A Brief Review of Resting-State Functional Magnetic Resonance Imaging Analysis in ADHD

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Abstract: Attention Deficit/Hyperactivity Disorder (ADHD) represents a brain-based disorder that is typically diagnosed based on reported behavioral symptoms, which is challenging due to the broad spectrum of symptoms and the presence of multiple subtypes. Thus, there is a growing interest in exploring its underlying mechanisms using advancements in brain imaging such as resting-state functional Magnetic Resonance Imaging (rs-fMRI). This technique) has become a central tool in investigating ADHD, enabling researchers to explore how intrinsic functional connectivity (FC) contributes to the disorder. Various methodologies, including model-driven and data-driven approaches, are available for analyzing rs-fMRI data. This research provides a brief overview of rs-fMRI analysis methodologies in ADHD research. It highlights the principal analytical methods and critically discusses their advantages and drawbacks in contributing to a more profound understanding of ADHD-specific FC profiles. By summarizing the recent trends and methodological advancements, this short review will help researchers familiarize themselves with these techniques and guide them in applying them effectively in clinical settings. Ultimately, this will improve the diagnostic potential of rs-fMRI in ADHD studies.

1 INTRODUCTION

ADHD lacks distinct imaging and physiological indicators [1], [2]. Thus, the diagnostic procedure depends on behavioral assessments and observed actions. Identifying distinct biomarkers in the ADHD brain remains a central, unresolved challenge in neuroscience. Researchers employ neuroimaging techniques to examine brain functions by capturing images of neural activity in a safe and non-invasive manner. This approach facilitates more profound insights into how specific brain areas, termed regions of interest (ROIs), contribute to cognitive and behavioral processes. A key technology is functional Magnetic Resonance Imaging (fMRI). This non-invasive imaging approach provides enhanced spatial and temporal precision by measuring brain fluctuations in the blood-oxgen-level-dependent (BOLD signals). These fluctuations correspond to neural activity, reflecting the brain's functional organization [3]. Brain parcellation can be explored using two primary forms of functional MRI, task-state and rest-state fMRI [4]. The rs-fMRI has become a prominent tool for probing the neurofunctional alterations associated with ADHD, as it holds promise for supporting objective classification and diagnosis strategies in the absence of external tasks [5]. Rs-fMRI's passive nature is helpful for research with children, where getting them to cooperate can be challenging [6]. Rs-fMRI investigations have consistently identified aberrant patterns of Functional Connectivity (FC) across multiple brain networks in individuals diagnosed with ADHD [7]-[9], often assessed through Resting-State Networks (RSNs) reflecting the disorder-specific connectivity patterns, as they are spatially distinct but functionally coherent brain regions [10]. The application of rs-fMRI has uncovered connectivity disruption associated with ADHD-affected brains, including several interconnected RSNs [11]-[15]. Studies have reported that disruption in FC spans multiple RSNs as the Default Mode- (DMN), Ventral Attention- (VAN), Dorsal Attention- (DAN), Fronto Partial- (FPN), and Sensorimotor- (SMN) networks have been extensively examined in ADHD subjects compared to TDC [15]. Dysregulation in these RSNs has been linked to ADHD core symptoms, categorized by variations in network homogeneity

and FC. Despite the availability of various parcellation methods for rs-fMRI analysis, anatomical and functional brain atlases remain the most used approaches that collectively aid in exploring those RSN patterns. Those atlases facilitated the parcellation of the brain into a structure of interest that effectively analyzes rs-fMRI. Moreover, the ADHD-200 Consortium has contributed to the field by developing a substantial rs-fMRI dataset that collected multiple research sites that aim to enhance research on ADHD [3], [16]. This initiative aims to enhance ADHD research by encouraging the standardization and reproducibility of findings. This work addresses the limitations of current analysis methods by exploring the concept that resting brains would offer a window into the underlying mechanisms of ADHD. It will examine various analysis techniques for rs-MRI to inform future research focused on identifying biomarkers associated with ADHD.

