

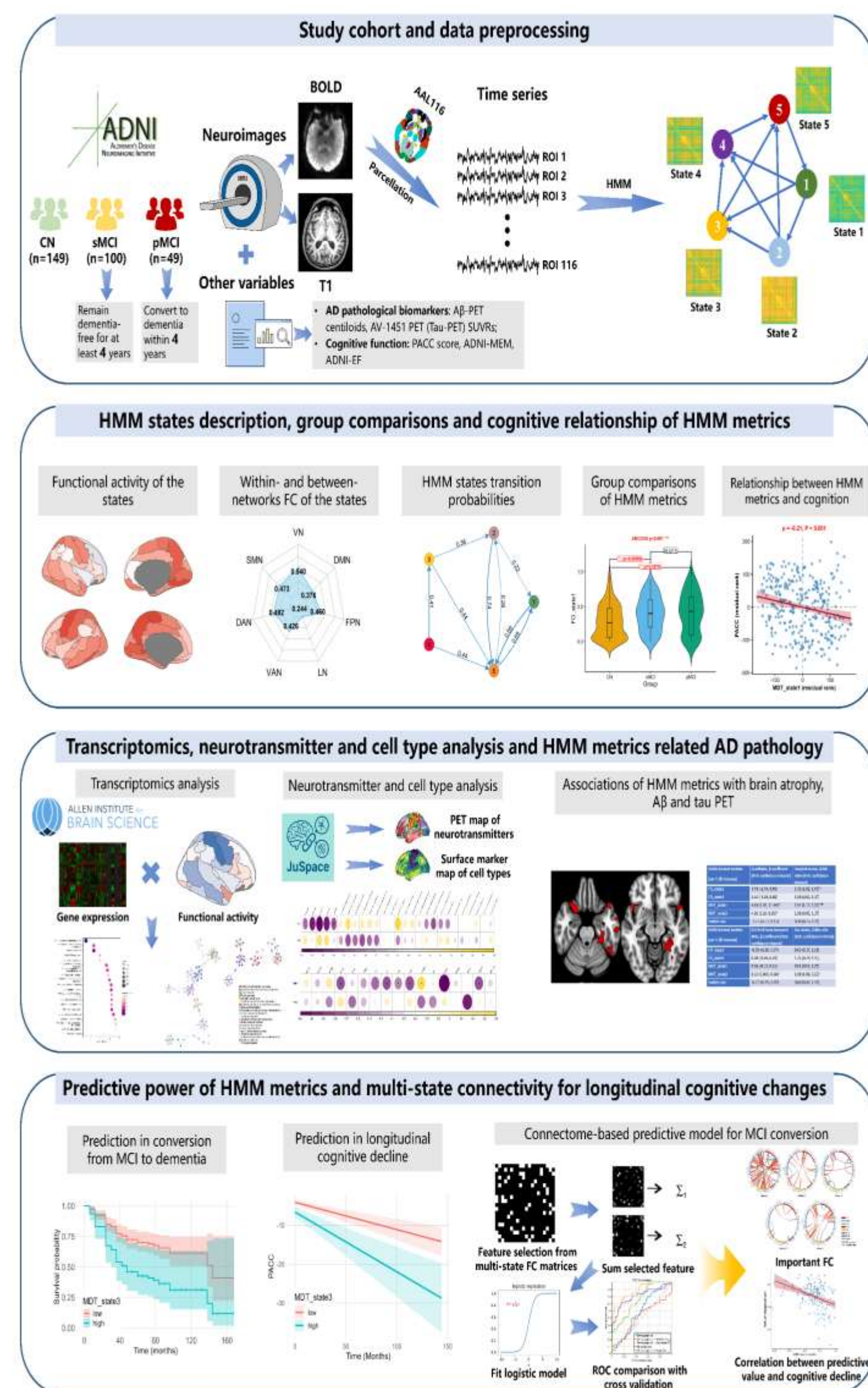
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Introduction

- Functional network analysis has become an essential tool for elucidating the pathological substrates of MCI.
- Conventional static functional connectivity approaches neglect the temporal variability of brain networks.
- Dynamic functional connectivity captures transient brain states and their switching patterns.
- Systematic investigations of dynamic functional networks and their underlying mechanisms in MCI remain limited.

