Network physiology to study neurological diseases and chronic pain investigating different brain scales and data.

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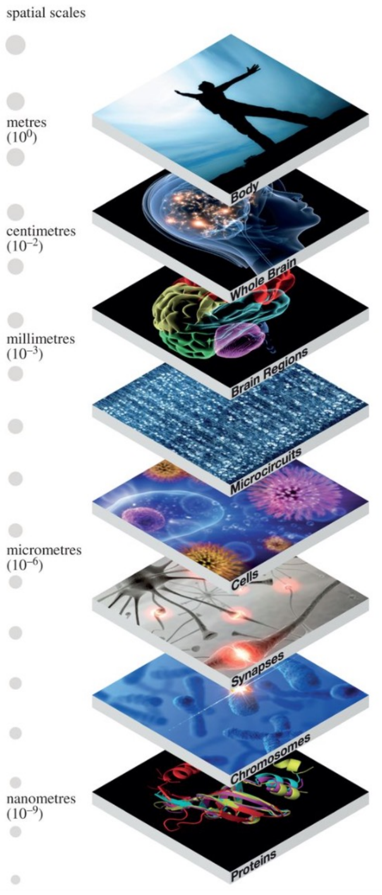
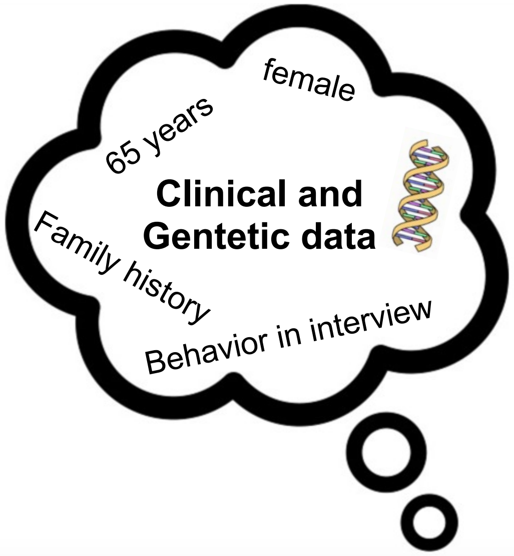
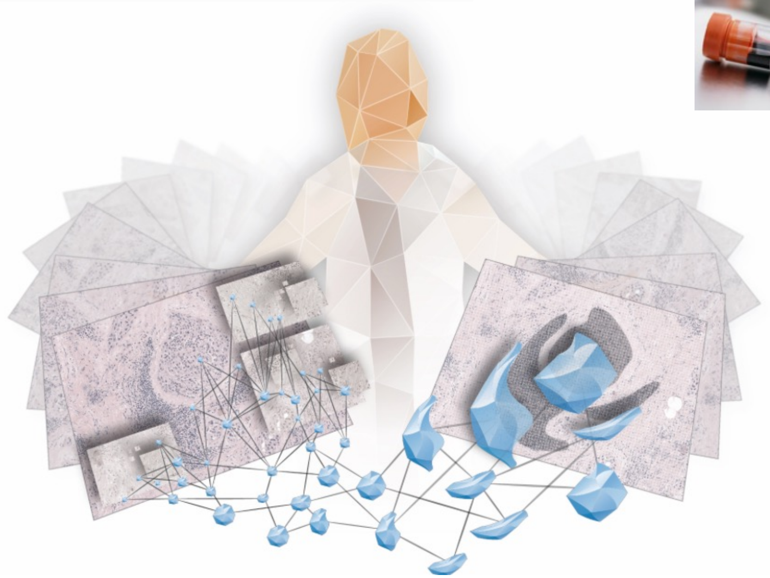
Complex Network in Neuroscience



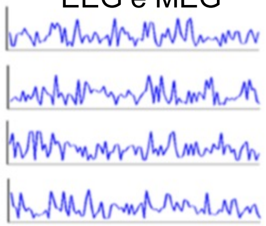
Multiple Scales



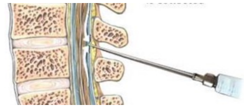


Multiple data types

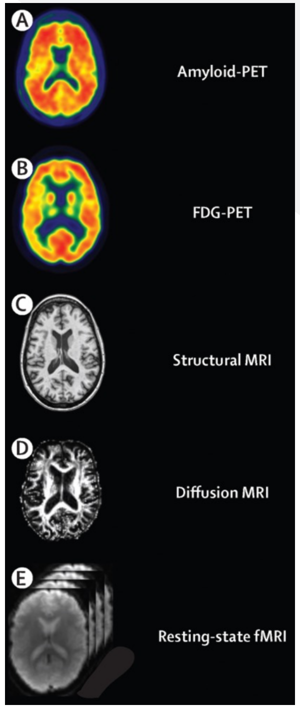
EEG e MEG



CSF



Blood test



Multiple databases

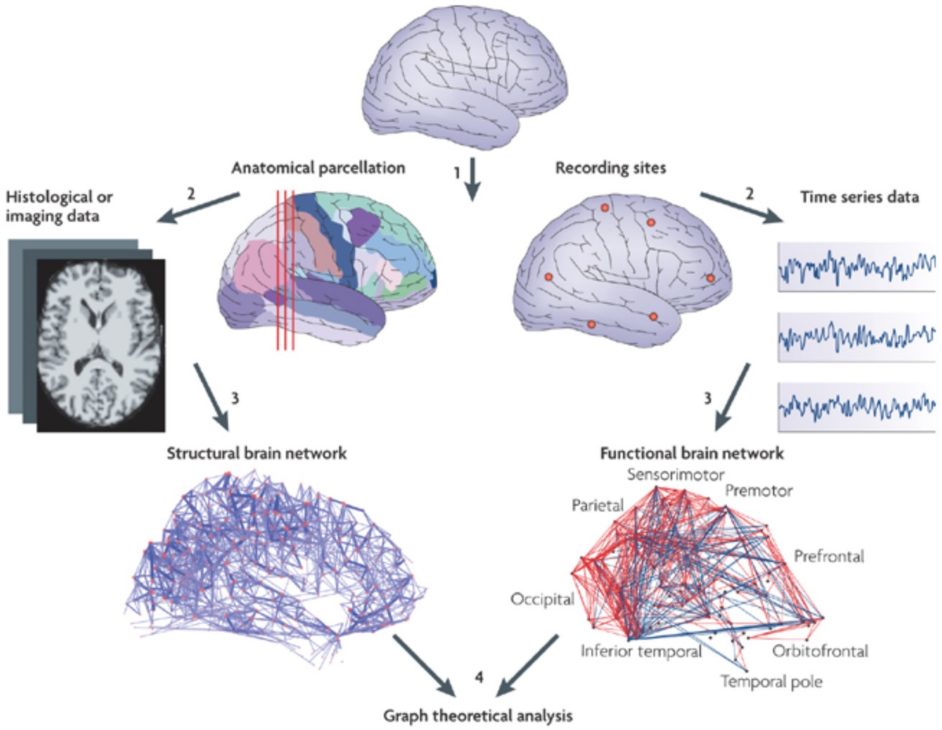
ADNI

PPMI

Necessity of quantitative methods to manage, process and analyze data of complex matter and great cardinality (Big Data).

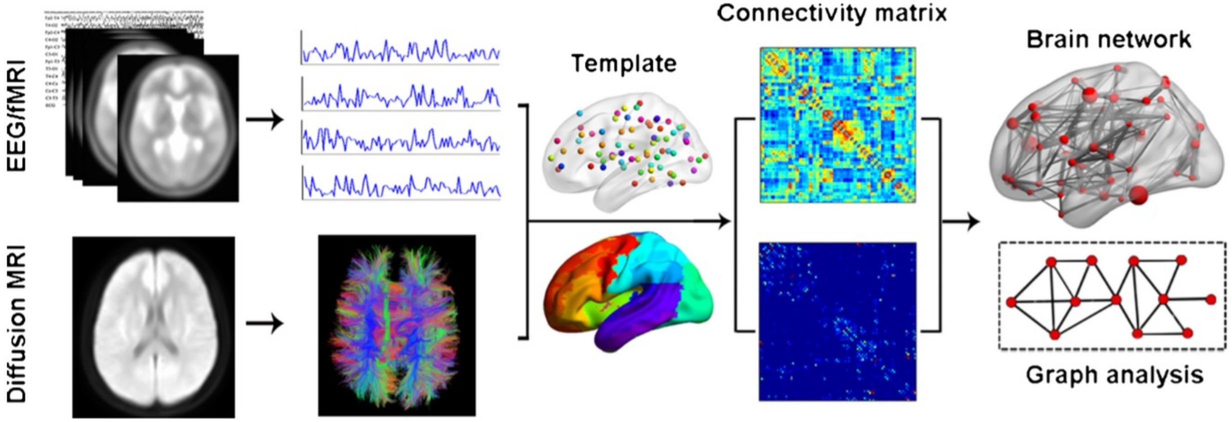
Complex Network in Neuroscience

A standard method to apply complex networks to neuro-data does not exist.

