Artificial
Intelligence in
Medicine

Association between Structural Connectivity and Generalized Cognitive Spectrum in Alzheimer's Disease

AIM3.T4

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AIM General Meeting - Oct 15-16, 2020

Motivations

- Several **scores assess the severity of the most important symptoms of AD**. The most used cognitive indexes include Alzheimer's Disease Assessment Scale cognitive total score (ADAS), Mini Mental State Exam score (MMSE) and Rey Auditory Verbal Learning Test (RAVLT) which measures cognitive impairment, attention, language and visuo-spatial functions and memory deficits.
- The **AD progression** can be also accurately observed by using **MRI features**: average regional cortical thickness, white matter (WM) volume, cortical surface area, tissue volume and gray matter density (GM).
- An ever-increasing number of works is dedicated to the study of **brain connectivity in AD**: the decline due to AD is related to a disrupted connectivity among brain regions, caused by WM degeneration.

GOAL: investigate the strength of association between DTI structural connectivity and cognitive spectrum in Alzheimer's disease.

Dataset

- **Diffusion-weighted scans** of a mixed ADNI cohort (191 subjects).
- **MRtrix3** software package for image preprocessing and structural connectome generation.
- We included the **10 clinical measures in the outcome matrix Y** of our analysis: CDR-SOB, ADAS-Cog-13, MMSE, MoCA, FAQ, RAVLT-immediate, RAVLT-learning, RAVLT-percforgetting, ECog-PT-total, ECog-SP-total.

	NC (48)	AD (39)	MCI (104)
Age	73.4 ± 5.7	75.4 ± 8.8	72.8 ± 7.4
Gender	$24M/24F$	$26M/13F$	$64M/40F$
CDR-SOB	0.04 ± 0.13	4.8 ± 1.3	1.41 ± 0.7
Adas-Cog 13	9 ± 4.7	30.9 ± 8.7	15.9 ± 6.7
MMSE	29 ± 1.1	23 ± 1.8	27 ± 1.6
MoCA	25.6 ± 2.1	17.5 ± 4.3	22.9 ± 2.7
FAQ	0.23 ± 0.92	15.1 ± 6.9	2.7 ± 4
RAVLT-immed	44.3 ± 10.4	21.3 ± 6.7	34.1 ± 9.6
RAVLT-learn	5.12 ± 2.3	2 ± 1.9	4.3 ± 2.1
RAVLT-percforg	36.2 ± 28.2	89 ± 19.4	56.8 ± 32
ECog-PT-total	1.2 ± 0.2	1.9 ± 0.6	1.8 ± 0.5
ECog-SP-total	1.2 ± 0.3	2.8 ± 0.5	1.7 ± 0.6

Network metrics

A **120 x 120 weighted symmetric connectivity matrix W** was obtained for each subject as output of the image processing steps. In order to assess the importance of the regions with respect the rest of the network, the following graph metrics have been extracted from each matrix W and for each node of the network:

- **Strength** of connections:

$$s_i = \sum_{j=1}^{N} w_{ij}$$

- **Eigenvector centrality**:

$$eig_i = \frac{1}{\lambda} \sum_{j=1}^{N} w_{ij} e_j$$

- **Local efficiency**:

$$E(G_i) = \frac{1}{n_i(n_i - 1)} \sum_{j \in G_i} \frac{1}{d(i,j)}$$

input of ML:

