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Predicting Cognitive Function in Aging from White Matter Microstructure with Explainable Machine Learning

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Abstract. Cognitive decline is one of the most significant challenges in aging populations, closely linked to structural and functional changes in the brain. White matter degeneration, which disrupts neural connectivity, is known to affect cognitive processes such as memory, attention, and executive function. Diffusion Tensor Imaging (DTI) provides a unique window into microstructural integrity through metrics like fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (L1), and radial diffusivity (L23m). In this study, we used DTI-derived features of 50 cognitively normal participants from the Open Access Series of Imaging Studies (OASIS) to investigate whether patterns of white matter organization can predict cognitive performance. Using four machine learning models—ridge regression, lasso regression, partial least squares (PLS), and random forest (RF)—we assessed model performance through five-fold cross-validation. SHAP (SHapley Additive exPlanations) analysis was employed to interpret the most influential features driving predictions. The Random Forest (RF) model achieved the highest cross-validated R^2 (0.35) for the Trail B-A task, demonstrating moderate predictive power and revealing non-linear relationships between DTI features and cognitive measures. SHAP analysis highlighted tracts such as the cingulum, inferior longitudinal fasciculus, and posterior corona radiata as key contributors. These findings demonstrate that explainable machine learning can uncover neurobiologically meaningful predictors of cognitive variation in healthy aging, providing a potential framework for early risk assessment of cognitive decline and differentiation from abnormal aging trajectories such as dementia.

Keywords: Diffusion Tensor Imaging, Cognitive Aging, Machine Learning, SHAP, OASIS Dataset

1. Introduction

Cognitive aging is an inevitable aspect of human development, reflecting gradual changes in neural structure and function that influence learning, attention, and problem-solving [1-3]. The integrity of cerebral white matter, which is essential for efficient neural communication, is postulated to be a key determinant of cognitive efficiency in later life [4,5]. The deterioration of white matter integrity—particularly in long-range association tracts—has been consistently linked to reduced processing speed, episodic memory decline, and impaired executive function in older adults[6–8].

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Diffusion Tensor Imaging (DTI) offers a non-invasive tool for quantifying microstructural changes in white matter through metrics such as fractional anisotropy (FA) and mean diffusivity (MD) [9-11]. High FA values typically indicate tightly organized and myelinated fiber bundles, whereas elevated MD suggests demyelination or axonal degeneration [12,13]. Longitudinal DTI studies have shown that white matter decline begins in midlife and accelerates during later decades, often preceding measurable cognitive symptoms [14,15].

Understanding these structure–function relationships is not only important for studying normal aging, but also for identifying abnormal aging trajectories, such as mild cognitive impairment (MCI) and dementia [16-18]. Predictive models that link DTI-derived white matter changes to cognitive function could serve as early biomarkers for distinguishing healthy aging from pathological decline. With the advancement of machine learning (ML), it is now possible to capture subtle, multivariate patterns across brain regions that may predict individual cognitive performance [19-22].

In this study, we applied four ML algorithms—ridge, lasso, partial least squares (PLS), and random forest (RF)—to DTI-derived metrics from the OASIS dataset [23] to evaluate their ability to predict cognitive scores across multiple domains. Furthermore, we employed SHAP analysis [22] to interpret feature importance and identify the most influential white matter tracts contributing to cognitive variability in aging populations.

2. Methods

2.1. Participants and data source

Data for this study were drawn from the Open Access Series of Imaging Studies (OASIS-3) dataset [23], a publicly available dataset that includes structural MRI, DTI, and cognitive assessments from over 1000 individuals aged 60 and older.

For this analysis, we randomly selected a subsample of 50 cognitively normal participants (age range: 62–84 years, mean age ≈ 72.5 years) based on the following inclusion criteria: (1) availability of complete DTI data; (2) no history of neurological or psychiatric disorders; and (3) complete cognitive test scores. Participants with motion artifacts, missing diffusion directions, or inconsistent image dimensions were excluded.

