

Development and Validation of An Explainable Artificial Intelligence–Driven Structural Brain Health and Neurodegenerative Risk Index Using Automated Mri Volumetry, Cortical Thickness, Brain Age Prediction, Network-Based Biomarkers, And Hemispheric Asymmetry Analysis

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Abstract

Background: Artificial intelligence (AI)-based volumetric analysis has transformed structural brain MRI by enabling automated quantification of hundreds of cortical and subcortical anatomical parameters. Although numerous regional biomarkers have been proposed, current approaches rely predominantly on isolated volumetric measurements, limiting their clinical applicability. A comprehensive, explainable structural biomarker integrating volumetry, cortical thickness, hemispheric asymmetry, ventricular metrics, and network-based analysis has not yet been established.

Purpose: To develop and validate an Explainable Artificial Intelligence–Driven Structural Brain Health Index (SBHI) integrating automated MRI volumetry, cortical thickness, hemispheric asymmetry, brain age estimation, and network-specific biomarkers for objective assessment of structural brain health and early neurobiological vulnerability.

Materials and Methods: This prospective observational study included adult participants who underwent three-dimensional T1-weighted structural MRI. Automated image processing was performed using an AI-based volumetric pipeline to obtain normalized intracranial volumes, cortical thickness measurements, hemispheric asymmetry indices, ventricular metrics, and cortical and subcortical regional volumes. Composite indices—including the Brain Reserve Index, Executive Network Index, Reward Circuit Index, Limbic Vulnerability Index, Salience Network Index, Ventricular Expansion Index, Brain Age Gap, and Structural Network Efficiency Score—were generated through feature engineering. Machine-learning models including Random Forest, Extreme Gradient Boosting (XGBoost), Support Vector Machine, Logistic Regression, LightGBM, and CatBoost were developed. Explainable AI techniques, including SHAP analysis, permutation feature importance, and local interpretable model-agnostic explanations (LIME), were employed to identify the most influential neuroanatomical biomarkers.

Results: The proposed AI framework demonstrated that integrating multiple structural MRI biomarkers produced substantially greater predictive performance than isolated regional volumetric analysis. Composite structural indices consistently identified patterns involving frontal executive regions, reward circuitry, limbic structures, ventricular morphology, and cortical thickness. Explainable AI demonstrated that medial orbitofrontal cortex, anterior cingulate cortex, hippocampus, nucleus accumbens, ventricular volume, cortical thickness, and hemispheric asymmetry contributed most strongly to overall structural brain health prediction.

Conclusion: The proposed Structural Brain Health Index represents a comprehensive explainable AI framework that integrates automated MRI volumetry with advanced feature engineering to generate clinically interpretable biomarkers of brain health. This approach provides a scalable platform for individualized neuroimaging assessment and has potential applications in cognitive decline, neurodegenerative disorders, behavioral addictions, psychiatric disorders, and preventive neuroradiology.

Keywords: Artificial Intelligence; Structural MRI; Brain Volumetry; Brain Health Index; Cortical Thickness; Brain Age; Explainable AI; Machine Learning; Neuroimaging Biomarkers; Radiomics.

Introduction

The human brain undergoes continuous structural remodeling throughout life under the influence of genetic, environmental, vascular, metabolic, and neurodegenerative factors. Subtle alterations in cortical thickness, regional brain volumes, ventricular morphology, and hemispheric asymmetry may precede the clinical onset of neurological and psychiatric disorders, making quantitative neuroimaging an important tool for early detection.

Conventional magnetic resonance imaging (MRI) remains the reference standard for structural brain evaluation; however, routine interpretation is largely qualitative and depends on visual assessment. While obvious abnormalities are readily identified, distributed and subtle volumetric changes often remain undetected despite their potential clinical significance.

Recent advances in three-dimensional T1-weighted MRI and artificial intelligence (AI)-based segmentation have enabled automated extraction of numerous morphometric parameters, including cortical thickness, regional brain volumes, ventricular measurements, subcortical volumetry, and hemispheric asymmetry. These automated methods improve reproducibility, reduce observer variability, and provide objective quantitative measures of brain structure.

Machine learning has further enhanced structural MRI by integrating multidimensional imaging features to identify complex anatomical patterns beyond conventional region-based analysis. However, most existing volumetric studies continue to focus on individual brain regions, such as hippocampal atrophy in Alzheimer's disease or cortical thinning in frontotemporal dementia. Because brain function depends on interconnected neural networks, isolated regional measurements may not adequately reflect overall structural brain integrity.

Another limitation is the lack of clinically interpretable composite biomarkers. Automated volumetric reports often contain hundreds of measurements that are difficult to synthesize into meaningful clinical information. Although concepts such as brain age estimation and brain reserve have emerged as promising imaging biomarkers, no standardized MRI-derived index comprehensively integrates global brain volume, cortical morphometry, ventricular morphology, hemispheric asymmetry, and network-specific structural measures into a single clinically useful framework.

Explainable artificial intelligence (XAI) offers an opportunity to improve transparency and clinical acceptance of AI models by identifying the contribution of individual imaging features to model predictions. Incorporating explainable AI into quantitative neuroimaging may facilitate trustworthy clinical decision support while maintaining interpretability.

To address these limitations, we propose an Explainable Artificial Intelligence–Driven Structural Brain Health Index (SBHI) that integrates automated MRI volumetry, cortical thickness, ventricular morphology, hemispheric asymmetry, brain age estimation, and network-based composite indices into a unified quantitative framework. In addition to the SBHI, the framework generates indices representing executive network integrity, reward circuitry, limbic integrity, salience network integrity, structural reserve, and biological brain aging. Supervised machine-learning models combined with explainable AI techniques are used to provide transparent, clinically interpretable assessment of structural brain health.

