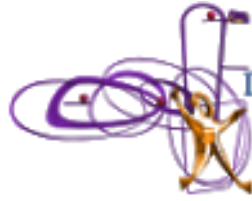




UNIVERSITÀ  
DEGLI STUDI DI BARI  
ALDO MORO



Dipartimento Interateneo di Fisica  
Michelangelo Merlin



# Artificial Intelligence and Complexity in Biological Systems

---

ANGELA LOMBARDI, PHD

UNIBA – INFN

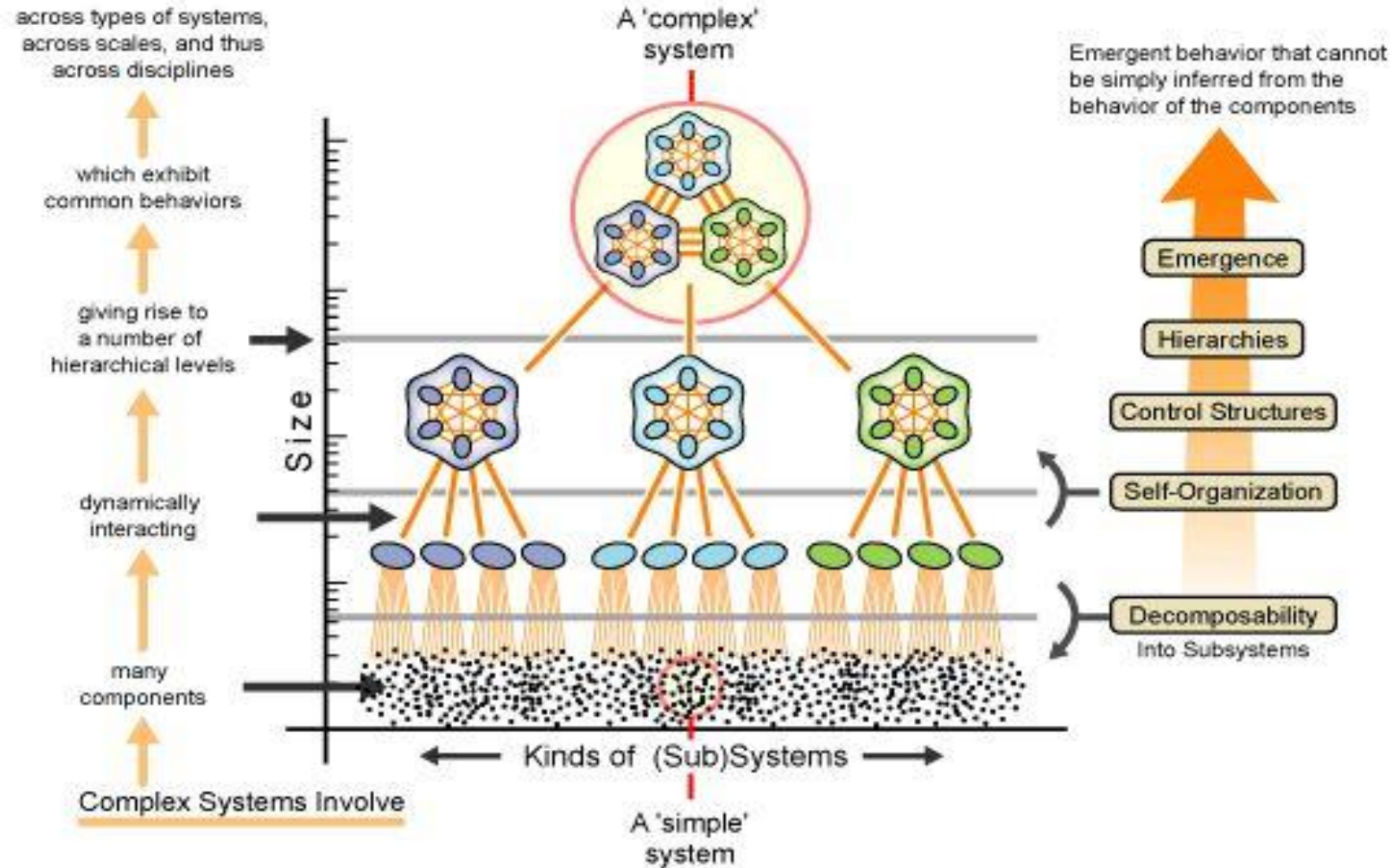
ON BEHALF OF MEDICAL PHYSICS RESEARCH GROUP

# Summary

- ✓ Complex systems
- ✓ The human brain as a complex network
- ✓ Nodes and links in brain networks
- ✓ Graph modeling
- ✓ Artificial intelligence and complexity
- ✓ Multidimensional neuroimaging pipelines in ReCaS datacenter
- ✓ Case Study 1: DTI connectivity networks in Alzheimer's Disease
- ✓ Case Study 2: Brain age prediction
- ✓ Conclusions

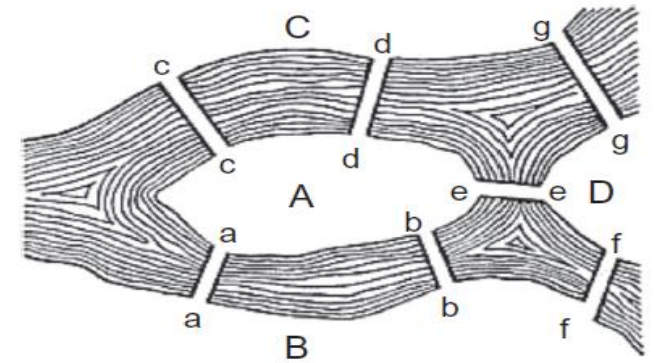
# Complex Systems

## Characteristics of Complex Systems

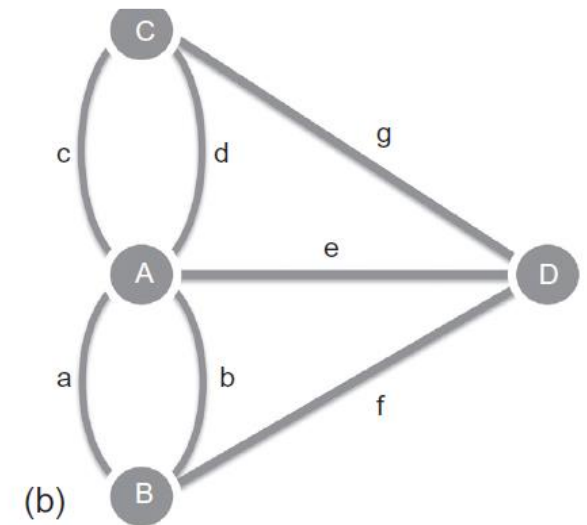


# Graphs as models of complex systems

- ✓ Complex systems have properties that are neither completely random nor completely regular, instead showing **nontrivial characteristics** that are indicative of a more elaborate, or complex, organization.
- ✓ An interdisciplinary field of **network science** has formed around the use of general analytic methods to model complex networks, and to explore the scope of common or near-universal principles of **network organization, function, growth, and evolution**. Principal among these general methods is **graph theory**.



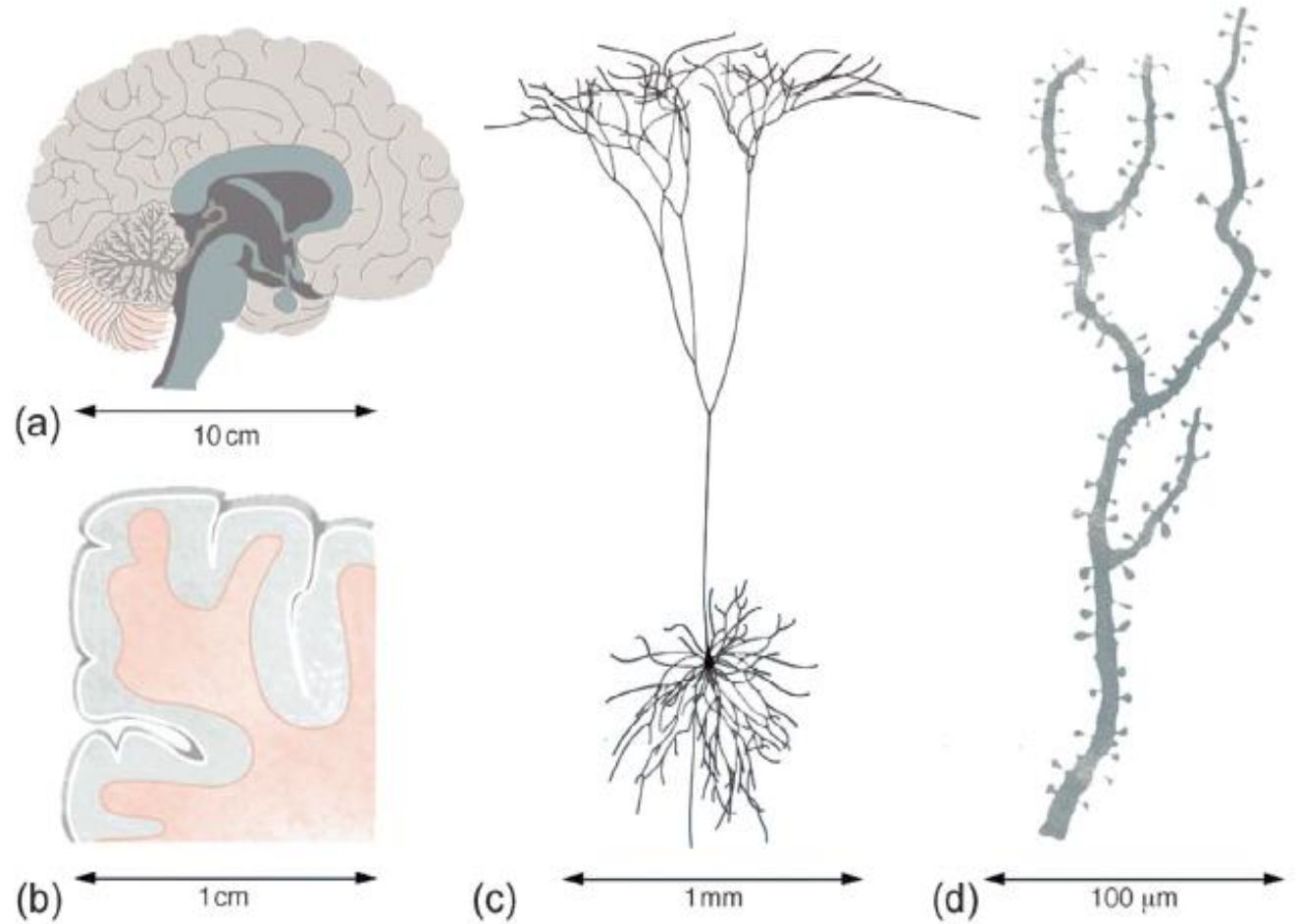
(a)



(b)

# Multiscale organization of the brain

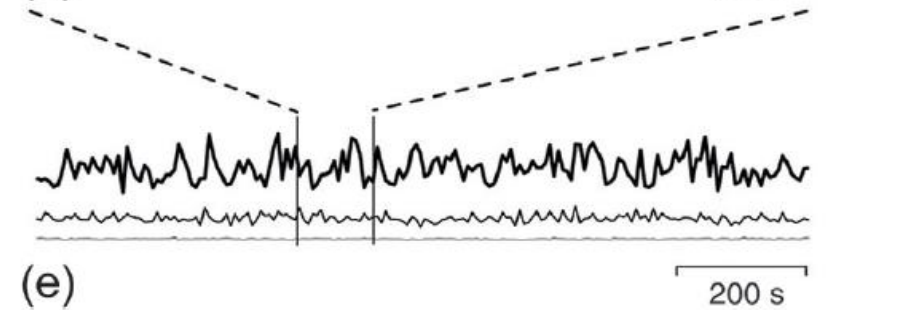
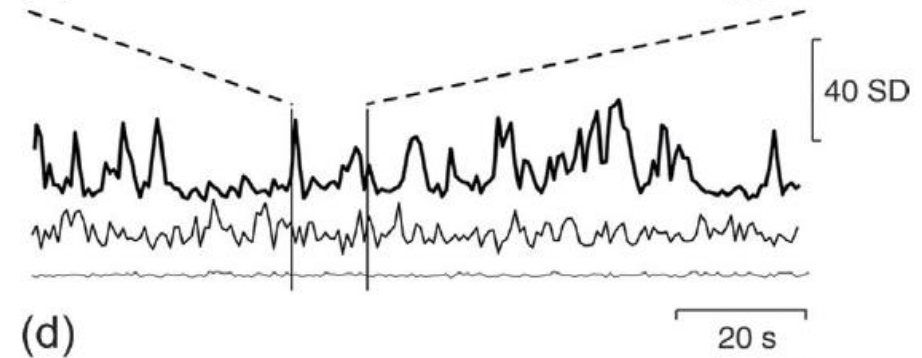
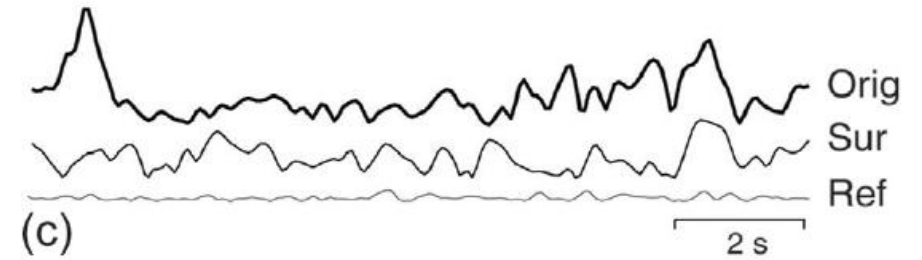
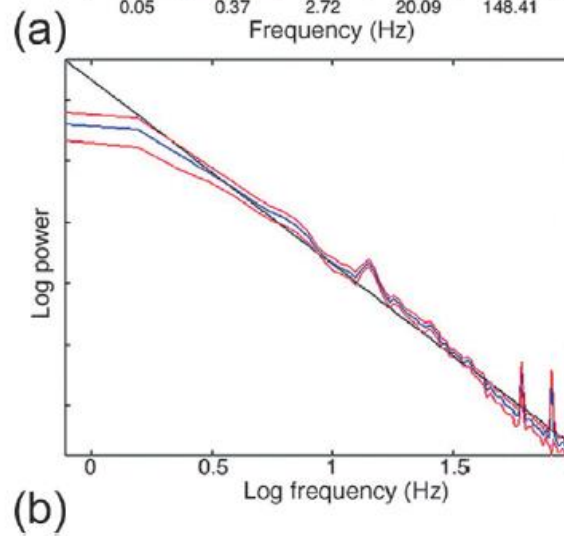
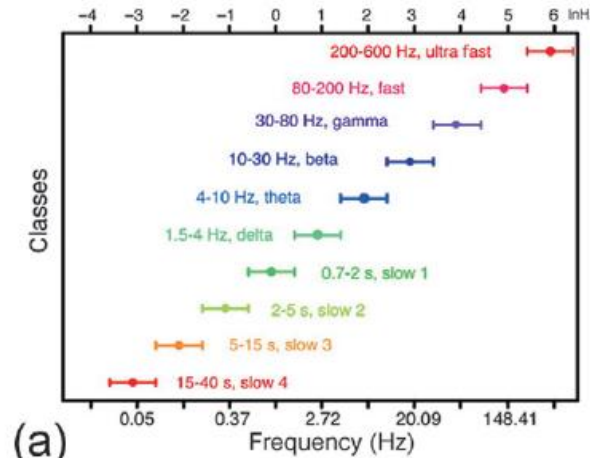
In humans, **neural anatomy** is organized over **six orders of magnitude**, from the level of individual neurons and synapses ( $<1\ \mu\text{m}$ ), through populations of neurons such as cortical columns and cytoarchitectonic regions (1 cm), to large-scale divisions such as lobes, systems, and hemispheres (10 cm).



