Proceedings of ICBioMed 2025 Symposium: Extended Reality (XR) Applications in Medical Imaging
DOI: 10.54254/2753-8818/2025.PJ25882

The Present State of Research Concerning the Use of Structural Magnetic Resonance Imaging (sMRI) for the Diagnosis of Mild Cognitive Impairment (MCI)

Wenzhi Li

School of Public Health, Fudan University, Shanghai, China
23301020061@m.fudan.edu.cn

Abstract: As the global population ages, cognitive impairment-particularly mild cognitive impairment (MCI)—has emerged as a pressing public health challenge. MCI, a transitional stage between normal aging and dementia, is characterized by subtle declines in cognitive functions such as memory and language, yet these deficits do not meet the diagnostic criteria for dementia. Structural magnetic resonance imaging (sMRI), a non-invasive neuroimaging technique, provides detailed brain anatomical information, making it a valuable tool for studying the relationship between brain structural changes and cognitive dysfunction. This review systematically examines current sMRI-based MCI diagnostic methods, including voxel-based morphometry (VBM), region of interest (ROI)-based analysis, and machine learning/deep learning approaches. Each method presents unique advantages and challenges. VBM enables automated whole-brain analysis but may miss subtle changes in complex regions. ROI analysis offers targeted insights but is subjective and narrow in focus. Machine learning and deep learning methods, despite their powerful feature extraction capabilities, require large public datasets and may suffer from black-box issues. Future research should prioritize optimizing deep learning models, integrating multi-modal and multi-omics data, and establishing multi-center, large-sample MRI databases. These advancements are expected to significantly contribute to the early diagnosis, intervention, and treatment of MCI, addressing the growing challenge of cognitive impairments worldwide.

Keywords: mild cognitive impairment, structural magnetic resonance imaging, sMRI analysis methods, machine learning, deep learning

1. Introduction

With the increasingly severe trend of population aging, cognitive impairment has become a crucial public health concern. According to the World Health Organization (WHO) 2019 guidelines "Risk Reduction of Cognitive Decline and Dementia", approximately 50 million people worldwide are affected by cognitive impairment, with around 10 million new cases reported each year. Without globally coordinated interventions, the number of dementia patients is estimated to reach 139-152 million by 2050 [1]. Mild Cognitive Impairment (MCI), an intermediate state between normal aging and dementia, is defined by the National Institute on Aging as a condition where patients exhibit

© 2025 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2025.PJ25882

mild memory or other cognitive declines that do not yet satisfy the diagnostic criteria for dementia [2]. Its core features include subtle impairments in single or multiple cognitive domains—such as memory, language, and executive function—and its current prevalence poses a growing concern. Epidemiological studies by Petersen [3]. demonstrate that MCI incidence increases with age, with 5%-15% progressing to Alzheimer's Disease (AD) within years. Early prevention during the initial cognitive decline phase could substantially improve cure rates.

Structural magnetic resonance imaging (sMRI), a non-invasive neuroimaging technique, captures detailed anatomical information of the brain by detecting signal differences among gray matter, white matter, and cerebrospinal fluid. This capability makes it an invaluable tool for investigating the relationship between structural brain changes and cognitive dysfunction. Compared with biomarker-based disease detection methods, sMRI offers greater accessibility and cost-effectiveness, making it widely applicable in neurological disease diagnosis and research. This review employs a dual approach of literature review and case study method to meticulously analyze the research process of sMRI diagnosis of cognitive impairment. The purpose of this review is to comprehensively systematize current sMRI-based MCI diagnostic methods, summarize existing limitations in various approaches, and provide informed perspectives on future directions, thereby offering valuable references for early MCI diagnosis, intervention, and treatment.

2. sMRI-based MCI diagnostic research methods

2.1. Voxel-based morphometry (VBM) method

The VBM method is a voxel-based statistical analysis technique for investigating brain structural changes. In sMRI-based diagnosis of mild cognitive impairment (MCI), its fundamental principle involves segmenting brain images into different tissue types, including gray matter, white matter, and cerebrospinal fluid, and then conduct statistical analysis on each voxel. The process begins with preprocessing steps for acquired sMRI images, such as motion correction, tissue segmentation, and spatial normalization, which align all subjects' brains into a standardized spatial framework. Subsequently, statistical comparisons are conducted to identify voxel-wise differences in gray/white matter volume or density between MCI patients and healthy controls. These differences reflect structural changes such as regional atrophy or cortical thickening, thereby providing diagnostic evidence for MCI [4].

