Brain Functional Imaging in the Big Data Era: Toward Clinical Applications for Psychiatric Disorders

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Abstract

Brain functional imaging encompasses multiple research modalities, among which functional magnetic resonance imaging (fMRI) technology, particularly resting-state fMRI, has been extensively applied in psychiatric disorder research due to its unique advantages of being safe and non-invasive, possessing relatively high spatial and temporal resolution, ease of clinical implementation, and facilitation of large-scale data accumulation. However, issues such as small effect sizes and suboptimal reproducibility have also hindered the further clinical translation and application of this technology in the diagnosis and treatment of psychiatric disorders. The author argues that refining the characterization of resting-state spontaneous thinking to improve the resting-state fMRI research paradigm, elucidating the physiological significance of resting-state fMRI metrics and developing novel indicators with greater neurobiological significance, accumulating large datasets and training deep learning classifiers to assist clinical diagnosis, and meticulously designing longitudinal studies to explore improvements in treatment protocols for psychiatric disorders, constitute viable approaches to promote the further clinical translation of resting-state fMRI technology for diagnostic and therapeutic applications.

Full Text

Functional Brain Imaging in the Big Data Era: Towards Applications in the Diagnosis and Treatment of Mental Disorders

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Abstract: Brain functional imaging encompasses multiple research modalities, among which functional magnetic resonance imaging (fMRI) technology, particularly resting-state fMRI, has been widely applied in mental illness research due to its unique advantages: safety and non-invasiveness, relatively high spatial and temporal resolution, ease of clinical implementation, and suitability for accumulating big data. However, issues such as small effect sizes and poor reproducibility have hindered further clinical translation of this technology in mental illness diagnosis and treatment. The author argues that refining resting-state spontaneous thought to improve resting-state fMRI research paradigms, clarifying the physiological significance of resting-state fMRI metrics and developing new metrics with greater neural relevance, accumulating big data and training deep learning classifiers to assist clinical diagnosis, and carefully designing longitudinal studies to explore improvements in mental illness treatment approaches are feasible pathways to advance resting-state fMRI technology towards clinical diagnosis and treatment applications.

Keywords: functional magnetic resonance imaging; resting-state; big data; mental disorders

Brain functional imaging is a technology for measuring neural functional activity in the brain, covering intracranial electrocorticography (ECoG), scalp electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), single-photon emission computed tomography (SPECT), functional near-infrared spectroscopy (fNIRS), and functional magnetic resonance imaging (fMRI) [1]. Among these, fMRI technology has been highly anticipated in clinical research to discover clinically useful disease imaging biomarkers, due to its safety, non-invasiveness, relatively high spatial and temporal resolution, and widespread availability of equipment [2,3]. fMRI technology is further divided into task-based fMRI and resting-state fMRI. In clinical applications, task-based fMRI has achieved certain success in preoperative functional area localization [4]. However, task-based fMRI requires relatively complex experimental design, demands active patient cooperation, and necessitates high requirements for MRI-compatible response devices, which somewhat limits its use. In contrast, resting-state fMRI only requires subjects to lie quietly in the MRI scanner for 5-10 minutes, offering unique advantages such as simple design, ease of accumulating big data, straightforward clinical implementation, and good patient compliance [5], making it a major focus for fMRI technology in clinical diagnosis and treatment research.

On the other hand, although mental disorders represent one of the greatest health threats to humanity in the 21st century, their diagnosis lacks objective biological indicators and relies primarily on symptom-based clinical observation. There is an urgent need to establish highly sensitive and specific objective markers based on abnormal brain mechanisms [6]. Since mental disorders are not amenable to invasive study methods, resting-state fMRI has become the preferred technical approach for characterizing spontaneous brain activity disturbances and establishing imaging markers, due to its unique combination of

safety, non-invasiveness, high spatiotemporal resolution, and simplicity. Moreover, it is foreseeable that until new revolutionary non-invasive brain imaging technologies emerge, resting-state fMRI will remain one of the irreplaceable primary methods for studying brain mechanisms of mental disorders for a considerable period.

However, despite numerous preclinical studies on the pathophysiological mechanisms of mental disorders using resting-state fMRI [5,7,8], the technology has yet to enter clinical practice. Notably, most previous resting-state fMRI studies on mental disorders have suffered from small sample sizes and weak statistical power, often yielding inconsistent conclusions. Some researchers have pointed out that small-sample studies produce varied results, are inherently unlikely to discover significant findings (due to insufficient statistical power), and even when significant results are found, their validity is low (low positive predictive value) [9]. Therefore, to establish generalizable clinical biological markers, it is necessary to accumulate large clinical datasets and adopt the currently emerging big data deep learning paradigm to achieve this goal.

