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Title: Statistical Method for Identification of Alzheimer's Disease in Mild Cognitive Impairment
with Multimodal Predictive Markers

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To appear in: **Basic and Clinical Neuroscience**

Received date: 2024/04/20

Revised date: 2024/10/15

Accepted date: 2024/10/26

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Please cite this article as:

Zarei, S., Shalhaf, R., Shalhaf, A. (In Press). Statistical Method for Identification of Alzheimer's Disease in Mild Cognitive Impairment with Multimodal Predictive Markers. *Basic and Clinical Neuroscience*. Just Accepted publication Jul. 10, 2024. Doi: <http://dx.doi.org/10.32598/bcn.2024.2034.7>

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Abstract

Predicting progression from Mild Cognitive Impairment (MCI) to Alzheimer's Disease (AD) is challenging, requiring reliable predictive markers for intervention. This study identifies predictive markers across various assessments, including demographics, Positron Emission Tomography (PET), genotyping, Magnetic Resonance Imaging (MRI), and neurocognitive tests from statistical methods. The primary goal is to discern markers effectively distinguishing stable MCI (sMCI) from progressive MCI (pMCI) to AD. We use the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset which individuals are meticulously categorized into sMCI (487 individuals) and pMCI to AD (348 individuals). In this study, we employ an innovative methodology that involves comprehensive data cleaning and engineering on the ADNI dataset. Area Under the Curve (AUC) and Wilcoxon testing as robust statistical methods are used to reveal distinct cognitive patterns between sMCI and pMCI. With a focus on 50 features, our findings highlight the discriminatory potential of PET, specifically Florbetaben (FBB), boasting an AUC value of 0.84. Neurocognitive tests, including Alzheimer's Disease Assessment Scale 13 items (ADAS13), ADNI-modified Preclinical Alzheimer Cognitive Composite with Trails B (mPACCtrailsB), ADAS cognitive subscale question 4 (ADASQ4), Logical memory delayed recall Total score (LDELTOTAL), and ADNI-modified Preclinical Alzheimer Cognitive Composite with Digit Symbol Substitution (mPACCdigit), exhibit substantial discriminatory power, each with AUC values of 0.83, 0.83, 0.82, 0.82, and 0.82, respectively. Consequently, diverse features, analyzed via robust methods, reveal cognitive markers for differentiating stable and progressive MCI, offering insights for improved early AD diagnosis and intervention.

Keywords: Alzheimer's Disease, Mild Cognitive Impairment, Predictive markers.

Introduction

Alzheimer's disease (AD), a severe form of dementia marked by rapid progression and profound cognitive impact, necessitates exploration of symptoms, rising incidence, diagnostic progress, and the urgent need for enhanced measures¹. AD is exceptionally severe, progressing swiftly and often leading to fatality with profound cognitive impairment. Individuals with AD experience various symptoms, underscoring the pressing need for improved diagnostic, preventive, and therapeutic measures. The rising incidence of AD mirrors the demographic shift toward an aging population. Recent statistics indicate that approximately 5 to 10 percent of individuals aged 65 and above meet the criteria for AD². Projections suggest a staggering 152 million people worldwide will be affected by 2050, underscoring the paramount importance of understanding AD's development and mechanisms³. Collaborative initiatives, exemplified by the Alzheimer's Disease Neuroimaging Initiative (ADNI)⁴, play a pivotal role in recruitment, assessment, and data management. ADNI's comprehensive approach significantly advances our comprehension of AD, bridging the gap between epidemiological trends and the intricate neurobiological processes underlying the disease. Concurrently, the field of AD diagnosis has progressed with the implementation of the International Working Group (IWG-2)⁵ criteria, representing a delicate balance between biomarkers and clinical phenotype. These criteria facilitate a nuanced understanding of the clinical heterogeneity inherent in AD⁶. The integration of biomarkers and clinical features is especially critical in comprehending the phases of AD⁷, influencing the design and execution of clinical trials, and shaping treatment considerations.

In elucidating the critical role of early detection and precise risk prediction within Alzheimer's research, there is an emphasis on recognizing Mild Cognitive Impairment (MCI) as a pivotal prodromal stage. Within the intricate domain of AD investigation, this emphasis consistently revolves around the imperative need for early detection and precise risk prediction⁸⁻¹⁰. The emphasis originates from the considerable economic and clinical advantages linked to timely identification and intervention, signaling a paradigm shift towards proactive healthcare strategies¹¹. Various scholarly discourses significantly contribute to this thematic exploration, converging on the challenging question of early AD diagnosis. This dialogue accentuates the importance of acknowledging MCI as a prodromal stage, representing a critical juncture in the temporal progression of AD^{12,13}. MCI, distinguished by noticeable cognitive decline exceeding age-related expectations without significant interference with daily life, emerges as a pivotal phase in comprehending and detecting early AD symptoms¹⁴.

Identifying individuals with MCI susceptible to the progression to AD is crucial for timely intervention. Although MCI is not a deterministic condition precursor to dementia¹⁵ and even sometimes reverses to normal cognitive¹⁶, the exploration of MCI to AD encompasses diverse modalities, including clinical/demographic factors^{17,18}, Positron Emission Tomography or Magnetic Resonance Imaging (PET/MRI) analyses¹⁹⁻²¹, genotyping²², along with neurocognitive assessments^{23,24}, and psychosocial elements²⁵⁻²⁷. Each modality carries distinct advantages and limitations. Clinical/demographic factors provide valuable contextual information and play a pivotal role in diagnostic decision-making. PET/MRI analyses furnish high-resolution neuroimaging data, yet, despite yielding precise images, entail considerations of cost and radiation exposure. Genotyping offers insights into genetic underpinnings but may lack specificity. Neurocognitive assessments unravel cognitive profiles, although they may exhibit variability in reliability. The intricate interplay and potential synergy among these modalities introduce complexities, presenting unique challenges in comprehending the progression from MCI to AD. It's

worth noting that, although our dataset doesn't directly assess psychosocial elements, we review relevant studies to ensure a comprehensive understanding of all features in our contextual analysis.

Embarking on a discussion of previous studies, Li et al.'s meta-analysis²⁶ reveals a suggested correlation between anxiety, Alzheimer's biomarkers, and cognitive decline in MCI. However, the study faces challenges due to the lack of specificity in MCI subtypes and inconsistencies in operational and diagnostic criteria, posing difficulties in forming robust conclusions. This leads to an inherent limitation, as relying on reported measures, rather than patient-administered assessments, may potentially result in false diagnostic assumptions. Transitioning to a different focus, M. Fei et al.'s literature synthesis integrates findings from eight studies exploring the association between the APOE ϵ 4-allele and the transition risk from MCI to AD²². The meta-analysis underscores a heightened AD risk in Amnesic MCI patients with the APOE ϵ 4-allele. Despite the robust findings, the study acknowledges limitations, such as the need for larger sample sizes and additional family-based Transmission/Disequilibrium Test (TDT) studies. It also highlights potential publication bias, originating from data sourced in English journals and the absence of family-based TDT studies. Shifting the focus to community-based follow-up surveys, C. Hu et al.'s study, spanning 17 communities, employed psychiatric medical staff with over 2 years of clinical experience, achieving a 43.8% follow-up rate²⁸. Challenges emerged as demographic differences surfaced among participants lost to follow-up. Among the 441 diagnosed with MCI, the study uncovered varied outcomes, with 17.5% progressing to dementia, 80.7% remaining stable, and 1.8% reverting to normal cognition. The findings also unveiled significant associations with diabetes, marital status, and occupational roles.

