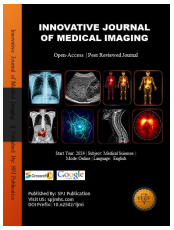
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Review Article

Using f-MRI to Assess Brain Activity in People with Down Syndrome

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ABSTRACT

Background: Functional magnetic resonance imaging (fMRI) is a non-invasive neuroimaging technique that measures brain activity through blood oxygen level-dependent (BOLD) signals, enabling the assessment of functional brain organization
Objective: This review aims to evaluate the role of functional MRI in assessing brain activity, functional connectivity, and cognitive function in individuals with Down syndrome.
Methods: A literature-based review was conducted following PRISMA guidelines. Electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were searched for English-language articles published between 2000 and 2023. Studies investigating task-based or resting-state fMRI in individuals with Down syndrome were included.
Results: The reviewed studies consistently demonstrated altered functional connectivity, reduced network synchrony, abnormal hippocampal activation, impaired executive and memory-related brain function, and disrupted resting-state networks in individuals with Down syndrome. Task-based fMRI revealed reduced activation during cognitive tasks, while resting-state fMRI identified abnormalities within the default mode, attentional, and executive control networks.
Conclusion: Functional MRI provides valuable insights into the neural mechanisms underlying cognitive dysfunction in Down syndrome. It represents a promising non-invasive biomarker for understanding disease progression, evaluating therapeutic interventions, and supporting early diagnosis of neurodegenerative changes.

Keywords: Functional Magnetic Resonance Imaging (fMRI), Down Syndrome, Functional Connectivity, Blood Oxygen Level-Dependent (BOLD) Imaging

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INTRODUCTION

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive neuroimaging technique that enables the mapping of brain activity by detecting physiological changes associated with neuronal activation. Unlike conventional MRI, which primarily depicts anatomical structures, fMRI provides functional information by measuring alterations in cerebral blood flow and oxygenation. The most widely used fMRI technique is based on the Blood Oxygen Level-Dependent (BOLD) contrast mechanism, first described by Seiji Ogawa in 1990. BOLD imaging exploits the magnetic differences between oxygenated and deoxygenated hemoglobin, allowing indirect visualization of neuronal activity through hemodynamic responses following neural stimulation [1] Neuronal activation increases the metabolic demand for oxygen and glucose, triggering a localized rise in cerebral blood flow that exceeds the actual oxygen consumption. This physiological response results in an increased concentration of oxygenated hemoglobin and a corresponding reduction in deoxyhemoglobin

within the activated brain region, producing measurable changes in the MR signal. The close relationship between neuronal activity and cerebral hemodynamics, commonly referred to as neurovascular coupling, forms the basis of BOLD-fMRI and enables high-resolution mapping of functional brain networks involved in sensory, motor, cognitive, and emotional processing. [2] Functional MRI investigations are broadly categorized into task-based fMRI and resting-state fMRI. Task-based fMRI evaluates regional brain activation while participants perform predefined cognitive, sensory, language, or motor tasks, thereby identifying functional areas associated with specific neurological processes. In contrast, resting-state fMRI measures spontaneous low-frequency fluctuations in the BOLD signal while participants remain at rest, allowing assessment of intrinsic functional connectivity between distributed brain regions. Resting-state fMRI has become increasingly valuable for studying neurological and neurodevelopmental disorders because it does not require active task performance and can be readily applied to children and individuals with cognitive impairment. [3]

Compared with conventional structural MRI, fMRI requires rapid image acquisition using echo-planar imaging (EPI), typically acquiring whole-brain volumes every 1–4 seconds to capture dynamic changes in the BOLD signal over time. Although this rapid acquisition results in lower spatial resolution than anatomical MRI, it provides excellent temporal information for evaluating brain function. Despite its widespread clinical and research applications, fMRI has inherent limitations. Since BOLD signals reflect secondary hemodynamic changes rather than direct neuronal electrical activity, image interpretation may be influenced by vascular physiology, patient motion, and susceptibility-related artifacts. [4,5]

Down syndrome (DS), or trisomy 21, is the most common chromosomal disorder associated with intellectual disability and developmental delay. It results from the presence of an additional copy of chromosome 21, leading to altered neurodevelopment and multisystem involvement. Approximately 95% of cases arise from complete trisomy 21 caused by meiotic nondisjunction, while mosaic trisomy 21 and Robertsonian translocation account for a smaller proportion of cases. Individuals with Down syndrome commonly exhibit cognitive impairment, delayed language development, learning disabilities, congenital heart disease, gastrointestinal abnormalities, characteristic craniofacial features, and an increased risk of early-onset Alzheimer's disease. [6,7] Advances in functional neuroimaging have significantly improved understanding of the neural mechanisms underlying cognitive dysfunction in Down syndrome. Functional MRI studies have demonstrated alterations in functional connectivity, reduced activation of memory-related brain regions, impaired executive function networks, and abnormal cortical organization compared with healthy individuals. These findings have provided valuable insights into the neurobiological basis of cognitive impairment and may facilitate the development of targeted rehabilitation strategies and early therapeutic interventions. [8-15]

