Representational similarity analysis between ADHD and SCZ based on functional brain network

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Abstract

Attention deficit hyperactivity disorder (ADHD) and schizophrenia (SCZ) have complex neural mechanisms. This study used fMRI data from resting state and 2-back working memory tasks to analyze the abnormal brain network characteristics of the two. The results showed that ADHD patients had dispersed functional connections under task conditions, and increased node degrees in the prefrontal cortex, insula, anterior cingulate gyrus, and cerebellum, indicating compensatory network reorganization. SCZ patients showed abnormal connections between the default mode network and the limbic cortex, and weakened coupling between the parietal lobe and the attention network, reflecting cognitive integration and emotion regulation defects. Through representational similarity analysis (RSA), it was found that the two diseases had shared abnormal connections in the prefrontal cortex, middle temporal gyrus, and hippocampus, which may be related to working memory regulation disorders. These findings provide potential biomarkers for targeted intervention.

Keywords: ADHD; SCZ; Functional connectivity; RSA; Working Memory;

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) and schizophrenia (SCZ) are both common neurodevelopmental disorders. Among them, ADHD is characterized by inattention, hyperactivity and impulsivity (Cooper & Bilton, 2013), while SCZ is mainly manifested by hallucinations, delusions and flat emotions (Insel, 2010). In recent years, the incidence of ADHD and SCZ has continued to rise, posing a huge challenge to the social function and cognitive development of individuals, and also causing a heavy burden on families and society. Studies have shown that both diseases are closely related to executive function deficits, especially in working memory (WM) (Alderson et al., 2013; Cortese et al., 2012). Working memory is an important basis for higher-order cognitive activities. Its multi-component model (Baddeley,2012) emphasizes the ability to temporarily store and process information, which is of key significance to the individual's learning and decision-making process. Neuroimaging studies have further revealed that delayed prefrontal development in ADHD patients (Wang et al., 2021) and abnormal thalamus-cortical networks in SCZ patients (Anticevic et al., 2014) may be the core mechanisms of their working memory deficits. Therefore, in-depth exploration of the differences in neural circuits at the working memory level between ADHD and SCZ is of great value for understanding and intervening in these two neurodevelopmental disorders.

Neuroimaging is crucial in studying brain functional connectivity and interaction patterns between different brain regions (Friston, 2011). Since its successful application in human brain research, functional magnetic resonance imaging (fMRI) has become an important tool for exploring the pathogenesis of neuropsychiatric diseases with its high spatial resolution, non-invasiveness, and good signal-to-noise ratio (Yen, Lin, & Chiang, 2023). In particular, the special paradigm of resting-state fMRI (rs-fMRI) can capture the temporal coherence between functionally related brain regions by measuring the spontaneous fluctuations of blood-oxygen-level-dependent (BOLD) signals in a task-free state (Lee, Smyser, & Shimony, 2013). Due to its low requirement for subject cooperation and strong repeatability, rs-fMRI has been widely used in the early diagnosis and prognosis evaluation of complex neuropsychiatric diseases such as ADHD and SCZ. However, resting-state fMRI cannot fully reflect the dynamic regulation of brain activity by cognitive processes such as working memory. In contrast, task-based fMRI allows researchers to more directly observe the activation patterns and connectivity changes of the brain when performing specific cognitive loads by designing specific cognitive tasks (D'Esposito & Postle, 2015), thus helping to reveal the underlying pathophysiological mechanisms.

In recent years, with the rapid development of machine learning and network science methods in the field of cognitive neuroscience, more and more scholars have begun to pay attention to how to extract features and recognize patterns from brain imaging data to assist in disease diagnosis and classification (Smith & Jones, 2022; Plis et al., 2021). In previous studies, common practices include traditional machine learning techniques such as support vector machines and random forests, as well as network models based on deep learning (Kim et al., 2020; Heinsfeld et al., 2022). These methods have achieved considerable results in disease discrimination and brain network analysis (BNA) (Dvornek et al., 2020; Zeng et al., 2023). However, there are still limited comparative or joint analyses of various neurodevelopmental disorders, especially ADHD and SCZ in terms of working memory-related functional connectivity (Cheng et al., 2023; Anticevic et al., 2021). Most task-based studies usually focus only on specific brain regions or local

