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Silhouettes, number Location, and cube analysis tests from the VOSP battery reveal visual object and space perception deficits in early Alzheimer's disease

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The Visual Object and Space Perception Battery (VOSP) is a widely used tool for evaluating higher visual processing. However, limited information exists regarding its diagnostic utility in differentiating mild cognitive impairment (MCI) and mild dementia (MD) due to Alzheimer's disease (AD) from cognitively normal older adults (CG). This study aimed to evaluate VOSP tests for object perception (silhouettes) and space perception (number location and cube analysis) as diagnostic tools for the early detection of AD. This study included 81 participants (28 with MD, 27 with MCI, and 26 in the CG). Our findings indicate that performance on the silhouettes, number location, and cube analysis tests showed good diagnostic properties in distinguishing CG from individuals with MCI or MD: AUC = 0.8, 0.79, and 0.82, respectively. Incorporating number location or cube analysis results into a multinomial regression model that included sex, age, education, and ADAS-Cog 13 scores improved correctly classified CG, MCI, and MD cases (from 76.5% to 80.2%). These results confirm that silhouettes, number location, and cube analysis tasks are suitable as additional tools for early diagnosis of AD, and space perception tasks improve diagnostic accuracy.

Keywords Alzheimer's disease, Cube analysis, Mild cognitive impairment, Number location, Silhouettes, VOSP

The pathological processes of Alzheimer's disease (AD) begin many years before individuals exhibit any symptoms[1]. Patients with AD who survive from 70 to 80 years of age typically experience the severe stage of the disease for approximately 40% of that decade[2]. The period from the onset of AD neuropathological changes to the severe stage presents a critical window for early identification, enabling patients and medical professionals to mitigate risks and manage the condition, including utilizing recent advancements in AD diagnostic tools and therapeutic interventions[3].

According to the National Memory Service Audit in England, the use of in vivo indicators of AD-related brain abnormalities (such as cerebrospinal fluid (CSF) analysis) remains limited, and the actual number of patients referred for these investigations in the audit was very low[4]. Disclosing AD biomarker results to patients without clinical evaluation and proper counseling can be detrimental[5]. The Revised criteria for the diagnosis and staging of AD, released in 2024 by the Alzheimer's Association Workgroup, do not endorse the routine clinical assessment of AD-related biomarkers in asymptomatic individuals. Such evaluations are currently recommended only within the framework of observational or interventional studies[6].

Cognitive testing remains essential; however, no single cognitive test is ideal for detecting the earliest stages of AD. Recent studies have provided growing evidence that visual perception is a promising noninvasive marker[7,8]. Fundamental aspects of visual perception include light perception, sensitivity to contrast, orientation of stimuli, visual acuity, and the ability to detect form, color, movement, and depth[9,10]. The gradual integration of visual data into the visual association cortex occurs through two principal pathways: the ventral stream, which identifies "what" is seen, and the dorsal stream, which determines "where" objects are located in space[11]. The rationale for utilizing visual perception and visuospatial tests for early AD detection is based on structural and functional changes in the parietal and temporal lobes early in the disease course[12,13]. Memon et al. recently

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	CG ($N=26$)	MCI ($N=27$)	MD ($N=28$)	Statistics ($\chi^2(2)$ /H(2), p)
Female (%)*	12 (46%)	19 (70%)	18 (64%)	3.09, 0.21
Age*	73 (9)	75 (11)	77 (9)	4.63, 0.10
Years of education*	16 (1)	15 (4)	15 (3)	4.37, 0.11
GDS*	4 (2)	5 (1)	4 (2)	1.40, 0.50
HIS*	1 (1)	1 (1)	1 (1)	1.84, 0.40

Table 1. Demographic and clinical data of the participants. The data are represented as median and interquartile range, except where otherwise noted. *Groups did not differ significantly. MD, mild dementia; MCI, mild cognitive impairment; CG, control group; GDS, Geriatric Depression Scale; HIS, Hachinski Ischemic Score.

	CG ($N=26$)	MCI ($N=27$)	MD ($N=28$)	Statistics (H(2), p)
MMSE*	29 (1)	25 (3)	22 (2)	72.02, < 0.001
ADAS-Cog 13*	12.5 (5.67)	22 (7.66)	31 (7.5)	74.26, < 0.001
CDR-SB*	0 (0)	1.5 (1)	4.5 (0.5)	53.07, < 0.001

Table 2. Cognitive tests results of the participants. The data are represented as median and interquartile range. *All three groups differed significantly. MD, mild dementia; MCI, mild cognitive impairment; CG, control group.

reported a connection between visual function and changes in AD biomarkers[14]. Visual perceptive ability and its deterioration in AD warrant particular attention, given the considerable adverse effects on the quality of life of patients[15]. However, neuropsychological tests evaluating overall cognition are predominantly verbal, with visual perception comprising only a minor component of the evaluation[16].

The Visual Object and Space Perception Battery (VOSP) serves as a common assessment tool for evaluating higher visual processing and consists of eight tests: four for visual object perception (incomplete letters, silhouettes, object decisions, and progressive silhouettes) and four for visual space perception (dot counting, position discrimination, number location, and cube analysis)[17]. The VOSP is easy to administer and is a paper-based battery that does not rely on language skills or motor abilities[17]. However, implementing the complete set of tasks is time-intensive, and typically, only a few or single tests are employed. Notably, object perception VOSP test results should be interpreted with caution, especially for Test 3 (object decision), as individuals with low visual acuity have an increased likelihood of scoring below the cutoff point owing to their visual limitations[18]. Quental et al. emphasized that the VOSP battery is a highly effective instrument for identifying visuospatial impairments in patients with mild dementia (MD) due to AD, with minimal interference from other cognitive domains[19]. According to this study, the silhouettes test demonstrated the most favorable diagnostic properties among object perception tests, with an area under the curve of 0.859, whereas other object perception tests scored below 0.8[19]. Additionally, the number location and cube analysis tests demonstrated the highest diagnostic accuracy in spatial perception assessments[19]. In our research, we selected VOSP tests that have also been identified in recent studies as potential measures for predicting the progression from MCI to AD or for predicting the pathological diagnosis of AD[20–22]. Nevertheless, limited information exists regarding its diagnostic properties in differentiating mild cognitive impairment (MCI) due to AD from cognitively normal older adults. These data would be valuable for disease-modifying treatment studies and clinical practice.

