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ORIGINAL RESEARCH

Agreement and Comparative Performance of Cognitive Testing, Visual MRI Rating, and Automated Brain Morphometry in Older Adults with Suspected Dementia in Uganda

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Background: Dementia diagnosis in sub-Saharan Africa is constrained by limited access to specialist neuroimaging interpretation and reduced specificity of brief cognitive tools in low-literacy populations. We evaluated the agreement, incremental value, and comparative performance of Mini Mental State Exam (MMSE), visual MRI medial temporal atrophy (MTA), and automated brain morphometry in older Ugandan adults with suspected dementia.

Methods: In this cross-sectional study, adults aged ≥50 years with suspected dementia were recruited from neurology and psychiatry clinics at two hospitals and from a community cohort. Participants underwent MMSE and standardized 1.5T brain MRI. Visual MRI ratings were performed by radiologists blinded to clinical data, and automated morphometry was generated using NeuroQuant® normative percentiles. Hippocampal occupancy (HOC <5th percentile) was used as a reference MRI biomarker for comparative classification. Agreement between visual and automated measures was assessed using Spearman correlation and intraclass correlation. Incremental value was assessed using regression models, and comparative performance using area under the curve (AUC).

Results: Sixty-three participants were included (mean age 75.6 ± 8.7 years; 49 female). Agreement between visual ratings and automated morphometry was poor. MMSE correlated inversely with MTA (ρ = −0.47; p = 0.049) and correlated positively with hippocampal volume percentile (ρ = 0.46; p = 0.056). Adding hippocampal volume to MTA did not improve model fit for MMSE (ΔR^2 = 0.028; p = 0.18). For comparative classification, MMSE alone was sensitive but poorly specific, while the combined MMSE-MTA model improved specificity and discrimination (AUC 0.70 vs 0.62 for either measure alone).

Conclusion: Visual and automated MRI measures were not interchangeable in this heterogeneous cohort. Automated hippocampal volumetry added limited value beyond visual MTA for global cognition, while combining MMSE with visual MTA showed modest improvement in comparative classification and warrants further validation.

Keywords: dementia, MMSE, medial temporal atrophy, visual MRI rating, automated brain volumetric analysis software, hippocampal occupancy, automated morphometry

Introduction

Globally, dementia is a growing public health challenge with over 55 million people affected, a figure expected to double every two decades due to an aging population.[1,2] Sub-Saharan Africa (SSA) is now experiencing a significant rise in

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dementia cases, driven by improved life expectancy and increasing burden of non-communicable diseases.[3,4] Despite this trend, dementia remains widely underdiagnosed across SSA, including Uganda, due to limited awareness, constrained diagnostic capacity, and inadequate access to neuroimaging and cognitive screening tools.[5–7] Dementia assessment and diagnosis remains a challenge in Uganda and similar SSA settings due to limited health worker training in dementia assessment and lack of validated diagnostic tools in African settings.[8,9] Despite these challenges, a high burden of undiagnosed cognitive impairment or dementia in community settings has been reported. For example, the DEPEND study led by Prynn et al (2025) reported significant levels of probable dementia, particularly in rural populations, alongside poor access to diagnostic infrastructure.[10] Similarly, Mubangizi et al (2024) noted poor classification of dementia subtypes and underuse of brain MRI among elderly patients presenting with cognitive symptoms.[11] Dementia diagnosis relies on cognitive screening tools like the mini-mental state exam and structural brain imaging to augment the diagnosis.

The Mini-Mental State Examination (MMSE) remains the most widely used cognitive screening tool in SSA due to its simplicity and minimal resource requirements.[12] However, MMSE performance is strongly influenced by literacy, language, and cultural context- factors that limit its diagnostic validity in many African settings where formal education is low.[13–18] Moreover, the MMSE lacks etiological specificity and does not reliably distinguish dementia subtypes, which can contribute to delayed recognition of underlying pathology and suboptimal clinical management. In this context, structural brain MRI provides complementary, objective markers of neurodegeneration and cerebrovascular injury, including medial temporal atrophy (MTA), ventricular enlargement, and white matter disease.[19–21] Among the imaging-based tools for dementia assessment, the Scheltens visual medial temporal atrophy (MTA) scale stands out for its simplicity, rapid application, and strong clinical utility.[22] Visual MTA scores are quick to apply in routine practice and have been validated against neuropathological findings, making them reliable indicators of Alzheimer's disease-related neurodegeneration. In parallel, NeuroQuant®, an FDA-cleared automated volumetric software by CorTechs Labs, provides age- and sex-adjusted normative measurements of hippocampal and cortical volumes that are increasingly used as supportive tools in dementia work-ups, particularly for quantifying regional volumes and supporting longitudinal assessment.[21,23] These automated tools generate reproducible, quantitative outputs and can detect subtle changes in hippocampal volume, cortical thinning, and ventricular enlargement, thereby enhancing early diagnosis and longitudinal tracking of neurodegeneration. Hippocampal occupancy (HOC) integrates hippocampal volume with inferior lateral ventricular enlargement and has been used in memory clinic settings as a supportive biomarker, although diagnostic performance can be variable and should be interpreted cautiously.[24]

Recent studies have validated both visual and automated methods for assessing medial temporal atrophy. Persson et al (2024) demonstrated a strong inverse correlation ($r = -0.75$) between automated brain volumetric analysis software measured hippocampal volume and MTA scores, with both methods achieving good diagnostic performance (AUCs of 0.88 and 0.80, respectively) in distinguishing Alzheimer's disease from non-dementia cases.[23] Pemberton et al have shown that automated volumetric tools are operationally viable and enhance diagnostic reproducibility in routine care.[25] Jerard et al further highlighted variability in inter-rater agreement for visual scales, emphasizing the value of automated, objective metrics to standardize dementia imaging workflows.[26] Their applicability to low-literacy, resource-constrained contexts such as Uganda where both radiologist training and cognitive tool validity may be limited remains underexplored.

