REVIEW ARTICLE

POSSIBLE CLINICAL APPLICATION OF RESTING-STATE fMRI IN NEUROPSYCHIATRIC DISORDERS

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ABSTRACT

Functional brain imagings studies have shown brain regions having greater neural activity during an experimental task than during rest or sensory-motor task with reduced cognitive demand. Based upon this hypothesis that supports the idea of “default mode of brain function" recent studies have focused on brain regions in which neuronal activity is greater during resting-state than during an experimental task with cognitive demand. Recent Studies have showed that resting-state connectivity is crucial for cognitive performance. To detect dysfunctional connectivity and activity in various resting-state networks in brain that has been suggested to be underlying pathophysiology of some neuropsychiatric disorders, resting-state fMRI could be considered as a relatively novel and beneficial tool for diagnosis of these disorders. In this article, brain resting-state networks are briefly introduced for better understanding of possible clinical applications of resting-state fMRI in diagnosis and early detection of some neuropsychiatric diseases that have been studied in recent years.

Keywords: Neuropsychiatric disorder, resting-state fMRI, cognitive impairment, and functional connectivity

Introduction

Human brain is optimized for a high level of information processing and information integration across the brain network. Despite of the fact that information is widely distributed in brain, functionally connected regions constantly process and transform information. Resting-state fMRI as a new tool is able to measure and examine functional connectivity between brain regions. A bold-oxygen-level- dependency (BOLD) displaying low-frequency spontaneous fluctuation during rest is a neurophysiology index in resting-state fMRI. Spontaneous fluctuation of BOLD signal in fMRI is shown to occur at the same time in distant parts of the brain during rest, a phenomenon known as “functional connectivity".[1] Ongoing functional connectivity between different brain regions during rest is also confirmed by observation of correlation of fMRI times-series between anatomically separated regions.[2]

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Resting-state networks

Several studies reported approximately eight resting state networks in brain.[3-5] Anatomically separated regions, but functionally connected brain regions with high level of functional connectivity during rest are known as resting state networks (Fig. 1).[3] Interestingly, there is extensive overlap between these resting-state networks with regions that are known to share common functions. Resting-state networks are made up of regional patterns that are believed to participate in sensory, attention and motor performance (Fig. 2).

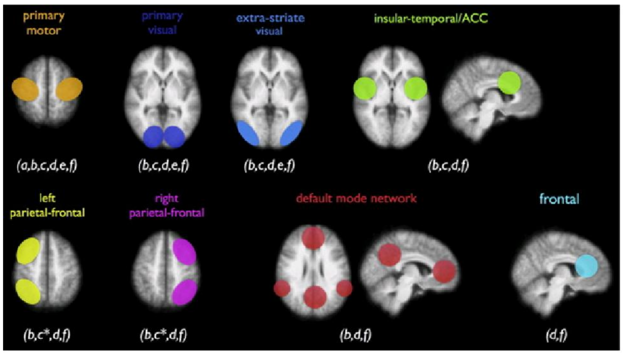

Figure 1: Resting-state networks showing the formation of functionally linked resting-state networks during rest.