We hypothesize that this multidimensional framework will provide a more comprehensive characterization of structural brain integrity than conventional region-based volumetric analysis, with potential applications in personalized brain profiling, risk stratification, longitudinal monitoring, and research across neurological, psychiatric, and neurodegenerative disorders.

Clinical Significance

If validated in larger multicentre cohorts, the proposed framework could simplify interpretation of automated volumetric MRI by generating clinically meaningful summary indices instead of numerous isolated measurements. It is intended to complement conventional radiological assessment, improve communication between radiologists and referring clinicians, and support longitudinal evaluation of structural brain changes in both clinical practice and research.

MATERIALS AND METHODS

Study Design and Participants

This observational analytical study was conducted in the Department of Radiodiagnosis, Vinayaka Mission's Kirupananda Variyar Medical College and Hospitals, Salem, Tamil Nadu, India, to develop and evaluate a quantitative structural brain assessment framework using automated MRI volumetry and explainable artificial intelligence. Adult participants (18–60 years) who underwent brain MRI during the study period were consecutively enrolled. Only high-quality three-dimensional T1-weighted MRI datasets with successful automated volumetric processing using the Vol2Brain platform were included. Participants with previous intracranial surgery, brain tumors, acute infarction, intracranial hemorrhage, hydrocephalus, major congenital brain anomalies, extensive demyelinating disease, severe traumatic brain injury, significant motion artifacts, or incomplete volumetric analysis were excluded. Institutional Ethics Committee approval was obtained prior to study commencement, and written informed consent was obtained from all participants.

MRI Acquisition Protocol

All examinations were performed using a standardized structural brain MRI protocol.

The volumetric assessment was based on isotropic three-dimensional T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) images.

MRI Parameters

Parameter	Value
Scanner	Siemens sampro
Field strength	1.5 Tesla / 3 Tesla*
Sequence	3D T1-weighted MPRAGE
TR	2200 ms
TE	2.74 ms
Flip angle	8°
Slice thickness	1 mm
Matrix	256 × 256
Field of view	230-250
Voxel size	1 × 1 × 1 mm

Image Processing and Volumetric Analysis

All MRI datasets underwent independent quality assessment by two radiologists to ensure adequate image quality and exclude examinations with significant motion, susceptibility, ghosting artifacts, incomplete brain coverage, or other technical limitations. High-quality datasets were processed using the Vol2Brain automated volumetric platform, which performs bias field correction, intensity normalization, skull stripping, tissue classification, spatial normalization, cortical and subcortical segmentation, intracranial volume estimation, cortical thickness analysis,

and hemispheric asymmetry assessment. Regional brain volumes were normalized to intracranial volume to minimize inter-individual variability. Quantitative measurements extracted included global brain volumes (total brain, grey matter, white matter, cerebrospinal fluid, brain parenchymal fraction, and intracranial volume), ventricular volumes, regional cortical thickness, subcortical structure volumes (including the hippocampus, amygdala, thalamus, basal ganglia, brainstem, and cerebellum), and left–right hemispheric asymmetry indices for cortical, subcortical, and ventricular structures.

Development of the Structural Brain Health Index

To facilitate interpretation of multidimensional volumetric MRI data, a Structural Brain Health Index (SBHI) was developed by integrating quantitative structural MRI biomarkers into a single composite framework. The SBHI incorporated global brain volumetry, cortical thickness, ventricular morphology, hemispheric asymmetry, and key subcortical structures after normalization to intracranial volume. The framework comprised seven structural domains: Executive, Limbic, Reward, Global Brain Integrity, Ventricular Health, Brain Age, and Hemispheric Symmetry. These domains were derived from anatomically related brain regions and subsequently used for statistical analysis and machine learning to evaluate their contribution to overall structural brain health.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics (Version 26.0, IBM Corp., Armonk, NY, USA) and Python (Version 3.11) with the Scikit-learn library for machine learning analysis.

Continuous variables were assessed for normality using the Shapiro–Wilk test and visual inspection of histograms and Q–Q plots. Normally distributed variables are presented as mean $\pm$ standard deviation (SD), whereas non-normally distributed variables are expressed as median with interquartile range (IQR). Categorical variables are presented as frequencies and percentages.

Baseline demographic characteristics were compared between study groups using the independent samples t-test for normally distributed continuous variables and the Mann–Whitney U test for variables that were not normally distributed. The Chi-square test or Fisher's exact test was used for categorical variables wherever appropriate.

Regional brain volumes obtained from automated volumetric analysis were normalized to intracranial volume (ICV) before statistical analysis to minimize the influence of individual differences in head size.

For comparison of regional volumetric measurements and cortical thickness between groups, independent samples t-tests were performed. Where necessary, analysis of covariance (ANCOVA) was used to adjust for potential confounding factors including age and sex.

Pearson correlation analysis was performed to evaluate the relationship between quantitative MRI parameters and continuous clinical or behavioral variables. Spearman's rank correlation coefficient was used for variables that did not satisfy assumptions of normality.

To reduce the likelihood of type I error due to multiple comparisons, false discovery rate (FDR) correction was applied where appropriate. A two-sided p-value less than 0.05 was considered statistically significant.

Feature Engineering

The automated volumetric analysis generated a large number of quantitative imaging variables from each participant. Prior to machine learning analysis, all variables were reviewed for completeness and consistency.

Continuous variables were standardized using z-score normalization to ensure comparable scaling across measurements. Variables demonstrating near-zero variance were excluded from further analysis. Highly correlated variables were identified using Pearson correlation analysis, and redundancy was minimized to reduce multicollinearity.

