



EEG-Based Brain Effective Connectivity Predicts PET Amyloid Status of Persons with Normal Cognition

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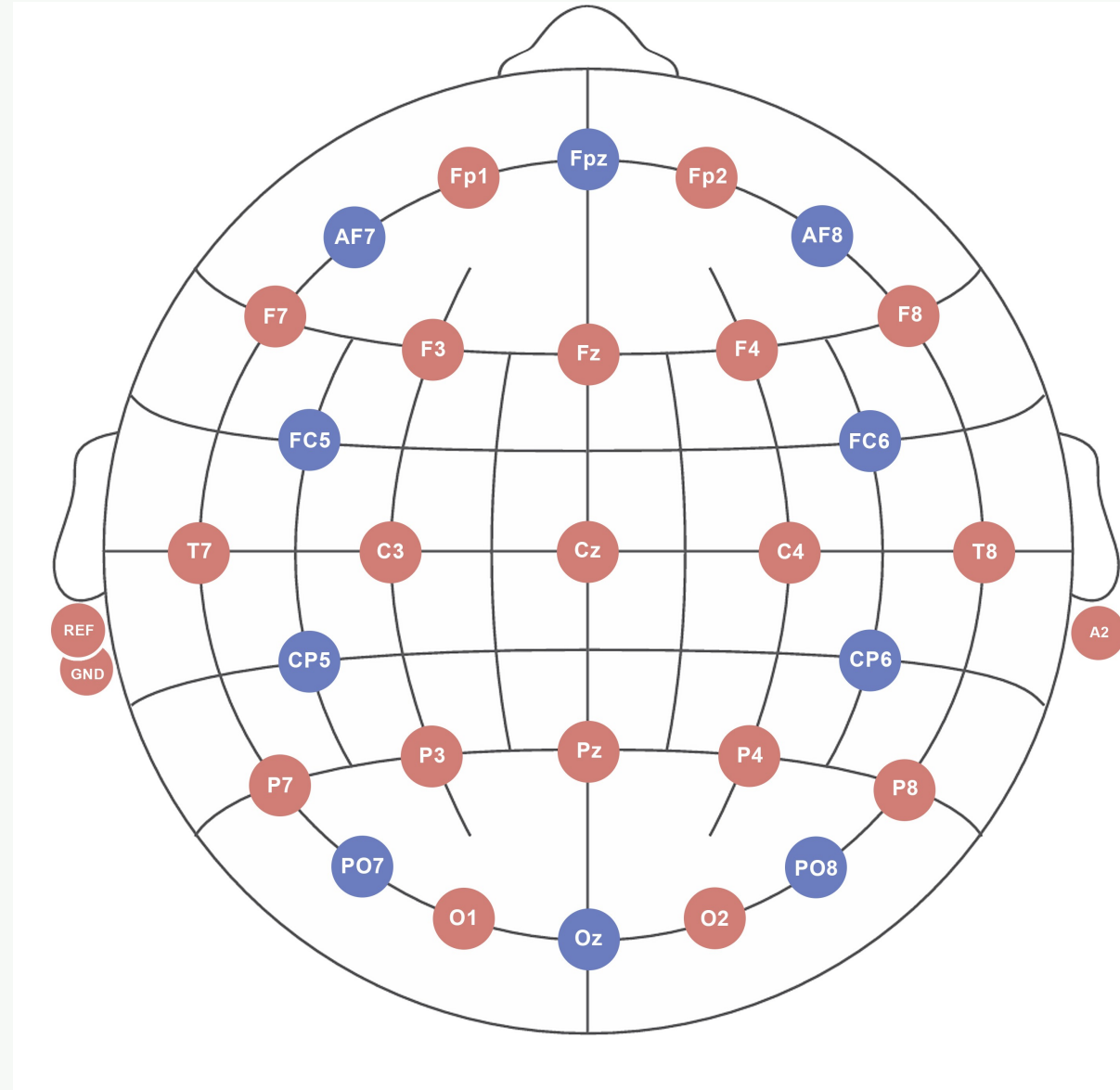
Background

- Early identification of amyloid-beta ($A\beta$) pathology is essential for timely intervention in Alzheimer's disease (AD), as $A\beta$ accumulation precedes clinical symptoms by years or even decades.
- Current methods (PET, CSF biomarkers) are accurate but costly, invasive, and unsuitable for broad screening; blood biomarkers are less invasive but may take additional processing time and cannot localize brain dysfunction.
- AD pathologies are often closely related to the weakening or loss of connectivity among critical brain regions, since the most vulnerable neurons in neurodegeneration are the association neurons with long projections that formulate the communication channels between the brain regions.
- In this study, we predicted $A\beta$ status, as determined by PET imaging, in cognitively normal individuals using non-invasive resting-state dry EEG.