This study aimed to evaluate the VOSP tests for object (silhouettes) and space (number location, and cube analysis) perceptions as diagnostic tools for the early detection of AD. In addition, we assessed their diagnostic properties and relationships with other cognitive test results.

Results

The analysis revealed no statistically significant differences in sex distribution between the three groups (chi-squared test, $p > 0.05$). Similarly, no significant differences were observed in educational background, age, depressive symptoms (as measured by the Geriatric Depression Scale), or Hachinski ischemic scores (Kruskal–Wallis $p > 0.05$). A comprehensive summary of the demographic and clinical data of the study participants is presented in Table 1.

Significant differences were observed in cognitive test results between the three groups (Kruskal–Wallis $p < 0.05$). The results of the cognitive tests are presented in Table 2.

Object perception: silhouettes

One-way analysis of variance (ANOVA) revealed significant differences in silhouettes test scores (mean and standard deviation: CG, 18.77 ± 5.64; MCI, 13.44 ± 4.85; MD, 12.07 ± 4.06; $F = 14.06$, $p < 0.001$). Post-hoc testing indicated significant differences between the CG and MCI groups as well as the CG and MD groups ($p < 0.001$ for both). However, no significant differences were observed between the MCI and MD groups ($p = 0.90$).

The silhouettes test consists of two components: the identification of 15 animals and 15 inanimate objects. Both components demonstrated statistically significant differences between the CG and MCI groups as well as the CG and MD groups. However, no significant differences were observed between the MCI and MD groups (one-way ANOVA for naming animals: $F = 11.49$, $p < 0.001$; CG vs. MCI, $p = 0.002$; CG vs. MD, $p < 0.001$; and MCI vs. MD, $p = 1$; one-way ANOVA for naming inanimate objects: $F = 9.65$, $p < 0.001$; CG vs. MCI, $p = 0.004$; CG vs. MD, $p < 0.001$; and MCI vs. MD, $p = 1$).

In the sample comprising all participants, silhouettes test scores demonstrated a moderate correlation with mini-mental state examination (MMSE) (Spearman's rho: 0.477; $p < 0.001$), clinical dementia rating–sum of boxes (CDR-SB) (Spearman's rho: -0.437; $p < 0.001$), The 13-item version of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 13) (Spearman's rho: -0.479; $p < 0.001$), and age (Spearman's rho: -0.404; $p < 0.001$), while a weak correlation was observed with education (Spearman's rho: 0.295; $p = 0.007$).

Multiple linear regression models were employed to assess whether silhouettes test scores could be predicted using cognitive test results. These models incorporated cognitive test scores (MMSE, CDR-SB, and ADAS-Cog 13) and were adjusted for sex, age, and education.

The adjusted models demonstrated statistical significance in the multiple linear regression analysis for MMSE ($R^2 = 0.489$, $F = 20.12$, $\beta = 0.381$, $p < 0.001$), ADAS-Cog 13 ($R^2 = 0.492$, $F = 20.38$, $\beta = -0.4$, $p < 0.001$), and CDR-SB ($R^2 = 0.444$, $F = 16.99$, $\beta = -0.316$, $p < 0.001$).

To assess the effectiveness of silhouettes test scores in distinguishing between the CG and patients with AD, including those with MCI or MD, as well as patients with MCI and MD, receiver operating characteristic (ROC) curve analysis was conducted. The ROC curves illustrating the silhouettes test performance for differentiating between participant groups are shown in Fig. 1.

A threshold score ≤ 16 on the silhouettes test was established as an indicator of AD (sensitivity 78%, specificity 73%, maximum Youden's $J = 0.51$). When applied to distinguish AD patients (including those with MCI or MD

