Resting state brain activity and functional brain mapping*

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Abstract Functional brain imaging studies commonly use either resting or passive task states as their control conditions, and typically identify the activation brain region associated with a specific task by subtracting the resting from the active task conditions. Numerous studies now suggest, however, that the resting state may not reflect true mental "rest" conditions. The mental activity that occurs during "rest" might therefore greatly influence the functional neuroimaging observations that are collected through the usual subtracting analysis strategies. Exploring the ongoing mental processes that occur during resting conditions is thus of particular importance for deciphering functional brain mapping results and obtaining a more comprehensive understanding of human brain functions. In this review article, we will mainly focus on the discussion of the current research background of functional brain mapping at resting state and the physiological significance of the available neuroimaging data.

Keywords: resting state brain activity, default mode brain networks, BOLD, deactivation, OEF.

Currently, many functional brain mapping approaches based on blood oxygen level-dependent (BOLD) contrasts, such as functional magnetic resonance imaging (fMRI), have been widely used in the mapping of human brain activity in normal physiological states, mental disorders and in cerebral injury research[1—4]. Functional neuroimaging studies mainly focus on the regions of the brain that show increased activity defined by an increase in signals during an active task compared with a passive baseline. Recently, however, many studies have suggested that even in resting or passive task states, the human brain is still functionally active. This phenomenon has therefore attracted much interest[5,6] in this field as investigators generally use a no task-related resting state or passive task state as the control conditions in functional brain imaging studies. Obviously, if there are specific mental operations that occur during either resting or passive task states, this would greatly influence any results arising from functional brain mapping studies of goal-directed tasks, and the subsequent interpretation of such data. Hence, exploring the nature of brain activity that occurs in resting state must now be regarded as critically important in functional neuroimaging studies. The purpose of our review is to briefly summarize the relevant research background, the supporting evidence, characteristics and physiological significance of the ongoing brain activity that exists during the resting state. In particular, we will focus on the progress that has been made in functional magnetic resonance imaging studies of the resting brain.

1 Task related fMRI and deactivation

1.1 Physiological basis and neural nature of BOLD signal

BOLD contrast is the basis of BOLD-fMRI methodology, which was originally described in 1990 by Ogawa et al.[7] from Bell Laboratories in the USA and refers to the magnetic resonance signal changes that result from blood oxygen level-dependent contrasts. The physiological mechanisms underlying BOLD reflect neuronal activity increases associated with increased brain activity, which are accompanied by hemodynamic changes, including an increase in the local cerebral blood flow, cerebral blood volume and oxygen supply. However, the increased blood oxygen available is actually in excess of the oxygen consumption required for neuronal activity. The excess of locally available oxygen results in a relatively increased amount of oxygenated hemoglobin and decrease in deoxygenated-hemoglobin in the microvasculature. Due to the diamagnetic properties of oxygenated-hemoglobin, an increase in its amount will change the magnetic properties of the regions sur-

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rounding it and directly accelerate the dephasing speed of the regional brain tissue, shortening the T2* relaxation time and decreasing the T2* weighted imaging signal. In contrast, when the deoxygenated hemoglobin levels are reduced, the dephasing speed becomes slower, resulting in an increased T2* relaxation time and stronger T2* weighted imaging signal.

The fMRI signals which are based on BOLD contrasts detect the local changes in the blood flow and metabolism underlying neuronal activity, but cannot measure directly neuronal activity itself. Logothetis and his colleagues[8] have suggested that the nature of the BOLD signals most likely reflect the activities of the synapses. The evidence in support of this contention that they present in their animal fMRI study is that a close correlation exists between the BOLD signal change and local field potentials (LFP), which are considered to reflect underlying synaptic activity.