Beyond the big data dimension, resting-state fMRI also has other limitations that hinder its clinical translation. Recently, Professor Lu Guangming and Professor Zhang Zhiqiang from Nanjing General Hospital of the People's Liberation Army also commented on this issue [10], proposing that advancing fMRI clinical applications requires translational applications based on individual analysis models, refined effective metrics and concise direct analysis procedures, as well as standardization of data acquisition and analysis. In these directions, the author and collaborators have completed some research work. We have proposed widely recognized and cited solutions in the field for a series of methodological issues troubling resting-state fMRI, such as head motion [11], standardization [12], and multiple comparison correction [13]. To address the cumbersome data processing steps and diverse parameter settings in resting-state fMRI, we standardized the process and established the DPARSF pipeline computing platform, which has been cited over a thousand times [14]. However, beyond this work, we believe the following points deserve further exploration to achieve clinical application of resting-state fMRI in mental disorders.

1. Refining Complex and Diverse Resting-State Spontaneous Thoughts to Study Mental Disorder-Specific Spontaneous Cognition

The current reliability of resting-state fMRI is not particularly ideal, with one important reason being the inherent complexity of psychological activity during the resting state [15]. Classic resting-state fMRI designs impose very simple requirements on subjects ("stare at a crosshair, stay awake" or "close eyes and rest"), making it difficult to control and determine subjects' mental states during scanning [16]. In this situation, subjects may engage in various types of spontaneous thought such as mind wandering, worry, rumination, etc. These

spontaneous thoughts are mixed together, collectively forming the resting-state mental condition [17-19]. Spontaneous thoughts have variable characteristics [5]; the same individual may generate different types of spontaneous thoughts during two resting-state scans, which significantly reduces intra-individual consistency across multiple resting-state measurements, thereby affecting the reliability of resting-state fMRI. On the other hand, for group comparison studies, if there are differences in spontaneous thought tendencies between groups, their spontaneous thought activities during rest will likely exhibit systematic inter-group differences, which will be reflected in their resting-state neural activity patterns. Many mental disorders are associated with abnormalities in spontaneous thought, meaning that patients' spontaneous thought tendencies differ from healthy individuals [7]. For example, compared with healthy people, patients with attention deficit hyperactivity disorder have more frequent spontaneous thoughts with greater variability; patients with anxiety disorders have spontaneous thoughts that excessively exaggerate personal harm from events, accompanied by strong worry; and patients with depression mostly have rumination traits, with their spontaneous thought content being more negative and past-oriented [8,9]. If the influence of resting-state spontaneous thoughts is not excluded, then group differences in resting-state measurement metrics between mental disorder patients and healthy individuals will be confounded by these different spontaneous thought tendencies and cannot truly reflect the neural basis of the mental disorder. Therefore, guiding subjects into specific spontaneous thought states, particularly those specific to certain mental disorders, is very helpful for improving the reliability of resting-state fMRI and thereby finding stable biological markers for mental disorders.

2. Clarifying the Physiological Significance of Resting-State fMRI Metrics to Advance Understanding of Mental Disorder Neural Mechanisms

Resting-state fMRI has proposed various brain imaging metrics, including but not limited to amplitude of low-frequency fluctuations (ALFF) [20], fractional ALFF (fALFF) [21], regional homogeneity (ReHo) [22], degree centrality (DC) [23], and voxel-mirrored homotopic connectivity (VMHC) [24]. However, the physiological significance of these metrics remains unclear, and even the neurophysiological mechanisms underlying the basis of these metrics—the blood oxygenation level dependent (BOLD) signal—are still ambiguous. The BOLD signal itself reflects changes in deoxyhemoglobin concentration rather than direct measurement of neural activity. Therefore, understanding the neural mechanisms of the BOLD signal and resting-state fMRI metrics based on it is fundamental to interpreting mental disorder brain mechanisms. Animal studies have shown that the BOLD signal is associated with local field potentials (LFP), particularly gamma rhythms (30-100Hz) [7-9]. Human studies using asynchronous ECoG-fMRI recordings during tasks also suggest that low-frequency oscillations in gamma and high-gamma rhythms are related to BOLD signal changes

[10-12], but this evidence is indirect and has not been proven by simultaneous fMRI-electrophysiology experiments. Mantini et al. [13] used simultaneous scalp EEG-fMRI technology and found that different functional networks in the resting state have different combinatorial relationships with different EEG rhythms. However, no study has yet effectively established a correspondence between resting-state fMRI metrics and neuroelectrical activity. Therefore, using simultaneous EEG-fMRI technology, or even simultaneous intracranial electrode ECoG-fMRI technology, to clarify the physiological significance of resting-state fMRI metrics from an electrophysiological perspective and to develop new fMRI algorithms and metrics that better represent neural activity is an important direction for advancing understanding of mental disorder neural mechanisms.