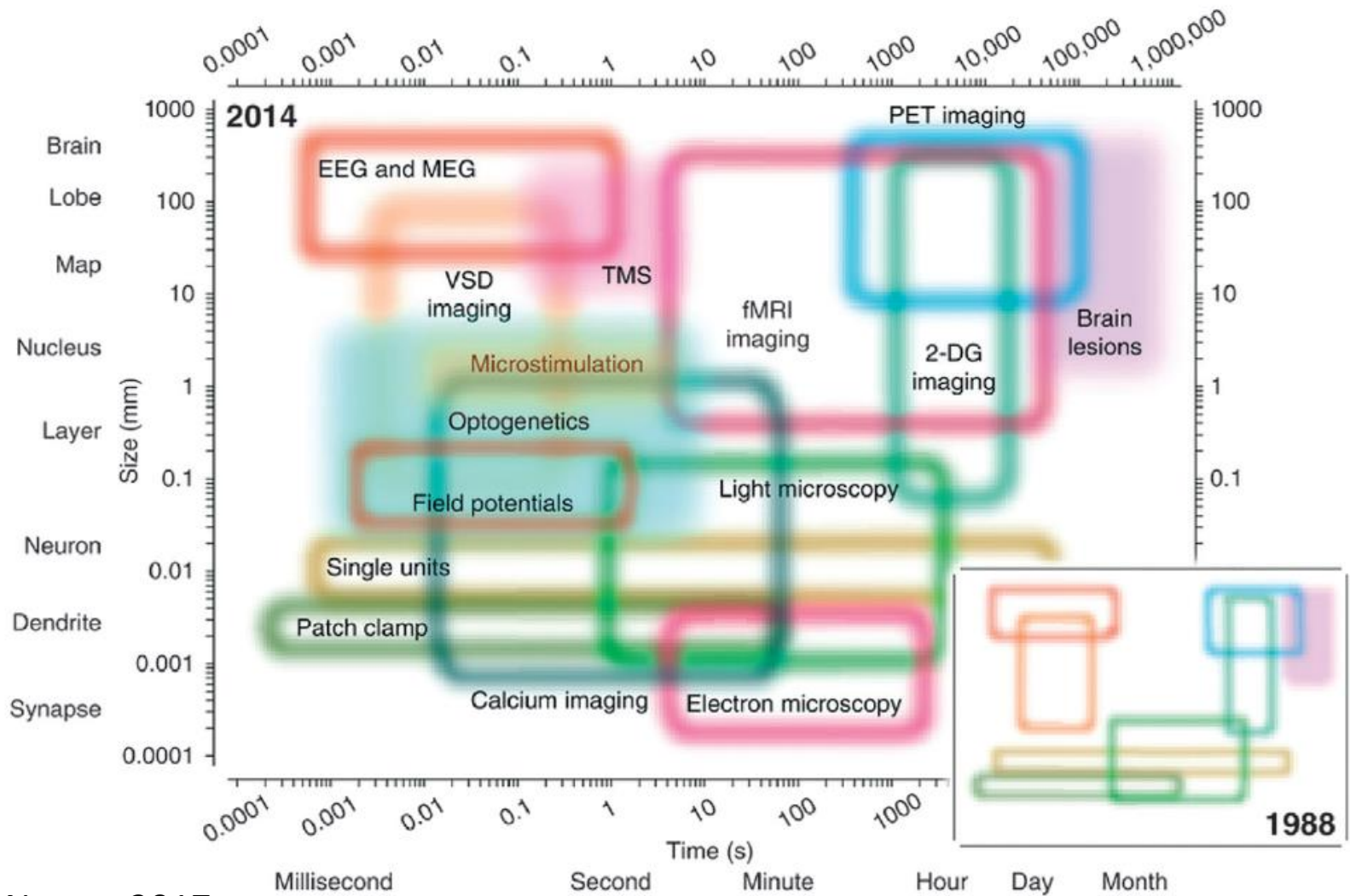
# Multiscale organization of the brain

The dynamics unfolding on these structures evolve over a similar range of temporal scales, spanning frequencies between 0.05 and 500 Hz .

This **multiscale organization** means that there is no single, privileged scale for the analysis of brain networks.



# Methods for studying the organization of the brain

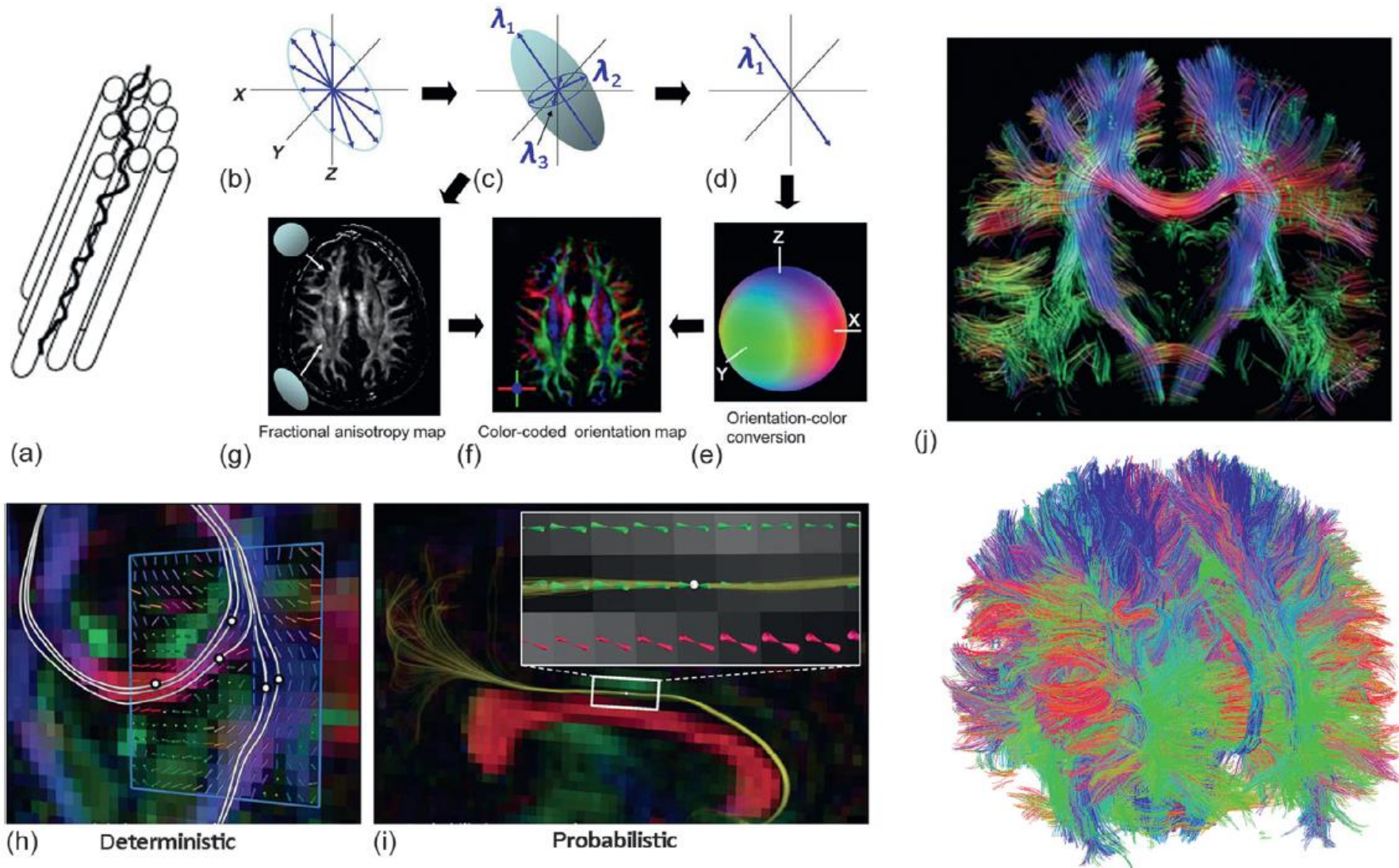


# Nodes in brain networks

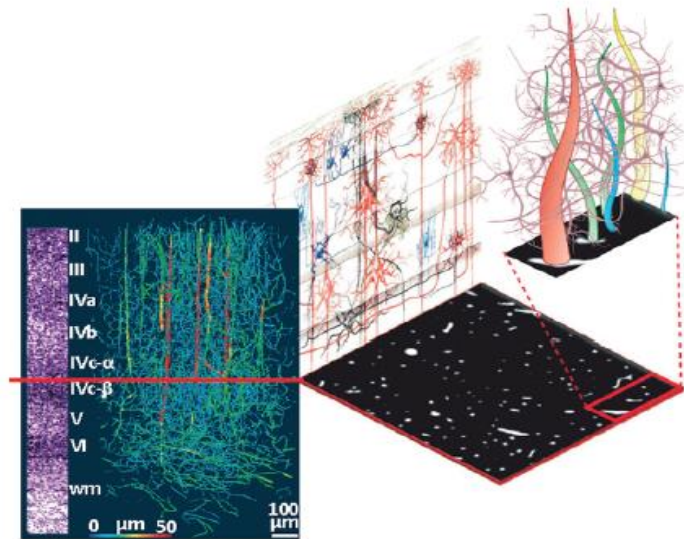
- ✓ Noninvasive imaging techniques, such as **MRI**, **EEG**, and **MEG**, offer a means for mapping connectivity across the entire brain, in vivo, in model species and humans alike.
- ✓ The advantages of these methods include their **clinical safety** and **tolerability**, **their coverage of the entire brain** (particularly MRI), and their flexibility in allowing studies of whole-brain connectivity across the lifespan and in relation to a wide range of human brain disorders.
- ✓ A typical **T1-weighted anatomical MRI** has a voxel resolution of about **1 mm x 1 mm x 1 mm**, which contains an estimated **20.000-30.000 neurons** and billions of synapses.



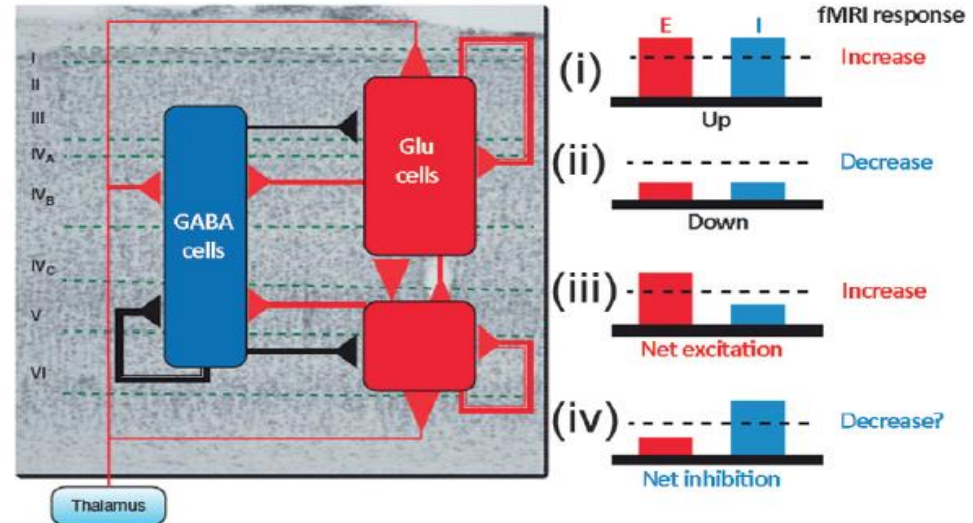
# Diffusion MRI



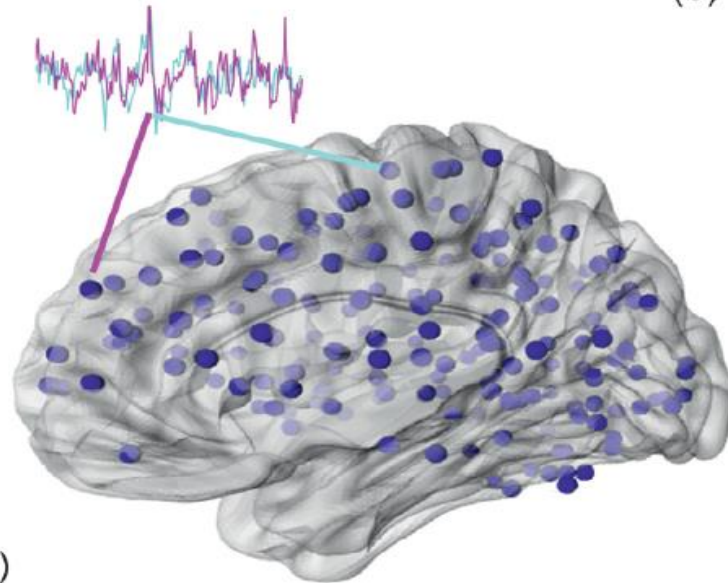
# Functional MRI



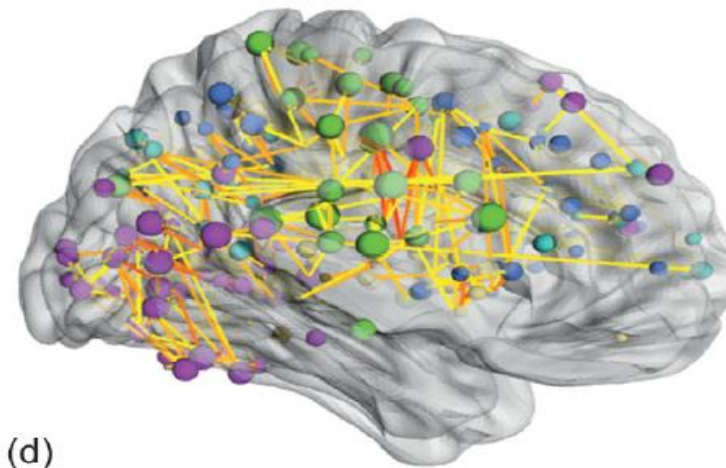
(a)