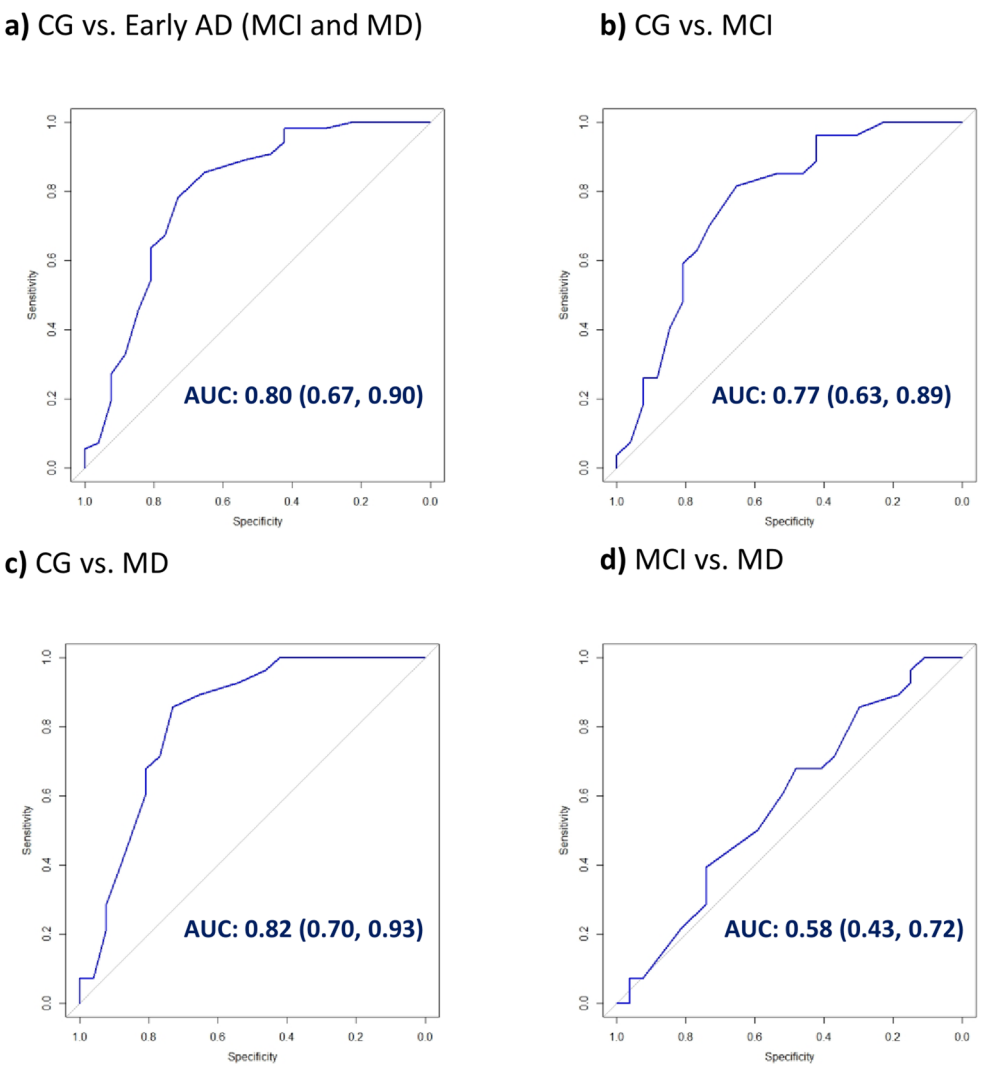

Fig. 1. Performance of the silhouettes test in differentiating between participants with AD from the CG. AD, Alzheimer's disease; CG, control group; MD, mild dementia; MCI, mild cognitive impairment.

due to AD) from CG participants, the silhouettes test demonstrated a sensitivity of 78.18% (95% CI: 64.99–88.19) and specificity of 73.08% (95% CI: 52.21–88.43%). Furthermore, the test yielded a negative predictive value of 61.29% (95% CI: 47.69–73.33%) and positive predictive value of 86% (95% CI: 76.26–92.16%). The overall accuracy of diagnosis was 76.54% (95% CI: 65.82–85.25%). A threshold score ≤ 13 on the silhouettes test was established for differentiating MCI from MD (sensitivity 68%, specificity 48%, maximum Youden's J = 0.16). All cutoff scores and diagnostic properties of the silhouettes test for comparisons between the diagnostic groups are presented in Table 3.

To examine the influence of predictor variables on group classification (CG, MCI, and MD), a multinomial logistic regression analysis was conducted. Initially, a model incorporating sex, age, education, and ADAS-Cog 13 scores as predictors was developed. The inclusion of these variables significantly enhanced the fit of the model compared to the intercept-only model ($X^2 = 87.79$, $p < 0.001$; Nagelkerke $R^2 = 0.744$). This model accurately classified 76.5% of cases overall, with correct classification rates of 92.3% for CG, 66.7% for MCI, and 71.4% for MD. Among the predictors, the ADAS-Cog 13 score emerged as the most robust and statistically significant ($X^2 = 78.83$, $p < 0.001$).

A second model incorporating sex, age, education, ADAS-Cog 13 scores, and silhouettes test scores demonstrated a notable enhancement in fit compared to a null model ($X^2 = 88.30$, $p < 0.001$; Nagelkerke $R^2 = 0.747$). This model accurately classified 76.4% of cases overall, with specific accuracies of 92.3% for CG, 63% for MCI, and 75% for MD. Within this model, ADAS-Cog 13 emerged as a robust and statistically significant predictor (X^2 61.77; $p < 0.001$), whereas the silhouettes test was not a significant predictor (X^2 0.465; $p = 0.793$).

Space perception: number location

Significant differences were observed in the number location test scores across the three groups. The median and interquartile ranges were as follows: CG, 9.5 (2); MCI, 8 (3); and MD, 6 (6). A Kruskal-Wallis test ($p < 0.001$) and subsequent post hoc analysis revealed statistically significant differences between all group pairs: CG versus MCI ($p = 0.007$), MCI versus MD ($p = 0.007$), and CG versus MD ($p < 0.001$).

A moderate correlation was observed between number location test scores and performance on the MMSE (Spearman's rho: 0.573; $p < 0.001$), CDR-SB (Spearman's rho: -0.5; $p < 0.001$), and ADAS-Cog 13 (Spearman's rho: -0.467; $p < 0.001$). No significant correlations were observed with age and education.

Multiple linear regression models were employed to assess whether silhouettes test scores could be predicted using cognitive test results. These models incorporated cognitive test scores (MMSE, CDR-SB, and ADAS-Cog 13) and were adjusted for sex, age, and education.