Methods

- Baseline resting-state functional magnetic resonance imaging (fMRI) and T1-weighted MRI were acquired from the ADNI database for 100 stable MCI (sMCI) participants, 49 progressive MCI (pMCI) participants, and 149 cognitively normal (CN) participants.
- Hidden Markov model (HMM) was used to construct dynamic functional networks and extract state-specific metrics.
- Group differences in dynamic metrics and associations with cognition, positron emission tomography (PET) pathology, brain structure, transcriptomic, neurotransmitter, and cell-type maps were examined. Connectome-based predictive modeling (CPM) was used to predict MCI-to-dementia conversion.



Results

- Five brain states were identified by HMM (Figure 1 & Figure 2).

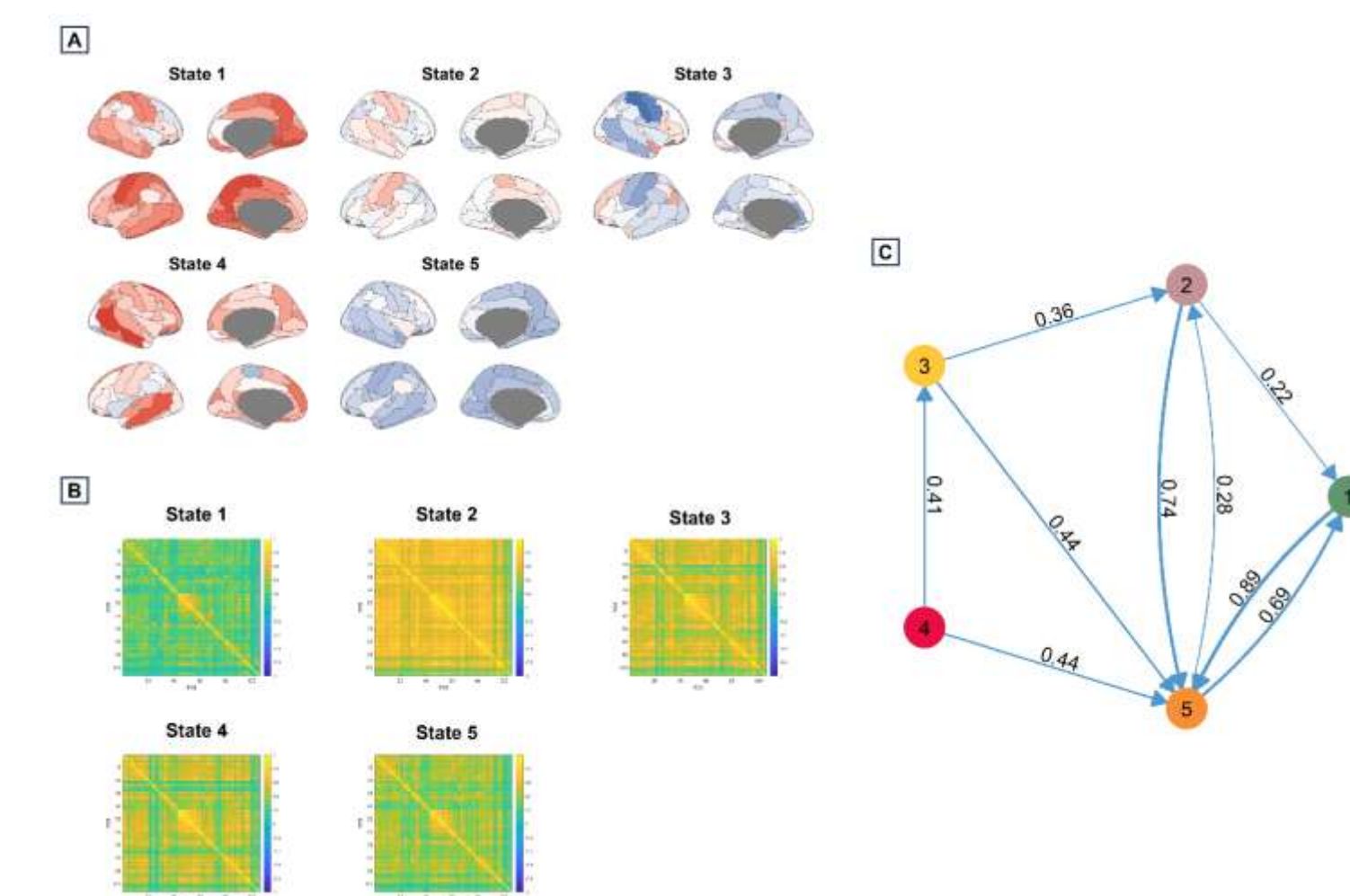


Figure 1 Multistate spatial characterization and between-state transition probabilities