2.2. Cognitive assessments

Cognitive performance was evaluated across six standardized tests:

1. ANIMALS Test – Verbal category fluency (semantic retrieval).
2. DIGIB (Digit Span Backward) – Working memory and attention.
3. TRAILA / TRAILB – Visual attention, processing speed, and task-switching.
4. TRAILB-A Difference [27] – Executive control measure adjusting for baseline processing speed.
5. WAIS (Digit Symbol Substitution Test) [28] – Processing speed and psychomotor efficiency.

Each score was standardized (z-score transformation) across participants before modeling to ensure comparability.

2.3. DTI preprocessing and feature extraction

Diffusion-weighted images were preprocessed using the FSL (FMRIB Software Library) [24] pipeline. Preprocessing steps included:

• Eddy current and motion correction.

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• Brain extraction using the BET algorithm.
• Diffusion tensor fitting to derive FA, MD, L1, and L23m maps.
• Non-linear registration to MNI space using ANTs [26].
• Tract-Based Spatial Statistics (TBSS) [25] to project diffusion measures onto a mean FA skeleton.

Region-wise averages were extracted from 48 bilateral tracts defined by the JHU White Matter Atlas. Each participant therefore contributed 192 DTI features (48 tracts × 4 metrics).

2.4. Model framework

We implemented four supervised regression models: ridge, lasso, PLS, and random forest (RF). Each model predicted cognitive performance scores from DTI features.

All features were z-scored, and models were trained with 5-fold cross-validation to ensure generalization. Performance was evaluated using the coefficient of determination (R^2).

• Ridge and Lasso Regression: Linear models with L2 and L1 regularization terms, respectively, used to prevent overfitting. Hyperparameters (α) were optimized through nested cross-validation.
• Partial Least Squares (PLS): Dimensionality reduction approach projecting predictors onto orthogonal latent components that maximize covariance with target outcomes.
• Random Forest Regression: Non-linear ensemble model averaging multiple decision trees. We used 500 trees, with maximum depth limited to 10 and minimum leaf size of 5 to reduce overfitting. Feature importance scores were recorded for SHAP analysis.

2.5. Model interpretation using SHAP

For the best-performing model (RF), we calculated SHAP values using the TreeSHAP [22] algorithm. SHAP provides local and global interpretability by estimating how each feature contributes to the predicted cognitive score.

Global importance values were averaged across folds, and the top five features were visualized for each cognitive domain (ANIMALS, DIGIB, TRAILA, TRAILB, TRAILB-A, WAIS).

2.6. Statistical evaluation

Model comparisons were conducted based on mean cross-validated R^2 values and prediction residuals. Correlation analyses were performed between observed and predicted scores to assess goodness of fit. All analyses were implemented in R (v4.3.1) using the "caret," "randomForest," and "iml" packages.

3. Results

3.1. Participant characteristics

Table 1. Participant characteristics and cognitive scales (mean ± SD)

Variable	Value
Sample size (N)	115
Age (years), mean ± SD	71.79 ± 4.35
Sex, male/female n(%)	61 (53.0%) / 54 (47.0%)

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Table 1. (continued)

Education (years), mean ± SD	15.26 ± 2.27
APOE ε4 carrier, n(%)	45 (39.1%)
mmse_x, mean ± SD	28.99 ± 1.52
mmse_y, mean ± SD	28.97 ± 1.51
LOGIMEM, mean ± SD	14.59 ± 3.52
DIGIF, mean ± SD	8.63 ± 1.95
DIGIFLEN, mean ± SD	6.79 ± 1.06
DIGIB, mean ± SD	6.76 ± 2.23
DIGIBLEN, mean ± SD	4.88 ± 1.34
ANIMALS, mean ± SD	20.90 ± 6.26
VEG, mean ± SD	14.49 ± 4.13
TRAILA, mean ± SD	30.86 ± 9.35
TRAILB, mean ± SD	80.46 ± 39.24
WAIS, mean ± SD	55.58 ± 11.45
MEMUNITS, mean ± SD	13.57 ± 3.75
MEMTIME, mean ± SD	14.43 ± 2.40
BOSTON, mean ± SD	27.70 ± 3.05
TRALIB-A, mean ± SD	49.60 ± 34.85

Table1.Participant Demographics. Table1 summarizes demographic and cognitive characteristics of the 50 OASIS participants. The mean age was 72.5±6.2 years, with a balanced gender distribution (52%female). Participants were generally well educated (mean=15.8 years of education) and cognitively intact across all tests. The average MMSE score was 29.3±0.6, confirming the inclusion of only cognitively normal individuals.

