes in cerebral blood flow or cerebral metabolism. AD patients show hypo-metabolism or hypo-perfusion in many brain regions, including the posterior cingulate cortex (PCC), parietal, temporal, and prefrontal cortices (Nestor, Scheltens, & Hodges, 2004). More recently, task based functional magnetic resonance imaging (fMRI) has been developed to detect local brain activities when performing a specific task. A large number of fMRI studies have revealed that the patterns of activation or deactivation[1] are changed in AD patients during the performance of tasks (Buckner, Snyder, Sanders, Raichle, & Morris, 2000; Gould, Brown, Owen, Bullmore, & Howard, 2006; Remy, Mirrashed, Campbell, & Richter, 2005; Rombouts, Goekoop, Stam, Barkhof, & Scheltens, 2005).

Abbreviations: AD, Alzheimer's disease; ROI, region of interest; ReHo, regional homogeneity.

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[1] Some previous task based PET and fMRI studies in healthy subjects have consistently demonstrated task specific increases in regional brain activity during goal-directed tasks. Researchers have also frequently found task-induced deactivation in some brain regions (Amedi et al., 2005; Kobayashi et al., 2006). Many deactivated brain regions appear to be largely task independent, varying little in their location across a wide range of tasks (for a review see Raichle & Mintun, 2006). These deactivations during specific tasks are considered to be an organized default mode of brain function.

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However, this method requires extensive participation of subjects, which may be difficult for some participants, especially for AD patients. Consequently, resting-state fMRI has been developed and has attracted considerable attention. Resting-state fMRI signals may reflect spontaneous neuronal activity (Biswal, Yetkin, Haughton, & Hyde, 1995; Wang et al., 2008) and/or the endogenous/background neurophysiological process of the human brain in the resting state (for a review see Fox & Raichle, 2007). This method has practical advantages for clinical applications because no stimulation and response are required; thus it can be performed easily by subjects, especially patients.

Although resting-state fMRI is a relatively young technique, many exciting findings have been reported in the past several years (for a review see Fox & Raichle, 2007). Biswal et al. (1995) found that spontaneous low-frequency fluctuations (SLFF) (<0.08 Hz) of the blood oxygen level dependent (BOLD) signals within the somatomotor system, measured during rest, were highly synchronous and concluded that these were physiologically meaningful. Since then, the SLFF of the resting-state fMRI signal have been used in healthy subjects to investigate the brain activities, within various functional systems, such as motor (Jiang, He, Zang, & Weng, 2004; Lowe, Mock, & Sorenson, 1998), auditory (Cordes et al., 2001), visual (Lowe et al., 1998), language (Hampson, Peterson, Skudlarski, Gatenby, & Gore, 2002) and limbic systems (Greicius, Krasnow, Reiss, & Menon, 2003; Tian, Jiang, Liu, et al., 2007; Wink, Bernard, Salvador, Bullmore, & Suckling, 2006). Interestingly, the SLFF of resting-state fMRI signals have also been used to characterize the pathophysiological changes of some diseases, such as multiple sclerosis (Lowe et al., 2002), epilepsy (Waites, Briellmann, Saling, Abbott, & Jackson, 2006), attention deficit hyperactivity disorder (Tian, Jiang, Liang, et al., 2007; Zang et al., 2007), schizophrenia (Liang et al., 2006; Salvador et al., 2007; Zhou, Liang, Jiang, et al., 2007; Zhou, Liang, Tian, et al., 2007), major depression (Anand et al., 2005; Greicius et al., 2007), blindness (Liu et al., 2007; Yu et al., 2007) and acute brainstem ischemia (Salvador et al., 2005). Thus, we believe that resting-state fMRI will be an increasingly important avenue for exploring the functional abnormalities of AD patients.