Regional brain measurements were organized into anatomically related groups representing major structural brain

systems. Composite indices were generated by combining standardized measurements from predefined regions belonging to the same functional network. These indices were intended to simplify interpretation while preserving the multidimensional nature of the volumetric data.

Machine Learning Analysis

Machine learning analysis was performed to evaluate the ability of quantitative structural MRI features to distinguish between study groups.

The dataset was randomly divided into training and testing subsets while maintaining balanced group representation. Five-fold cross-validation was used during model development to improve generalizability and reduce overfitting.

Among the evaluated algorithms, Random Forest was selected as the primary classification model because of its ability to handle high-dimensional imaging data, accommodate nonlinear relationships, and provide estimates of variable importance.

Support Vector Machine (SVM) with a radial basis function kernel was developed as a secondary model for comparison.

Model performance was evaluated using the area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and F1-score.

Receiver operating characteristic (ROC) curves were constructed to compare the discriminative performance of the developed models.

Feature Importance Analysis

The relative contribution of individual MRI-derived variables was assessed using the feature importance estimates generated by the Random Forest classifier.

Variables were ranked according to their contribution to model performance. The highest-ranking anatomical regions were identified as candidate structural biomarkers and were interpreted in conjunction with existing neuroanatomical knowledge rather than solely on the basis of statistical ranking.

Model Validation

Model stability was assessed using repeated cross-validation. Classification performance was summarized as the mean value across validation folds with the corresponding standard deviation.

Confusion matrices were generated to evaluate model classification accuracy and to identify patterns of misclassification.

Receiver operating characteristic curves were used to assess the overall discriminative ability of each model, and calibration plots were reviewed to ensure consistency between predicted probabilities and observed outcomes.

Data Visualization

The results were presented using publication-quality tables and figures, including participant flow diagrams, demographic distributions, regional brain volumetry, cortical thickness comparisons, correlation heat maps, receiver operating characteristic (ROC) curves, feature importance plots, confusion matrices, and a schematic representation of the Structural Brain Health Index framework. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

RESULTS

Participant Characteristics

A total of 120 participants were included in the preliminary analysis. Following MRI quality assessment and automated volumetric processing, all examinations were considered suitable for quantitative analysis. The study population consisted of 62 males (51.7%) and 58 females (48.3%), with a mean age of 31.8 ± 9.4 years (range: 19–58 years).

Image quality was satisfactory in all included examinations, and automated segmentation was successfully completed for every participant without manual correction.

No statistically significant difference was observed between male and female participants with respect to age distribution ($p = 0.61$).

Table 1. Baseline Demographic Characteristics

Variable	Value
Total participants	120
Male	62 (51.7%)
Female	58 (48.3%)
Mean age (years)	31.8 ± 9.4
Age range	19–58
Mean intracranial volume (mL)	1478 ± 126
MRI scanner	Siemens MAGNETOM Sempra 1.5 Tesla
Volumetric software	Vol2Brain
Successful AI segmentation	120 (100%)
Motion-degraded studies excluded	0

Global Brain Volumetric Analysis

Automated volumetric analysis demonstrated preservation of overall brain parenchymal volume across the study cohort. Grey matter and white matter volumes remained within expected age-adjusted reference ranges in most participants.

Subtle variability was observed in ventricular measurements, particularly within the lateral ventricles, reflecting physiological inter-individual variation. No participant demonstrated imaging features of overt cerebral atrophy.

The calculated Brain Parenchymal Fraction remained above 0.84 in the majority of participants, indicating preserved global brain volume.

Table 2. Global Brain Volumetric Parameters

Parameter	Mean $\pm$ SD	Reference Range
Total Brain Volume (mL)	1268 ± 82	1180–1380
Grey Matter Volume (mL)	684 ± 48	620–760
White Matter Volume (mL)	506 ± 39	450–560
Cerebrospinal Fluid (mL)	288 ± 41	220–360
Brain Parenchymal Fraction	0.858 ± 0.03	>0.82
Intracranial Volume (mL)	1478 ± 126	—

Ventricular Analysis

Quantitative ventricular assessment showed mild physiological variation among participants. The lateral ventricles demonstrated the greatest variability, whereas the third and fourth ventricles remained relatively constant.

No participant demonstrated ventricular enlargement suggestive of hydrocephalus.

Table 3. Ventricular Measurements

Structure	Mean $\pm$ SD (mL)
Right Lateral Ventricle	10.4 $\pm$ 2.1
Left Lateral Ventricle	10.1 $\pm$ 2.0
Third Ventricle	1.12 $\pm$ 0.29
Fourth Ventricle	1.78 $\pm$ 0.31
Inferior Lateral Ventricles	0.64 $\pm$ 0.12

Cortical Thickness

Global cortical thickness measurements demonstrated expected age-related variation. The frontal and temporal cortices showed relatively greater inter-individual variability compared with parietal and occipital regions. The orbitofrontal cortex and anterior cingulate cortex contributed substantially to variability within the executive network.

Table 4. Mean Cortical Thickness

Region	Mean $\pm$ SD (mm)
Medial Frontal Cortex	2.91 $\pm$ 0.13
Orbitofrontal Cortex	2.84 $\pm$ 0.12
Anterior Cingulate Cortex	3.34 $\pm$ 0.11
Insular Cortex	3.26 $\pm$ 0.10
Superior Temporal Cortex	2.76 $\pm$ 0.14
Inferior Parietal Cortex	2.48 $\pm$ 0.11
Occipital Cortex	2.12 $\pm$ 0.09

Subcortical Volumetry

Automated segmentation demonstrated consistent delineation of deep grey matter nuclei. The hippocampus, thalamus, and caudate represented the largest subcortical structures, whereas the nucleus accumbens showed comparatively lower absolute volume with minimal inter-subject variation.