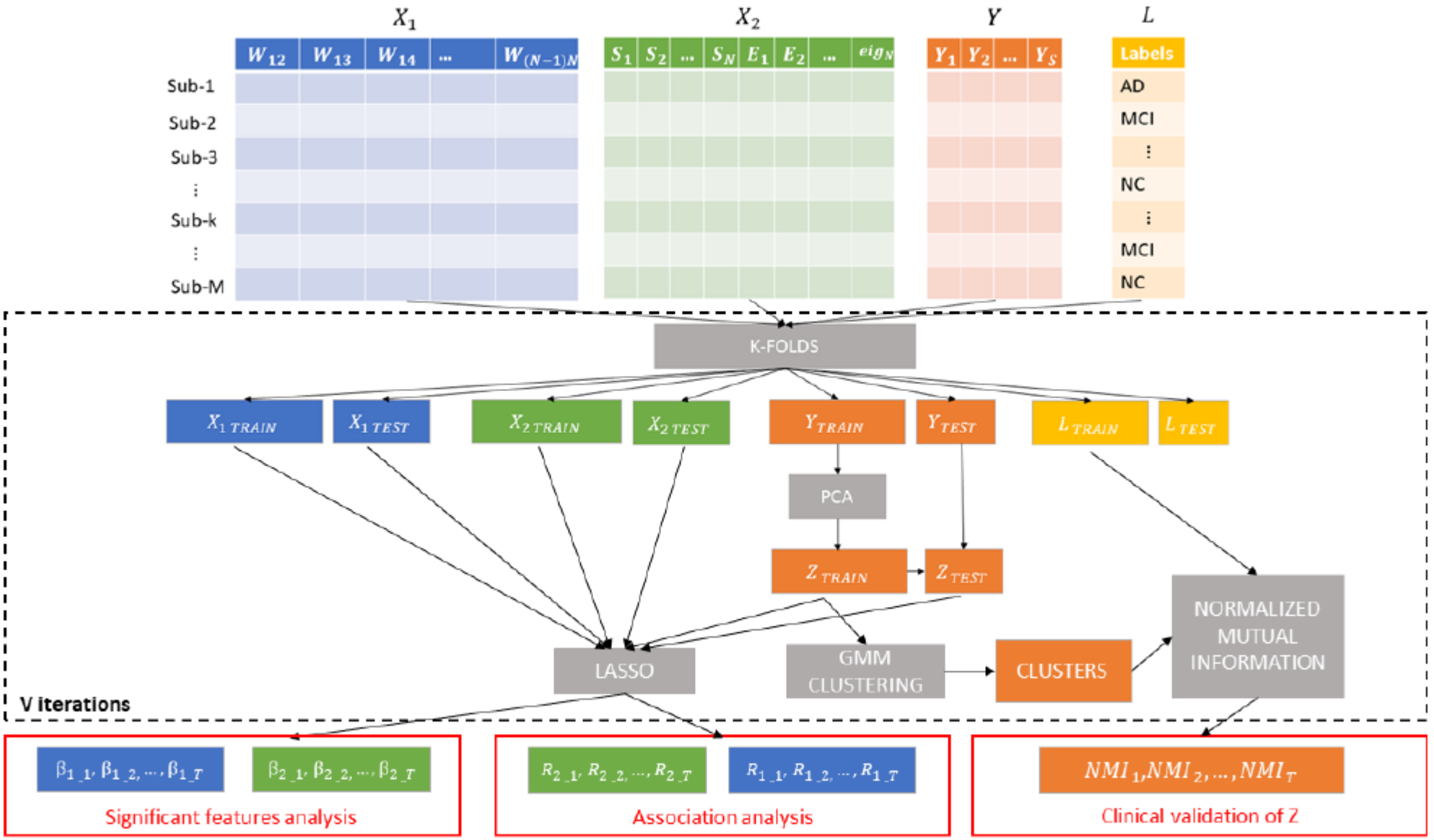
matrix X_1 $M \times P_1, (M = 191, P_1 = 7140)$

