Validation Of the Tau Heterogeneity Evaluation in Alzheimer's Disease (THETA) Score Using Longitudinal and Histopathology Data

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http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Abstract

Introduction: We recently developed a novel tau-PET summary measure THETA, capturing regional heterogeneity and identifying tau status, using ground truth visual assessments from a large single-center cross-sectional dataset and validated on independent cohorts [1, 2]. In this study, we aimed to evaluate the performance of THETA on longitudinal and histopathology data.

Methods: We included longitudinal tau-PET ([^{18}F]flortaucipir) data from 696 Mayo Clinic Study of Aging (MCSA) and ADRC participants, with histopathology in n=90. Fig. 1 shows the model that uses regional standard uptake value ratios (SUVR) and a target of binary class of tau positivity for prediction of THETA. This model was applied to predict tau status on each followup scan. Slopes of the meta-ROIs' tau SUVRs and THETA were evaluated by diagnostic group and as a function of baseline amyloid SUVR in discordant CU participants (where meta-ROI and visual assessments did not match at baseline) and in incident-THETA+ CU participants (whose THETA moved from below to above 1 over serial tau-PET scans). We evaluated tau measurements as a function of Braak stages for neurofibrillary tangles.

Results: Longitudinal plots of meta-ROIs for diagnostic groups were very similar, but the expanded range of THETA based on visual positivity prediction clearly identified tau positive or tau-negative scans. In discordant-CU (n=97) and incident-THETA+ CU participants (n=14 all amyloid positive at follow-up but only 65% at baseline), the relationship between baseline amyloid and rate of tau increase was stronger for THETA than temporal meta-ROI (Fig.2). Separation between baseline and follow-up was greater for THETA (t-statistics=90) compared to temporal meta-ROI (t-statistics=20) ($p<0.01$) in the incident-THETA+ CU participants. THETA showed a slightly stronger association with Braak stage than meta-ROIs (rho=0.87 vs. ≤0.83, $p<0.05$), with better separation of clinical diagnoses (Fig.3).

Conclusions: THETA remained clearly negative or positive in MCI and AD, providing consistent information on underlying etiology of impairment at both baseline and follow-up. Although binary in its construction, THETA both provided separation of values based on tau status and its change correlated with baseline amyloid burden especially in discordant-CU where tau deposition is not in typical meta-ROIs. Further work is needed to confirm if THETA captures early tau changes.

