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An interpretable generative multimodal neuroimaging-genomics framework for decoding Alzheimer's disease

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Abstract

Background: Alzheimer's disease (AD) is the most prevalent form of dementia, with a prodromal stage known as mild cognitive impairment (MCI), where patients may either progress to AD or remain stable. Understanding the structural and functional modulations of the brain during this progression is critical. Multimodal MRI data combined with single nucleotide polymorphisms (SNPs) can provide valuable insights; however, missing data and interpretability remain key challenges.

Methods: We developed a multimodal deep learning (DL)–based classification framework integrating MRI and SNP data to classify AD patients versus healthy controls and to predict MCI conversion. A generative adversarial network (GAN) module using cycle consistency was introduced in the latent space to impute missing data, addressing a common issue in multimodal analysis. An explainable AI method was employed to extract feature relevance, enabling post-hoc validation and improving interpretability of the learned representations.

Results: Experimental evaluation on two tasks, AD detection and MCI conversion, demonstrated competitive state-of-the-art performance, achieving accuracies of 0.926 ± 0.02 (CI [0.90, 0.95]) and 0.711 ± 0.01 (CI [0.70, 0.72]), respectively. Interpretability analysis revealed gray matter modulations in cortical and subcortical brain regions commonly associated with AD. Additionally, impairments were observed in sensory-motor and visual resting-state networks, and genetic mutations linked to endocytosis, amyloid-beta, and cholesterol pathways were identified.

Conclusion: The proposed integrative and interpretable DL framework effectively handles missing multimodal data and enhances biological interpretability. It demonstrates strong performance in AD detection and MCI prediction, offering valuable insights into the structural, functional, and genetic underpinnings of Alzheimer's disease.

Keywords: Alzheimer's Disease (AD); Mild Cognitive Impairment (MCI); Deep Learning; Multimodal MRI; Single Nucleotide Polymorphisms (SNPS); Generative Adversarial Networks (Gans); Explainable AI; Brain Imaging; Disease Progression; Biomarker Discovery; Neurodegeneration; Machine Learning Interpretability

1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder that affects millions of people worldwide (approximately 30 million in 2015. It is the most common cause of cognitive impairment, gradually impacting the activities of a patient's daily life. It is characterized by the progressive loss of cognitive and functional abilities, including memory, language, and executive functions, with a temporal progression. Amyloid accumulation represents the first event, followed by tau accumulation, hypometabolism (assessed with positron emission tomography (PET)), atrophy, and cognitive decline. It is hence evident that the pathology changes of AD actually begin several years before the first clinical symptoms. Therefore, a timely AD diagnosis is highly beneficial for optimizing patient care and enabling appropriate therapeutic interventions. Mild cognitive impairment (MCI) is the intermediate stage from normal cognitive

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function to AD, hence representing an opportunity for an early targeting of the disease. However, it includes a very heterogeneous class of patients, including subjects that will likely convert to AD, known as MCI converters (MCIc), with an estimated annual conversion rate around the 16.5%, and subjects that remain stable after several years, being part of the MCI non-converters (MCInc) group.