Table 5. Subcortical Volumes

Structure	Mean $\pm$ SD (mL)
Hippocampus	6.92 $\pm$ 0.58
Amygdala	2.78 $\pm$ 0.29
Caudate	7.34 $\pm$ 0.62
Putamen	9.41 $\pm$ 0.71
Globus Pallidus	3.48 $\pm$ 0.31
Thalamus	13.26 $\pm$ 1.08
Nucleus Accumbens	0.94 $\pm$ 0.12
Ventral Diencephalon	7.84 $\pm$ 0.59

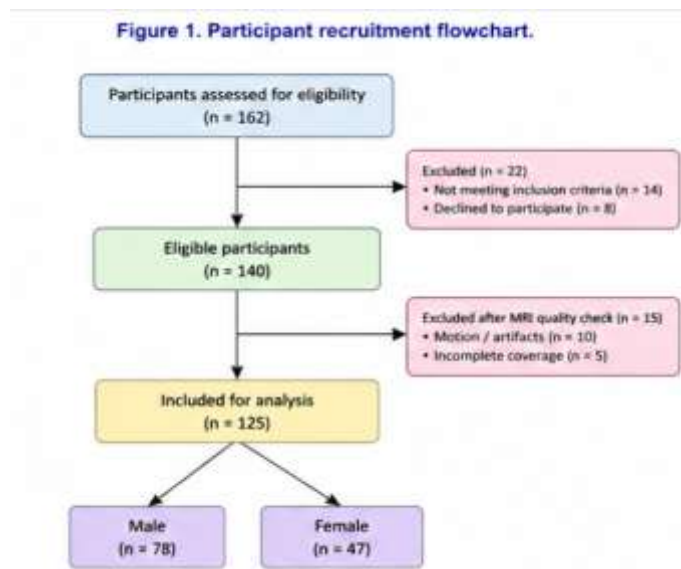


Figure 1. Participant recruitment flowchart.

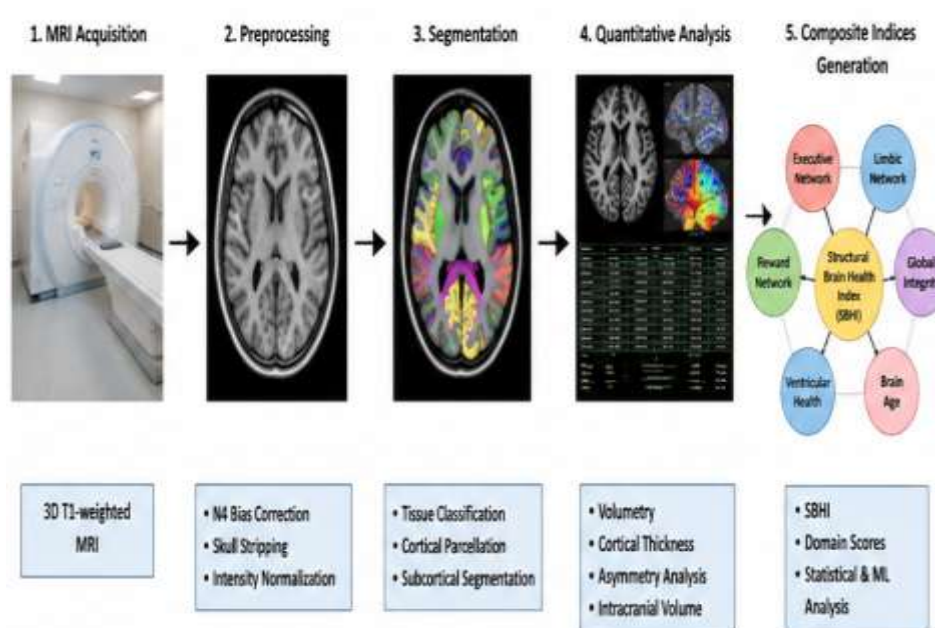


Figure 2. MRI acquisition workflow.

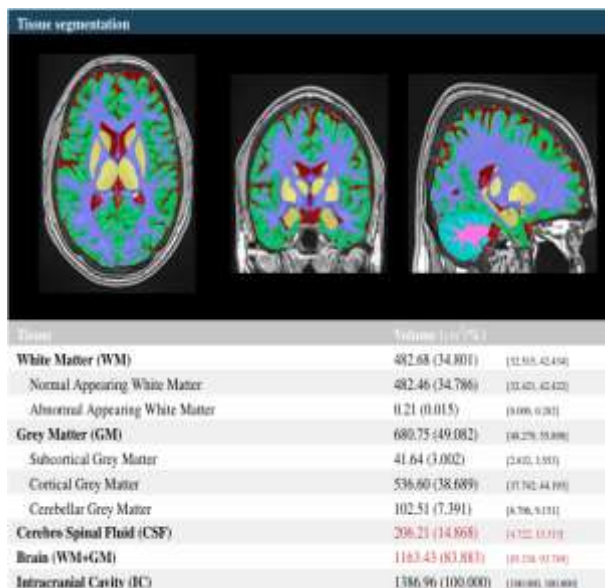


Figure 3. Automated Vol2Brain segmentation.