Continuing in a longitudinal context, T. Gabryelewicz and colleagues conducted an extensive study involving 105 individuals with MCI, subjecting them to comprehensive assessments and following up every 12 months²⁷. Over the 3 years, the study observed a significant trend: individuals identified with multiple-domains MCI (MD-MCI) displayed a notably increased likelihood of progressing to dementia, emphasizing the clinical significance of this classification. This shift in focus from community-based surveys to more targeted assessments contributes to a nuanced understanding of MCI progression. Shifting gears to a six-year investigation, MP Ates et al. observed seventy-six individuals aged 57 and above diagnosed with MCI²⁹. The study's results revealed that 44.7% progressed to dementia, while 55.3% maintained an MCI diagnosis. Noteworthy associations were found between dementia cases and advanced age, vascular diseases, and shorter education duration. Additionally, patients with dementia exhibited a notably higher prevalence (94.1%) of vascular systemic diseases compared to those persisting with MCI. This prolonged study duration allows for a comprehensive examination of the factors influencing MCI outcomes. Transitioning to another longitudinal study by H Xue et al., encompassing a 5-year biannual follow-up of 437 MCI patients¹⁷, 24.3% progressed to AD. This study identified transition risk factors, including gender, age, reading habits, smoking, drinking, cerebrovascular disease, hyperlipidemia, and diabetes. Moreover, it highlighted education as a protective factor, while advanced age and the presence of cerebrovascular disease significantly influenced the transitions from MCI to AD and death. This nuanced exploration of various factors affecting MCI outcomes contributes to a richer understanding of the complexities involved. Finally, RO Roberts spearheaded a study involving thorough assessments of residents aged 70 to 89¹⁶. This comprehensive evaluation covered demographic information, memory inquiries, clinical ratings, and neuropsychological tests. MCI classifications included amnesic and non-amnesic MCI, along with single- and multiple-domain MCI. Participants underwent assessments at 15-month intervals,

uncovering an elevated risk of dementia in those with a history of MCI, particularly among women aged 80 to 89. This community-based approach, coupled with detailed assessments, provides a bridge between community-based surveys and more targeted clinical investigations, offering a holistic view of MCI progression.

Recent investigations have adopted multimodal strategies to predict AD progression by integrating neuroimaging, genetic data, and neurocognitive assessments, which closely aligns with our methodology of utilizing PET, MRI, genotyping, and neurocognitive tests to differentiate between sMCI and pMCI³⁰⁻³³. Techniques such as MRI have demonstrated efficacy in detecting structural and functional brain changes, while the incorporation of MRI with genetic markers has significantly improved prediction accuracy for AD progression³¹. Longitudinal studies combining structural MRI with neurocognitive assessments or PET biomarkers have also shown enhanced predictive capacity for neuropsychological outcomes^{32,33}. Additionally, approaches informed with advanced methods such as 3D-convolutional neural networks have further refined the ability to predict conversion from MCI to AD³⁴. A systematic review of deep learning approaches shows how the combination of MRI and clinical data can yield early predictions of conversion from MCI to AD³⁵. Our study further extends this work by employing a robust statistical framework for a comprehensive evaluation of these multimodal features, underscoring the importance of integrated and longitudinal approaches for early diagnosis and targeted therapeutic interventions.

Concluding this integrated discussion, SJ Lee's study utilizing data from ADNI-1 focused on 382 participants with amnesic MCI³⁶. Over a 2.9-year follow-up, 46.9% progressed to probable AD. Factors influencing progression encompassed demographic, symptomatic, functional, and neuropsychiatric domains. The clinical index, though less accurate than the full index with neuroimaging measures, underscored the importance of their inclusion for heightened predictive precision. This transition from community-based assessments to more refined clinical investigations demonstrates the intricate interplay of factors influencing MCI outcomes, showcasing the complexity of predicting progression to dementia.

We employ an innovative approach, delving into various modules to foster a holistic understanding of the intricate interplay among demographics, PET, genotyping, MRI, and neurocognitive tests. This comprehensive exploration seeks to identify effective markers that distinguish participants into two cohorts: those consistently maintaining a MCI diagnosis, termed stable MCI (sMCI), and those progressing from MCI to AD, known as progressive MCI (pMCI). Each module serves as a unique lens for our investigation: demographics enhance our understanding of prevalence and risk, PET sheds light on functional and metabolic nuances, genotyping delves into genetic and molecular realms, MRI unveils intricate structural details, and neurocognitive tests assess cognitive function. Our exhaustive statistical scrutiny rigorously evaluates the significance of these modalities, pinpointing their value in identifying AD within the spectrum of MCI. This holistic exploration, empowered by statistical methods, enables us to distill the most potent predictive markers, refining early detection strategies for AD. By navigating diverse modalities and conducting a nuanced analysis, our innovative investigation aims to uncover optimal predictors for AD within the context of MCI, contributing to a more profound comprehension of the disease and advancing early detection efforts.

Materials and Methods

ADNI: Cohort Collaboration, Data Integration, and Access Protocols

The ADNI initiative stands as a groundbreaking collaborative effort, aiming to revolutionize our understanding of AD by advancing early diagnostic capabilities, standardizing data sharing, enhancing clinical trial methodologies, and fostering collaborative research endeavors. Integral to this initiative, the ADNI-MERG dataset plays a pivotal role in consolidating a diverse array of data into a unified repository. The manuscript's framework provides efficient access to a comprehensive dataset, including demographic information, PET, genotyping, MRI, and neurocognitive assessments, minimizing the need for complex data integration. Each dataset entry corresponds to a participant's visit across different ADNI phases, providing crucial details like participant ID, site visited, examination date, original study protocol, and data collection study protocol. Furthermore, the dataset includes extensive baseline data from all tests conducted during each participant's visit, establishing a robust groundwork for focused exploration of patterns and relationships aligned with the study's objectives. Accessing ADNI data involves submitting a formal request to the ADNI team, and outlining research goals and methodologies. Following a thorough approval procedure, the ADNI team grants necessary permissions for data access.

Inside ADNI MERG Data: Exploration, Cleaning, and Trajectory Insights

The ADNI-MERG dataset includes a comprehensive array of data types, with baseline (BL) fields extending beyond demographic information. Time-related fields, such as visit codes and examination dates, provide a longitudinal perspective, while "Update_stamp" fields offer insights into the last modification of entries. The "DX" column indicates diagnostic categories, with "NA" denoting missing values, underscoring the need for careful analysis, and prompting researchers to consider imputation techniques or exclusion criteria.