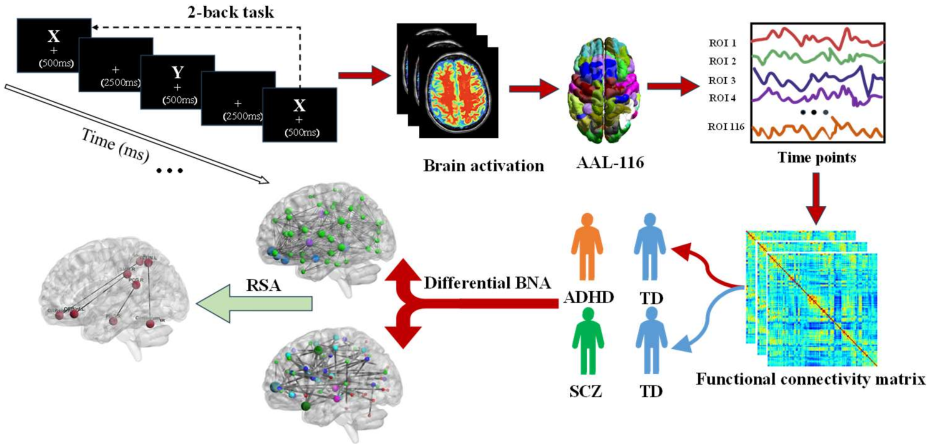

Figure 1: Analytical Framework.

pathways, lacking a holistic examination of the whole brain functional network in the execution of working memory tasks (Bullmore & Sporns, 2020; Bassett et al., 2021). Therefore, functional connectivity analysis methods have gradually become a hot topic of research, which can quantify the temporal coordinated changes between different brain regions and provide a new perspective for understanding the interaction and integration of brain information (Zhou et al., 2023; Fornito et al., 2022). With the advancement of neuroimaging, especially the combination of functional magnetic resonance imaging (fMRI) and representational similarity analysis (RSA), we have gained a new research perspective to gain a deeper understanding of the working memory mechanisms in ADHD and SCZ (Kriegeskorte et al., 2021; Walther et al., 2022). Representational similarity analysis has become an effective tool for exploring the mechanisms of these neural disorders by quantifying the similarity of neural activation patterns under different task conditions (Haxby et al., 2020; Nili et al., 2023). However, the existing RSA studies mainly focus on the topological characteristics of static functional networks and the analysis of local activation patterns in specific brain regions, and rarely involve the dynamic activation patterns of the brain under different task states (Zuo et al., 2021; Lurie et al., 2023). Therefore, combining dynamic functional connectivity analysis and representational similarity methods may provide a new perspective for revealing the dynamic neural mechanisms of ADHD and SCZ in working memory tasks.

This study aims to fill the gap in existing research and propose a new method that combines RSA with brain activation states under different tasks. By analyzing the brain activation patterns of ADHD and SCZ patients in working memory tasks, we explore their neural characteristics under different task conditions. Specifically, our work contributes as follows:

1) We studied the functional connection network of ADHD and SCZ patients under the 2-back task, identified differential connection characteristics, and compared them with the resting state network to explore the impact of working memory load on brain network information flow.

2) From the perspective of cross-disorder and task load, we analyzed the dynamic differences of the two neurodevelopmental disorders in the whole brain network, providing a new perspective for understanding the pathological mechanisms of ADHD and SCZ.

3) We used RSA to visualize and verify differential connections, further clarifying the role of these connections in working memory processes and disease manifestations, and providing a basis for accurately locating diseased brain areas and networks.

Method

This paper analyzes the differential connectivity of ADHD and SCZ subjects under 2-back memory load. First, we explore the most different functional connections between ADHD and SCZ and construct differential functional brain networks, and compare them with the resting functional brain networks of the two diseases to explore the information flow of brain functional connections under memory tasks. Then, we use RSA to study the relationship between the differential connections shared by the two diseases. See Figure 1 for the process.