There is a dearth of published literature from sub-Saharan Africa that has systematically examined how brief cognitive screening (MMSE), pragmatic visual MRI scoring, and automated volumetry compare and complement one another in clinically suspected dementia. We therefore addressed the following objectives: (i) to quantify agreement between visual medial temporal atrophy (MTA) and automated hippocampal-centred morphometry metrics, focusing on their consistency as alternative MRI biomarkers rather than prevalence; (ii) to evaluate the incremental contribution of automated morphometry beyond visual MTA and MMSE in explaining variability in cognitive performance and cognitive severity; and (iii) to determine whether multivariable models integrating MMSE, visual MTA, and automated morphometry improve prediction of cognitive impairment severity compared with MMSE-only models, emphasizing incremental discrimination (ΔAUC) and classification performance rather than diagnostic accuracy against a gold standard. Collectively, these aims support scalable multimodal assessment strategies advocated by African dementia researchers and aligned with the WHO Brain Health Initiative.[27–29]

Methods

Study Design and Setting

This cross-sectional study with comparative performance analyses was conducted between 09 January 2025 and 25 June 2025 in Uganda. Participants were recruited from three sources: (1) the adult Neurology and Psychiatry outpatient clinics at Mulago National Referral Hospital (MNRH), (2) the Neurology Clinic at St. Francis Hospital Nsambya (SFHN), and (3) a community-based cohort enrolled under the Recruitment and Retention of Alzheimer's Disease Diversity Genetic Cohorts in the Alzheimer's Disease Sequencing Project (READD-ADSP). To ensure protocol consistency, eligible participants from MNRH and READD-ADSP underwent MRI at SFHN, where all scans were acquired on a single 1.5T Siemens Magnetom Sempra scanner using a standardized automated brain volumetric analysis software -compatible protocol.

Participants and Eligibility

A total of 72 adults aged ≥50 years with clinically suspected dementia were recruited consecutively into the study. Participants were eligible if they had completed the Mini-Mental State Examination (MMSE) and undergone brain MRI suitable for visual rating and automated morphometry. "Clinically suspected dementia" refers to individuals referred for cognitive complaints by neurology or psychiatry clinicians, or identified through community screening with concern for cognitive impairment; no external biomarker or longitudinal diagnostic adjudication was used in this cross-sectional analysis. The ≥50-year threshold was selected to capture both typical and early-onset presentations and is consistent with geriatric definitions applied in African population-based studies.[30–32] Exclusion criteria included prior stroke, intracranial tumor, major head injury, neurodevelopmental disorders, and major psychiatric illness judged unrelated to dementia. Imaging-level exclusions were applied for pronounced motion artifact, incomplete brain coverage, or segmentation failures preventing reliable automated brain volumetric analysis software morphometry outputs. Nine participants were excluded (four motion-degraded scans, one large falx meningioma, three irrecoverable segmentation failures, and one participant aged 102 years outside the software analytic limits), leaving 63 participants with complete MMSE data and interpretable MRI for analysis.

Cognitive Assessment

MMSE was administered by trained clinicians in each participant's primary language (primarily Luganda or English) using validated versions and standardized administration procedures. Given low educational attainment in this population, education-adjusted interpretation thresholds were used to support classification of impairment severity.[33] An unauthorized version of the MMSE was used by the study team without permission, however this has now been rectified with Psychological Assessment Resources (PAR). The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR.

MRI Acquisition and Processing

The MRI protocol was optimized for 1.5T acquisition and automated brain volumetric analysis software processing, and included a high-resolution 3D T1-weighted MPRAGE sequence for volumetric morphometry, supplemented by axial FLAIR, T2-weighted, diffusion-weighted imaging, susceptibility-weighted imaging, and proton density sequences. Core structural sequences were selected to align with internationally accepted dementia imaging recommendations while remaining feasible on available hardware.[34,35] Scans were anonymized and exported in DICOM format prior to visual scoring and automated processing.