(b)



(c)



(d)

# Graph modeling

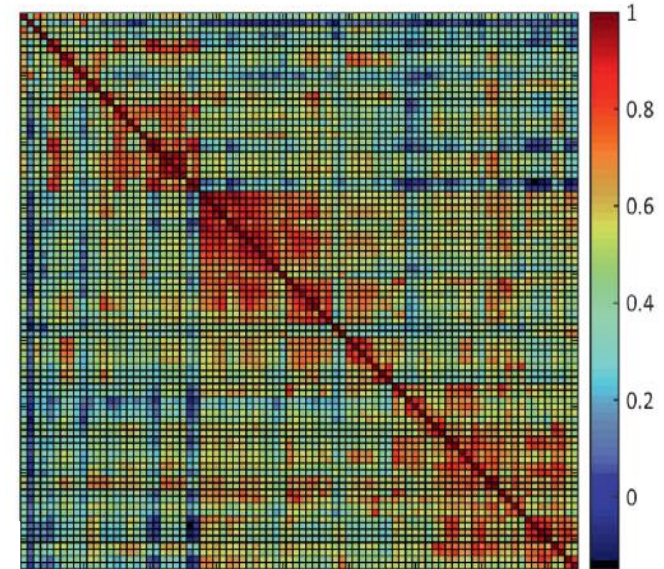
The **connectivity matrix** offers a compact description of the pairwise connectivity between all nodes of a network. To build a connectivity matrix,  $C$ , for a brain network comprising  $N$  nodes, we start by constructing a **two-dimensional array**, called a square matrix, which comprises  $N$  rows and  $N$  columns.

Directionality

Connectivity Weights

Diagonal and Off-Diagonal

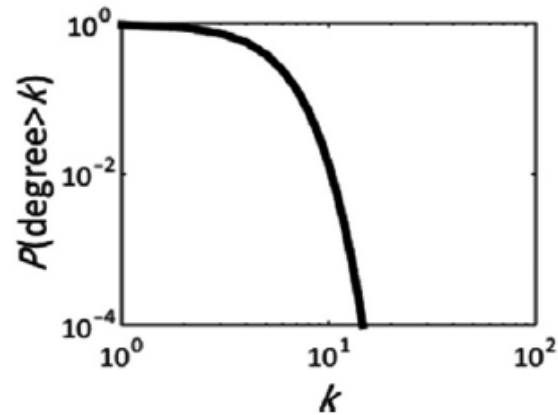
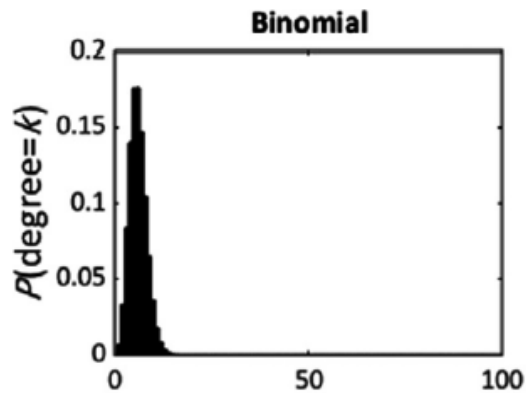
$$C_{ij} = \begin{bmatrix} C_{11} & C_{12} & \cdots & C_{1N} \\ C_{21} & C_{22} & & C_{2N} \\ \vdots & & \ddots & \vdots \\ C_{N1} & C_{N2} & \cdots & C_{NN} \end{bmatrix}.$$



# Graph metrics: degree distribution

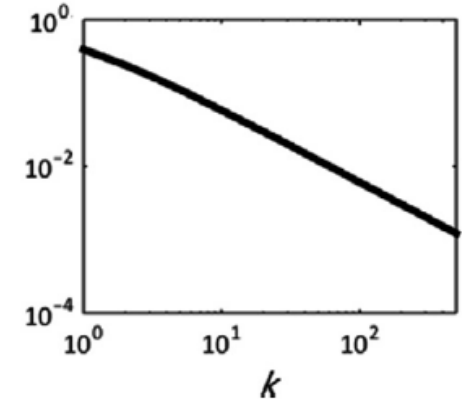
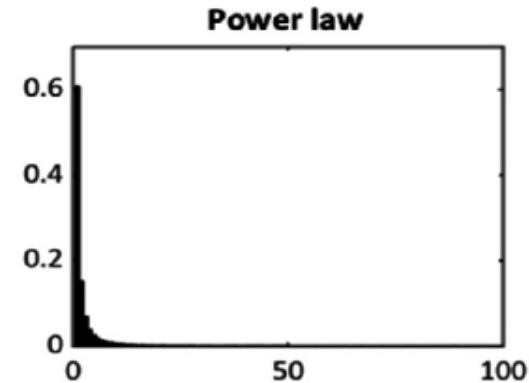
The Erdos-Renyi graph is a classic example of a **single-scale network**. The degree distribution of this network follows a binomial distribution.

$$P(\text{degree} = k) = \binom{N-1}{k} p^k (1-p)^{N-1-k}, \quad k \leq N-1,$$



Barabasi and Albert (1999) showed that the degree distribution of many real-world networks is better approximated by a **power law** with the form:

$$P(\text{degree} = k) \sim k^{-\gamma},$$

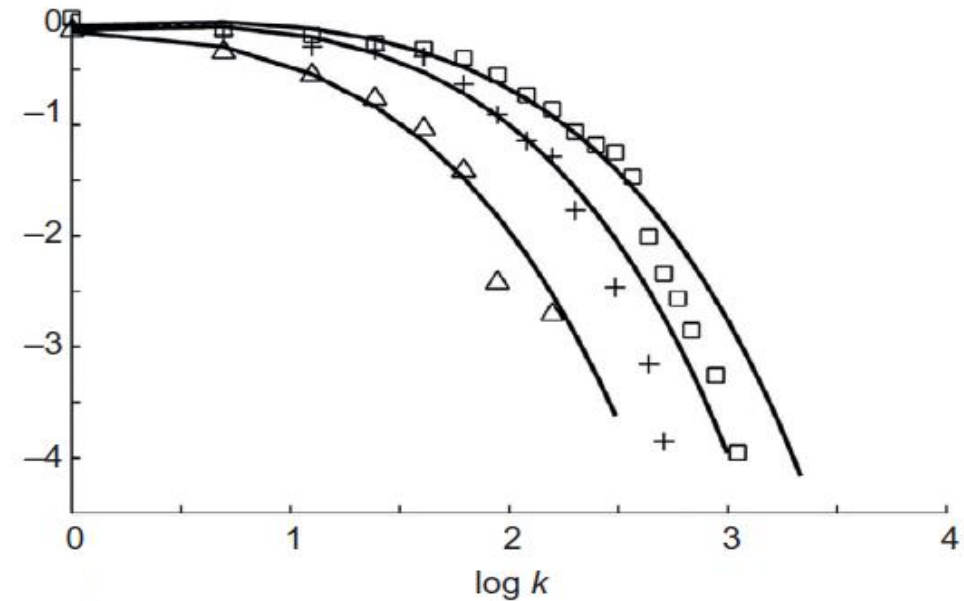
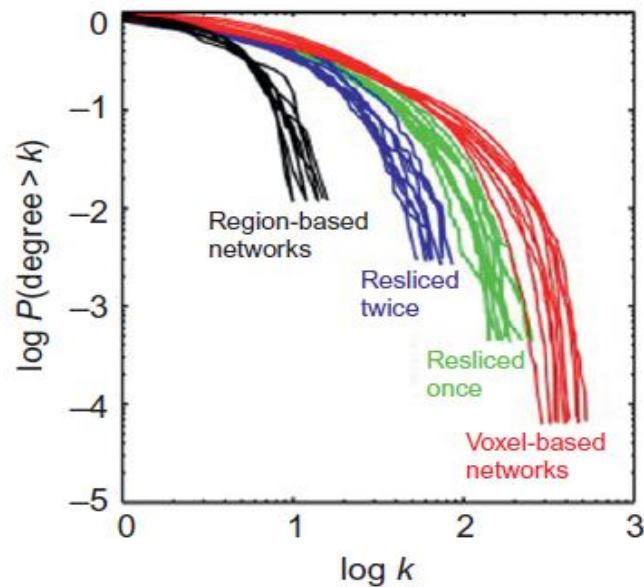


# Graph metrics: degree distribution

Nervous systems are physically embedded, and both spatial and metabolic constraints limit the number of connections that any single neural element can possess.

In different studies with several imaging modalities, was found an exponentially truncated power-law degree distribution of the form:

$$P(\text{degree} = k) \sim k^{-\gamma} e^{-k/k_c},$$



# Clustering coefficient

The clustering coefficient captures the degree to which the neighbors of a given node link to each other.

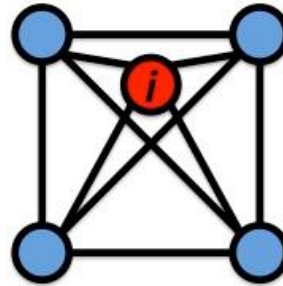
\* what fraction of your neighbors are connected?

\* Node  $i$  with degree  $k_i$

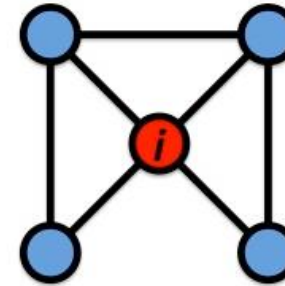
\*  $e_i$  the number of links between the  $k_i$  neighbors of node  $i$ .

\*  $C_i$  in  $[0,1]$

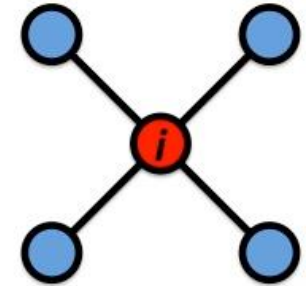
$$C_i = \frac{2e_i}{k_i(k_i - 1)}$$



$$C_i = 1$$



$$C_i = 1/2$$



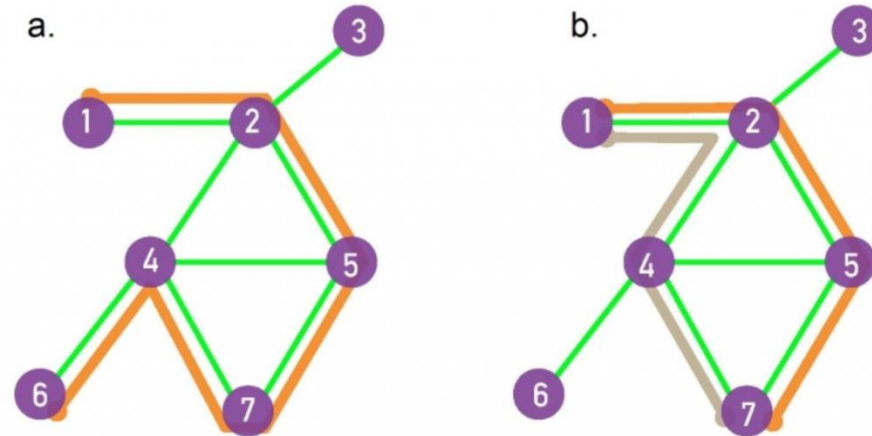
$$C_i = 0$$

# Path and distance

A **path** between nodes  $i_0$  and  $i_n$  is an ordered list of  $n$  links :