1.2 Brain activation and deactivation in task related fMRI

In general, fMRI signals are commonly obtained by data analysis methods based on mathematic calculations and statistical inferences. The common method in present functional brain mapping studies is a model-driven data analysis technique[9], for example, statistical parameter mapping (SPM) with a linear model or general linear model[10—12]. This kind of method typically maps the activated brain regions by detecting fMRI signal differences between two conditions, the task of interest and the control condition (usually, the awake resting state with eyes closed, passive viewing of a visual task or visual fixation). In the context of functional brain imaging, the term "activation" indicates that the task related neural activities increase in the brain regions involved in the specific task, and can be measured by comparing the two conditions with each other. Moreover, in these experiments, the resting state in which no specific task set is commonly defined as the control state, and activated brain regions are identified by subtracting the control condition from the task of interest. Recently, numerous investigators have noted that when performing a reverse minus, namely, subtracting the task of interest condition from the control condition, activated brain regions can in fact be identified. This situation has frequently been encountered in functional brain imaging studies and is typically referred to as "deactivation". Many investigators have noted two groups of deactivation[13—17]. One of which is task-specific and varies in location depending on the demands of the task, another is task-independent and varies little in location across a wide range of tasks. For example, language processing, memory, and attention tasks deactivate similar regions in the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC) and medial parietal cortex.

1.3 The physiological implications of the neural mechanisms underlying deactivation

It is widely recognized that brain activation is a reflection of an increase in neuron's activity accompanied by the increase in blood flow and the change in the blood oxygen level. However, the physiological mechanisms underlying deactivation are not yet clear. There are several physiological explanations of deactivation. The first concerns the hemodynamic changes that occur in the brain[18]. It has been observed[18] that when the curtain brain regions perform specific functions, the blood supply to related regions of the brain will increase as a result of a vascular-stealing effect, and the blood flow will decrease in adjacent tissues to meet the needs of activated brain regions. This phenomenon exists at the level of the microvasculature[19], but it cannot fully explain the occurrence of deactivation during functional brain imaging for several reasons. First, there is a vast vascular reserve present in the brain, and relative to the overall blood flow to the brain, the local blood flow changes produced by goal directed tasks is quite small[20] (approximately 10%). Consequently, there is no real physiological requirement for shunting blood from the surrounding tissues to supply functionally active regions. Moreover, the blood capacity of the brain is large enough to supply almost twice the blood requirement for performing specific functions[21,22]. And the large cortical areas showing decreased activity can be observed far from the active regions, and can also be present without any associated increase in activity. Hence, these observations cannot be explained simply by blood flow redistribution[23].

Another possible explanation for deactivation is based upon the physiological and functional significance of the brain. It is assume that both the activated and deactivated brain regions together comprise an intact network that can perform particular functions.

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The deactivation regions that operate in this network may reflect a suppression or "gating" of information processing in regions that are not involved in task performance[14]. In addition, the filtering out of unattended sensory input may facilitate the processing of information that is expected to result in behavior performance.

We noticed that the two possible explanations for deactivation mentronal above are not truely correct. The hemodynamic theory of vascular-stealing fails to account for certain phenomena discussed above. In the case of the suppression or "gating" theory of deactivation, this emphasizes the functional significance of deactivated regions only and does not focus on the physiological mechanisms that result in deactivation. In addition, some investigators have hypothesized that deactivation may reflect the activities of inhibitory neurons[24,25]. However, it is well known that all neuronal activity requires an energy source, which will be accompanied by an increased supply of blood flow and oxygen within the given region of the brain. Moreover, the inhibitory neuron theory does not explain the deactivation phenomena that are frequently observed in functional neuroimaging studies involving the detection of hemodynamic changes (including BOLD contrast fMRI) that accompany neuronal activity. Consequently, in this instance in the context of functional neuroimaging, it is activation but not deactivation that should be observed during inhibitory neuronal activity.

