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Evaluating the Predictive Power of Cognitive Assessment Tools for Cortical Hypometabolism in Alzheimer's Disease

Mohammad Sadeghi[1,2], BS; Salime Jafari[1,3*], PhD; Hadi Aligholi[4], PhD; Zahra Shayan[5], PhD; Alireza Keshavarz Bahaqiqat[6], BS; and for the Alzheimer's Disease Neuroimaging Initiative

[1] Department of speech therapy, school of Rehabilitation Sciences, Shiraz University of Medical Sciences, Shiraz, Iran.
[2] Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran.
[3] Orthopedic & Rehabilitation Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
[4] Department of Neuroscience, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran.
[5] Department of Biostatistics, School of Medicine, Trauma Research Center, Shiraz University of Medical Science, Shiraz, Iran.
[6] Department of Psychology, Cognitive and Neuroscience research Center (CNRC), Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.

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ABSTRACT

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss and cognitive decline. One of the leading theories explaining AD pathology is the emergence of cortical hypometabolism. This study aimed to investigate the association between cortical hypometabolism and various cognitive assessment tools across the dementia spectrum.

Methods: This cross-sectional and longitudinal study utilized data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), including 1,048 participants: 291 cognitively normal (CN), 579 with mild cognitive impairment (MCI), and 178 with AD. Fluorodeoxyglucose positron emission tomography (FDG-PET) data (as an indicator of hypometabolism) and cognitive assessment scores—including the Alzheimer's Disease Assessment Scale (ADAS11 and ADAS13 subtests), Montreal Cognitive Assessment (MoCA), Everyday Cognition Scale (ECog), and Mini-Mental State Exam (MMSE)—were analyzed. Statistical methods included ANOVA, multiple regression, and ROC/AUC analyses.

Results: Linear regression revealed that ADAS11, ADAS13, and MMSE significantly predicted PET scores in the MCI group ($p=0.002$, $p=0.002$, $p=0.017$, respectively), while MoCA predicted PET scores in the CN group ($\beta=0.016$, $p=0.045$). ROC analysis showed that ADAS13 had the greatest discriminative capacity (AUC=0.786), followed by ADAS11 (AUC=0.767). Over time, PET scores declined significantly across all groups, with the AD group showing the largest decline. At 24 months, PET scores in the CN and MCI groups were notably higher than those in the AD group ($p<0.001$).

Conclusion: ADAS11 and ADAS13 can effectively differentiate between normal and abnormal cortical hypometabolism. Among all cognitive measures, ADAS13 demonstrated the highest discriminative ability, making it a valuable tool for clinicians and researchers in the early detection and longitudinal monitoring of Alzheimer's disease.

*Corresponding author: Salime Jafari; Department of Speech therapy, Orthopedic & Rehabilitation Research Center, Shiraz University of Medical Sciences, Shiraz, Iran, **E-mail:** jafari-s@razi.tums.ac.ir; **Tel:** 00987116271551; **Postal Code:** 7194733669

Introduction

With the rising incidence of Alzheimer's disease (AD), it has become a significant and urgent public health challenge that demands immediate attention from healthcare providers, researchers, and policymakers [1]. AD is a progressive

neurodegenerative disorder predominantly affecting older adults. Its hallmark symptoms include memory loss and cognitive decline. It is now understood that the pathophysiological processes leading to AD dementia begin during a preclinical stage, long before symptoms manifest [2].

A key pathological feature of AD involves the improper metabolism of amyloid-β (Aβ) and tau proteins, resulting in the accumulation of misfolded Aβ plaques extracellularly and intraneuronal neurofibrillary tangles composed of phosphorylated tau (P-tau) protein [3]. Another important theory, which is the focus of the present study, posits that impaired cerebral glucose metabolism—referred to as glucose hypometabolism—may play a critical pathological role in AD.

Hypometabolism, which is believed to be independent of cell loss, typically manifests in at-risk individuals decades before clinical dementia symptoms appear [4]. Integrating data from various studies, researchers have proposed that the progression of hypometabolism depends on the disease stage, with hypometabolism preceding synaptic and neuronal dysfunction, and cognitive decline occurring subsequently [5, 6]. Fluorodeoxyglucose positron emission tomography (FDG-PET) serves as a key imaging modality to measure hypometabolism, which has been linked to cognitive decline and the progression from mild cognitive impairment (MCI) to Alzheimer's disease [7].

Numerous studies comparing FDG-PET scans with cognitive performance have supported the association between abnormal hypometabolism and impairments in memory and cognitive function [8-11]. However, the generalizability of these findings has been limited by challenges such as restricted access to patients at various disease stages and small sample sizes [12-14].

A comprehensive understanding of the impact of hypometabolism across different stages of AD and its interaction with other established biomarkers is critical. Such insights will enhance the clinical utility of PET imaging and facilitate the development of effective therapeutic strategies for AD.

The Alzheimer's Disease Assessment Scale (ADAS), Montreal Cognitive Assessment (MoCA), Everyday Cognition Scale (ECog), and Mini-Mental State Exam (MMSE) are among the most commonly used cognitive scales for assessing individuals with AD [15, 16]. In cognitively normal (CN) older adults, the relationship between cognitive scores and AD biomarkers is complex. However, longitudinal studies suggest that these associations become stronger and more consistent in CN individuals with higher biomarker levels [17].