The dataset encompasses essential demographic variables, including AGE (Mean Age), PTEDUCAT (Participant's Years of Education), PTETHCAT (Participant's Ethnic Category), PTGENDER (Participant's Gender), PTMARRY (Participant's Marital Status), and PTRACCAT (Participant's Racial Categories). Cognitive assessments comprise ADAS11 (11 items), ADAS13 (13 items), and ADASQ4 (Cognitive Subscale Question 4) from the Alzheimer's Disease Assessment Scale, along with CDRSB (Clinical Dementia Rating - Sum of Boxes), DIGITSCOR (Digit Symbol Substitution Test), FAQ (Functional Assessment Questionnaire), LDELTOTAL (Logical memory I and II, delayed recall), MMSE (Mini-Mental State Examination), TRABSCOR (Trail Making Test-B-Score), MOCA (Montreal Cognitive Assessment), mPACCtrailsB (ADNI modified Preclinical Alzheimer Cognitive Composite with Trails B), and mPACCdigit (ADNI modified Preclinical Alzheimer Cognitive Composite with Digit Symbol Substitution). Also RAVLT.immediate (RAVLT Immediate), RAVLT.learning (RAVLT Learning), RAVLT.forgetting (RAVLT Forgetting), and RAVLT.perc.forgetting (RAVLT Percent Forgetting) from the Rey Auditory Verbal Learning Test. Everyday cognition test Participant Self-Report assessments encompass EcogPtMem (EcogPT Memory test), EcogPtLang (EcogPT Language test), EcogPtVisspat (EcogPT Visual-spatial and perceptual abilities test), EcogPtPlan (EcogPT Planning test), EcogPtOrgan (EcogPT Organization test), EcogPtDivatt (EcogPT Divided attention test), and EcogPtTotal (EcogPT Total test mean score). Additionally, EcogSPMem (EcogSP Memory test), EcogSPLang (EcogSP Language test), EcogSPVisspat (EcogSP Visual-spatial and perceptual abilities test), EcogSPPlan (EcogSP Planning test), EcogSPOrgan (EcogSP Organization test), EcogSPDivatt (EcogSP Divided attention test), and EcogSPTotal (EcogSP Total test mean score) represent assessments from the Everyday Cognition Study Partner Report. PET and

genotype features encompass AV45 (Florbetapir), FBB (Florbetaben), FDG (Fluorodeoxyglucose), PIB (Pittsburgh Compound B), APOE4 (Apolipoprotein E), ABETA (Amyloid β peptide), PTAU (Blood phosphorylated tau), and Total tau (TAU). Brain region volume measurements include Entorhinal (Entorhinal cortex), Fusiform (Fusiform gyrus), Hippocampus, ICV (Intracranial Volume), MidTemp (Middle temporal gyrus), Ventricles (Brain ventricles), and Whole Brain.

The meticulous preparation of the dataset involved a rigorous data cleaning process to enhance its quality and relevance. Duplicate entries were systematically eradicated using participant ID (RID) and visit code as distinctive identifiers to guarantee the distinctiveness of each participant's visit. Coherence was enhanced by excluding subjects lacking a diagnosis, while the omission of participants with a solitary diagnosis enriched dataset diversity and encompassed a broader spectrum of diagnostic transitions. The exclusion of rows with complete missing values was essential to maintain the accuracy and integrity of the data set. These judiciously applied criteria contribute to a meticulously curated dataset, void of redundancies, inclusive of participants with meaningful diagnostic information, and devoid of incomplete or uninformative entries, aligning with the precise goals and analytical requisites of the study. Significant work on the ADNI-MERG dataset included the implementation of enhancements to enrich the understanding of participant trajectories and diagnostic alterations within the ADNI study. These updates provided an in-depth insight into participant involvement and diagnostic shifts, introducing additional metrics such as visit frequency, participant engagement duration, and unique visit identifiers. This not only enriched the dataset but also expanded the ability to assess participant progressions thoroughly. Incorporating group labels to identify transitions between diagnostic states and records of diagnosis conversions significantly fortified the dataset's capability to capture and illuminate the intricacies of participants' diagnostic changes. Importantly, the categorization of participants into progressive and stable MCI groups provided a more refined analysis of participant paths and their diagnostic alterations throughout their involvement in the study, which is discussed in detail later.

Exploring ADNI Data Dynamics: In-Depth Analysis and Visualization

The baseline diagnoses of 2070 participants in the ADNI dataset include various cognitive states, with Late Mild Cognitive Impairment (LMCI) being the most prevalent diagnosis (624 individuals), followed by Early Mild Cognitive Impairment (EMCI) with 362 participants. Together, LMCI and EMCI form the largest group of individuals with MCI, totaling 986 participants. Additionally, there are 485 individuals classified as Cognitively Normal (CN), 357 participants diagnosed with AD, and 242 participants with Subjective Memory Concerns (SMC). Figure 1(a) illustrates these baseline diagnoses, providing essential context for understanding the cognitive states of participants, which is crucial for subsequent analyses of cognitive decline. Figure 1(b) shows how these baseline diagnoses are distributed across different ADNI phases: ADNI1 predominantly includes LMCI, CN, and AD diagnoses; ADNI2 has a broader distribution with significant numbers of EMCI, AD, and SMC cases; ADNI3 has a notable prevalence of SMC cases; and ADNIGO primarily features EMCI, underscoring the variability in diagnoses across the ADNI phases.

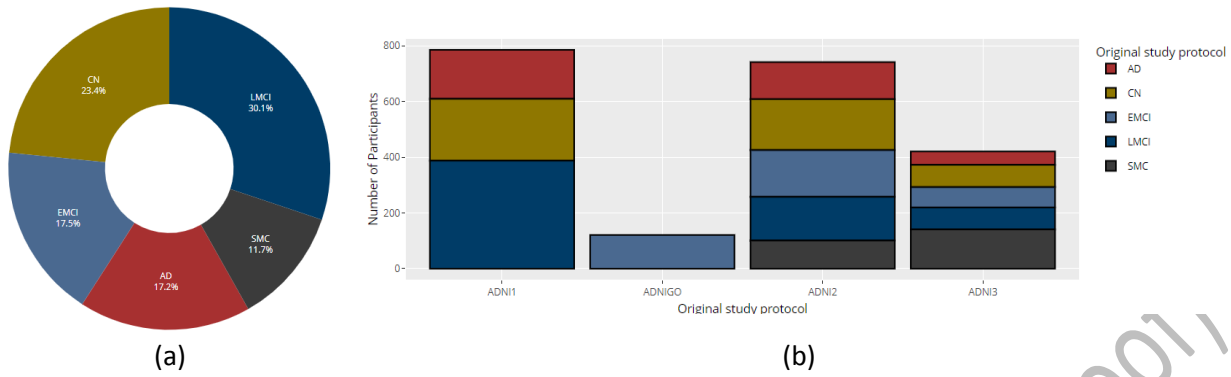


Fig1. a) Visualizing baseline diagnosis distribution in the ADNI cohort b) Baseline diagnosis distribution across ADNI phases