Studies by Busato and Ferreira, which compared gray matter volumes between MCI patients and controls, consistently detected atrophy in medial temporal lobe structures (e.g., hippocampus, parahippocampus, amygdala, entorhinal cortex) at early disease stages. Notably, Ferreira's study revealed more pronounced atrophy in the left hippocampus and parahippocampal gyrus, while Busato et al. proposed that AD pathology spreads from the medial temporal lobe to association cortices, supporting the neurodegenerative cascade hypothesis [4,5]. Furthermore, Guo challenged the traditional focus on gray matter bydemonstrating extensive white matter involvement in AD pathology, elucidating gray-white matter degradation coupling mechanisms to improve detection [6].

VBM enables automated whole-brain analysis without predefined regions of interest, eliminating observer bias and objectively detecting subtle structural changes. This makes it particularly suitable for exploratory studies. However, its whole-brain focus may fail to capture fine-grained alterations in morphologically complex regions (e.g., limbic system, thalamus), limiting diagnostic accuracy for related disorders. Contemporary VBM research has evolved beyond merely detecting regional volume changes in MCI. Recent studies leverage whole-brain volumetric patterns to identify biomarker variations. For instance, Bailey integrated data from 12 VBM studies to systematically

DOI: 10.54254/2753-8818/2025.PJ25882

investigate APOEε4 allele effects on gray matter atrophy in MCI patients, proposing imaging biomarkers for precise subtyping of cognitive impairment [7].

2.2. Region of interest (ROI)-based analysis method

In comparison with the whole-brain automated analysis of the VBM method, the region of interest (ROI)-based analysis method prioritizes the examination of specific brain regions. The principles and application scenarios of the ROI-based analysis method possess distinctive characteristics. ROI-based morphometry is a technique that segments images into predefined regions for analysis, based on the principle that each region shares homogeneous features (e.g., color, texture, intensity) with spatial continuity. This method leverages intra-region similarity and inter-region discontinuity for segmentation. The critical step involves defining anatomically informed ROIs (e.g., hippocampus) based on prior knowledge or hypotheses, followed by extracting quantitative features (volume, cortical thickness, density) within these ROIs for statistical comparisons.

The hippocampus, a key structure responsible for memory formation and spatial navigation, exhibits significant atrophy during MCI progression, making it a predominant ROI in MCI research. Traditional whole-hippocampus volumetry suffers from limited sensitivity/specificity. La Joie innovatively subdivided hippocampal subfields (including CA1 and subiculum) using high-resolution MRI orthogonal to the hippocampal long axis, covering both head and body regions. Their CA1-focused analysis showed superior sensitivity in distinguishing MCI from controls compared to whole-hippocampus metrics ($p=0.05$) [8].

ROI-based methods offer targeted insights into the structure-function relationships within specific brain regions, generating results that are easy to interpret. However, ROI selection heavily depends on researchers' anatomical priors, introducing subjectivity. This approach may overlook cross-regional interactions and whole-brain changes. Current MCI research increasingly combines ROI-based findings with advanced network analyses.

2.3. Machine learning and deep learning-based analysis methods

As technology advances, machine learning and deep learning methods have emerged as novel approaches to sMRI analysis, complementing traditional VBM and ROI methods. Recent advances in machine learning (ML) have enabled automated extraction of latent neuroimaging biomarkers from sMRI data for classification purposes. The ML algorithms applied to sMRI include traditional methods—such as Support Vector Machines (SVM) and Random Forests (RF)—and deep learning architectures optimized for complex data.

SVM works by identifies hyperplanes that maximize the margin between different classes, achieving optimal classification performance, and it is particularly effective for small-scale linear datasets. RF enhances accuracy through ensemble decision trees, demonstrating robustness against noise in high-dimensional nonlinear data (e.g., sMRI features). Comparative studies by Givian and Calbimonte revealed SVM's exceptional performance in CN vs AD classification (mean ACC 95%, peak 100%), validating hippocampal biomarkers' diagnostic specificity. Conversely, RF achieved 71.5% mean ACC (peak 83.3%) in EMCI vs LMCI classification, reflecting the challenge of distinguishing MCI subtypes [9]. The near-perfect performance of SVM in CN vs AD classification (95% ACC) is likely attributable to the pronounced hippocampal atrophy observed in AD cohorts, whereas the relatively lower accuracy of RF in EMCI vs LMCI differentiation (71.5% ACC) stems from the subtlety of neuroanatomical differences between these subtypes.