The adjusted models demonstrated statistical significance in the multiple linear regression analysis with MMSE ($R^2 = 0.384$, $F = 13.47$, $\beta = 0.483$, $p < 0.001$), ADAS-Cog 13 ($R^2 = 0.288$, $F = 9.08$, $\beta = -0.383$, $p < 0.001$), and CDR-SB ($R^2 = 0.364$, $F = 12.46$, $\beta = -0.46$, $p < 0.001$).

To assess the effectiveness of the number location test score in distinguishing between the CG and patients with AD, including those with MCI or MD, as well as patients with MCI and MD, ROC curve analysis was conducted. The ROC curves illustrating the number location test performance for differentiating participant groups are shown in Fig. 2.

A threshold score ≤ 8 on the number location test was established to indicate AD (sensitivity 65%, specificity 73%, maximum Youden's J = 0.39). When applied to distinguish patients with AD (including those with MCI or MD due to AD) from CG participants, the number location test demonstrated a sensitivity of 65.45% (95% CI: 51.42–77.76) and specificity of 73.08% (95% CI: 52.21–88.43%). Furthermore, the test yielded a negative predictive value of 50% (95% CI: 39.36–60.64%) and positive predictive value of 83.72% (95% CI: 72.63–90.88%). The overall accuracy of diagnosis was 67.9% (95% CI: 56.60–77.85%). A threshold score ≤ 7 on the number location test was established for differentiating MCI from MD (sensitivity 71%, specificity 67%, maximum Youden's J = 0.38). All cut-off scores and diagnostic properties of the number location test for comparisons between the diagnostic groups are presented in Table 4.

To examine the influence of predictor variables on group classification (CG, MCI, and MD), a multinomial logistic regression analysis was conducted. Initially, a model incorporating sex, age, education, and ADAS-Cog 13 scores as predictors was developed. Including these variables significantly enhanced the fit of the model

	CG vs. early AD (MCI and MD), cut-off ≤ 16	CG vs. MCI, cut-off ≤ 16	CG vs. MD, cut-off ≤ 16	MCI vs. MD, cut-off ≤ 13
Sensitivity	78.18% (64.99–88.19%)	70.37% (49.82–86.25%)	85.71% (67.33–95.97%)	67.86% (47.65–84.12%)
Specificity	73.08% (52.21–88.43%)	73.08% (52.21–88.43%)	73.08% (52.21–88.43%)	48.15% (28.67–68.05%)
Negative predictive value	61.29% (47.69–73.33%)	70.37% (55.94–81.63%)	82.61% (65.05–92.38%)	59.09% (42.61–73.75%)
Positive predictive value	86% (76.26–92.16%)	73.08% (57.92–84.26%)	77.42% (64.13–86.80%)	57.58% (46.54–67.9%)
Overall diagnostic accuracy	76.54% (65.82–85.25%)	71.7% (57.65–83.21%)	79.63% (66.47–89.37%).	58.18% (44.11–71.35%)

Table 3. Diagnostic properties of the silhouettes test for differentiating between participants with AD and CG. Data are presented as percentage and 95% confidence interval. MD, mild dementia; MCI, mild cognitive impairment; CG, control group.