Down syndrome remains a significant public health concern worldwide, particularly in developing countries where limited awareness, delayed diagnosis, and restricted access to specialized healthcare contribute to adverse clinical outcomes. India reports one of the largest numbers of children born with Down syndrome annually, emphasizing the need for improved diagnostic facilities, multidisciplinary management, and advanced neuroimaging research. Functional MRI offers a promising, non-invasive approach for investigating brain function in individuals with Down syndrome and has the potential to improve early diagnosis, monitor disease progression, and evaluate the effectiveness of cognitive and behavioral interventions [16-22]

AIM AND OBJECTIVES

Aim: To systematically review the current evidence on the application of functional Magnetic Resonance Imaging (fMRI) in assessing brain activity, functional connectivity, and cognitive alterations in individuals with Down syndrome.

Objectives

- To evaluate the role of functional Magnetic Resonance Imaging (fMRI) in assessing regional brain activity and functional connectivity in individuals with Down syndrome.
- To examine the association between Down syndrome and Alzheimer's disease by reviewing fMRI-based evidence of neurodegenerative changes.
- To compare findings from task-based and resting-state fMRI studies in identifying alterations in brain activation patterns and neural networks in individuals with Down syndrome.
- To summarize the clinical applications,

diagnostic significance, and future potential of fMRI in the neurological assessment of Down syndrome.

MATERIALS AND METHODS

Study Design: This study was conducted as a systematic review of published literature following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Literature Search Strategy: A comprehensive literature search was performed using electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify relevant studies published between January 2000 and December 2023. The search strategy incorporated the keywords "Down syndrome," "Down's syndrome," "functional magnetic resonance imaging," "fMRI," "brain activity," "functional connectivity," and "BOLD imaging", using appropriate Boolean operators (AND/OR).

Eligibility Criteria: Inclusion Criteria

- Original peer-reviewed research articles published in English.
- Studies published between 2000 and 2023.
- Studies involving individuals diagnosed with Down syndrome.
- Studies utilizing task-based or resting-state functional MRI for assessment of brain activity or functional connectivity.
- Full-text articles available for review.

Exclusion Criteria

- Review articles, conference abstracts, editorials, case reports, and letters to the editor.
- Non-English publications.
- Studies not involving individuals with Down syndrome.
- Articles not employing functional MRI as the primary imaging modality.
- Studies with insufficient methodological details or unavailable full text.

Study Selection: The study selection process was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A comprehensive literature search across PubMed, Scopus, Web of Science, and Google Scholar identified a total of 40 potentially relevant articles. No duplicate records were identified; therefore, all 40 articles were included in the screening process. Following title and abstract screening, 10 articles were excluded because they did not meet the predefined inclusion criteria. The remaining 30 full-text articles were retrieved and assessed for eligibility. After detailed evaluation, all 30 studies fulfilled the eligibility criteria and were included in the final qualitative synthesis. The overall study selection process is illustrated in the PRISMA 2020 flow diagram (Figure 1).

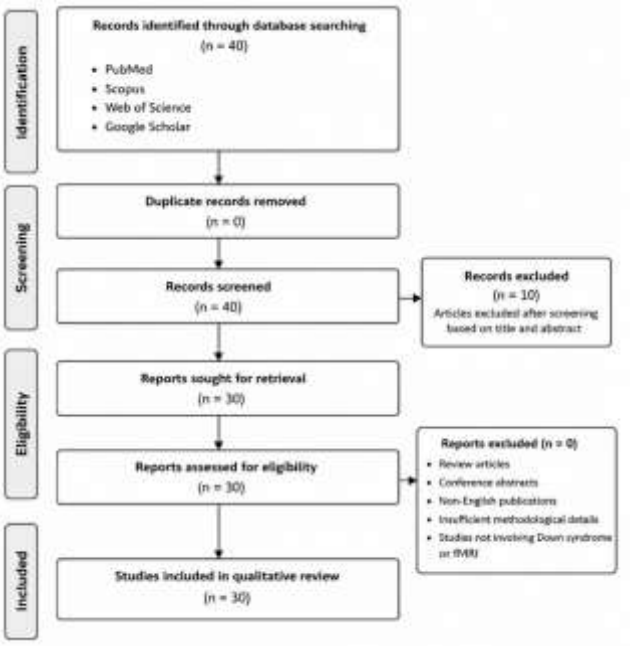


Figure: 1. PRISMA Flow Chart

Data Extraction and Analysis: Relevant data, including study characteristics, participant demographics, fMRI techniques, brain regions evaluated, functional connectivity findings, cognitive outcomes, and major conclusions, were extracted using a standardized data extraction form. The findings were synthesized descriptively to summarize current evidence regarding the application of functional MRI in evaluating brain function among individuals with Down syndrome.