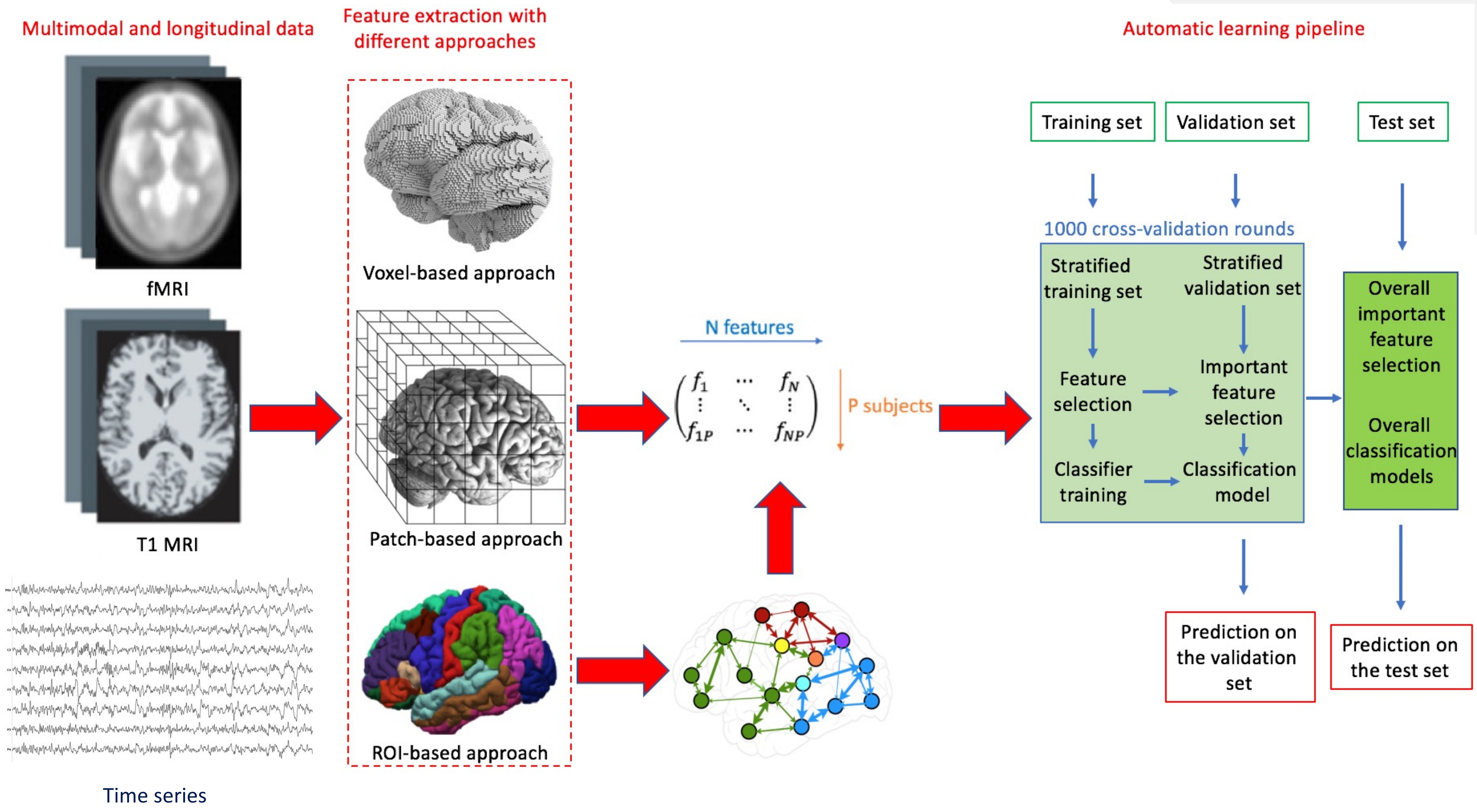


(Bullmore E. , Sporn O. , Nat. Rev. Neurosci.; 2009).

(Cao M. et al.; Mol. Neurobiol.; 2014).



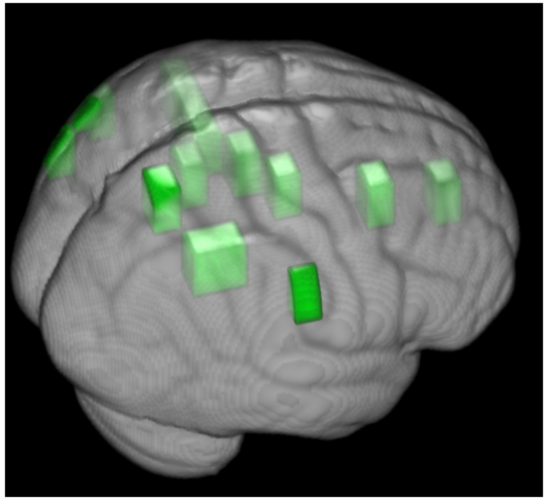
Complex Networks and machine learning



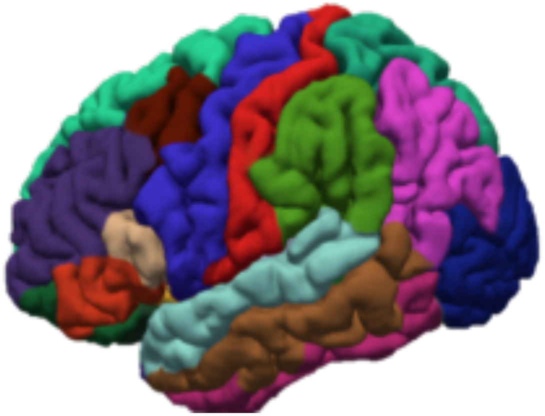
Complex Networks and machine learning

Anatomical Interpretation

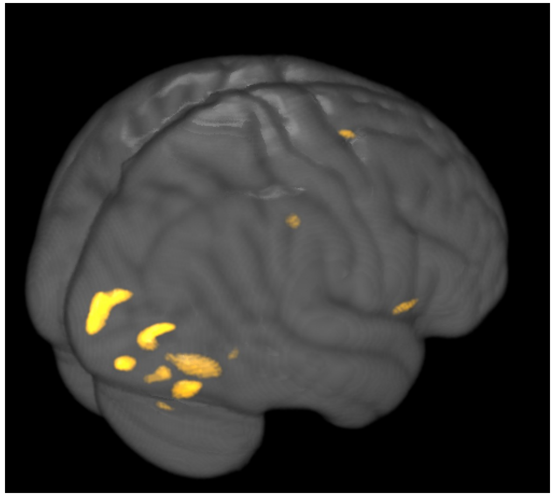
By identifying which brain areas correspond to the important features obtained from the machine leaning models, it is possible to have clinical interpretations