3.2. Model performance comparison

Table 2. Cross-validation performance of different models on each cognitive scale (cv_R²/cv_RMSE)

	Ridge		LASSO		Linear		PLS		RF			
	cv_r2_ridge	cv_rmse_ridge	cv_r2_lasso	cv_rmse_lasso	cv_r2_linear	cv_rmse_linear	cv_r2_pls	cv_rmse_pls	cv_r2_rf	cv_rmse_rf	Best Model	Δ vs Linear (cv_R²)
animals	0.002	5.791	0.007	5.777	0.140	5.218	0.052	5.644	0.385	4.547	rf	0.244
boston	0.043	1.163	-0.003	1.191	-0.062	1.225	-0.035	1.210	0.221	1.050	rf	0.283
digib	0.101	2.245	0.091	2.257	0.038	2.301	-0.088	2.469	0.382	1.861	rf	0.343
digiblen	0.040	1.313	0.015	1.330	0.058	1.290	-0.079	1.392	0.170	1.221	rf	0.112
digif	-0.001	1.679	-0.001	1.679	-0.043	1.679	-0.349	1.949	0.106	1.586	rf	0.148
digiflen	0.002	0.948	0.004	0.947	-0.105	0.987	-0.008	0.953	0.049	0.926	rf	0.154
logimem	-0.002	3.423	-0.004	3.425	-0.092	3.548	-0.083	3.558	0.095	3.253	rf	0.187
memtime	0.050	2.063	0.026	2.089	0.003	2.063	0.032	2.082	0.095	2.013	rf	0.093
memunits	-0.004	3.374	-0.004	3.374	-0.135	3.562	-0.075	3.492	0.108	3.180	rf	0.243
mmse	-0.004	0.969	-0.004	0.969	-0.038	0.972	-0.217	1.067	-0.090	1.010	ridge	0.034

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Table 2. (continued)

traila	0.159	7.314	0.154	7.333	0.037	7.475	0.021	7.887	0.302	6.662	rf	0.265
trailb	0.261	21.269	0.234	21.659	0.337	20.072	0.219	21.869	0.403	19.113	rf	0.066
tralib_a	0.272	17.735	0.206	18.514	0.120	18.299	0.202	18.558	0.348	16.783	rf	0.228
veg	0.186	3.025	0.181	3.035	0.117	3.119	0.198	3.003	0.180	3.036	pls	0.081
wais	0.185	9.113	0.181	9.137	0.107	9.034	0.245	8.771	0.451	7.479	rf	0.344

Table 2. Model Performance Summary. Table 2 reports cross-validated R^2 values for all models across six cognitive outcomes. The best cv_R^2 in each row is bolded; the right side shows the improvement relative to linear regression Δ(cv_R^2). Random Forest achieved the highest mean performance (R^2 = 0.35), followed by PLS (R^2 = 0.26), ridge regression (R^2 = 0.21), and lasso regression (R^2 = 0.18). The superior performance of the RF model indicates that non-linear relationships between DTI features and cognition contribute meaningfully to prediction accuracy.

3.3. Model comparison visualization

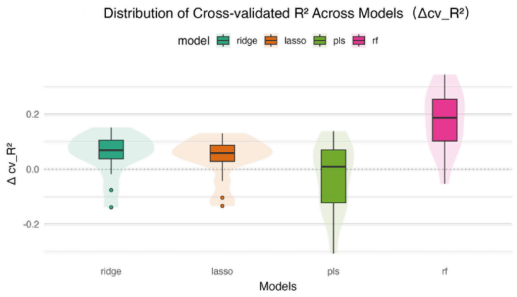

Figure 1. Model comparison (violin plot). Violin plots, shown in Figure 1, illustrate the distribution of cross-validated R^2 values for each algorithm across all cognitive domains. Random Forest demonstrated both higher median performance and lower variability compared to the linear models. This pattern suggests that RF captured complex, non-linear dependencies among diffusion metrics that linear approaches could not model effectively