2 ADHD BACKGROUND: FROM BEHAVIORAL TO NEURODEVELOPMENTAL PERSPECTIVE

2.1 The Evolution of ADHD Subjective Diagnosis

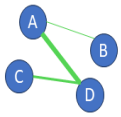
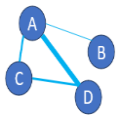
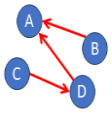
This section clarifies the historical shift in ADHD subjective diagnostic criteria. In 1902, it was known as "Hyperkinetic Disorder," as documented by Sir George Still, a UK pediatrician [17]. Initially, ADHD was described as a childhood condition that was associated with "moral control." However, by 1980, the American Psychiatric Association (APA) released the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III); shifting the disorder from the "hyperkinetic reaction" to "Attention Deficit Disorder" (ADD), which reflects the recognition that hyperactivity did not consistently present the core symptom [18]. Later, in 1987, the APA updated the DSM-III once again, merging attention issues with hyperactivity under the new term "Attention-Deficit/ Hyperactivity Disorder (ADHD)". The DSM-III-R combines symptoms into a single list, shifting towards a more inclusive definition [19]. The modern framework for diagnosing and categorizing ADHD, grounded in the DSM-IV, was released in 2000. The clinical framework for ADHD distinguishes three subtypes: predominantly inattentive (ADHD-I), hyperactive/impulsive (ADHD-HI), and combined presentation type (ADHD-C). These subcategories remain central to guiding clinical ADHD diagnosis today. Substantial evidence from prior studies a pronounced genetic factor among first-degree relatives, when parents and siblings have ADHD [20]. The more recent revision of DSM-V redefined ADHD as a part of the neurodevelopmental disorders domain, reflecting an enhanced understanding of the condition by incorporating more comprehensive symptom descriptions and situational contexts than those outlined in DSM-IV, thereby improving diagnostic precision [20].

2.2 Toward Objective Diagnosis: Neural Biomarker of ADHD

The World Health Organization (WHO) classifies ADHD as a part of a wider category of mental health conditions, grouping it with other related conditions like depression, bipolar disorder, and schizophrenia. These conditions can vary significantly in their symptoms, severity, and duration, ranging from episodic with short-term to long-standing chronic issues [21]-[23]. Foundational research conducted by Paloyelis, et al. [24] has provided essential insights into the neurobiological underpinnings of ADHD. Their work emphasized the methodological difficulties in comparing neural activation profiles between subjects diagnosed with ADHD and controls when relying on fMRI. Although extensive neuroscience research has demonstrated functional and structural irregularities in the brains of subjects with ADHD through clinical data [25], these findings still need to gain widespread acceptance and be trusted in clinical routine practices.

Studies utilizing fMRI have been extensively used to investigate how neuronal connections differ between ADHD and typically developing individuals (TDC) [3], [26]. This imaging technique captures brain activity by assessing brain functions indirectly by monitoring the hemodynamic responses, particularly through the Blood-Oxygen-Level-Dependent (BOLD) signal, which indirectly reflects the neural processes. The fMRI experiments generally fall into two main categories: task-based (i.e., real-time), which records brain responses during specific cognitive or behavioral, and resting-state, which measures brain activity while the subject is not performing any cognitive task. These insights have revealed altered FC in ADHD subjects across various RSNs by analyzing fluctuations associated with BOLD levels to infer the underlying neural processes [15], [27].

Table 1: Summary of the three principal brain connectivity models.

Aspect	Structural	Functional	Effective
Definition	Examines the brain's physical wiring by tracing anatomical pathways to depict various brain regions.	Quantifying the statistical relationships between activity patterns in different regions over time.	Model the direct influence or causal interactions across brain regions.
Visual Representation			
Imaging	"DTI, MRI"	"fMRI, MEG, PET"	"fMRI, MEG, PET"
Output	White matter pathways, tract density	Temporal association, statistical synchronization	Supervised information flow and causal influence
Analysis Techniques	Tractography algorithms	Correlation, coherence, and F network analysis	Granger causality analysis, dynamic causal modeling (DCM), Bayesian modeling approach
Matrix Type	Undirected Structural Connectivity, Symmetric	Undirected FC, Symmetric	Directed influence, Asymmetric
Advantages	Reveals brain's anatomical wiring; detects structural abnormalities and guides neurosurgical planning	Identifies functional connections and synchronized brain activity	shows insights into the directed influence and causal overlapping neural functions.
Constraints	Restricted by available anatomical information	Correlations alone cannot determine direct causal or directional influence	Requires additional assumptions and may involve complex modeling
Key Utilization	Detecting lesions, tumors, or structural abnormalities. Mapping white matter pathways.	Studying task-related brain activity, RSNs, and evaluation of neurological disorders.	Understanding cognitive processes, decision-making, and brain stimulation.