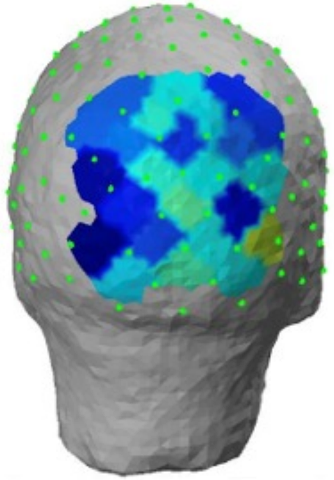
Patch level



ROI level



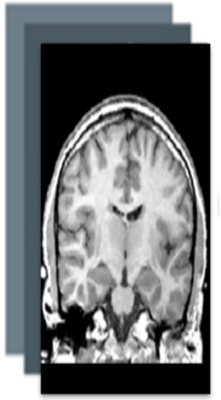
Voxel level



Sensor level

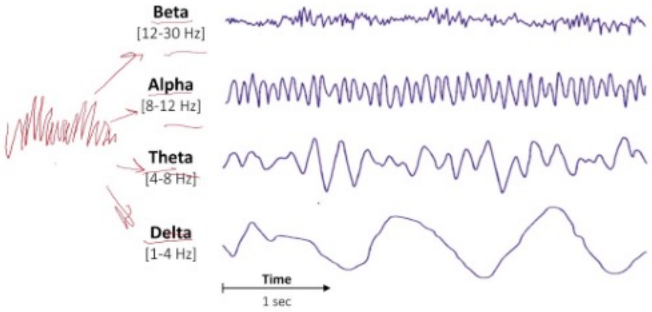
Multiplex Networks

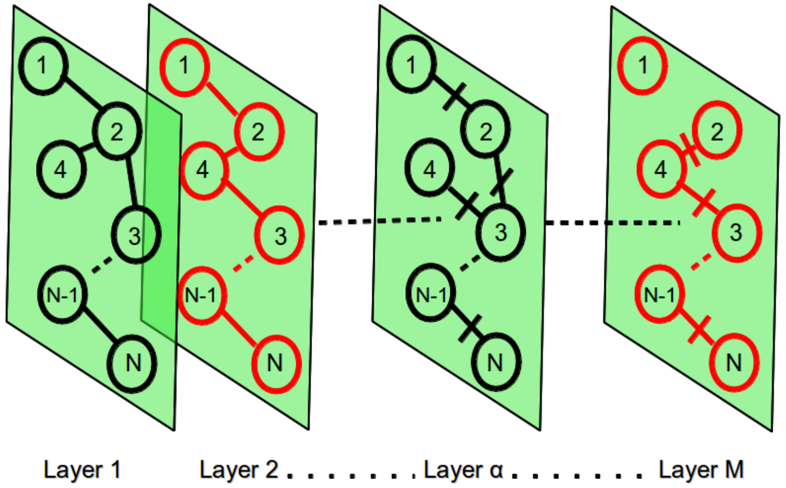
Multiple subjects



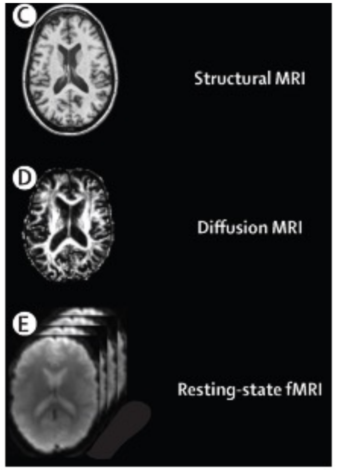
Existing approaches are not able to study the same nodes as interactions change.

Multiple frequency bands





Multiple modalities

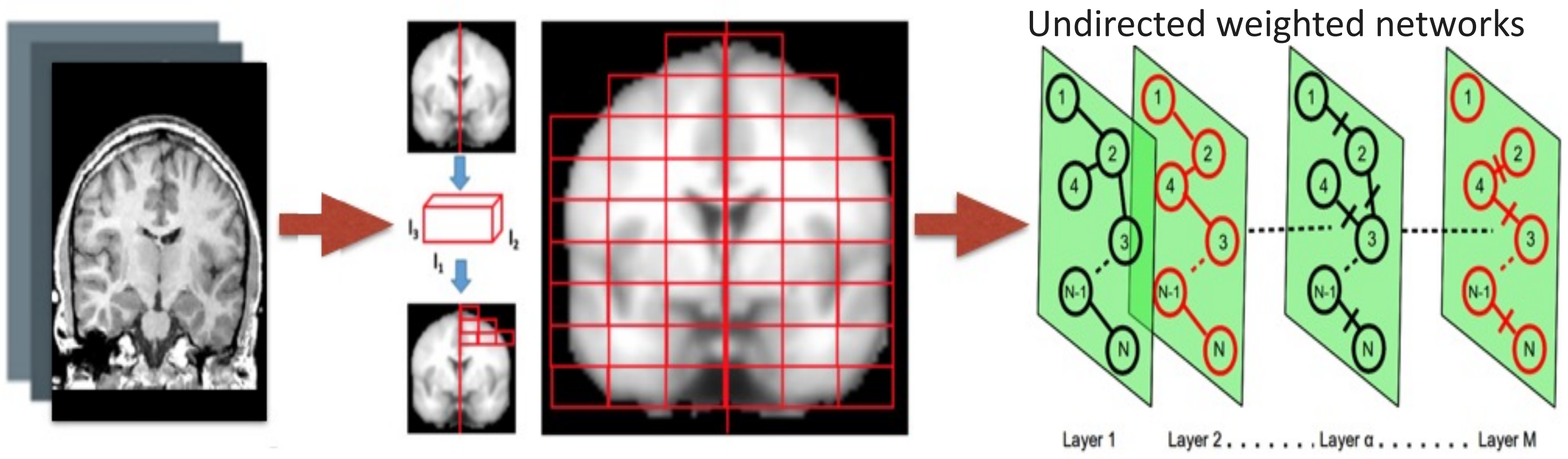


Multiplex Networks are an innovative investigation instrument able to provide context information among networks with fixed nodes and variable connections.

Alzheimer case study

Data: T1 MRI of normal controls, Alzheimer disease (AD) subjects, Mild cognitive impairment (MCI) subjects who will develop AD. These data come from Alzheimer's Disease Neuroimaging Initiative (ADNI).

Goal: early detection of the disease in order to test new treatments when they can be truly effective.



(N. Amoroso, M. La Rocca et al., Frontiers in Aging Neuroscience, 2018)

Nodes: Patches, Rectangular parallelepipeds which images can be regularly divided into

Connections: Pearson's correlation coefficient r_{ij} between pairs of nodes.

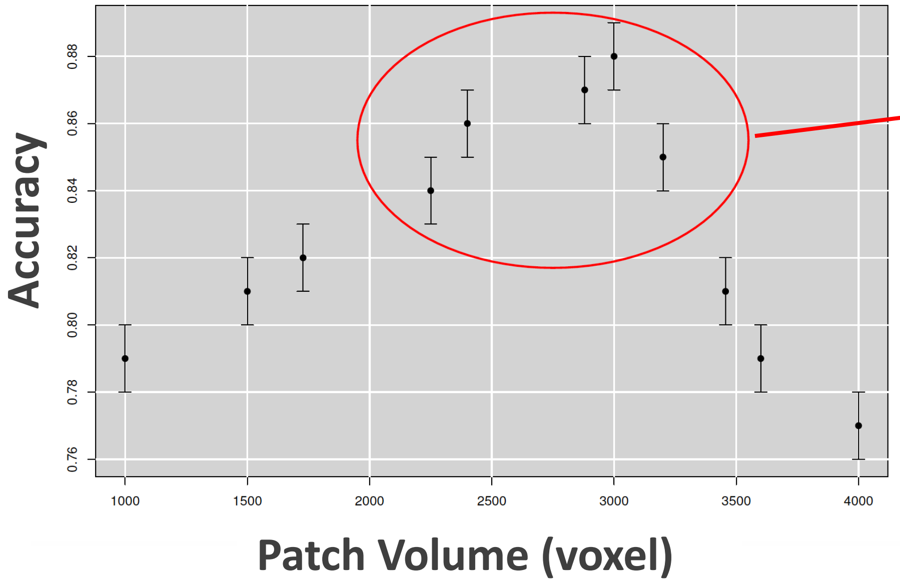
$$r_{i,j} = \frac{\sum_{k=1}^{D}(p_i^k - \bar{p}_i)(p_j^k - \bar{p}_j)}{\sqrt{\sum_{k=1}^{D}(p_i^k - \bar{p}_i)^2}\sqrt{\sum_{k=1}^{D}(p_j^k - \bar{p}_j)^2}}$$

p_i^k e p_j^k are voxel intensity at k position of the patches *i* and *j*.
D patch size.