matrix X_2 $M \times P_2, (M = 191, P_2 = 360)$

ML framework: goals

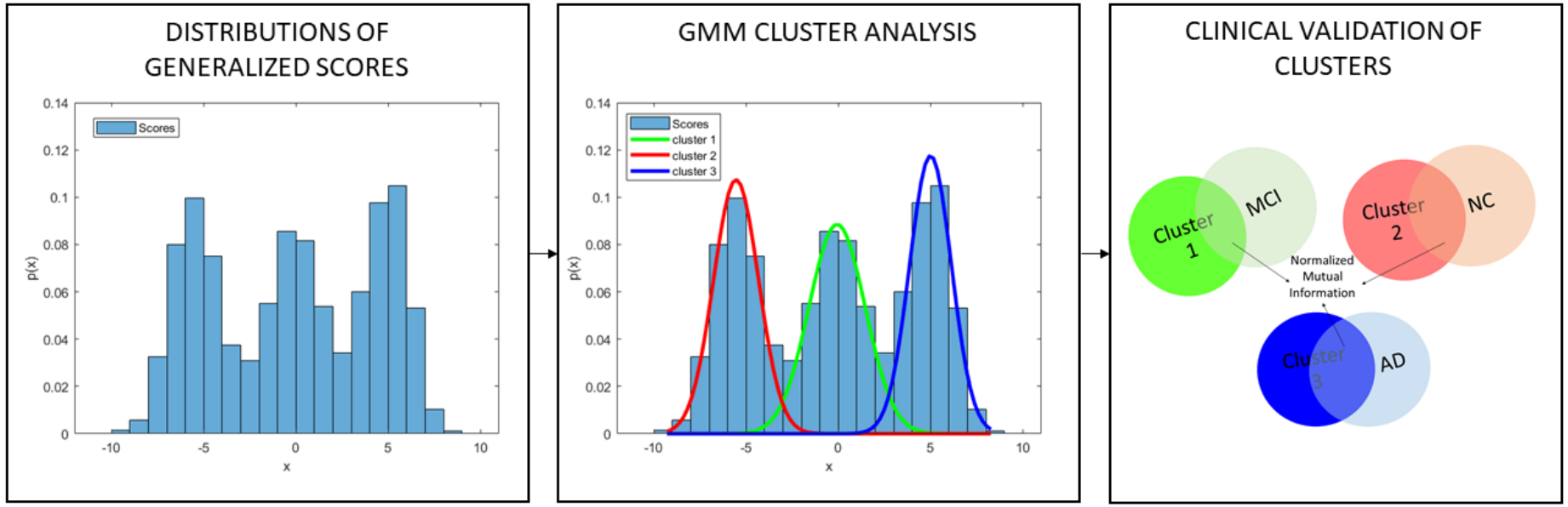
- Identify a **generalized index** that effectively summarizes **the cognitive spectrum of the population under investigation**;
- find **significant associations between the identified index and the features** derived from the structural connectivity of the subjects;
- **identify the most significant features** among the total set of features in order to understand the strongest biological associations between the structural connectivity and cognitive spectrum.

ML Framework



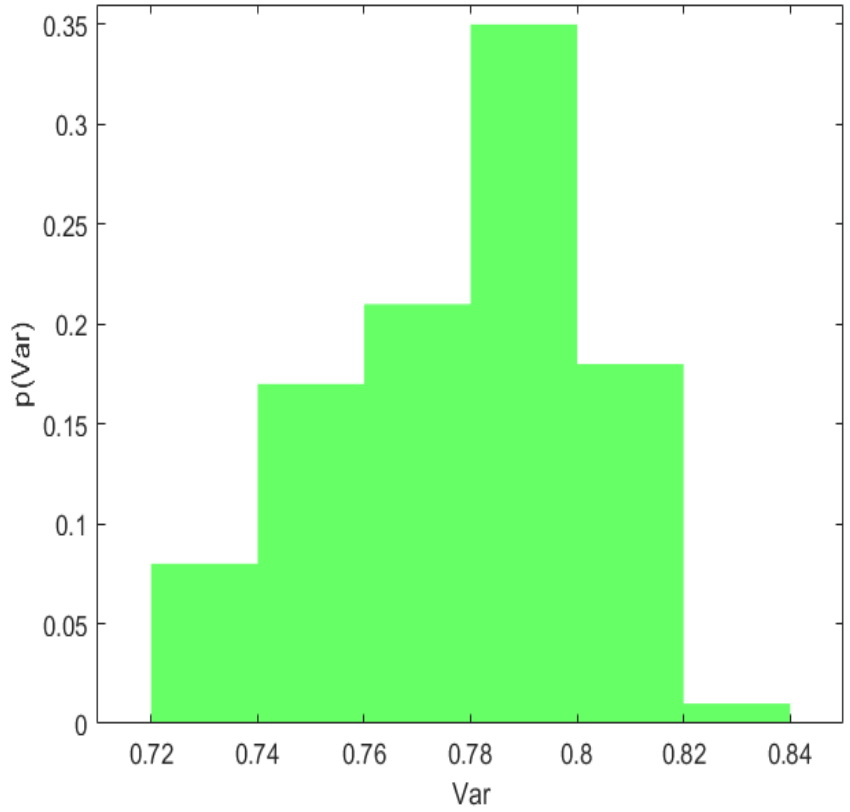
Identification of the generalized cognitive index

- We computed the **first PCA component** of the matrix of the clinical scores within each training fold (i.e., YTRAIN) to compute the vector of the generalized scores ZTRAIN for the training samples. Then, the generalized scores ZTEST for the test data were computed by using the coefficients obtained from the PCA of the training dataset.
- Clustering analysis in order to provide a clinical validation of the computed score:

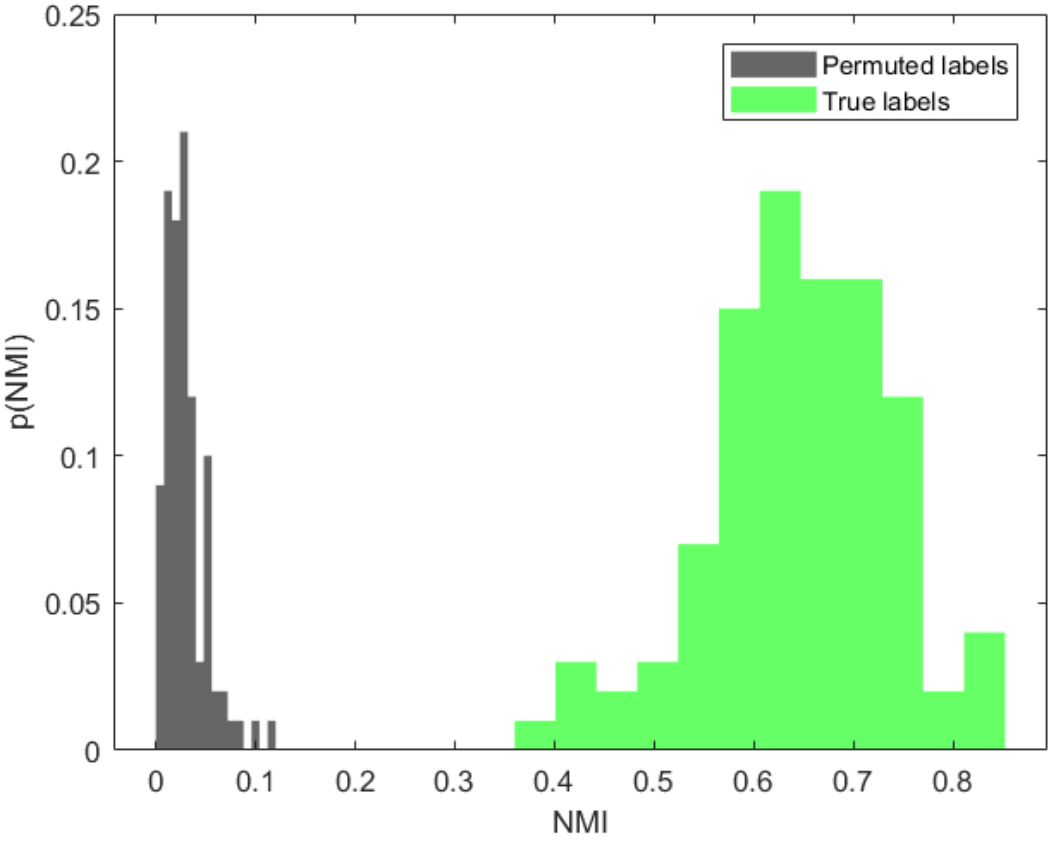


Identification of the generalized cognitive index

The average percentage of explained variance of the first component over all the rounds is Var = 0.78 +/- 0.02 :the first latent variable may explain the relationship between the ten observed variables.