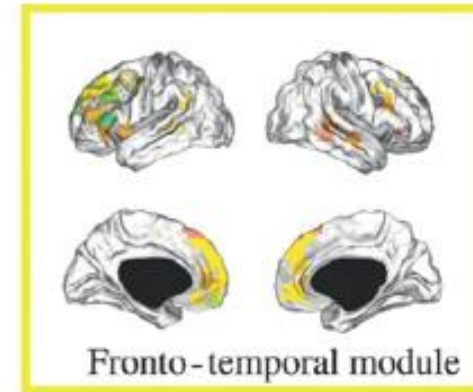
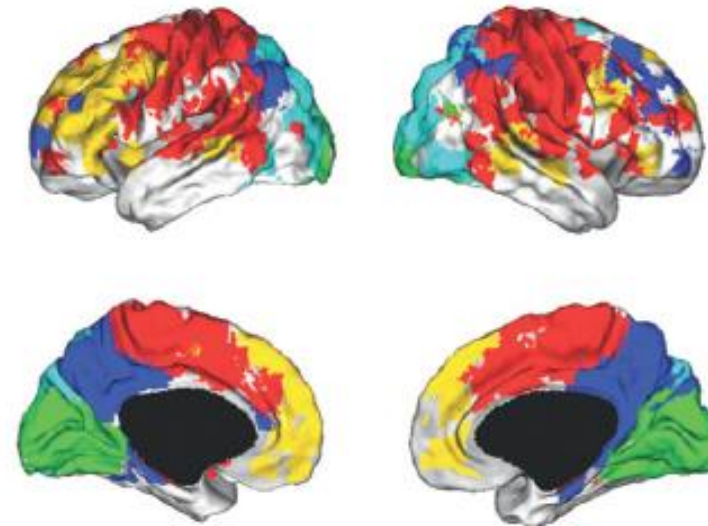
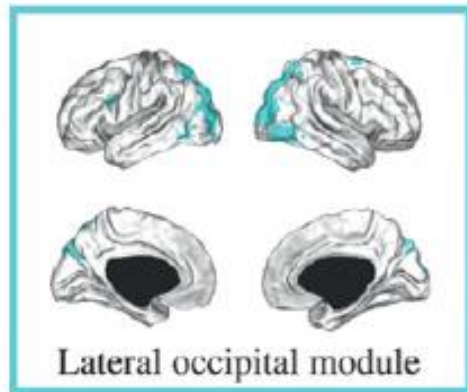
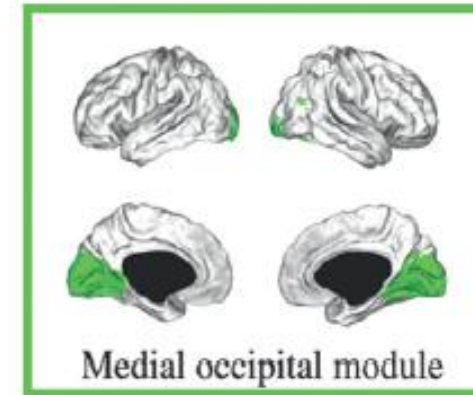
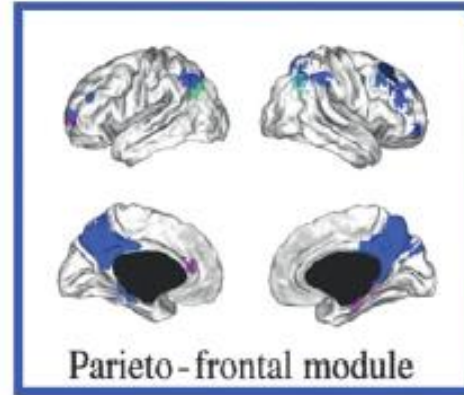
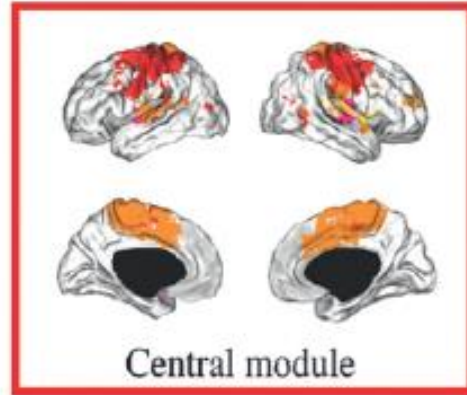
$$P_n = \{(i_0, i_1), (i_1, i_2), (i_2, i_3), \dots, (i_{n-1}, i_n)\}$$

The length of this path is  $n$ . The path shown in orange in (a) follows the route  $1 \rightarrow 2 \rightarrow 5 \rightarrow 7 \rightarrow 4 \rightarrow 6$ , hence its length is  $n = 5$ .



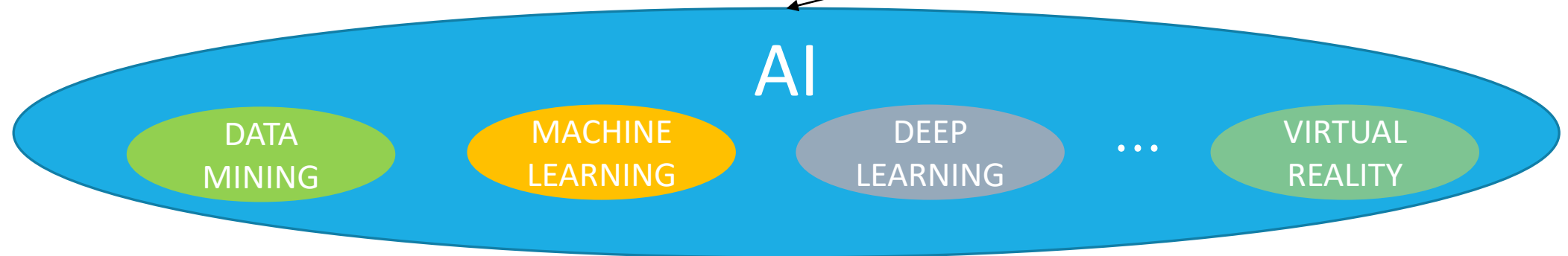
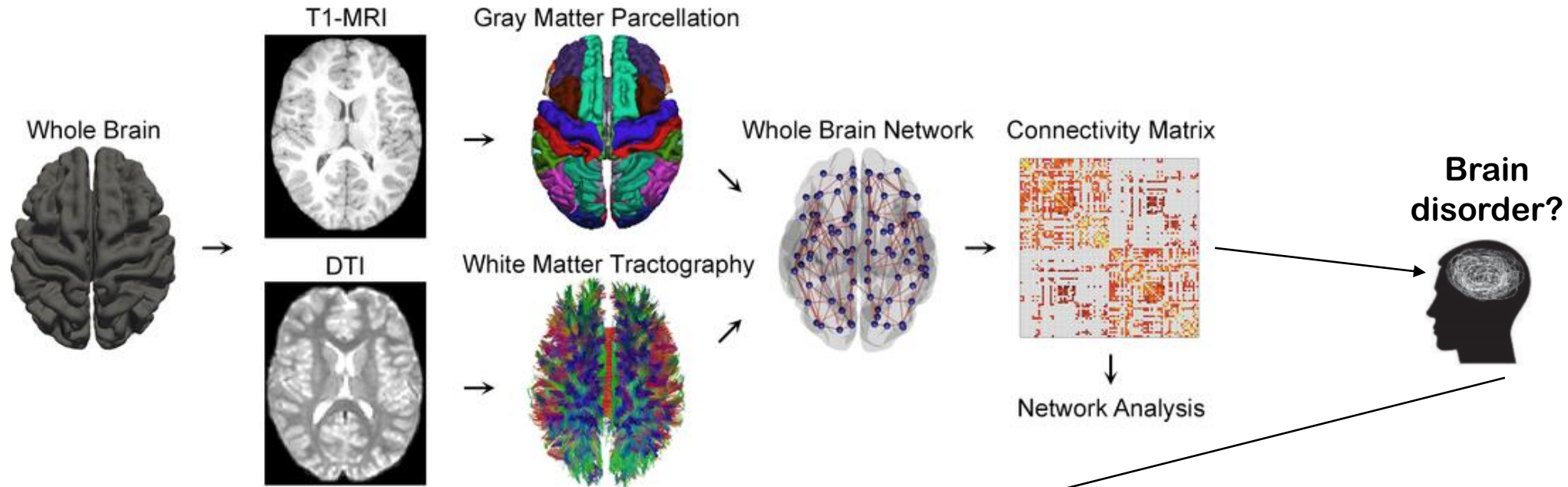
The **shortest paths** between nodes 1 and 7, or the distance  $d_{17}$ , correspond to the path with the fewest number of links that connect nodes 1 to 7. The shortest path is often called the **distance** between nodes  $i$  and  $j$ , and is denoted by  $d_{ij}$ , or simply  $d$ . We can have multiple shortest paths of the same length  $d$  between a pair of nodes.

# Graph metrics: modularity



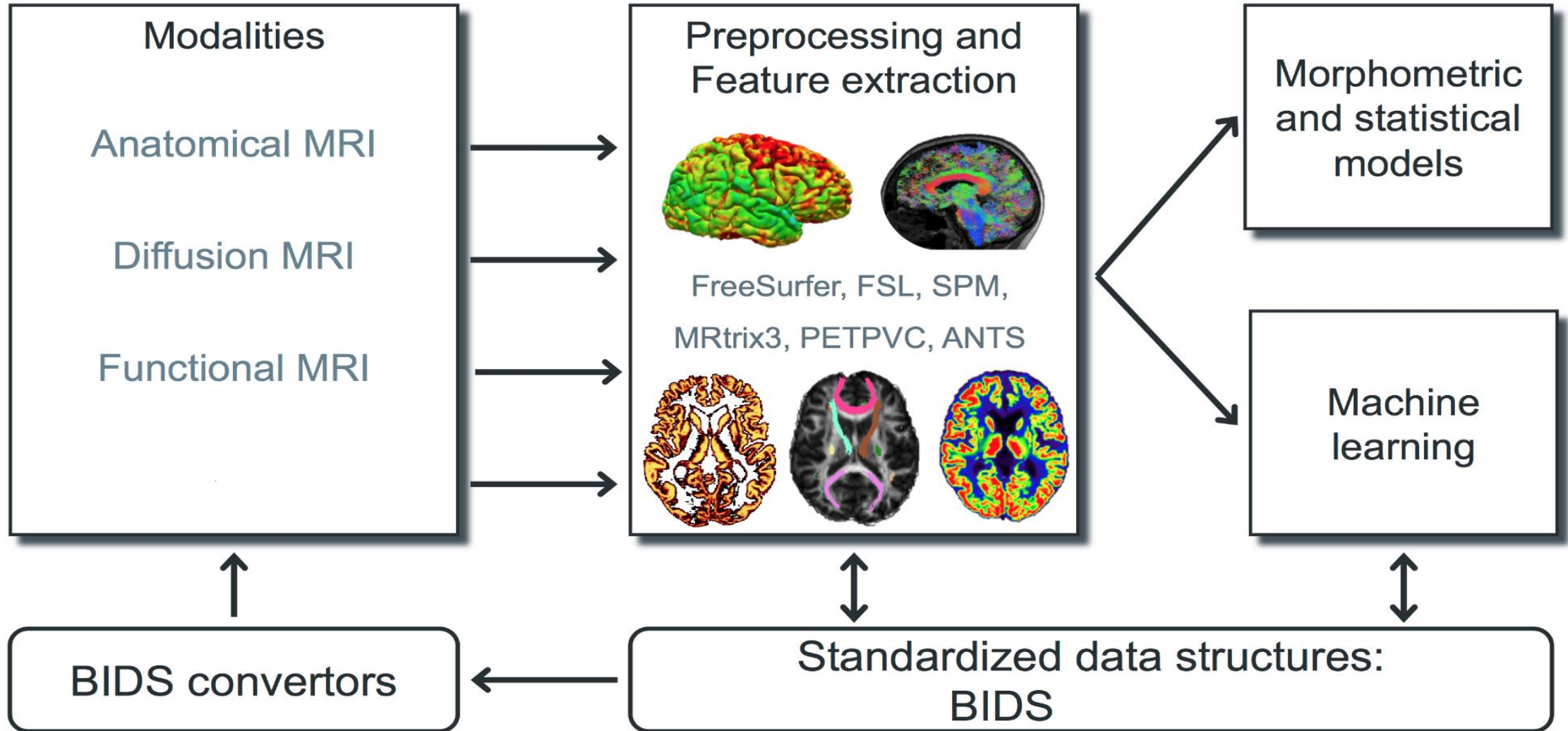


# Artificial Intelligence meets Complexity



Extract information, patterns and relationships that can be used to make decisions, they have different approaches and functionalities.

# Multidimensional neuroimaging processing in ReCaS



# Case study 1 – DTI connectivity and AD

## COGNITION

Several tests provide information about the neuropsychological conditions of patients and *measure the severity of the most important symptoms of AD*:

- Alzheimer's Disease Assessment Scale cognitive total score (ADAS);
- Mini Mental State Exam score (MMSE);
- Rey Auditory Verbal Learning Test (RAVLT) which measures cognitive impairment, attention, language and visuo-spatial functions and memory deficits.

## IMAGING

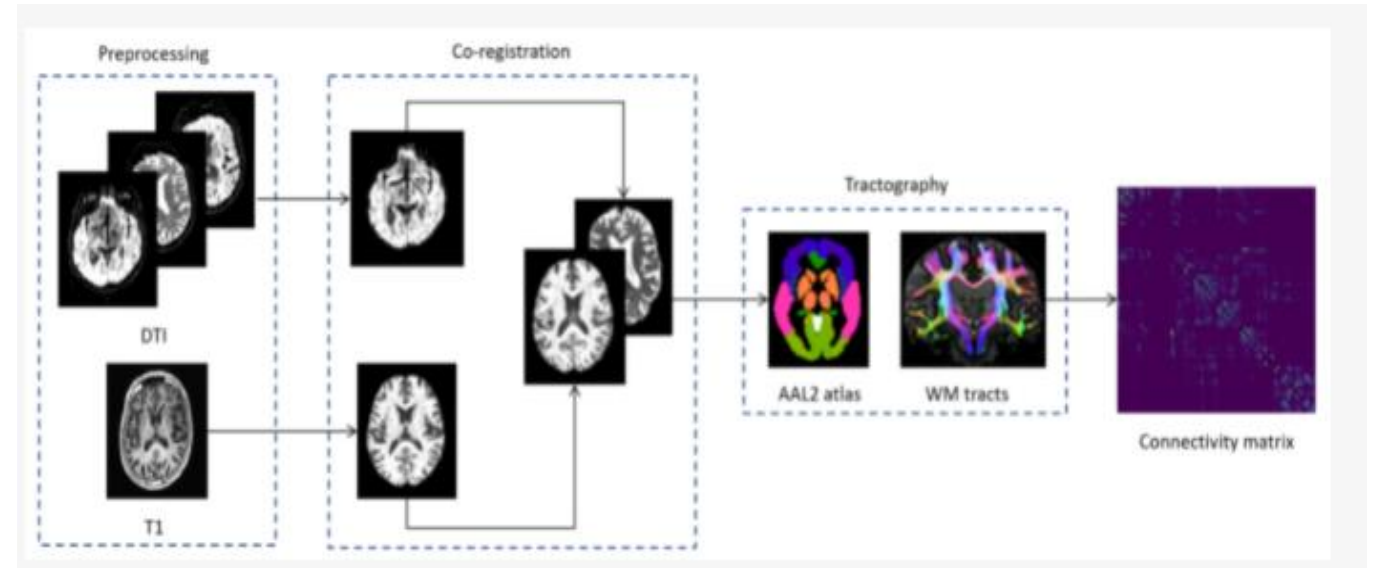
- The AD decline is associated to *disrupted connectivity among brain regions caused by degeneration of white matter (WM)*.
- *Diffusion weighted imaging (DWI)* has become the most popular technique *to investigate the physical connection among WM fibers*, i.e, the structural connectivity.
- DWI and tractography algorithms are combined to define diffusion **tensor imaging (DTI) structural networks that could be analyzed through complex network models**.
- Connectivity patterns could be investigated by using several topological network metrics describing the roles of the regions, the structure of paths connecting them and their importance for the network integrity.