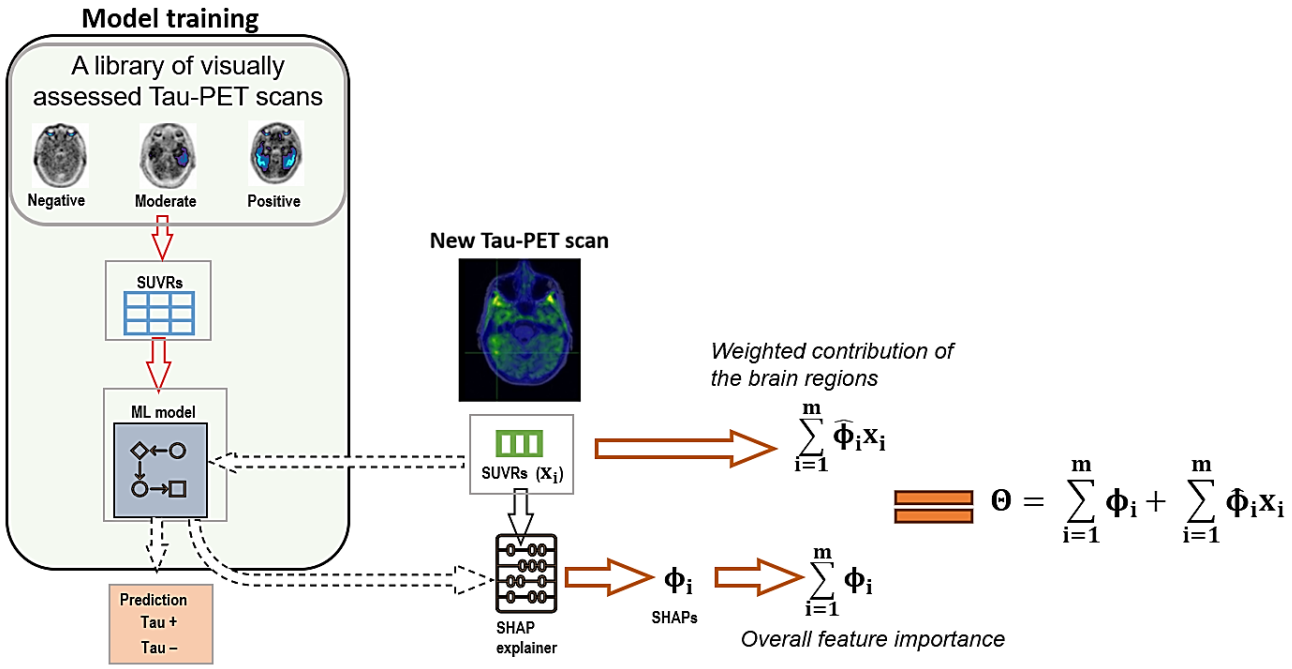

Figure 1. Schematic of showing the processes starting from model training up to THETA (θ). We first trained the machine learning model with SUVR values obtained from a library tau-PET scans that were visually assessed by raters for tau status positivity. After training the model, we used SHAP an AI explainer to generate the individual feature importance in order to formulate THETA [1, 2].

[1] Gebre, et al. PREPRINT [https://doi.org/10.21203/rs.3.rs-3290598/v1]

[2] Gebre et al. HAI 2024 Page 502 [https://www.paperturn-view.com/?pid=ODc8773894&v=18.1]