Multi and single layer metrics concerning node importance and weight uniformity were extracted to train the machine learning system

Alzheimer case study

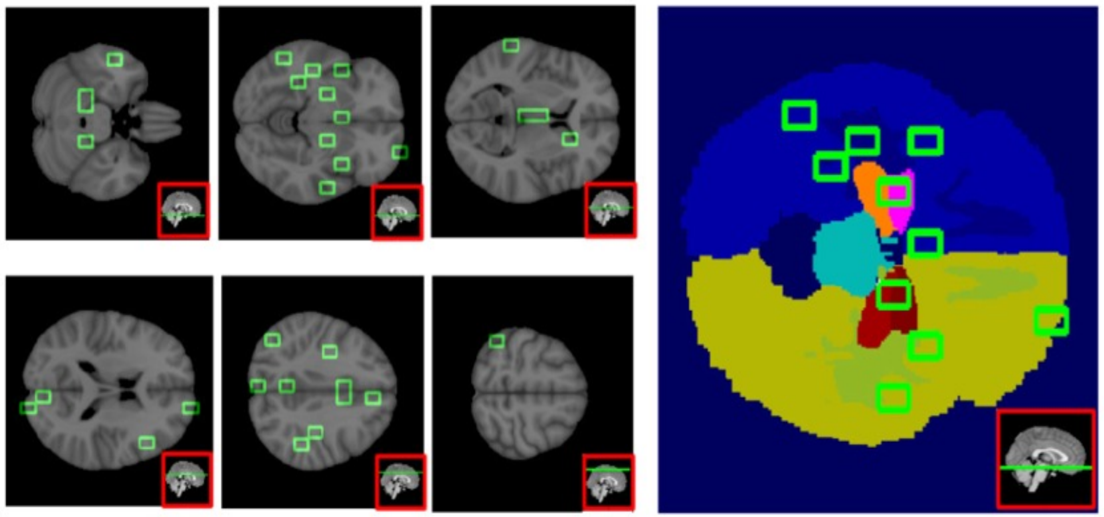
(N. Amoroso, M. La Rocca et al., Frontiers in Aging Neuroscience, 2018)



A fairly stable region in the range of [2250, 3500] voxel. The optimal performance was achieved for a volume of 3000 voxel and an accuracy of 0.88±0.01 significantly greater than that obtained with standard methods like Free Surfer (0.83±0.01).

1) identification of a privileged scale to detect disease effects.

Classification accuracy on an independent dataset	
NC-AD	NC-cMCI
0.86 ± 0.01	0.84 ± 0.01



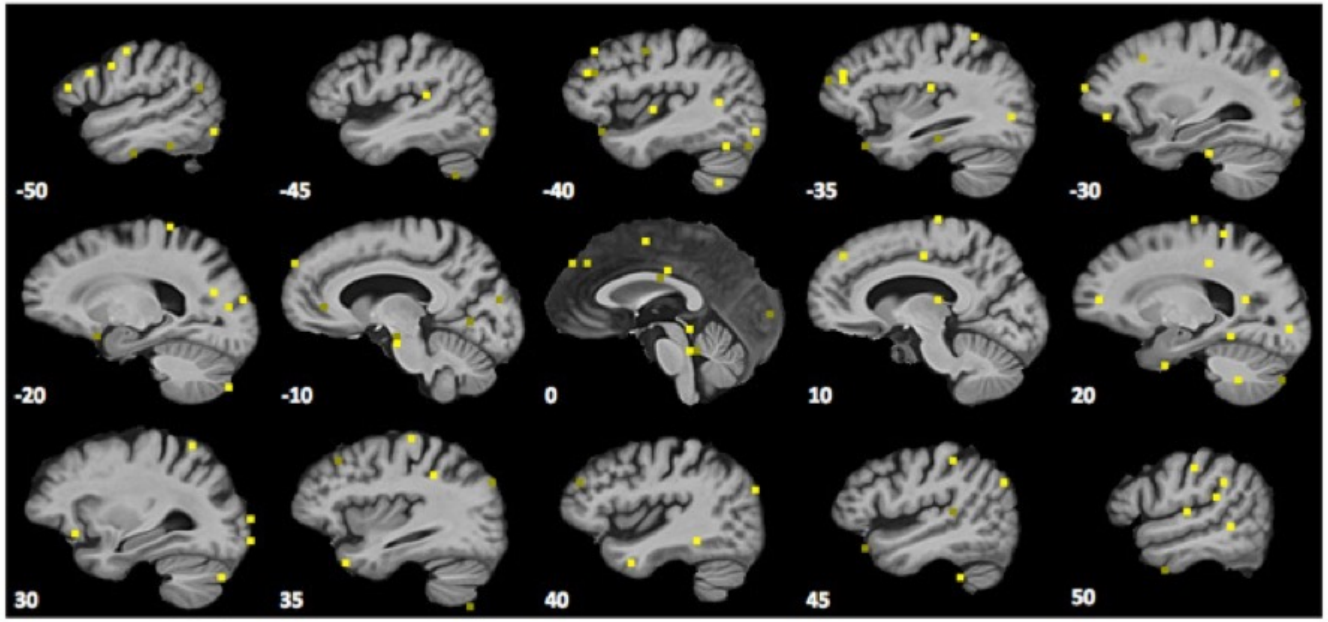
2) Compared to standard methods, it detects more disease-related anatomical regions with an unsupervised segmentation method.

3) The method is reliable and lends itself well to becoming predictive.

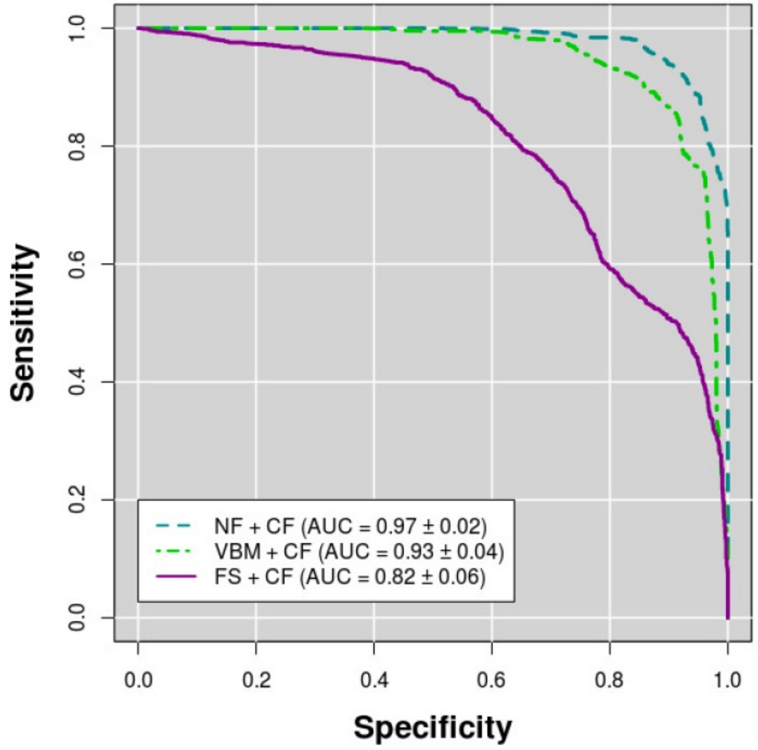
Parkinson case study

Data: T1 MRI of Normal controls, Parkinson disease (PD) subjects at the first stages of the disease. Data come from the Parkinson's Progression Markers Initiative (PPMI).

Goal: early detection of the disease in order to test new treatments when they can be truly effective.



This method outperform conventional methods such as FreeSurfer or Voxel Based Morphometries.



Accuracy
NC-PD
0.832 ± 0.004

The best accuracy was reached of a volume of 125 voxels.