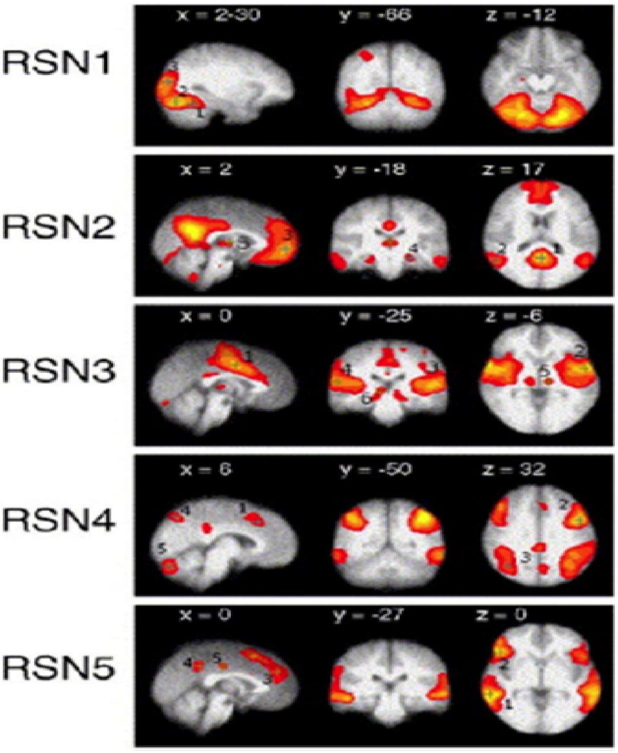

Figure 2: Group resting state network maps. From top to bottom: (1) RSN 1 including visual cortical areas. The RSN reported here includes the main visual functional network. (2) RSN 2 including visuospatial and executive system. The RSN reported here includes the emotion/visuospatial processing functional network. (3) RSN 3 including sensory and auditory system. (4) RSN 4 including the dorsal pathway. (5) RSN 5 including ventral pathway. The crosses indicate the positions of the centers of the major clusters, and the corresponding coordinates are reported in for each corresponding map (map obtained with alternative hypothesis threshold P > 0.5).

Previous study[6] showed that there is an organized, baseline default mode of brain function suspended during some specific goal directed behaviours.[6] Therefore unlike other resting-state networks, and default mode network is more active during rest than cognitive task duration. Default mode network consists of posterior cingulate cortex (PCC)/precuneus, medial frontal, inferior parietal regions and temporal regions that are functionally connected to each other. Resting-state functional connectivity, especially within default mode network, is shown to be related to cognitive and emotional measures. For example, the regions that are linked to PCC in default mode network are responsible to support the ongoing mental processes during the rest (Fig. 3 and 4).[2]

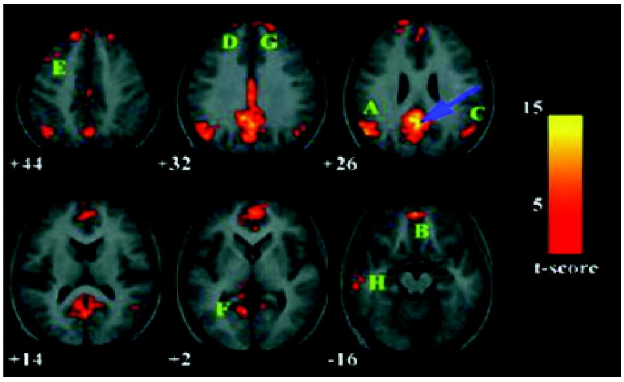

Figure 3: Map of the resting-state neural connectivity for the PCC. The blue arrow indicates the approximate location of the PCC peak [-2 -51 27]. The approximate locations of the eight significant clusters are labeled A–H in descending order of the cluster's t score (A corresponds to the cluster with the highest t score). A [-51 -65 27], left IPC. B has a maximum at [-2 55 -18] in the OFC, but extends superiorly into the MPFC and the vACC (seen at z = +2). C [53 -61 27], right IPC. D [-16 49 38], MPFC just left of midline. E [-44 20 41], left DLPFC. F [-12 -35 0], posterior left PHG. G [18 54 32], MPFC just right of midline. H [-58 -18 -14], left ITC.[2]