Visual MRI Rating

Three consultant radiologists with experience in brain MRI interpretation, blinded to clinical data, independently applied validated visual rating scales on structural MRI (MTA, GCA, Koedam posterior atrophy, and Fazekas WMH). Prior to scoring, readers completed a training and standardization session using reference cases and published rating atlases to harmonize interpretation. For this comparative manuscript, MTA was prespecified as the primary visual rating used in

predictive models; other visual scales were used descriptively and to support exploratory visual-automated comparisons, avoiding duplication with a separate descriptive structural MRI manuscript. MTA was considered abnormal if ≥2 in participants <75 years and ≥3 in those aged ≥75 years, consistent with published validation studies.[22] Fazekas ≥2 was considered abnormal.[36]

Inter-Rater Reliability

Inter-rater reliability for visual ratings was assessed using the intra-class correlation coefficient (ICC) with a two-way random-effects model and absolute agreement, interpreted according to Koo and Li (2016).[37] For the primary visual scale used in the comparative analyses, inter-rater reliability of independent MTA ratings from the three radiologists was specifically examined prior to any consensus discussion to aid interpretation of visual-versus-automated agreement.

Automated Morphometry

Automated volumetric morphometry was performed using automated brain volumetric analysis software version 4.1.2 (CorTechs Labs Inc., San Diego, CA), an FDA-cleared tool that generates regional brain volumes and age- and sex-adjusted normative percentiles normalized to intracranial volume. For the primary analyses, automated hippocampal volume and hippocampal occupancy score (HOC) were analyzed as normative percentiles, with values <5th percentile considered abnormal (higher percentiles indicating larger/better-preserved structures). Additional regional cortical and ventricular percentiles (eg., inferior lateral ventricle and lobar cortical percentiles) were available and were treated as exploratory variables, primarily used to support agreement analyses rather than prevalence reporting, to maintain distinction from the descriptive manuscript.

Reference MRI Biomarker (HOC) and Justification

For comparative model evaluation, hippocampal occupancy (HOC <5th percentile) was used as a reference MRI biomarker of medial temporal neurodegeneration rather than as a diagnostic gold standard for dementia. HOC was selected because it integrates hippocampal volume with inferior lateral ventricle enlargement, providing a robust composite marker of medial temporal atrophy severity that is less sensitive to variability in a single structure than hippocampal volume alone. This framing was intended to benchmark the relative performance of MMSE, visual MTA, and combined models, without adjudicating clinical dementia diagnosis.

Statistical Analysis

Analyses were performed in STATA version 17. Normality of continuous variables was assessed using visual inspection and Shapiro–Wilk testing. MMSE and several MRI measures were not normally distributed; therefore, non-parametric statistics were applied where appropriate for correlation analyses. For Objective 1 (agreement), correspondence between visual MTA and automated morphometry measures was assessed using Spearman rank correlations and intraclass correlation coefficients (ICC), given the ordinal nature of visual scores and non-normality of several measures.

For Objective 2 (incremental value), automated hippocampal volume percentile was examined as a candidate predictor in nested linear regression models to assess incremental explanatory value beyond visual MTA for MMSE performance (Model 1: MTA; Model 2: MTA plus hippocampal volume percentile). Assumptions for linear regression were evaluated at the model level by inspection of residual plots, including assessment of residual distribution and homoscedasticity. Model comparison used ΔR^2 and likelihood-ratio testing, with Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) reported as supportive indices.

These regression models were intentionally unadjusted for age, sex, and education because the aim was to examine the incremental contribution of automated hippocampal volume beyond visual MTA within a parsimonious exploratory framework rather than to estimate independent causal associations. Given the modest sample size, additional covariate adjustment was avoided to reduce the risk of overfitting. However, this may introduce residual confounding and should be considered when interpreting the findings.

HOC was reserved for comparative classification analyses (Objective 3) and was not included in regression models to avoid redundancy.

Results

Participants and Data Completeness

Sixty-three participants with clinically suspected dementia had complete MMSE data and analyzable brain MRI studies. The mean age was 75.6 years (SD 8.7; range 56–98), 49/63 (77.8%) were female, and the mean MMSE score was 13.9 (SD 6.1; range 0–29), consistent with substantial cognitive impairment in the cohort. Participants had a mean of 6.9 years of formal education (SD 4.5; range 0–16), and 3/63 (4.8%) had no formal schooling (Table 1). Visual inspection of the MMSE distribution and formal normality testing (Shapiro–Wilk) indicated non-normality; accordingly, non-parametric methods were used for correlation analyses.

Agreement Between Visual MRI Ratings and Automated Morphometry

Agreement between visual atrophy ratings and automated morphometry measures was poor across all paired comparisons. Spearman analysis showed weak association between MTA scores and automated hippocampal volume ($\rho = 0.22$, $p = 0.085$). Intraclass correlation coefficients were near zero for all visual-automated pairs, including MTA versus hippocampal volume and hippocampal occupancy score, GCA versus whole-brain percentile, and Koedam versus parietal cortex percentile (Table 2). Importantly, inter-rater reliability for visual MTA scoring among the three radiologists was good (ICC 0.872, 95% CI 0.737–0.931), indicating that the poor agreement observed between visual and automated measures was unlikely to be explained primarily by instability of visual scoring. Additional agreement analyses are provided in Figures S1–S3.

Association Between MRI Markers and Cognitive Performance

MMSE was inversely correlated with visual MTA ($\rho = -0.47$, $p = 0.049$) and showed a similar-magnitude positive correlation with automated hippocampal volume percentile that did not reach conventional statistical significance ($\rho = 0.46$, $p = 0.056$) (Table 3).

A representative discordant case illustrating mismatch between cognitive performance and MRI-based measures is shown in Figure 1.