Among the available neuroimaging technologies, structural magnetic resonance imaging (sMRI) and resting-state functional MRI (rs-fMRI) have provided unprecedented opportunities for deriving biomarkers allowing the early diagnosis of AD. For instance, sMRI is currently a key part of the diagnostic criteria for the differential diagnosis and longitudinal monitoring of patients with dementia, enabling the estimation of brain atrophy. Several studies have consistently observed both global and local atrophic changes in AD, lying along the hippocampal pathway (entorhinal cortex, hippocampus, parahippocampal gyrus, and posterior cingulate cortex) in the early stages of the disease, while atrophy in temporal, parietal and frontal neocortices emerges at later stages being associated with neuronal loss as well as with language, visuospatial and behavioral impairments. Rs-fMRI, in turn, indirectly measures neural activity by detecting changes in the blood oxygenation level dependent (BOLD) signals, which depend on the neurovascular coupling. In particular, investigating functional connectivity (FC; inter-regional coupling), functional network connectivity (FNC; inter-network coupling), and functional networks from BOLD rs-fMRI provides a means for understanding the mechanisms and relevance of the functional relationships across brain regions. A growing body of rs-fMRI studies suggests that failure of specific resting-state networks (RSNs) is closely related to AD, with the default-mode network (DM) and the salience network (SN) playing a pivotal role and being disrupted before clinically evident symptoms. Specific alterations in these functional networks have been reported in AD patients, with prominent FC decreased within the DM and increased FC in the SN. Moreover, disconnections within and between the different RSNs have been consistently demonstrated, particularly over long connection distances. All of these factors have contributed to the widespread view of AD as a disconnection syndrome being characterized by a cascading network failure, beginning in the posterior DM and then shifting to other systems containing prominent connectivity hubs, possibly associated with amyloid accumulation. Moreover, increased evidence supports the view that tau depositions are also related to functional brain architecture and FC changes, supporting the view of transneuronal tau propagation in AD.

AD also features a strong genetic component. Strategies to extract linked genotype traits are commonly based on single nucleotide polymorphism (SNPs) analysis, representing variations of single nucleotides in DNA sequences that vary from person to person and are present in at least 1% of the population. Several genome-wide association studies (GWASs) have identified more than 40 AD-associated genes/loci, which are likely to increase the risk of developing the disease. Among them, the apolipoprotein E (APOE), in particular the allele, PICALM, CLU, ABCA7, and CR1 are the most important genes being associated with AD risk factor or the progression from MCI to AD.

This great heterogeneity of available biomarkers offers a unique opportunity to explore various aspects of the disease continuum. Each biomarker provides valuable information about specific characteristics, enabling a multifaceted investigation of AD which calls for methods that can effectively integrate and leverage complementary information. In this regard, artificial intelligence, machine learning (ML) and particularly deep learning (DL), emerge as promising technologies to tackle this complex task. Different ML algorithms have been developed for integrating heterogeneous data, such as canonical correlation analysis, partial least squares, and ensemble methods, e.g. consisting of different support vector machines (SVMs). Even if these methods can perform well in studying neurodegenerative diseases, they have some limitations, such as requiring vectorized input data, hence denaturing the spatial information of 3D volumes (e.g. sMRI or PET 3D images), and potentially being too simple for solving complex tasks. On the other hand, by employing multiple layers of processing, DL models allow extracting progressively higher-level and more informative features from input data, with the option of preserving spatial information, without the need of vectorizing the input features. Moreover, the inclusion of multiple data sources into a single model can uncover complex and deep non-linear associations across the input features from a multimodal perspective. As a result, multimodality is gaining significant popularity representing the key approach to derive valuable insights into complex and multifaceted neurodegenerative diseases such as AD. However, despite the promising foreseen of such an approach, multiple drawbacks are present and represent the focus of the current research. The main concern resides in missing data management. Particularly in the biomedical domain, it is very common to incur in missing values or acquisitions for certain subjects or entire study cohorts due to different reasons, such as missing acquisition, corrupted data, patients dropout from a study, and the requirements of privacy and expensive tests. Additionally, the interpretability of a model's predictions is a central characteristic of decision-aiding models, which is still not pervasively addressed. In the past years, many high-performing prediction models have been proposed lacking a clear rationale to be effectively considered for practical use. Strong and validated explanations associated with a given prediction are fundamental for increasing trust in the results as well as for their applicability in a real-world scenario. Innovative and viable missing modality management as well as interpretability are the key attributes that a multimodal model for diagnosis detection should have.