Functional Brain Network Construction

We used 116 anatomical divisions based on the AAL (Automated Anatomical Labeling) standard brain atlas, including 90 cerebral cortex and subcortical regions and 26 cerebellar regions, as the basic units for brain function analysis. In the signal preprocessing stage, the blood oxygen level dependent (BOLD) signals in each brain region were first spatially integrated, and the arithmetic mean of the time series of all voxels in each brain region was calculated to generate the average BOLD signal time series representing the brain region. Subsequently, Z-score standardization was performed to eliminate the differences in baseline signal intensity between individuals and ensure the comparability of signals between different individuals. Then, the Pearson correlation coefficient between the 116 brain region time series of each subject was calculated, and a 116×116 functional connection matrix was constructed.

In the inter-group comparison stage, we compared the functional network differences between the ADHD and SCZ groups by a two-sample t-test, with the significance level set at p<0.05, and FDR correction was performed to ensure the reliability and validity of the statistical results.

Difference Classification Based on Bayesian SVM

Due to the small data sample, the traditional machine learning methods were used for classification in this study. To prevent overfitting, in this study, a Bayesian support vector machine (Bayesian SVM) was used to classify the functional connectivity features of ADHD and SCZ. The Bayesian optimization improves the classification performance and prevents overfitting by optimizing the hyperparameters of the SVM (the regularization parameter C and the kernel function parameter γ). Its kernel function is defined as:

$$k(x_i, x_j) = exp\left(-\gamma \|x_i - x_j\|^2\right) \tag{1}$$

Given the training set $D = \{(x_i, y_i)\}_{i=1}^{N}$, where $x_i \in R^d$ denotes the sample features. The optimization formula for the standard SVM is as follows:

$$\min_{w,b} \frac{1}{2} |\boldsymbol{w}|^2 \tag{2}$$

Constraints are:

$$y_i(\boldsymbol{w}^T \boldsymbol{x}_i + b) \geq 1, \quad i = 1, \ldots, n$$

Where $\boldsymbol{w}$ is the normal vector of the hyperplane and b is the bias term. $y_i \in \{-1,1\}$ Show the label.

The Bayesian SVM conducts probabilistic modeling of the hyperparameters by introducing Bayesian inference, and the optimization goal is to maximize the posterior distribution $(p\ (\theta \mid \mathcal{D})$, where $\theta = \{\boldsymbol{w}, b, C, K\}$ represent the model parameters, and D is the training data. The posterior distribution $p\ (\theta \mid \mathcal{D})$ is expressed as:

$$p(\theta|\mathcal{D}) = \frac{p(\mathcal{D}|\theta)p(\theta)}{p(\mathcal{D})} \tag{3}$$

Among them, $p\ (\mathcal{D} \mid \theta)$ is the likelihood function, $p\ (\theta)$ is the prior distribution of the hyperparameters, and $p\ (\mathcal{D})$ is the marginal likelihood of the data. The goal of Bayesian optimization is to optimize the hyperparameters by maximizing the posterior probability:

$$\hat{\theta} = argmax_{\theta} p(\mathcal{D} \mid \theta) p(\theta) \tag{4}$$

The best hyperparameters are selected by variational inference. Finally, to evaluate the performance of the Bayesian SVM classifier, we applied ten-fold cross-validation and further analyzed the classification contributions of different brain regions by clustering the feature space and mapping to the AAL116 standard brain atlas. The contribution of each brain region was obtained by calculating the absolute value of categorical weights for each brain region and averaging them. Ultimately, brain regions with retention contributions over 2% were reconstructed as key brain regions.

Inter-group RSA based on differential connectivity

Representational similarity analysis (RSA) quantifies the differences in neural activation patterns under different stimulation conditions by constructing a representational dissimilarity matrix (RDM). Since fMRI signals are insensitive to amplitude, the Pearson correlation coefficient is usually used to compare neural responses under different stimulation categories (Kriegeskorte et al., 2021). The RSA method can be flexibly applied to task-based fMRI in block-design and event-related designs (Nili et al., 2023). By aggregating individual RDMs to generate group-level RDMs, RSA can not only reveal neural activation patterns at the individual level, but also further support inter-group analysis, revealing the similarities or differences in activation patterns of different groups (such as ADHD and SCZ) in specific brain regions (Walther et al., 2022).