Table 1 Participant Characteristics

Characteristic	Statistic	Value
Age, years	Mean (SD); range	75.6 (8.7); 56–98
Sex	n (%)	Female 49 (77.8%); Male 14 (22.2%)
MMSE score	Mean (SD); range	13.9 (6.1); 0–29
Education, years	Mean (SD); range	6.9 (4.5); 0–16
No formal education	n (%)	3 (4.8%)

Table 2 Agreement Between Visual MRI Ratings and Automated Morphometry

Visual Rating vs Automated Measure	n	ICC	95% CI	p_Value	Interpretation
MTA (visual) vs Hippocampal Volume	63	0.025	−0.187–0.247	0.41	Poor
MTA (visual) vs Hippocampal Occupancy Score	63	−0.017	−0.155–0.150	0.59	Poor
GCA vs Whole-brain percentile	63	−0.004	−0.048–0.060	0.56	Poor
Koedam vs Parietal cortex percentile	63	−0.003	−0.067–0.087	0.53	Poor

Abbreviations: MTA, medial temporal atrophy; GCA, global cortical atrophy; ICC, intraclass correlation coefficient; CI, confidence interval.

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Table 3 Spearman Correlations Between MRI Markers and Cognitive Performance in Older Adults with Suspected Dementia

Variables	Spearman ρ	p-Value
MMSE vs MTA	−0.471	0.049
MMSE vs Hippocampal volume	0.459	0.056

Notes: Spearman rank correlation was used due to the ordinal nature of visual ratings and non-normality. Automated hippocampal volume was expressed as an age-adjusted NeuroQuant normative percentile (higher values indicate larger/better-preserved hippocampi; values <5th percentile were considered abnormal).

Incremental Value of Automated Morphometry Beyond Visual Rating

While hippocampal occupancy (HOC) served as the reference MRI biomarker for classification analyses, hippocampal volume was examined in Table 4 as an automated predictor of MMSE performance beyond visual MTA. Accordingly, Model 1 included MTA alone and Model 2 added hippocampal volume as a nested extension. In linear regression, higher MTA scores were associated with lower MMSE performance in Model 1 (β = −1.46, 95% CI −2.98 to 0.06; p = 0.06). After adding hippocampal volume (Model 2), MTA remained independently associated with MMSE (β = −1.65, 95% CI −3.19 to −0.11; p = 0.036), whereas hippocampal volume was not (β = 0.082, 95% CI −0.039 to 0.202; p = 0.18). Model fit improved minimally ($\Delta R^2 = 0.028$) and was not significantly better by likelihood-ratio testing (p = 0.18), with no meaningful change in information criteria (Table 4). The findings suggest that visual MTA captures most of the MMSE-related variance attributable to medial temporal neurodegeneration in this cohort, with minimal additional contribution from automated hippocampal volume.

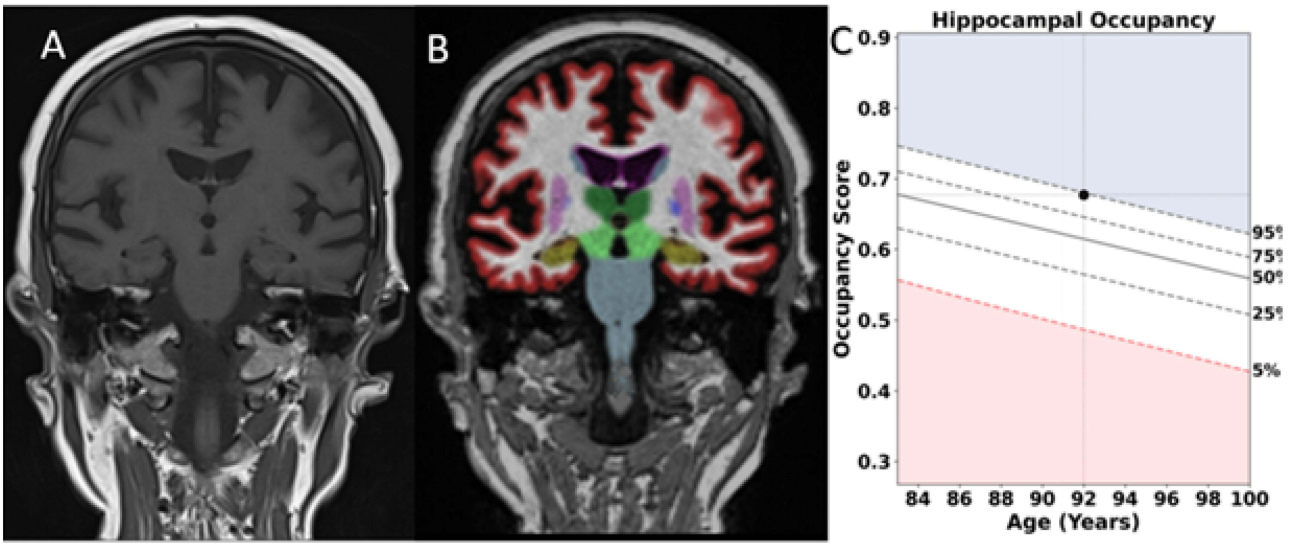

Figure 1 Representative discordant case illustrating disagreement between cognitive screening, visual MRI rating, and automated morphometry. A 92-year-old woman with limited formal education (Primary Three level) had an MMSE score of 8 (severe range). (**A**) Coronal T1-weighted image shows mild medial temporal atrophy (visual MTA grade 1). (**B**) Automated morphometry output indicates hippocampal volumes within expected ranges. (**C**) Automated brain volumetric analysis software percentile plot shows hippocampal occupancy within the reference range. This case is presented to demonstrate discordance between MMSE and MRI-based measures and to underscore that MMSE performance may be influenced by education and language context; it is not intended to adjudicate diagnosis.