# Case study 1 – DTI connectivity and AD

## COGNITION

	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

## IMAGING

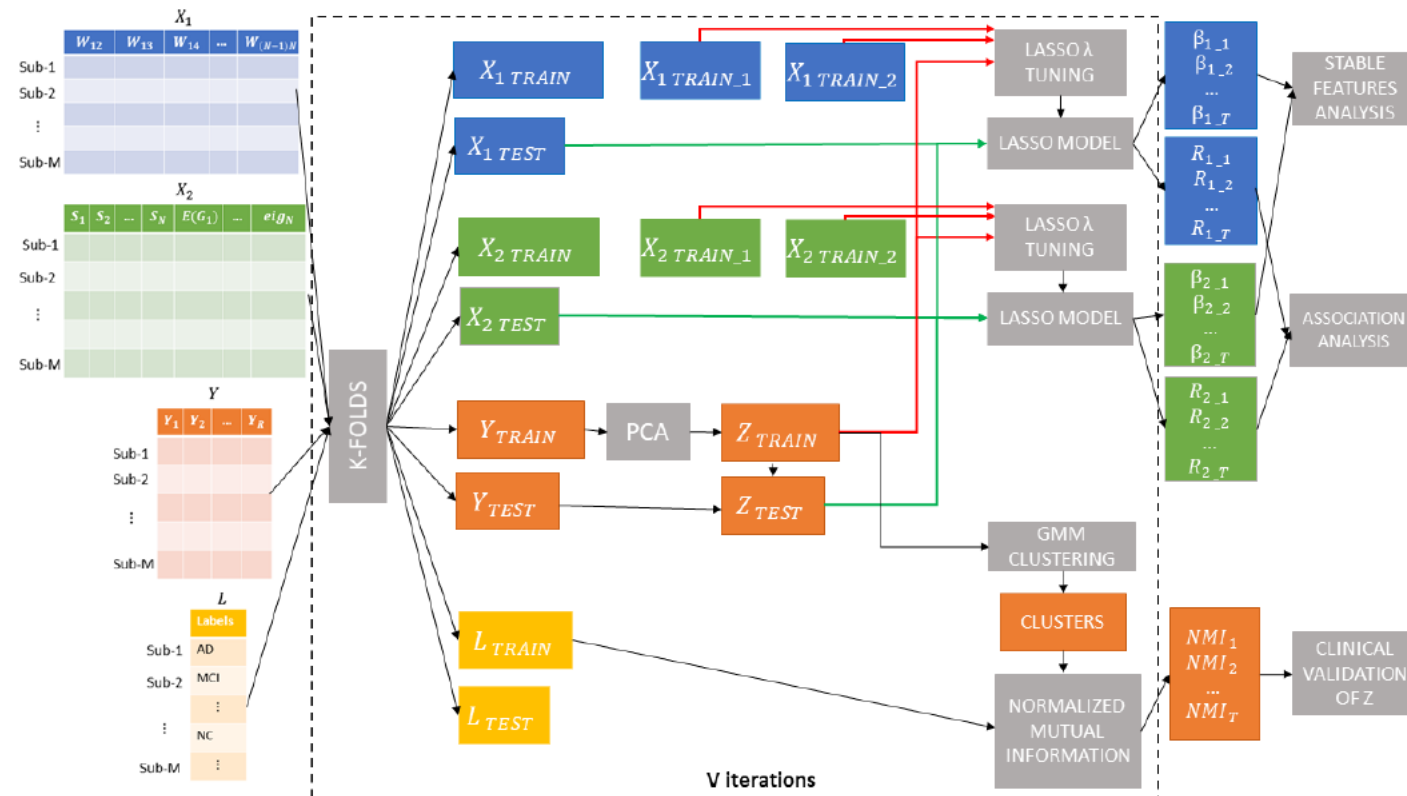


A. Lombardi, et al. "Association between Structural Connectivity and Generalized Cognitive Spectrum in Alzheimer's Disease." *Brain Sciences* 10.11 (2020): 879.

# Case study 1 – DTI connectivity and AD

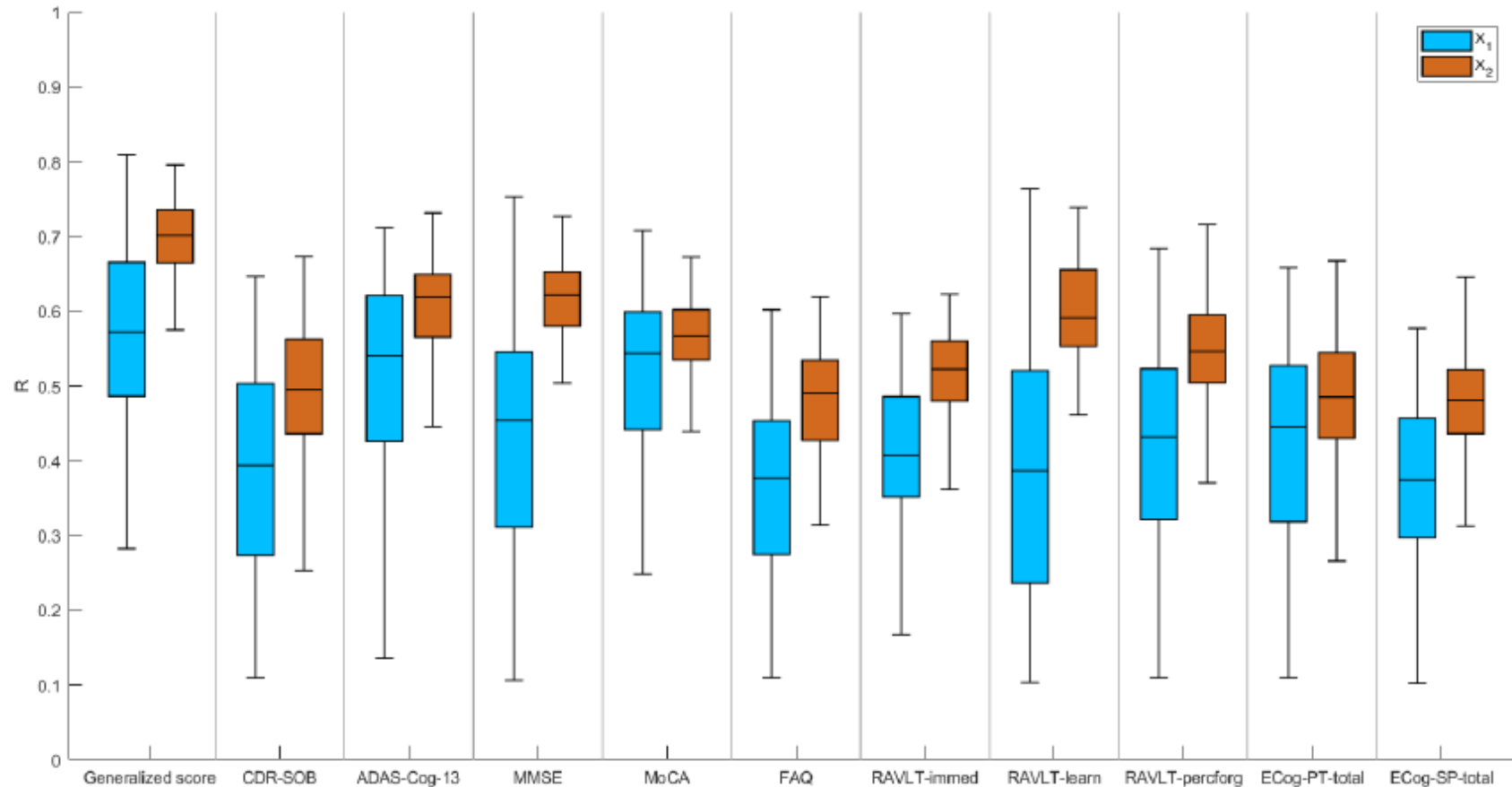
## ML FRAMEWORK

1. identify a generalized index that effectively summarizes the cognitive spectrum of the population under investigation;
2. find significant associations between the identified index and the features derived from the structural connectivity of the subjects;
3. identify the most important features in order to understand the strongest biological associations between the structural connectivity and cognitive spectrum.



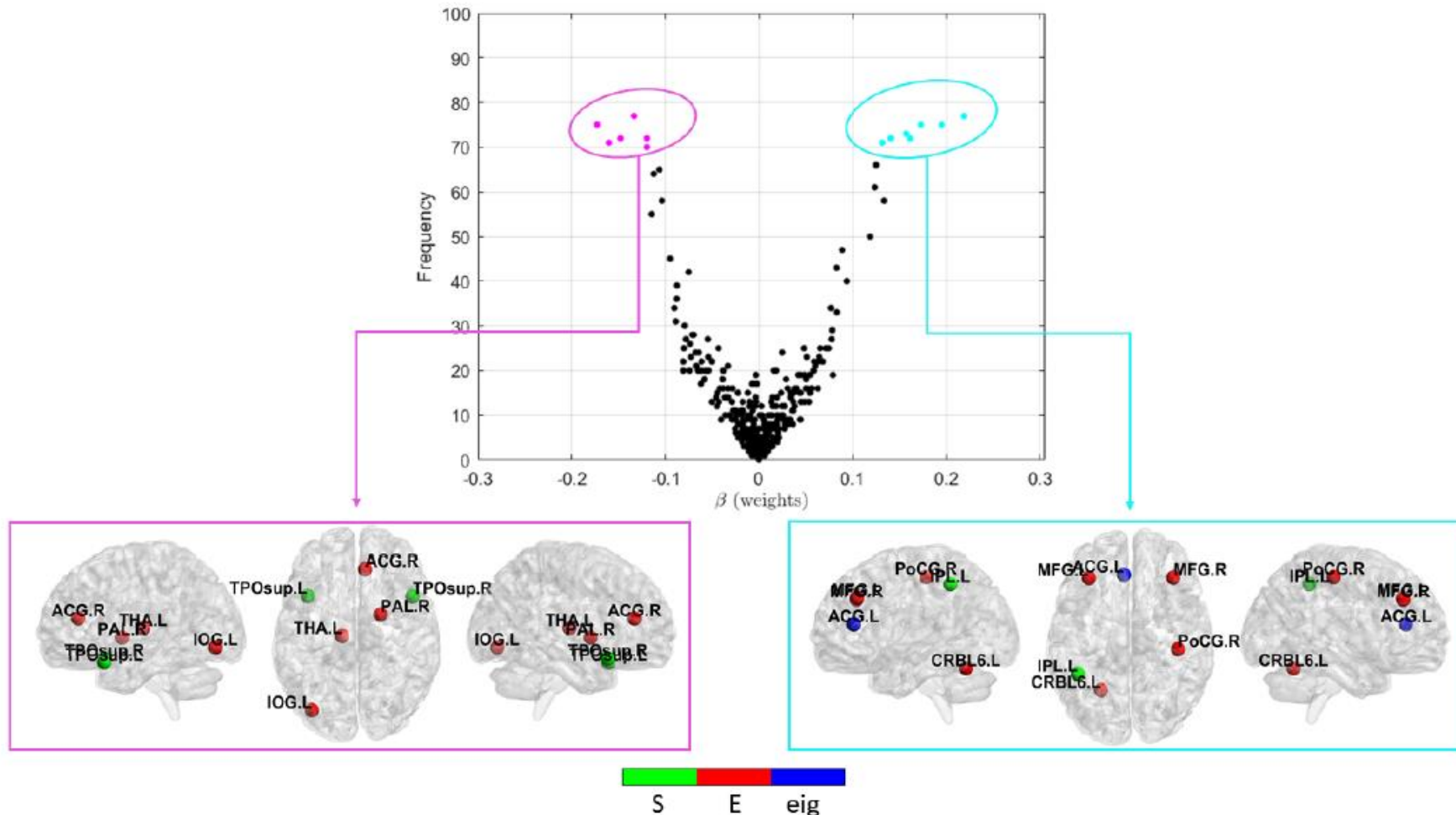
# Case study 1 – DTI connectivity and AD

Correlation between the actual values and the values predicted by Lasso algorithm of the generalized cognitive score and each of the ten clinical indexes by using both connectivity weights (matrix X1) and local graph metrics (matrix X2) as features.



# Case study 1 – DTI connectivity and AD

The relative frequency of the selected features and their average weights were evaluated across the validation rounds to rank the importance of each feature for the most performing matrix X2.



# Case study 2 – Brain age prediction

The last few decades have seen significant advances in neuroimaging methodologies and machine learning (ML) techniques focused on identifying structural and functional features of the brain associated with the age.

- **Age prediction** is typically performed using a **multivariate set of features derived from one or multiple imaging modalities**. A dataset is then specified by including the characteristics of different subjects and their chronological ages.
- The dataset is employed to train one or more **supervised machine learning** algorithms which attempt to **predict a given subject's brain age by using the brain imaging features** while minimizing the difference from the true age and preventing overfitting.