3 ANALYTICAL APPROACHES TO MODELING BRAIN NETWORKS

A groundbreaking study by Biswal, et al. [28] represented a significant milestone in neuroimaging by discovering low-frequency correlations (< 0.1 Hz) among motor cortex seeds in rested brains. This finding fundamentally transformed our understanding of brain function and laid the foundation for subsequent studies on inpatient and healthy individuals using modern rs-fMRI. Modeling brain activity involves diverse approaches alongside advanced imaging techniques. A summary of three distinct types of brain connectivity is listed in Table 1.

3.1 Model-Driven Approach

3.1.1 Seed-Based Analysis

This approach is commonly acknowledged as a reliable way to investigate irregular brain activity in rs-fMRI paradigms, specifically on ADHD and various brain disorders [29]. Connectivity analysis in rs-fMRI is generally conducted after parceling the entire cortex. This can be done using a broad level covering the whole brain or targeting a specific brain region- or network- of interest (i.e., ROI- or network-based approaches). One commonly applied method in ADHD studies is voxel-wise correlation analysis, which examines the neural mechanisms of ADHD at the voxel level. The voxel-wise analysis entails the evaluation of numerous measurements within individual voxel features. Several voxel-based metrics have been used in ADHD studies, including Amplitude of Low-Frequency Fluctuation (ALFF), its fractional version (fALFF), Regional Homogeneity (ReHo), degree centrality, and voxel-mirrored homotopic connectivity [30]-[37]. However, when applied to multiple sites datasets such as ADHD-200, results have often been inconsistent, raising concerns about the reliability of voxel-wise findings in capturing the spontaneous brain activity in the ADHD population [38]. Another analytical strategy centers on defining seeds as regions of interest (ROIs), clusters of neighboring voxels based on anatomical or functional relevance (e.g., conventionally standardizing an ROI to around 27

voxels to be represented). These ROIs can be derived from prior studies, anatomical references, or specific considerations. Still, even minor changes in ROI placement can lead to noticeable variations in analysis outcomes. One of the major limitations of the ROI-based analysis lies in its subjective determination of regions to be examined. However, variability in experts' judgments can result in overlapping the ROIs for similar analyses, leading to inconsistencies and reducing reproducibility among studies. Moreover, a notable drawback is relying on expert-driven decisions, where researchers have to define ROIs subjectively, which possess a conceptual grasp of abstract targets that may not be universally applicable. In addition to those technical issues, the last limitation is the inherent inter-subject variability, as the spatial configuration and extent of functional brain regions can vary across subjects. Earlier seed-based FC studies suffered from ambiguity in defining the selected seeds' dimensions and spatial placement, which could lead to misleading results or biased interpretations [39]. Modern neuroscience addressed these challenges using standardized brain atlases, which provide systematically defined ROIs based on anatomical landmarks or functional characteristics [40]. These atlases serve as a reference framework that ensures consistent delineation of brain regions across studies [41], thereby enhancing the reliability and reproducibility of FC analysis.