Table 4 Linear Regression Models Predicting MMSE and Model Comparison Model definitions:Model 1: MMSE ~ MTA. Model 2: MMSE ~ MTA + Hippocampal Volume Percentile

Panel A. Regression coefficients (Outcome: MMSE)						
Model	**Predictor**	**β (Estimate)**	**95% CI**	**p-value**		
1	MTA	−1.46	−2.98 to 0.06	0.06		
2	MTA	−1.65	−3.19 to −0.11	0.036		
2	Hippocampal volume percentile	0.082	−0.039 to 0.202	0.18		
Panel B. Model fit and comparison						
Model	**R^2**	**Adj R^2**	**ΔR^2**	**AIC**	**BIC**	**LRT p-value**
1	0.057	0.042	-	407.1	413.6	-
2	0.085	0.055	0.028	407.2	415.8	0.18

Notes: Model 2 is nested within Model 1. Hippocampal volume is an age- and sex-adjusted normative percentile (higher values indicate larger/better-preserved hippocampi). β estimates represent the change in MMSE per 1-unit increase in the predictor.
Abbreviations: MMSE, Mini Mental State Exam; MTA, Medial Temporal Atrophy; CI, Confidence Interval; R^2, Coefficient of determination; Adj R^2, Adjusted coefficient of determination; ΔR^2, Change in coefficient of determination; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; LRT, Likelihood ratio test.

Comparative Classification Performance

Using hippocampal occupancy (HOC <5th percentile) as a reference MRI biomarker, MMSE alone showed high sensitivity (83.3%) but low specificity (41.0%). The combined series cross-method model achieved higher overall discrimination (AUC 0.70) and improved specificity (76.9%) compared with either measure alone (Table 5 and Figure 2).

Results Takeaway

Across comparative analyses, MMSE-only models showed high sensitivity but limited specificity, while visual MTA alone had modest discrimination. Models combining MMSE and MTA improved specificity and showed the best overall discrimination among the approaches evaluated, suggesting complementary clinical-imaging value. Automated hippocampal volumetry provided limited incremental value beyond visual MTA for explaining MMSE performance in this cohort.

Table 5 Comparative Classification Performance of MMSE, Visual MTA, and Combined MMSE-MTA Models Using Hippocampal Occupancy (HOC <5th Percentile) as a Reference MRI Biomarker

Model	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**AUC (95% CI)**	**LR+ (95% CI)**	**LR- (95% CI)**
MMSE alone	83.3 (62.6, 95.3)	41.0 (25.6, 57.9)	0.62 (0.51, 0.73)	1.41 (1.03, 1.94)	0.41 (0.15, 1.07)
MTA alone	70.8 (48.9, 87.4)	53.8 (37.2, 69.9)	0.62 (0.50, 0.75)	1.53 (1.00, 2.35)	0.54 (0.27, 1.08)
MMSE OR MTA (parallel)	91.7 (73.0, 99.0)	17.9 (7.5, 33.5)	0.55 (0.46, 0.63)	1.12 (0.92, 1.35)	0.40 (0.10, 2.05)
MMSE AND MTA (series)	62.5 (40.6, 81.2)	76.9 (60.7, 88.9)	0.70 (0.58, 0.82)	2.71 (1.41, 5.20)	0.49 (0.28, 0.84)

Notes: HOC (<5th percentile) was used as a *reference MRI biomarker* for comparative analyses and does not represent a diagnostic gold standard for dementia. Parallel combination used the OR rule (positive if either test is positive). Series combination used the AND rule (positive only if both tests are positive).
Abbreviations: MMSE, Mini-Mental State Examination; MTA, Medial temporal atrophy; CI, Confidence interval; AUC, Area under the curve; LR+, Positive likelihood ratio; LR−, Negative likelihood ratio.

