Exploring the Multimodal Integration of VR and MRI biomarkers for Enhanced Early Detection of Mild Cognitive Impairment

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ABSTRACT

Early detection of mild cognitive impairment (MCI) is crucial to impede dementia progression. Virtual reality (VR) biomarkers are adept at detecting impairments in instrumental activities of daily living (IADL), whereas magnetic resonance imaging (MRI) biomarkers excel in measuring observable structural changes in the brain. However, the efficacy of integrating VR and MRI biomarkers to improve early MCI detection remains unclear. This study aims to evaluate and compare the effectiveness of VR and MRI biomarkers and investigates the potential of their combined use for more accurate early MCI detection. Through support vector machine analysis, distinct characteristics were observed. For identifying MCI, VR biomarkers demonstrated high specificity (90.0%), whereas MRI showed high sensitivity (90.9%). The combination of both biomarkers yielded superior results in accuracy (94.4%), sensitivity (100.0%), and specificity (90.9%). Drawing from these results, we suggest a sequential diagnostic approach, employing VR for initial screening and MRI for subsequent confirmation of MCI.

CCS CONCEPTS

• **Human-centered computing**; • **Virtual reality**;; • **Computing methodologies**; • **Machine learning approaches**;; • **Applied computing**; • **Health informatics.**;

KEYWORDS

Virtual reality, Magnetic resonance imaging, Biomarker, Mild cognitive impairment

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1 INTRODUCTION

Mild cognitive impairment (MCI) represents a critical juncture in cognitive decline, lying between the normal cognitive aging process and Alzheimer's disease (AD). This stage is characterized by symptoms such as memory loss and difficulty in performing complex daily activities [1–3]. The progression of MCI towards AD complicates the reversal of cognitive decline [4, 5], significantly impacting patient independence [6]. Therefore, intervening during the MCI stage is essential to potentially slow down cognitive decline. Early MCI detection is not only crucial to hinder its progression to AD but also imperative for initiating timely interventions aimed at reinstating cognitive functions to a normal aging level [7].

Traditionally, MCI diagnosis has depended on biomarkers such as neuropsychological tests and magnetic resonance imaging (MRI) [8]. While neuropsychological tests are effective in quantitatively evaluating cognitive functions [9], they necessitate extensive examination periods and can yield varied interpretations depending on the professionals involved [10]. MRI, in contrast, identifies MCI by detecting structural brain alterations, especially in memory-related

areas [11, 12], but its use is restricted by its costly nature and [13, 14]. This has led to a growing need for alternative biomarkers that can economically and accurately detect MCI based on observable behavioral patterns in day-to-day activities [16, 17].

Recent advancements have seen the incorporation of virtual reality (VR) technology into traditional diagnostic approaches, such as MRI, to collect behavioral data pertinent to instrumental activities of daily living (IADL) and enhance early MCI detection through machine learning techniques [16–18]. For example, Kim et al. [16] developed a virtual kiosk test for tasks like food ordering, achieving a 93.3% success rate in differentiating MCI patients from healthy controls based on hand and eye movements, as well as task performance. Research by Castegnaro et al. [19] and Howett et al. [20] investigated the impact of brain damage on performance in VR tasks, observing significant declines, particularly in those with entorhinal cortex impairment. Additionally, Cavedoni et al. [17] highlighted the importance of integrating VR and MRI biomarkers in understanding MCI. Our study, therefore, seeks to examine the use of a multimodal learning approach that integrates VR and MRI biomarkers for enhanced clinical effectiveness and more accurate early detection of MCI.

Our study is driven by two key objectives. First, we aim to conduct a comparative analysis of VR and MRI biomarkers against the standard neuropsychological tests used in MCI diagnosis, to identify the unique strengths and limitations of each modality. The second objective is to assess the potential of a multimodal learning model that utilizes the distinctive characteristics of VR and MRI biomarkers to improve early MCI detection. This integrated approach aims to amalgamate the superior attributes of both modalities, endeavoring towards a more precise and reliable MCI diagnostic method. The findings of our study propose a novel clinical approach that furnishes clinicians with an improved framework for MCI detection, employing VR as the primary screening tool followed by secondary diagnosis via MRI.