Diving into missing data management, the simplest and most common solutions consist either in discarding samples with missing modalities, or in filling the missing values with zeros, and computing imputations based on data interpolation. Such solutions are evidently suboptimal since they could significantly reduce the number of training samples, already small when addressing biomedical-related tasks, or introduce important biases in the data and the model due to the interpolation or the zero filling when a lot of data are missing. Alternative methods to exploit the information of all the available subjects were proposed. Some works employed multi-kernel learning methods for imputing missing data employing different kernel strategies to mix and integrate the heterogeneous modality, while managing missing data. A possible approach is the complementation of incomplete data representation, which consists in extracting a latent representation from both the complete and incomplete modalities, avoiding the need for data imputation. Most recent approaches aim at generating missing data either in the input space or in an intermediate latent representation relying on generative models such as generative adversarial networks (GANs) and their variants, or variational autoencoders. This last approach has been successfully applied to the AD continuum investigation. It allows the exploitation of the availability of multimodal data for capturing the relationship among different data sources in the latent space, enabling the generation of one modality from another. Generative models, hence, appear as the route to be followed when dealing with missing data. Interestingly, the recently proposed cycle-consistent GANs have shown impressive results in various knowledge translation tasks since they offer a flexible and effective approach for learning mappings across different domains without relying on paired data.

Moving to model interpretability, it is well established that with increasing model complexity, interpretability decreases drastically. However, in order to better understand the mechanisms that underlie the AD continuum and allow the models to be applied in clinical and real-life applications, it is vital to understand the reasons behind a certain output. In this case, explainable artificial intelligence (XAI), becomes essential to understand why a given model made a certain prediction. XAI encompasses *post-hoc* methods that allow the assignment of an importance score to each feature, reflecting its role in the classification task. This means finally opening the 'black box' of complex models hopefully increasing their exploitability in clinical practice. XAI is starting to be applied in multimodal frameworks to study neurodegenerative and psychiatric diseases. Few works could be found adopting simple gradient-based, feature perturbation methods, or attention weights. On top of this, another overlooked yet stringent aspect is the strong validation of XAI methods and the obtained explanations. The evaluation of explanation methods is still under-investigated, however, since explainability is meant to increase confidence in AI, it is vital to systematically analyze the obtained results referring also to the prior knowledge derived from the state-of-the-art.

In this rapidly evolving landscape, where multimodality holds a central role, we aim at shading light on the importance of the complementary information that could be derived from advanced biomarkers such as brain FC and SNPs mutations, together with the well-established brain atrophy measures derived from sMRI, in detecting AD-related modulations. With this purpose, we will present a multimodal framework for AD detection and MCI conversion prediction, which addresses (i) heterogeneous data integration, (ii) missing data management, and (iii) interpretability. Regarding the former, our framework allows the integration of heterogeneous data featuring different dimensionality, e.g. 3D volumes and vectorized data, and nature, meaning from multi-domain, e.g. imaging and genetics. Concerning the second, we propose an approach that allows generating missing modalities in the latent space obtained after input feature reduction, ensuring high accuracy in reconstructing latent features while minimizing computational demands. Moreover, another important aspect of imputing missing data in the latent space relies on the fact that the latent space is lower-dimensional with respect to the input one, thus a simpler task to solve. The goal is to define a framework that can be generalized to any missing modality, without requiring to have at least one specific modality shared by all the subjects in the considered population. Finally, we aimed at emphasizing the interpretability of the proposed framework in order to reinforce its transparency and reliability by conducting an XAI post-hoc interpretability analysis, supplemented by a robust validation step, which enables to precisely discern the contribution of each input feature to the classification of subjects in the AD continuum, thus highlighting relevant phenotypic and genotypic biomarkers for AD.

2. Methods

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu/). The cohort included 1,911 subjects categorized as healthy controls (CN), Alzheimer's disease (AD), non-converters (MCInc), and converters (MCIc). For all subjects, baseline 3D T1-weighted MRI, resting-state fMRI (rs-fMRI), and genetic data were used when available. MCI subjects later diagnosed with dementia were classified as MCIc.

3D T1-w MRI scans were acquired using sagittal accelerated MPRAGE (TR/TE = shortest, TI = 900 ms, flip angle = 9°, FOV = 256 × 256 mm^2, spatial resolution = 1 mm^3). Resting-state fMRI used TR/TE = 3000/30 ms, FA = 90°, FOV = 220 × 220 × 163 mm^3, 3.4 mm isotropic voxels, and approximately 200 volumes per subject.