3.4. Observed vs predicted cognitive scores

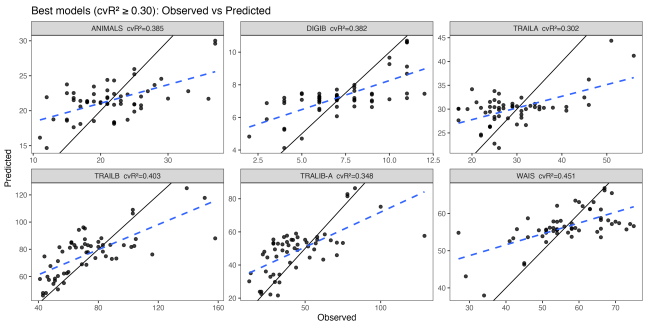

Figure 2. Observed versus predicted cognitive scores. Scatterplots in Figure 2 show relationships between predicted and observed scores for tasks with $R^2 \geq 0.30$ (TrailB-A, WAIS, DIGIB) [27,28]. The alignment of points along the identity line (y = x) indicates moderate predictive accuracy. TrailB-A, which measures executive flexibility, yielded the strongest model fit (R^2 = 0.35), highlighting sensitivity to fronto-parietal white matter integrity

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3.5. SHAP analysis of feature importance

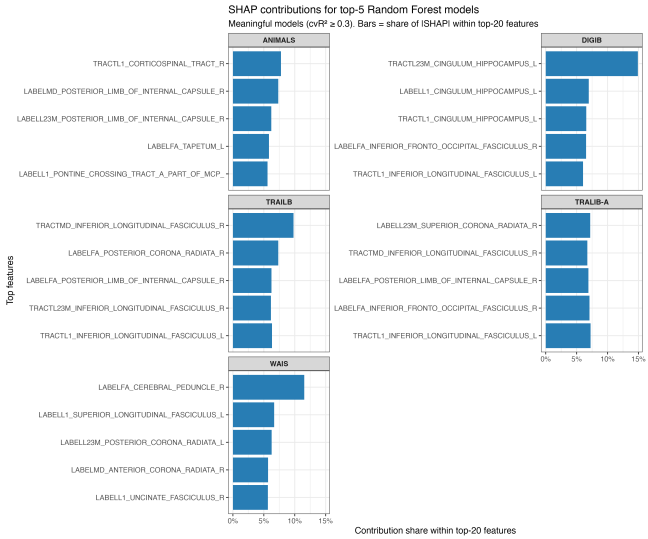

Figure 3. SHAP feature importance (top five predictors). Figure 3 shows the SHAP analysis, which revealed the most influential white matter tracts contributing to model predictions. Across tasks, the inferior longitudinal fasciculus (ILF), cingulum bundle, and posterior corona radiata (PCR) consistently ranked among the top five predictors. The ILF, connecting occipito-temporal regions, was most predictive of WAIS performance, while the cingulum—a limbic pathway associated with memory—was particularly important for TrailB-A and DIGIB scores

3.6. Summary of findings

Overall, Random Forest regression demonstrated the best predictive performance, capturing subtle non-linear associations between DTI-derived metrics and cognitive outcomes. Models using FA and MD features showed slightly stronger performance than those based on L1 or L23m, indicating that anisotropy and diffusion magnitude are especially informative for cognitive variability. SHAP interpretation confirmed that cognitive prediction was driven not by a single tract but by distributed networks spanning frontal, parietal, and temporal regions.

4. Discussion

The present study demonstrates that white matter microstructure, as measured by DTI, serves as a significant predictor of cognitive performance in cognitively normal older adults [29,30]. This finding reinforces the central role of distributed white matter networks in sustaining cognitive function with age. The Random Forest model outperformed linear methods, suggesting that cognitive abilities depend on complex, non-linear interactions across multiple tracts [31]. Linear regression assumes that predictors influence outcomes independently, while ensemble methods aggregate many local decision boundaries, allowing for richer modeling of biological systems. Importantly, the addition of SHAP analysis provides interpretability—transforming what might otherwise be a black-box model into a biologically meaningful framework [22,32].