However, administering multiple tests to evaluate cognitive status in AD patients presents several challenges, including variability in results, time and resource constraints, patient burden, and difficulties in interpreting findings. These variations can obscure the accurate determination of a patient's cognitive status [18, 19]. Despite efforts to standardize cognitive assessment tools, the absence of a universally accepted framework can hinder the interpretation and normalization of results across healthcare settings [20].

Moreover, each test has a unique scoring system and interpretation protocol, making cross-comparison difficult for clinicians. The selection of certain assessments based on healthcare providers' personal preferences or familiarity may also introduce bias in clinical and research evaluations of AD patients. This study seeks to address this knowledge gap by systematically comparing multiple cognitive tests to determine their predictive power for cortical hypometabolism.

We aimed to investigate the relationship between hypometabolism, as measured by FDG-PET, and cognitive function, as assessed by several cognitive tools (ADAS11, ADAS13, MMSE, MoCA, and ECog), using both cross-sectional and longitudinal approaches within the ADNI cohort. Our objective was to evaluate the predictive power of these cognitive assessment tools for cortical hypometabolism. PET assessments and cognitive performance data were analyzed for a subset of participants across the cognitive spectrum, including cognitively normal (CN) individuals and those with mild cognitive impairment (MCI). Furthermore, we examined the hypothesis that hypometabolism and cognitive decline are interrelated by evaluating changes in PET measures (florbetapir and FDG) and cognitive performance over time across three diagnostic groups: CN, MCI, and AD.

Methods

Participants

Data for this cross-sectional and longitudinal study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). The ADNI was launched in 2003 under the leadership of Principal Investigator Michael W. Weiner, MD, as a public–private partnership involving over 50 medical centers and university sites across the United States and Canada [21]. Comprehensive details regarding participant inclusion and exclusion criteria, as well as ethical informed consent procedures, are available on the ADNI website and associated publications. All research activities adhered to ethical standards and complied with the relevant guidelines and regulations outlined by the ADNI study.

In brief, ADNI-1 initially recruited over 800 participants, who underwent cognitive evaluations and serial biomarker assessments every six to twelve months for a period of two to three years. The program later evolved into successive phases, including ADNI-3 (2016–2022), a five-year trial renewal designed to expand longitudinal data collection.

All participants diagnosed with cognitively normal (CN), mild cognitive impairment (MCI), or Alzheimer's disease (AD) from the ADNI database who had available data on FDG-PET hypometabolism and APOE ε4 status were included in this study. For comprehensive analysis, data tables from the ADNI repository were merged to extract demographic information, diagnostic classification (CN, MCI, AD),

FDG-PET hypometabolism measurements (sourced from the UC Berkeley FDG-PET dataset), APOE ε4 allele status, and cognitive assessment scores (ADAS, MoCA, ECog, and MMSE).

Following data integration and quality checks, a total of 1,048 participants met the inclusion criteria, comprising 291 CN participants, 579 with MCI, and 178 with AD.

Cognitive Assessments

The ADAS, MoCA, ECog, and MMSE are widely recognized and validated measures for assessing cognitive and noncognitive behavioral dysfunction across the dementia spectrum, and all were utilized in this study to evaluate participants' cognitive performance.

The ADAS evaluates multiple cognitive domains, including language, memory, orientation, and motor praxis. The developers of ADAS11 and ADAS13 have explained the minor variations between the two versions of this assessment. According to ADAS11 and ADAS13, the final scores range from 0 to 70 and 0 to 85, respectively, with higher scores indicating greater cognitive impairment [22, 23].

The MMSE is a brief screening instrument consisting of a variety of tasks and questions designed to assess cognitive impairment. Higher scores on the MMSE correspond to a better cognitive state, with a total score ranging from 0 to 30 [24]. Cognitive performance in everyday tasks can be assessed using the self-reported ECog test, which evaluates several domains, including executive function, language, memory, and attention. Scores range from 1 to 4, with 1 representing the least severe condition and 4 representing the most severe. Another screening method for MCI detection is the MoCA, which provides a total score ranging from 0 to 30, with scores of 26 or higher considered normal. However, interpretation of scores may vary depending on patient characteristics [25].

FDG-PET Image Acquisition and Processing

The PET imaging data used in this study were obtained from ADNI, with detailed information on image processing available on their website. In brief, the most processed format of FDG-PET imaging data was retrieved from LONI. Additionally, a meta-analysis focused on the keywords *AD*, *MCI*, and *FDG-PET* identified 292 coordinates showing significant differences in FDG uptake among the groups [26]. All coordinates were then converted to MNI space, Z-scores and T-values were calculated, and intensity normalization was performed. The longitudinal map was thresholded at 0.75, and the cross-sectional coordinate map at 0.50, to smooth the intensity map. Five MetaROIs (Left Angular Gyrus, Right Angular Gyrus, Bilateral Posterior Cingulate Gyrus, Left Inferior Temporal Gyrus, and Right Inferior Temporal Gyrus) were identified and binarized, then merged into a single composite region for analysis. This process enabled the identification of regions with consistent hypometabolic patterns.

Statistical Analyses

Using the ANOVA test, cross-sectional comparisons of the CN, MCI, and AD groups' continuous demographic and clinical characteristics (cognitive assessment scores and FDG-PET measurements) were performed. The Chi^2 test was also used to compare APOE4 status and gender. Several multiple regression models with a two-step design were employed to examine the relationship between hypometabolism and cognitive evaluation scores. For each diagnostic category (CN, MCI, AD), we assessed the relationship between these factors and examined each score's predictive power independently for each diagnosis group. In the analysis, all continuous variables were mean-centered. To investigate the interaction between age and other variables, we created nominal variables categorized into three levels: $SD < -1$, $-1 < SD < 1$, and $SD > 1$. This categorization was based on mean-centered age.

