

Alzheimer's Disease signatures in Subjective Cognitive Decline: a multimodal plasma, cognitive, and empathy approach.

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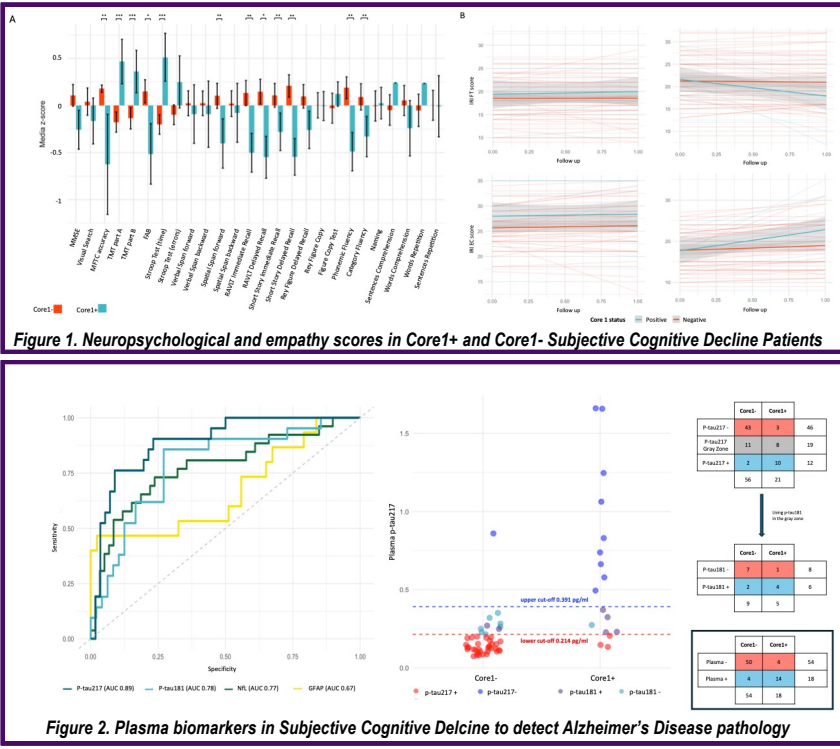
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Background and Aims

With disease-modifying therapies now available, identifying Alzheimer's disease (AD) biology at the earliest stages has become a clinical priority. Subjective cognitive decline (SCD) is an optimal but heterogeneous target. We assessed whether plasma biomarkers, neuropsychological, and socio-emotional indicators improve identification of underlying AD pathology in SCD.

Results

SCD Core1+ patients were older at baseline. They showed subtle, normal-range inefficiencies in memory and executive tasks (Stroop test, FAB, TMT part A and B, phonemic and category fluency, Rey Auditory Learning Test and Short Story) (Figure 1A). Longitudinally, Core1+ patients exhibited declining Perspective Taking scores ($p<0.001$) and increasing Personal Distress scores ($p<0.001$). Plasma p-tau217 had the highest AUC (0.89, 95% CI 0.81–0.97) when compared with the other plasma biomarkers (Figure 2A). The two-cutoff strategy led to an accuracy of 91.40% a PPV of 83.33% and an NPV of 93.48%

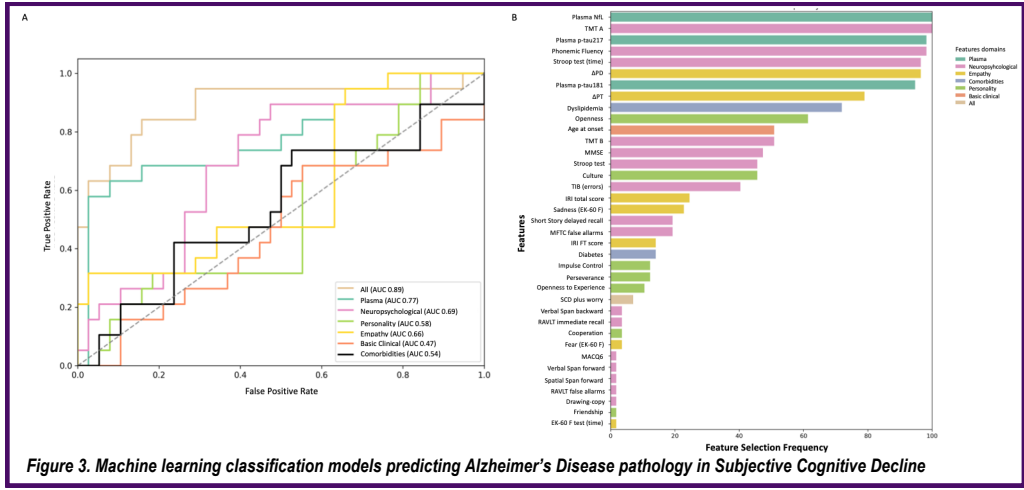


Methods

We enrolled 97 SCD patients who underwent CSF biomarkers and/or amyloid-PET and were classified as Core1+ or Core1-. Participants underwent demographic, neuropsychological, and emotional assessments, including Interpersonal Reactivity Index. Plasma p-tau217 (CLEIA) and plasma p-tau181, NfL, and GFAP (Simoa) were quantified. Comparative analyses and machine learning (ML) models (random forest, XGBoost) were used to predict AD pathology from multimodal data.

The gray zone included 22.58% of patients. The use of plasma p-tau181 allowed the reclassification of 78.54% gray zone cases that were previously indeterminate (McNemar's test $p=0.002$).

The multimodal ML model achieved the best performance (accuracy 84%, AUC 0.89). Regarding single-domain models, the model trained on plasma biomarkers achieved the highest discriminative ability (accuracy 81%, AUC 0.77), followed by the neuropsychological and empathy domains. Plasma biomarkers, executive and empathy-related features ranking among top predictors.



Discussion

SCD with AD appears as a biologically distinct transitional stage marked by early executive and socio-emotional vulnerability. Plasma p-tau217 supports a scalable first-line rule-out strategy, with p-tau181 improving gray-zone resolution. Integrating plasma biomarkers with higher-order cognitive and empathy measures may improve diagnostic confidence and support a multimodal, person-centered workflow for early AD detection.