Data Acquisition and Preprocessing

- We studied 38 cognitively normal participants (13 Amyloid-positive ($A\beta+$) and 25 Amyloid-negative ($A\beta-$), determined by $A\beta$ -PET Centiloid units, ages 65-88). All participants were recruited through MADRC.

- Prior to further analysis, the current source density (CSD) was computed from the scalp voltage of the EEG signal for all the ROIs.



- Each participant was recorded for 3 minutes of eye-closed resting-state Dry EEG system (the S-BP-100-5010 CGX Quick-32r system). 27 of 38 completed a blood draw at the baseline visit.

Quantifying Effective Connectivity using Causalized Convergent Cross-Mapping (cCCM)

- cCCM is a robust and effective tool for measuring effective connectivity and evaluating the directed information transfer in the brain network.
- Consider two dynamically coupled variables X and Y which share the same attractor manifold M . Let $X^n = [X_1, X_2, \dots, X_n]$ and $Y^n = [Y_1, Y_2, \dots, Y_n]$ be the time series consisting of samples of X and Y , respectively.
- Construct the shadow manifolds with respect to X^n and Y^n , M_x and M_y .
- For each vector x_t , find its $E + 1$ nearest neighbors and denote the time indices (from closest to farthest) by $t_1, \dots, t_{E+1}$, where $t_i < t$ for $i = 1, 2, \dots, E + 1$.

cCCM-based effective connectivity (Cont.)

- If X and Y are dynamically coupled, then the nearest neighbors of x_t in M_x would be mapped to the nearby points of Y_t on M . The estimated Y_t based on M_x , or say the cross-mapping from X to Y , is defined as:

$$\hat{Y}_t | M_x = \sum_{i=1}^{E+1} w_i Y_{t_i}$$

where

$$w_i = \frac{u_i}{\sum_{j=1}^{E+1} u_j}, \text{ with } u_i = \exp\left\{-\frac{d(x(t), x(t_i))}{d(x(t), x(t_1))}\right\},$$

here d denotes the Euclidean distance between two vectors. The cross-mapping from Y to X can be defined similarly.

- As n increases, it is expected that $\hat{X}_t | M_y$ and $\hat{Y}_t | M_x$ would converge to X_t and Y_t , respectively.
- The cross-mapping correlations are defined as

$$\rho_{cCCM}(X \rightarrow Y) = \rho(Y^n, \hat{Y}^n) \text{ and } \rho_{cCCM}(Y \rightarrow X) = \rho(X^n, \hat{X}^n)$$