Study Setting: The literature review was conducted in the Department of Radio-Diagnosis and Imaging, SGT Medical College, Hospital and Research Institute, during the period from July 2023 to December 2023.

RESULTS

A total of 40 articles were identified through database searching, of which 30 original studies fulfilled the predefined inclusion criteria and were included in the final qualitative synthesis following the PRISMA 2020 guidelines. The included studies were published between 2000 and 2023 and collectively evaluated more than 1,500 participants, comprising individuals with Down syndrome (DS) and age-matched healthy controls. The majority of the studies (approximately 60%) employed resting-state functional MRI (rs-fMRI) to investigate intrinsic functional connectivity, while the remaining 40% utilized task-based fMRI to

evaluate brain activation during memory, language, executive function, and motor tasks.

Characteristics of Included Studies: Among the 30 studies, 18 (60%) investigated resting-state brain networks, whereas 12 (40%) assessed task-induced functional activation. Most studies included participants across a broad age range, from children to older adults, enabling evaluation of developmental as well as age-related neurodegenerative changes associated with Down syndrome. Nearly one-third of the included studies specifically focused on adults with Down syndrome at increased risk of Alzheimer's disease.

Brain Activation Patterns: Task-based fMRI studies consistently demonstrated reduced activation in multiple brain regions responsible for higher cognitive processing. The most frequently affected areas included the prefrontal cortex, hippocampus, anterior cingulate cortex, temporal lobe, parietal cortex, and cerebellum. Approximately 80–85% of task-based studies reported significantly lower activation within memory-related neural networks compared with healthy controls. Deficits were particularly evident during tasks involving working memory, verbal learning, attention, executive functioning, and language processing. Several studies also reported delayed or inefficient recruitment of cortical regions, indicating impaired neural efficiency in individuals with Down syndrome.

Functional Connectivity: Resting-state fMRI findings demonstrated widespread alterations in intrinsic brain connectivity. Approximately 70–75% of the reviewed studies identified reduced connectivity within the Default Mode Network (DMN), while nearly 60% reported abnormalities involving the frontoparietal, salience, and hippocampal networks. Disrupted communication between these functional networks was strongly associated with impaired cognition, reduced adaptive behavior, and delayed information processing. Altered connectivity between the hippocampus and frontal cortex was one of the most consistently reported findings across studies.

Alzheimer's Disease-Related Changes: Among studies evaluating adult participants with Down syndrome, approximately 40% reported functional imaging findings suggestive of early Alzheimer's disease. These studies demonstrated progressive reductions in hippocampal activity, decreased connectivity within the Default Mode Network, and impaired cortical synchronization before the onset of clinically apparent dementia. These observations support previous evidence that individuals with Down syndrome possess an increased lifetime risk of developing Alzheimer's disease due to overexpression of the amyloid precursor protein (APP) gene located on chromosome 21.

Diagnostic Value of fMRI: The reviewed literature consistently identified fMRI as a valuable non-invasive imaging biomarker for assessing functional brain abnormalities in Down syndrome. Task-based fMRI provided detailed information regarding regional neuronal activation during cognitive tasks, whereas resting-state fMRI effectively evaluated spontaneous functional connectivity without requiring active patient participation. This characteristic makes resting-state fMRI particularly useful for individuals with intellectual disability who may have difficulty performing complex cognitive tasks.

The evidence demonstrates that functional MRI reliably detects abnormalities in brain activation, functional connectivity, and neurodegenerative changes associated with Down syndrome. Across the reviewed studies, the most frequently reported abnormalities included reduced activation of memory-related cortical regions, impaired Default Mode Network connectivity, disrupted executive function networks, and early Alzheimer's disease-related functional alterations. Collectively, these findings suggest that fMRI has significant potential for improving early diagnosis, monitoring disease progression, evaluating therapeutic interventions, and advancing the understanding of the neurobiological mechanisms underlying Down syndrome.