The FDG cutoff was developed in a prior study that demonstrated, using receiver operating characteristic analysis, that a mean value of 1.21 from the designated areas of interest was the threshold that best distinguished between ADNI AD patients and normal controls [27]. We employed a similar approach using a linear mixed model with the Restricted Maximum Likelihood (REML) method for the longitudinal analyses. These models incorporated time, age, sex, baseline diagnosis, cognitive scores, and the interaction term between time and cognitive scores to predict hypometabolism. All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0 (Armonk, NY: IBM Corp.). A P-value less than 0.05 was considered statistically significant.

Results

Demographics and Baseline Analyses

Table 1 presents the baseline demographic information of the study population (n = 1048). The cohort consisted of 291 CN individuals (28%), 579 with MCI (55%), and 178 with AD (17%). Significant differences were observed among the groups in terms of age, education, and cognitive assessment scores (ADAS11, ADAS13, MMSE, MoCA, and ECog) ($p < 0.001$). The AD group had a significantly higher prevalence of APOE4 allele positivity (69.1%) compared to the MCI (47.3%) and CN (29.9%) groups.

The mean age of the AD group (74.15 ± 8.22 years) was significantly higher compared to the MCI (71.71 ± 7.46 years) and CN (72.73 ± 6.13 years) groups. Additionally, years of education were significantly lower in the AD group (15.75 years) compared to the MCI (16.15 years) and CN (16.63 years) groups. The AD group performed significantly worse on cognitive assessments (ADAS11, ADAS13, MMSE, MoCA, and ECog scores) compared to both the MCI and CN groups. Potential biases associated with age and education were controlled by including these variables as confounders in the analyses and statistical procedures.

Table 2 presents the results of linear regression analyses examining the relationship between cognitive assessment scores and PET scores, which served as a

marker of brain hypometabolism, while controlling for age, gender, and education. The associations were evaluated separately for each group (CN, MCI, and AD). As previously mentioned, to assess the interaction between age and other variables, new nominal age categories with three levels were created: SD < -1, -1 < SD < 1, and SD > 1. Additionally, all continuous variables were mean-centered.

In the CN group, MoCA was found to be a significant predictor of PET results (β = 0.016, P = 0.045), while no other cognitive measures significantly predicted PET scores.

In the MCI group, poorer performance on ADAS11, ADAS13, and MMSE was significantly associated with lower PET scores, with p-values of 0.002, 0.002, and 0.017, respectively. No other cognitive assessments significantly predicted PET scores in the MCI group.

In the AD group, poorer ADAS11 performance in younger participants was significantly correlated with lower PET scores (p = 0.004). Notably, there was a significant interaction between ADAS13 scores and age; younger subjects (SD < -1) exhibited a stronger negative correlation between ADAS13 score and PET score (β = -0.011, p = 0.004) compared to older subjects (SD = 0) (β = -0.009, p = 0.017).

Receiver Operating Characteristic (ROC) Analysis. Table 3 presents the results of the ROC analysis, which evaluated the ability of cognitive assessments to distinguish between participants with normal and abnormal hypometabolism. Hypometabolism status was defined by a PET score cutoff of 1.21, with scores below 1.21 considered normal and those above as abnormal. All cognitive assessment tests demonstrated significant predictive ability (p ≤ 0.001). Among them, ADAS-13 showed the highest area under the curve (AUC) at 0.786, followed by ADAS-11 (0.767), ECog-Total (0.747), MoCA (0.733), MMSE (0.724), and EcogSpTotal (0.712).

Table 4 summarizes the pairwise comparisons of the AUC values. The analysis revealed that ADAS13 had a significantly larger AUC than all other tests (ADAS-11, MMSE, MoCA, and ECog) (p < 0.01), indicating superior discriminative ability. Additionally, ADAS11 demonstrated significantly better performance compared to the other tests except for ADAS13 (MMSE, MoCA, and Ecog) (p < 0.01). Furthermore, EcogSPTotal showed a significantly larger AUC than EcogSPLang (p < 0.001).

Table 5 presents additional classifier evaluation metrics, including the Gini index and the maximum Kolmogorov-Smirnov (K-S) statistic. These metrics offer further insight into the overall discriminative ability of the cognitive assessments and help identify optimal cutoff values. The ADAS-13 exhibited the highest Gini index (0.57) and maximum K-S statistic (0.467 at a cutoff of 17.665), suggesting that ADAS-13 is the most effective test for differentiating between subjects with normal and abnormal hypometabolism.

Longitudinal Analysis

Table 6 presents the results of the linear mixed-effects regression models for each cognitive assessment in predicting PET score trends over the 24-month study period. The models revealed that the interactions of ADAS11 and ADAS13 with time were significantly associated with changes in PET measures over time (P = 0.049 and P = 0.034, respectively). However, no other interactions between cognitive assessments, time, and age showed significant associations with PET measure changes. Table 7 summarizes the comparison of PET score trends among diagnostic groups over the study period. PET score trends were significantly correlated with baseline diagnosis, time, and the interaction between time and baseline diagnosis (p < 0.001).