(N. Amoroso, M. La Rocca et al., Medical image analysis, 2018)

Post-traumatic epilepsy case study

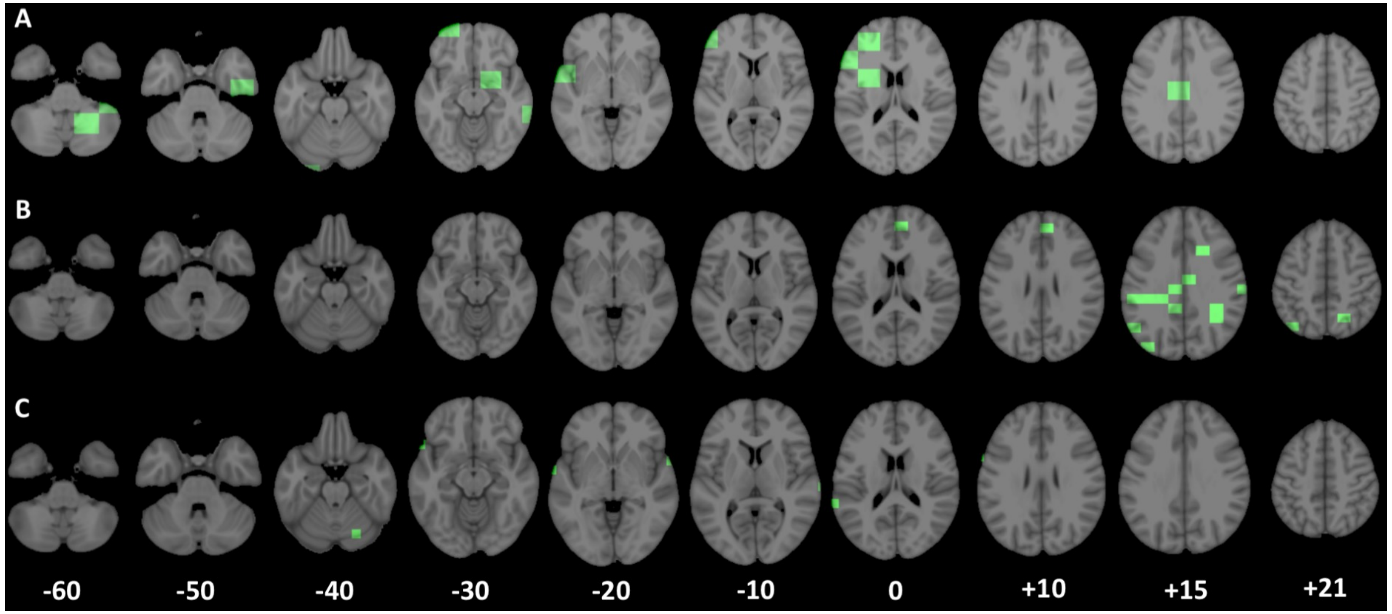
Data: T1 MRI of traumatic brain injury (TBI) patients who developed seizures and seizure-free TBI patient. Data come from The Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx) .
Goal: Identify relevant biomarkers of epileptogenesis after traumatic brain injury (TBI).

Features	Accuracy	Specificity	Sensitivity	AUC
FreeSurfer	0.67 ± 0.03	0.61 ± 0.05	0.71 ± 0.04	0.71 ± 0.03
VBM	0.60 ± 0.02	0.54 ± 0.03	0.67 ± 0.03	0.62 ± 0.03
Complex network (1000 voxels)	0.70 ± 0.03	0.74 ± 0.04	0.66 ± 0.04	0.75 ± 0.02
Complex network (3000 voxels)	0.68 ± 0.03	0.70 ± 0.04	0.67 ± 0.04	0.76 ± 0.02
Complex network (5000 voxels)	0.70 ± 0.03	0.68 ± 0.04	0.69 ± 0.04	0.75 ± 0.02

Regions related to the pathology have been confirmed in literature.

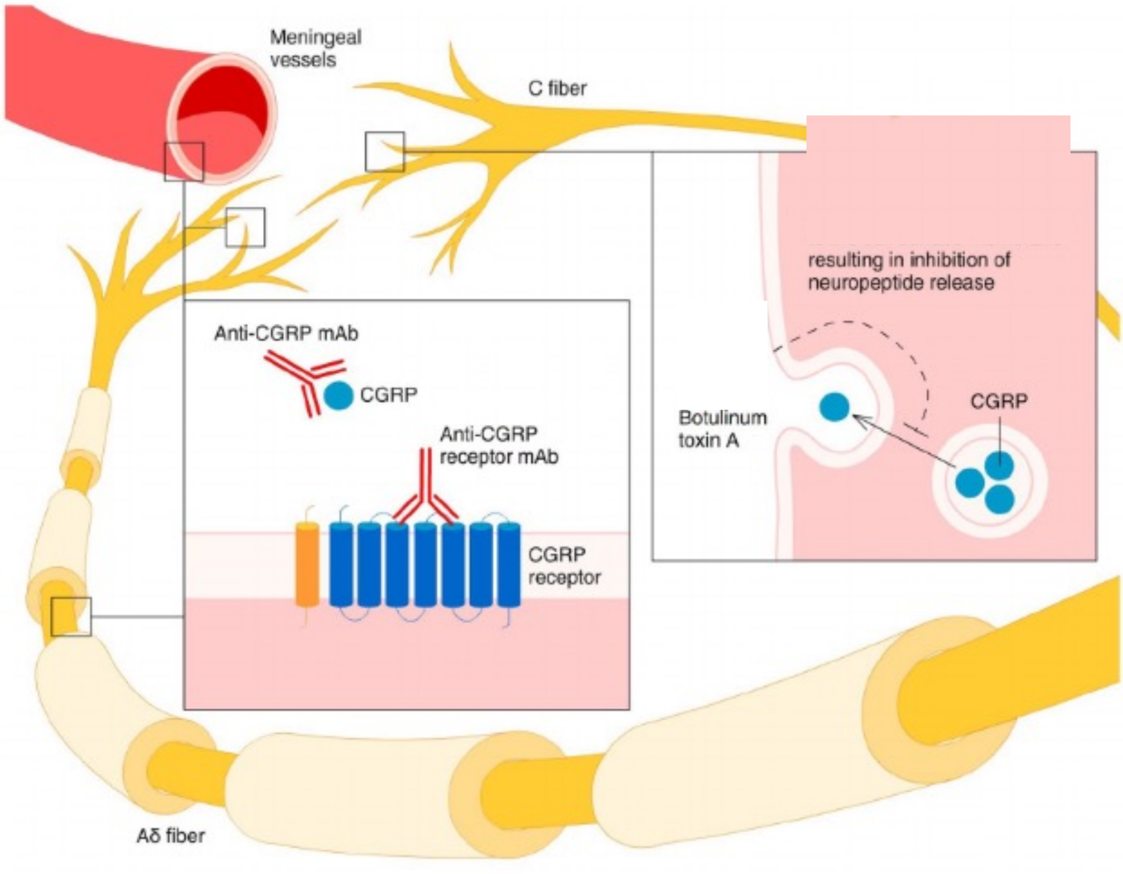
The best classification performances were obtained at three scales: 1000, 3000, and 5000 voxels, proving that the study of seizure development in TBI patients requires multi-variate analyses since brain lesions can have different sizes.

(M. La Rocca et al., Frontiers in Neuroscience, 2020)



Migraine case study

The identification of Calcitonin Gene-Related Peptide (CGRP) as a possible target for migraine treatment has revolutionized the therapeutic scenario.

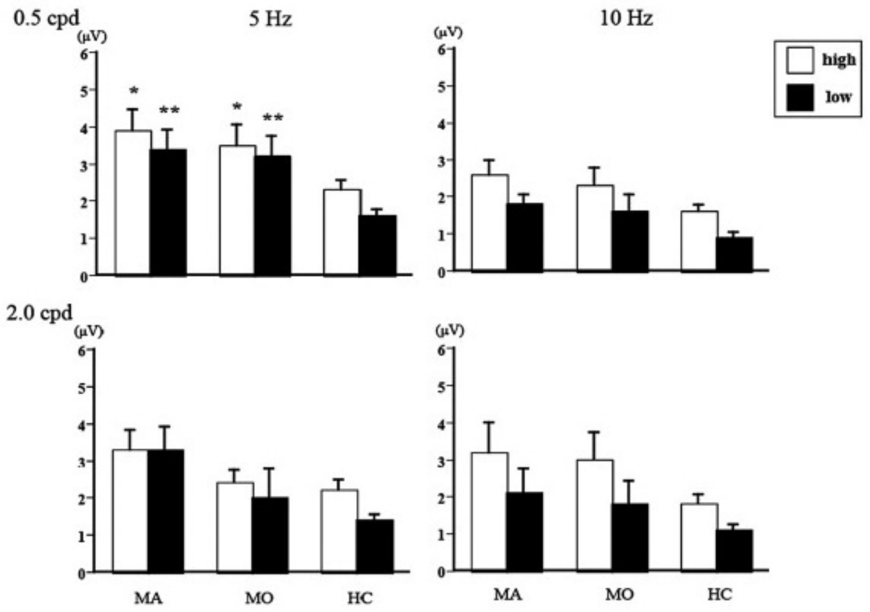


To date, all new therapies directed against CGRP or its receptor for the treatment of migraine have produced positive results.