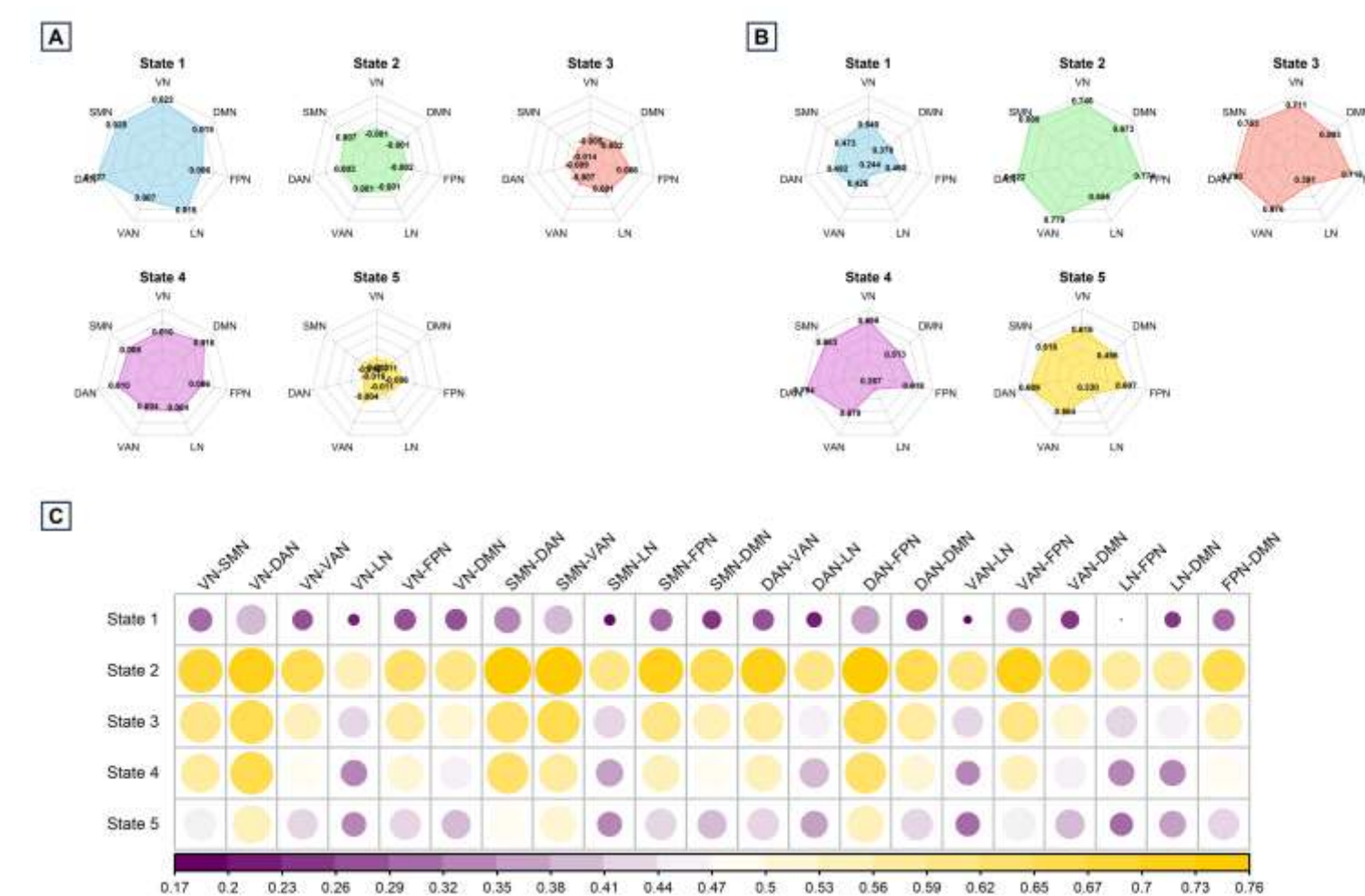


Figure 2 Within-network mean functional activity, within-network functional connectivity, and between-network functional connectivity across states

- Compared with CN, both sMCI and pMCI showed higher occupancy and temporal stability of a weakly connected state with relatively high mean functional activity (state 1). Compared with sMCI, pMCI showed increased temporal stability of a strongly connected state with low functional activity (state 3) (Figure 3).