In the past several years, many researchers, including ourselves, have begun to study the pathophysiology of AD by investigating changes in the SLFF of resting-state fMRI signals (Greicius, Srivastava, Reiss, & Menon, 2004; He, Wang, et al., 2007; Li et al., 2002; Maxim et al., 2005; Wang, Jiang, et al., 2006; Wang et al., 2007; Wang, Zang, et al., 2006) (extended details about these studies can be found in Table 1). In this paper, we will review resting-state fMRI studies on AD from the following perspectives: in Section 2, we will review AD-related changes of the regional coherence of resting fMRI signals. In Section 3, we will describe findings based on functional connectivity analysis. In Section 4, we will review the discriminative analysis of AD based on resting-state fMRI data. Finally, limitations, conclusions, and future work will be discussed in Sections 5 and 6.

2. Regional coherence

Because there is no specific stimulus in the resting state, traditional model-driven methods for task-related data analysis may

Table 1
Published results of AD–related resting-state fMRI study

Authors	Patients (AD/NC)	Method	Main conclusions
Li et al. (2002)	10/9	Cross-correlation coefficients of SLFF analysis	The cross-correlation coefficients of SLFF in mild cognitive impairment were significantly higher than those of AD patients, but significantly lower than those of control subjects
Greicius et al. (2004)	14/14	Independent component analysis	Default-mode network activity is abnormal in AD. The activity in the default-mode network ultimately proved to be a sensitive and specific biomarker for incipient AD
Maxim et al. (2005)	9/12	Wavelet-based maximum likelihood of fractional Gaussian noise	AD patients had greater persistence of resting fMRI noise in the medial and lateral temporal lobes, insula, dorsal cingulate/medial premotor cortex, and left pre- and post-central gyrus
Wang, Jiang, et al. (2006)	14/14	Correlation and Fisher linear discriminative analysis	Correlation/anti-correlation pattern of the two intrinsically anti-correlated networks is a sensitive feature for the discriminative analysis of early AD
Wang, Zang, et al. (2006)	13/13	Correlation analysis based on ROI	Decreased activity in default mode network activity offers a clue to reduced integrity in hippocampus-related networks in early AD
Wang et al. (2007)	14/14	Correlation analysis of the whole brain	AD patients show decreased functional connectivity between anterior–posterior regions but increased connectivity between within-lobe regions, and a disruption of the anti-correlation patterns between two intrinsically anti-correlated networks during the resting state
He, Wang, et al. (2007)	15/15	ReHo analysis of the whole brain	AD patients exhibited changes in regionally low-frequency fluctuation coherence in the PCC/PCu, the occipital and temporal lobes
Allen et al. (2007)	8/8	Correlation analysis based on ROI	Healthy subjects showed hippocampal functional connectivity with diffuse cortical, subcortical, and cerebellar sites, while patients demonstrated markedly reduced functional connectivity, including an absence of connectivity with the frontal lobes

ROI, region of interest; AD, Alzheimer's disease; NC, normal controls.

not be suitable for analyzing resting-state fMRI data. Thus, data-driven methods have been proposed for studying resting-state fMRI signals (He, Wang, et al., 2007; Zang, Jiang, Lu, He, & Tian, 2004).

2.1. Cross-correlation coefficient method

By measuring the cross-correlation coefficients (a measure of functional synchrony) between pairs of voxel time courses within regions of the hippocampus, Li et al. (2002) found that the cross-correlation coefficients of SLFF within the hippocampus were significantly lower in AD patients compared with healthy subjects. In addition, they also found that for mild cognitive impairment (MCI), the functional synchrony of SLFF within the hippocampus was significantly higher than that in AD patients, but significantly lower than those in healthy subjects. Additionally, they found that an exponential curve could describe the relationship between the cross-correlation coefficients of SLFF and Mini-Mental Status Examination (MMSE) scores[2], which indicated a rapid decrease in cognitive capacity in AD. This study indicated for the first time that the cross-correlation coefficients of SLFF could be regarded as quantitative markers for the early diagnosis of AD.