The exact physiological mechanisms underlying deactivation require significantly further study. However, existing functional neuroimaging studies do have the capacity also to improve our insights into such mechanisms. In summarizing the presently available views and research results, we have noted the following three important trends: First, in a brain network involved in specific tasks, some of the regions involved have a relatively high degree of activity during task conditions compared with the control state, thus these regions exhibit activation. In contrast, some brain regions within this network have a relatively low degree of activity from the same measurements and thus show deactivation. Second, the location of the task-dependent deactivation brain regions changes as a result of different stimuli. In comparison, the location of the task-independent deactivation brain regions is relatively invariable; changing little with different task stimuli. Third, although the hemodynamic mechanisms of task-dependent and task-independent deactivation might be similar, the underlying functional implications of these two types of deactivation seem to be quite different. The regions showing task-dependent deactivation can only be observed in the presence of a specific task. However, brain regions that demonstrate task-independent deactivation have a higher resting metabolism and blood flow in the resting state but certain goal-directed tasks can suppress their activity. The consistency with which certain brain regions show task-independent deactivation suggests the existence of organized brain activity during resting. This possibility has prompted Raichle and colleagues to propose the hypothesis of default mode activity networks in the human brain[26].

2 Brain activities in the resting state

2.1 Two types of deactivation in functional neuroimaging

In fMRI studies, investigators typically use the "resting state" as their control conditions. It is thus of critical importance to properly define the concept of resting state prior to fMRI study. The resting state is commonly defined as the conditions under which the subject is awake, lies quietly within the scanner with closed eyes, and is typically instructed to refrain from any thought. However, the question arises as to whether it is reasonable to assume that rest periods represent an actual zero-activity condition without any functional brain activity. Significantly in this regard, the deactivation phenomena that are frequently observed in function imaging suggest the existence of fundamentally functional brain activity during resting periods.

As stated above, from the viewpoint of the physiological mechanisms underlying BOLD and the subtraction strategies employed for fMRI data acquisition, the neural information that is directly reflected by deactivation is that the regional blood-flow and BOLD signal are higher during baseline conditions relative to specific task conditions. This description could also be restated as that the regional blood flow, BOLD signal and local neural activity are attenuated in the presence of specific tasks in comparison with the so-called baseline conditions. In fact, such decreases can arise under two circumstances (Fig. 1). In the first instance, activity in a certain region is above baseline during control conditions and the task

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of interest produces a decreased activity relative to the control state (Fig. 1(a)). In the second case, the brain activity is below the mean baseline under the control condition and task of interest involves a greater decrease in activity relative to the control state (Fig. 1(b)).

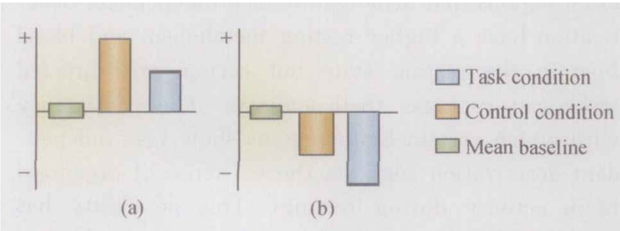

Fig. 1. Two possible circumstances in which deactivation can occur. Blue bars indicate task of interest condition. Orange bars denote the control condition. The green bars represent the mean baseline of the brain. The graph is adapted from Ref. [27] with minor modifications.

The important and key issue of which of these two circumstances occurs under resting baseline conditions would thus need to be addressed. The first case highlighted in Fig. 1(a) suggests that there may be some brain regions that have a higher activity than others in the resting states and there are indeed substantial reasons to suppose that mental processes do occur in the brain in the absence of specific external stimuli. The second situation depicted in Fig. 1(b) might occur in a brain network involved in a specific external task. In the following sections, however, we mainly focus on the first scenario shown in Fig. 1 (a).

2.2 Evidence for the existence of a resting brain activity network

2.2.1 Physiological basis of the resting brain activity network

Although the human brain accounts for only 2% of body weight, it consumes large amounts of energy in the awake resting state. For example, the human brain receives 11% of the cardiac output and accounts for 20% of the total oxygen consumption of the entire body[28]. This raises the question of why the brain requires such a large amount of energy in baseline or resting conditions, which has been typically regarded as a "zero" activity state and commonly serves as the control in most functional neuroimaging studies. It is well known that the human body is an efficient, accurate and economical biology system and so the larger consumption of oxygen and energy by the brain in the resting state must have significant functional implications. A possible explanation comes from the previous observations that up to 50% of this baseline energy consumption contributes to the functional aspects of synaptic transmission[29—31], also implying a significant degree of functionality in the baseline or resting state brain.