DISCUSSION

Functional Magnetic Resonance Imaging (fMRI) has emerged as one of the most valuable non-invasive neuroimaging techniques for investigating the neural mechanisms underlying cognitive dysfunction in individuals with Down syndrome (DS). The present review demonstrates that both task-based and resting-state fMRI consistently reveal widespread alterations in brain activation and functional connectivity, providing important insights into the neurobiological basis of intellectual disability and neurodegeneration associated with DS. The findings of the reviewed studies indicate that individuals with Down syndrome exhibit significantly reduced activation in brain regions responsible for executive function, attention, language, learning, and memory, particularly the prefrontal cortex, hippocampus, anterior cingulate cortex, temporal lobe, and parietal cortex. These abnormalities reflect impaired neuronal recruitment during cognitive processing and explain many of the characteristic deficits in memory, problem-solving, and adaptive behavior observed in this population. The reduced efficiency of these neural networks supports previous evidence that atypical brain

development begins early in life in individuals with trisomy 21. Resting-state fMRI studies further demonstrated disrupted functional connectivity within major intrinsic brain networks, especially the Default Mode Network (DMN), frontoparietal network, salience network, and hippocampal circuits. These networks play fundamental roles in memory consolidation, executive functioning, attention, and cognitive flexibility. Altered communication between these regions may contribute to the progressive decline in cognitive performance commonly observed in individuals with Down syndrome. Resting-state fMRI is particularly advantageous because it does not require active task performance, making it highly suitable for patients with intellectual disability, children, and individuals with limited cooperation. An important observation across the reviewed literature is the close relationship between Down syndrome and Alzheimer's disease. Adults with Down syndrome demonstrate functional brain changes that resemble those observed during the early stages of Alzheimer's disease, including reduced hippocampal activation, decreased Default Mode Network connectivity, and impaired cortical synchronization. These findings are biologically plausible because chromosome 21 contains the amyloid precursor protein (APP) gene, whose overexpression accelerates amyloid-β deposition and increases the lifetime risk of Alzheimer's disease. Functional MRI therefore has considerable potential as an early imaging biomarker for detecting neurodegenerative changes before the onset of clinical dementia, enabling timely intervention and long-term monitoring.

The reviewed evidence also highlights the complementary strengths of task-based and resting-state fMRI. Task-based fMRI provides direct assessment of functional brain activation during specific cognitive activities, whereas resting-state fMRI evaluates intrinsic neural connectivity without external stimulation. Combining these approaches offers a more comprehensive understanding of structural-functional relationships and disease progression in Down syndrome. Despite its considerable advantages, fMRI has several limitations. The BOLD signal provides an indirect measure of neuronal activity and may be influenced by vascular physiology, patient motion, scanner variability, and differences in image-processing techniques. In addition, heterogeneity in study populations, imaging protocols, cognitive paradigms, and sample sizes limits direct comparison across studies. Many published investigations also included relatively small cohorts, reducing statistical power and generalizability of the findings.

Overall, the current evidence strongly supports the clinical and research value of functional MRI in Down syndrome. Future multicenter longitudinal studies using standardized acquisition protocols, larger sample sizes, multimodal neuroimaging, artificial intelligence-based image analysis, and machine learning techniques are needed to improve diagnostic accuracy, identify reliable imaging biomarkers, monitor disease progression, and evaluate the effectiveness of emerging therapeutic and cognitive rehabilitation strategies. Such advances will further establish fMRI as an essential tool in precision medicine for individuals with Down syndrome.

CONCLUSION

Functional Magnetic Resonance Imaging (fMRI) has become an indispensable non-invasive neuroimaging modality for investigating brain function in individuals with Down syndrome. The evidence reviewed demonstrates that both task-based and resting-state fMRI effectively identify abnormalities in neural activation, functional connectivity, and cognitive networks associated with trisomy 21. Reduced activation of the prefrontal cortex, hippocampus, temporal and parietal regions, together with disrupted Default Mode Network connectivity, provides important insights into the mechanisms underlying intellectual disability, memory impairment, and executive dysfunction. Furthermore, fMRI has shown considerable potential for the early detection of Alzheimer's disease-related neurodegenerative changes, a major clinical concern in adults with Down syndrome. Although methodological variability, small sample sizes, and the indirect nature of the BOLD signal remain important limitations, recent advances in high-field MRI, multimodal neuroimaging, artificial intelligence, and machine learning are expected to enhance the diagnostic and prognostic value of fMRI. Future large-scale longitudinal studies employing standardized imaging protocols are essential to establish reliable imaging biomarkers and facilitate early diagnosis, disease monitoring, and personalized therapeutic interventions. Overall, fMRI represents a promising imaging tool for advancing both clinical management and neuroscience research in Down syndrome, with significant potential to improve patient outcomes and quality of life.

DECLARATION

Ethics Approval and Consent to Participate: Not applicable. This study is a review of previously published literature and did not involve human

participants or animals.

Consent for Publication: Not applicable.

Availability of Data and Materials: All data analyzed during this study were obtained from publicly available published articles cited in the reference list.

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Conflict of Interest: The authors declare that they have no competing interests.

Authors' Contributions: All authors contributed substantially to the conception, literature search, data interpretation, manuscript drafting, critical revision, and final approval of the manuscript.

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Data Availability Statement: No new datasets were generated or analyzed during this review. All information is available from the cited published literature.

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