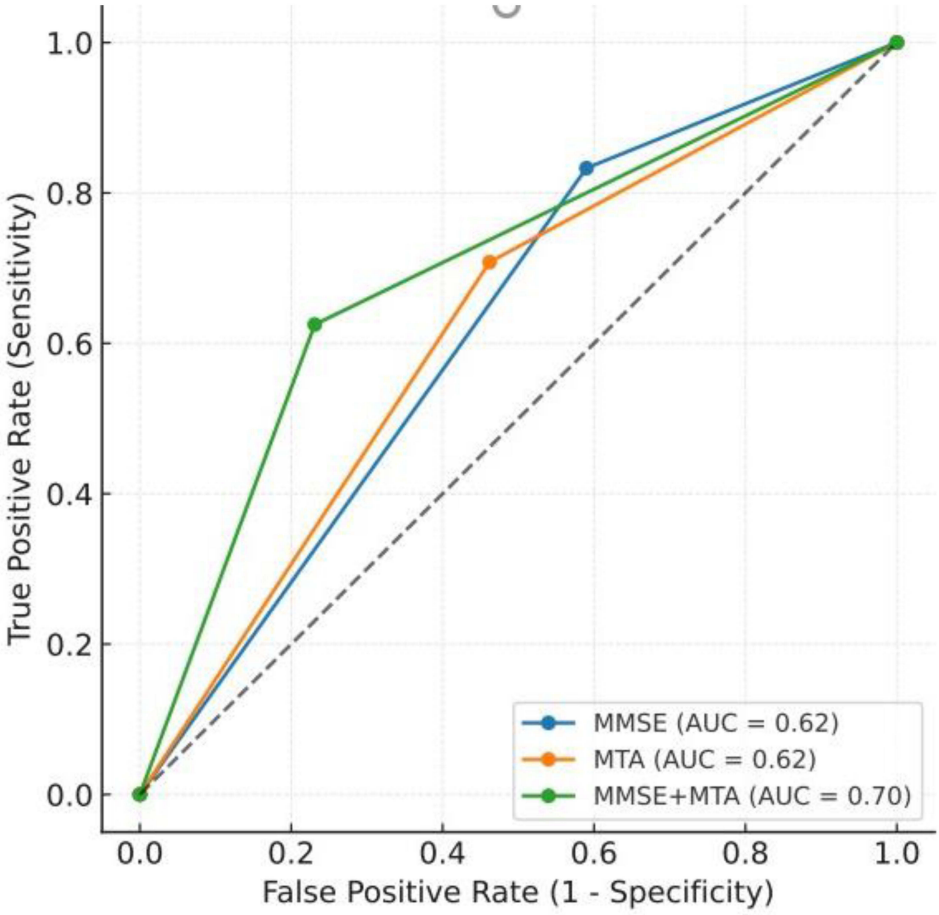

Figure 2 ROC curves for comparative classification performance. Receiver operating characteristic (ROC) curves comparing MMSE alone, visual medial temporal atrophy (MTA) alone, and the combined MMSE–MTA model for classification of abnormal hippocampal occupancy (HOC <5th percentile), used as a reference MRI biomarker. MMSE and MTA each showed modest discrimination (AUC 0.62), while the combined MMSE–MTA model demonstrated improved discrimination (AUC 0.70).

Discussion

This study examined how a brief cognitive screen (MMSE), a pragmatic visual MRI rating (medial temporal atrophy (MTA)), and automated morphometry outputs compare and complement one another in older adults with clinically suspected dementia in Uganda. Three key findings emerged; First, agreement between visual and automated MRI metrics was poor across all paired comparisons, with intraclass correlation coefficients close to zero for MTA versus hippocampal volume and HOC, and similarly low agreement between other visual scales (GCA, Koedam) and their automated counterparts (Table 2). Second, cognitive performance related to medial temporal markers, but the pattern depended on whether markers were visual or automated: MMSE correlated inversely with MTA ($\rho = -0.47$; $p = 0.049$) and showed a similar-magnitude positive correlation with automated hippocampal volume percentile that did not reach conventional statistical significance ($\rho = 0.46$; $p = 0.056$) (Table 3). Third, in comparative classification using HOC as the reference MRI biomarker, MMSE alone was sensitive but poorly specific, whereas combining MMSE with MTA improved specificity and overall discrimination (Table 5 and Figure 2).

Rather than treating MRI as a diagnostic gold standard, we used automated hippocampal occupancy (HOC) as a reference MRI biomarker to support consistent comparative classification across tools. HOC was selected because it integrates hippocampal volume with inferior lateral ventricular enlargement, providing a composite marker of medial temporal neurodegeneration severity. In this heterogeneous cohort, HOC was used solely as a comparative anchor and not to adjudicate clinical dementia diagnosis. MTA was prespecified as the primary visual marker for modeling; other scales are reported for agreement analyses only.

Interpretation in the Context of a Heterogeneous Dementia Cohort

Two contextual features likely explain the modest effect sizes and weak cross-method agreement. First, the cohort had advanced cognitive impairment overall (mean MMSE 13.9; Table 1), which compresses variability and reduces the ability of any single structural marker to explain cognition. Second, the clinical population included multiple dementia subtypes and frequent mixed pathology. While medial temporal atrophy is most characteristic of Alzheimer's disease, it is not specific to AD in advanced or mixed dementia; accordingly, medial temporal measures (MTA, HOC, hippocampal volume percentiles) are best interpreted here as indicators of overall neurodegeneration severity rather than Alzheimer's disease-specific biomarkers. Because physiological brain atrophy increases with age, we interpreted visual atrophy scales using age-adjusted thresholds rather than absolute scores alone. In particular, MTA scores of 0–1 were considered within normal limits in participants aged <75 years, whereas scores up to 2 could be age-appropriate in those aged ≥75 years; scores of 3–4 were considered abnormal across age groups. Similarly, mild global cortical atrophy was interpreted in an age-aware manner, recognizing that a GCA score of 2 may be within normal limits in older individuals but potentially abnormal in younger participants. Automated morphometric measures were likewise interpreted using age- and sex-adjusted normative percentiles. These steps do not eliminate age-related confounding, but they reduce the risk of misclassifying physiological aging as pathology. Under these conditions, weak associations do not necessarily signal measurement failure; they may reflect true clinical heterogeneity, overlapping pathologies, and downstream effects of education and comorbidity on cognitive screening performance. Prior studies in low-education populations have demonstrated that hippocampal volume may remain relatively preserved at comparable levels of cognitive impairment, consistent with cognitive reserve theory, which may partly explain why automated hippocampal volumetry did not independently improve cognitive prediction beyond visual MTA in the present cohort.[38]