2.2.2 Evidence from functional neuroimaging studies

The remarkably consistent results of two large PET meta-analysis studies conducted respectively by Shulman and by Mazoyer with their colleagues[13,17,23,32] have provided with important basic information for understanding functional brain activity in the resting state. The study of Shulman et al.[13] involved 132 volunteers for the purpose of searching for common brain deactivation regions under various visual stimulation tasks (e.g. detecting target, sequencing task operations, attention establishment and language processes). Two types of condition were used as the control: passive viewing of visual stimuli without attention to particular aspects of the stimuli and simple visual fixation. The systematic reanalysis results described in this study revealed that no common brain regions showed increased activity outside the visual cortex. The location of the activated brain regions changed with different tasks. However, a consistent set of brain regions showing the decreased activity were observed under different task stimuli[13].

The study of Mazoyer et al. employed the resting state as the task of interest, in which the subjects were instructed to "keep their eyes closed, to relax, to refrain from moving, and to avoid structured mental activity such as counting, rehearsing, etc."[17]. A range of visual, auditory, and imagery tasks was used as the control conditions. They found activation occured in almost the same regions as that had been observed by Shulman et al.[13]. However, because the study of Mazoyer utilized the resting state as the task of interest, their results were reported as activation rather than deactivation. The common regions in these two studies include the posterior cingulate cortex, the dorsomedial frontal cortex in the midline, the superior frontal cortex, the rostral anterior cingulate cortex and the angular cortex[17]. The posterior cingulate gyrus extends ventrally to the cortex precuneus, and the angular gyrus spreads anteriorly into

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the supramarginal gyrus in the study of Shulman et al. and posteriorly into the superior occipital cortex in the study of Mazoyer et al. The consistency with these sets of regions showing similar changes at rest with eyes closed, as well as during visual fixation and passive viewing of simple visual stimuli, suggested that there might be an organized mode of brain function active under the rest or passive task conditions, but attenuated during various goal-directed performance conditions. Moreover, compared with the transient brain activity response to the specific task stimuli, the brain activity that occurs under the resting or passive task conditions is continuous or ongoing.

Based on previous studies of deactivation with PET and the work of themselves, Raichle et al. have proposed a default model network activity hypothesis[26] which assumes that there exists organized brain activity in the human brain under the awake resting state. The organized brain activity is thought to be supported by a consistent set of brain region networks, which comprise specific areas such as the posterior cingulate cortex, anterior cingulate cortex and bilateral inferior parietal cortex. Despite the fact that the precise functional roles of this brain regional network are not well understood, it has also been widely proposed that such internal activity might be involved in many processes, including monitoring of the external environment, the body image and the emotional states. In addition, an ongoing "thought" processing that humans experience during rest consciousness has been noted and emphasized in some reports[5].

Recently, several researchers have also performed studies using noninvasive brain mapping techniques to characterize default model network activity, and several lines of evidence in support of such a network have been accumulated. Greicius et al.[33] using a functional connection MRI (fcMRI) analysis approach have observed BOLD signal fluctuations occur with a high temporal coherence within the medial frontal, lateral parietal, and medial parietal/posterior cingulated cortex under passive or resting conditions. These temporal correlation regions are consistent with the observations of previous PET studies[13,17]. Moreover, the deactivation magnitude has been found to increase with the increasing cognitive demands of the task, suggesting that the cognitive processes that are ongoing during the resting state require attention resources, and thus allow deactivation to occur via a passive mechanism of reallocation of these resources[34]. Brain regions that show task-related increases in brain activity are inversely correlated with the default mode network, particularly the posterior cingulate cortex which plays a central role in this network. These observations provide compelling evidence for the concept that the reallocation of resources occurs during deactivation. Some specific tasks that have been designed to target processes that are thought to be subserved in the default mode network, such as those involved in emotion processing or self-referential mental processing can activate the medial prefrontal cortex, which is one part of the default mode network[35,36]. With the use of PET Kjaer et al. found that the neural correlates of reflective self-awareness was similar to the brain regions showing highly metabolic activity in the resting consciousness state[36]. These findings suggest that these brain regions are associated with mental self awareness and episodic memory, which is considered to be one of the vital functions of the default mode network.