The visit progress for selected participants within the ADNI study is presented in Figure 2, which illustrates participant retention and transitions across various ADNI study phases. The figure highlights the longitudinal participation of individuals starting from baseline in each ADNI phase (ADNI1, ADNIGO, ADNI2, ADNI3), showing how participants move through sequential visits over time. For example, ADNI1 initially enrolled 786 participants, and as the study progressed, a portion of these participants transitioned to subsequent phases such as ADNIGO, ADNI2, and ADNI3. ADNI GO began with 121 participants, ADNI2 with 742, and ADNI3 with 410. The plot effectively visualizes participant follow-up within and across these phases, as indicated by the continuous lines. Larger, bolded dots represent baseline visits for each ADNI phase, while smaller points indicate follow-up visits over time. This figure underscores the continuity of the cohort and the attrition or retention of participants as they progress through the study phases.

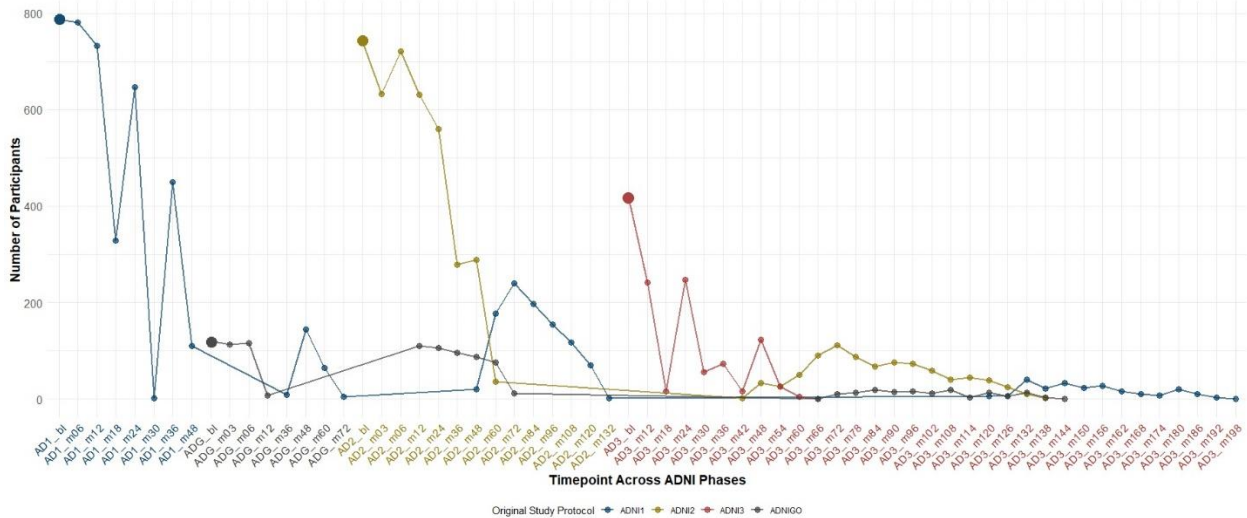


Figure 2: Participant distribution across ADNI phases. The x-axis represents time points for each phase (ADNI1, ADNIGO, ADNI2, ADNI3), with enrollment numbers of 819, 110, 730, and 410, respectively. Bold dots indicate baseline visits, while continuous lines track participant follow-up and transitions across phases, illustrating longitudinal retention.

Examining diagnosis conversions during participant visits in the ADNI study reveals notable patterns. The frequent transitions from MCI to MCI (3635 instances) and CN to CN (2971 instances) suggest prevalent stability in cognitive states across visits. These repeated transitions indicate that many participants

remained in the same cognitive state over multiple visits, reflecting either the slow progression of the disease or a lack of significant change in their condition during the observation period. Additionally, the persistence of AD to AD transitions (1590 instances) underscores the stability of this cognitive state. Of particular interest is the MCI to Dementia transition (419 instances), signifying a substantial progression in cognitive decline. Conversely, rare transitions, such as CN to Dementia (6 instances) and Dementia to CN (1 instance), raise concerns about potential reporting errors or misclassifications. The presence of NA values (1180 instances) further complicates the analysis, emphasizing the challenges in accurately categorizing cognitive changes.

ADNI Group Distinction: Categorizing Cognitive Progression Paths

In this phase, we undertake the categorization of participant groups within our dataset, with a specific focus on individuals initially diagnosed with MCI. Within this subgroup, our attention is directed towards two distinct cohorts: those who consistently maintain an MCI diagnosis throughout their visits and those who undergo a conversion from MCI to AD. For the MCI to MCI group, we apply stringent criteria. Participants are required to have a minimum of one year's worth of available data, ensuring a comprehensive temporal perspective. Furthermore, their diagnosis should consistently remain MCI from baseline through all available records, precluding any transitions to alternative states such as normal cognition.

In contrast, the MCI to AD group was meticulously selected based on specific criteria, requiring participants to exhibit an MCI to Dementia conversion and maintain a consistent diagnosis post-conversion. This approach aims to derive meaningful insights from the dataset regarding the trajectories and factors associated with these cognitive progression paths. Table 1 provides an overview of the number of participants in various diagnostic transition groups, emphasizing the 'MCI to MCI' and 'MCI to AD' categories. These groups represent distinct cognitive progression paths, with the former indicating individuals who remained stable in the MCI category across visits and the latter depicting those who progressed from MCI to AD. The total number of participants included in the analysis is 835, with each category carefully selected based on specific criteria related to cognitive progression.

Table 1. Number of participants in groups

Group	Number of participants
MCI to MCI	487
MCI to AD	348
Total number	835

Defining Stable and Progressive MCI States: Precision in Labeling for Insights

In the process of labeling the data for pMCI and sMCI, we shift our focus from participants to individual records, recognizing the multifaceted nature of participants' cognitive trajectories. Within the MCI to MCI group, every record is uniformly designated as sMCI, irrespective of the participant's visit duration, ensuring a consistent representation of the sustained MCI state for each recorded visit, even if the engagement extends beyond three years. On the other hand, for the MCI to AD group, a precise

temporal criterion guides the labeling. Only records preceding the AD diagnosis and those within the three-year window before the conversion event receive labels.

In conclusion, the comprehensive analysis of the ADNI-MERG dataset, from exploration and cleaning to the categorization of cognitive progression paths, is succinctly depicted in Figure 3, providing a visual representation of the intricate flow of our study.