2.2. Regional homogeneity method

Regional homogeneity (ReHo)[3] measures the functional coherence of a given voxel with its nearest neighbors and can be used to evaluate resting-state brain activities (Zang et al., 2004) based on the hypothesis that significant brain activities would more likely occur in clusters than in a single voxel. The pattern of resting-state brain activities obtained by using the ReHo method (He, Zang, Jiang, Liang, & Gong, 2004; He, Zang, Jiang, Lu, & Weng, 2004; Zang et al., 2004) is very similar to that of previous PET studies in which earlier researchers found that some brain regions deactivated when the subject was performing certain tasks (Amedi, Malach, & Pascual-Leone, 2005; Kobayashi, Bagshaw, Grova, Dubeau, & Gotman, 2006; Raichle et al., 2001; Shulman et al., 1997). This indicates that the ReHo index could be regarded as a measure for investigating human brain activities in the resting state and may be useful for revealing the complexity of human brain function.

He, Wang, et al. (2007) used the ReHo index to investigate the pattern of regional coherence of SLFF in AD patients. The results demonstrated that AD patients showed significant decreases in regional coherence in the posterior cingulate cortex/precuneus (PCC/PCu) when compared with healthy subjects (Fig. 1). In healthy subjects, the PCC/PCu had the highest metabolic rates (Raichle et al., 2001; Shulman et al., 1997) and was considered as a central node in a default-mode network during rest (Raichle & Snyder, 2007). Moreover, this region had the highest mean ReHo value in younger (He, Zang, Jiang, Liang, et al., 2004) and older adults (He, Wang, et al., 2007). They also found the ReHo index of the PCC/PCu significantly decreased with the progression of this disease as measured using MMSE scores. Importantly, all the results from the PCC/PCu remained significant even after correcting for the effect of regional atrophy (He, Wang, et al., 2007). The AD patients also showed increased SLFF coherence in the bilateral cuneus, left lingual gyrus and right fusiform gyrus compared with healthy subjects (Fig. 1). These regions are consistent with previous findings of AD-related increased activation during cognitive tasks, as explained in terms of a compensatory-recruitment hypothesis (Backman, Almkvist, Nyberg, & Andersson, 2000; He, Wang, et al., 2007; Prvulovic et al., 2002).

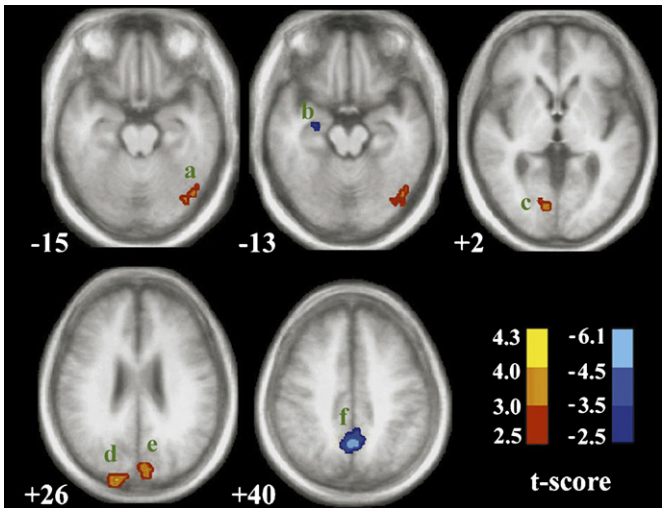

Fig. 1. *T*-statistical difference map between AD patients and healthy subjects. The AD patients showed a significantly increased ReHo in the left FG (a), right LG (c), right cuneus (d) and left cuneus (e) and decreased ReHo in the PCC/PCu (f). *T*-score bars are shown on the right. Hot and cold colors indicate AD-related ReHo increases and decreases, respectively. Reprinted from; He, Wang, et al. (2007), with permission from Elsevier.