2 METHOD

2.1 Participants

We recruited 54 participants aged 50 and above from Hanyang University Hospitals in Seoul and Guri over the period from January 2022 to July 2023. These participants were selected through a combination of voluntary sign-ups and outpatient clinic referrals at the hospitals. To diagnose MCI, we enlisted two neurologists with extensive experience of 18 and 22 years. They followed the MCI diagnostic criteria of Albert et al [21], using the Seoul Neuropsychological Screening Battery-Core (SNSB-C), a standardized assessment tool for the Korean population [22, 23]. Eligible participants were required to demonstrate the ability to engage with VR technology through visual and auditory prompts. We excluded individuals with a history or predisposition towards neurodegenerative diseases or brain surgeries. Each participant was thoroughly informed about the study and provided written consent. The study received ethical clearance from the Institutional Review Board of Hanyang University Hospital, Republic of Korea, in accordance with the Declaration of Helsinki (HYUH-2021-08-020-004).

2.2 Neuropsychological tests

This study utilized the SNSB-C, a neuropsychological test specifically designed and standardized for the Korean population. The SNSB-C was utilized to evaluate five cognitive domains through separate assessments, including: 1) Digit Span Test: Backward (DST: B) for attention; 2) Short form of the Korean-Boston Naming Test (S-K-BNT) for language function; 3) Rey Complex Figure Test (RCFT) for visuospatial function; 4) Seoul Verbal Learning Test-Elderly's version: Delayed Recall (SVLT-E: DR) for memory; and 5) Digit Symbol Coding (DSC) for frontal/executive function.

2.3 VR biomarkers

Our study made use of the virtual kiosk test, a VR tool developed in previous research [24], to gather VR biomarkers. This test simulates the process of ordering at a virtual kiosk, aiming to identify early signs of MCI. The setup included a laptop with an Intel i7-12700H processor, 16 GB of RAM, and an NVIDIA GeForce RTX 3080 graphics card. For an immersive VR experience, participants used a head-mounted display with eye-tracking features (HTC VIVE Pro Eye) and interacted with the kiosk using a hand controller (see Figure 1). Their movements were tracked by two base stations throughout the test, which they performed while seated.

The virtual kiosk involved six sequential steps, excluding the initial 'Start' and final 'End' stages (see Figure 2). These steps were: 1) selecting a place to eat; 2) choosing a burger item; 3) picking a side item; 4) selecting a drink item; 5) deciding on a payment method; and 6) entering a four-digit payment password. Before starting the test, participants were verbally provided with the following instructions: "The place to eat is a restaurant. Please use the kiosk to order a shrimp burger, cheese sticks, and a Coca-Cola. Use a credit card as the payment method, and the card payment password is 6289." Participants were not allowed to take notes or inquire about the instructions again.

Four key VR biomarkers were derived from the behavioral data collected during the test (refer to Appendix A's Figure 4). The first biomarker was *hand movement speed*, determined by dividing the total hand movement distance by the overall duration of the test [16, 24]. The second biomarker, *scanpath length*, measured the total distance covered by the participants' gaze during the test [26, 27]. The third metric, *the time to completion*, indicated the time taken by participants to finish all six steps [28]. Lastly, we counted *the number of errors* made during the test [24]. These biomarkers are indicative of various cognitive functions, including perception and processing speed.

2.4 MRI biomarkers

MRI scans for our study was conducted at Hanyang University Hospital in both Guri and Seoul, using the PHILIPS Ingenia CX 3T scanner. We applied the 3D T1-weighted magnetization prepared rapid gradient echo technique for these scans, with each location following a specific protocol. At Guri Hospital, the parameters were TE/TR=2.9ms/6.3ms, a flip angle of 9°, field of view at 256×256mm, with 211 slices and a voxel size of $1\times1\times1mm^3$. Seoul Hospital's protocol involved TE/TR=4.1ms/6.9ms, a flip angle of 8°, field of view at 300×299mm, 170 slices, and a voxel size of $0.8\times0.8\times1mm^3$. The MRIs were processed using AQUA 3.0 software, which assisted in

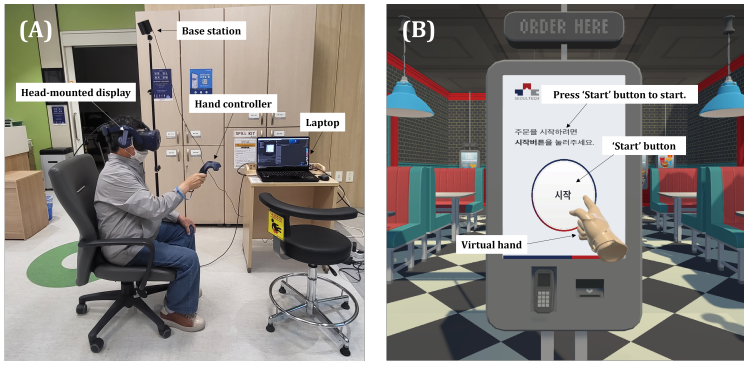

Figure 1: Layout of the virtual kiosk test setup. (A) Various components used in the experiment; (B) The virtual kiosk and virtual hand within the VR environment.

