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Application of Resting-State fMRI in Auxiliary Diagnosis of Dissociative Disorders: Advances in Cerebral Biomarker Research and Clinical Implications

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Abstract. Dissociative disorders (DDs), a group of trauma-related psychiatric conditions, are characterized by disruptions in consciousness, memory integration, identity coherence, and perceptual continuity. These disorders present significant diagnostic challenges due to symptom overlap with other psychiatric conditions and the lack of objective biomarkers. Resting-state functional magnetic resonance imaging (rs-fMRI), a non-invasive neuroimaging modality, has emerged as a transformative tool for investigating the neurobiological underpinnings of DDs. By capturing low-frequency oscillations (0.01–0.1 Hz) in spontaneous neural activity, rs-fMRI enables the identification of functional network abnormalities, including default mode network (DMN) dysregulation, regional connectivity alterations, and compensatory neural mechanisms. This review synthesizes recent advancements in rs-fMRI biomarker research, highlighting its applications in differential diagnosis, therapeutic target identification, and prognostic evaluation. Critical limitations—such as sample heterogeneity, methodological variability, and insufficient causal inference—are discussed, with proposed solutions emphasizing multimodal data integration, genetic-epigenetic correlates, and interventional validation. The review concludes with a roadmap for advancing precision psychiatry in DDs management through innovative neuroimaging frameworks.

Keywords: Dissociative disorders; Resting-state fMRI; Default mode network; Translational biomarkers; Neurocircuitry; Precision psychiatry.

1. Introduction

Since their formal classification in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) in 1994, dissociative disorders (DDs) have remained enigmatic within the psychiatric landscape. Clinically, DDs manifest as dissociative amnesia, identity fragmentation, derealization, or depersonalization—symptoms that frequently co-occur with post-traumatic stress disorder (PTSD) and borderline personality disorder (BPD), complicating both diagnosis and mechanistic research [1]. Despite their profound impact on quality of life, DDs receive disproportionately less research attention compared to depression or anxiety disorders, leaving critical gaps in understanding their neurobiological foundations.

Traditional diagnostic frameworks rely heavily on subjective symptom reporting and psychological assessments, which are prone to misclassification due to the absence of objective biomarkers [2]. This diagnostic ambiguity underscores the urgent need for neuroimaging tools capable of capturing the neural correlates of dissociation. The advent of rs-fMRI has revolutionized neuropsychiatric research by enabling non-invasive mapping of resting-state neural networks. Unlike task-based fMRI, which requires active participant engagement, rs-fMRI bypasses task-related confounds, making it uniquely suited for studying populations with limited compliance, such as severely ill psychiatric patients [3].

2. Key Methodological Innovations in RS-fMRI

Functional connectivity profiling: Quantifying information transfer efficiency between brain regions through temporal correlation analyses.

Regional homogeneity (ReHo): Measuring local neuronal synchrony by assessing the similarity of time-series signals within spatially adjacent voxels.

Amplitude of low-frequency fluctuation (ALFF): Characterizing the energy distribution of spontaneous neural activity within the 0.01–0.1 Hz frequency band [4].

These approaches have not only elucidated neuroplastic anomalies in DDs but also catalyzed the development of data-driven diagnostic models and personalized neuromodulation protocols.

3. Epidemiological Insights and Cultural Modulation

The prevalence of DDs varies markedly across cultural contexts and diagnostic criteria. According to the World Health Organization (WHO), the lifetime prevalence of DDs in the general population ranges from 1% to 3%, escalating to 10%–20% among individuals exposed to severe trauma, such as combat veterans or survivors of sexual violence [5]. In China, epidemiological studies indicate that DDs account for 2%–5% of psychiatric hospitalizations, with a striking female predominance (female-to-male ratio: 3:1) [6]. These disparities highlight the interplay between environmental stressors, genetic susceptibility, and diagnostic practices in shaping DDs epidemiology.