With the use of our previous fMRI study of anxiety data[37], we have observed the same regions of deactivation in our patient subjects, compared with the normal controls, during the processing of emotionally neutral and threat-related words. These patterns were consistent with the default model network (Fig. 2), and our results thus extend the default model network to anxiety patients.

3 Characteristics of default mode network activity

Based on the data that we have already described, it is necessary to keep in mind that during awake and resting states, some human brain regions are actually active and operate specific mental processes that are critical for human activity. These brain regions are organized and comprise a functional network, the default mode network. In reviewing the previous brain mapping literature, we have noted several properties of this default network as follows: First, it consists regularly of curtain brain regions, such as the medial prefrontal, parietal/posterior cingulate regions, together with the bilateral occipital and parietal regions. Relative to other regions, the posterior cingulate cortex may play an important role in this network[33]. Additionally, the neural activity levels in these regions are significantly higher than other regions of the brain. Second, this default net-

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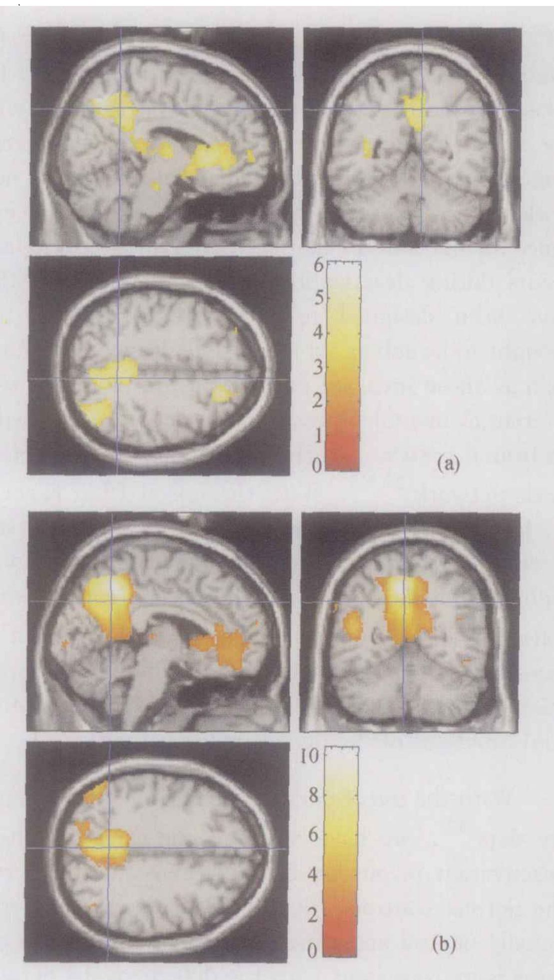

Fig. 2. Averaged reverse subtraction images showing significant deactivation regions in the medial prefrontal, posterior cingulate and inferior parietal cortices in normal controls (a) and anxiety patients (b). $P<0.001$, uncorrected.

work performs specific functions that have not been well understood up until recently. Many processes might be considered to be involved, for example, the retrieval of episodic memory, the monitoring of the environment, self-reference[38—43] and emotion processing[44—50]. Third, the brain regions that comprise this network are task-independent, and the locations of the related regions change little across different tasks and modalities. However, the deactivation levels in this network are modulated by the degree of difficulty of the goal-directed task stimuli, i.e. the higher the demands of the task are, the greater the extent of the deactivation will be[26,33]. Lastly, the performance of tasks with low cognitive demands, such as finger-tapping, vision fixation and simple passive viewing, does not disrupt or alter this default network[33].