Figure 2: Six sequential steps of the virtual kiosk test.

accurately identifying and delineating the brain regions of interest [35].

For this study, we focused on MRI biomarkers linked to brain areas susceptible to early atrophy in AD [30]. The selected MRI biomarkers included the amygdala [31], hippocampus [32], entorhinal cortex [33], parahippocampal gyrus [33], fusiform gyrus [34], and the superior, middle, and inferior temporal gyrus [35], as detailed in Appendix A's Figure 5. These biomarkers were sourced from both hemispheres of the brain, culminating in a total of 16 distinct biomarkers for the study. Additionally, we factored in the intracranial volume (ICV), encompassing the total volume of white matter, gray matter, and cerebrospinal fluid [36], to account for overall brain size. All MRI biomarkers were then normalized relative to the ICV to mitigate variations in brain volume that could arise from differences in age and gender [14].

2.5 Procedures

Each participant in our study first completed the SNSB-C. Two neurologists then diagnosed MCI according to the criteria set by Albert et al. [21], utilizing the results from the SNSB-C. Following this, participants were involved in both the virtual kiosk test and MRI scans, executed in a counter-balanced sequence. The neurologists who made the MCI diagnosis also administered the virtual kiosk test. A radiologist with 16 years of expertise conducted the MRI scans. To familiarize participants with the VR technology and environment, two practice sessions were conducted prior to the virtual kiosk test. While participants had the option to take breaks or stop the experiment if they experienced any discomfort or dizziness, all participants completed the experiment without needing breaks, with the entire process averaging 54.32 minutes.

2.6 Statistical analysis

The statistical analysis was carried out using IBM SPSS Statistics 27 software. We began with a chi-square (χ^2) test and independent sample t-tests to assess differences in demographic characteristics between healthy controls and MCI patients. Following this, we conducted analyses of covariance (ANCOVA) with age factored in as a covariate, to evaluate the variances in neuropsychological characteristics, VR biomarkers, and MRI biomarkers between healthy controls and MCI patients. This approach was instrumental in identifying specific attributes of each biomarker. Furthermore, we performed a Pearson correlation analysis to investigate the interrelationship between VR and MRI biomarkers.

2.7 Multimodal integration

In our research, Python 3 was employed for the purpose of multimodal learning, focusing on the integration of VR and MRI biomarkers that showed statistical significance. We selected the support vector machine (SVM) algorithm as our machine learning model [37–39]. The hyperparameters were determined through grid search, settling on a radial basis function kernel with C = 1 and gamma = 0.1. To ensure external validation, we conducted external validation by employing a train/test split with a ratio of 7:3. Specifically, 38 participants were assigned to the train subcohort, while the remaining 16 participants formed the test subcohort. During the

Table 1: Comparative analysis of demographic characteristics between healthy controls and MCI patients, presented as Mean (SD).

Characteristics	Healthy controls (n = 22)	MCI patients (n = 32)	*p*-value
Demographic characteristics			
Gender (Female) (n (%))	14 (63.63)	14 (43.75)	.151
Age (years)	69.86 (6.72)	73.47 (8.39)	.070
Education level (years)	12.09 (4.46)	9.47 (5.12)	.057

Table 2: Comparative analysis of VR biomarkers between healthy controls and MCI patients, presented as Mean (SD).

VR biomarkers	Healthy controls (n = 22)	MCI patients (n = 32)	*p*-value
Hand movement feature			
Hand movement speed (m/s)	0.23 (0.06)	0.17 (0.06)	.001
Eye movement feature	23.66 (14.29)	60.36 (54.58)	.010
Scanpath length (m)			
Performance feature	39.48 (18.96)	105.39 (86.35)	.003
The time to completion (s)			
The number of errors	1.73 (1.61)	4.00 (2.81)	.003

biomarker integration process, we compared the performances of models that used either VR or MRI biomarkers individually. These models were evaluated based on various metrics, including accuracy, sensitivity, specificity, precision, F1-score, and the area under the receiver operating characteristic curve (AUC).