Why Visual and Automated MRI Measures May Disagree

The near-zero ICC values (Table 2) indicate that visual and automated scores were not interchangeable in this dataset. This does not imply that one method is "wrong"; rather, they quantify related but non-identical constructs. Importantly, inter-rater reliability for visual MTA scoring in this cohort was good, suggesting that the low agreement between visual MTA and automated hippocampal metrics is unlikely to be explained mainly by reader inconsistency. Visual ratings integrate pattern recognition such as sulcal widening, ventricular enlargement, and regional atrophy patterns across sequences and hemispheres, whereas automated tools apply segmentation-based quantification relative to a reference population. Differences in image quality, head position, atrophy distribution, and normative references (particularly when derived from non-African populations) can contribute to disagreement, especially on 1.5T datasets and in brains with vascular lesions or mixed pathology. While higher field strength improves sensitivity for subtle atrophy, use of a single 1.5T scanner reflects real-world practice in many LMIC settings and supports external validity for similar health systems. Accordingly, we present additional agreement visualizations (Bland-Altman and supplementary plots) as supportive material rather than as primary evidence.

Associations with Cognition and Incremental Value of Automated Hippocampal Volume

In correlation analyses, the hippocampal volume percentile showed a positive association with MMSE (Table 3), consistent with its definition (higher percentiles indicate larger, better-preserved hippocampi). Importantly, the distinction from MTA was one of direction and statistical uncertainty rather than magnitude; both associations were of similar absolute size. In regression modelling, adding hippocampal volume to MTA produced only minimal improvement in explained variance ($\Delta R^2 = 0.028$) and did not improve fit by likelihood-ratio testing ($p = 0.18$), with no meaningful change in information criteria (Table 4). In practical terms, within this cohort and analytic approach, automated hippocampal volume did not add explanatory value beyond what was captured by visual MTA for global cognition.

International studies have reported added value of automated morphometry, particularly in early or biomarker-confirmed Alzheimer's disease and in high-resource settings using higher field strength scanners and population-matched norms.[23,25] However, recent clinic-based evidence using automated brain volumetric analysis software suggests

that hippocampal volumetry and hippocampal occupancy scores (HOC) should be interpreted cautiously as supportive tools: Schaffert et al (2025) found lower hippocampal volumes and HOC in amnestic MCI and Alzheimer's disease, but only modest correlations with memory performance and variable sensitivity and specificity for objective memory impairment.[24] This aligns with our observation that single-region volumetry provided limited incremental value beyond a structured visual MTA assessment for global cognition.

Cohort composition and context are also critical. Falgàs et al (2019) reported that hippocampal atrophy had limited usefulness as a diagnostic biomarker in early-onset Alzheimer's disease, and that hippocampal measures may lose specificity across non-amnestic phenotypes and heterogeneous dementia cohorts even when biological confirmation is available.[39] Conversely, Chirila et al (2022) demonstrated that morphometric biomarkers can still identify Alzheimer's disease even among mixed dementia patients, highlighting that automated approaches may add value depending on the biomarker definition, analytic strategy, and target outcome.[40] Finally, education-related effects may attenuate structure-cognition relationships: Mondragón et al (2017) showed that hippocampal volumetry can behave differently in people with low education, consistent with cognitive reserve effects and potential MMSE misclassification in low-literacy populations.[38] Taken together, these data support the interpretation that the incremental value of hippocampal volumetry is context-dependent and may be limited in real-world, heterogeneous, moderate-severe clinical cohorts such as ours, where structured visual ratings may already capture the dominant neurodegenerative signal.

Comparative Classification Performance and What is "Comparative" Here

The comparative element of this paper is not diagnostic accuracy against a definitive clinical or pathological standard; rather, it is a head-to-head comparison of how commonly used tools classify individuals relative to a consistent reference MRI biomarker (HOC <5th percentile), and how performance changes when tools are combined. MMSE alone prioritized sensitivity (83.3%) but misclassified many individuals without abnormal HOC (specificity 41.0%). MTA alone showed similarly modest discrimination (AUC 0.62). The combined MMSE-MTA model showed the highest specificity (76.9%), AUC (0.70), and LR+ (2.71) among the approaches evaluated, although discrimination remained moderate and sensitivity was lower than MMSE alone (Table 5 and Figure 2). These findings suggest a potentially complementary role for combining cognitive screening with structured visual MRI rating in comparative classification, but this approach requires further validation before any clinical workflow recommendations can be made.