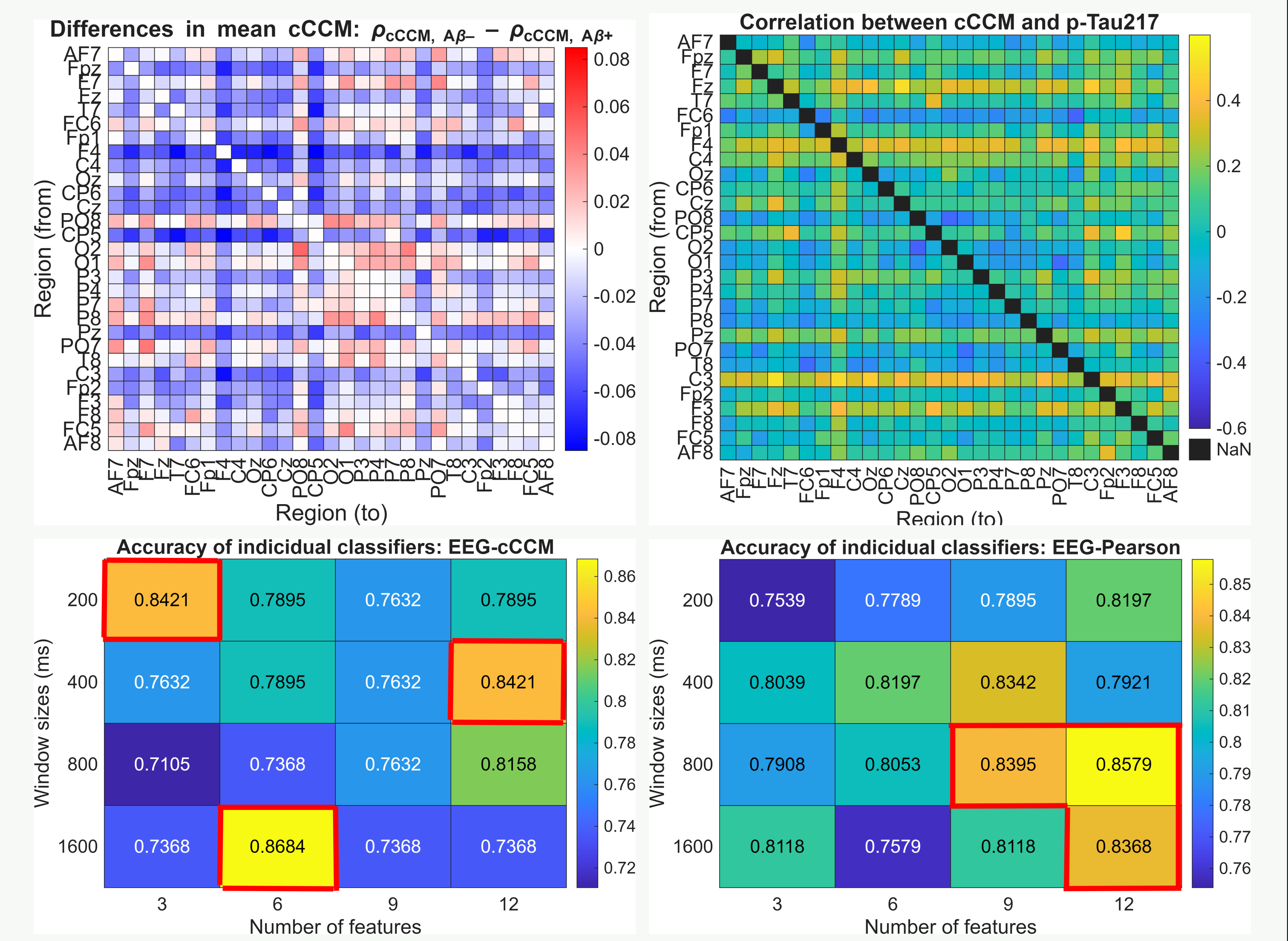
where ρ denotes the Pearson correlation.

Prediction of Amyloid Status using EEG

- In this research, we applied a multiscale analysis, using **window sizes** $L = 200, 400, 800, 1600$ ms and the number of selected features $M = 3, 6, 9, 12$.
- We partitioned the CSD signals into blocks of size L . For each participant, we evaluated the dynamic brain functional and effective connectivity for each directed region pair, represented as a cCCM sequence.
- For each window size, the mean, maximum, and minimum of the cCCM time series for each directed region pair were first extracted as **primitive features**.
- Next, a t-test was applied to select features that maximized the differences between the $A\beta+$ and $A\beta-$ groups. More specifically, M primitive features with the lowest p-values were selected as **features** to construct **EEG-based machine learning models** for predicting the PET $A\beta$ status of each participant.
- A diagonal linear discriminant analysis (Diag LDA) model was adopted due to its superior performance. A total of $4 \times 4 = 16$ EEG-based $A\beta$ prediction models were developed.
- Three of the 16 best-performing models were selected as voters, and the final prediction was obtained through a **weighted majority voting** scheme, where the weight assigned to each model was its classification accuracy.
- We conducted multiple methods, **EEG-cCCM**, **EEG-Pearson**, **EEG-cCCM-Pearson** and **EEG-cCCM-Wavelet**, for the prediction of $A\beta$ status.

Results

- The $A\beta+$ group exhibits lower effective connectivity than $A\beta-$ across certain brain-region pairs, but higher effective connectivity in others, which may reflect compensatory brain mechanisms;
- EEG-based models can predict amyloid positivity with accuracy comparable to, or in some cases exceeding, that of plasma p-Tau217, depending on the model.



Methods	Machine Learning	Prediction Accuracy of	Study Power
	Models	5-fold Cross-Validation	
EEG-cCCM	Diag LDA	88.03%	0.9784
EEG-Pearson	Diag LDA	85.92%	0.9785
EEG-cCCM-Pearson	Diag LDA	93.03%	0.9851
EEG-cCCM-Wavelet	Diag LDA	94.87%	1
BBM p-Tau217	Linear SVM	88.89%	1

Conclusions

- Beyond near-real-time $A\beta$ inference, the framework identifies the most affected brain regions and connections associated with neurodegeneration, offering complementary information to blood-based biomarkers and supporting its potential as an affordable tool for early AD detection.