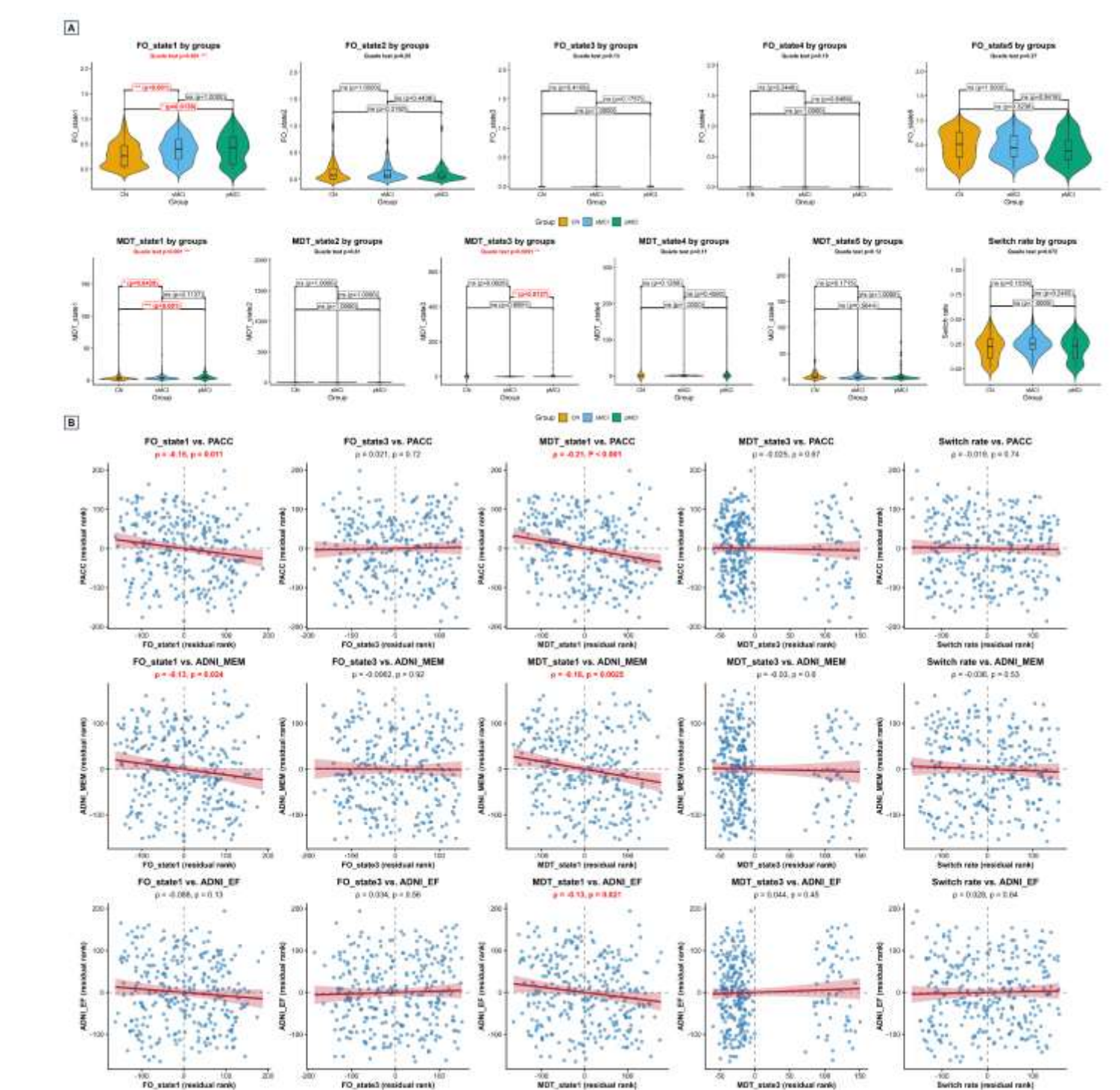


Figure 3 Between-group comparisons of brain dynamic metrics and their associations with cognitive function