3 RESULTS

3.1 Demographic and neuropsychological characteristics

Analysis of demographic characteristics using chi-square tests and independent sample t-tests showed no significant differences between healthy controls and MCI patients (see Table 1). However, when evaluating neuropsychological characteristics using ANCOVA, with age as a control variable, there was a clear distinction between healthy controls and MCI patients (refer to Appendix B's Table 4). Notably, MCI patients displayed considerable deficits in all five assessed cognitive domains. These included attention ($F_{1,51} = 24.181$; $p < .001$), language function ($F_{1,51} = 14.993$; $p < .001$), visuospatial function ($F_{1,51} = 19.115$; $p < .001$), memory ($F_{1,51} = 32.542$; $p < .001$), and frontal/executive function ($F_{1,51} = 20.584$; $p < .001$), all showing significant impairment when compared to healthy controls.

3.2 Differences in VR biomarkers between healthy controls and MCI patients

When evaluating VR biomarkers using ANCOVA, accounting for age as a covariate, there were notable differences between healthy controls and MCI patients (see Table 2). In the virtual kiosk test, MCI patients demonstrated considerably slower hand movement speed ($F_{1,51} = 13.426$; $p = .001$), longer scanpath length ($F_{1,51} = 7.108$; $p = .010$), prolonged time to completion ($F_{1,51} = 9.447$; $p = .003$), and a larger number of errors ($F_{1,51} = 9.438$; $p = .003$) in comparison to healthy controls.

3.3 Differences in MRI biomarkers between Healthy Controls and MCI Patients

Using ANCOVA with age as a control variable, we examined differences in ICV and its proportion between healthy controls and MCI patients. While MCI patients showed an increased ICV compared to healthy controls, this difference was not statistically significant. However, there was noticeable atrophy in the proportion of ICV among MCI patients. Table 3 highlights the MRI biomarkers with statistically significant differences from the total set of 16 biomarkers (refer to Appendix B's Table 5). Notably, significant differences were observed in the left entorhinal cortex ($F_{1,51} = 7.821$; $p = .007$), right entorhinal cortex ($F_{1,51} = 11.103$; $p = .002$), left hippocampus ($F_{1,51} = 11.926$; $p = .001$), right hippocampus ($F_{1,51} = 8.244$; $p = .006$), left amygdala ($F_{1,51} = 7.979$; $p = .007$), and right amygdala ($F_{1,51} = 6.618$; $p = .013$).

3.4 Correlation between VR and MRI biomarkers

A Pearson correlation analysis was carried out among the previously identified statistically significant VR and MRI biomarkers. Each VR biomarker showed significant correlations with one or more MRI biomarkers (detailed in Appendix B's Table 6). Particularly striking was the left hippocampus, which exhibited significant correlations with all four VR biomarkers: hand movement speed ($r = .396$, $p = .003$), scanpath length ($r = -.284$, $p = .038$), the time to completion ($r = -.379$, $p = .005$), and the number of errors ($r = -.392$, $p = .003$).

3.5 Multimodal integration performance of VR and MRI biomarkers

In our study, the SVM model, which was trained using SNSB-C components (RCFT and SVLT-E: DR) and regarded as the gold standard, demonstrated strong performance with accuracy of 94.4%,

Table 3: Comparative analysis of MRI biomarkers between healthy controls and MCI patients, presented as Mean (SD).

MRI biomarkers	Healthy controls (n = 22)	MCI patients (n = 32)	*p*-value
Raw volume (cc)			
ICV	1490.96 (127.40)	1511.49 (128.89)	.566
The proportion of ICV (%)			
Left Amygdala	0.24 (0.02)	0.21 (0.03)	.001
Right Amygdala	0.12 (0.01)	0.11 (0.01)	.002
Left Hippocampus	0.24 (0.02)	0.21 (0.03)	.001
Right Hippocampus	0.24 (0.02)	0.22 (0.03)	.006
Left Entorhinal cortex	0.15 (0.02)	0.13 (0.02)	.007
Right Entorhinal cortex	0.13 (0.01)	0.11 (0.02)	.013