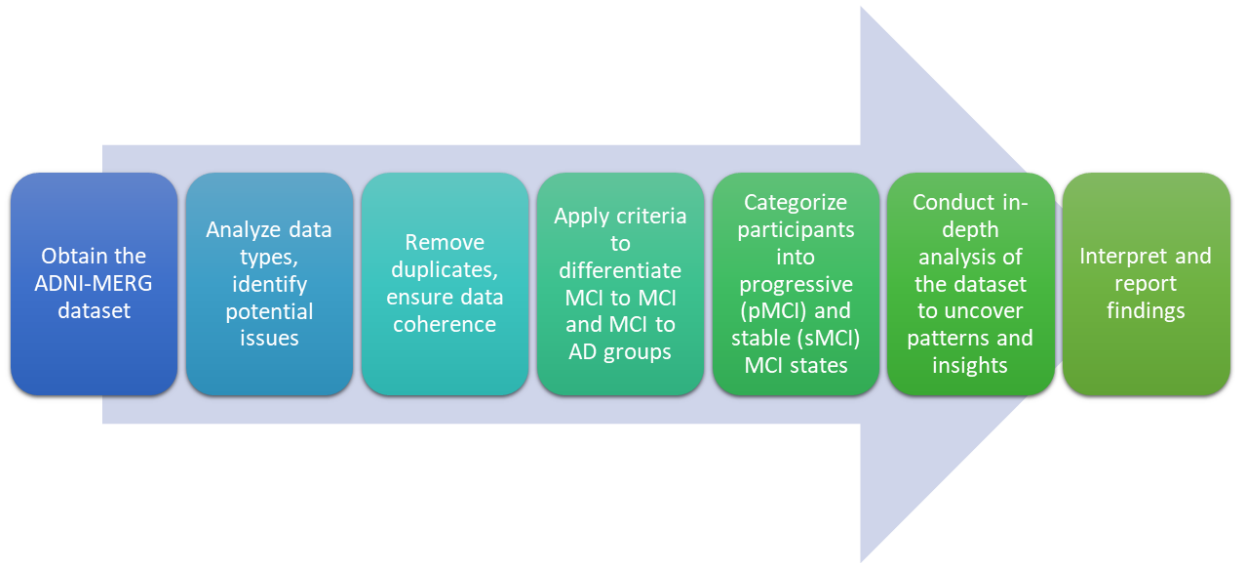


Figure3: Flowchart describing the process of study selection and their relevance to the approach taken in the manuscript

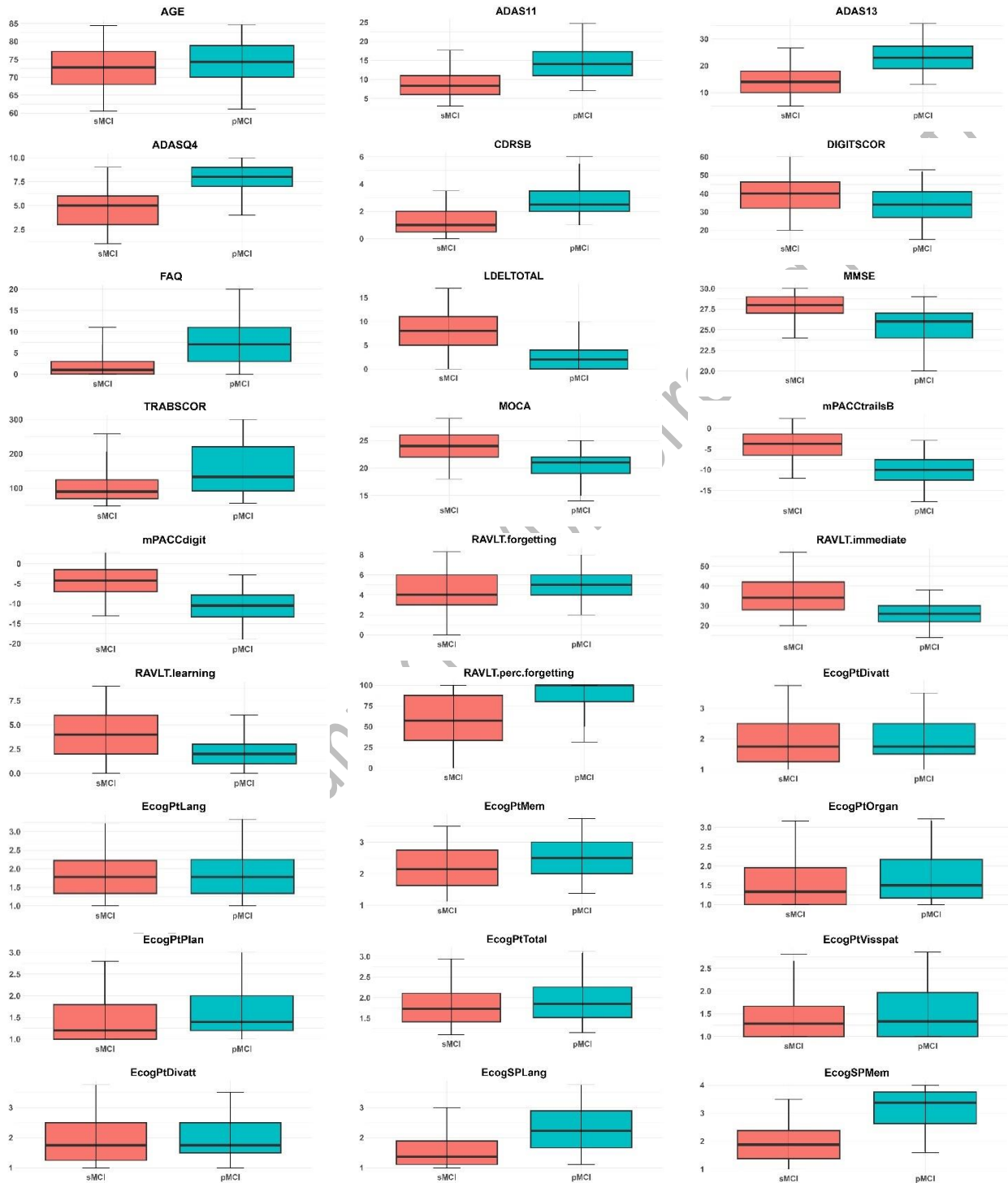
Statistical analyses

In the statistical analysis, we utilized descriptive statistics such as distribution histograms and box plots to compare the cognitive impairment patterns between sMCI and pMCI groups. Employing the Wilcoxon test³⁷ in R version 4, we scrutinized differences in the AUC, setting a stringent significance level (alpha) at 0.005. Our hypothesis testing aimed at detecting significant disparities in AUC, considering values approaching 1 as indicating more statistically significant differences. Ethical considerations guided our research, ensuring informed consent within the ADNI, upholding strict privacy measures, and prioritizing participant confidentiality and welfare throughout the analysis.

Result

In this section, we dedicate our focus to a comprehensive exploration of the ADNI Merge dataset, specifically examining patterns and differences between individuals diagnosed with sMCI and pMCI. Our approach involves meticulous labeling and stratification of the dataset based on these diagnostic categories. The analysis is organized into five key domains that are critical for understanding cognitive impairment: demographics, PET imaging, genotyping, MRI brain analysis, and neurocognitive tests. To facilitate a clear and effective comparison between the sMCI and pMCI groups, we present the data through a comprehensive box plot figure (Figure 4). This visualization illustrates the distribution of key variables across the two groups, highlighting the 5th to 95th percentiles and offering a clear depiction of group mean differences and variability in each domain. These visual aids play a crucial role in revealing

the differences across cognitive, imaging, and genetic measures, enhancing our understanding of the factors that distinguish sMCI from pMCI.