As a summary of this section, these resting-state fMRI studies showed abnormal changes in the hippocampus and PCC of AD patients, which is consistent with some previous PET studies in which hypo-metabolism or hypo-perfusion was found in these two brain regions in AD (Chetelat et al., 2005, 2008; Matsuda, 2001, 2007; Mosconi, Brys, et al., 2007; Mosconi, De Santi, et al., 2007; Mosconi, Tsui, et al., 2007; Nestor, Fryer, Smielewski, & Hodges, 2003). Significant correlations between the indexes of regional coherence and MMSE indicate that these measures could be useful for monitoring disease progression in AD patients.

The regional coherence indexes reflect the similarity of the fMRI series of a voxel with its neighbor voxels. Other measures of resting-state fMRI signals might also help us understand the abnormal changes of brain activity in AD. For example, Maxim

[2] The staging of AD can be assessed by the Mini-Mental State Examination (MMSE), which is a brief composite measure of mental status (maximum score is 30). People with AD generally score 26 points or less.

[3] For a given voxel, ReHo = A/B where $A = \sum R_i^2 - n \cdot \bar{R}$, $B = k^2(n^3 - n)/12$; which is the Kendall's coefficient of a given voxel and its nearest neighbors, ranging from 0 to 1. $R_i = \sum_{j=1}^{k} r_{ij}$ is the sum rank of the ith time point and r_{ij} is the rank of the ith time point of the jth voxel; $\bar{R} = (n+1)k/2$ is the mean of the R_i; n is the length of the time series; k is the number of voxels within the measured cluster (Zang et al., 2004).

et al. (2005) used a wavelet-based maximum likelihood to estimate the Hurst exponent of the fMRI signal and demonstrated that the Fractional Gaussian noise (FGn)[4] is a very attractive model for resting fMRI time series. They found that AD patients had greater noise in the medial and lateral temporal lobes, insula, dorsal cingulate/medial premotor cortex, and left pre- and postcentral gyrus than healthy subjects (Maxim et al., 2005). The disturbance of the long memory dynamics properties in fMRI time series may reflect neurodegenerative changes in the neuronal systems of AD patients, which might indicate that the brain activity has become less dynamically complex as a consequence of AD (Maxim et al., 2005). The combination of the FGn model and ReHo or cross-correlation coefficients of SLFF might strengthen the understanding of the brain activity in the resting-state in future studies.

3. Functional connectivity

In functionally related brain regions, even located remotely, the SLFF of the BOLD signal in the resting-state are synchronous, which implies the existence of neuronal connections that facilitate coordinated activity. In light of this, the correlation of spontaneous activity can provide insight into the fundamental functional architecture of healthy subjects and of some diseases (for a review see Fox & Raichle, 2007). What are the changes in functional connectivity in patients with AD? In what follows, we provide some answers to this question from results derived from both region of interest (ROI) and whole brain analyses.

3.1. Region of interest (ROI) analysis

Region of interest analysis is the most common method for investigating the functional connectivity pattern of a specific region by selecting this region as a 'seed' and evaluating the correlation map between the this region and every other voxel of the brain. Many studies have demonstrated that the hippocampus is an important node in the memory network (Buckner et al., 2005; Celone et al., 2006; Greicius et al., 2004), and that memory impairment is one of the earliest and most devastating symptoms of AD (Grady, Furey, Pietrini, Horwitz, & Rapoport, 2001). Previous studies have shown morphological abnormalities in this structure in AD patients (for a review see Chetelat & Baron, 2003). Since the hippocampus is one of the earliest loci affected by the accumulation of AD lesions (for a review see De Lacoste & White, 1993), the functional connectivity pattern of the hippocampus with other brain regions might be affected in subjects with MCI and AD. However, the pattern of functional connectivity in the resting-state between the hippocampus and other parts of the whole brain in AD had remained unclear till recent studies by Wang, Zang, et al. (2006) and Allen et al. (2007). In those two studies, the authors selected the bilateral anterior hippocampus as a 'seed' region and investigated the patterns of functional connectivities of the hippocampus in AD (Allen et al., 2007; Wang, Zang, et al., 2006).