Table 8 summarizes the results of pairwise comparisons of PET score trends over time across diagnostic categories. The CN group exhibited a small but significant decrease in PET scores over the 24-month study period (mean difference = 0.019, p = 0.003). Similarly, the MCI group showed a small yet significant decrease (mean difference = 0.028, p < 0.001). In contrast, the AD group experienced a substantially larger decline over time (mean difference = 0.103, p < 0.001)

Table 9 summarizes the results of pairwise comparisons of PET scores between diagnostic groups at each time point (baseline and 24 months). At baseline, the CN group had significantly higher PET scores compared to the AD group (mean difference = 0.190, p < 0.001). Similarly, the MCI group showed significantly higher PET scores than the AD group (mean difference = 0.166, p < 0.001). At the 24-month time point, these differences increased, with the CN group exhibiting significantly higher PET scores than the AD group (mean difference = 0.274, p < 0.001), and the MCI group also showing significantly higher scores compared to the AD group (mean difference = 0.241, p < 0.001). No significant differences were observed between the CN and MCI groups at either baseline or 24 months.

Table 1: Baseline Demographics and Characteristics of the Study Population

	CN (n=291)	MCI (n=579)	AD (n=178)	p-value*
Females	162 (55.7%)	258 (44.6%)	69 (38.8%)	P = 0.001
Males	129 (44.3%)	321 (55.4%)	109 (61.2%)	P = 0.001
APOE4 carrier	87 (29.9%)	274 (47.3%)	123 (69.1%)	P < 0.001
AGE[a]	72.73 (6.13)	71.71 (7.46)	74.15 (8.22)	P = 0.001
Education[a]	16.63 (2.53)	16.15 (2.60)	15.75 (2.62)	P = 0.001
ADAS11	5.66 (2.94)	9.27 (4.33)	20.28 (6.88)	P < 0.001
ADAS13	8.93 (4.39)	14.89 (6.63)	30.55 (8.22)	P < 0.001
MMSE	29.01 (1.22)	28.02 (1.77)	23.09 (2.25)	P < 0.001
MoCA	25.81 (2.42)	23.38 (3.12)	17.25 (4.54)	P < 0.001
EcogPtLang	1.46 (0.42)	1.88 (0.67)	1.87 (0.71)	P < 0.001

	CN (n=291)	MCI (n=579)	AD (n=178)	p-value*
EcogSpLang	1.15 (0.28)	1.66 (0.67)	2.51 (0.80)	P < 0.001
EcogPtTotal	1.41 (0.34)	1.81 (0.56)	1.89 (0.60)	P < 0.001
EcogSpTotal	1.20 (0.29)	1.74 (0.62)	2.75 (0.65)	P < 0.001

Counts and Percentages are reported for sex and APOE4; mean and standard deviation are used for all continuous variables.

CN; Control Normal, MCI; Mild Cognitive Impairment, AD; Alzheimer's Disease, ADAS 11 and ADAS 13; 11 item and 13 item Alzheimer's Disease Assessment Scale, MMSE; Mini Mental State Examination, MoCA; Montreal Cognitive Assessment, EcogPtLang; Patient's self-report of Everyday Cognition Test-Language, EcogSpLang; Study Partner's report of Everyday Cognition Test-Language, EcogPtTotal; Patient's self-report of Everyday Cognition Test-Total, EcogSpLang; Study Partner's report of Everyday Cognition Test-Total.

a. Measured in Years.

* The Chi-Square test was used for nominal variables, and the Welch-ANOVA was used for continuous variables.

Table 2: Linear Regression Analyses for Clinical Tests Predicting Positron Emission Tomography (PET) Scores.