Migraine case study

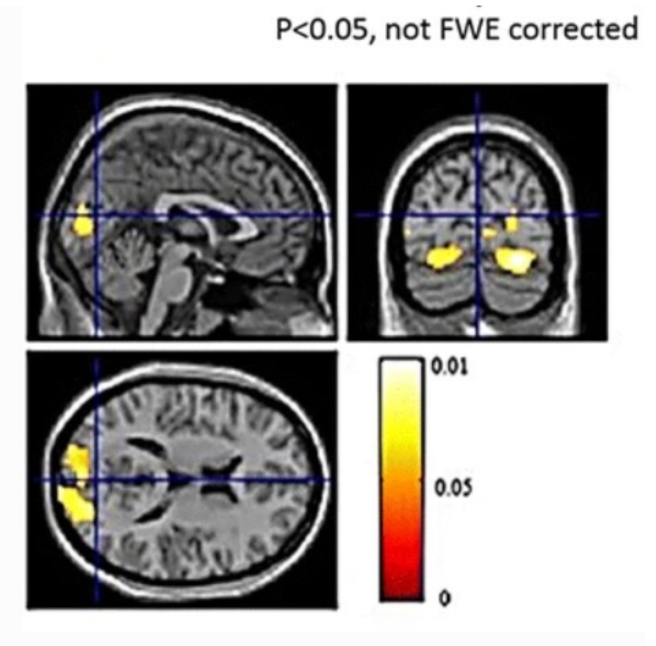
OCCIPITAL CORTEX IS A CRUCIAL SITE IN MIGRAINE: Increased amplitude of steady state visual evoked potentials, increased metabolic response and altered connectivity of occipital cortex were found

Abnormal visual processing in migraine with aura: A study of steady-state visual evoked potentials

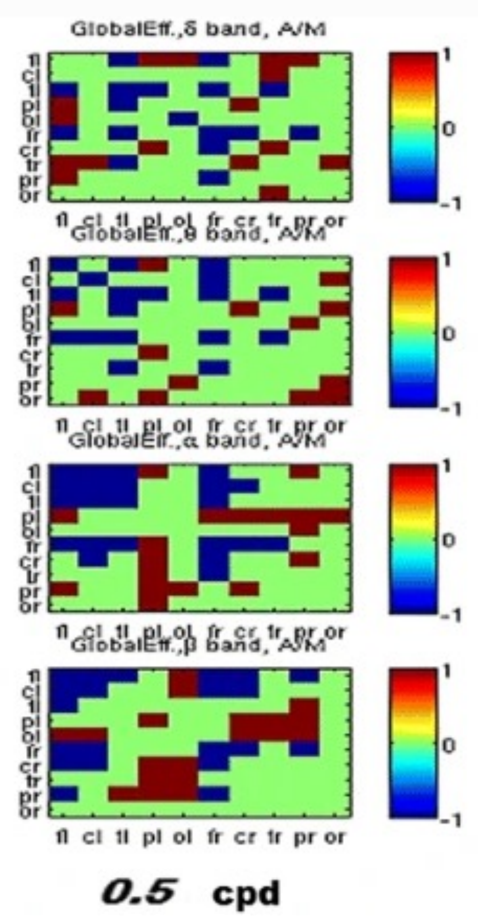


The mean amplitude at 5 and 10 Hz for 0.5 and 2.0 cpd and two different contrasts in migraine with aura (MA), without aura (MO) and healthy controls (HC)

(K. Shibita et al., Journal of the Neurological Sciences, 2008)



Statistical probability maps reporting the comparison of bold signal changes in migraine with aura vs migraine without aura



Comparison of global efficiency in migraine with aura vs migraine without aura

Brain networking analysis in migraine with and without aura

(M. De Tommaso et al., The Journal of Headache and Pain, 2017)

Migraine case study

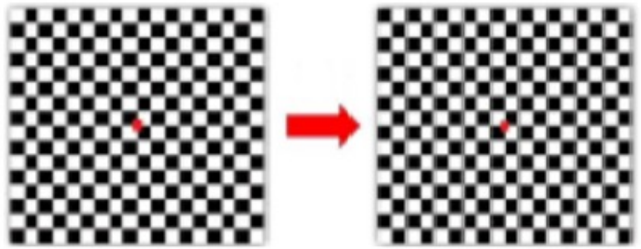
How can CGRP antagonists modify occipital cortex excitability in migraine?

Our goal has been to test the effect of 3 months Galcanezumab or GCA therapy on migraine patients by evaluating cerebral electrical (EEG) and hemodynamic activities (functional near infrared spectroscopy, fNIRS) during checkerboard pattern-reversal stimulation at 5 Hz with spatial frequency of 0.5 cycle per degree.

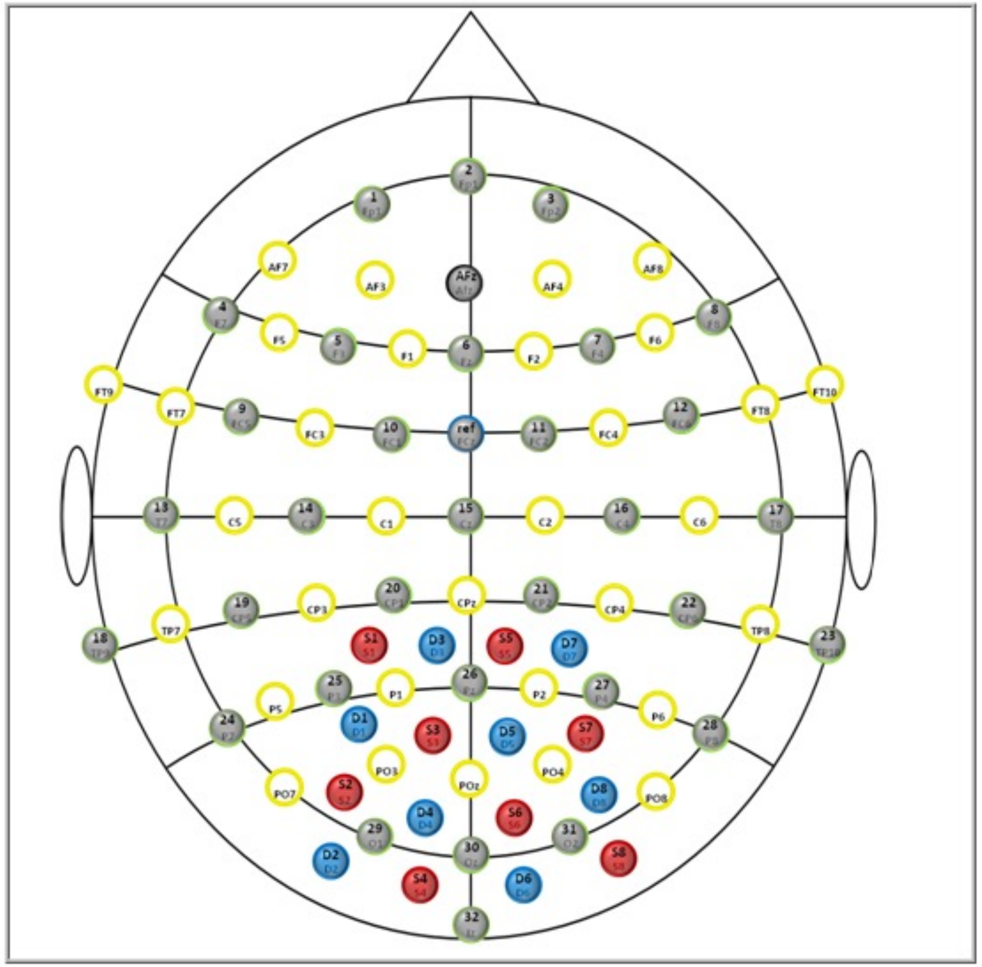
10 healthy volunteers and 13 drug patients were selected at the Headache Center of Applied Neurophysiology and Pain Unit of Bari Policlinico General Hospital from December 2020 to April 2021 during the routine clinical practice

Migraine patients underwent clinical and neurophysiological examination in basal condition (T0) , 1 hour after GCA injection (T1) and after 3 months of GCA treatment (T2). Controls were examined once.