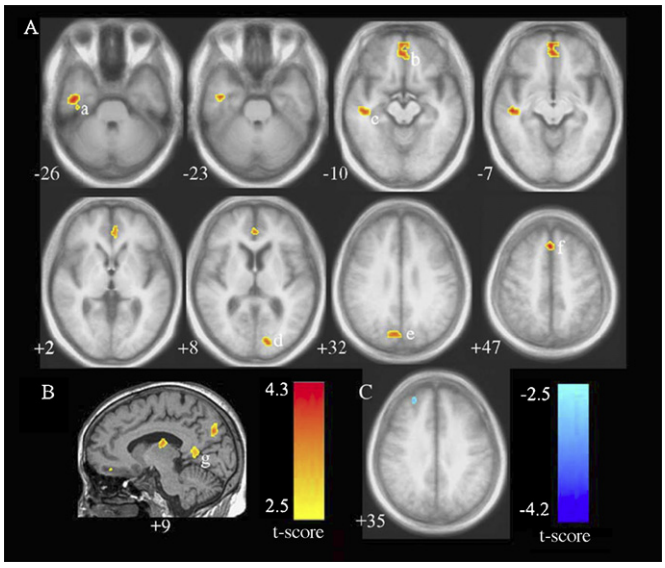

Fig. 2. Alterations in hippocampal connectivity in mild AD subjects. Regions showing decreased connectivity to the right hippocampus in AD subjects are indicated with hot color. Regions showing increased connectivity with the left hippocampus in AD subjects are indicated with cool color. (A) Regions that had decreased connectivity to the right hippocampus include the dorsal MPFC, MPFC/vACC, right cuneus extending into precuneus, left cuneus, right ITC, right STG and MTG in the AD group. a = ITC (including area inferior temporal gyrus (BA 20) and perirhinal cortex); b = MPFC and vACC; c = STG and MTG; d = left cuneus; e = right cuneus extending into precuneus, f = dorsal MPFC. (B) A sagittal view obtained from a representative subject highlights a 10-voxel cluster (270 mm^3) in the right PCC that survived the height but not the extent threshold. g = PCC (i.e., the right retrosplenial cortex). (C) A region with a 20-voxel cluster (540 mm^3) in the right lateral prefrontal cortex (BA 9) shows significantly increased connectivity to the left hippocampus in the AD group. Voxels with $|t(24)| > 2.492$ ($P < 0.02$) and cluster size >513 mm^3 were considered to be significantly different in hippocampal connectivity between the two groups. These criteria met a corrected threshold of $P < 0.05$. There was no significantly decreased functional connectivity between the left hippocampus and other regions in the whole brain. Reprinted from; Wang, Zang, et al. (2006), with permission from Elsevier.

Wang and co-workers found that the functional connectivities between the right hippocampus and a set of regions such as the medial prefrontal cortex (MPFC), ventral anterior cingulate cortex (vACC), right infrotemporal cortex, right cuneus/precuneus, left cuneus, right superior and middle temporal gyrus and PCC were disrupted in AD patients (Fig. 2A). Disrupted hippocampal connectivities to the MPFC, vACC and PCC provided further support for decreased activity in the default mode network, as previously shown in AD (Celone et al., 2006; Greicius et al., 2004). Decreased functional connectivities between the hippocampus and the visual cortices could indicate reduced integrity of hippocampus-related cortical networks in AD. Increased functional connectivities between the left hip-

[4] Fractional Gaussian noise (FGn), first advanced by Mandelbrot and Van Ness (1968), was the first comprehensive model for stationary increments of a self-similar process parameterized by the Hurst exponent (H, self-similarity) and variance (Mandelbrot and Van Ness, 1968). For FGn with $H < 0.5$, the time series is characterized by high frequency fluctuations and demonstrates a negatively autocorrelated or antipersistent property; for FGn with $H > 0.5$, the times series is characterized by stationary long memory ($1/f$) properties at low frequencies; and an FGn with $H = 0.5$ corresponds to the classic Gaussian white noise process (Maxim et al., 2005; Percival and Walden, 2000).

pocampus and the right lateral prefrontal cortex have also been found in AD (Fig. 2C). This increased connectivity could be interpreted as a compensatory recruitment of cognitive resources to maintain task performance in AD patients. This is consistent with the assumption that AD patients may be able to use additional neural resources in prefrontal regions to compensate for losses in cognitive function (Grady et al., 2003).