In this study, we attempted to extend RSA from individual studies to the group level. First, we established RDMs of different individuals with ADHD and SCZ under working memory load through first-order RSA. Then, the RDMs of the subjects in different groups were averaged to generate group-level RDMs. In the subsequent second-order RSA, we used these RDMs to compare the brain regions with greater classification contributions under the working memory task obtained by SVM decoding to identify the representational relationships between brain regions (Haxby et al., 2020).

To evaluate the performance of multiple model RDMs, we used a nonparametric permutation test (Nichols & Holmes, 2022). When calculating, the diagonal and upper triangle of the RDM were excluded, and only the lower triangle was calculated to avoid repeated comparisons and false positive interference. By randomly permuting the order of the rows and columns of the RDM of each subject (5000 iterations), the null distribution was generated and the significance p-value of the actual RDM was calculated (Winkler et al., 2014). When the number of permutations was greater than 5000, the convergence of the p-value was significantly improved, ensuring the reliability of the results. Finally, the Spearman correlation coefficient was used to quantify the similarity of RDM under different conditions (e.g., high/low memory load) and further verify its statistical significance (Zuo et al., 2021).

Experiment

Dataset

The data for this study are from two public datasets on the OpenNeuro platform（Working memory in healthy and schizophrenic individuals - OpenNeuro）.The ADHD data (ds002424/1.2.0) includes 20 patients with attention deficit hyperactivity disorder diagnosed by the ADHD rating scale and DSM-V structured interview and 20 age/sex matched healthy controls (TD). The sample size meets the statistical requirements (effect size 0.25, α=0.05, post hoc test power 0.94) verified by G*Power. The SCZ data comes from the dataset of the School of Medicine at Washington University in St. Louis, including 19 patients with schizophrenia diagnosed by the DSM-IV structured clinical interview (disease duration 4.79±2.98 years), 28 non-psychotic siblings of SCZ patients, 10 TD and their 17 siblings. All functional magnetic resonance imaging data were acquired by a

Siemens Allegra 3T scanner using a gradient echo planar imaging (EPI) sequence with key parameters including: repetition time (TR) 2.0s, echo time (TE) 30 ms, and flip angle 80°.

Experimental Paradigm

All subjects completed a standardized 2-back working memory task. The experiment used a letter matching task. The specific process was as follows: the computer presented letters in a random order, and each letter was displayed on the screen for a fixed time. At the beginning of the experiment, the letters were displayed one by one until a predetermined number was reached. The subjects were required to judge whether the current letter was the same as the letters displayed twice before. If they were the same, they pressed the corresponding button; if they were different, they did not respond. This task aims to examine the memory ability under working memory load, especially the ability to maintain and compare the previous and subsequent stimuli. The experiment used E-Prime 2.0 for stimulus presentation and response recording.

Data Processing

Functional magnetic resonance imaging (fMRI) data were preprocessed using SPM12 and DPABI toolbox. The specific steps are as follows: First, the first 10 time points were removed to eliminate the magnetic saturation effect at the beginning of the scan. Then, temporal slice correction was performed to synchronize the time series of different slices. Subsequently, the Friston-24 parameter model was applied to correct for head motion to remove artifacts caused by head motion. Subjects with a translation greater than 2 mm or a rotation greater than 2° were excluded. The next step was spatial registration, where the functional images were registered to the MNI standard space and the voxel size was resampled to $3 \times 3 \times 3$ mm^3. Then, spatial smoothing was performed using a 6mm full width at half maximum (FWHM) Gaussian kernel to improve the signal-to-noise ratio. Then, potential interference factors such as white matter, cerebrospinal fluid, whole brain signals, and head motion parameters were regressed out. After that, the linear trend in the time series was removed to eliminate possible linear drift. Finally, a 0.001-0.1 Hz bandpass filter was performed to effectively suppress high-frequency noise, thereby ensuring the quality of the data and the accuracy of the analysis.

Evaluation Metrics

The classifier was evaluated using common metrics used in classification tasks, including accuracy (ACC), sensitivity (SEN), and specificity (SPE).