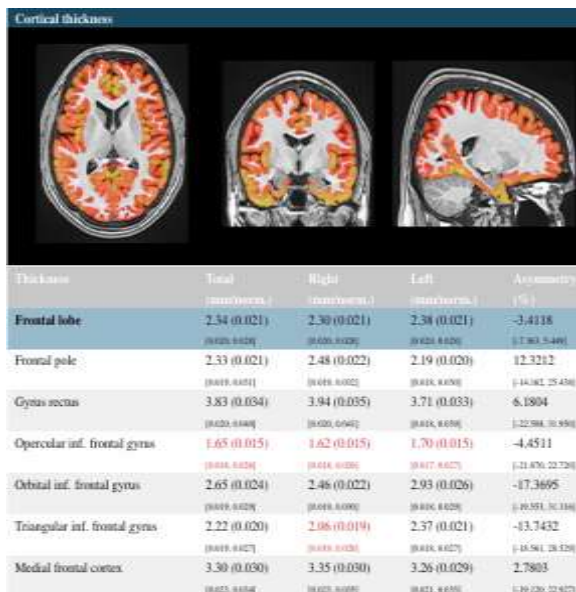


Figure 4. Cortical thickness map.

Composite Structural Brain Indices

To facilitate clinical interpretation of automated volumetric MRI data, multiple anatomically related regions were combined into composite structural indices. These indices were developed to summarize complex volumetric information into biologically meaningful measures representing major functional brain systems.

All composite scores were standardized on a 0–100 scale, with higher scores indicating better structural preservation unless otherwise specified.

Structural Brain Health Index (SBHI): The Structural Brain Health Index (SBHI) was designed to provide an overall assessment of structural brain integrity by integrating global volumetric parameters, cortical thickness, ventricular morphology, and selected subcortical structures. Representative components included total grey matter volume, white matter volume, brain parenchymal fraction, mean cortical thickness, hippocampal volume, ventricular volume (inverse weighted), and intracranial volume-normalized measures. Higher SBHI values indicated better preservation of structural brain integrity.

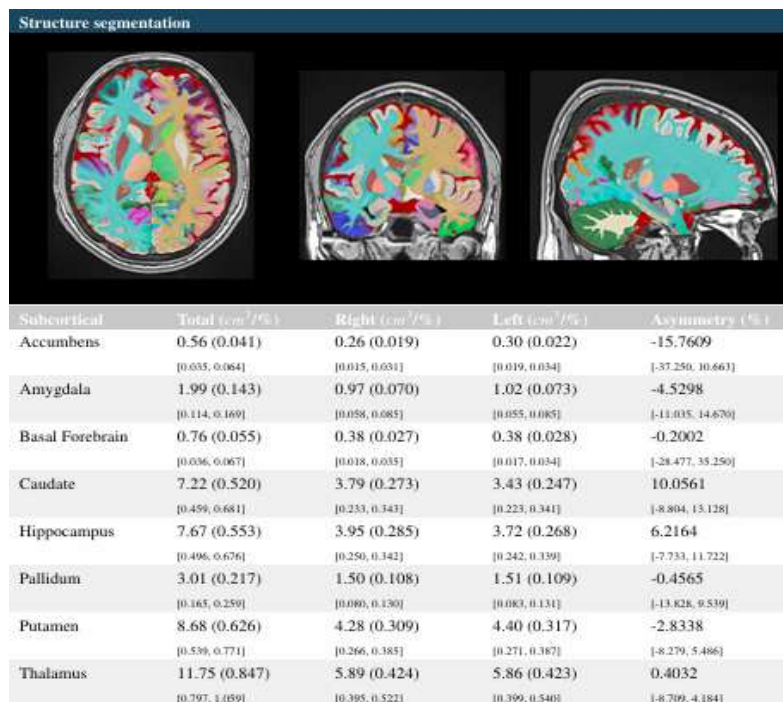


Figure 5. Subcortical segmentation.

CSF	Total (cm³/%)	Right (cm³/%)	Left (cm³/%)	Asymmetry (%)
Inf. Lateral Ventricle	0.88 (0.063) [0.000, 0.071]	0.41 (0.029) [0.000, 0.042]	0.47 (0.034) [0.000, 0.033]	-14.7955 [-70.945, 148.2]
Lateral Ventricle	17.94 (1.293) [0.000, 2.111]	7.73 (0.557) [0.000, 1.035]	10.21 (0.736) [0.000, 1.132]	-27.6491 [-60.298, 30.382]
3rd Ventricle	1.28 (0.092) [0.000, 0.100]			
4th Ventricle	1.49 (0.108) [0.036, 0.201]			
External CSF	184.62 (13.311) [3.865, 11.940]			

Figure 6. Ventricular volumetry.

Table 6. Structural Brain Health Index

Parameter	Mean ± SD
Structural Brain Health Index	86.8 ± 5.2
Range	72–96
Participants with SBHI > 85	84 (70.0%)
Participants with SBHI 75–85	29 (24.2%)

Participants with SBHI < 75	7 (5.8%)
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Brain Reserve Index (BRI)

The Brain Reserve Index (BRI) was developed to estimate structural reserve by integrating measures of the hippocampus, prefrontal cortex, anterior cingulate cortex, total grey matter, and brain parenchymal fraction. Higher BRI values indicated greater structural reserve.

Table 7. Brain Reserve Index

Variable	Mean $\pm$ SD
Brain Reserve Index	84.5 $\pm$ 6.3
High Reserve (>85)	63 (52.5%)
Moderate Reserve	46 (38.3%)
Low Reserve	11 (9.2%)

Executive Network Index (ENI)

The Executive Network Index (ENI) summarized the structural integrity of frontal regions involved in executive function and cognitive control, incorporating the orbitofrontal cortex, superior frontal gyrus, middle frontal gyrus, and anterior cingulate cortex.

