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NEUROIMAGING

Regional Deep Atrophy: Using Temporal Information to Automatically Identify Regions Associated with Alzheimer's Disease Progression from Longitudinal MRI

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Abstract

Background: Assessment of longitudinal hippocampal atrophy is a well-studied biomarker for Alzheimer's disease (AD). However, most state-of-the-art measurements calculate changes directly from MRI images using image registration/segmentation, which may misreport head motion or MRI artifacts as neurodegeneration. We present a deep learning method Regional Deep Atrophy (RDA) that (1) estimates atrophy sensitive to progression by quantifying time-associated changes in images, especially in preclinical AD stage (as in DeepAtrophy (Dong et al., 2021)), and (2) identifies regions where longitudinal changes significantly influence temporal inference.

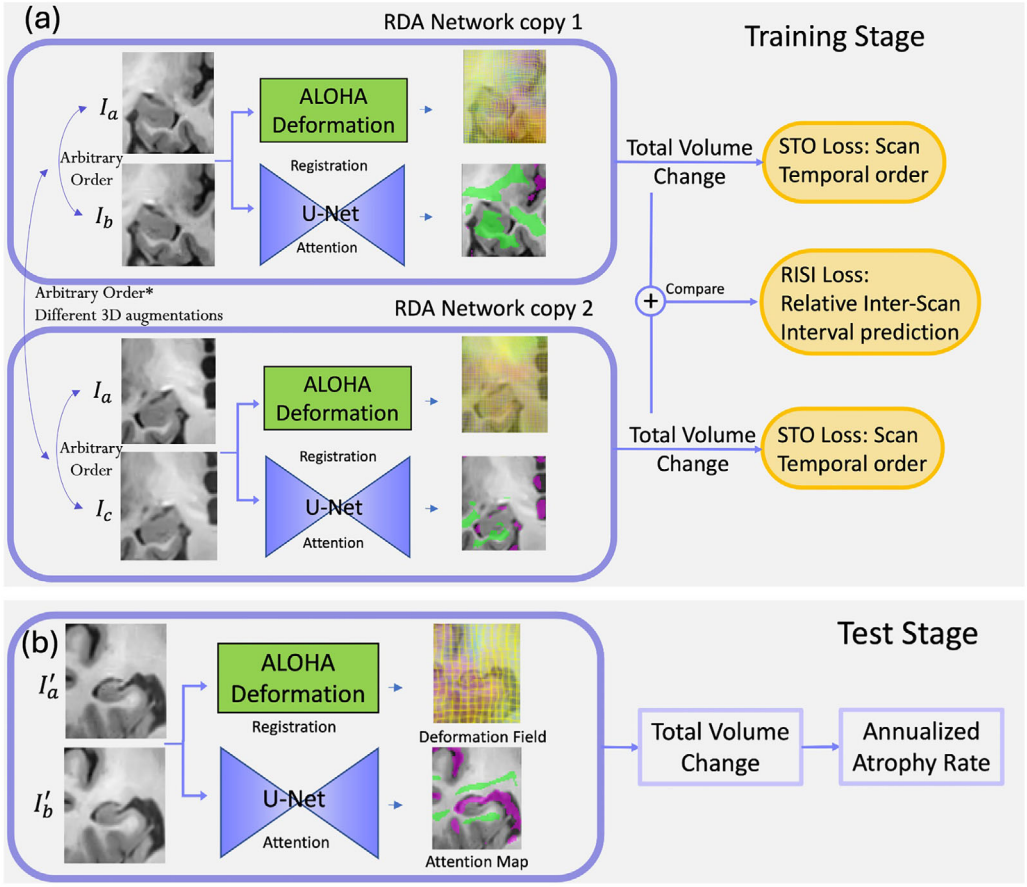
Method: RDA was trained on longitudinal T1-weighted MRI from 155 ADNI participants and evaluated on 326 participants (Figure 1(c)). During training, two image pairs from the same participant are fed into two instances of the RDA network in arbitrary temporal order. Within each RDA network, a U-Net is applied to one image pair of arbitrary order to predict attention regions informative of shrinkage/expansion. Attention regions are used to mask a deformation field computed by ALOHA (Das et al., 2012), and derive a total volume change measurement for attention areas. The attention regions are optimized by the Scan Temporal Order (STO) loss for one scan pair to evaluate if volume changes align with input image order, and the Relative Interscan Interval (RISI) metric to determine if larger volume changes correspond to longer interscan intervals for the whole RDA model (Figure 1). Only one longitudinal image pair is required for testing, directly generating the total volume change as atrophy measurement.