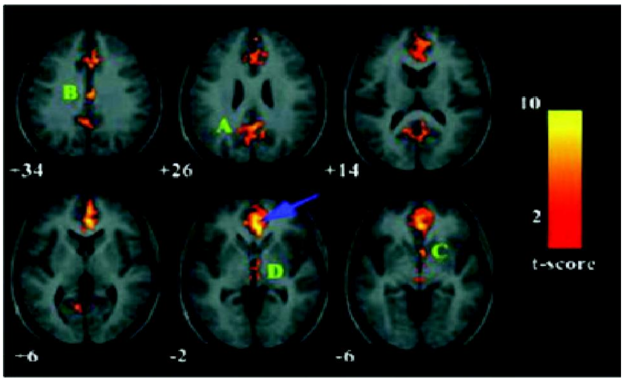

Figure 4: Map of the resting-state neural connectivity for the vACC. The blue arrow indicates the approximate location of the vACC maximum [2 38 -2]. A [2 -51 27], PCC extending into the precuneus. B [4 -14 34], rostral PCC. C [4 9 -6], nucleus acumens. D [4 -16 -3] is in the hypothalamus with some extension into the rostral midbrain.[2]

Regarding exciting evidences, to explore abnormalities of functional connectivity in resting-state networks, particularly in default mode network, resting-state fMRI as a relatively novel technology could be an appropriate choice. It is considered to have clinical applicability in diagnosis and assessment of treatment of neuro-psychiatric diseases especially with altered functional connectivity and activity of default mode network and presumably involved in their patho-physiology.

Resting-state functional connectivity and activity in neuropsychiatric disorders: evidence from resting-state fMRI.

(i) Alzheimer's Disease

It was presumed that abnormality of default mode network has been associated to Alzheimer's disease. To test the hypothesis, in a group of 13 subjects with mild Alzheimer' disease and in a group of 13 age matched control resting-state activity in regions within default mode network were studied by using independent component analysis (ICA). The Alzheimer group showed decreased resting-state activity in posterior cingulate and hippocampus.[5] This study introduced capacity of resting-state fMRI for examination of abnormalities of resting-state functional connectivity in Alzheimer patients.

(ii) Mild cognitive impairment

Mild cognitive impairment (MCI) is a transitional stage between cognitive health and more serious cognitive problem caused by Alzheimer' disease. By using resting-state fMRI, it was showed that PCC activation is the least intensive in Alzheimer patients compared to MCI and healthy control subjects, and it is less intensive in MCI subjects compared to healthy control subjects.[7] Based on studies done on Alzheimer' disease and MCI, it can be concluded that early detection of changes in resting-state functional connectivity with the aid of resting-state fMRI may result in earlier intervention and finally slow progression of Alzheimer' diseases in populations at risk.

(iii) Schizophrenia

Schizophrenia is known as a potential disconnection disease. 17 schizophrenic patients and 17 healthy volunteers were tested with fMRI at rest. In healthy volunteers spontaneous low frequency fluctuations of BOLD signals at rest in posterior cingulate were simultaneous with the low frequency fluctuations in the lateral parietal, medial prefrontal, and cerebellar regions. Unlike healthy control subjects, spontaneous low frequency fluctuations in posterior cingulate were significantly less correlated with spontaneous low frequency fluctuations in the later parietal, medial prefrontal and cerebellar regions in schizophrenic patients. This observation indicates remarkable functional disconnectivity in default mode network in schizophrenic patients.[8] Whitfield-Gabrieli and colleagues also compared resting state functional connectivity within default mode network in schizophrenic patients, their relative and control subjects (Fig. 5).[9]