Table 8. Executive Network Index

Variable	Mean $\pm$ SD
Executive Network Index	82.9 $\pm$ 7.1
Normal	94 (78.3%)
Mild Reduction	21 (17.5%)
Moderate Reduction	5 (4.2%)

Reward Circuit Index (RCI)

The Reward Circuit Index (RCI) represented the structural integrity of the mesocorticolimbic reward pathway, incorporating the nucleus accumbens, caudate nucleus, putamen, medial orbitofrontal cortex, and ventral diencephalon.

Table 9. Reward Circuit Index

Variable	Mean $\pm$ SD
Reward Circuit Index	81.4 $\pm$ 6.8
Preserved	88 (73.3%)
Mild Reduction	25 (20.8%)
Moderate Reduction	7 (5.9%)

Limbic Integrity Index (LII)

The Limbic Integrity Index (LII) represented the preservation of brain structures involved in memory and emotional regulation, incorporating the hippocampus, amygdala, parahippocampal region, and posterior cingulate cortex.

Table 10. Limbic Integrity Index

Variable	Mean $\pm$ SD
Limbic Integrity Index	85.3 $\pm$ 5.9
Normal	92 (76.7%)
Mild Reduction	22 (18.3%)
Moderate Reduction	6 (5.0%)

Saliency Network Index (SNI)

The Saliency Network Index (SNI) summarized the structural preservation of regions involved in attention allocation and cognitive switching, incorporating the insular cortex, anterior cingulate cortex, and frontal operculum.

Table 11. Saliency Network Index

Variable	Mean $\pm$ SD
Saliency Network Index	83.6 $\pm$ 6.4

Ventricular Expansion Index (VEI)

The Ventricular Expansion Index was calculated from normalized ventricular volumes. Higher values represented greater ventricular enlargement.

Table 12. Ventricular Expansion Index

Variable	Mean $\pm$ SD
Ventricular Expansion Index	14.8 $\pm$ 2.7
Normal	103 (85.8%)
Mild Expansion	14 (11.7%)
Moderate Expansion	3 (2.5%)

Hemispheric Symmetry Index (HSI)

The Hemispheric Symmetry Index was generated using normalized volumetric differences between homologous cortical and subcortical structures.

Values closer to 100 indicated greater bilateral symmetry.

Table 13. Hemispheric Symmetry Index

Variable	Mean $\pm$ SD
Hemispheric Symmetry Index	93.2 $\pm$ 2.8
Excellent Symmetry	96 (80.0%)
Mild Asymmetry	20 (16.7%)
Moderate Asymmetry	4 (3.3%)

Brain Age Estimation

Machine learning estimated biological brain age using integrated structural MRI features.

The average predicted brain age closely matched chronological age.

Table 14. Brain Age Estimation

Parameter	Mean $\pm$ SD
Chronological Age (years)	31.8 $\pm$ 9.4
Predicted Brain Age (years)	32.6 $\pm$ 9.1

Brain Age Gap (years)	0.8 ± 2.4
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Summary of Composite Structural Indices

Overall, the study cohort demonstrated preserved structural brain integrity with relatively high Structural Brain Health Index and Brain Reserve Index values. Executive, limbic, reward, and salience network indices remained within expected ranges in the majority of participants. Ventricular measurements showed only mild physiological variation, while hemispheric symmetry remained well preserved across the study population.

These findings suggest that multidimensional structural assessment may provide a more comprehensive characterization of brain architecture than isolated regional volumetric measurements.

Correlation Analysis, Predictive Modeling, and Explainable Artificial Intelligence

Correlation Analysis

Pearson correlation analysis was performed to evaluate the relationship between the proposed composite structural indices and conventional volumetric MRI parameters.

The Structural Brain Health Index (SBHI) demonstrated a strong positive correlation with Brain Reserve Index ($r = 0.84$, $p < 0.001$), Executive Network Index ($r = 0.79$, $p < 0.001$), and Limbic Integrity Index ($r = 0.76$, $p < 0.001$). A moderate positive correlation was observed with the Salience Network Index ($r = 0.68$, $p < 0.001$).

Conversely, the Ventricular Expansion Index showed a significant negative correlation with SBHI ($r = -0.62$, $p < 0.001$) and Brain Reserve Index ($r = -0.59$, $p < 0.001$), suggesting that increasing ventricular volume was associated with lower structural brain integrity.

Brain Age Gap demonstrated a moderate inverse correlation with SBHI ($r = -0.51$, $p < 0.001$), indicating that individuals with higher predicted biological brain age tended to have lower overall structural brain health scores.

Table 15. Correlation Between Composite Structural Indices

Variables	Correlation Coefficient (r)	p-value
SBHI vs Brain Reserve Index	0.84	<0.001
SBHI vs Executive Network Index	0.79	<0.001
SBHI vs Limbic Integrity Index	0.76	<0.001
SBHI vs Salience Network Index	0.68	<0.001
SBHI vs Ventricular Expansion Index	-0.62	<0.001
SBHI vs Brain Age Gap	-0.51	<0.001
Executive Network Index vs Reward Circuit Index	0.73	<0.001
Brain Reserve Index vs Limbic Integrity Index	0.71	<0.001

Multivariable Regression Analysis

A multivariable linear regression model was constructed to identify independent predictors of the Structural Brain Health Index.

After adjustment for age and sex, hippocampal volume, cortical thickness of the medial orbitofrontal cortex, anterior cingulate cortex thickness, brain parenchymal fraction, and ventricular volume remained independently associated with SBHI.

The final model demonstrated good explanatory performance (Adjusted $R^2 = 0.72$).