Results and Analysis

Classification Results

We used the Bayesian SVM classifier to classify the functional connectivity features of the ADHD and TD groups, and the SCZ and TD groups, and performed statistical analysis using a one-tailed two-sample T-test. By selecting functional connectivity at different p values as classification features, the most differential features were selected, with a p value range of 0.005 to 0.05 and a step size of 0.005.

The performance of the classifier is estimated by 10x cross-validation. The classification performance of the two groups of diseases is shown in Figure 2.

For the ADHD and TD groups, when the p value is 0.005, the selected functional connectivity features are the least and the classification performance is the worst. When the differential connectivity features are selected at a p value of 0.035, the classification performance is the best, with an accuracy of ACC = 64.48±1.33%, a sensitivity of SEN = 64.83±1.45%, and a specificity of SPE = 64.14±1.17%.For the SCZ and TD groups, when the p-value is 0.005, the classification performance is also the worst. When the differentially connected features were selected at a p-value of 0.04, the classification was the best, with an accuracy of ACC = 76.90±2.67%, a sensitivity of SEN = 76.55±2.54%, and a specificity of SPE = 77.24±2.64%.

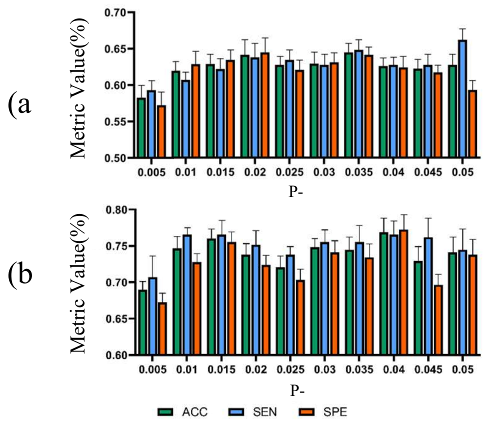

Figure 2: The change of feature classification metrics with p-value. (a) ADHD and TD; (b)SCZ and TD

Differential Brain Network Results

For the ADHD and TD groups, we took the functional connectivity at p=0.035 to construct the differential network, and the total number of functional connections in the task state was 426. For the SCZ and TD groups, we took the functional connectivity at p=0.04 to construct the differential network, and the total number of functional connections in the task state was 681. According to previous studies (Zhao et al., 2022), we visualized the 50 most differential functional connections and compared them with the resting state brain network. The results are shown in Figure 3.

We observed distinct functional connectivity patterns in attention-deficit hyperactivity disorder (ADHD) and schizophrenia (SCZ) patients during working memory tasks, reflecting disease-specific cognitive deficits. In ADHD patients, functional connections exhibited scattered distributions with pronounced frontoparietal connectivity. Important regions including the prefrontal cortex, insula, anterior cingulate gyrus, caudate nucleus, putamen, and