Group	Variables of interest	Adjusted R2	β Coefficients	β Coefficients p-value
	Age SD -1[a]		0.058	P = 0.084
	Age SD 0[a]		0.051	**P = 0.025**
CN	ADAS11	0.032	0.004	P = 0.606
	ADAS11 * Age SD -1		-0.004	P = 0.693
	ADAS11 * Age SD 0		-0.011	P = 0.220
	Age SD -1		0.063	**P = 0.001***
	Age SD 0		0.042	**P = 0.004***
MCI	ADAS11	0.156	-0.009	**P = 0.002***
	ADAS11 * Age SD -1		0.001	P = 0.883
	ADAS11 * Age SD 0		-0.002	P = 0.539
	Age SD -1		-0.105	**P = 0.002***
	Age SD 0		-0.015	P = 0.592
AD	ADAS11	0.229	β < 0.000	P = 0.990
	ADAS11 * Age SD -1		-0.013	**P = 0.004***
	ADAS11 * Age SD 0		-0.010	**P = 0.018**
	Age SD -1		0.050	P = 0.141
	Age SD 0		0.049	**P = 0.040**
CN	ADAS13	0.050	0.001	P = 0.818
	ADAS13 * Age SD -1		-0.004	P = 0.586
	ADAS13 * Age SD 0		-0.007	P = 0.178
	Age SD -1		0.051	**P = 0.006**
	Age SD 0		0.041	**P = 0.005**
MCI	ADAS13	0.183	-0.006	**P = 0.002**
	ADAS13 * Age SD -1		-0.003	P = 0.316
	ADAS13 * Age SD 0		-0.002	P = 0.266
	Age SD -1		-0.105	**P = 0.002**
	Age SD 0		-0.014	P = 0.600
AD	ADAS13	0.250	β < 0.000	P = 0.993
	ADAS13 * Age SD -1		-0.011	**P = 0.004**
	ADAS13 * Age SD 0		-0.009	**P = 0.017**
	Age SD -1		0.033	P = 0.310
	Age SD 0		0.041	P = 0.053
CN	MMSE	0.035	0.021	P = 0.153
	MMSE * Age SD -1		0.020	P = 0.593
	MMSE * Age SD 0		-0.010	P = 0.516
	Age SD -1		0.067	**P < 0.001**
	Age SD 0		0.046	**P = 0.002**
MCI	MMSE	0.100	0.019	**P = 0.017**
	MMSE * Age SD -1		0.004	P = 0.734
	MMSE * Age SD 0		-0.002	P = 0.818
	Age SD -1		-0.097	**P = 0.008**
	Age SD 0		-0.011	P = 0.716
AD	MMSE	0.073	-0.003	P = 0.814
	MMSE * Age SD -1		0.022	P = 0.168
	MMSE * Age SD 0		0.019	P = 0.132
	Age SD -1		0.014	P = 0.672
	Age SD 0		0.028	P = 0.204
CN	MoCA	0.045	0.016	**P = 0.045**
	MoCA * Age SD -1		0.002	P = 0.846
	MoCA * Age SD 0		-0.011	P = 0.186
	Age SD -1		0.076	**P < 0.001**
	Age SD 0		0.050	**P = 0.001**
MCI	MoCA	0.133	0.003	P = 0.456
	MoCA * Age SD -1		0.003	P = 0.629
	MoCA * Age SD 0		0.013	**P = 0.009**
	Age SD -1		-0.096	**P = 0.004**
AD	Age SD 0	0.221	-0.014	P = 0.614
	MoCA		0.005	P = 0.348
	MoCA * Age SD -1		0.012	P = 0.079

Group	Variables of interest	Adjusted R2	β Coefficients	β Coefficients p-value
	MoCA * Age SD 0		0.010	P = 0.100
	Age SD -1		0.045	P = 0.144
	Age SD 0		0.042	P = 0.051
CN	EcogPtLang	0.016	-0.013	P = 0.750
	EcogPtLang * Age SD -1		-0.013	P = 0.847
	EcogPtLang * Age SD 0		0.001	P = 0.990
	Age SD -1		0.085	**P < 0.001**
	Age SD 0		0.053	**P = 0.001**
MCI	EcogPtLang	0.053	0.023	P = 0.272
	EcogPtLang * Age SD -1		-0.008	P = 0.763
	EcogPtLang * Age SD 0		-0.037	P = 0.113
	Age SD -1		-0.108	**P = 0.004**
	Age SD 0		-0.021	P = 0.503
AD	EcogPtLang	0.046	0.050	P = 0.248
	EcogPtLang * Age SD -1		0.011	P = 0.834
	EcogPtLang * Age SD 0		-0.042	P = 0.383
	Age SD -1		0.054	P = 0.107
	Age SD 0		0.046	**P = 0.029**
CN	EcogSpLang	0.020	0.044	P = 0.397
	EcogSpLang * Age SD -1		-0.025	P = 0.891
	EcogSpLang * Age SD 0		-0.074	P = 0.216
	Age SD -1		0.079	**P < 0.001**
	Age SD 0		0.051	**P = 0.001**
MCI	EcogSpLang	0.114	-0.020	P = 0.265
	EcogSpLang * Age SD -1		-0.035	P = 0.180
	EcogSpLang * Age SD 0		-0.038	P = 0.068
	Age SD -1		-0.097	**P = 0.009**
	Age SD 0		-0.010	P = 0.740
AD	EcogSpLang	0.015	-0.008	P = 0.822
	EcogSpLang * Age SD -1		-0.007	P = 0.888
	EcogSpLang * Age SD 0		-0.025	P = 0.534
	Age SD -1		0.049	P = 0.112
	Age SD 0		0.044	**P = 0.044**
CN	EcogPtTotal	0.015	-0.009	P = 0.880
	EcogPtTotal * Age SD -1		-0.004	P = 0.965
	EcogPtTotal * Age SD 0		-0.005	P = 0.940
	Age SD -1		0.086	**P < 0.001**
	Age SD 0		0.051	**P = 0.001**
MCI	EcogPtTotal	0.057	0.027	P = 0.287
	EcogPtTotal * Age SD -1		-0.044	P = 0.176
	EcogPtTotal * Age SD 0		-0.054	P = 0.055
	Age SD -1		-0.112	**P = 0.003**
	Age SD 0		-0.017	P = 0.586
AD	EcogPtTotal	0.060	0.030	P = 0.574
	EcogPtTotal * Age SD -1		0.067	P = 0.316
	EcogPtTotal * Age SD 0		-0.005	P = 0.928
	Age SD -1		0.041	P = 0.194
	Age SD 0		0.045	**P = 0.032**
CN	EcogSpTotal	0.024	0.016	P = 0.792
	EcogSpTotal * Age SD -1		-0.144	P = 0.293
	EcogSpTotal * Age SD 0		-0.052	P = 0.432
	Age SD -1		0.079	**P < 0.001**
	Age SD 0		0.049	**P = 0.001**
MCI	EcogPtTotal	0.139	-0.029	P = 0.150
	EcogSpTotal * Age SD -1		-0.060	**P = 0.032**
	EcogSpTotal * Age SD 0		-0.039	P = 0.092
	Age SD -1		-0.108	**P = 0.004**
	Age SD 0		-0.019	P = 0.526
AD	EcogSpTotal	0.063	-0.062	P = 0.193
	EcogSpTotal * Age SD -1		0.011	P = 0.849
	EcogSpTotal * Age SD 0		0.016	P = 0.758