- Higher state 1 metrics were associated with poorer cognition, neurodegeneration-related gene expression, neurotransmitter systems, microglial, oligodendroglial, and endothelial markers, and temporo-parieto-occipital atrophy. Metrics of both states were associated with amyloid- β PET, whereas state 3 metrics were additionally associated with tau PET, subcortical atrophy, longitudinal cognitive decline, and MCI-to-dementia conversion. (Figure 3, Figure 4, Figure 5 & Figure 6)

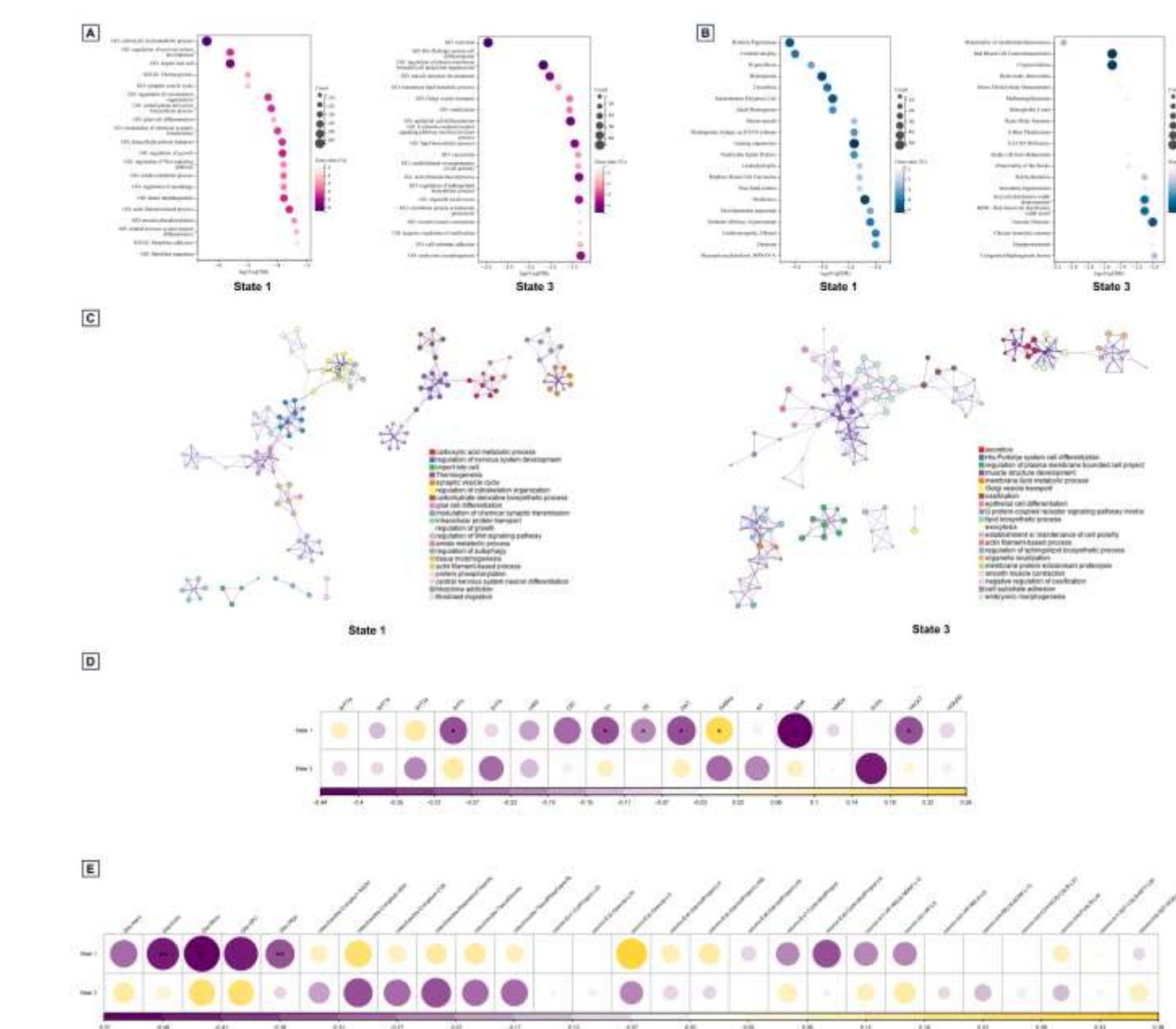


Figure 4 Transcriptomic, neurotransmitter, and cell-type associations with mean functional activity across brain regions