3.1.2 Atlas-Based Methodology

Atlases are standardized brain templates within a shared space. The human cerebral cortex is systematically partitioned into distinct regions based on either anatomical landmarks or FC profiles [42]. Adopting atlas-based approaches has been revolutionized by establishing standardized parameters for seed placements are crucial in comparative and meta-analysis studies [43]. Those atlases are [40], [42]: The Automated Anatomical Labeling (AAL), Eickhoff-Zilles (EZ), and Harvard-Oxford (HO) [16], [44], [45] Anatomical brain atlases, where AAL is a high-resolution atlas since it provides more detailed parcels. Alternatively, functional brain parcellations such as Craddock 200 (CC200), Craddock 400 (CC400), Yeo7, and Power [44], [46]-[48] are constructed using functional data. Figure 1 visualizes that brain atlases retrieved from [49]. Registering rs-fMRI to a brain atlas is a crucial pre-processing step before constructing the connectivity matrix. The choice of brain atlas significantly impacts the analysis result, as it determines the seed from which the time-series is extracted. Subsequently, several statistical methods are available for quantifying the correlation between time-series signals, including the Pearson Correlation Coefficient (frequently symbolized by r), Kendall's Tau, and Spearman's Rank Correlation (Table 2). Although all these methods are widely cited in the literature. Among these person's r remains the most prevalent in estimating the FC in ADHD studies.

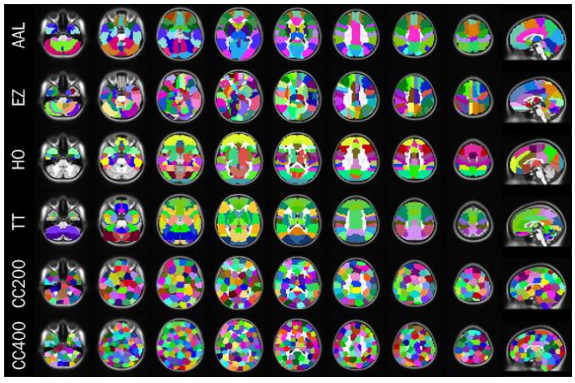


Figure 1: The precomputed brain atlases that are widely applied in model-driven studies on ADHD.

Table 2: Quantitative metrics utilized to assess the Functional Connectivity (FC).

Operation Domain	Normalized Range	Analytical Metric	Description and Advantages
Time	[-1,1]	Pearson correlation	Quantifies the linear association between two signals.
		Spearman correlation	Measures the monotonic relationship
		Partial correlation	Quantifies direct relationships while controlling
		Mutual Information	Estimates the shared information
Frequency	[0,1]	Coherence	Measures phase consistency between signals at specific frequencies.
		Mutual Information	Derived to include non-linear association.
Time-frequency		Wavelet Coherence	Combines time and frequency for dynamic-based analysis

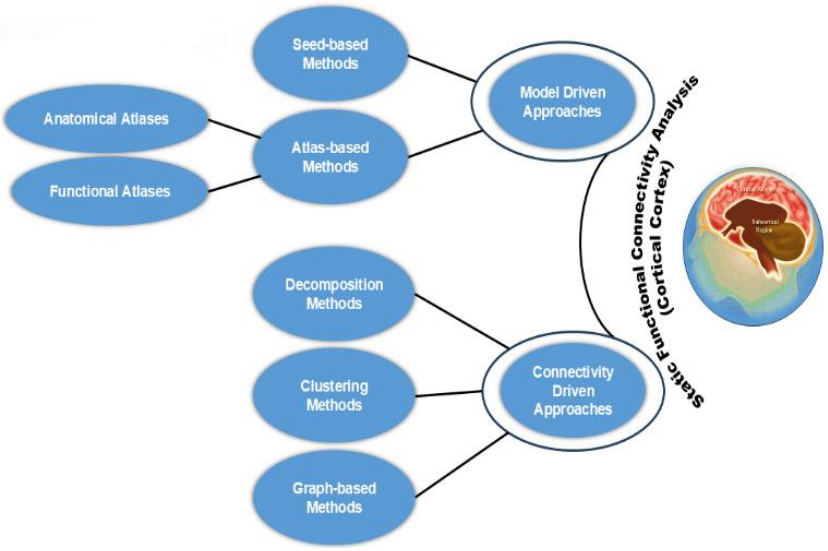


Figure 2: The categorization of approaches on rs-fMRI Analysis.