sensitivity of 100.0%, specificity of 85.7%, precision of 91.7%, F1-score of 95.7%, and AUC of 0.93. When utilizing only VR biomarkers (hand movement speed, scanpath length, and number of errors), the best-performing SVM model attained accuracy of 88.9%, sensitivity of 87.5%, specificity of 90.0%, precision of 87.5%, F1-score of 87.5%, and AUC of 0.84. On the other hand, an SVM model using only MRI biomarkers (specifically the left hippocampus and left entorhinal cortex) achieved the best results with accuracy of 83.3%, sensitivity of 90.9%, specificity of 71.4%, precision of 83.3%, F1-score of 87.0%, and AUC of 0.79. Remarkably, the integration of both VR and MRI biomarkers led to the highest performance, resulting in accuracy of 94.4%, sensitivity of 100.0%, specificity of 90.9%, precision of 87.5%, F1-score of 93.3%, and AUC of 0.89.

4 DISCUSSION

This study aimed to evaluate the effectiveness of a multimodal learning approach that integrates both VR and MRI biomarkers for the improved detection of early MCI. The findings showed that, in VR biomarkers, MCI patients demonstrated significantly reduced hand movement speed, increased scanpath length, longer time to complete tasks, and more errors in the virtual kiosk test compared to healthy controls. Similarly, MRI biomarkers revealed substantial atrophy in key areas such as the bilateral amygdala, hippocampus, and entorhinal cortex in MCI patients. The integration of VR and MRI biomarkers through a multimodal learning framework yielded excellent early MCI detection performance, achieving 94.4% accuracy, 100.0% sensitivity, 90.9% specificity, 87.5% precision, a 93.3% F1-score, and an AUC of 0.89. This integration proved advantageous in facilitating quicker MCI detection than longer neuropsychological tests like SNSB-C, typically taking about 2 hours [40]. Furthermore, it demonstrated superior performance compared to the integration of VR with other biomarkers such as electroencephalogram [41].

Both VR and MRI biomarkers displayed unique strengths in identifying MCI. VR biomarkers showed a high level of specificity (90.0%), in line with previous studies highlighting their effectiveness in VR-based IADL tasks [15, 42, 43]. MRI biomarkers, conversely, demonstrated a higher sensitivity (90.9%), effectively identifying MCI patients, surpassing the sensitivity rates of recent MRI studies [44, 45]. Our methodological approach, including separate measurements of each hemisphere, the use of sensitive regions like the hippocampus and entorhinal cortex as MRI biomarkers, and ICV normalization to adjust for individual brain volume differences [46–49], likely contributed to this improved sensitivity in detecting MCI compared to traditional methods. In summary, our findings underscore the unique benefits of each biomarker and robustly support the integration of VR and MRI biomarkers as a potent means to enhance MCI detection.

Our findings also revealed significant correlations between VR biomarkers and brain changes observed in MRI biomarkers, as depicted in Figure 3. Specifically, a strong correlation was found between VR biomarkers and the left hippocampus. Participants with reduced size in the left hippocampus were found to have slower hand movement speed, increased scanpath length, longer time to complete tasks, and more errors in the virtual kiosk test. These findings align with prior research [50, 51], suggesting that damage to the hippocampus can lead to cognitive impairments affecting daily tasks like hand and eye coordination. Furthermore, there was a notable correlation between eye movement attributes, MRI biomarkers (especially the left hippocampus), and SNSB-C outcomes, supporting recent studies that emphasize the role of eye movements in detecting MCI during complex daily activities [52, 53]. Additionally, a significant link was found between the number of errors in the virtual kiosk test and the size of the right amygdala; participants with a smaller right amygdala tended to make more errors, which is in line with studies [54, 55] that relate decreased amygdala volume to cognitive decline. Utilizing VR biomarkers derived from augmented or virtual reality tests that simulate daily tasks presents a novel method for early MCI [56, 57], bridging the gap between behavioral anomalies and key changes in brain structure [58, 59].

The distinct benefits of VR and MRI biomarkers suggest their effectiveness as sequential tools in a two-phase diagnostic process, as described by Galvin and colleagues [60]: the 'Detection' phase and the 'Assessment & Differentiation' phase. During the Detection phase, VR biomarkers serve as a quick screening method to evaluate the risk of MCI in a broader elderly population. Their short test duration and high specificity effectively distinguish between healthy individuals and those who may have MCI, warranting further investigation. Implementing VR biomarkers in local dementia centers could help in identifying individuals at risk, facilitating their referral to hospitals for detailed dementia evaluations. Moreover, VR's capability for effortless data visualization makes it suitable for long-term monitoring purposes. In the subsequent Assessment & Differentiation phase, individuals suspected of having MCI are