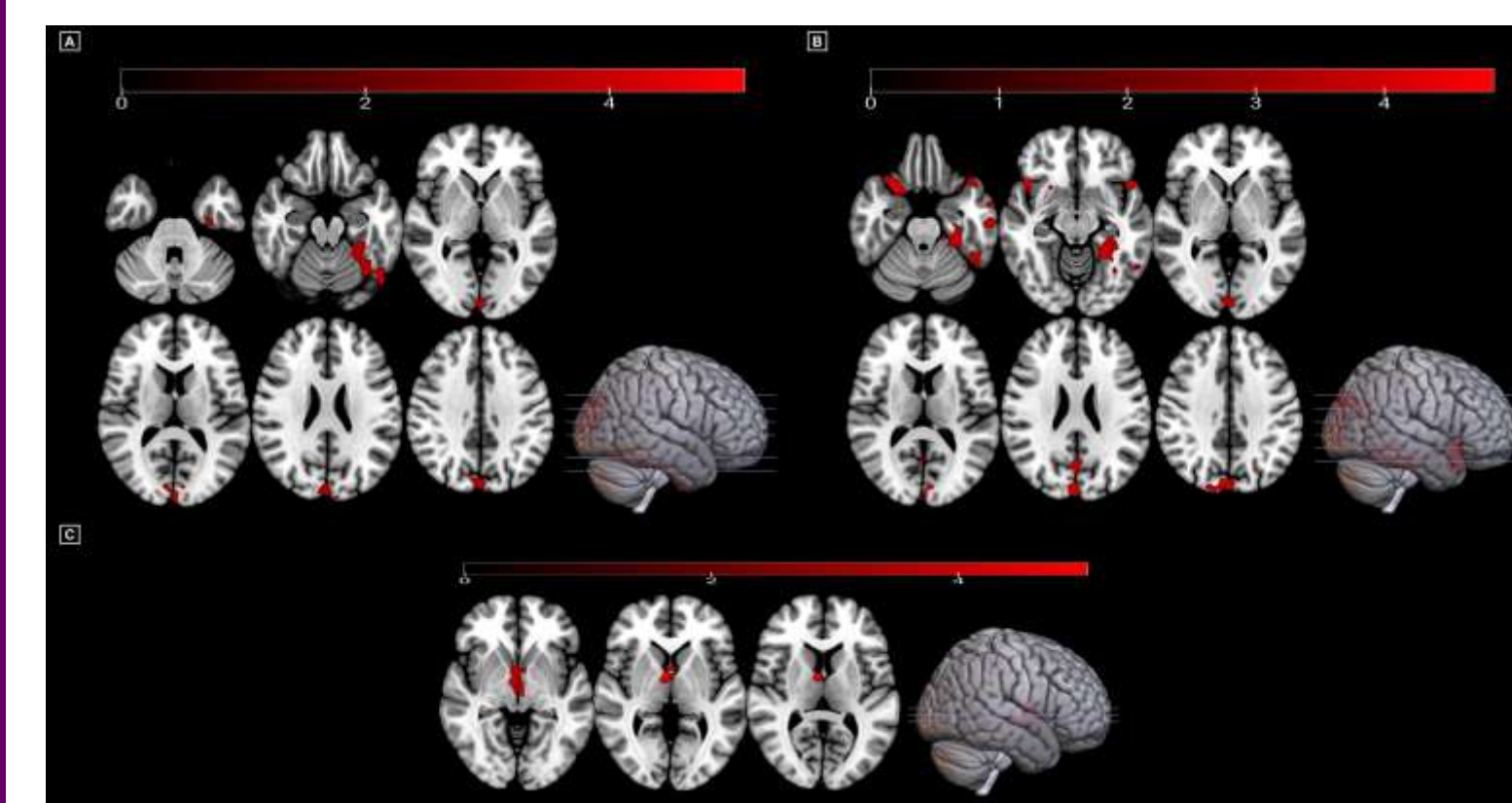


Figure 5 Comparison of whole-brain voxel-wise gray matter volume between high and low levels of dynamic metrics