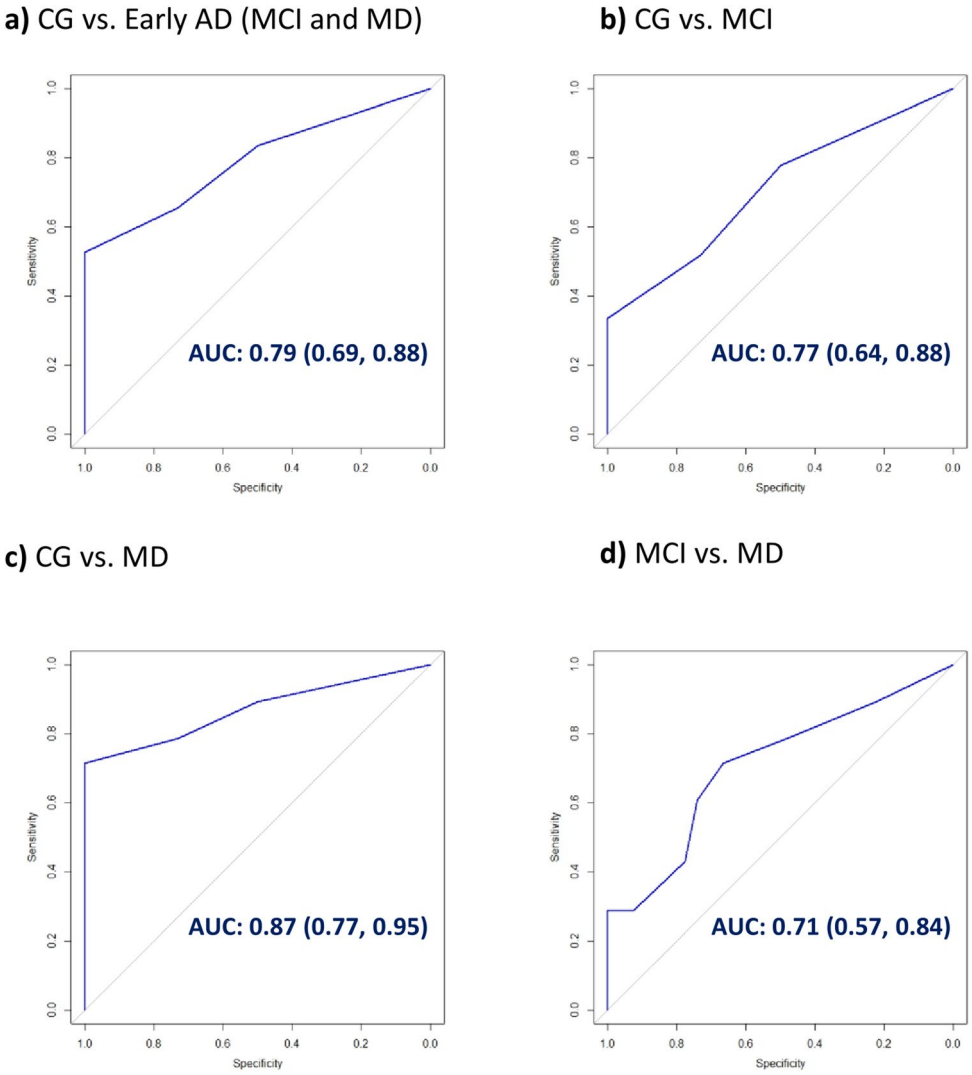

Fig. 2. Performance of the number location test in differentiating between participants with AD from the CG. AD, Alzheimer's disease; CG, control group; MD, mild dementia; MCI, mild cognitive impairment.

	CG vs. early AD (MCI and MD), cut-off ≤ 8	CG vs. MCI, cut-off ≤ 8	CG vs. MD, cut-off ≤ 8	MCI vs. MD, cut-off ≤ 7
Sensitivity	65.45% (51.42–77.76)	51.65% (31.95–71.33%)	78.57% (59.05–91.7%)	71.43% (51.33–86.78%)
Specificity	73.08% (52.21–88.43%)	73.08% (52.21–88.43%)	73.08% (52.21–88.43%)	66.67% (46.04–83.48%)
Negative predictive value	50% (39.36–60.64%)	59.38% (48.1–69.75%)	73.08% (52.21–88.43%)	69.23% (54.18–81.07%)
Positive predictive value	83.72% (72.63–90.88%)	66.67% (49.07–80.59%)	75.86% (61.84–85.9%)	68.97% (55.38–79.92%)
Overall diagnostic accuracy	67.9% (56.6–77.85%)	62.29% (47.89–75.21%)	75.93% (62.36–86.51%)	69.09% (55.19–80.86%)

Table 4. Diagnostic properties of the number location test for differentiating between participants with AD and CG. Data are presented as percentage and 95% confidence interval. MD, mild dementia; MCI, mild cognitive impairment; CG, control group.

compared to the intercept-only model ($X^2 = 87.79$, $p < 0.001$; Nagelkerke $R^2 = 0.744$). This model accurately classified 76.5% of cases overall, with correct classification rates of 92.3% for CG, 66.7% for MCI, and 71.4% for MD. Among the predictors, the ADAS-Cog 13 score emerged as the most robust and statistically significant ($X^2 = 78.83$, $p < 0.001$).

A second model incorporating sex, age, education, ADAS-Cog 13 scores, and number location test scores demonstrated a notable enhancement in fit compared to a null model ($X^2 = 104.76$, $p < 0.001$; Nagelkerke $R^2 = 0.816$). This model accurately classified 80.2% of cases overall, with specific accuracies of 92.3% for CG, 70.4% for MCI, and 78.6% for MD. Within this model, ADAS-Cog 13 and number location tests were statistically significant predictors (X^2 68.22, $p < 0.001$; X^2 16.97, $p < 0.001$, respectively).

Space perception: cube analysis

The cube analysis test scores differed significantly between the groups (medians and interquartile ranges: CG, 10 (1); MCI, 8 (3); MD 7 (5); Kruskal–Wallis $p < 0.001$). Post-hoc analysis revealed significant differences between CG vs. MCI and CG vs. MD, $p < 0.001$, but not between MCI vs. MD, $p = 0.094$).

The cube analysis scores moderately correlated with MMSE (Spearman's rho: 0.579; $p < 0.001$), CDR-SB (Spearman's rho: -0.489; $p < 0.001$), ADAS-Cog 13 (Spearman's rho: -0.521; $p < 0.001$), while a weak correlation was observed with age (Spearman's rho: -0.337; $p = 0.002$), and education (Spearman's rho: 0.346; $p = 0.002$).

Multiple linear regression models were employed to assess whether cube analysis test scores could be predicted using cognitive test results. These models incorporated cognitive test scores (MMSE, CDR-SB, and ADAS-Cog 13) and were adjusted for sex, age, and education.

The adjusted models demonstrated statistical significance in the multiple linear regression analysis with MMSE ($R^2 = 0.376$, $F = 13.03$, $\beta = 0.471$, $p < 0.001$), ADAS-Cog 13 ($R^2 = 0.29$, $F = 9.16$, $\beta = -0.382$, $p < 0.001$), and CDR-SB ($R^2 = 0.296$, $F = 9.4$, $\beta = -0.376$, $p < 0.001$).

To assess the effectiveness of the cube analysis test score in distinguishing between the CG and patients with AD, including those with MCI or MD, as well as patients with MCI and MD, ROC curve analysis was conducted. The ROC curves illustrating the cube analysis test performance for differentiating participant groups are shown in Fig. 3.