4 Brain activities in the resting state and a definition of the physiological baseline of the brain

Brain activity in the resting state is an ongoing activity, which occurs from the physiological baseline of the brain. The neural activities arise from particular goal-directed tasks can show both increased and decreased activities, corresponding to activation and deactivation during functional brain mapping. It is necessary to determine a reference point or baseline from which these decreases or increases in activities might arise. An inherent problem has been the lack of agreed characteristics to define such a baseline. Gusnard et al.[27] have suggested a criterion in terms of the oxygen extraction fraction (OEF) to define such a baseline, on the basis of quantitative circulation and metabolism.

4.1 The physiological baseline of the human brain activity

Gusnard et al.[27] defined the physiological baseline of the human brain in the absence of brain activation and were the first to introduce the concept of the oxygen extraction factor (OEF) to describe activation and deactivation in functional imaging studies. The oxygen extract factor can be expressed as the percentage of the oxygen delivered to the local region that is used by the brain. In short, the OEF is the ratio of oxygen utilization to blood flow (BF) and oxygen delivered. It can also be simply presented in the following equation, $OEF=$ utilization of oxygen/$BF \times C_A$, in which BF is the blood flow that is delivered to the specific brain site, C_A is the measurement of arterial blood oxygen content, and utilization of oxygen represents the extent to which delivered oxygen has been consumed. During the resting state, there are considerable variations in oxygen consumption and blood flow within gray matter and an almost four-fold difference in blood flow and oxygen consumption between the gray matter and white matter. However, the spatial uniformity of the OEF can be measured in the brain during resting states regardless of distinct brain regions and gray or white brain matter. Raichle et al.[26] using PET have revealed OEF values almost equal to "1" across distinct brain regions (except for the visual cortex), and have proposed that such spatial uniformity of OEF in the brain during the resting states indicates that metabolic equilibrium has been reached between the local metabolic requirements nec-

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essary to sustain a long-term level of neuronal activity and the level of blood flow in a particular brain region. The equilibrium between local metabolic requirements and blood flow satisfies the demand for long-lasting and ongoing neuronal activity in the specific region. As discussed in detail in their recent review, Gusnard et al.[27] have argued for the use of such a metabolic equilibrium to define the baseline of brain activity.

4.2 Relationship between the oxygen extraction factor and the activation and deactivation

In the context of functional brain imaging studies, the mapping of brain activation is derived from discrepancy or mismatch between blood oxygen supply and its consumption, in which the supplied oxygen exceeding the metabolic oxygen demand. These changes can be quantitatively described in the equation, OEF = utilization of oxygen/$BF \times C_A$. That is increased BF and C_A accompanyed with relatively decreased utilization of oxygen. On the base of these changes, Gusnard et al. described the activated regions as "those areas with a reduced OEF relative to the mean OEF of the brain (the brain mean OEF)", and stated that "those areas that do not differ from the brain mean OEF are considered to be at baseline". Hence, areas with increased OEF over the brain mean can be defined as regions of deactivation. Accordingly, those activation regions with decreased OEF have a higher activity relative to the baseline level and deactivation regions with increased OEF show a lower activity relative to the baseline level.

5 Conclusions and future implications

The studies of deactivations and resting state brain function are frequent topics of interest in the field of functional brain mapping. Increasing research evidence indicates that even during the resting state (with the awake subject lying quietly in the scanner with eyes closed), which has served as the control condition in many functional brain mapping studies, there exist mental process activities. Neuroimaging researchers need to consider this in the design of experimental paradigms and the interpretation of functional imaging study results. If rest periods are actually periods of complex cognitive operation, the use of rest as a control condition may be inappropriate in some studies and will affect the interpretation of the data. This is of concern because in most functional imaging studies activity within the brain regions is identified by simple subtraction of the resting neural activity from the task-related activity. Therefore, it is of particular importance to better understand the nature of cognitive processing that occurs during the resting state. Furthermore, the resting state default mode activity itself has many important functions, such as the processes of self awareness, episodic memory and monitoring of the environment, many of which are crucial for human survival. The further elucidation of these activities is therefore vital. In particular, the search for the nature of resting state processes may be very useful in identifying the neural correlates of consciousness of human brain[51] and the underlying neural mechanism of some diseases such as Alzheimer's disease and psychiatric disorders[52—55].