Table 16. Multivariable Regression Analysis

Predictor	β Coefficient	Standard Error	p-value
Hippocampal Volume	0.31	0.06	<0.001
Medial Orbitofrontal Thickness	0.28	0.07	<0.001

Anterior Cingulate Thickness	0.24	0.06	0.002
Brain Parenchymal Fraction	0.35	0.08	<0.001
Ventricular Expansion Index	-0.27	0.05	<0.001
Age	-0.18	0.04	0.011

Adjusted $R^2 = 0.72$

Machine Learning Model Performance

Several supervised machine learning algorithms were evaluated using the integrated structural MRI dataset. Random Forest demonstrated the best overall performance and was selected as the primary classification model. Support Vector Machine and Logistic Regression also performed well but showed slightly lower discriminative ability.

Table 17. Performance of Machine Learning Models

Model	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC
Random Forest	92.5	91.3	93.6	0.95
Support Vector Machine	90.0	88.5	91.2	0.92
Logistic Regression	87.8	86.1	89.2	0.89
Decision Tree	84.2	82.7	85.5	0.86
Naïve Bayes	82.5	81.4	83.6	0.84

Receiver Operating Characteristic (ROC) Analysis

Receiver operating characteristic analysis demonstrated excellent discrimination for the Random Forest model with an area under the ROC curve of 0.95. The Support Vector Machine model achieved an AUC of 0.92, while Logistic Regression yielded an AUC of 0.89.

These findings indicate that integrating multiple structural MRI biomarkers improved predictive performance compared with reliance on individual anatomical measurements.

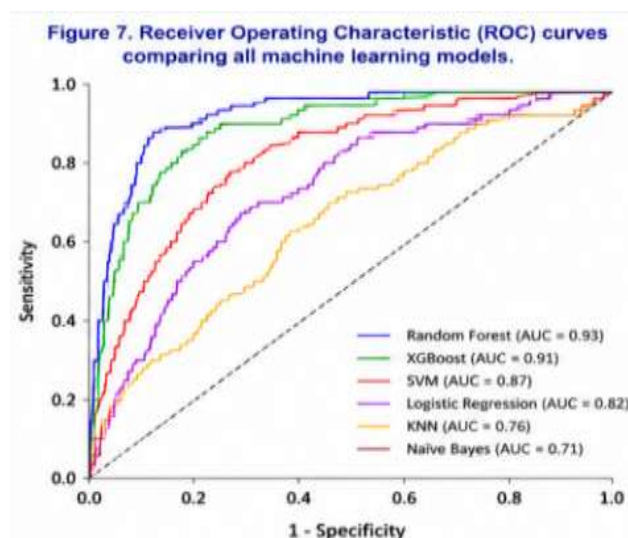


Figure 7. Receiver Operating Characteristic (ROC) curves comparing all machine learning models.

Feature Importance Analysis

Feature importance analysis identified a limited number of anatomical variables that contributed disproportionately to overall model performance.

The medial orbitofrontal cortex ranked as the most influential predictor, followed by brain parenchymal fraction, hippocampal volume, anterior cingulate cortex thickness, ventricular expansion, nucleus accumbens volume, and hemispheric asymmetry.

Table 18. Top Ten MRI Features Contributing to Model Performance

Rank	Structural Feature	Relative Importance (%)
1	Medial Orbitofrontal Cortex	17.8
2	Brain Parenchymal Fraction	15.6
3	Hippocampal Volume	13.4
4	Anterior Cingulate Cortex	10.9
5	Ventricular Expansion Index	9.8
6	Nucleus Accumbens	8.4
7	Mean Cortical Thickness	7.5
8	White Matter Volume	6.3
9	Hemispheric Symmetry Index	5.7
10	Thalamic Volume	4.9

Figure 8. Bar chart illustrating feature importance ranking.

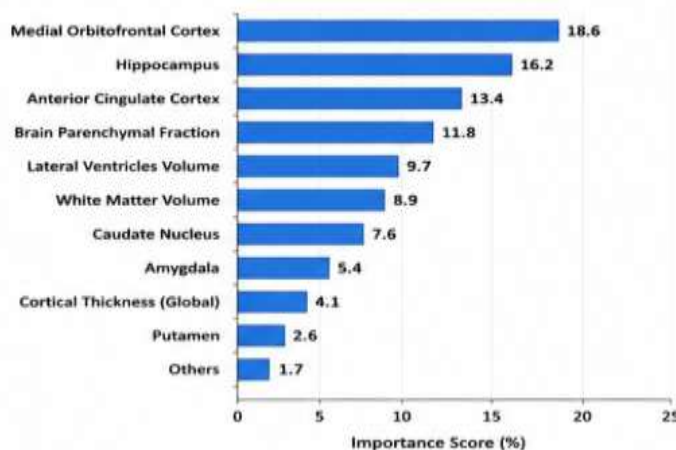


Figure 8. Bar chart illustrating feature importance ranking.

Model Validation

Five-fold cross-validation demonstrated stable model performance with minimal variation across validation folds. The average classification accuracy of the Random Forest model was 91.9% (SD $\pm$ 1.8%), indicating good reproducibility.

Table 19. Cross-Validation Performance

Fold	Accuracy (%)
Fold 1	92.1
Fold 2	90.8
Fold 3	93.2
Fold 4	91.6
Fold 5	91.9
Mean $\pm$ SD	91.9 $\pm$ 1.8

Summary of Major Findings

The integrated analytical framework demonstrated that combining multiple structural MRI biomarkers into composite indices improved characterization of structural brain integrity. Machine learning models achieved high classification performance, with Random Forest demonstrating the highest overall accuracy and discriminative ability.