Checkboard pattern stimulations of 60s preceded by 60 s of resting state were performed for each patient and for each condition.



Migraine case study



Signal Acquisition

EEG data were acquired simultaneously with fNIRS data, using a co-recording cap and a black over-cap to mitigate possible interferences generated by ambient light on the fNIRS acquisition.

EEG data were recorded by 62 scalp electrodes, according to the enlarged 10–20 system (nasion as reference and Fpz as ground). Electrooculogram (EOG) was recorded and EEG sampling rate was 256 Hz

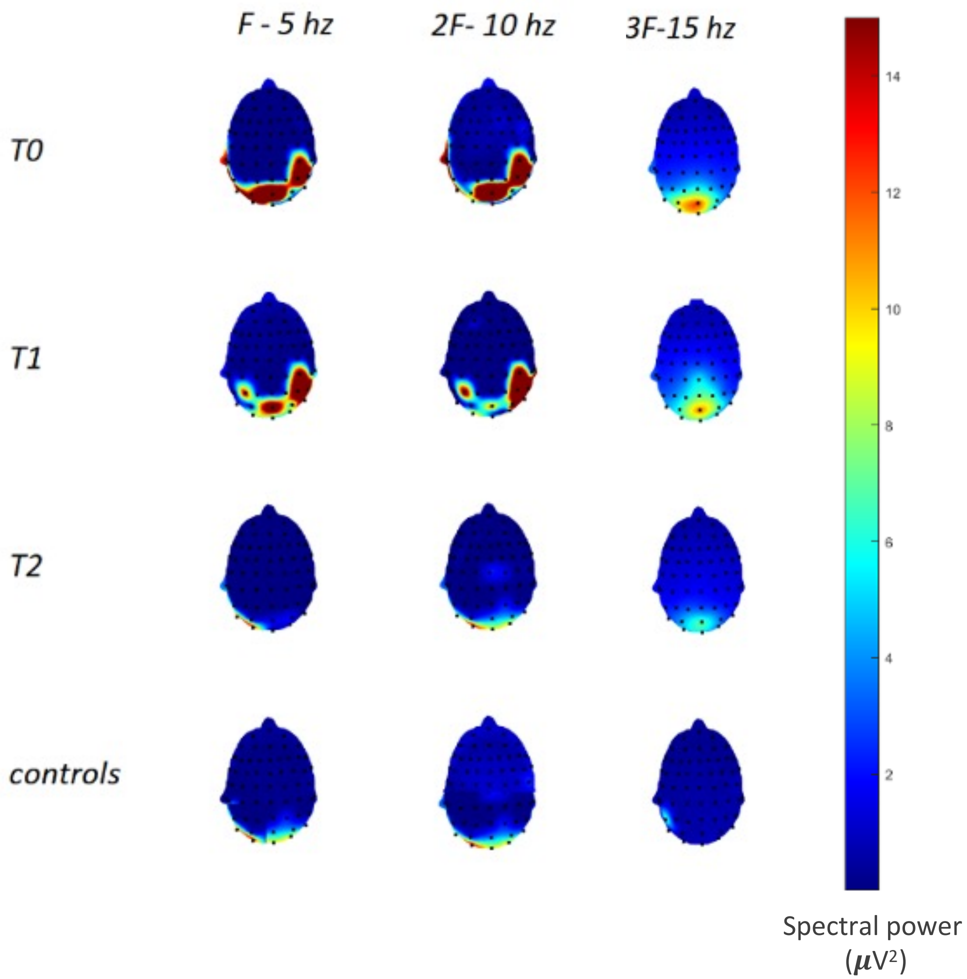
fNIRS data were recorded by 24 channels given by the arrangement of 8 sensors and 8 detectors. An inter-optode distance of 30 mm and a sampling rate of 7.8 Hz were used.

Migraine case study

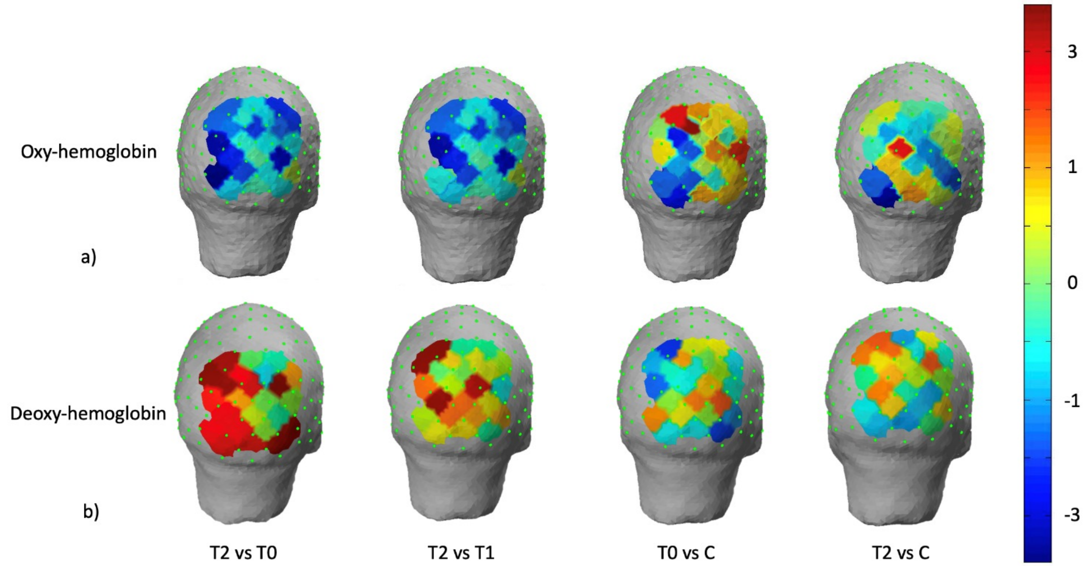
Statistical analysis for EEG and fNIRS data

(M. De Tommaso, M. La Rocca et al., The Journal of Headache and Pain, 2022)

We can observe a significant reduction of the spectral power at T2, as compared to T0 and T1 conditions for all the 3 frequencies (p<0.05).



T-statistic map of the brain regions wherein the significant increases and decreases in deoxy and oxyhemoglobin concentrations are indicated in intense red and in intense blue, respectively.



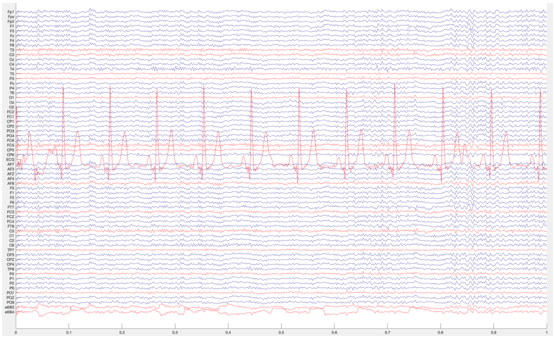
The paired Student's t test showed a general reduction of the oxyhemoglobin concentration at T2 compared with T0 and T1 , with significance (p<0.05) and a general increase in deoxyhemoglobin at T2 on different occipital channels.