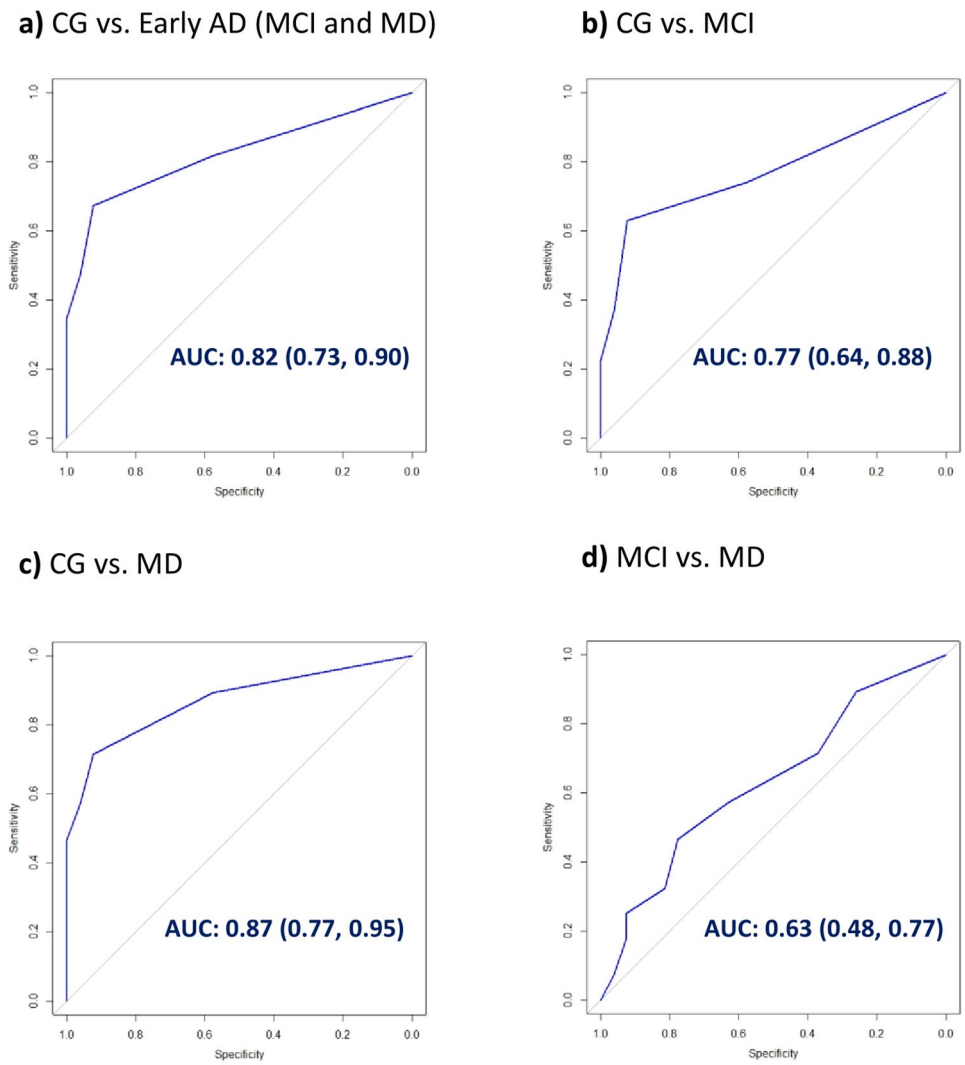

Fig. 3. Performance of cube analysis test in differentiating between participants with AD from the CG. AD, Alzheimer's disease; CG, control group; MD, mild dementia; MCI, mild cognitive impairment.

	CG vs. early AD (MCI and MD), cut-off ≤ 8	CG vs. MCI, cut-off ≤ 8	CG vs. MD, cut-off ≤ 8	MCI vs. MD, cut-off ≤ 7
Sensitivity	67.27% (53.29–79.32%)	62.96% (42.37–80.60%	71.43% (51.33–86.78%)	57.14% (37.18–75.54%)
Specificity	92.31% (74.87–99.05%)	92.31% (74.87–99.05%)	92.31% (74.87–99.05%)	62.96% (42.37%–80.6%)
Negative predictive value	57.14% (47.32–66.43%)	70.59% (59.18–79.89%)	75.00% (62.31–84.48%)	58.62% (45.81–70.36%)
Positive predictive value	94.87% (82.83–98.61%)	89.47% (68.51–97.08%)	90.91% (72.12–97.48%)	61.54% (47.07–74.22%)
Overall diagnostic accuracy	75.31% (64.47–84.22%)	77.36% (63.79–87.72%)	81.48% (68.57–90.75%)	60% (45.91–72.98%)

Table 5. Diagnostic properties of the cube analysis test for differentiating between participants with AD and CG. Data are presented as percentage and 95% confidence interval. MD, mild dementia; MCI, mild cognitive impairment; CG, control group.

A threshold score ≤ 8 on the cube analysis test was established to indicate AD (sensitivity 67%, specificity 92%, maximum Youden's J = 0.59). When applied to distinguish patients with AD (including those with MCI or MD due to AD) from CG participants, the test demonstrated a sensitivity of 67.27% (95% CI: 53.29–79.32%) and specificity of 92.31% (95% CI: 74.87–99.05%). Furthermore, the test yielded a negative predictive value of 57.14% (95% CI: 47.32–66.43%) and positive predictive value of 94.87% (95% CI: 82.83–98.61%). The overall accuracy of diagnosis was 75.31% (95% CI: 64.47–84.22%). A threshold score ≤ 8 on the cube analysis test was established for differentiating MCI from MD (sensitivity 57%, specificity 63%, maximum Youden's J = 0.2). All cut-off scores and diagnostic properties of the cube analysis test for comparisons between the diagnostic groups are presented in Table 5.

To examine the influence of predictor variables on group classification (CG, MCI, and MD), a multinomial logistic regression analysis was conducted. Initially, a model incorporating sex, age, education, and ADAS-Cog 13 scores as predictors was developed. The inclusion of these variables significantly enhanced the fit of the model compared to the intercept-only model ($X^2 = 87.79$, $p < 0.001$; Nagelkerke $R^2 = 0.744$). This model accurately classified 76.5% of cases overall, with correct classification rates of 92.3% for CG, 66.7% for MCI, and 71.4% for MD. Among the predictors, the ADAS-Cog 13 score emerged as the most robust and statistically significant ($X^2 = 78.83$, $p < 0.001$).