Consequently, selecting the brain atlas is critical in rs-fMRI analysis, as it influences the FC pattern and interpretation [40]. The framework in Figure 2 categorizes various rs-fMRI analytical methods.

3.2 Data-Driven Approach

This parcellation methodology is designated as connectivity-driven parcellation due to its empirical foundation in observed neural relationships [50]. These parcellation methods do not rely on the required predefined node locations, which are commonly characterized based on statistical features derived from the rs-fMRI data. Data-driven approaches offer flexibility and adaptability across various datasets, but small sample sizes may restrict the broader applicability of results [51]. The following section outlines key methodologies that have been widely adopted for brain parcellation:

3.2.1 Decomposition Methods

Principal Component Analysis (PCA) and Independent Component Analysis (ICA) are powerful techniques for decomposing fMRI data. PCA is often applied in pre-processing as a dimensionality reduction and noise-filtering strategy [50]. An ICA-based analysis has emerged as a data-driven signal processing approach extensively employed in the field of rs-fMRI analysis to extract statistically independent patterns from complex multivariate data [15] to find relevant components without relying on predefined seeds or models (i.e., blind source information) [52]. Numerous ICA-based algorithms have been available, and discussing them exceeds the boundaries of this study; thus, interested readers could explore comparative reviews [53]. The effectiveness of ICA in ADHD research is evident in identifying the latent brain networks in ADHD and TDC by decomposing the rs-fMRI data into spatially Independent Components (ICs), enabling the definition of RSNs that reflect the pathogenesis of ADHD. Even ICA enables the identification of all networks relevant to subjects, ensuring that functionally significant patterns are extracted [54]. Researchers have to manually locate the components and distinguish the noise from the hemodynamic signals. This manual step, though subjective, is often regarded as a benefit of ICA. A study by [55] applied an ICA-based FC mapping to derive FC maps as features using ICA to represent the prominent clusters in the ADHD cohort. Findings reflect inter-subject variability within ADHD subjects, affecting the consistency and interpretability of fMRI results. Besides, a work referenced in [15] employed ICA to investigate and examine the primary RSNs connectome between ADHD subtypes and TDC subjects. Findings revealed significant differences in six RSNs among TDC, ADHD-Combined, and ADHD-Inattentive in FC of the six networks. The dataset was obtained from the ADHD-200 consortium NYU site and included 67 control subjects, 56 individuals diagnosed with ADHD-Combined, and 32 individuals diagnosed with ADHD-Inattentive, all aged between 7 and 17 years. These findings aligned with current views on atypical network patterns observed in ADHD subjects. One drawback is that ICA-driven spatial maps display

neural and non-neuronal signals in non-contiguous and overlapped components, requiring careful interpretation. To address this drawback, researchers should increase the number of components or select components manually to avoid incorporating noise into functional data analysis.

3.2.2 Clustering Methods

Recent advancements in brain mapping have seen a growing emphasis on Connectivity-Driven Parcellations (CDP) from rs-fMRI data [55], since results from this approach will characterize a specific population as the data provides the information. These methods aim to segment the brain based on intrinsic connectivity, and their alignment does not consistently correspond with the underlying neuronal architecture. Studies using rs-fMRI to examine brain state dynamics in ADHD have applied several clustering algorithms [56]. Recent advancements in rs-fMRI have promoted CDP techniques, which aim to segment the brain into functionally distinct regions based on connectivity profiles. These methodologies conceptualize the brain as a dynamic network of interacting regions where spatially distributed voxels are grouped according to their functional coherence. This segmentation strategy offers a data-driven pathway to generate parcellation maps using healthy or disordered brains that can be generated as a reference framework for localizing disrupted or affected brain regions (i.e., lesion-specific maps). The processing workflow is strengthened by narrowing the analytical focus to the targeted region, reducing dimensionality and computational complexity. Riaz, et al. [45] stated a noticeable gap in the literature about applying clustering algorithms on ADHD-200 or other comparable neuroimaging datasets. Many algorithmic strategies have been developed for analyzing brain connectivity, each characterized by its advantages and limitations; among them are k-means, spectral, hierarchical, and fuzzy clustering commonly utilized on rs-fMRI [50], [57]-[59]. The research adopted cluster-based analysis, which demonstrated the efficiency of the k-means clustering methodology in distinguishing between ADHD subjects and TDC through the analysis of discrete FC using FC analysis, as reported in studies referenced by [60]-[62]. The rs-fMRI data of a cohort of 113 ADHD children and 76 TDC were employed for brain parcellation analysis.