Implications for Practice and Capacity Building

These findings support a tiered approach to dementia assessment in settings where subspecialty neuroradiology and advanced biomarker testing are limited. Routine dementia MRI could be reported using standardized visual scales (including MTA, and depending on local aims, GCA/Koedam/Fazekas) by general radiologists after structured training and inter-reader standardization, while automated morphometry can be reserved for diagnostically uncertain cases, longitudinal monitoring, or research cohorts. Given the poor interchangeability observed between visual and automated measures (Table 2), implementation should emphasize complementarity: using automated outputs to support, not replace, a structured visual report and clinical context.

Strengths and Limitations

Strengths of this study include integrating a routine cognitive screen with both pragmatic visual MRI rating and automated morphometry in a sub-Saharan African setting, using a standardized acquisition protocol on a single 1.5T scanner platform. Key limitations include the modest sample size and a cohort enriched for moderate to severe presentations (Table 1), which may compress variability and attenuate structure-cognition associations. We used an MRI reference biomarker (HOC <5th percentile) to support consistent comparative classification across tools rather than an external diagnostic gold standard; therefore, findings should not be interpreted as diagnostic validation or causal inference. Normative percentiles produced by automated tools are derived largely from non-African reference datasets, which may affect percentile interpretation and may partly contribute to weak cross-method agreement (Table 2). Although visual scales were interpreted using age-adjusted thresholds and automated outputs were age- and sex-normalized, residual confounding from physiological aging cannot be fully excluded given the broad age range and

cross-sectional design. Visual ratings were performed by calibrated general radiologists rather than subspecialty neuroradiologists; residual reader variability, particularly for subtle medial temporal changes, may also contribute to disagreement between methods.

MMSE performance is influenced by education and language, which may underlie the sensitivity-specificity trade-offs observed (Table 5). In this cohort, participants had a mean of 6.9 years of formal education, and 4.8% had no formal schooling (Table 1), underscoring the need for caution when interpreting MMSE-based comparisons in a low-resource setting. Domain-level MMSE sub scores were not examined. In addition, the regression analyses were intentionally unadjusted for age, sex, and education to preserve a parsimonious exploratory model in a modest sample; however, residual confounding from these factors may have influenced the observed associations. Age-related effects on cognition may also have contributed to observed structure-cognition relationships, independent of underlying neurodegenerative pathology. Because eligibility was based on referral or screening concern rather than formal multidisciplinary diagnostic adjudication, the cohort may have included individuals with mild cognitive impairment or subjective cognitive complaints in addition to dementia. Although MMSE was independently administered prior to recruitment to improve consistency of cognitive screening, this does not eliminate clinical heterogeneity or possible misclassification.

Finally, because the study was designed around a clinically suspected cohort without formal diagnostic adjudication or a cognitively normal comparison group, the results should be interpreted as head-to-head comparative performance within a clinical referral/screen-positive population rather than as population-level diagnostic accuracy or dementia-specific validation.

Future Research

Future studies should (i) validate these comparative findings in larger, multi-site cohorts spanning earlier disease stages; (ii) include locally appropriate cognitive batteries (Rowland Universal Dementia Assessment Scale (RUDAS) and the Community Screening Instrument for Dementia (CSI-D)) and evaluate which tools best align with MRI markers in low-literacy settings; (iii) develop or test regionally representative normative MRI datasets to improve interpretation of automated percentiles; and (iv) assess the added value of automated morphometry in prespecified use-cases (diagnostically uncertain cases, longitudinal monitoring, and research cohorts), ideally using standardized clinical adjudication and, where feasible, biomarker-supported subtype classification. Emerging low-cost biomarkers, such as retinal imaging combined with AI-based analysis, offer promising, scalable approaches for assessing neurodegenerative and cerebrovascular changes and may complement MRI in resource-limited settings.[41,42]

Conclusion

In older Ugandan adults with clinically suspected dementia, visual and automated MRI measures showed poor agreement, indicating that these approaches were not interchangeable in this heterogeneous cohort. For comparative classification using HOC as a reference MRI biomarker, MMSE alone was sensitive but non-specific, while combining MMSE with visual MTA was associated with higher specificity and modestly improved overall discrimination. These findings suggest that visual MRI ratings and brief cognitive screening may provide complementary information in comparative dementia assessment, while the role of automated morphometry remains supportive and warrants further evaluation in larger, diagnostically adjudicated cohorts.

Data Sharing Statement

De-identified individual-level data underlying the analyses reported in this study are available from the corresponding author upon reasonable request and subject to approval by the Makerere University School of Medicine Research Ethics Committee, due to participant privacy and consent restrictions. Summary data supporting the findings are included within the manuscript and its Supplementary Materials.

Ethics and Consent Statements

The study was approved by the Makerere University School of Medicine Research and Ethics Committee (Mak-SOMREC-2022-337) and the Uganda National Council of Science and Technology (UNCST; HS4777ES). All

participants or their caregivers provided written informed consent prior to enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki and its later amendments. The recruitment strategy was designed to capture a clinically and demographically diverse sample, including both hospital-based and community-based cases, men and women, and individuals with varying levels of education. This ensured representation of populations at high risk of underdiagnosis in sub-Saharan Africa, addressing heterogeneity in disease presentation and access to diagnostic services.

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An unauthorized version of the MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

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