A similar study by Allen et al. (2007) also found that healthy subjects showed hippocampal functional connectivity with diffuse cortical, subcortical, and cerebellar sites, while AD patients demonstrated markedly reduced functional connectivity, including an absence of connectivity with the frontal lobes (Allen et al., 2007). In contrast to the study by Wang, Zang, et al. (2006), Allen et al.'s (2007) study indicated a more extensive disruption of hippocampal connectivity in AD, with no regions of increased connectivity and an absence of hippocampal-frontal connectivity. This may have been caused by differences in the severity of symptoms of the subjects in these two studies. According to Allen et al. (2007), the subjects in their study had a greater disease severity than those in Wang et al.'s, supporting the notion that the functional connectivity of the hippocampus declines progressively throughout the disease. Another possible explanation is that sample size, 16 (8 AD) subjects in Allen et al.'s study (2007) compared with 26 (13 AD) subjects in Wang, Zang, et al.'s (2006) study, might have had an effect on the statistical results within/between the groups.

These findings suggest that resting-state fMRI could be an appropriate approach for studying the pathophysiological changes of AD. Dysfunctional circuitry connecting the hippocampus with other brain regions is a likely contributor to deficits in learning, memory and the other areas of cognition characteristic of AD and supports the hypothesis that disconnection is a possible explanation for the impairment of memory and other higher cognitive functions observed in AD (for reviews see Delbeuck, Van der Linden, & Collette, 2003; Delbeuck, Collette, & Van der Linden, 2007; Grady et al., 2001). The pattern of hippocampus functional connectivity may ultimately to be an in vivo marker for diagnosis and monitoring of AD progression.

3.2. Whole brain network analysis

Considering the possibility that abnormalities in functional connectivities may exist in widely distributed regions in AD, it is helpful to study functional connectivity from the perspective of the whole brain for a better understanding of the pathophysiology of AD. In a recent study, Wang et al. (2007) divided the whole brain using an anatomically labeled template, paired every region with every other region and calculated correlation coefficients between each pair of brain regions, in both AD patients and elderly healthy subjects. The results indicated that AD patients show many decreased correlations; nearly half of which were between the prefrontal lobe and the parietal lobe. These results are consistent with previous studies that have suggested an anterior–posterior disconnection in AD patients, either under task conditions or in the resting-state (Horwitz, Grady, Schlageter, Duara, & Rapoport, 1987; Horwitz et al., 1995). In addition, AD patients showed some increased correlations. Compared with the decreased ones, the increased correlations were mainly between regions within lobes, such as the prefrontal lobe, the parietal lobe, the occipital lobe and the temporal lobe. Such increased functional connectivities within the prefrontal lobe have been found in many previous studies and have been interpreted as a compensatory effect of early AD patients (Grady et al., 2001, 2003; Horwitz et al., 1995). These results suggest that the compensatory effect was not restricted to the prefrontal lobe but was also distributed in other lobes. More interestingly, in addition to these altered correlations, the authors also found some altered anti-correlations, many of which were between two intrinsically anti-correlated networks (the task-positive network and its anti-correlated network). According to two previous studies by Fox et al. (2005) and Fransson (2005), the balance between these two intrinsically anti-correlated networks may be associated with the attention process. Therefore, we suggest that the disturbance of the balance between the intrinsically anti-correlated networks may be associated with attention deficits in AD patients.

4. Discriminative analysis

One of the ultimate goals of research in this area is to find objective and quantitative indexes for the early diagnosis and therapeutic evaluation of AD patients. From the analyses of resting-state fMRI data, it is possible that we may find some indexes that have a relatively high sensitivity and specificity for monitoring the evolution of the disease.