3. Accumulating Big Data in Mental Illness Brain Imaging and Training Deep Learning Classifiers for Artificial Intelligence-Assisted Diagnosis

Building on the first two points regarding experimental paradigms and development of new fMRI metrics that better represent neural activity, the most promising direction for pushing resting-state fMRI towards clinical application is undoubtedly big data and deep learning. In terms of big data accumulation, multiple data sharing initiatives (such as FCP/INDI, CORR, ABIDE, HCP, ADNI, FBIRN, UK Biobank, etc.) have been successfully implemented and applied to studies of healthy individuals [25], attention deficit hyperactivity disorder [26], autism [27], and schizophrenia [28]. This model accumulates raw data from multiple sites and then performs unified analysis and modeling, thus placing extremely high demands on data organization, transmission, and storage. Moreover, the raw data have enormous dimensions and raise concerns about subject privacy leakage [29]. Beyond these factors, researchers' willingness to share raw data varies, limiting larger-scale raw data sharing. In the structural imaging field, the ENIGMA meta-analysis model [30] has emerged, where participating sites perform standardized data processing and regression analysis on structural brain data according to a unified model, then share p-values and regression coefficients for meta-analysis. This approach has enabled big data applications in structural abnormalities in depression [31], schizophrenia [32], and autism [33]. Unfortunately, due to various methodological and standardization issues in resting-state fMRI, the ENIGMA model has not yet been applied to resting-state fMRI research. Leveraging our strengths in resting-state fMRI methodological research, the author and collaborators standardized the data processing procedure and established the DPARSF pipeline computing platform, which has been cited over a thousand times. Building on DPARSF, we constructed the Resting-State fMRI Maps Project (http://rfmri.org/maps). Following the ENIGMA model, each site uniformly processes data according to the established standardized pipeline and then aggregates the resulting resting-state fMRI metrics into big data. Currently, resting-state imaging data from 4,770 subjects have been shared. Recently, based on this big data sharing plat-

form, the author, together with Professor Zang Yufeng from Hangzhou Normal University, Professor Zhao Jingping from the Second Xiangya Hospital of Central South University, and Researcher Zuo Xinian from the Institute of Psychology, Chinese Academy of Sciences, invited psychiatric experts nationwide to launch the REST-meta-MDD project—a multicenter meta-analysis of resting-state fMRI data in depression. This project aims to address the unreliability of conclusions from small-sample depression studies, establish a multicenter large-sample database, reanalyze and re-mine existing resting-state fMRI data in depression, and strive to establish a probabilistic whole-brain resting-state activity abnormality map for Chinese depression patients, thereby pushing resting-state fMRI further towards clinical application in depression. By collaborating with 25 depression research groups from 17 domestic hospitals, we successfully aggregated brain imaging data from 1,300 patients with depression and 1,128 healthy controls, establishing the world' s largest resting-state fMRI database for depression. In the future, the author and collaborators will further expand the depression database and accumulate resting-state big data covering multiple mental disorders (such as bipolar disorder, schizophrenia, obsessive-compulsive disorder, etc.) to examine the specificity of brain imaging biological markers. On the established big data, using deep learning to train deep neural networks can help identify biologically specific markers for diagnosis. Recently, deep learning has revolutionized artificial intelligence, achieving unparalleled recognition capabilities by leveraging large-scale multi-layer artificial neural networks, massive training data, and powerful parallel computing tools [34]. However, deep learning requires large amounts of training data, and its performance on small samples is even worse than traditional shallow network algorithms, thus limiting its application in brain imaging. In the future, training clinically specific classifiers on big data from multiple mental disorders using deep learning algorithms such as deep convolutional networks, stacked autoencoders, and transfer learning is an important direction for achieving artificial intelligence-assisted diagnosis of mental disorders.

4. Small-Sample Mental Illness Brain Imaging Research in the Big Data Era: Within-Subject Longitudinal Design

Although the neuroimaging field is vigorously promoting the multicenter big data research model, not all researchers can engage in big data research, and not all scientific questions are suitable for the big data model. The author believes that carefully designed small-sample studies remain highly necessary even in the big data era. In our previous research [13], we found that the popular between-subjects design small-sample studies ($N < 80$) in the brain imaging field have unsatisfactory reproducibility and statistical power, with a low probability that discovered significant results are true. However, once within-subject designs are adopted (such as examining differences between eyes-open and eyes-closed conditions), due to their much larger effect sizes and statistical power compared to between-subjects designs, even small-sample data with $N = 30$ have far greater reproducibility than between-subjects designs (such as sex dif-

ferences) with large samples. Therefore, even in the big data era, carefully designed small-sample longitudinal studies still hold great value. In mental disorder research, longitudinal follow-up studies can be conducted to examine the impact of disease progression on brain activity [35]. More importantly, we can examine the effects of treatment modalities (such as psychotropic medications, cognitive behavioral therapy, and brain stimulation therapies) on brain activity [36,37], elucidate the neural mechanisms underlying treatment efficacy, and help further improve treatments for mental disorders.

Of course, the above four points only represent the author' s preliminary views, and many other directions may be worth exploring. Nevertheless, improving resting-state fMRI research paradigms, clarifying the physiological significance of resting-state fMRI metrics and developing new metrics with greater neural relevance, utilizing big data and deep learning to assist clinical diagnosis, and employing longitudinal studies to explore improvements in mental disorder treatment approaches are important pathways through which resting-state fMRI can effectively contribute to the diagnosis and treatment of mental disorders.

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