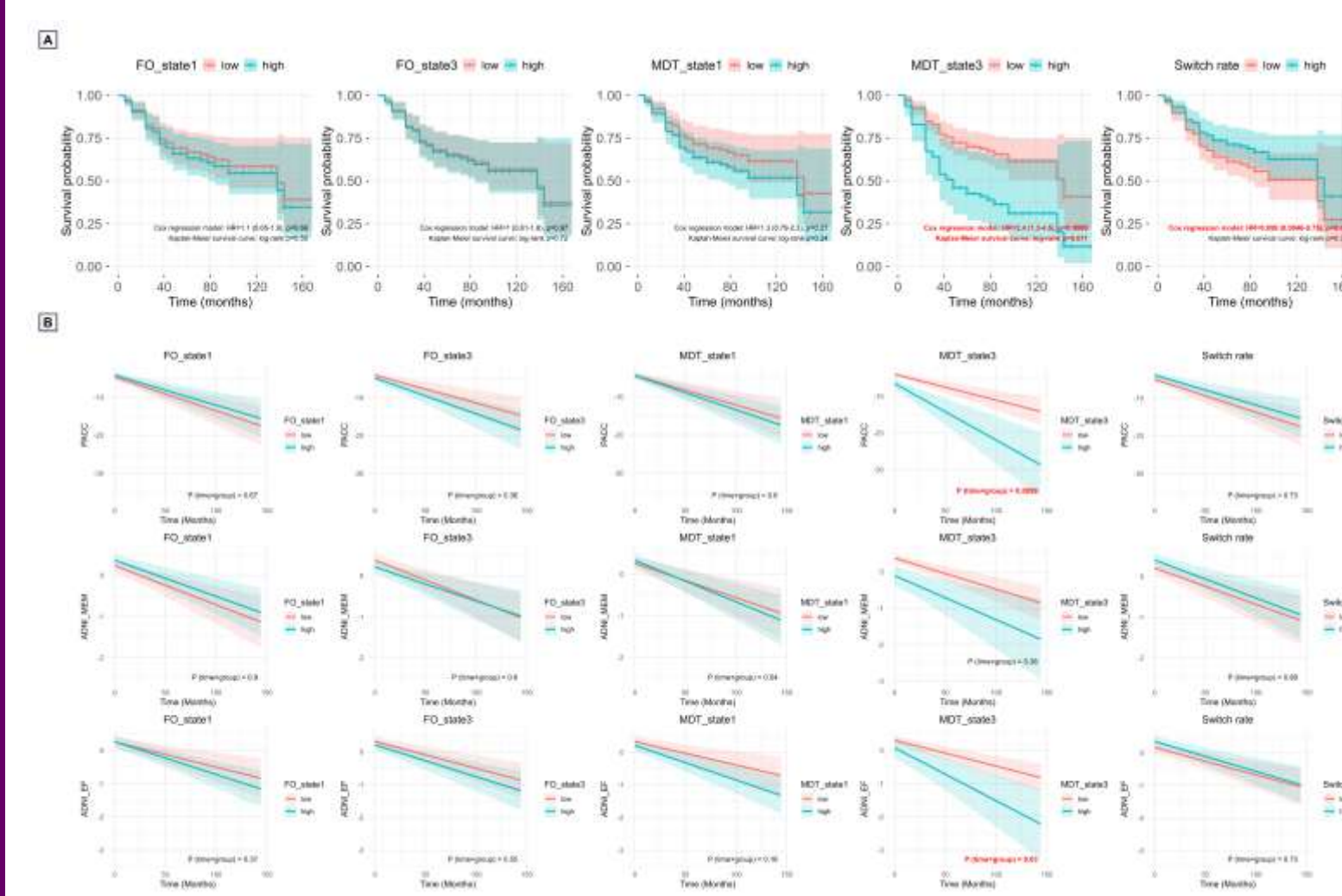


Figure 6 Associations between brain dynamic metric levels and longitudinal cognitive change

- A CPM model based on multistate functional connectivity achieved high predictive accuracy (AUC = 0.879), outperforming models using static connectivity or dynamic metrics (Figure 7).

