

Multimodal Integration of Blood-based Biomarker and Subcortical MRI features for Predicting Clinical Phenotype in Alzheimer's Disease and Related Dementias

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KEY TAKE AWAY: A multimodal framework combining subcortical functional integrity and cerebrovascular burden can provide additional value in populations with co-pathology.

INTRODUCTION

Neuropathological evidence indicates that the co-pathology of Alzheimer's disease (AD) and cerebral small vessel disease (CSVD) is highly prevalent in the aging population. This real-world study aimed to determine whether a multimodal integration of plasma ptau217, subcortical neural activity measured by the amplitude of low-frequency fluctuation (ALFF), and CSVD burden (quantified as WMH volume) improves the prediction of clinical cognitive phenotypes across the ADRD spectrum.

METHODS

We enrolled 247 older adults (151 cognitively unimpaired [CU], 82 with mild cognitive impairment [MCI], and 14 with dementia). Participants underwent neuropsychological assessments, multimodal MRI, and ptau217 measured using the Lumipulse platform. Resting-state fMRI data were preprocessed (SPM12/DPABI) to generate ALFF maps. Mean ALFF values were extracted from 116 regions of interest (AAL atlas) for correlation analysis. Logistic regression models were constructed to differentiate cognitively impaired (CI) individuals (MCI and dementia) from CU controls.

RESULTS

Significant ALFF abnormalities were identified in subcortical and limbic regions, including the thalamus, amygdala, caudate, putamen, and pallidum, which correlated with neuropsychological test scores ($p < 0.05$). In discriminating CI from CU, individual predictors yielded the following Area Under the Curve (AUC) values: hippocampal ALFF (0.635), amygdalar ALFF (0.636), p-tau217 (0.599), and WMH burden (0.663). An integrated model combining subcortical ALFF and WMH significantly improved classification performance. Notably, in a subgroup analysis specifically distinguishing individuals with AD-related cognitive impairment from pure normal controls without AD pathology, a combined model of amygdalar ALFF and WMH yielded a superior AUC of 0.781.

CONCLUSIONS

Our results highlight the substantial contributions from widespread subcortical regions to cognitive phenotypes, with amygdalar ALFF contributing predictive value comparable to hippocampal ALFF. Subcortical ALFF and WMH served as complementary biomarkers, and their integration enhanced classification performance. The relatively limited additive contribution of ptau217 within the combined model suggests that in heterogeneous, real-world aging populations characterized by co-pathology, a comprehensive framework incorporating both subcortical functional integrity and cerebrovascular burden is more effective than reliance on a single plasma biomarker.

FIGURE

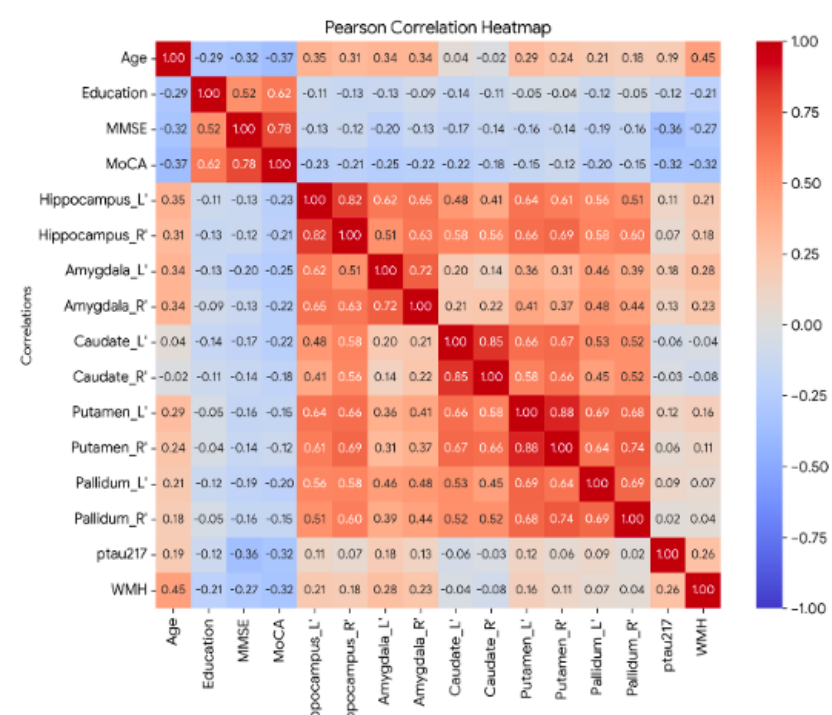


Figure 1. Pearson Correlation Matrix of Clinical, Cognitive, and Neuroimaging Biomarkers
This heatmap displays Pearson correlation coefficients (r) between demographic factors (Age, Education), cognitive scores (MMSE, MoCA), subcortical ALFF values, plasma p-tau217, and WMH burden. The color scale indicates the strength and direction of the relationship: red represents positive correlations (e.g., between Age and WMH), while blue represents negative correlations (e.g., between Age and MoCA). Values inside the cells indicate the specific correlation coefficient.
Abbreviations: ALFF = Amplitude of Low-Frequency Fluctuation; L = Left; R = Right

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