A second model incorporating sex, age, education, ADAS-Cog 13 scores, and cube analysis test scores demonstrated a notable enhancement in fit compared to a null model ($X^2 = 94.08$, $p < 0.001$; Nagelkerke $R^2 = 0.773$). This model accurately classified 80.2% of cases overall, with specific accuracies of 92.3% for CG, 70.4% for MCI, and 78.6% for MD. Within this model, ADAS-Cog 13 and cube analysis test were statistically significant predictors (X^2 59.93, $p < 0.001$; X^2 6.29, $p = 0.043$, respectively).

Discussion

Our study demonstrated that the VOSP battery tests (silhouettes, number location, and cube analysis) are appropriate additional tools for early diagnosis of AD. These three tests demonstrated similar diagnostic potential in differentiating MCI from CG (area under the curve (AUC) = 0.77 for all). In contrast, the cube analysis test exhibited the highest diagnostic accuracy in distinguishing CG from MCI and MD diagnostic groups (AUC silhouettes = 0.8, number location = 0.79, and cube analysis = 0.82).

The findings of this study indicate that performance on the silhouettes test is impaired at the MCI stage, with no significant differences observed between the MCI and MD groups. Compared with the study by Quental et al., the cutoff score for differentiating CG from early AD was identical in the silhouettes test, and our diagnostic accuracy results fell within the confidence interval range[19]. A longitudinal study by Eckerström et al. evaluating the conversion of MCI or subjective cognitive decline to dementia using CSF biomarkers and cognitive testing showed that silhouettes test results were significantly worse in the amyloid beta aggregation (A), tau aggregation (T), and neurodegeneration (N) positive (A + T + N+) groups than in the group with negative biomarkers (A-T-N-) at baseline evaluation[23]. In our study, a moderate negative correlation was observed between age and performance on the silhouette test, and a weak or no correlation between demographic data and number location or cube analysis tests. In a study by Herrera-Guzmán et al., educational level was a significant predictor of performance in a population with normal cognitive function for silhouettes and object decision tests[24]. Multinomial logistic regression analysis, incorporating demographic data, ADAS-Cog 13 scores, and silhouettes test results, accurately classified 76.4% of cases; however, the silhouettes test was not a significant predictor in this model. The specific accuracies showed poor performance in classifying MCI (92.3% for CG, 63% for MCI, and 75% for MD). Consequently, this test is influenced by demographic characteristics and object perception impairment occurs early in the course of AD.

Performance on the number location task differed significantly across the three groups, suggesting its potential utility for the very early diagnosis of AD. In this study, lower cut-off scores in number location and cube analysis tests were used to differentiate CG from early AD (MCI and MD) compared to the study by Quental et al.[19]. A cutoff value ≤ 8 was selected to indicate early AD, whereas Quental et al. reported a cutoff score of 9 for distinguishing CG from MD in both tasks[19]. Incorporating number location or cube analysis task results into a multinomial regression model with age, education, sex, and ADAS-Cog 13 scores improved

correctly classified CG, MCI, and MD cases from 76.5% to 80.2% (specific accuracies: 92.3% for CG, 70.4% for MCI, and 78.6% for MD). Both space perception tests improved the diagnostic accuracy of the models. As previously mentioned, cube analysis provided the best AUC results, differentiating CG from early AD, and improved group classification. This test stands out among spatial tests because of its unique requirement for three-dimensional perception despite being presented as a two-dimensional image. In addition, it involves the detection of hidden cubes, which must be deduced rather than observed directly[17]. In the human brain, the parieto-occipital junction is responsible for stereoscopic processing, which is crucial for spatial reasoning[25].

In addition to our finding that the number location and cube analysis tests enhance diagnostic accuracy in amnestic early AD, evidence demonstrates their substantial efficacy in diagnosing early atypical presentations of AD[22,26,27]. Recent studies with pathological confirmation of the diagnosis provide evidence that atypical AD variants with prominent visual agnosia (posterior cortical atrophy) and motor AD variant (corticobasal syndrome) can be clinically diagnosed using VOSP tests[22,26,27]. Boyd et al. reported that, in a clinicopathological investigation of individuals with corticobasal syndrome, poor performance on incomplete letters and all spatial VOSP tests correlated with an increased likelihood of underlying AD pathology, with cube analysis emerging as the most effective (sensitivity: 100%; specificity: 77%)[22].

This study had a few limitations. First, CSF biomarker analysis was not performed within the framework of this study owing to its exploratory nature. Medical records with CSF biomarker data were available for only a limited number of patients because of the invasiveness and cost of the procedure, and positron emission tomography biomarkers were not used. Using CSF biomarkers for all participants would have excluded MCI due to dementia with Lewy bodies, which may be challenging to differentiate from MCI due to AD with cognitive testing using visual perceptual function tests. However, none of the participants fulfilled the 2017 revised criteria for the clinical diagnosis of dementia with Lewy bodies[28]. In addition, while the study's sample size was adequate to demonstrate significant changes, additional research involving a larger group of participants would be beneficial in validating these results. Moreover, the study's cross-sectional design restricts its capacity to draw conclusive inferences regarding the progression of AD. Despite the promising outcomes of this study, longitudinal investigations are necessary to confirm the effectiveness of silhouettes, number location, and cube analysis tests as valuable assessment tools. The strengths of this study include the separation of visuoperception from language and motor abilities using VOSP, which provides a better understanding of early AD-related changes and improved diagnostic accuracy.