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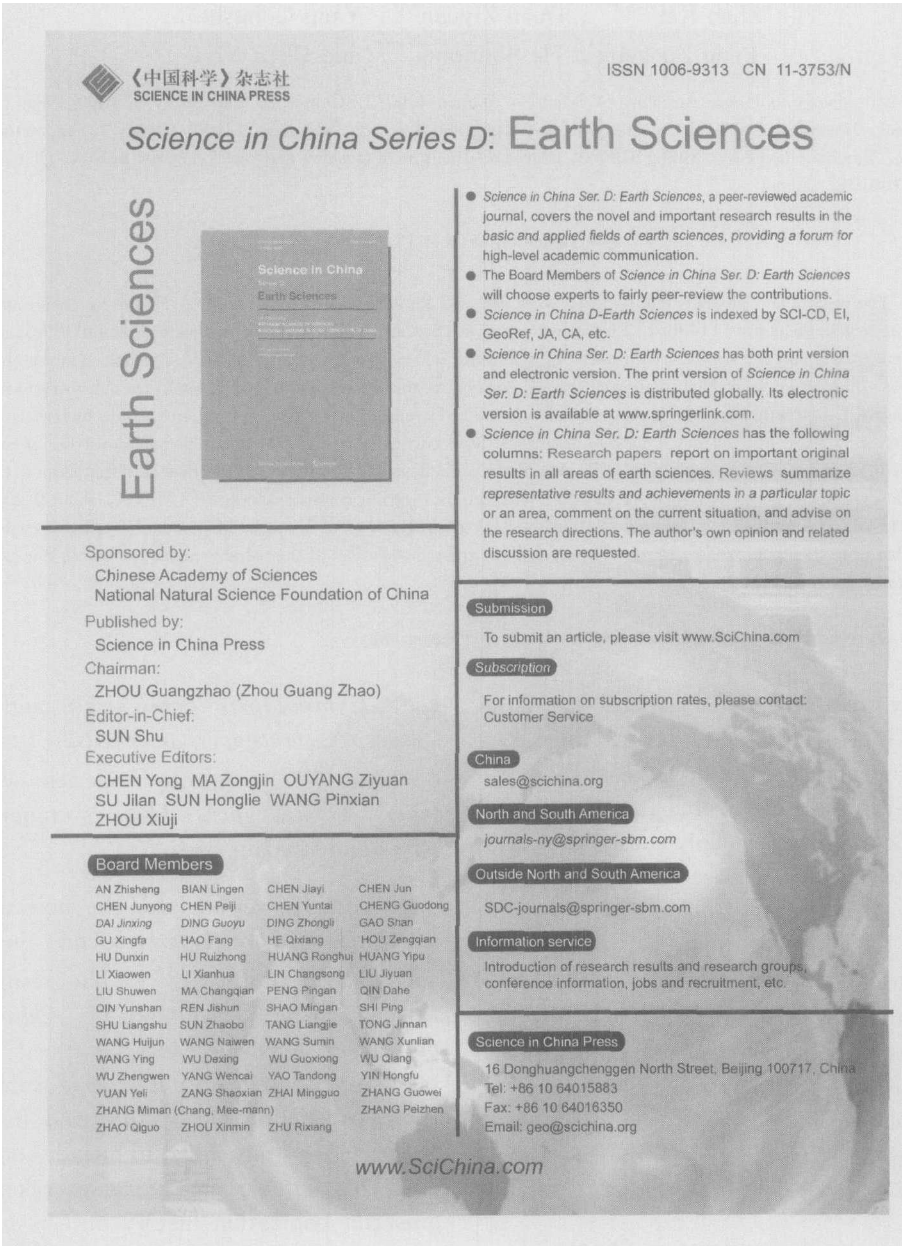

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