DOI: 10.54254/2753-8818/2025.PJ25882

Deep learning employs hierarchical neural networks to learn high-level feature representations, excelling in capturing spatial correlations within imaging data. Most current models analyze single timepoint sMRI scans for MCI prediction. Zhentao Hu. proposed the VGG-TSwinformer model, integrating CNN-based local feature extraction with Transformer-driven global temporal dependencies. This hybrid architecture achieved 77.2% classification accuracy, outperforming standalone 3D CNN+RNN (70.1%) and Attention Transformer models (73.5%) [10].

ML and DL algorithms automate the feature extraction process, reducing manual intervention. However, they require large datasets and computational resources, with inherent challenges including model interpret-ability ("black-box" features) and over-fitting.

3. Future perspectives

3.1. Technological innovation directions

Current deep learning models, including convolutional neural networks (CNNs) and Transformers, have demonstrated promising results in MCI diagnosis, yet further refinements remain imperative. Future efforts will focus on optimizing model architectures to design more efficient networks capable of extracting complex features from sMRI data. Enhanced spatial-resolution feature extractors and hybrid architectures combining attention mechanisms with geometric deep learning could improve the models' capability to capture subtle structural changes, thereby advancing diagnostic precision. Beyond architectural optimization, addressing the "black-box" limitation of deep learning models is critical for clinical translation. Integrating explainable AI (XAI) techniques —such as gradient-weighted class activation mapping (Grad-CAM) and layer-wise relevance propagation (LRP)—can illuminate the specific brain regions or structural features driving model predictions. For instance, applying Grad-CAM to CNN models could visualize which voxels or anatomical regions (e.g., hippocampal subfields, entorhinal cortex) are prioritized during MCI classification, bridging the gap between computational outputs and neurobiological interpretability. To improve model robustness to data variability, domain adaptation algorithms and lightweight designs are needed. Leveraging longitudinal sMRI data to model dynamic structural changes over time is also potential. Temporal modeling techniques can capture temporal trajectories of brain structural changes, improving early detection sensitivity. Multimodal fusion within model architectures can provide a more holistic representation of brain integrity, enhancing diagnostic specificity and predicting MCI conversion to AD.

3.2. Multi-omics data integration

Future research will increasingly integrate sMRI with functional MRI (fMRI), diffusion tensor imaging (DTI), and other neuroimaging modalities. Multimodal fusion analysis using deep canonical correlation analysis (DCCA) or graph neural networks (GNNs) may unravel the pathophysiological interplay between structural degeneration and functional network disruptions in MCI. Beyond imaging, incorporating genomics (e.g., APOE ε4 carrier status), proteomics (amyloid-β42/tau ratios), and metabolomics data could enable systems-level biomarker discovery. For instance, longitudinal metabolomic profiling of cerebrospinal fluid (CSF) has revealed that decreased N-acetylaspartate (NAA) concentrations—a marker of neuronal mitochondrial dysfunction—correlate with accelerated hippocampal atrophy rates. Spatial mapping further identified that glutamate/glutamine imbalances in the posterior cingulate cortex (PCC) mediate gray matter volume loss in prodromal MCI, suggesting excitotoxicity as a modifiable pathological driver

DOI: 10.54254/2753-8818/2025.PJ25882

[11]. Such integration may reveal novel therapeutic targets through cross-omics interaction networks, facilitating personalized interventions tailored to individual molecular profiles [12].

3.3. Multicenter large-sample cohort trends

Current MRI studies of MCI often suffer from limited sample sizes and heterogeneous data acquisition protocols across institutions. Establishing standardized multicenter consortia—such as an ADNI (Alzheimer's Disease Neuroimaging Initiative)-equivalent framework for preclinical MCI—will address reproducibility challenges. Federated learning platforms with harmonized imaging protocols (e.g., harmonzied 3D T1-weighted sequences) and centralized quality control pipelines can mitigate site-specific biases while preserving data privacy [4,12]. Large-scale datasets would empower robust validation of edge-AI diagnostic tools across diverse populations.

4. Conclusion

This review has comprehensively examined the application of structural magnetic resonance imaging (sMRI) in diagnosing mild cognitive impairment (MCI), systematically evaluating three core methodologies: voxel-based morphometry (VBM), region-of-interest (ROI) analysis, and machine/deep learning approaches. Each method contributes uniquely to understanding MCI-related brain changes: VBM enables unbiased whole-brain exploration of gray and white matter alterations, particularly in regions like the medial temporal lobe; ROI analysis offers targeted insights into critical structures such as the hippocampus and its subfields, enhancing sensitivity to early atrophy; and machine/deep learning methods leverage complex feature extraction to improve classification accuracy, though their "black-box" nature and reliance on large datasets remain limiting. Despite these advancements, significant challenges persist. First, dataset heterogeneity—stemming from scanner variability, demographic imbalances, and inconsistent clinical criteria—hinders the reproducibility of findings across studies, with volumetric measurement errors reaching ±7.3% due to field strength differences. Second, the interpretability of advanced models like 3D CNNs remains inadequate, limiting their clinical translation. Third, current approaches often focus on isolated structural changes, failing to capture the multi-faceted pathophysiology of MCI, which involves interactions between structural, functional, and molecular processes.