To evaluate the regression performance, two different metrics were employed:

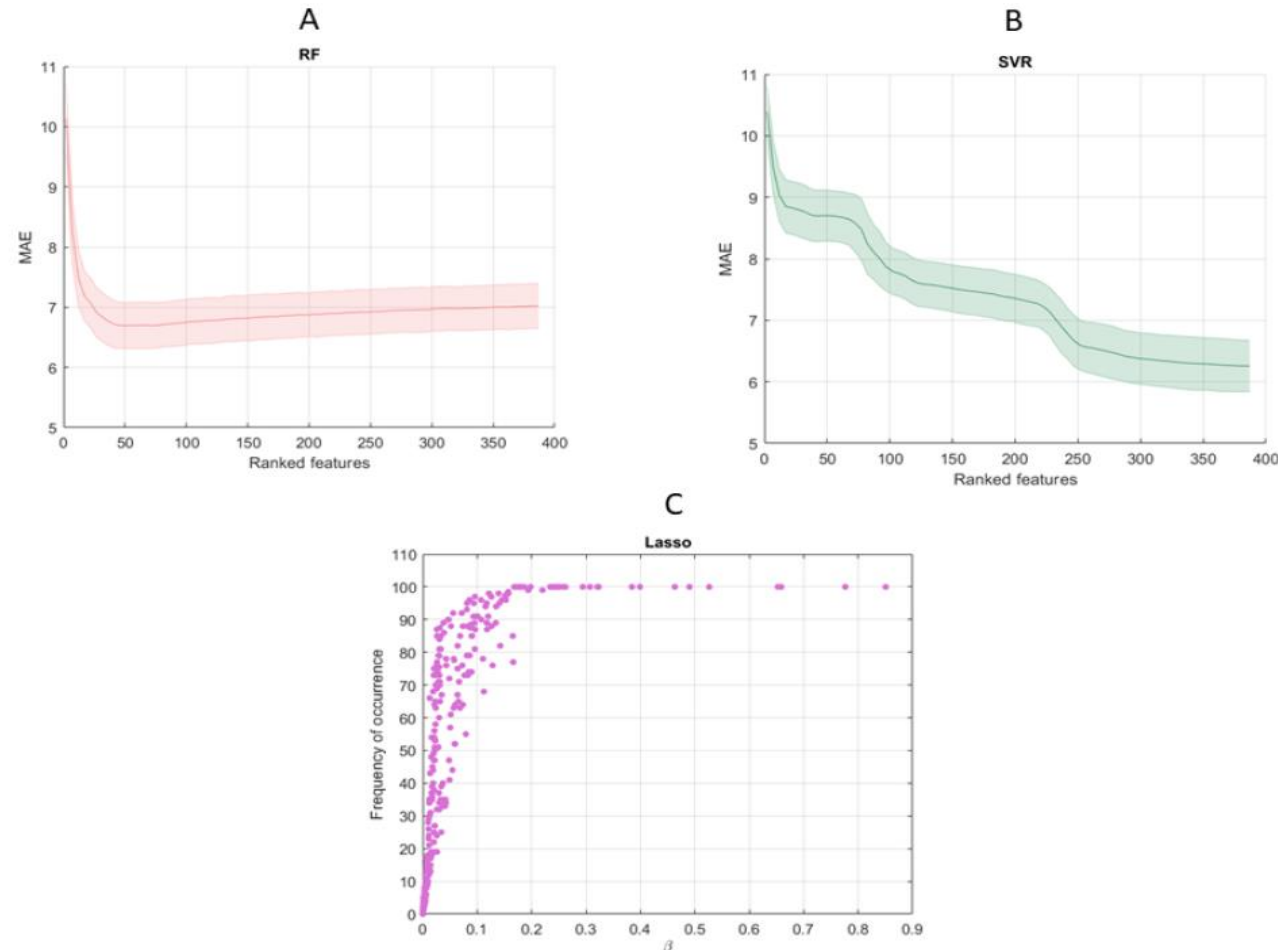
$$MAE = \frac{1}{N} \sum_{i=1}^N |y_i - \hat{y}_i|$$

$$R = \frac{\sum_{i=1}^N (y_i - \bar{y})(\hat{y}_i - \bar{\hat{y}})}{\sqrt{\sum_{i=1}^N (y_i - \bar{y})^2} \sqrt{\sum_{i=1}^N (\hat{y}_i - \bar{\hat{y}})^2}}$$



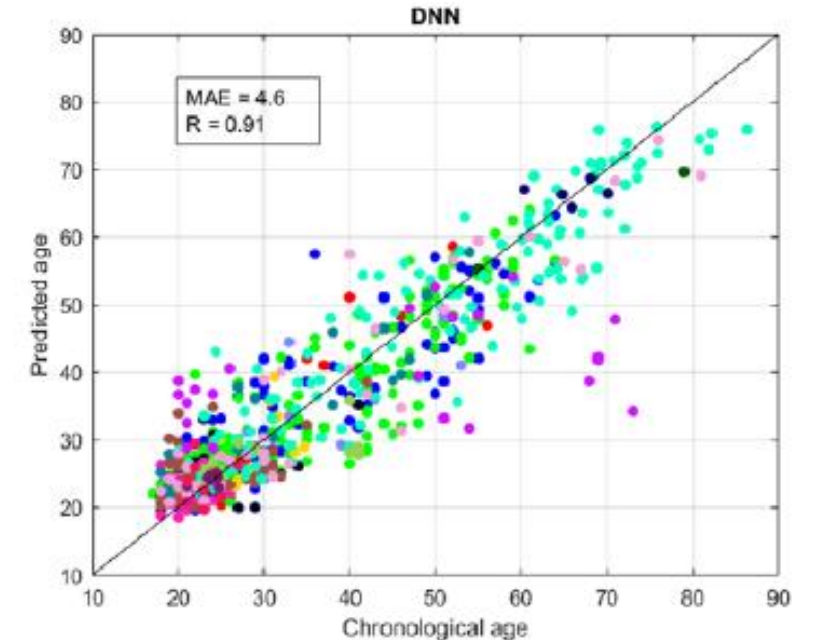
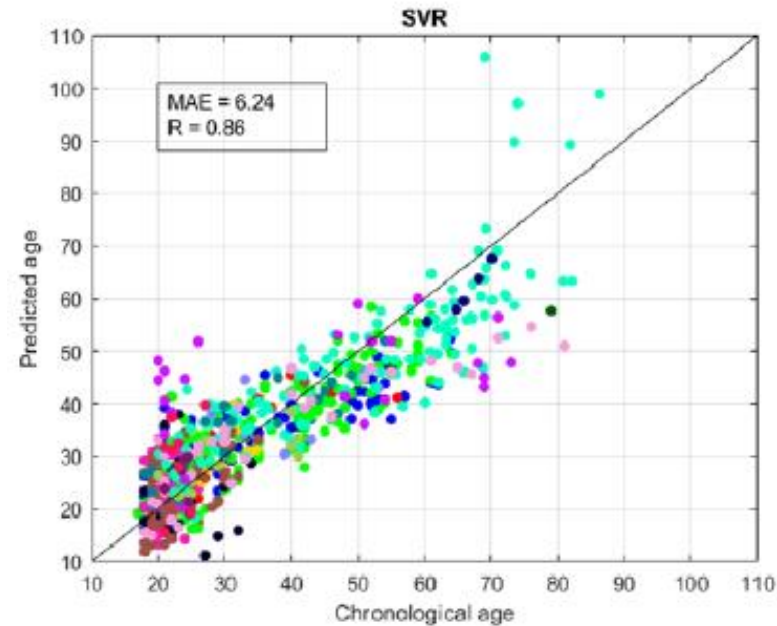
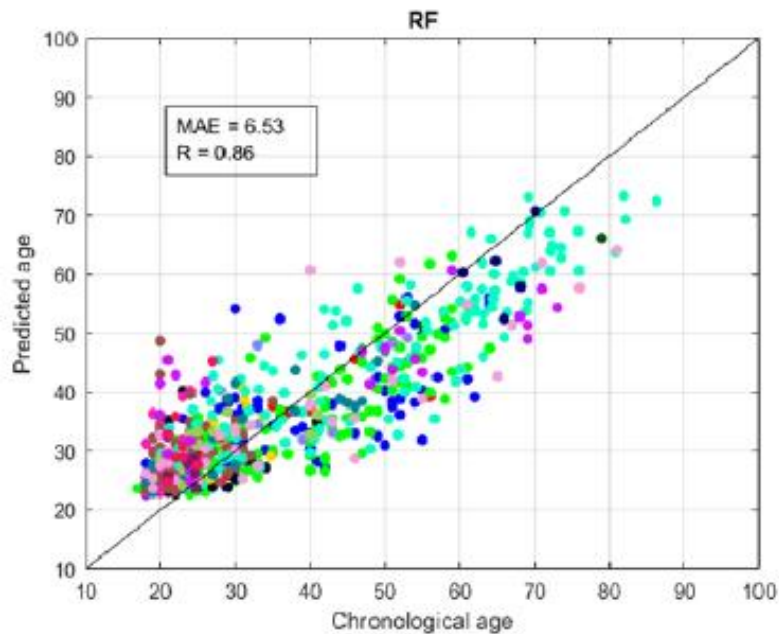
# Case study 2 – Brain age prediction

Four different regression models support vector regression (SVR), random forest (RF), Lasso and deep neural networks (DNN) were evaluated to predict brain ages of  $N$  subjects  $Y \in \mathbb{R}^N$  based on the matrix of predicting variables  $X \in \mathbb{R}^{N \times P}$ .



# Case study 2 – Brain age prediction

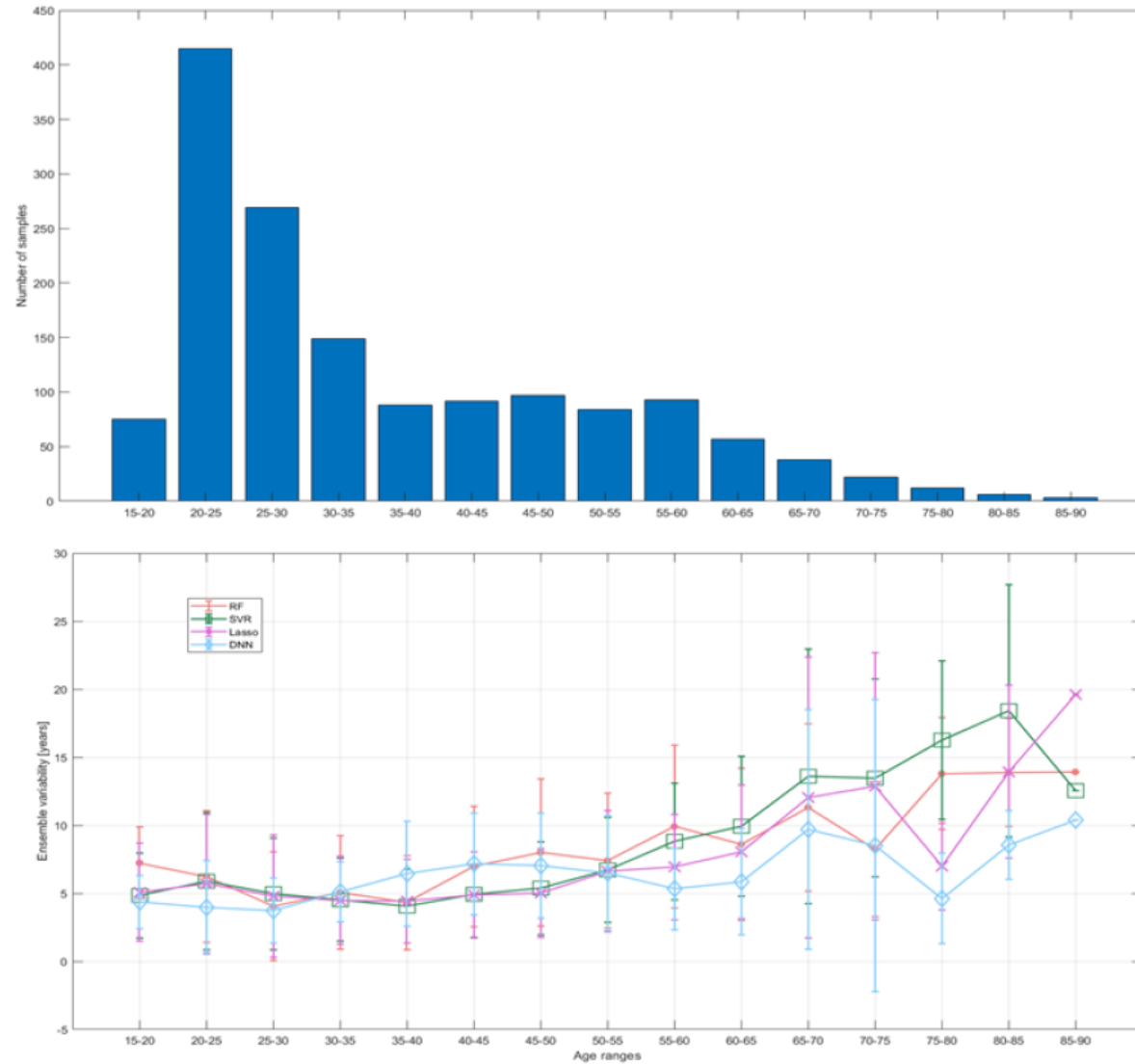
DNN models outperform the other regression algorithms



A. Lombardi, et al. "Brain Age Prediction With Morphological Features Using Deep Neural Networks: Results From Predictive Analytic Competition 2019." *Frontiers in Psychiatry* 11 (2020): 1613.