Result: RDA achieves the similar ability to detect differences in atrophy between stages on the AD continuum as DeepAtrophy, especially in preclinical AD (Figure

2), while having additional explainability in the form of heatmaps that summarize expansion/shrinkage regions in the brain that contribute to the RDA change measurement (Figure 3). These heatmaps, derived in a fully data-driven manner, largely recapitulate the areas of atrophy and expansion in the MTL reported by prior studies.

Conclusion: RDA has similar prediction accuracy as DeepAtrophy, but its additional interpretability makes it more acceptable for use in clinical settings, and may lead to more sensitive biomarkers for disease monitoring and progression understanding in preclinical AD.

Figure 1. (a) The overall architecture of the Regional Deep Atrophy (RDA) pipeline involves two pairs of images of the same subject, which are input to two copies of the RDA network in an arbitrary order. For each copy, the image pair is fed into a U-net-like Attention Network. A total volume change is computed from the deformation field generated by ALOHA, alongside the shrinkage (green) or expansion (purple) attention maps produced by the Attention Network. Updates of attention areas are based on the Scan Temporal Order (STO) loss for one image pair and the Relative Interscan Interval (RISI) loss for two image pairs from the same subject, both of which use temporal information to guide attention training. (b) During the testing stage, only a longitudinal image pair is needed. (c) Characteristics of the selected ADNI2/GO participants whose T1 MRI scans were used for the Regional Deep Atrophy (RDA) and comparison experiments for this paper. Numbers in parentheses are standard deviations. All subjects in the training and test set had 2-6 scans between 0.25 and 6 years from the baseline. Abbreviations: n = number of subjects; A+/A-: β-amyloid positive/negative; CU = cognitively unimpaired adults; eMCI = early mild cognitive impairment; lMCI = late mild cognitive impair; Edu = years of education; MMSE = mini-mental state examination.



(c)	Training Set (n = 155)				Test Set (n = 326)			
	A- CU (n = 64)	A+ CU (n = 0)	A+ eMCI (n = 49)	A+ lMCI (n = 42)	A- CU (n = 103)	A+ CU (n = 85)	A+ eMCI (n = 79)	A+ lMCI (n = 59)
Age (years)	71.5 (5.7)	-	73.3 (7.4)	71.9 (7.2)	72.4 (6.3)	75.2 (5.8)**	74.0 (6.9)	72.5 (6.5)
Sex	27F 37M	-	16F 33M	21F 21M	56F 47M	58F 27M	39F 40M	28F 31M
Edu (years)	17.4 (2.3)	-	16.2 (3.0)*	16.8 (2.7)	16.8 (2.4)	16.0 (2.7)*	15.3 (2.9)***	16.4 (2.7)
MMSE	29.1 (1.2)	-	28.0 (1.5)****	26.7 (1.8)****	29.1 (1.2)	29.0 (1.1)	28.1 (1.6)****	27.3 (1.9)****

Figure 2. (a) and (b) Area under the receiver operating characteristic (ROC) curve (AUC) for (a) inference of the correct scan temporal order (STO); (b) inference of which scan pairs have longer relative interscan interval (RISI) for all four models. (c) and (d) Comparison of four models to detect differences in rates of progression from follow-up measurements (c) within 180 to 400 days and (d) within 400 to 800 days. For DeepAtrophy, age-adjusted Predicted-to-actual interscan interval rate (PAIIR), and for the rest four methods, age-adjusted annualized atrophy rate was applied to differentiate groups. Abbreviations: ALOHA = Automatic Longitudinal Hippocampal Atrophy software/package; RDA = Regional Deep Atrophy; RISI = Relative Interscan Interval; A + /A- = β-amyloid positive/negative; CU = cognitively unimpaired older adults; eMCI = early mild cognitive impairment; lMCI = late mild cognitive impair.