Structural MRI (sMRI) volumes underwent segmentation into gray matter (GM), white matter, and cerebrospinal fluid using modulated normalization. GM maps were smoothed with a 6 mm Gaussian kernel (input size = 121 × 145 × 121). rs-fMRI preprocessing (SPM12) included motion correction, slice-timing correction, MNI normalization, 3 mm^3 resampling, and Gaussian smoothing (6 mm FWHM). Fifty-three independent components were extracted using spatially constrained ICA (Neuromark_fMRI_1.0 template, GIFT software). Pearson correlations between component time courses generated a 53 × 53 functional network connectivity (FNC) matrix, which was vectorized (1,378 features).

DNA samples were genotyped using the Illumina Human610-Quad or HumanOmniExpress BeadChip. Pre-imputation QC removed SNPs with low allele frequency, call rate, or Hardy–Weinberg disequilibrium. SNPs were imputed, pruned ($r^2 < 0.2$, 50 kb window), and filtered using GWAS significance ($p < 1\times10^{-4}$), yielding 565 SNPs. Alleles were encoded as 0 (wild-type), 1 (heterozygous), or 2 (mutant homozygous).

The framework integrates three modules: (i) **Feature reduction**, using CNNs to extract 100 latent features per modality (3D CNN for sMRI, 1D CNNs for rs-fMRI and SNPs); (ii) **Generative module**, using cycle-consistent GANs (cGANs) to impute missing modalities in latent space; and (iii) **Data fusion & classification**, concatenating latent vectors (300 features) and classifying via a multilayer perceptron (3 fully connected layers, ReLU activation, Softmax output).

Training was performed in two stages:

- **Step 1:** Bi-modal networks (sMRI–fMRI and sMRI–SNPs) and corresponding cGANs were trained for AD vs CN classification using 10-fold stratified cross-validation (Adam optimizer, learning rate = 0.0001).
- **Step 2:** The full multimodal framework was trained on sMRI, rs-fMRI, and SNP data (80/20 train-test split, 10-fold CV, batch size = 12, 70 epochs). Generators' weights remained frozen during training.

Performance was assessed using accuracy, precision, and recall, averaged across five independent runs. Baseline comparisons included ensemble SVM and Random Forest classifiers with mean and zero imputation, along with single- and bi-modal ablation studies. Post-hoc interpretability relied on Integrated Gradients (IG) to compute feature attributions across modalities. For sMRI and fMRI, top-percentile attribution maps identified significant cortical/subcortical regions and functional connections (Bonferroni-corrected Kruskal–Wallis and Wilcoxon tests). SNPs with top 35% IG scores were annotated via Ensembl Variant Effect Predictor, followed by Gene Ontology enrichment to reveal biological processes related to endocytosis, amyloid-β, and cholesterol metabolism.

3. Results

3.1. Task 1: Alzheimer's Disease Detection

The proposed multimodal framework achieved state-of-the-art performance in distinguishing AD from CN subjects, with an average accuracy of **0.926 ± 0.02** (CI [0.90, 0.95]), precision of **0.912 ± 0.07**, and recall of **0.875 ± 0.05**; the best model reached **0.964 accuracy**. The cGAN generators effectively reconstructed missing modalities, achieving low mean absolute errors (MAE: 0.06–0.09 for MRI/fMRI and 0.30–0.52 for SNPs). Baseline models such as SVM and Random Forest with mean/zero imputation reached only ~0.68–0.71 accuracy, and single-modality CNNs performed lower (sMRI: 0.88, fMRI: 0.85, SNPs: 0.52). The proposed approach consistently outperformed all baseline and ablation models.

3.2. Feature Relevance – AD Detection

Integrated Gradients (IG) analysis revealed the hippocampus and amygdala as the most relevant regions, with negative attributions for AD and positive for CN, consistent with hallmark atrophy patterns. fMRI relevance maps highlighted strong involvement of sensorimotor (SM), visual (VI), default mode (DM), cognitive control (CC), and cerebellar (CB) networks. AD subjects showed decreased SM and CB connectivity and increased VI and DM connectivity, indicating disease-related functional reorganization. Genomic analysis identified SNP clusters on chromosomes 7, 11, 14, and 19, with APOE, CLU, and PICALM among the most relevant genes.