CN; Control Normal, MCI; Mild Cognitive Impairment, AD; Alzheimer's Disease, ADAS 11 and ADAS 13; 11 item and 13 item Alzheimer's Disease Assessment Scale, MMSE; Mini Mental State Examination, MoCA; Montreal Cognitive Assessment, EcogPtLang; Patient's self-report of Everyday Cognition Test-Language, EcogSpLang; Study Partner's report of Everyday Cognition Test-Language, EcogPtTotal; Patient's self-report of Everyday Cognition Test-Total, EcogSpLang; Study Partner's report of Everyday Cognition Test-Total.
a. Age SD -1; Age less than -1 Standard Deviation, Age SD 0; Age between -1 to +1 Standard Deviation, note that Age more than +1 Standard Deviation is reference level.

Table 3: Receiver Operating Curve Analyses Predicting Hypometabolism

ADAS11		ADAS13		MMSE*		MoCA*	
Area	**p-value**	**Area**	**p-value**	**Area**	**p-value**	**Area**	**p-value**
0.767	P < 0.001	0.786	P < 0.001	0.724	P < 0.001	0.733	P < 0.001

EcogSpLang		EcogSpTotal`	
Area	**p-value**	**Area**	**p-value**
0.712	P < 0.001	0.747	P < 0.001

The Y variable is the PET scores transformed into two categories: positive and negative hypometabolism, using a cut-off score of 1.21.
* Please note that MMSE and MoCA are reversed codded to be comparable with other clinical tests.
ADAS 11 and ADAS 13; 11 item and 13 item Alzheimer's Disease Assessment Scale, MMSE; Mini Mental State Examination, MoCA; Montreal Cognitive Assessment, EcogPtLang; Patient's self-report of Everyday Cognition Test-Language, EcogSpLang; Study Partner's report of Everyday Cognition Test-Language, EcogPtTotal; Patient's self-report of Everyday Cognition Test-Total, EcogSpLang; Study Partner's report of Everyday Cognition Test-Total.

ADAS11		ADAS13		MMSE*		MoCA*	
Area	**p-value**	**Area**	**p-value**	**Area**	**p-value**	**Area**	**p-value**
0.767	P < 0.001	0.786	P < 0.001	0.724	P < 0.001	0.733	P < 0.001
EcogSpLang		**EcogSpTotal`**					
Area	**p-value**	**Area**	**p-value**				
0.712	P < 0.001	0.747	P < 0.001				

The Y variable is the PET scores transformed into two categories: positive and negative hypometabolism, using a cut-off score of 1.21.
* Please note that MMSE and MoCA are reversed codded to be comparable with other clinical tests.
ADAS 11 and ADAS 13; 11 item and 13 item Alzheimer's Disease Assessment Scale, MMSE; Mini Mental State Examination, MoCA; Montreal Cognitive Assessment, EcogPtLang; Patient's self-report of Everyday Cognition Test-Language, EcogSpLang; Study Partner's report of Everyday Cognition Test-Language, EcogPtTotal; Patient's self-report of Everyday Cognition Test-Total, EcogSpLang; Study Partner's report of Everyday Cognition Test-Total.

Table 4: Paired-Sample Area Difference Under the ROC Curves

Test Result Pair(s)*	z	P value	AUC Difference
ADAS11 - ADAS13	-4.437	**P < 0.001**	-0.019
ADAS11 - MMSE	2.961	**P = 0.003**	0.043
ADAS11 - MOCA	2.597	**P = 0.009**	0.034
ADAS11 - EcogSPLang	3.378	**P = 0.001**	0.055
ADAS11 - EcogSPTotal	1.332	P = 0.183	0.020
ADAS13 - MMSE	4.352	**P < 0.001**	0.062
ADAS13 - MOCA	4.214	**P < 0.001**	0.053
ADAS13 - EcogSPLang	4.628	**P < 0.001**	0.074
ADAS13 - EcogSPTotal	2.662	**P = 0.008**	0.039
MMSE - MOCA	-0.601	P = 0.548	-0.009
MMSE - EcogSPLang	0.646	P = 0.518	0.012
MMSE - EcogSPTotal	-1.357	P = 0.175	-0.023
MOCA - EcogSPLang	1.227	P = 0.220	0.021
MOCA - EcogSPTotal	-0.877	P = 0.381	-0.014
EcogSPLang - EcogSPTotal	-4.158	**P < 0.001**	-0.035

* Please note that MMSE and MoCA scores are reversed codded to be comparable with other clinical tests.
ADAS 11 and ADAS 13; 11 item and 13 item Alzheimer's Disease Assessment Scale, MMSE; Mini Mental State Examination, MoCA; Montreal Cognitive Assessment, EcogPtLang; Patient's self-report of Everyday Cognition Test-Language, EcogSpLang; Study Partner's report of Everyday Cognition Test-Language, EcogPtTotal; Patient's self-report of Everyday Cognition Test-Total, EcogSpLang; Study Partner's report of Everyday Cognition Test-Total.