Some previous studies suggested that atrophy of the medial temporal lobe might be a sensitive marker for AD (Chetelat & Baron, 2003; Scheltens, Fox, Barkhof, & De Carli, 2002; Scheltens, Barkhof, & Fazekas, 2003). Several PET studies indicated that changes in blood flow or glucose metabolism might be biomarkers to discriminate AD patients from normal controls (De Santi et al., 2001; Herholz et al., 2002; Mosconi, Brys, et al., 2007; Reiman et al., 2004; Small, 1999, 2004; Small et al., 2006). Some task fMRI studies have regarded changes in brain activity as biomarkers of AD (Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005; Rombouts, Goekoop, et al., 2005). In resting-state fMRI studies, the measures that we will discuss below have also been found to be sensitive and specific biomarkers for AD (Greicius et al., 2004; Li et al., 2002; Wang, Jiang, et al., 2006).

As described previously, Li et al. (2002) found an exponential curve that described the relationship between MMSE scores and the cross-correlation coefficients of the hippocampus. On the basis of the receiver operating characteristic curve, the cross-correlation coefficients index test will provide an 80% true-positive rate at a level 10% false-positive rate, as suggested by Li et al. (2002). This result indicates that the cross-correlations of SLFF could be taken as a noninvasive quantitative marker for the preclinical stage of AD.

Greicius et al. (2004) applied a goodness-of-fit analysis of the default mode network between AD patients and normal controls at the individual subject level and discriminated the AD patients at a sensitivity of 85% and a specificity of 77%. This result

suggests that the activity in the default mode network in the resting-state may be a sensitive and specific indicator of AD.

In the early stages of the disease, AD patients show attention deficits, which may be a factor underlying other cognitive deficits (Balota & Faust, 2001; Perry & Hodges, 1999). As introduced above, some previous studies have suggested that the balance between intrinsically anti-correlated networks is associated with the attention process (Fox et al., 2005; Fransson, 2005; Lustig et al., 2003). Wang, Jiang, et al. (2006) used the correlation/anti-correlation coefficients between all pairs of regions in the two networks as a classification feature and proposed a discriminative approach to distinguish AD patients from healthy subjects. The correct prediction ratios were 93% and 79%, respectively, for AD patients and elderly healthy subjects, and the average correct prediction ratio was 83%.

In summary, these studies have shown that functional imaging has potential for the early detection of AD patients, which might open a new avenue into the study of the pathophysiology of AD or other cognitive diseases. However, the translation of resting fMRI studies from the research laboratory to clinical practice is still in the preliminary stages (Matthews, Honey, & Bullmore, 2006; Rombouts, Barkhof, et al., 2005). Big challenges remain for future studies.

5. Limitations

It should be noted that the methods introduced in this review have some limitations. For example, the temporal and spatial resolutions of voxel time courses obtained using different acquisition parameters may strongly affect the values of the cross-correlation coefficients of SLFF (Li et al., 2002). In the ROI analysis method, the results might be affected by the reproducibility of the selection of ROIs. In addition, the results of the whole brain functional connectivity analysis, based on a selected template (Wang et al., 2007), might also be affected by the time-course variability within each region of the template.

Although resting-state fMRI has brought important progress in understanding the normal human brain and psychiatric diseases, limitations in this technique should be noted. Some inevitable noise, such as cardiac and/or respiratory cycle-related pulsations and instrumental and thermal sources of noise; and head movement (rotation or translation) of the subject during scanning, will affect the stability of resting-state fMRI signals, although we can use some methods such as regression to reduce these noises. New and better methods need to be developed to further reduce these sources of noise.

Another limitation is that we cannot completely remove the effects of heterogeneity in clinical symptoms, duration of illness, severity of symptoms, and medication among the patients that are being measured; although with time and an increased number of samples, some of the effects of this heterogeneity will be minimized. Similarly, imaging measures of brain function may be sensitive to constitutional or chronic differences between individuals, in areas such as genetics, intelligence or educational levels, learning, mood or medication.