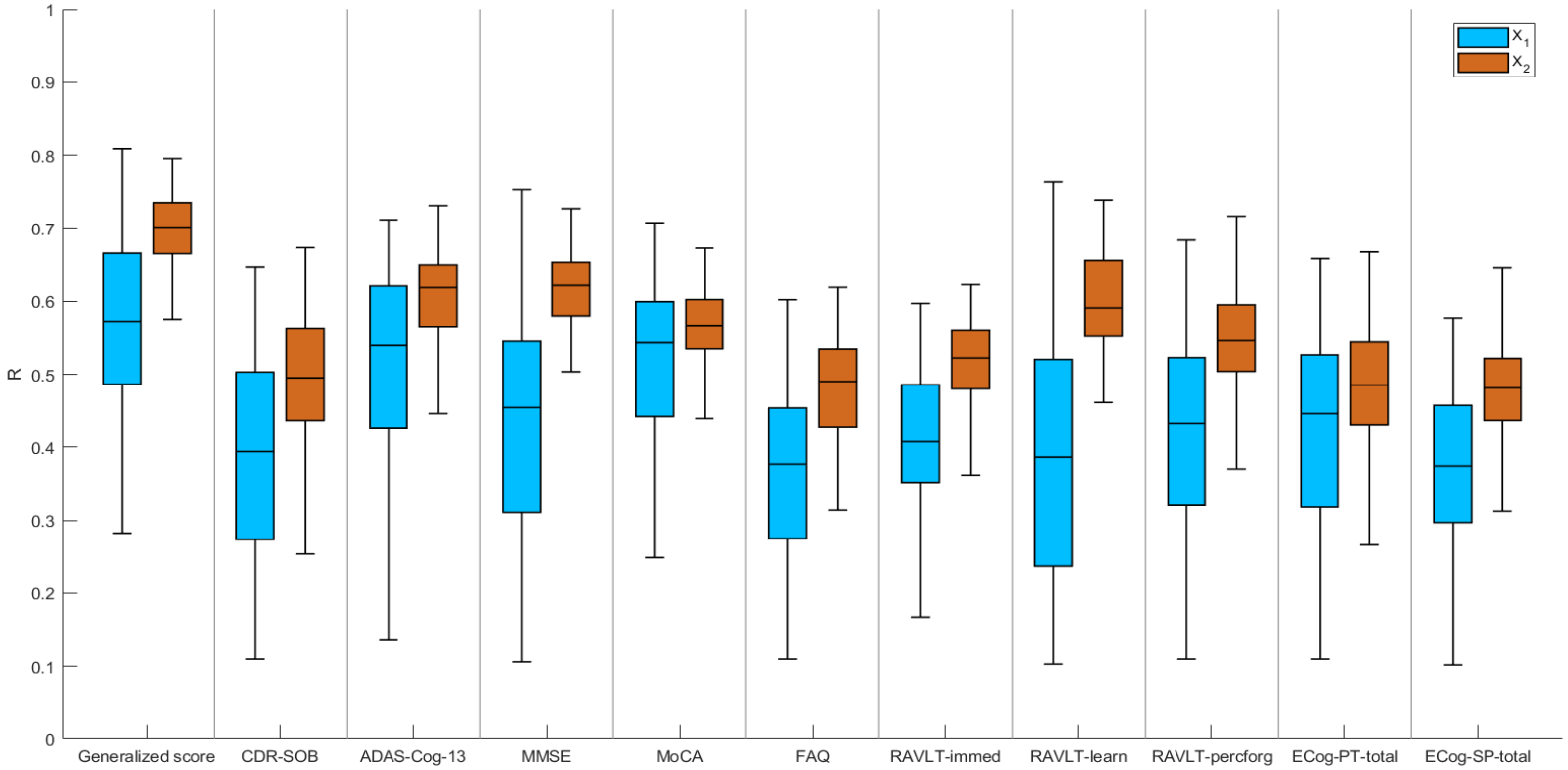


A significant overlap between the GMM clusters and the clinical groups was obtained with an average NMI value = 0.65 +/- 0.09(p = 0).