In conclusion, the VOSP serves as an inexpensive and efficient clinical assessment instrument, allowing easy and fast evaluation of visuoperceptual function in early AD. We recommend using silhouettes and space perception tasks (number location and cube analysis) as additional tools to improve early AD diagnosis. Combining multiple diagnostic tools, including verbal cognitive, visual object, and space perception tests (number location, and cube analysis), may provide the most accurate and early diagnosis of AD.

Methods

Participants

This study included three groups: 28 participants diagnosed with MD due to AD, 27 with amnestic MCI, and 26 cognitively normal older adults who served as the CG.

Individuals diagnosed with MD met the National Institute on Aging and Alzheimer's Association (NIA/AA) criteria for probable AD[29] and scored 1 on the clinical dementia rating total score (CDR-TS). Those classified as having MCI met the NIA/AA clinical and cognitive criteria for MCI due to AD[30] and received a CDR-TS of 0.5. Cognitively healthy older adults in the CG reported no cognitive issues, scored 0 on the CDR-TS, and showed no neurological abnormalities.

The study participants were recruited from the Memory Clinic of the Vilnius University Hospital, Santaros Klinikos. A cognitive neurologist diagnosed probable AD based on criteria for probable AD dementia with increased certainty[29], supported by the observed progression of cognitive decline, suggesting an ongoing and active pathological process[29]. For a subset of patients with MD (7/28 (25%)), medical records included positive AD CSF biomarker status, confirming AD diagnosis according to the 2018 NIA-AA research framework[31]. The diagnosis of MCI due to AD was established by applying clinical and cognitive criteria, with its etiology determined to be consistent with the pathophysiological process of AD[30]. This diagnosis involved ruling out vascular, traumatic, and medical causes of amnestic MCI along with documented longitudinal cognitive deterioration[30]. The biomarkers indicated an intermediate likelihood of MCI due to AD, as structural MRI revealed signs of neuronal injury (medial temporal lobe atrophy) in all cases. Medical records with positive AD CSF biomarker status were available for a subset of patients with MCI (8/27 (30%)), confirming AD diagnosis[31].

The exclusion criteria included neurological disorders affecting the central nervous system (except for MCI and MD); cerebrovascular issues (indicated by a Hachinski Ischemic Score ≥ 4); history of head injury; major psychiatric conditions (such as schizophrenia, delirium, psychosis, or depression with a Geriatric Depression Scale score exceeding 9); vision and hearing disorders impairing cognitive testing; diagnosis or any symptoms of substantial cardiovascular, hepatic, or metabolic disorders; drug or alcohol abuse; and use of psychoactive medications. The study was conducted in accordance with the Declaration of Helsinki (1975) and approved by the Vilnius Regional Bioethics Committee (Approval Number 2022/1-1405-877). All participants provided written informed consent before participating in the study.

Assessments of cognitive function

The MMSE test was used to evaluate overall cognition. The ADAS-Cog 13 was administered to the participants for detailed cognitive evaluation. The ADAS-Cog 13 includes word recall, commands, constructional praxis, delayed word recall, naming, ideational praxis, orientation, word recognition, remembering test instructions, comprehension of spoken language, word-finding difficulty, spoken language ability, and number cancellation.

ADAS-Cog 13 scores ranged from 0 to 85. The Clinical Dementia Rating Sum of Boxes (CDR-SB) scale was used to assess the extent of functional impairment and cognitive decline.

Assessment of VOSP battery tests: silhouettes, number location, and cube analysis

Silhouettes: Black shadows of animals and inanimate objects from unusual angles were shown to the participants. The test consisted of 15 silhouettes of animals and 15 silhouettes of inanimate objects. Participants may name, mimic, gesture, or describe the object. The test boards were organized from the easiest to the most challenging, and the examination was discontinued after five mistakes. To establish the threshold scores, we implemented all boards even when the participant made > five errors (maximum score: 30).

Number location: This test consists of 10 boards, each featuring two vertically aligned squares. The upper square displayed a random arrangement of numbers ranging from 1 to 9. The lower square contains a black dot that corresponds to the location of a specific number. The participants were required to identify the number aligned with the position of the black dot. One point was awarded for each correct identification, with a total of ten boards presented (maximum score: 10).

Cube analysis: Each board displayed a configuration of solid objects. Participants were required to determine the total number of cubes on each board, including those that were not visible. A series of ten boards was presented, with the complexity increasing progressively from one board to the next. (maximum score = 10).

Data analysis

The Shapiro–Wilk test was used to evaluate whether the data followed a normal distribution. Group differences in demographic and clinical data, as well as test results were analyzed using one-way ANOVA, Kruskal–Wallis, or chi-square tests. Spearman's rank correlation coefficient was used to evaluate the associations between the variables. Subsequently, linear regression models, adjusted for demographic data, were used to predict continuous dependent variables. Multinomial logistic regression was employed to examine the association between independent variables and classification into the three groups. Diagnostic test performance was evaluated using ROC curve analysis. The optimal threshold for each test was determined by maximizing Youden's J statistic (J = sensitivity + specificity − 1). Statistical significance was set at $p < 0.05$.

Data availability

The datasets used and analyzed in this study are available from the corresponding author upon reasonable request.

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Author contributions
V. S. and G. K. conceived and designed the study. V.S., E.A., and G.P.-K. collected the data. V.S., E.A. and G.P.-K. analyzed the data. V. S. and G. K. prepared the manuscript. E.A. and G.P.-K. revised the manuscript. All the authors have approved the final manuscript.

Declarations

Competing interests
The authors declare no competing interests.

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