6. Conclusions and future perspectives

In conclusion, we have provided a brief review of recent resting-state fMRI studies on AD. These studies demonstrated that the regional coherence of the fMRI signal are significantly altered in AD patients. Altered patterns of functional connectivities based on ROI and whole brain analysis indicate that AD may be a disconnection syndrome. These results have improved our understanding of the pathophysiological basis of AD. Although much is known, more has yet to be discovered, and the following research directions show promise for interesting discoveries in the near future.

One potential future direction would be to develop new methods for detecting intrinsic noise and reducing physiological artifacts effects, such as acquiring images at a higher sampling rate (TR < 1 s) (Cordes et al., 2001; Rombouts et al., 2003), or using certain robust methods that have been reported in recent studies such adaptive filter (Deckers et al., 2006), regression (Shmueli et al., 2007), or cued the subjects to breathe at a relatively constant rate and depth (Birn, Diamond, Smith, & Bandettini, 2006) so as to partly reduce these physiological effects in resting-state fMRI data.

A second direction would be to attempt to understand the neuroanatomical basis for resting-state brain activities. Using resting-state fMRI, several recent studies have demonstrated that the human brain is strongly symmetrical, subtended predominantly by low-frequency time series components and has an efficient small-world topology (Achard & Bullmore, 2007; Salvador et al., 2005). Moreover, the organization of brain functional networks, as derived from resting-state fMRI data, has been found to have a large degree of topological and anatomical similarity with the organization of large-scale structural brain networks (He, Chen, Evans, 2007; Sporns & Honey, 2006). Thus, one can suspect that the AD-related functional alterations found by resting-state fMRI are likely to be associated with structural disruptions. Future studies could be conducted to examine the associations between structure and function in patients, using anatomical and functional data measured from the same subjects. Such investigations would provide crucial insights into the understanding of how brain function is affected in AD patients, if the underlying structural basis is disrupted.

Another recommendation involves combining fMRI and PET/SPECT as a way to compare different measures of brain function concurrently. Functional brain imaging has contributed to a greater understanding of regional brain function at rest, during normal sensorimotor and cognitive function, and in disease states (see a review in Fox & Raichle, 2007). PET can measure cerebral blood flow, cerebral blood volume, cerebral glucose metabolism and cerebral oxygen metabolism. Clinical researchers from the University of Pennsylvania Health System were the first to combine fMRI and PET scanning, creating a way to compare different measurements of the brain's function at the same time. Their result demonstrated that there is a relative plateau in metabolic values in brain regions in which cerebral blood flow rates were higher (Newberg et al., 2005). Therefore, we suggested that combining such PET/SPECT and resting-state

fMRI analyses might lead to a clearer diagnosis and therapeutic evaluation of AD.

A fourth recommendation for future research would be to carry out longitudinal studies. Those at greatest risk for the development of AD are known to be individuals with MCI. MCI progresses to AD with a prevalence about 10–15% annually (Gauthier et al., 2006; Petersen, 2007). Nearly half of MCI patients will convert to AD within 3–5 years (Petersen et al., 2001). A longitudinal study from healthy elderly subjects to MCI and finally to AD patients could further support our previous results and enrich our understanding of the pathophysiological basis of this disease.

A further recommendation would be to combine resting-state fMRI with genetic studies to predict the progress of AD. The APOE (4 allele, present in 50–75% of AD patients, can be used to predict when, but not if, a person is predisposed to develop AD (Bookheimer et al., 2000; Meyer et al., 1998; Reiman et al., 2001, 2004, 2007; Small et al., 2000). In the future, it would be interesting to explore brain activity in subjects with APOE (4 using resting-state fMRI.

Finally, given the small sample size of AD patients, statistical power is of potential concern. Larger sample sizes could reduce individual effects on the results and allow us to develop effective and applicable biomarkers for psychiatric diseases. This could be of great importance, especially for the early diagnosis of AD.

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