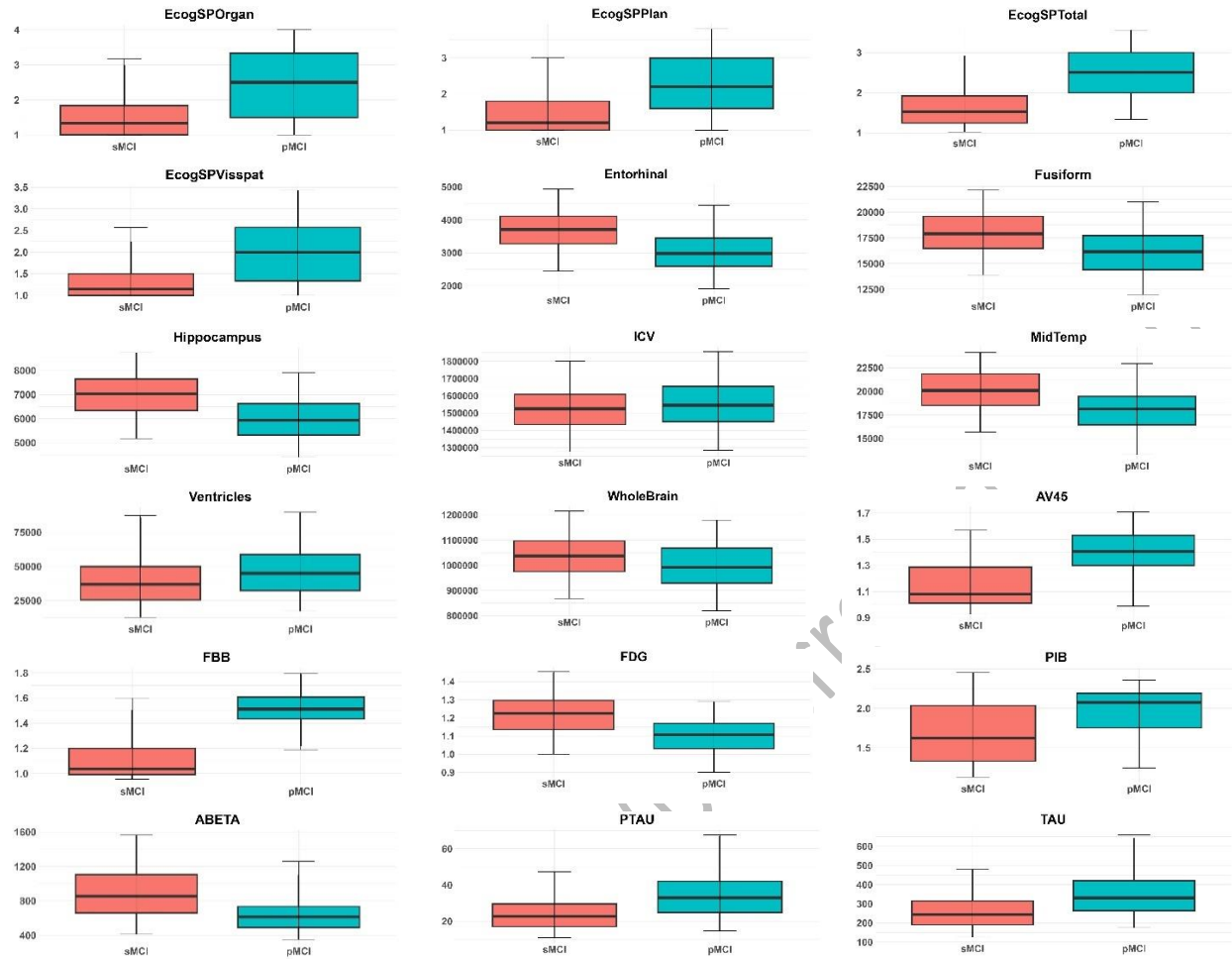


Figure 4: Consolidated box plots for all variables comparing sMCI and pMCI. This figure provides a comparative analysis using box plots for all examined variables, highlighting group mean differences and distributions between sMCI and pMCI, facilitating a comprehensive understanding of group differences.

Following the box plot analysis, we present an extensive statistical evaluation in Table 2, which provides AUC values and corresponding p-values for the key features in the dataset. This table highlights the discriminative power of clinical features between the sMCI and pMCI groups, particularly in cognitive assessments such as mPACtrailsB, ADAS13, and LDELTOTAL, alongside memory-related tasks like RAVLT immediate and RAVLT learning. The high AUC values demonstrate the robust capability of these features to differentiate between cognitive statuses, reinforcing their relevance in understanding cognitive decline and its progression.

Table 2: AUC and p-values analysis for discrimination of features in the ADNI dataset. This table highlights the discriminative power of various features in different categories, with AUC values indicating the accuracy of each metric in differentiating between sMCI and pMCI groups, and p-values assessing statistical significance

Features	AUC	p_value	
Demographic	AGE	0.56	0.005
	PTEDUCAT	0.51	0.356
	PTETHCAT	0.5	0.352
	PTGENDER	0.49	0.53
	PTMARRY	0.49	0.191
	PTRACCAT	0.49	0.023

Features	AUC	p_value	
MRI Brain Analysis	Entorhinal	0.73	0.005
	Fusiform	0.69	0.005
	Hippocampus	0.75	0.005
	ICV	0.54	0.005
	MidTemp	0.71	0.005
	Ventricles	0.6	0.005
	WholeBrain	0.61	0.005

Features	AUC	p_value	
Rey Auditory Verbal Learning Test	immediate	0.77	0.005
	learning	0.72	0.005
	forgetting	0.57	0.005
	perc.forgetting	0.75	0.005

Features	AUC	p_value	
Cognitive Tests	CDRSB	0.8	0.005
	DIGITSCOR	0.63	0.005
	FAQ	0.8	0.005
	LDELTOTAL	0.82	0.005
	MMSE	0.76	0.005
	TRABSCOR	0.67	0.005
	MOCA	0.77	0.005
	mPACctrailsB	0.83	0.005
	mPACCdigit	0.82	0.005

Features	AUC	p_value	
Everyday Cognition Participant Self-Report	EcogPtMem	0.58	0.005
	EcogPtLang	0.5	0.819
	EcogPtVisspat	0.55	0.005
	EcogPtPlan	0.58	0.005
	EcogPtOrgan	0.55	0.001
	EcogPtDivatt	0.49	0.393
	EcogPtTotal	0.55	0.005