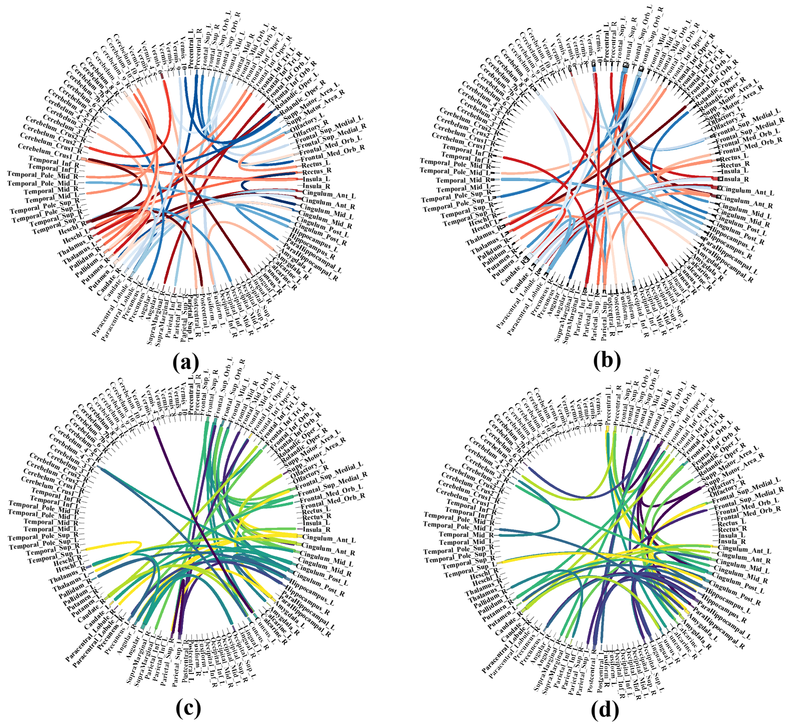

Figure 3: The 50 most significant functional connections in the brain network between ADHD and SCZ. (a) Resting-state ADHD;(b) Task-based ADHD;(c) Task-based SCZ;(d) Resting-state SCZ;

cerebellar subregions demonstrated elevated nodal centrality, corresponding to their roles in executive control and attentional processes (Fair et al., 2023). Notably, cerebellar functional connectivity was significantly attenuated during the 2-back task compared to resting state, suggesting weakened integration of executive-attentional networks during working memory demands, potentially reflecting core deficits in these domains (Castellanos et al., 2022). This altered connectivity pattern may represent a compensatory mechanism through selective regional hyperconnectivity to offset functional impairments in attention regulation and executive control (Sonuga-Barke et al., 2021).

Conversely, SCZ patients displayed unique connectivity signatures characterized by heightened resting-state coupling between the limbic cortex and default mode network (DMN), potentially underlying spontaneous attention and emotional dysregulation (Anticevic et al., 2021). Task engagement revealed enhanced limbic-executive/dorsal attention network (DAN) connectivity, yet attenuated frontoparietal coordination within DAN, indicative of impaired attentional maintenance (Repovs et al., 2023). Enhanced limbic-parietal connectivity and hyperactivation of prefrontal, superior parietal, and hippocampal regions were observed during tasks, accompanied by deficient DMN suppression, potentially driving aberrant frontoparietal interactions across both resting and task states (Whitfield-Gabrieli et al., 2022). These patterns suggest compromised neural integration mechanisms critical for cognitive control, attention modulation, and information processing (Barch et al., 2021). The preserved nodal centrality in prefrontal and superior parietal regions further highlights their pivotal yet dysfunctional roles in SCZ pathophysiology, potentially contributing to characteristic cognitive and mnemonic impairments (Cheng et al., 2023; Rubia et al., 2022).

RSA Results for Shared Connections

In order to investigate the differences in brain networks between the ADHD group and the SCZ group in the resting state and the 2-back task, We conducted an RSA analysis. In the ADHD group, as shown in Figure 4 (a), there were four functional connections that were significantly similar in the resting state and the task state, involving the prefrontal cortex and the default mode network, mainly related to memory encoding, retrieval, and visual spatial processing. In the SCZ group, as shown in Figure 4 (b), there were significant connections related to the frontoparietal network and the executive control network in the resting state and the task state, involving attention maintenance, spatial perception, and cognitive control.

When comparing the differences between the ADHD and SCZ groups in the 2-back task, a total of six functional connections had significant similarities, as shown in Figure 4 (c), of which four were SCZ>ADHD, namely, the right anterior cingulate and paracingulate gyrus to the right dorsolateral superior frontal gyrus, the left temporal pole middle temporal gyrus to the left amygdala, the right temporal middle temporal gyrus to the right hippocampus, and the right caudate nucleus to the right cuneus. The two lines for ADHD>SCZ are from the left thalamus to the left anterior cingulate and paracingulate gyrus, and from the left