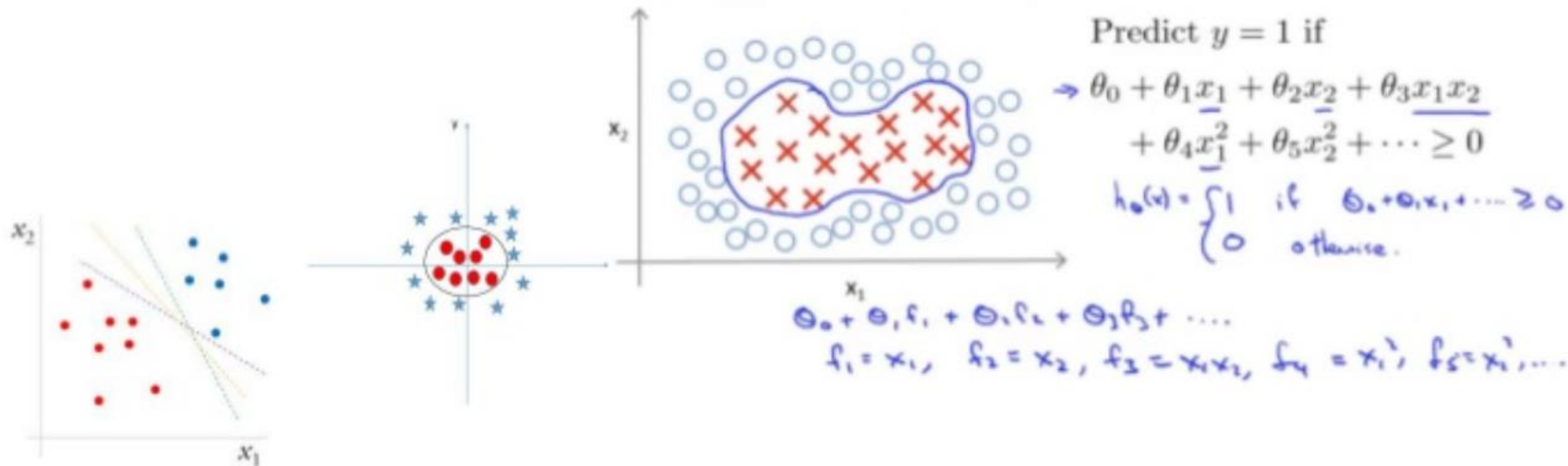
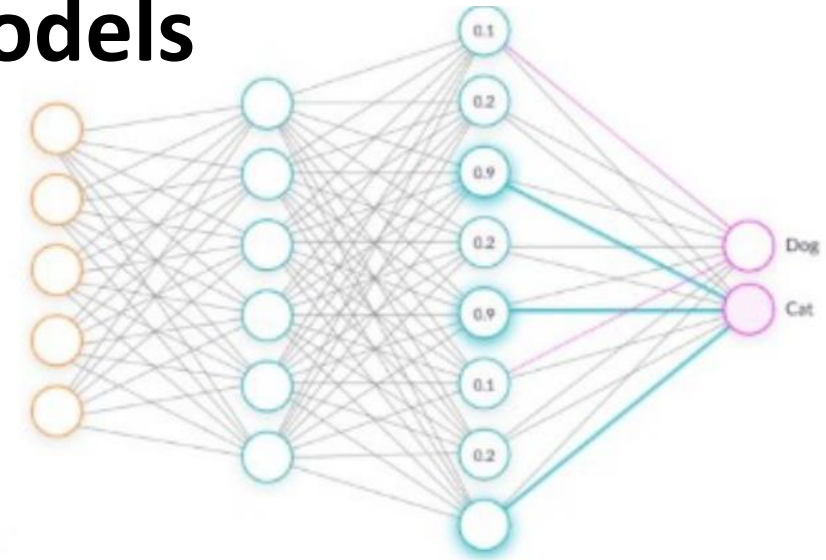
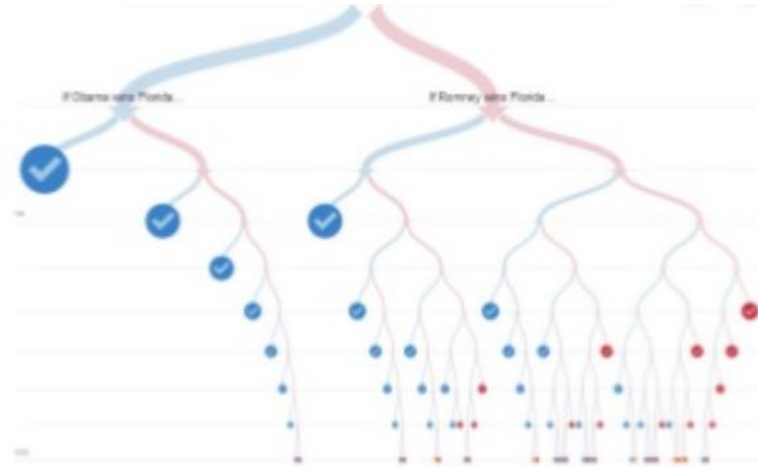
# Case study 2 – Brain age prediction

DNN models perform better even on age groups with fewer samples.



# Accuracy VS Interpretability of the ML models

ML creates functions to combine features in sophisticated ways.



It is difficult to disaggregate the final predictions to single feature contribution and untangle interaction among features!

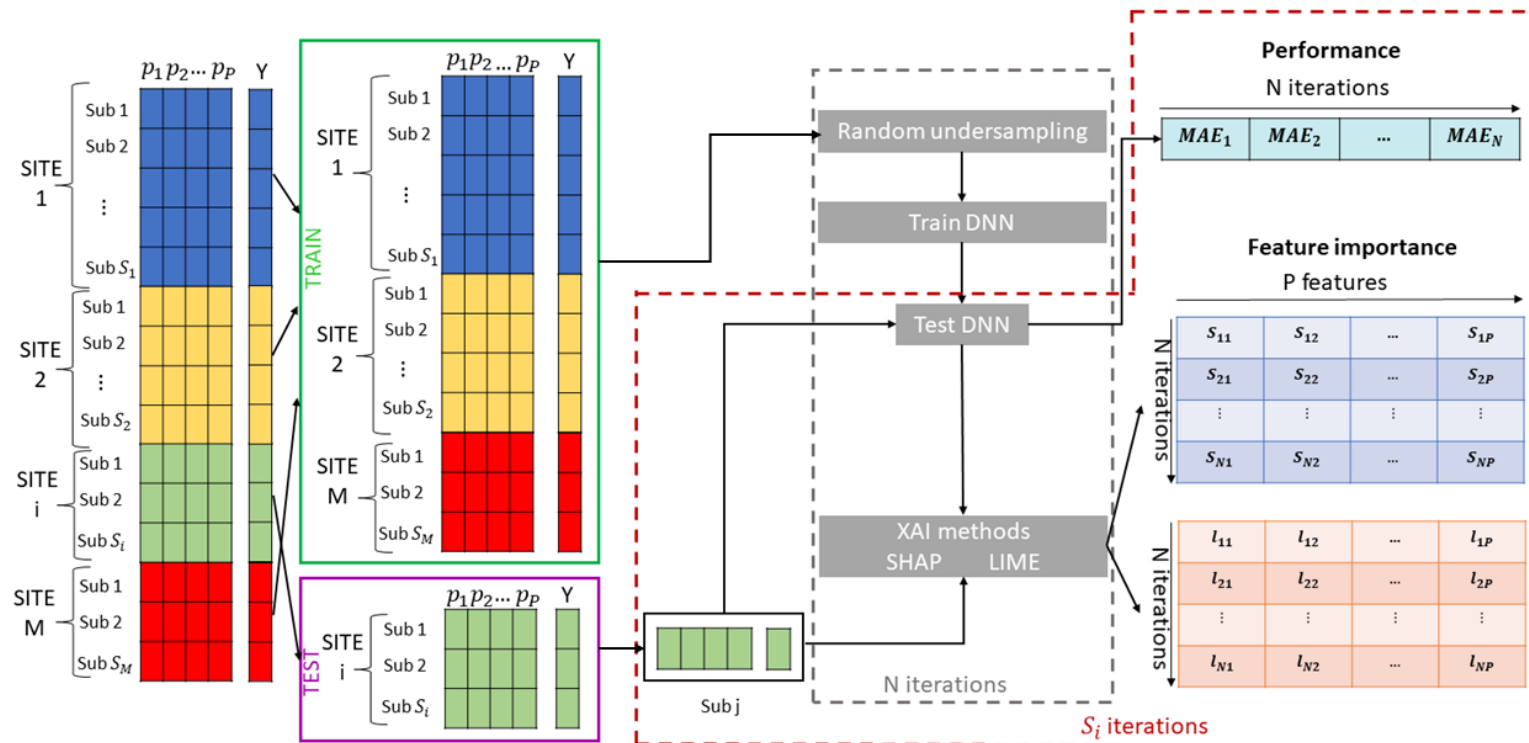
# Towards Explainability of DNN for age prediction

- Several works have shown that *DL models improve performance and reduce model bias compared to other less complex ML methods*, however, current **DL approaches** applied to neuroimaging **are black boxes** as they typically do not provide an in-depth understanding of the underlying mechanisms and how they contributed to the outcome.
- **Explainable Artificial Intelligence (XAI)** comprises many techniques that *combines ML algorithms with explanatory techniques to develop explainable solutions* that have been extensively applied in different domains.
- There has been little analysis of the **reliability and robustness of the explanation methods** in computational neuroscience, making their utility for critical applications unclear.

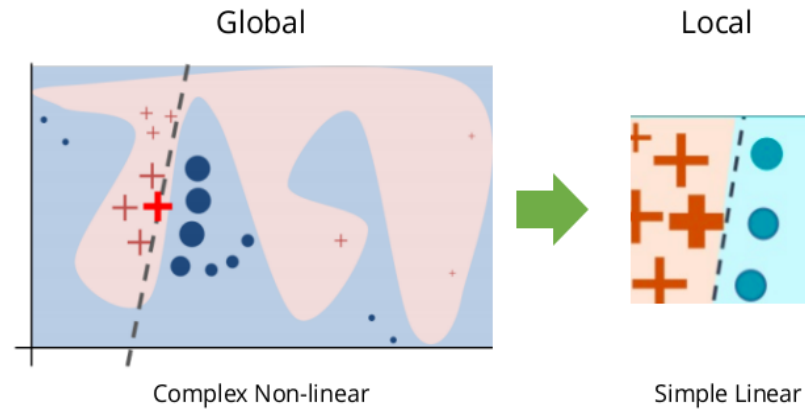
A. Lombardi, et al. "Explainable Deep Learning for Personalized Age Prediction With Brain Morphology." *Frontiers in neuroscience* 15 (2021).

# XAI for personalized brain age prediction

- Explainable DNN framework to predict the age of a healthy cohort of subjects from ABIDE I database by using morphological features extracted from their MRI scans.
- Two **local XAI methods** to explain the outcomes of the DNN models and **determine the contribution of each brain morphological descriptor to the final predicted age of each subject.**
- Complete architecture to **compare the two methods, determine their reliability and to extract information on the importance of the most age-related morphological descriptors** in order to encourage the use of DL models in clinical settings.



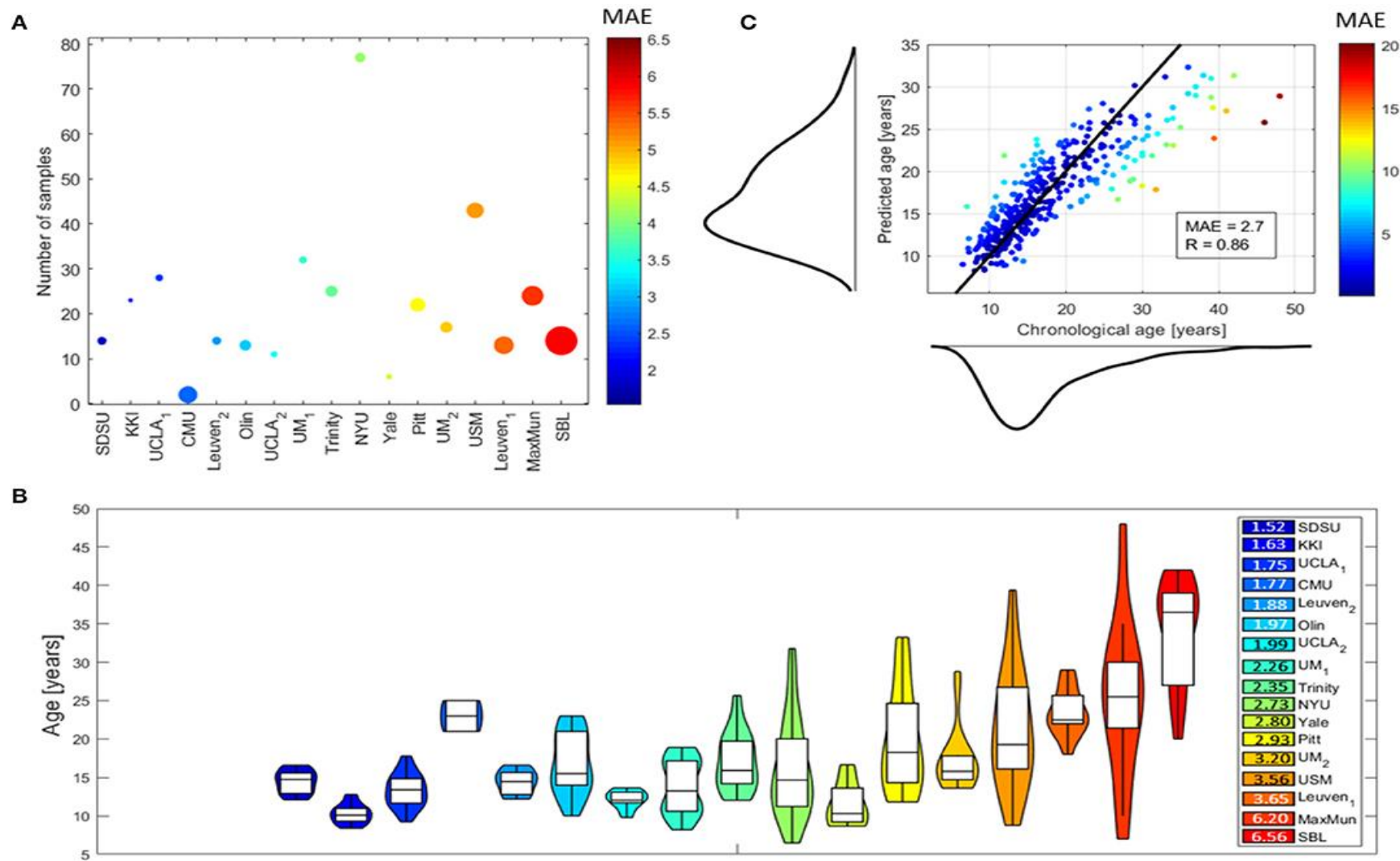
# How local XAI methods work?



SHAP and LIME are **local model-agnostic** as they explain predictions at individual level regardless the selected models. Basically, the two methods learn an interpretable linear model around each test instance and estimate feature importance at local level.