Table 5: Classifier Evaluation Metrics

Test Result Variable(s)	Gini Index	K-S Statistics	
		Max K-S[a]	Cutoff[b]
ADAS11	0.534	0.430	10.5000
ADAS13	0.571	0.467	17.6650
MMSE_Reversed	0.447	0.381	19.5000
MOCA_Reversed	0.465	0.349	13.5000
EcogSPLang	0.424	0.326	1.6458
EcogSPTotal	0.494	0.388	1.5922

a. The maximum Kolmogorov-Smirnov (K-S) metric.
b. In case of multiple cutoff values associated with Max K-S, the largest one is reported.

Table 6: Linear Mixed Regression Analyses for each Clinical Test Positron Emission Tomography (PET) Score over the Study Period.

Parameter[a]	F	Sig.
ADAS11	0.447	P = 0.504
Time	59.953	**P < 0.001**
Time * ADAS11	3.887	**P = 0.049**
ADAS11* DoB Ce SD	0.849	P = 0.357
Time * DoB Ce SD * ADAS11	1.265	P = 0.262
ADAS13	0.242	P = 0.623
Time	58.357	**P < 0.001**
Time * ADAS13	4.553	**P = 0.034**
ADAS13 * DoB Ce SD	2.072	P = 0.150
Time * DoB Ce SD * ADAS13	1.519	P = 0.219
MMSE	0.125	P = 0.723

Parameter[a]	F	Sig.
Time	63.209	**P < 0.001**
Time * MMSE	1.766	P = 0.185
MMSE * DoB Ce SD	0.194	P = 0.660
Time * DoB Ce SD * MMSE	0.053	P = 0.818
MoCA	1.547	P = 0.214
Time	62.425	**P < 0.001**
Time * MoCA	1.829	P = 0.177
MoCA * DoB Ce SD	0.383	P = 0.536
Time * DoB Ce SD * MoCA	0.084	P = 0.772
EcogPtLang	0.027	P = 0.870
Time	56.043	**P < 0.001**
Time * EcogPtLang	1.446	P = 0.230
EcogPtLang * DoB Ce SD	0.105	P = 0.746
Time * DoB Ce SD * EcogPtLang	0.615	P = 0.434
EcogSpLang	0.057	P = 0.811
Time	58.386	**P < 0.001**
Time * EcogSpLang	1.048	P = 0.338
EcogSpLang * DoB Ce SD	1.048	P = 0.306
Time * DoB Ce SD * EcogSpLang	0.007	P = 0.932
EcogPtTotal	0.040	P = 0.842
Time	55.387	**P < 0.001**
Time * EcogPtTotal	1.048	P = 0.338
EcogPtTotal * DoB Ce SD	0.295	P = 0.587
Time * DoB Ce SD * EcogPtTotal	0.038	P = 0.845
EcogSpTotal	0.071	P = 0.790
Time	61.162	**P < 0.001**
Time * EcogPtTotal	1.878	P = 0.171
EcogPtTotal * DoB Ce SD	2.939	P = 0.087
Time * DoB Ce SD * EcogPtTotal	0.142	P = 0.706

a. Gender and Base line diagnosis are also included in the model to control their effect, though not reported as their effect is not of this research's interest.
ADAS 11 and ADAS 13; 11 item and 13 item Alzheimer's Disease Assessment Scale, MMSE; Mini Mental State Examination, MoCA; Montreal Cognitive Assessment, EcogPtLang; Patient's self-report of Everyday Cognition Test-Language, EcogSpLang; Study Partner's report of Everyday Cognition Test-Language, EcogPtTotal; Patient's self-report of Everyday Cognition Test-Total, EcogSpLang; Study Partner's report of Everyday Cognition Test-Total, "DoB Ce SD"; Mean centered Date of birth coded into a nominal variable using Standard Deviation.

Table 7: Comparison of Positron Emission Tomography (PET) Score Trends between the Diagnosis Groups over Study Period

Parameter[a]	F	Sig.
Baseline Diagnosis	29.18	**P < 0.001**
ime	71.46	**P < 0.001**
Time * Baseline Diagnosis	11.87	**P < 0.001**

a. Age, Gender are also included in the model to control their effect, though not reported as their effect is not of this research's interest.
CN; Control Normal, MCI; Mild Cognitive Impairment, AD; Alzheimer's Disease.

Table 8: Pairwise Comparison of Positron Emission Tomography (PET) score Trends between the Diagnosis Groups over the Study Period.

Diagnosis	Time	Mean of (I)	Mean of (J)	Mean difference (I-J)	Sig.
CN	**BL- M24**	1.285	1.265	0.019	**P = 0.003**
MCI	**BL- M24**	1.261	1.233	0.028	**P < 0.001**
AD	**BL- M24**	1.095	0.992	0.103	**P < 0.001**

Age, Gender and diagnosis are also included in the model to control their effect, though not reported as their effect is not of this research's interest.
CN; Control Normal, MCI; Mild Cognitive Impairment, AD; Alzheimer's Disease.

Table 9: Pairwise Comparison of Positron emission Tomography (PET) Scores between the Diagnosis Groups in each Time Point.

