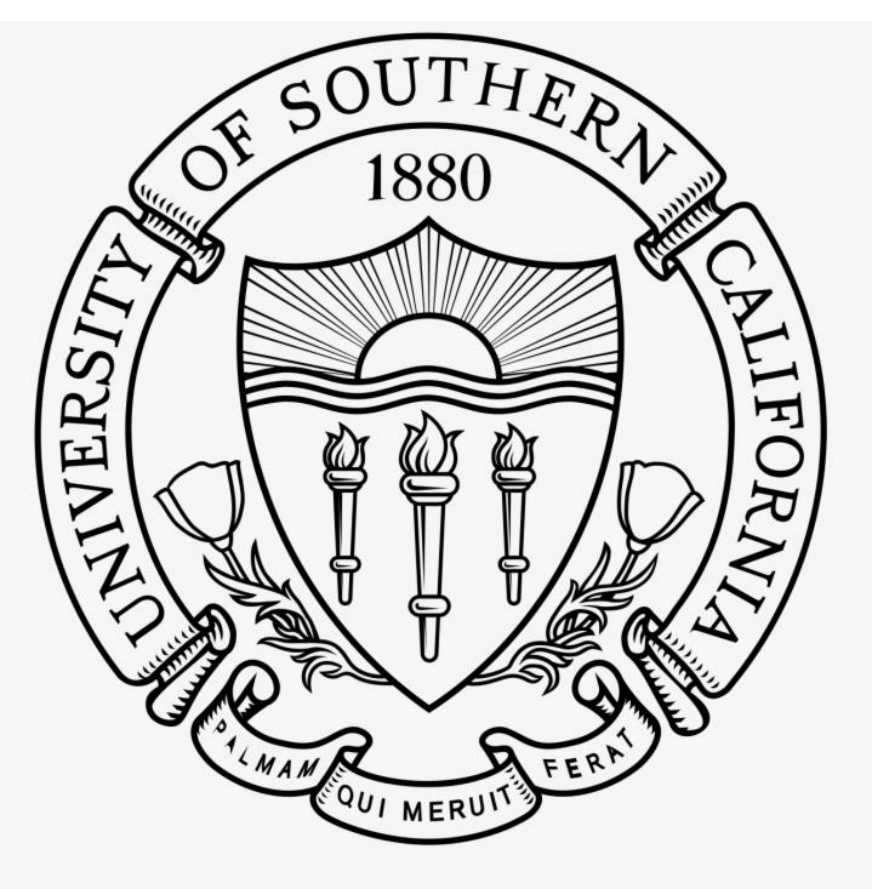




Novel Signature Of Limbic-predominant Age-related TDP-43 Encephalopathy Neuropathological Change (LATE-NC) On Postmortem MRI



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Hippocampal subfield radiomics identifies region-specific microstructural patterns associated with LATE pathology, particularly in Entorhinal cortex and CA1 section.

INTRODUCTION

Limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) is a highly prevalent, underdiagnosed neurodegenerative disease that closely mimics AD but lacks validated in-vivo biomarkers.

MRI radiomics enables quantitative assessment of tissue microstructural alterations not appreciable on conventional MRI. We hypothesized that radiomics could detect LATE-NC related changes within medial temporal lobe regions, distinguishing individuals with and without LATE-NC.

METHODS

• 32 participants from the 90+Study: 16 LATE+ and 16 LATE-, balanced for AD pathology, and none had hippocampal sclerosis.

• Manual segmentation of the hippocampal subfields, posterior cingulate gyrus, and amygdala performed on high-resolution isotropic T2W images.

• Radiomic features (n=151) were extracted using the Cancer Imaging Phenomics Toolkit across eight feature families: first-order intensity, histogram, gray-level co-occurrence matrix (GLCM), gray-level run length matrix (GLRLM), gray-level size zone matrix (GLSZM), neighboring gray tone difference matrix (NGTDM), volumetrics and morphometrics.

• Group comparisons used independent t-tests or Wilcoxon rank-sum tests (depending on normality), with Benjamini-Hochberg correction. Effect sizes (Cohen's d) visualized via heatmaps.

RESULTS

The entorhinal cortex (ETC) exhibited consistent association across intensity-based, GLCM, GLSZM, and NGTDM for TDP43+, with larger heterogeneity in radiomic signatures from those feature classes (p < 0.01(adjusted), d > 1.3).

CA1 showed more feature-specific effect sizes, clustering within GLSZM and GLRLM metrics with Zone Size Entropy, Small Zone Emphasis, and Grey Level Mean quantifying patchy regional tissue and enhanced brightness in T2 signal (p < 0.01(adjusted), d > 1.80) and high Short Run Emphasis indicating fragmentation of organized tissue layers (adjusted p < 0.01, d = 3.16).

Near-zero effect sizes across most metrics were observed in the PCG, supporting its role as internal negative control.

CONCLUSIONS

Distinct radiomic textures, independent of volume loss, detect LATE-NC, highlighting microstructural disorganization missed by conventional morphometry and volumetry.

Radiomics identifies region-specific microstructural patterns changes with strongest effects in:

ETC align with expected increases in entropy and textural disarray from TDP43 proteinopathy.

CA1 consistent with altered cellular architecture, scarring and gliosis as well as fragmentation of organized tissue layers.

Overall, GLRLM, GLSZM, and NGTDM contain the most informative radiomics for differentiating LATE pathology.