A notable feature of DDs is their high comorbidity with PTSD, major depressive disorder (MDD), and generalized anxiety disorder (GAD). Approximately 30%–50% of PTSD patients exhibit dissociative symptoms, such as emotional numbing or depersonalization, suggesting shared yet distinct neurobiological pathways [1]. Furthermore, cultural factors profoundly influence symptom expression. In collectivist societies, patients often present with somatic symptoms (e.g., functional paralysis or blindness), whereas identity disturbances and memory fragmentation predominate in individualistic cultures [7]. This cultural modulation complicates cross-national research and underscores the necessity of culturally sensitive diagnostic frameworks.

Despite these insights, epidemiological data on DDs remain sparse and fragmented. Large-scale, multinational cohorts integrating genetic, epigenetic, and psychosocial variables are urgently needed to refine risk stratification models and disentangle the biological mechanisms underlying DDs heterogeneity.

4. Technical Foundations and Historical Evolution of RS-fMRI

Resting-state fMRI (rs-fMRI) is grounded in the neurovascular coupling mechanism, wherein neuronal activity triggers localized changes in cerebral blood flow and oxygenation. These hemodynamic responses are captured via blood oxygenation level-dependent (BOLD) signals, forming the basis for mapping spontaneous neural activity [8]. Methodological rigor—encompassing advanced data acquisition protocols, preprocessing pipelines (e.g., motion correction, global signal regression), and quantitative analytics (e.g., graph theory, dynamic connectivity modeling)—enables precise characterization of spatiotemporal network dynamics.

The theoretical foundation of rs-fMRI rests on the hypothesis that low-frequency oscillations (0.01–0.1 Hz) in resting-state neuronal assemblies encode functional coherence across distributed brain regions [4]. This premise challenges earlier views of the resting brain as a passive "baseline," instead positing it as a dynamic state rich in organized neural activity. Unlike task-based paradigms requiring explicit cognitive engagement, rs-fMRI circumvents task-related confounds, rendering it uniquely suited for studying populations with limited compliance, such as children, elderly patients, or individuals with severe psychiatric conditions [9].

5. The Evolution of rs-fMRI Spans Three Transformative Phases

Methodological validation (1995–2005): Seminal work by Biswal et al. (1995) demonstrated synchronized BOLD fluctuations in bilateral motor cortices during rest, debunking the notion of rest as a passive baseline [10]. The landmark discovery of the default mode network (DMN) by Raichle et al. in 2001 catalyzed a paradigm shift toward whole-brain network analysis [11]. Using positron emission tomography (PET) and fMRI, Raichle’s team identified the DMN—a network of regions (e.g., medial prefrontal cortex, posterior cingulate cortex) that exhibit heightened activity during rest and suppressed activity during goal-directed tasks.

Network topology exploration (2005–2015): The integration of independent component analysis (ICA) and graph theory enabled systematic decomposition of functional networks (e.g., DMN, sensorimotor network) and quantification of topological metrics such as global efficiency, modularity, and small-worldness [12]. Bullmore and Sporns’ "economical brain network" theory further posited that evolutionary pressures optimize brain networks for cost-efficient information transfer [13].

Dynamic and multimodal integration (2015–present): Contemporary research prioritizes dynamic functional connectivity (dFC) and cross-modal data fusion. Techniques like sliding-window analysis and machine learning algorithms (e.g., support vector machines, deep neural networks) now enable real-time tracking of network reconfigurations and disease subtyping [14]. Multimodal approaches integrating rs-fMRI with diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) have further elucidated structure-function relationships and neurochemical correlates of DDs [15].

6. Neuroimaging Biomarkers in DDs: Mechanistic Insights

6.1. Default Mode Network (DMN) Dysregulation

The DMN, anchored in the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), precuneus, and inferior parietal lobule, is central to self-referential processing, autobiographical memory retrieval, and social cognition [16]. Convergent evidence from rs-fMRI studies highlights DMN hypoconnectivity in DDs, particularly between the mPFC and PCC. For instance, Jang et al. (2011) demonstrated that reduced prefrontal DMN connectivity correlates with self-disintegration in schizophrenia patients at high genetic risk, suggesting DMN dysfunction as a transdiagnostic marker shared across psychiatric disorders [17]. Notably, DMN abnormalities are not unique to DDs; similar patterns are observed in Alzheimer’s disease and PTSD with dissociative symptoms, implicating the DMN as a "hub" for psychopathology [18].