Addressing these challenges requires multi-pronged efforts. Optimizing deep learning architectures with hybrid designs (e.g., combining attention mechanisms and geometric deep learning) will enhance sensitivity to subtle neurodegenerative changes. Integrating sMRI with functional neuroimaging (fMRI, DTI) and multi-omics data (genomics, proteomics, metabolomics) can unravel the interplay between structural degeneration, functional network disruptions, and molecular biomarkers—such as APOE ε4 status or CSF tau levels—enabling systems-level understanding. Establishing standardized multi-center databases, modeled after initiatives like ADNI but expanded for preclinical MCI, will mitigate dataset variability and support large-scale validation of diagnostic tools.

Future research must prioritize advancing deep learning architectures to enhance sensitivity for early neurodegeneration detection, fusing multi-modal imaging (fMRI/DTI) with multi-omics data (genomic/proteomic profiles) to elucidate pathophysiological mechanisms, and establishing standardized multi-center MRI databases through large-scale collaborative initiatives like the Alzheimer's Disease Neuroimaging Initiative framework. These integrated advancements will significantly improve diagnostic accuracy, reliability, and reproducibility, ultimately translating neuroimaging innovations into clinically actionable tools for early MCI intervention and

DOI: 10.54254/2753-8818/2025.PJ25882

personalized treatment strategies, thereby mitigating the global burden of age-related cognitive disorders.

References

[1] Risk reduction of cognitive decline and dementia: WHO guidelines. Geneva: World Health Organization; 2019. Licence : CC BY-NC-SA 3.0 IGO.
[2] National Institute on Aging, 2021. What is mild cognitive?https: //www.nia.nih.gov/health/memory-loss-and-forgetfulness/what-mild-cognitive-impairment.
[3] PETERSEN R C, ROBERTS R O, KNOPMAN D S, et al. Mild cognitive impairment: ten years later [J]. Arch Neurol, 2009, 66(12): 1447-55.
[4] [BUSATTO G F, DINIZ B S, ZANETTI M V. Voxel-based morphometry in Alzheimer's disease [J]. Expert Rev. Neurother., 2014, 8(11): 1691-702.
[5] FERREIRA L K, DINIZ B S, FORLENZA O V, et al. Neurostructural predictors of Alzheimer's disease: A meta-analysis of VBM studies [J]. Neurobiol. Aging, 2011, 32(10): 1733-41
[6] GUO X, WANG Z, LI K, et al. Voxel-based assessment of gray and white matter volumes in Alzheimer's disease [J]. Neurosci. Lett., 2010, 468(2): 146-50
[7] BAILEY M, ILCHOVSKA Z G, HOSSEINI A A, et al. The impact of APOE ε4 in Alzheimer's disease: a meta-analysis of voxel-based morphometry studies [J]. medRxiv, 2024.
[8] La JOIE R, PERROTIN A, de La SAYETTE V, et al. Hippocampal subfield volumetry in mild cognitive impairment, Alzheimer's disease and semantic dementia [J]. NeuroImage: Clinical, 2013, 3: 155-62.
[9] GIVIAN H, CALBIMONTE J. Early diagnosis of Alzheimer's disease and mild cognitive impairment using MRI analysis and machine learning algorithms [J]. Discover Applied Sciences, 2025, 7(1): 27.
[10] ZHANG L, WANG L, GAO J, et al. Deep Fusion of Brain Structure-Function in Mild Cognitive Impairment [J]. Med. Image Anal., 2021, 72: 102082.
[11] KANTARCI K, JACK C R J, XU Y C, et al. Regional metabolic patterns in mild cognitive impairment and Alzheimer's disease: A 1H MRS study [J]. Neurology, 2000, 55(2): 210-7.
[12] JONES A, ALI M U, MAYHEW A, et al. Environmental risk factors for all-cause dementia, Alzheimer's disease dementia, vascular dementia, and mild cognitive impairment: An umbrella review and meta-analysis [J]. Environ. Res., 2025, 270: 121007