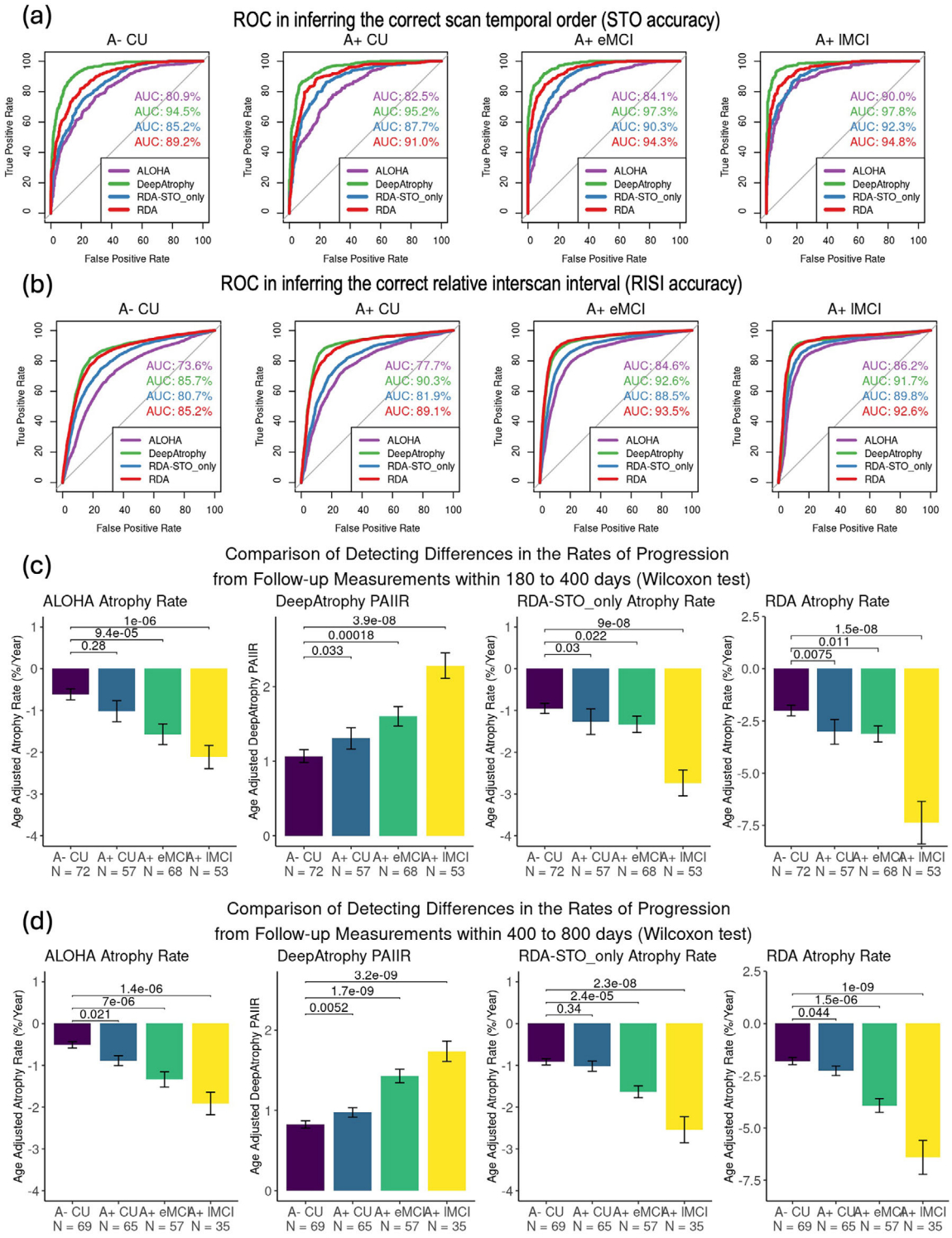


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Figure 3. Regional Deep Atrophy (RDA) predictions depicted through attention maps of (b) averaged medial temporal lobe (MTL) in the template space of A- CU group, (a, c) the difference heatmap between all other diseased groups and the A- CU group, and (d) example attention maps as direct outputs of RDA. In panel (a), the MTL template, average segmentation (in red) on the template, and heatmap of shrinkage (in red) and expansion (in purple) areas are presented. In panels (a) and (c), areas with no change are denoted in, while regions with more prominent heatmap are depicted in hot colors (red), and lighter heatmap areas compared to the A- CU group are shown in cool colors (blue). For a single subject in panel (d), shrinkage areas are overlaid on MRI images in green, and expanding areas are overlaid in red (refer to color-printed version for details).