Features	AUC	p_value	
Everyday Cognition Study Partner Report	EcogSPMem	0.82	0.005
	EcogSPLang	0.74	0.005
	EcogSPVisspat	0.77	0.005
	EcogSPPlan	0.76	0.005
	EcogSPOrgan	0.76	0.005
	EcogSPDivatt	0.74	0.005
EcogSPTotal	0.81	0.005	

Features	AUC	p_value	
Alzheimer Disease Assessment Scale	ADAS11	0.8	0.005
	ADAS13	0.83	0.005
	ADASQ4	0.82	0.005

Features	AUC	p_value	
Genotyping	ABETA	0.72	0.005
	PTAU	0.72	0.005
	TAU	0.7	0.005

Features	AUC	p_value	
PET Brain Analysis	AV45	0.77	0.005
	FBB	0.84	0.005
	FDG	0.75	0.005
	PIB	0.66	0.015

The subsequent sections will explore the detailed findings for each domain, discussing the specific results and their implications for differentiating between sMCI and pMCI, while providing insights into potential early markers of Alzheimer's disease. In the cognitive assessment domain, a range of tests, including ADAS11, ADAS13, and ADASQ4, demonstrates significant potential in identifying individuals at risk for Alzheimer's disease (AD) within the MCI spectrum. With AUC values of 0.80, 0.83, and 0.82, respectively, these tests effectively differentiate between sMCI and pMCI participants, with the pMCI group consistently showing higher median scores across the board. Other cognitive measures, such as mPACCdigit, mPACctrailsB, FAQ, and LDELTOTAL, further highlight the divergence between the two groups, as evidenced by their non-overlapping distributions. Additionally, TRABSCOR, MMSE, CDRSB, and MOCA provide clear separation between sMCI and pMCI cohorts, underscoring the value of these cognitive variables in differentiating individuals with varying degrees of cognitive impairment. The

RAVLT group also reveals consistent disparities in cognitive function, with individuals in the pMCI group exhibiting greater forgetfulness, lower immediate recall, and more difficulty in learning new information compared to those with sMCI.

In the EcogPt assessments, individuals with sMCI report slightly better performance in memory, language, and planning than those with pMCI. While differences in organization, language, and divided attention are subtle, the overall cognitive functioning, reflected by EcogPtTotal, shows clearer distinctions between the groups. Study partner reports provide stronger evidence of cognitive impairments in individuals with pMCI across multiple domains compared to those with sMCI. AUC values for these assessments range from moderate to good accuracy, suggesting the utility of study partner evaluations in detecting cognitive decline. Both EcogPt and EcogSP total scores indicate cognitive difficulties in the pMCI group, though study partner reports exhibit greater sensitivity in identifying cognitive impairment.

Beyond cognitive tests, analyses of demographic, PET imaging, genotyping, and MRI brain data offer additional insights. Demographic factors, such as age and PTEDUCAT, serve as moderate predictors of cognitive impairment, with AUC values of 0.56 and 0.51, illustrating their limited standalone predictive strength. PET imaging variables, particularly FBB and AV45, emerge as promising markers for distinguishing between sMCI and pMCI, with FBB scores elevated in the pMCI group and AV45 scores declining in the sMCI group, pointing to their utility in monitoring MCI progression. Genotyping variables, including ABETA, PTAU, and TAU, show consistent AUC values around 0.70-0.72, further supporting their relevance in cognitive impairment. Lastly, MRI brain analysis uncovers structural differences between the two groups, with higher Ventricles scores and lower Hippocampus scores in the pMCI group, suggesting potential structural changes associated with cognitive decline, particularly in midbrain regions.

We further employed the Wilcoxon rank-sum test to statistically compare AUC values greater than 0.8 between different diagnostic groups. The results indicated that AUC values exceeding 0.8, with p-values below 0.005, were significantly distinct from each other, confirming meaningful differences in the discriminatory power of these features. Moreover, the statistical significance of these metrics, reflected in low p-values, strengthens the confidence in their ability to differentiate between cognitive statuses. In conclusion, this comprehensive analysis highlights the broad range of features that contribute to the identification and differentiation of cognitive status within the ADNI dataset, offering valuable insights for both future research and potential clinical applications.

Discussion

Decoding ADNI-MERG: Patterns, Implications, and Cognitive Assessment Dynamics

The exhaustive exploration of the ADNI-MERG dataset aimed at understanding patterns among individuals diagnosed with sMCI and pMCI. Our methodology involved meticulous labeling and stratification, enabling a detailed analysis across various domains. Various studies, such as those by Hu et al.²⁸, Gao et al.³⁸, Hu et al.³⁹, and Pandya et al.⁴⁰, report varying ratios of MCI to AD progression (34%, 4%, 35%, and 17.5%, respectively). These disparities may stem from differences in diagnostic criteria, assessment processes, regional variations, and participant backgrounds. However, the collective emphasis on understanding MCI to AD progression underscores the significance of continuous research efforts in this critical domain. The intricate dynamics within the ADNI cohort highlight a nuanced

landscape of cognitive decline. Assessments such as ADAS13, mPACCtrailsB, and FBB exhibit discriminative prowess, emphasizing the importance of diverse tools to capture distinct facets of cognitive impairment. While our analysis focuses on individual features, acknowledging the holistic nature of cognitive decline, it is noteworthy that some studies explore interactions among features, emphasizing the potential benefits of a more comprehensive evaluation^{41,42}. Furthermore, classifying MCI to AD participants into strong and weak categories provides an additional layer of insight, with the strong group representing cases of consistent AD progression and the weak group indicating fewer clear trajectories, which may warrant a focused analysis to understand differing contributing factors.

Comprehensive Insights: Unraveling Cognitive, Demographic, Imaging, and Genetic Factors in Cognitive Impairment

In our study, akin to previous research^{43,44}, MoCA and MMSE scores prove crucial in discerning MCI converters from non-converters. Our study aligns with a systematic review⁴⁵ emphasizing the significance of cognitive tests, such as RAVLT, in predicting dementia with high sensitivity and specificity. The contrasting patterns in participant self-reports and study partner reports highlight the subjective nature of cognitive experiences, offering valuable insights into an individual's perception of cognitive function. Despite modest AUC values for age⁴⁶, education⁴⁷, and marriage status²⁸, our findings concur with established literature, affirming the influential roles of female sex and lower educational levels in facilitating conversion. Demographic factors, though playing a role, have limited standalone predictive strength. The combined influence of age and year of education underscores the intricate relationship between individual characteristics and broader cognitive trends.