3.2.3 Graph Theory Methods

Despite the above-mentioned analytical methods, graph theory can provide a powerful tool for diagnosing biomarkers and insight into treating brain disorders for rs-fMRI data. The brain lends itself to graph theory approaches due to its natural network structure, which can be represented as a graph of interconnected nodes and edges [63]. This section provides an overview of the current state of graph theory methods in analyzing rs-FC in ADHD research. Brain networks can be represented as: $G = (N, E)$; nodes N typically represent brain regions, and E symbolizes the connections among those nodes. Graph theory reveals network disturbances in ADHD [64]. Graph local and global metrics are the frequently used approaches for characterizing the functional brain network. Previous research has indicated decreased global efficiency alongside increased local efficiency in the brain networks of ADHD subjects [65]. An accurate node definition is key to modeling functional organization using graphs [66]. A fundamental challenge in rs-fMRI analysis is determining the optimal strategy for defining and grouping voxels to construct a meaningful and anatomically valid brain parcellation.

4 EVALUATIONS OF PARCELLATION

No agreement exists on which evaluation strategy is used to evaluate the resultant parcellation [58], [67]. However, various parcellation algorithms yield varying numbers of parcels by the intended granularity to achieve optimal granularity, driven by the data used. Therefore, different studies produced brain references that characterized the used fMRI dataset; Figure 3 showcases a comparison of four brain atlases developed by various parcellation algorithms, fine and coarse granularity, and different research labs, as other colors reflecting different parcels, regions, or even networks with either functional connectivity or anatomical landmarks.

For instance, reproducibility was adopted to assess the stability of the parcellation algorithm across different datasets for the generalization of results. In contrast, functional homogeneity measures the consistency of BOLD signals across parcels, which is an essential criterion in rs-fMRI studies. Moreover, effectiveness is measured using parcel/region separation metrics, like the Silhouette coefficient or modularity, to evaluate the identified parcels' distinctiveness [47], [50], [58], [67].

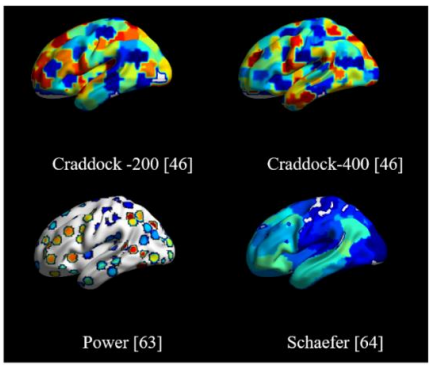


Figure 3: The sagittal representation of the left hemisphere across four distinct Brain atlases, illustrating how various methodological and anatomical considerations influence variations in brain parcellations.

5 CONCLUSIONS

Researchers are growing interested in the reliability of subjective assessments in diagnosing ADHD, as their interpretation varies depending on clinicians, cultural context, and countries. Therefore, objective diagnostic methods are essential for accurately identifying ADHD. One of the most cited issues in ADHD studies is the inconsistencies in how researchers define and label RSNs. Variability in parcellation schemas can significantly impact the FC analysis. Moreover, different atlases affect the selected brain parcels, influencing the study's results and conclusions. Future research should focus on developing a uniform and customized approach, such as creating condition-specific brain references with specific brain networks of interest. Hybrid approaches are also advisable, combining various analytical techniques, such as seed-based methods with ICA or atlas-based methods with clustering-based algorithms and graph-theory approaches. Finally, developing a tailored atlas would provide a robust framework for understanding brain patterns in the ADHD cohort. This strategy is recommended for capturing ADHD-related variations and improving consistency in research findings.

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