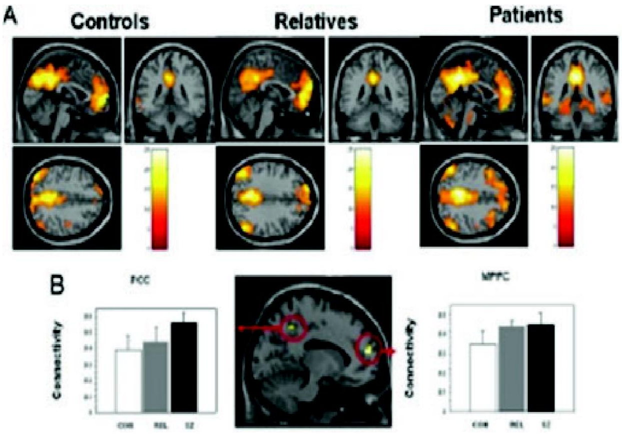

Fig. 5. Functional connectivity with default network during rest. (A) Areas showing positive connectivity with default network areas (averaged across 4 ROI seeds) in controls (CON), relatives (REL), and patients (SZ). (B) *(Middle)* Regions within default network showing significant connectivity differences between groups. Connectivity with default network (with 95% confidence intervals) in MPFC (*Right*, peak: [-12, 54, 15]) and PCC/precuneus (*Left*, peak: [-9, -51, 48]).[9]

(iv) Attention deficit hyperactivity disorder (ADHD)

One study examined boys with ADHD by using resting-state fMRI and regional homogeneity (ReHo) method. ReHo reflects temporal synchrony of regional BOLD signal. Decreased ReHo in the prefrontal-striatal-cerebellar circuits observed in this study demonstrated functional disconnectivity in resting-state in ADHD boys.[10] Gastellanos and his colleagues also found strong evidence for resting-state functional disconnectivity between anterior cingulate and posterior component of default mode network in ADHD.[11] Although, present studies do not provide consistent findings for using resting state fMRI in ADHD, but resting state fMRI has potential to be used in examination of functional disconnectivity for diagnosis and early detection in ADHD in future.

(v) Multiple sclerosis (MS)
To compare resting-state functional connectivity of MS patients with control group, spontaneous low frequency BOLD fluctuation signals in both the resting state and during finger tapping were studied. Control group showed high functional connectivity between left and right hemisphere at least in one of the spontaneous low frequency BOLD fluctuations images. MS patients showed lower synchrony of spontaneous low frequency BOLD fluctuations between the same regions.[12]

Structural impairment and dysfunctional connectivity in neuropsychiatric disorders
Several studies show that anatomically separated regions communicate with each other. It is also suggested that a structural support is essential for effective communication between different brain regions. The structural support is particularly referred to white matter.[4] Since in neurological disorders such as MS, impaired white matter integrity is well known characteristic of this disease, it can be concluded that effective functional connectivity might relate to white matter integrity up to certain extent.

Future use of resting-state fMRI for diagnosis of neuropsychiatric disorders

(i) Cognitive impairment after traumatic brain injury
It was showed that chronic white matter disruption is related to cognitive impairment after traumatic brain injury. Regarding the notion that functional connectivity may be disrupted due to white matter impairment, resting-state fMRI may have advantage over conventional neuroimaging tools in early detection of abnormalities of functional connectivity after traumatic brain injury.[13]

(ii) Focal structural damage
In addition to white matter impairment and other structural impairments that affect resting state functional connectivity in some neuropsychiatric disorders such as Alzheimer', schizophrenia and even in normal ageing, focal lesions may also affect resting-state functional connectivity. Dysfunctional connectivity of brain regions connected to the area of the focal lesion has been observed in stroke. Dysfunctional connectivity in somatomotor network and dorsal attention network was strongly connected to behavioural impairment in stroke patients. Use of resting-state fMRI in acute phase of stroke may contribute to evaluation of severity of neuropsychiatric disorders and to undertake more appropriate therapeutic approach.[14]

Conclusion

Since dysfunctional connectivity and activity between different parts within resting-state networks particularly default mode network and other brain regions can be pathophysiology of some neuropsychiatric diseases, resting-state fMRI could be potentially useful in the diagnosis of neuropsychiatric disorders. Although, all preliminary results have not been quite consistent in some neuropsychiatric diseases but resting-state fMRI has progressed well in terms of clinical applicability. Resting-state fMRI is more patient and clinician friendly to be used in clinic compared to task-activated fMRI, because subjects do not have to perform a task. Significant advanced studies are warranted to use resting-state fMRI in diagnosis of neuropsychiatric disorders in a more effective way.

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