6.2. Local Synchrony and Oscillation Anomalies

Regional homogeneity (ReHo) and amplitude of low-frequency fluctuation (ALFF) metrics provide complementary insights into local neural dynamics. In DDs aberrant ReHo/ALFF values are observed in visual-processing regions (e.g., cuneus, calcarine cortex) and emotion-regulation hubs (e.g., amygdala, anterior cingulate cortex). Lanius et al. reported enhanced amygdala-medial PFC connectivity in PTSD patients with dissociation, correlating with intrusive traumatic recollections—a finding that underscores the amygdala’s role in fear memory encoding [19]. Additionally, hippocampal-prefrontal decoupling, as proposed by Schacter et al., may underlie dissociative amnesia by disrupting autobiographical memory integration [20].

6.3. Compensatory Network Reconfiguration

RS-fMRI studies reveal adaptive neural strategies in DDs, such as hyperconnectivity within sensorimotor networks compensating for DMN-visual decoupling. For example, Karmonik et al. (2010) observed similar network switching anomalies in epilepsy patients with dissociative symptoms, suggesting shared compensatory mechanisms across disorders [21]. However, the clinical relevance of such plasticity—whether adaptive or maladaptive—remains debated and warrants longitudinal investigation.

7. Clinical Translation: From Bench to Bedside

Diagnostic Refinement: rs-fMRI biomarkers augment symptom-based criteria (DSM-5/ICD-11), enhancing subtype discrimination. For instance, rs-fMRI distinguishes dissociative neurological symptom disorder from conversion disorder by revealing distinct functional connectivity patterns in sensory-motor cortices .

Therapeutic Targeting: Aberrant prefrontal-amygdala pathways identified via rs-fMRI guide interventions such as cognitive-behavioral therapy (CBT) and real-time fMRI neurofeedback. Pilot studies demonstrate that modulating DMN activity can ameliorate self-integration deficits in DDs patients .

Prognostic Stratification: Longitudinal rs-fMRI studies show that dynamic network reconfigurations predict symptom chronicity. Multimodal imaging (e.g., DTI for white matter integrity, MRS for glutamate levels) further refines prognostic models, enabling personalized treatment plans .

8. Challenges and Future Directions

Heterogeneity Management: DDs’ symptom diversity and comorbidity patterns necessitate stratified cohorts integrating genomics, epigenetics, and phenomics. Initiatives like the ENIGMA-Dissociation Consortium, which aims to aggregate multimodal data from 10,000 participants, exemplify progress toward harmonized datasets .

Methodological Harmonization: Standardizing preprocessing pipelines (e.g., motion correction thresholds) and analytical parameters (e.g., ICA dimensionality) is vital for reproducibility. Open-source toolkits like DPABI and CONN are advancing this goal .

Causal Validation: Interventional studies using transcranial magnetic stimulation (TMS) or pharmaco-fMRI must establish causality between network anomalies and symptom profiles. For example, suppressing amygdala hyperactivity could test its role in dissociative flashbacks .

Multimodal Synthesis: Converging rs-fMRI with structural MRI, MRS, and EEG data will optimize diagnostic specificity. Emerging techniques like fMRI-EEG co-registration capture cross-scale neural dynamics, offering unprecedented mechanistic insights.

9. Conclusiom

RS-fMRI has illuminated core neural signatures of DDs, including DMN hypoconnectivity, hippocampal-prefrontal decoupling, and sensorimotor compensatory plasticity. To translate these insights into clinical practice, future research must prioritize: Multimodal Integration: Combining rs-fMRI with electrophysiology (e.g., EEG microstates) to capture oscillatory coupling mechanisms. Data Scalability: Leveraging federated learning for privacy-preserving multicenter data aggregation. Interventional Innovation: Linking DMN modulation to clinical outcomes via closed-loop neuromodulation systems.

A tripartite strategy—incorporating DMN metrics into diagnostics, dynamic connectivity for personalized interventions, and longitudinal imaging for relapse prevention—promises to transform DDs care from symptom management to mechanism-driven precision medicine. By bridging the gap between neurobiological discovery and clinical application, rs-fMRI stands poised to redefine psychiatric practice in the 21st century.

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