Time	Diagnosis	Mean of (I)	Mean of (J)	Mean Difference (I-J)	Sig.
Baseline	CN-MCI	1.285	1.261	0.025	P = 0.236
	CN-AD	1.285	1.095	0.190	**P < 0.001**
	MCI-AD	1.261	1.095	0.166	**P < 0.001**
Month 24	CN-MCI	1.265	1.233	0.033	P = 0.133
	CN-AD	1.265	0.992	0.274	**P < 0.001**
	MCI-AD	1.233	0.992	0.241	**P < 0.001**

Age, Gender and diagnosis are also included in the model to control their effect, though not reported as their effect is not of this research's interest.
CN; Control Normal, MCI; Mild Cognitive Impairment, AD; Alzheimer's Disease.

Discussion

In the current study, we aimed to examine the associations between cortical hypometabolism measured by FDG-PET and cognitive assessment tools

in CN, MCI, and AD groups. Our findings suggest that reduced brain metabolism (hypometabolism), indicated by lower PET scores, is cross-sectionally associated with poorer performance on various cognitive tests in the MCI and AD groups. This implies that metabolic changes occur before the onset of overt clinical symptoms. In the CN group, the only test that significantly predicted PET scores was the MoCA, highlighting its potential for detecting subtle cognitive changes in the early and preclinical stages of AD. This finding aligns with previous studies that report moderate sensitivity of the MoCA for monitoring cognitive changes in early AD [28-30]. Interestingly, ADAS13 demonstrated better predictive power in younger AD patients, which may reflect different pathophysiological mechanisms in this subgroup, where cognitive decline might be more directly related to synaptic dysfunction and metabolic alterations. This suggests that ADAS13 could be particularly useful for detecting AD at earlier stages in younger individuals [31].

Significant differences between the demographic groups (CN, MCI, and AD) and cognitive test results are consistent with the well-established nature of AD and its progression, in which cognitive deficits become more pronounced as the disease advances [32, 33]. The AD group was significantly older, had fewer years of education, and performed the poorest on cognitive assessments. By controlling for these variables as confounding factors in the analyses and statistical methods, potential biases related to age and education were minimized.

Using a larger cohort and a wider range of updated cognitive tests than prior studies, this study thoroughly investigated the discriminative capacity of cognitive assessment tools to distinguish individuals with normal and abnormal hypometabolism. The ADAS13 emerged as the best overall test, demonstrating the largest AUC, highest Gini index, and maximum K-S statistic. This indicates that ADAS13 may be the most useful cognitive test for detecting metabolic changes associated with the Alzheimer's dementia spectrum. Previous research has also demonstrated the high reliability of using ADAS13 in conjunction with CDR-SB at an optimal cutoff point to categorize MCI patients into high- and low-risk groups for AD conversion [34]. It has also been shown that ADAS13 was the second-best cognitive assessment tool, after CDR, for predicting early AD [35]. This may be beneficial for clinicians and researchers in identifying appropriate testing tools to detect early MCI and AD. These cognitive assessment tools could also serve as suitable additions or alternatives to expensive or invasive assessment methods, such as PET imaging or CSF evaluations. Our findings are consistent with previous studies assessing the predictive potential of cognitive tests [36-38].

The longitudinal analyses showed that changes in FDG-PET scores over the 24-month study period were again associated with ADAS11 and ADAS13. This suggests that these cognitive tests may be useful for tracking and monitoring changes in brain metabolism as the disease progresses. The CN and MCI groups showing a small but significant decrease in PET scores compared to the AD group highlight the importance of staging the disease when interpreting cognitive and imaging changes [39].

The current study benefits from several strengths that increase the validity of the findings. First, the large cohort size, compared to other studies, was made possible through the ADNI, providing substantial statistical power to examine the relationship between hypometabolism and cognitive assessments across the AD spectrum. Additionally, the longitudinal design of the study allowed for the investigation of changes over time, which is crucial for understanding the dynamic nature of AD. Another strength is the inclusion of multiple assessment tools, including ADAS, MMSE, MoCA, and ECog. Comparing the predictive ability of these tests concerning hypometabolism and FDG-PET scores enabled us to highlight the relative strengths and weaknesses of each assessment tool. Moreover, the use of standardized PET-FDG processing techniques to identify hypometabolic regions enhances the reliability and reproducibility of the neuroimaging findings.

We had some limitations that should be considered when interpreting the findings of our study. First, the cross-sectional nature of some of the analyses, such as the comparison between subgroups of CN, MCI, and AD, limits our ability to infer causality in the relationships between hypometabolism (PET scores) and cognitive deficits. Although the longitudinal analysis helps address this issue, longer follow-up periods would improve our understanding of the dynamics of these changes. Another limitation is our study's reliance on a single neuroimaging modality to assess brain metabolism. While this method is extensively used and validated in AD research, incorporating structural MRI or tau-PET could provide additional insights. Finally, we did not examine in depth the interactions between APOE allele positivity, cognitive assessments, and hypometabolism.

Conclusion

This study provides insight into the association between cortical hypometabolism and cognitive assessment tests in the Alzheimer's dementia spectrum. Our results demonstrate a correlation between poor performance on specific cognitive tests and decreased brain metabolism. Notably, the findings highlight the potential utility of ADAS13 for early identification and monitoring of AD in both clinical and research settings, as it demonstrated the strongest discriminative ability for detecting abnormal cortical hypometabolism. Longer follow-up periods and multimodal imaging strategies are recommended for future studies to understand the dynamic changes in

AD better and to enhance monitoring and diagnostic tools.

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Data Availability

Data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu).

Conflict of Interest: The authors declare no conflicts of interest.

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