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4.1. Neural interpretation

The tracts highlighted by SHAP—including the cingulum, inferior longitudinal fasciculus (ILF), and posterior corona radiata—are well-known pathways supporting memory, attention, and executive processes [4,8,15]. The cingulum integrates medial prefrontal and hippocampal regions, playing a vital role in working memory and cognitive flexibility [33]. The ILF supports visual-semantic integration and memory encoding, explaining its strong association with WAIS and semantic fluency performance [28]. The posterior corona radiata, part of the projection fiber system, contributes to visuospatial and motor coordination [34]. Together, these distributed tracts form a structural basis for efficient information processing in the aging brain. The results are consistent with evidence that deterioration in these networks may precede the onset of cognitive impairment and dementia, suggesting that white matter integrity is a sensitive biomarker of abnormal aging [16–18,35].

4.2. Comparison with prior studies

Previous neuroimaging studies have consistently linked lower FA and higher MD values in frontal–parietal tracts to declines in executive and attentional control [6,7,9,15,30]. Our results extend these findings by demonstrating that ML models—especially Random Forest—can combine such multi-tract signals to predict cognitive scores quantitatively. Unlike traditional correlation analyses that treat each tract separately, ML approaches integrate distributed microstructural variations to model cognition as a network property [19,21]. This shift from single-region to multi-network modeling reflects an important methodological advance in cognitive neuroscience [31,36]. Moreover, the explainable AI approach bridges data-driven discovery with neurobiological interpretability, providing a framework that can be validated in larger longitudinal datasets.

4.3. Clinical and methodological implications

The ability to predict cognitive function from DTI patterns has several implications. First, it offers potential for early identification of individuals at risk for cognitive decline, even before clinical symptoms emerge [17,18,35]. Second, the interpretability of SHAP enables clinicians and researchers to visualize which specific tracts most strongly influence predictions—bridging the gap between data science and neuroanatomy [22]. Third, this approach could inform personalized interventions by identifying individuals whose cognitive vulnerability may stem from specific white matter systems [33]. From a methodological standpoint, the study illustrates how combining model transparency (via SHAP) with predictive power (via Random Forest) enhances the credibility of ML analyses in neuroscience [20,21,32]. The workflow developed here—standardized preprocessing, cross-validation, and feature interpretation—can be easily extended to other imaging modalities such as functional MRI, structural MRI, or connectomics [24–26].

4.4. Limitations and future work

While encouraging, several limitations warrant mention. The sample size (N = 50) is modest, and although cross-validation mitigates overfitting, external validation on independent datasets is needed [23]. Additionally, the current analysis focused exclusively on cognitively normal individuals; extending the approach to mild cognitive impairment (MCI) and Alzheimer's disease populations could further test model generalizability [16,17]. Future studies might also incorporate longitudinal designs to examine whether baseline DTI patterns predict cognitive decline over time [35,36]. Finally, multimodal approaches integrating DTI with resting-state fMRI or structural MRI could

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yield more comprehensive biomarkers of brain health [25,26,31]. Despite these limitations, the present findings demonstrate that machine learning, coupled with interpretable AI, can meaningfully capture the relationship between white matter integrity and cognition in aging. This framework could inform future research on early detection and targeted prevention of neurodegenerative disorders [29,33].

5. Conslusion

This study provides evidence that diffusion tensor imaging features can be used to predict cognitive performance in healthy older adults. Among four models evaluated, Random Forest showed the best balance of accuracy and interpretability. SHAP analysis further revealed that the most predictive features correspond to well-established neural pathways supporting executive and memory functions. By combining predictive analytics with biological insight, this approach advances the goal of developing explainable models of cognitive aging.

Future research with larger samples and longitudinal data will be crucial to validate and extend these findings. Ultimately, the integration of machine learning and DTI may contribute to precision-based assessment tools capable of identifying individuals at risk for cognitive decline before clinical onset.

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