Our study demonstrates a significant AUC value of 0.75 for FDG features, aligning with the emphasis on FDG's pivotal role in MCI diagnosis and risk prediction in a related study⁴⁸. Nevertheless, in line with recommendations from another survey⁴⁹, we recognize the imperative of judicious FDG-PET use, especially in cases with less certain risk. The inclusion of neuroimaging biomarkers, such as FBB from PET brain analysis and structural metrics from MRI brain analysis, adds a visual dimension to our understanding. FBB's exceptional discriminative power suggests its potential as a key marker for early detection, aligning with the increasing importance of imaging techniques in identifying cognitive impairment. The presence of White Matter Hyperintensities (WMH) appears linked to dementia progression in older adults with MCI^{50,51}. The resilience of structural metrics, as illustrated by the Hippocampus⁵¹ and Entorhinal⁴¹ in my study, aligns with observations from two supplementary studies. This coherence underscores the essential contribution of alterations in brain structures to cognitive status determination, establishing a pivotal link between neuroimaging and cognitive assessments. Specific genetic differences could influence the chances of MCI advancing to AD⁵². Genotyping variables, including ABETA, PTAU, and TAU, introduce a genetic layer to our exploration. Their consistent relevance implies a shared role in the development of cognitive impairment, suggesting a convergence of various factors contributing to the complexity of cognitive decline.

Navigating Cognitive Complexity for Optimized Clinical Strategies

Comparing the various facets, it becomes clear that no single measure possesses universal discriminatory strength. Instead, a comprehensive understanding of cognitive decline emerges from combined insights from demographics, PET, genotyping, MRI, and neurocognitive tests. The integration

of multiple modalities provides significant advantages, as it captures the diverse aspects of Alzheimer's disease progression, making it more robust than relying solely on individual markers. FBB's prominence in PET brain analysis and the collective strength of certain cognitive assessments indicate potential avenues for prioritizing markers in future diagnostic strategies. However, our approach also presents drawbacks, including the potential for increased complexity and the necessity for comprehensive data that may not always be available in all clinical settings. The need for integrating multiple data types, while advantageous for accuracy, also presents logistical challenges related to data availability, cost, and computational resources. From a clinical perspective, understanding the performance of specific tests in different groups enables targeted and informed decision-making. Clinicians can enhance predictive accuracy by prioritizing assessments with higher AUC values, exemplified by ADASQ4, and mPACtrailsB. The distinction between strong and weak groups plays a pivotal role in the performance of machine learning models. Machine learning models should be trained and validated with careful consideration of these nuances, incorporating a dynamic approach that accounts for the varying strengths of predictors. Focusing on specific features or subsets of the dataset, especially those from the strong group, may enhance model accuracy and reliability. Additionally, addressing potential challenges posed by the weak group, such as employing tailored imputation techniques or adjusting decision thresholds, could further improve the model's predictive capabilities. In summary, the intricate relationships observed among various factors emphasize the necessity for a holistic approach to understanding and addressing cognitive decline. Integrating diverse assessments, along with a nuanced interpretation of subjective and objective measures, forms a foundation for developing targeted interventions and diagnostic strategies tailored to the unique profiles of individuals at different stages of cognitive impairment within the ADNI cohort. The motivation behind this work is to enhance clinical decision-making through a deeper understanding of the predictive power of various markers and to ultimately contribute to more personalized and effective treatment strategies for Alzheimer's disease.

Limitations

It is crucial to recognize the constraints of our study. The modest sample sizes within specific groups may compromise the statistical power required for discerning significant differences, particularly in the context of utilizing AUC for distinctions. As a result, the applicability of our findings to broader populations is circumscribed, necessitating further validation in more extensive cohorts

Suggestions for Future Research

In future studies, a comprehensive strategy entails concurrently analyzing cognitive facets such as all ADAS features or RAVLT scores. Moreover, exploring synergies by combining factors across diverse cognitive dimensions could unveil valuable insights, while understanding the temporal evolution of this conversion process over time remains essential for enhancing our understanding of predictive markers for dementia.

Conclusion

In conclusion, our exploration of the MCI to AD transition underscores the critical importance of a holistic perspective in understanding and addressing cognitive decline. By investigating data from multiple modules including demographics, PET, genotyping, MRI, and neurocognitive tests within the ADNI cohort, we unveiled distinct cognitive patterns distinguishing sMCI from pMCI, encompassing a total of 50 features. The investigation into AUC values for individual features across diverse groups

sheds light on the nuanced predictive potential within the transition from MCI to AD. In the demographic group, features display modest predictive values, suggesting a limited impact of demographic factors on AD prediction, with AUC ranging from 0.49 to 0.56. The MRI and PET groups demonstrate diverse AUC ranges, substantiating their respective performances. In the realm of MRI features, the AUC spans from 0.54 to 0.75, with the Hippocampus exhibiting the highest AUC value. Meanwhile, PET features showcase an AUC range of 0.66 to 0.84, with FBB presenting the highest AUC value in this group. The genotyping group, including features like ABETA and PTAU, falls within an intermediate AUC range of 0.70 to 0.72. In neurocognitive tests, the ADAS group demonstrates robust predictive power (AUC range from 0.80 to 0.83). Diverse AUC values within the cognitive tests group, including CDRSB, FAQ, and mPACtrailsB, collectively enhance predictive capability, with AUC ranging from 0.63 to 0.83. The RAVLT group shows moderate predictive capability, with AUC ranging from 0.57 to 0.77. EcogPT features align with modest predictive capability, with AUC ranging from 0.49 to 0.58. Conversely, the EcogSP group exhibits high individual predictive values, contributing to commendable performance, with AUC ranging from 0.74 to 0.82. Features with high individual predictive power, such as those from neurocognitive tests including the ADAS, cognitive tests, EcogSP, and PET, play pivotal roles in enhancing the overall predictive capability of their respective groups. However, it's essential to note that not all groups exhibit equally strong predictive capabilities. In particular, the demographic and EcogPT groups, characterized by lower individual predictive values, reflect a comparatively modest overall predictive performance. Consequently, this nuanced analysis underscores the varied contributions of different modalities, guiding a refined understanding of the complex interplay between diverse assessments in predicting the MCI to AD transition. These insights contribute to a refined understanding of the intricate interplay between diverse assessments, guiding future research and personalized approaches for early AD diagnosis and intervention strategies.

Data availability statement

The data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu/>). Researchers interested in accessing the data can request it through the ADNI website, following their established procedures. The data are available to qualified investigators for purposes of scientific research, subject to approval and compliance with ADNI data use policies and agreements. Details on how to request and access the ADNI data can be found on the ADNI website or by contacting the ADNI Data Coordinating Center.

Author contributions

Dr. Ahmad Shalbaf, Dr. Reza Shalbaf, and Soheil Zarei contributed equally to the conceptualization, design, and execution of the study. Dr. Ahmad Shalbaf provided valuable guidance and supervision throughout the research process. Zarei conducted data collection, analysis, and interpretation, with input and oversight from Dr. Ahmad Shalbaf and Dr. Reza Shalbaf. All authors actively participated in drafting and revising the manuscript. Dr. Ahmad Shalbaf, Dr. Reza Shalbaf, and Zarei approved the final version of the manuscript and shared accountability for the accuracy and integrity of the work.

Competing interests

The authors declare that they have no competing interests

Ethics Approval declaration

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Acknowledgment

This research is financially supported by " Shahid Beheshti University of Medical Sciences" (Grant No 43007906).

Accepted Manuscript (Uncorrected Proof)

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