Best model selection

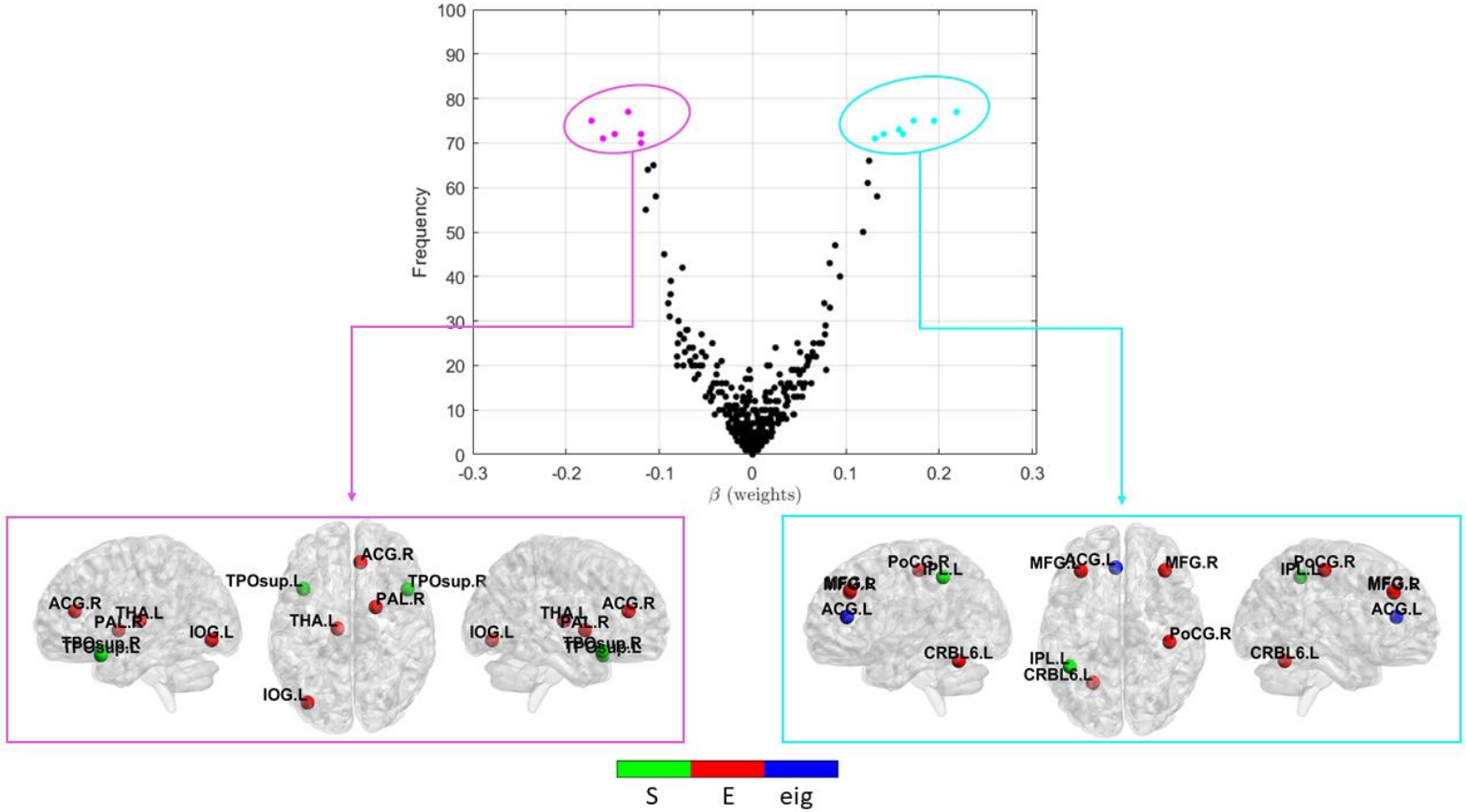
Lasso (Least Absolute Shrinkage and Selection Operator) was employed to find significant associations between the connectivity features and the proposed generalized cognitive score. Correlation coefficients between the actual and predicted score is reported.



Clinical index	X_1	X_2
Generalized score	0.57 ± 0.11	0.70 ± 0.05
CDR-SOB	0.39 ± 0.14	0.49 ± 0.09
Adas-Cog 13	0.51 ± 0.13	0.60 ± 0.07
MMSE	0.42 ± 0.15	0.60 ± 0.07
MoCA	0.50 ± 0.13	0.56 ± 0.06
FAQ	0.36 ± 0.11	0.47 ± 0.07
RAVLT-immed	0.40 ± 0.10	0.51 ± 0.07
RAVLT-learn	0.39 ± 0.18	0.59 ± 0.07
RAVLT-percforg	0.42 ± 0.14	0.54 ± 0.07
ECog-PT-total	0.41 ± 0.14	0.48 ± 0.08
ECog-SP-total	0.37 ± 0.11	0.47 ± 0.08

Clinical interpretability

We computed the relative frequency occurrence of the features selected and their average weights across the validation rounds in order to show the importance ranking of each feature for the most performing matrix X2.



Main findings and next steps

- The generalized cognitive score obtained in a data-driven manner by combining the available clinical cognitive scores is more significantly associated with structural connectivity.
- Some local topological descriptors of structural connectivity can effectively track cognitive impairment in Alzheimer's disease (R=0.7).

Next steps:

1. Further investigations on structural DTI networks to identify markers to capture cognitive decline associated with AD.
2. Test more complex nonlinear machine learning models on a larger data sample.
3. Find aging effective descriptors.

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Deadline for manuscript submissions: **20 December 2020**.

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Research Topic

Explainable Artificial Intelligence (XAI) in Systems Neuroscience

Submission Deadlines

09 September 2020	Manuscript
11 January 2021	Manuscript Extension