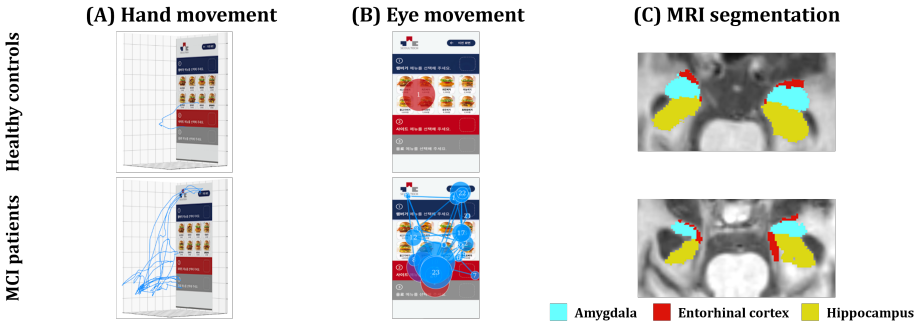

Figure 3: Comparison of hand and eye movements, and MRI findings between healthy controls and MCI patients. (A) A 3D representation of hand movement trajectories; (B) Participant gaze points with dots, where red, blue, and purple signify the start, middle, and end of gaze respectively. Dot size reflects fixation duration; (C) Notable atrophy observed in MCI patients.

subjected to an in-depth diagnostic procedure. Here, MRI biomarkers, known for their increased sensitivity, play a crucial role in detecting MCI and providing insights into brain structural changes. These biomarkers contribute to an accurate diagnosis of MCI, thus aiding in the development of tailored treatment plans. Integrating VR biomarkers in the initial screening (Detection phase) and MRI biomarkers in the detailed diagnostic stage (Assessment & Differentiation phase) substantially improves early detection. This integrated approach not only saves time and reduces costs for patients but also offers essential support to healthcare professionals in making accurate diagnoses for the aging population. Additionally, incorporating neuropsychological tests like SNSB-C into an intermediate phase between VR and MRI could further bolster clinical application.

This study has certain limitations that should be acknowledged. Primarily, it lacked a diverse sample in terms of racial diversity [60] and did not include individuals with various neurodegenerative diseases [61]. Additionally, there is a potential need to explore and compare other methods to improve classification performance, such as employing Contrastive Language-Image Pre-training [62]. Future research should aim to include a more diverse range of participants and further investigate the complex interactions between biomarkers using multimodal approaches. Despite these limitations, our study makes a significant contribution by demonstrating enhanced performance through the integration of VR and MRI biomarkers via multimodal learning, outperforming the individual performance of each biomarker. This integrated approach achieved noteworthy results, with an accuracy of 94.4%, sensitivity of 100.0%, specificity of 90.9%, precision of 87.5%, an F1-score of 93.3%, and an AUC of 0.89. These results highlight the combined benefits of using both VR and MRI biomarkers. Furthermore, our correlation analysis sheds light on how changes in brain structure may be reflected in behavioral patterns in daily activities. We suggest a novel clinical application that employs VR biomarkers, which exhibit high specificity (90.0%) in the initial Detection phase, followed by MRI biomarkers, showing optimal sensitivity (90.9%) in the Assessment & Differentiation phase. This stepwise approach could potentially reduce the time and financial burden on individuals and assist clinicians in making more accurate diagnoses. In summary, our study underscores the improved effectiveness of early MCI detection through the combined use of VR and MRI biomarkers in a multimodal learning framework.

5 CONCLUSION

Our study highlights the significance of integrating VR and MRI biomarkers for the early detection of MCI. The findings indicate that selecting appropriate biomarkers for different stages of the diagnostic process is advantageous. VR biomarkers, characterized by their high specificity, are well-suited for initial screenings, whereas MRI biomarkers, known for their high sensitivity, are more apt for confirming an MCI diagnosis. The most effective strategy, however, emerges from the integration of both types of biomarkers. This approach significantly enhances the accuracy of early MCI detection, illustrating the potential of multimodal learning in improving diagnostic processes. Furthermore, our study sheds light on the relationship between VR and MRI biomarkers, offering insights into how changes in brain structure can translate into behavioral differences. By adopting a multimodal learning approach that incorporates a variety of biomarkers, our study provides valuable contributions to the field, particularly in enhancing the performance of early MCI detection.

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