Code will be released here: https://github.com/RobelGebre/THETA

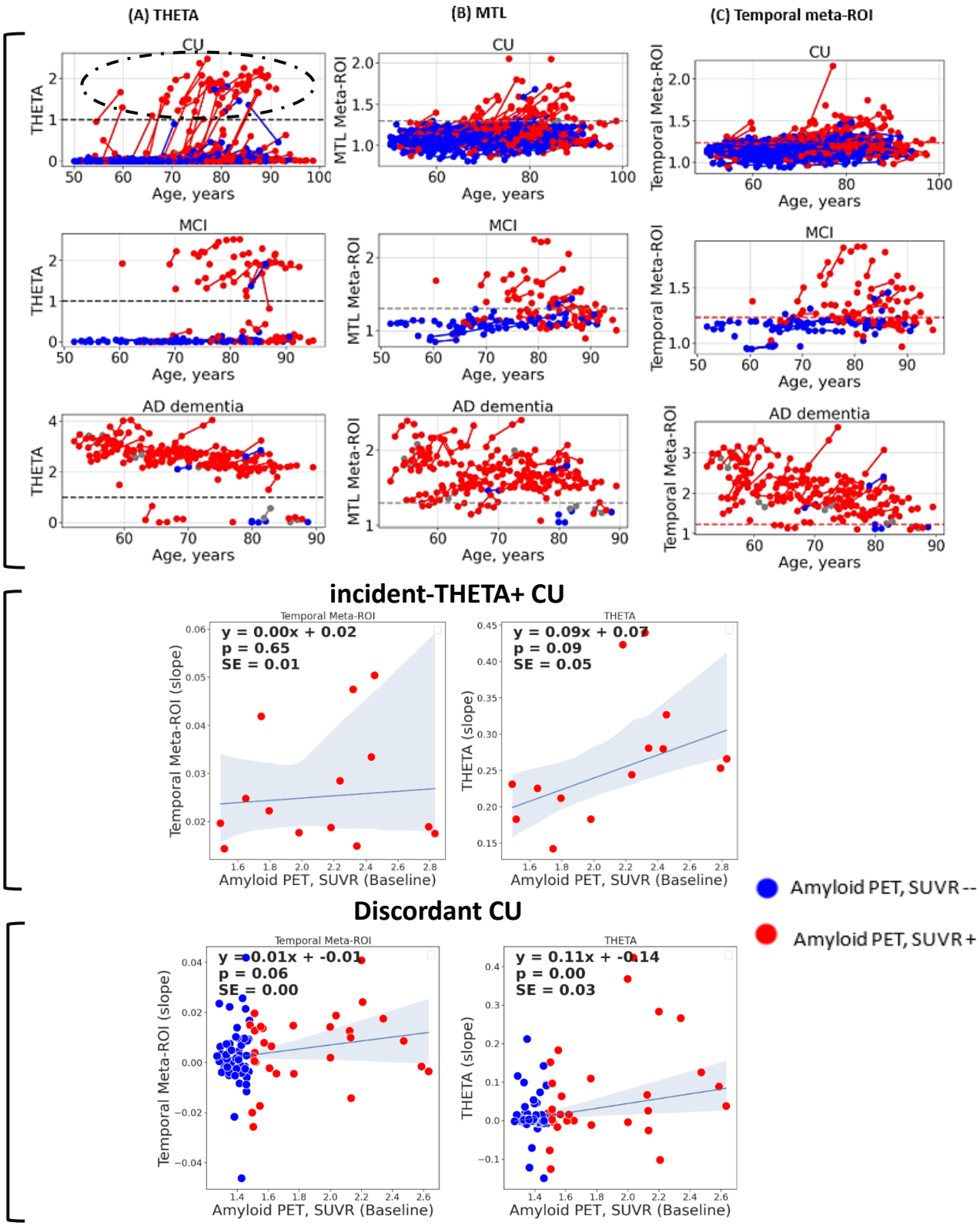

Figure 2. The top panel shows longitudinal plots for the meta-ROIs and THETA against age. The middle panel shows the relationship between the slope of temporal meta-ROI and THETA as a function of amyloid PET SUVR at baseline for the CU participants encircled in the top panel. The bottom panel shows a similar relationship for the discordant cognitively unimpaired (CU) participants. Discordance was defined from the cross-sectional visual reads where complete disagreement was found between the visual rating and the meta-ROIs. *SE: Standard error of estimated slope*

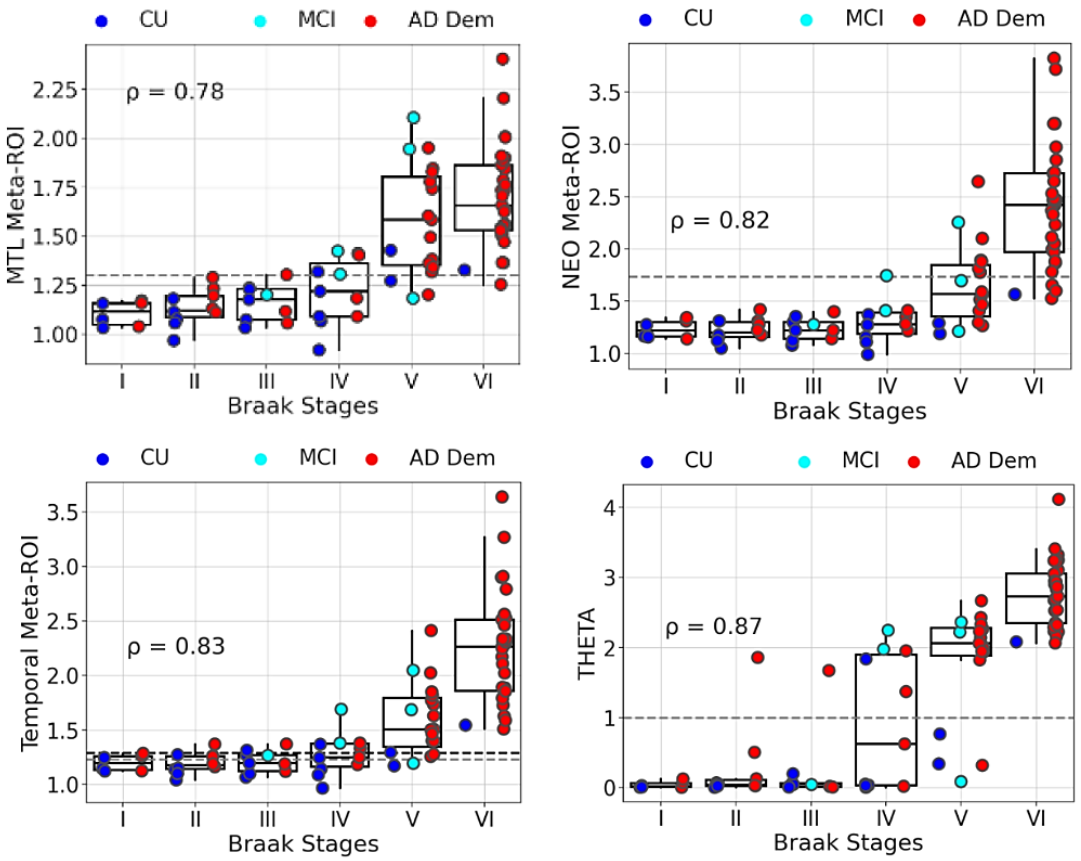

Figure 3. Shows the association of meta-ROIs and THETA to Braak stages (I to VI). The cutoff points for positivity for each metric are shown by dotted lines (MTL at 1.30 SUVR, NEO at 1.37 SUVR, Temporal at 1.23 SUVR and, and THETA at 1.0). The diagnostic groups (CU, MCI, and AD Dementia) are shown in blue, cyan, and red respectively.