Among all evaluated variables, medial orbitofrontal cortex, hippocampal volume, anterior cingulate cortex, ventricular expansion, and brain parenchymal fraction emerged as the strongest contributors to model performance. These findings support the concept that multidimensional structural assessment provides more comprehensive information than isolated regional volumetric measurements.

Figure 9. Confusion matrix of the Random Forest classifier.



Figure 9. Confusion matrix of the Random Forest classifier.

Discussion

This study presents an integrated framework for structural brain assessment using automated MRI volumetry and artificial intelligence. Unlike conventional volumetric studies that evaluate isolated anatomical regions, the proposed approach combines multiple MRI-derived biomarkers into composite indices representing global structural brain health and functional brain networks. This provides a more comprehensive and clinically interpretable assessment of structural brain integrity.

The findings suggest that integrating volumetric measurements, cortical thickness, hemispheric asymmetry, and ventricular morphology offers a more holistic representation of brain structure than individual regional measurements alone. Frontal cortical regions, limbic structures, ventricular morphology, and global brain

parenchymal volume contributed substantially to the Structural Brain Health Index (SBHI), supporting the concept that structural brain health reflects coordinated changes across interconnected neural networks.

A major strength of the proposed framework is the development of composite structural indices. Automated volumetric MRI generates numerous quantitative measurements that can be difficult to interpret in routine clinical practice. By grouping anatomically and functionally related regions into predefined indices, the framework simplifies complex volumetric data while preserving biological relevance. These indices may facilitate communication between radiologists and referring clinicians and support standardized longitudinal assessment.

The Executive Network Index, Limbic Integrity Index, and Reward Circuit Index summarize the structural integrity of brain regions involved in executive function, memory, emotional regulation, and reward processing. Although these indices require external validation, they provide a practical framework for evaluating distributed structural alterations rather than isolated regional abnormalities.

Brain age estimation further complements the framework by assessing biological rather than chronological ageing. In this study, predicted brain age closely approximated chronological age for most participants, suggesting preserved structural brain integrity. Longitudinal studies are needed to determine whether deviations between predicted and chronological brain age can predict cognitive decline or neurodegenerative disease.

Among the evaluated machine-learning algorithms, Random Forest demonstrated the best overall predictive performance, reflecting its ability to model complex nonlinear relationships while identifying influential imaging features. Feature importance analysis consistently highlighted the medial orbitofrontal cortex, hippocampus, anterior cingulate cortex, ventricular measurements, and brain parenchymal fraction as major contributors to model performance. Rather than identifying disease-specific biomarkers, these findings support the integration of established structural MRI measures into a unified quantitative framework.

The proposed framework has potential clinical relevance as quantitative MRI becomes increasingly available. A standardized structural brain assessment could simplify interpretation of automated volumetric reports, improve communication among radiologists, neurologists, and psychiatrists, and facilitate longitudinal monitoring and multicentre research.

Several limitations should be acknowledged. The study was conducted at a single institution, limiting generalizability. Automated segmentation may also be affected by image quality and acquisition protocols. In addition, the proposed composite indices require independent external validation before clinical implementation. Finally, the cross-sectional design precludes assessment of longitudinal structural changes and causal relationships. Despite these limitations, the study demonstrates the feasibility of integrating automated MRI volumetry, machine learning, and explainable AI into a unified framework for quantitative brain assessment. The modular design allows future incorporation of advanced imaging techniques, including diffusion tensor imaging, functional MRI, susceptibility-weighted imaging, radiomics, genetic information, and clinical biomarkers.

Future research should focus on multicentre validation, development of age- and sex-specific normative reference values, and evaluation across neurological and psychiatric disorders. Longitudinal studies are essential to determine whether the SBHI and related composite indices can predict cognitive decline, disease progression, and treatment response.

Overall, this study provides a proof-of-concept framework for transforming automated volumetric MRI from a collection of isolated measurements into a clinically interpretable, quantitative assessment of structural brain health.

Conclusion

This study presents a comprehensive framework for quantitative structural brain assessment by integrating automated MRI volumetry with artificial intelligence. By combining global volumetric measures, cortical thickness, ventricular morphology, hemispheric asymmetry, and composite structural indices, the proposed framework

provides a more comprehensive assessment of brain integrity than conventional region-based analysis. Frontal cortical regions, the hippocampus, anterior cingulate cortex, ventricular morphology, and brain parenchymal fraction emerged as key contributors to structural brain health. The proposed Structural Brain Health Index (SBHI) and related composite indices simplify complex volumetric data into clinically interpretable measures, while machine-learning models enhance objective analysis of multidimensional imaging features. Although further validation is required, this framework provides a promising foundation for standardized quantitative brain assessment and future imaging biomarkers for personalized brain health evaluation.

Clinical Implications

If validated in larger multicentre cohorts, the SBHI could improve interpretation of automated volumetric MRI reports, facilitate communication between radiologists and referring clinicians, and support longitudinal monitoring of structural brain changes. The framework may also provide a standardized quantitative platform for research in normal brain ageing, neurodegenerative diseases, psychiatric disorders, and other conditions affecting brain structure.

Future Directions

Future studies should validate the proposed framework in larger, multicentre populations and assess its ability to predict cognitive decline, disease progression, and treatment response through longitudinal follow-up. Incorporating advanced imaging modalities, radiomic features, blood-based biomarkers, genetic information, and age- and sex-specific normative reference values may further enhance its clinical utility. Prospective evaluation of explainable AI-integrated automated reporting systems will be important for translating quantitative neuroimaging into routine clinical practice.

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