- *Dataset*  $D = [(x_1, y_1), (x_2, y_2), \dots, (x_T, y_T)]$ , where  $x_i$  is the feature vector for the sample  $i$  and  $y_i$  the corresponding age;
- the generic pre-trained model  $f$  returns a prediction  $f(x_i)$  based on a single input sample  $x_i$ ;
- SHAP and LIME aim at finding a linear model  $g$  to explain  $f$  by using a simplified inputs  $x'$  that map the original inputs through a mapping function  $x = h(x')$  trying to ensure  $g(z') \approx f(h(z'))$  whenever  $z' \approx x'$

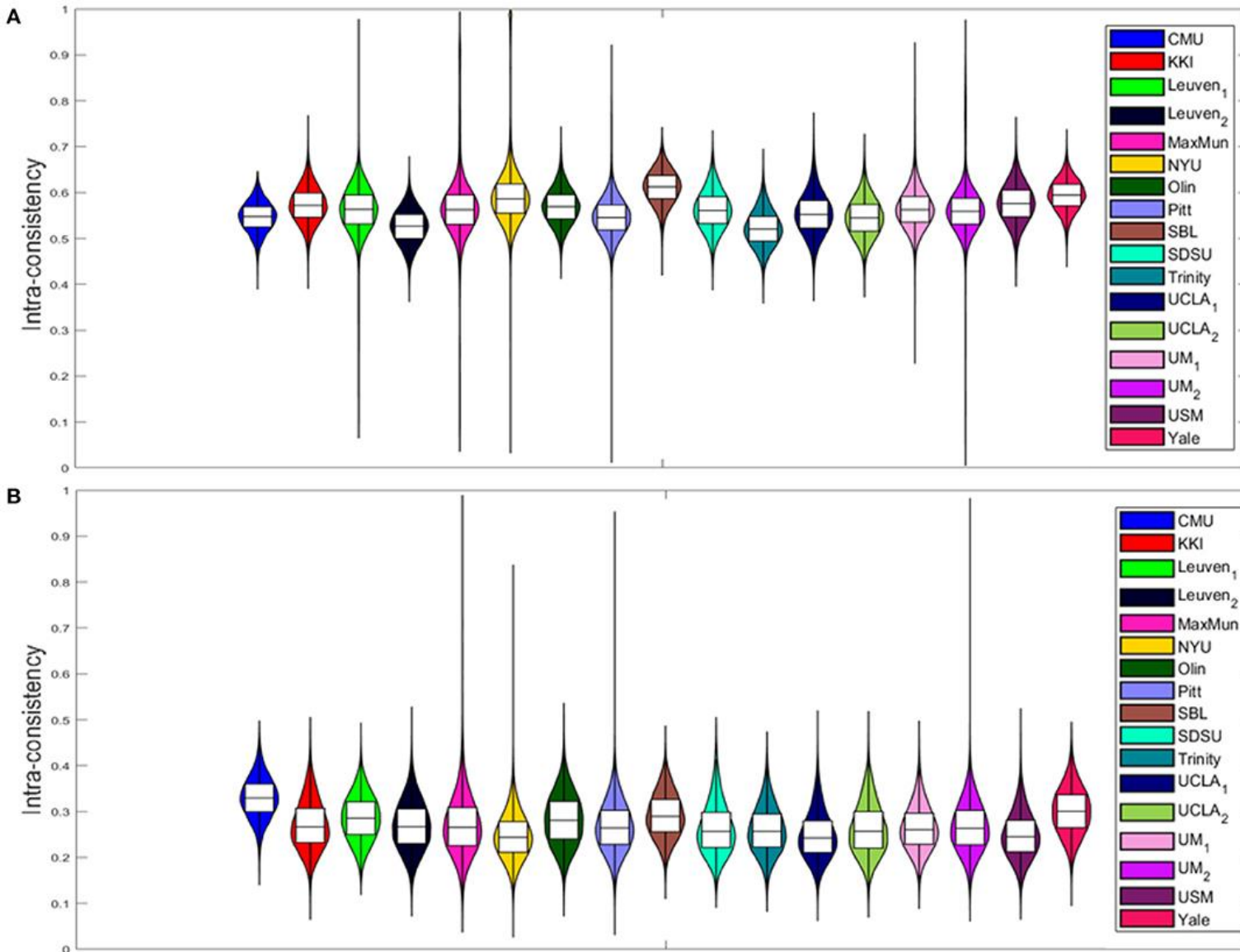
# Accuracy of the DNN models



MAE values are related to age range within each site: the higher the age range, the higher the average MAE within a site.



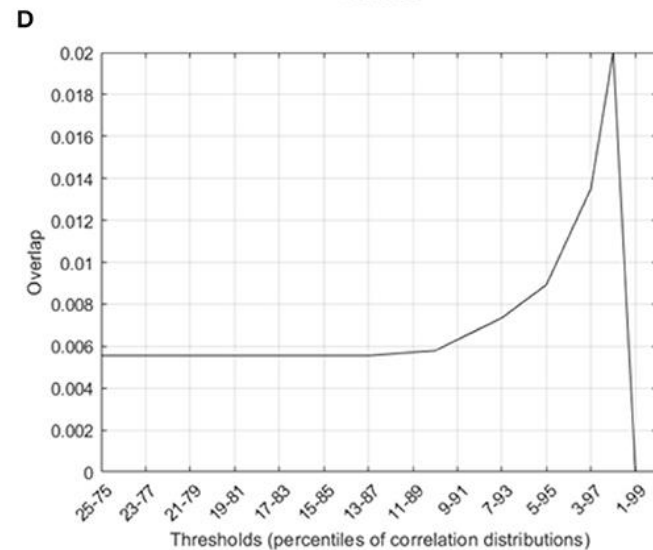
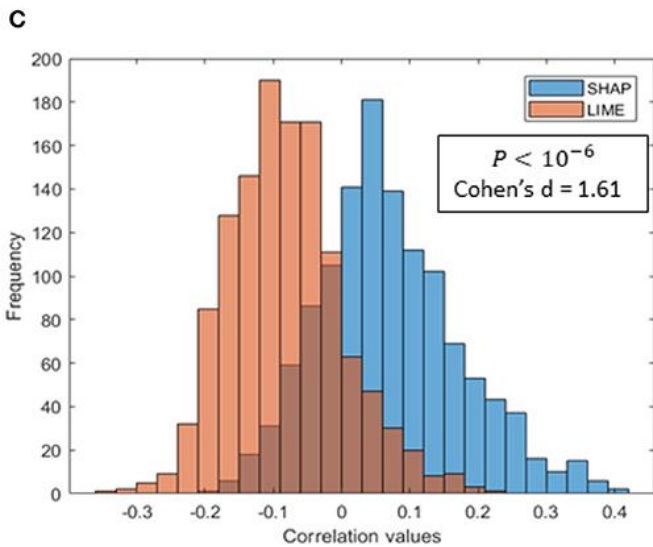
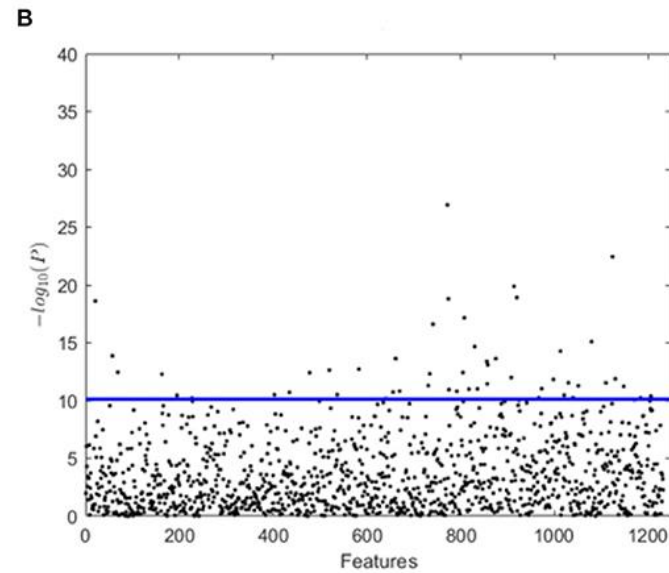
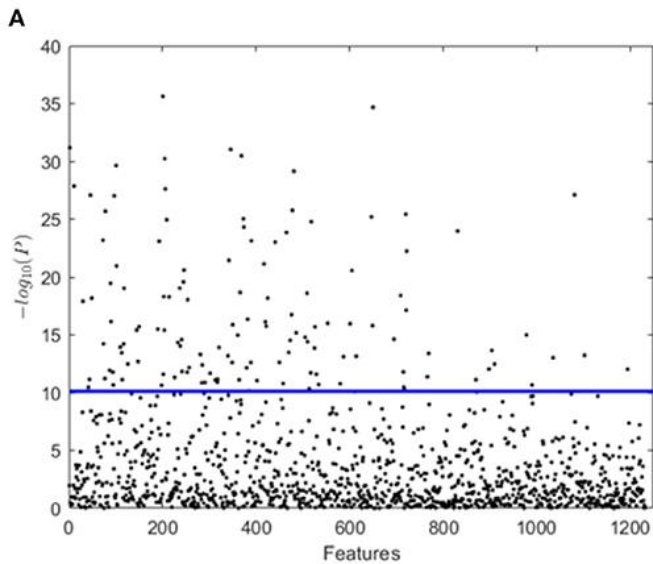
# Explainability: intra subject consistency



The intra-consistency coefficients of the XAI scores provide indices of consistency of the feature importance as the training set varies from round to round.

The LIME scores show consistently lower intra-consistency values (lower than 0.4 for all the sites) than those exhibited by the SHAP scores (greater than 0.5 for all the sites).

# Explainability of brain age: the XAI algorithm matters!



Results about the correlation analysis between the XAI scores and the age of the subjects:

- The distribution of coefficient values between the SHAP scores of the morphological features and the age of the subjects is significantly higher than the distribution of coefficient values between the LIME scores and the age.

- A higher number of features statistically related to the age resulted from SHAP values than from the LIME values as presented in Figures A and B.

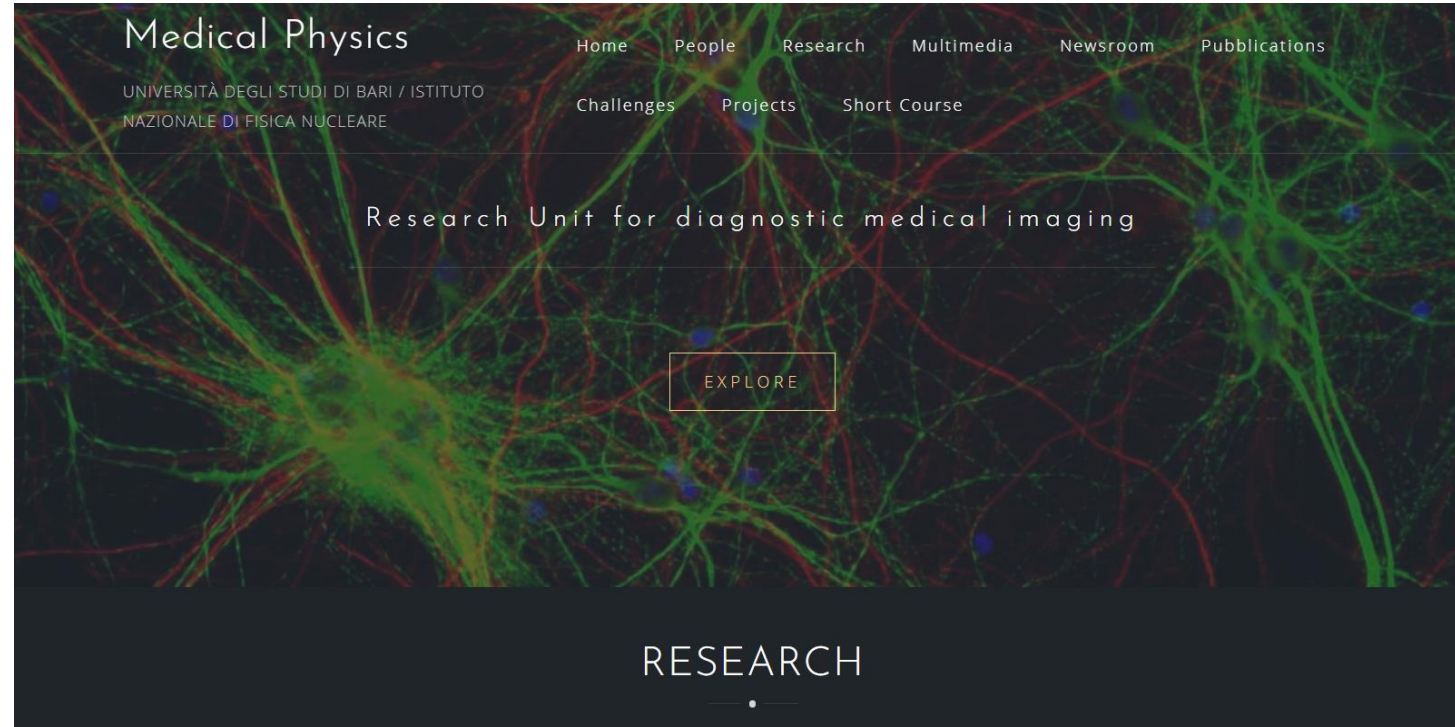
- The sets of age-related features for the two XAI methods exhibit a remarkably low overlap.

# Conclusions

- Biological complexity can be explored using a wide variety of topological indices that provide quantitative and detailed information at different scales.
- It is often difficult to identify quantitative indices to be used for a specific clinical problem. The different descriptions of a complex system are used as features for one or more ML/DL algorithms, which are then applied to optimize the accuracy of the classification/regression problem.
- **The accuracy of the algorithms is not enough:** identifying the set of descriptors of the physical system related to the classification and regression results is also very crucial in biological contexts.
- **Explainable Artificial Intelligence (XAI)** can provide clear and interpretable explanations about the links between features and outcomes.

# Thank you for your attention!

<http://medphys.ba.infn.it/>



Angela Lombardi

[angela.lombardi@ba.infn.it](mailto:angela.lombardi@ba.infn.it)

# Case study 1 – DTI connectivity and AD

## ASSOCIATION BETWEEN CONNECTIVITY AND GENERALIZED COGNITIVE SCORES

- Lasso (Least Absolute Shrinkage and Selection Operator) to find significant associations between the connectivity features and the proposed generalized cognitive score.
- Lasso is a regularization method that was introduced to solve both overfitting and multicollinearity problems in ordinary least square regression.
- This approach involves a penalty term that controls the complexity of the model by introducing sparsity. This term penalizes the coefficients of the least significant variables shrinking some of them to zero so only the most important features are retained.
- The outcome is a subset of the predictors that contribute mostly to the regression model, so the algorithm is also used as embedded feature selection method. The goal of this method is to minimize the residual sum of squares (RSS) to find the coefficients of the predictors:

$$RSS = \frac{1}{2} \|Z_{TRAIN} - \beta X_{TRAIN}\|_2^2 - \lambda \|\beta\|_1$$