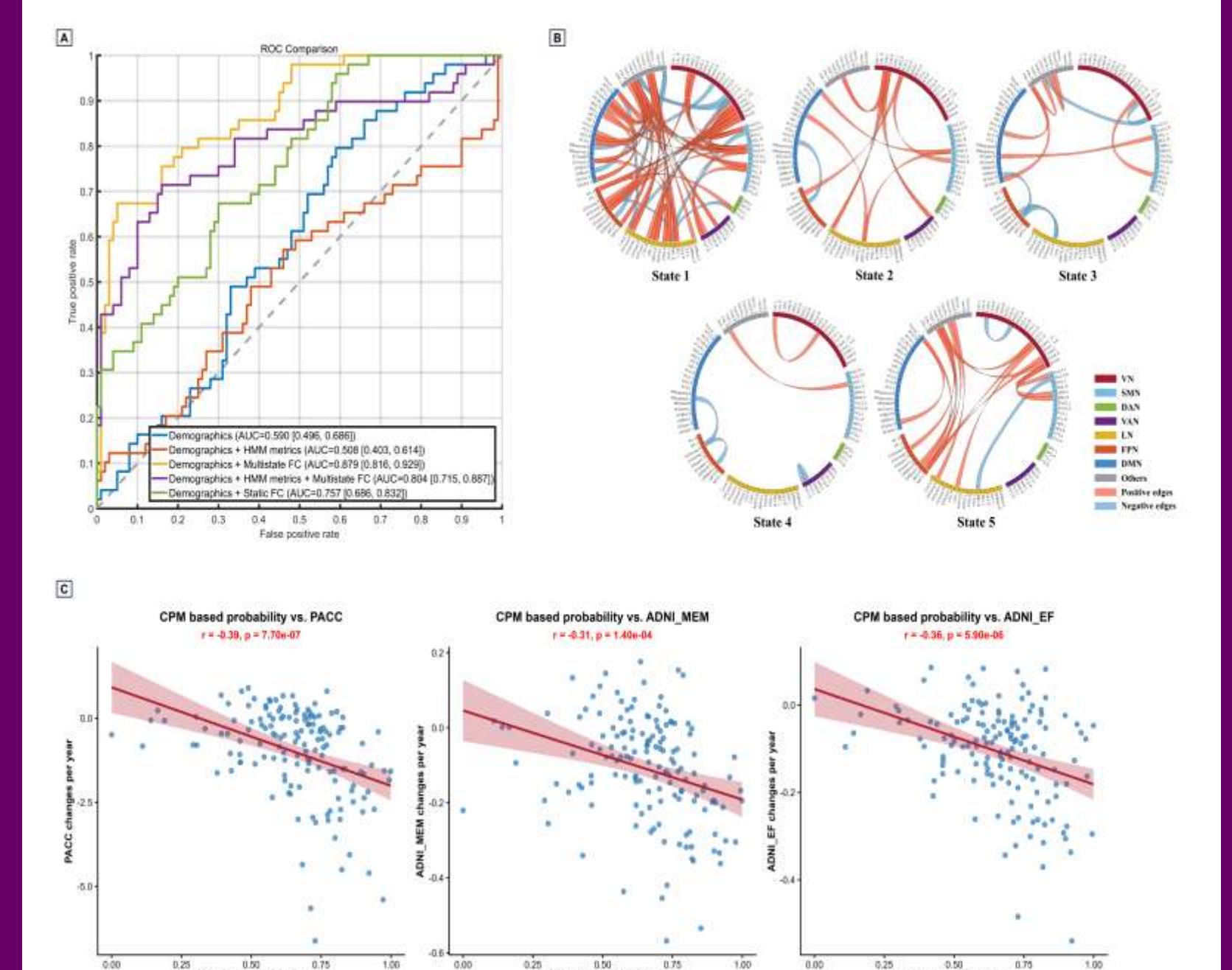


Figure 7 Predictive models for MCI-to-dementia conversion based on dynamic brain characteristics

Conclusion

- There is altered brain dynamic in sMCI and pMCI, which links to molecular and pathological substrates.
- Brain dynamic features provide strong predictive power for MCI conversion, offering a promising approach for risk stratification of MCI.

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