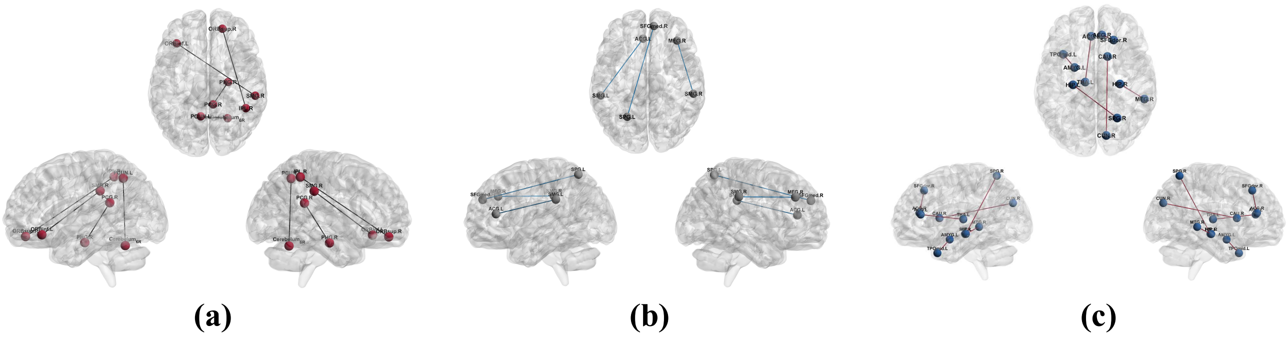

Figure 4: The 2-back task-state resting-state functional connectivity (RSA) results for ADHD and SCZ compared with TD, as well as between ADHD and SCZ, are as follows: (a) RSA results between ADHD and TD; (b) RSA results between SCZ and TD; (c) RSA results between ADHD and SCZ.

hippocampus to the right superior parietal gyrus. The dorsolateral superior frontal gyrus, amygdala, middle temporal gyrus, caudate nucleus, hippocampus and other brain regions may show abnormal functional connectivity in working memory tasks, which is related to executive control of working memory and memory retrieval. The coordinates of these brain regions are shown in Table 1.

Table 1: Significant brain regions of differential functional connectivity between ADHD and SCZ

Brain Region	MNI coordinates	Brain Region	MNI coordinates	P-Value
ACG.R	8.46,37.01,15.84	SFGdor.R	-18.45, 34.81,42.2	0.009
TPOmid.L	-36.32, 14.59,34.08	AMYG.L	-23.27, -0.67, -17.14	0.006
MTG.R	57.47, -37.23, -1.47	HIP.R	29.23, -19.78, -10.33	0.011
CAU.R	14.84, 12.07, 9.42	CUN.R	13.51, -79.36, 28.23	0.016
THA.L	-10.85, -17.56, 7.98	ACG.L	-4.04, 35.4, 13.95	0.009
SPG.R	26.11, -59.18, 62.06	HIP.L	-25.03, -20.74, -10.13	0.003

Preliminary results show that ADHD and SCZ have significant overlapping features at the neural circuit level. Compared with the general population, SCZ patients show a higher incidence of ADHD symptoms (Smith et al., 2020), and this comorbidity phenomenon suggests that the two may share some neural mechanisms. Through RSA, it was found that both types of patients showed abnormal patterns of prefrontal-limbic system connections when performing working memory tasks. Specifically, weakened functional connectivity from the anterior cingulate gyrus to the dorsolateral prefrontal cortex may jointly lead to executive control disorders, while abnormal connectivity between the middle temporal gyrus and the hippocampal-amygdala circuit may cause memory processing deficits (Thompson et al., 2021). These findings suggest that prefrontal dysfunction and attention network damage may be the common neural basis of ADHD and SCZ.

Conclusion

This study investigated the distinct and shared neural mechanisms underlying ADHD and SCZ through task-based and resting-state fMRI, combined with representational similarity analysis (RSA). ADHD patients exhibited dispersed functional connectivity under working memory load, with increased nodal centrality in prefrontal, insular, anterior cingulate, and cerebellar regions, suggesting compensatory hyperconnectivity to offset executive-attentional deficits. In contrast, SCZ patients showed disrupted coupling between the default mode network and limbic cortex, alongside impaired frontoparietal coordination, reflecting deficits in cognitive integration and emotion regulation. RSA revealed overlapping abnormalities in prefrontal, middle temporal, and hippocampal circuits, implicating shared dysregulation in working memory and memory retrieval processes. These findings highlight disease-specific network reorganization and common neural substrates, providing potential biomarkers for targeted interventions. However, the small sample size and cross-sectional design limit generalizability. Future studies should validate these results in larger cohorts and explore dynamic network interactions across developmental stages to refine mechanistic models of neurodevelopmental disorders.

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