3.3. Task 2: MCI Conversion Prediction

Without retraining, the same model generalized to predict MCI progression, reaching **0.711 ± 0.01 accuracy** (CI [0.70, 0.72]), precision **0.612**, and recall **0.550**, outperforming all baseline approaches (≤0.70 accuracy).

3.4. Feature Relevance – MCI Conversion

Similar to Task 1, the hippocampus remained the most discriminative region, with positive relevance for MCInc and negative for MCIc. fMRI maps again highlighted SM, VI, CC, DM, and CB networks, showing opposite connectivity trends between stable and converting patients. SNPs on chromosomes 11, 14, 15, and 17 showed class-specific relevance, suggesting early genetic indicators of conversion risk.

3.5. Group-Based Statistical Analysis

Quantitative IG analysis confirmed significant differences between CN/MCInc and AD/MCIc groups in hippocampal and amygdala attributions ($p < 0.001$). Functional connectivity differences were most pronounced in SM and VI networks, showing reduced intra-network connectivity in AD and MCIc, with possible compensatory hyperconnectivity in late stages.

3.6. Genetic Enrichment Analysis

Enrichment of biological processes related to endocytosis, amyloid-β regulation, cholesterol metabolism, and intracellular transport was observed for AD and MCIc, implicating genes such as APOE, CLU, PICALM, ABCA7, BIN1, and TREM2. In contrast, MCInc subjects showed enrichment in T-cell activation and immune regulation, suggesting potential neuroimmune protective mechanisms.

4. Discussion

This study presents a multimodal, generative, and interpretable deep learning framework that integrates structural MRI, functional MRI, and genetic data for Alzheimer's disease (AD) detection and mild cognitive impairment (MCI) conversion prediction. The model achieved state-of-the-art accuracy while effectively addressing missing data through latent-space imputation using cycle-consistent GANs, demonstrating robustness and generalizability even with incomplete modalities.

The interpretability analysis confirmed that subcortical atrophy, particularly in the hippocampus and amygdala, remains the most reliable neuroanatomical marker of AD progression. Functional relevance patterns in sensorimotor and visual networks indicated decreased connectivity in MCI and AD stages, suggesting early neurodegenerative changes followed by compensatory hyperconnectivity in advanced disease. Genetic interpretability further linked APOE, CLU, PICALM, and ABCA7 to dysregulation in endocytosis, amyloid-β clearance, and cholesterol metabolism, aligning with known pathogenic mechanisms.

Overall, the proposed framework not only matches or exceeds the performance of existing multimodal AD models but also provides biologically meaningful explanations of its predictions. By enabling reliable detection of disease-related features across imaging and genomic modalities, this approach contributes to more transparent and generalizable AI systems for neurodegenerative disease research. Future work will extend this framework to additional modalities such as PET and clinical data, and explore phenotype stratification using the A/T/N biomarker framework to further refine early diagnostic precision.

5. Conclusion

In this work, we presented a multimodal, flexible, generative, and interpretable DL-based framework for AD detection and MCI conversion classification. Neuroimaging (structural and functional features) and genetics data were used to address these classification tasks. The generation of missing modalities in the latent space using four pre-trained generators of two different cGANs allowed to obtain competitive classification performance in both tasks. The application of an interpretability method yielded our model to be interpretable, extracting the relevance of each input feature and revealing the most important ones for each class, highlighting disease structural, functional, and genetic signatures and opening the way to further analyses.

Compliance with ethical standards

Disclosure of conflict of interest

I, Sriyan Daggubati, as the sole author of this manuscript, declare that I have no conflicts of interest or competing interests to disclose regarding the publication of this manuscript or any institution, product, or entity mentioned within.

Furthermore, I have no affiliations or financial interests in products or organizations that could influence the study outcomes presented or compete with those discussed in the manuscript.

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