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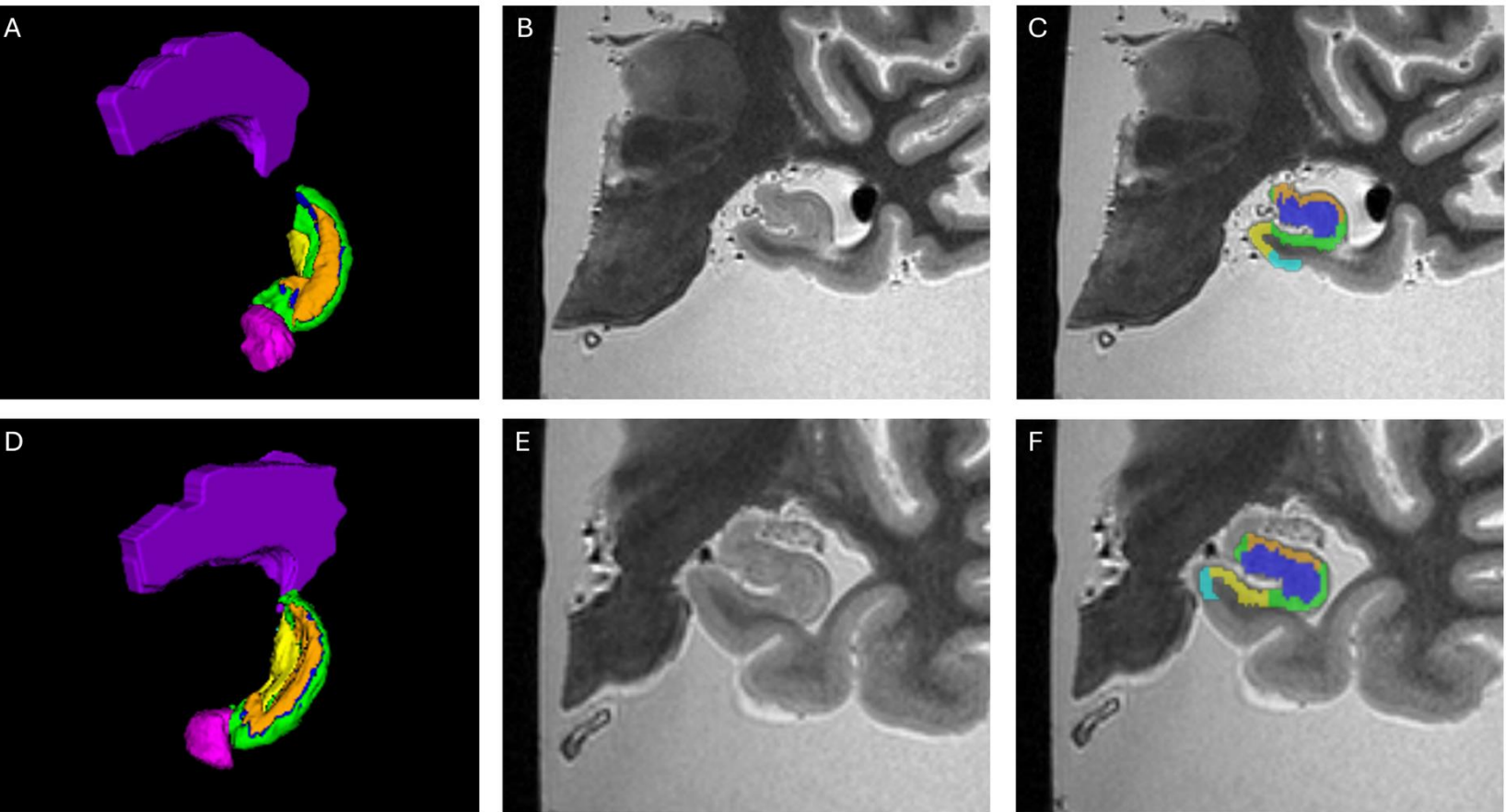


Figure 1. Visualization of Hippocampal Subfields and the Subtlety of LATE-NC Pathology. Comparison of a TDP-43 positive case (A–C) and a TDP-43 negative control (D–F). (A, D) 3D volumetric renderings of the medial temporal lobe. (B, E) Coronal T2-SPACE MRI sequences. Visual inspection reveals only marginal differences in contrast and morphology, highlighting the challenge of diagnosing LATE using standard radiological viewing. (C, F) Corresponding segmentation masks used for quantitative radiomic feature extraction.

		TDP-43 Positive (N=16)	TDP-43 Negative (N=16)	Full sample (N=32)
Age at death (mean)		99 (4.2)	96.3 (3)	97.7 (3.8)
Sex	Male	5 (31.25%)	7 (43.75%)	12 (37.5%)
	Female	11 (68.75%)	9 (56.25%)	20 (62.5%)
TDP-43 Stage	Stage 0: Absent	0 (0%)	16 (100%)	16 (50%)
	Stage 1: Amygdala	3 (18.75%)	0 (0%)	3 (9.38%)
	Stage 2: Amygdala + Hippocampus	12 (75%)	0 (0%)	12 (37.5%)
	Stage 3: Into Middle Frontal Gyrus	1 (6.25%)	0 (0%)	1 (3.13%)
Clinical Dementia Status	No Dementia	7 (43.75%)	10 (62.5%)	17 (53.13%)
	Dementia Present	9 (56.25%)	6 (37.5%)	15 (46.88%)
Alzheimer's Severity	Low	6 (37.5%)	6 (37.5%)	12 (37.5%)
	Intermediate	5 (31.25%)	6 (37.5%)	11 (34.38%)
	High	5 (31.25%)	4 (25%)	9 (28.13%)
Braak Stage for Lewy Body Disease	0: No LBD pathology	13 (81.25%)	11 (68.75%)	24 (75%)
	Stage 1	1 (6.25%)	3 (18.75%)	4 (12.5%)
	Stage 6	2 (12.5%)	2 (12.5%)	4 (12.5%)