No significant differences in spectral power and hemodynamic signal were found between the conditions T2 and controls

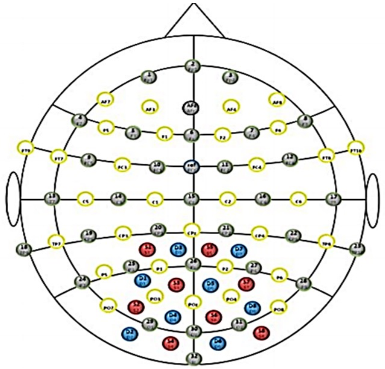
Migraine case study

EEG connectivity

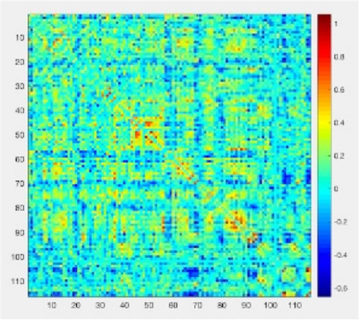
Processed EEG signal

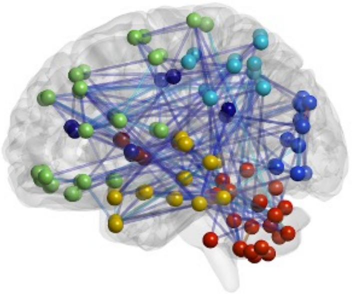


EEG electrodes to define network nodes

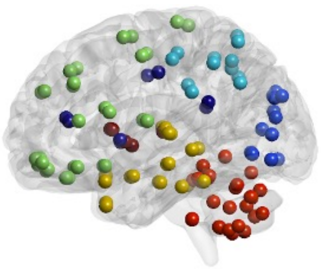


magnitude squared coherence was used to define network links





Network metrics:
Strength
Global Efficency
Clustering Coefficient

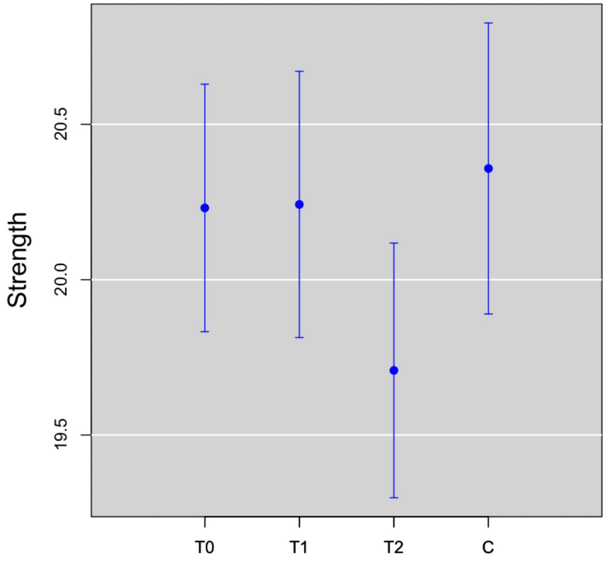


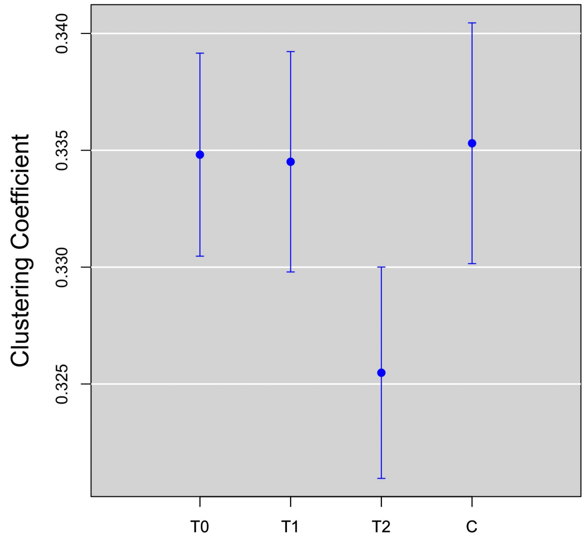
For each EEG frequency band (delta, theta, alpha, beta), we built a weighted network

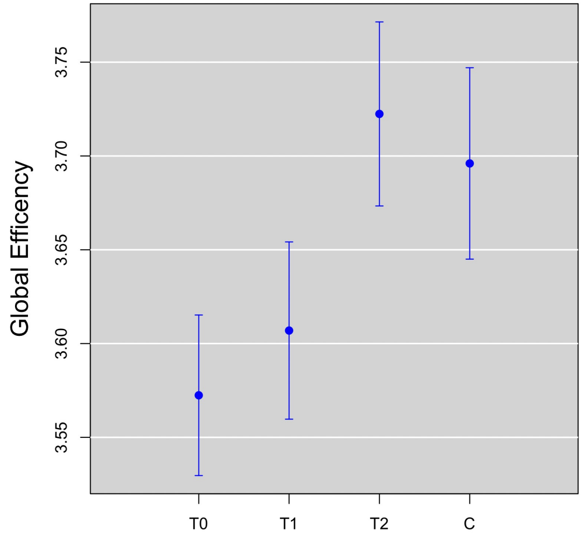
Migraine case study

EEG connectivity

Theta band (4-7 Hz)

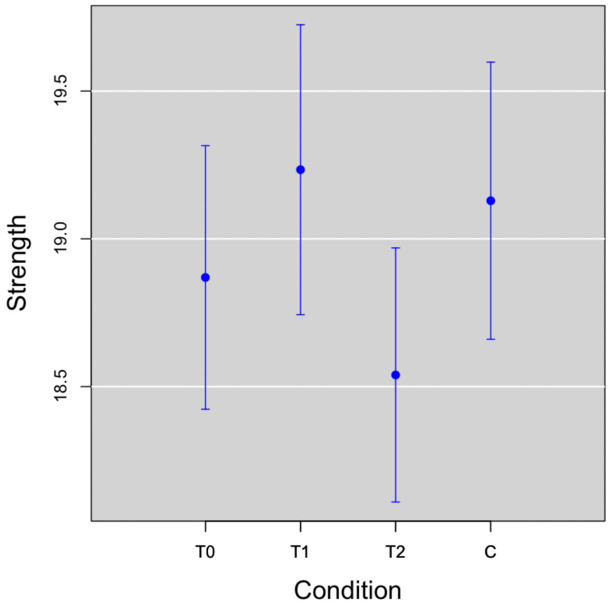


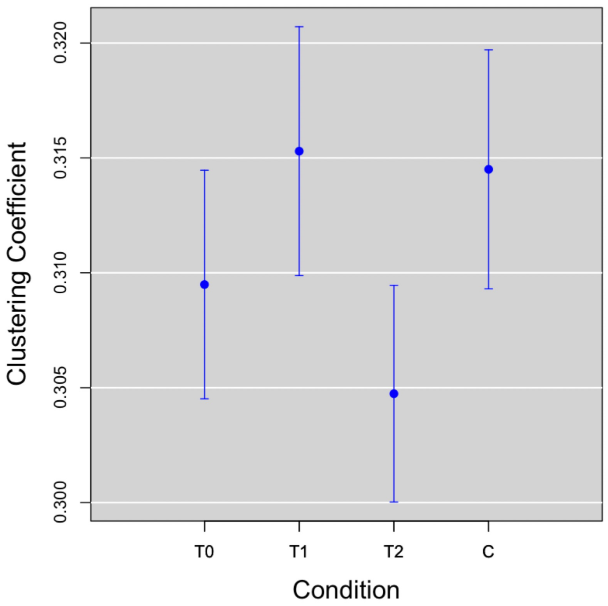


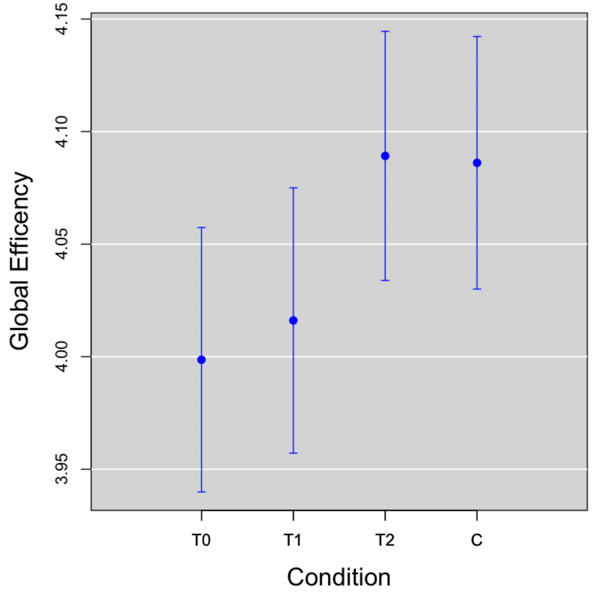


For both bands, GCA has the effect to increase network integration and decrease node coeherence and network segregation.

Alpha band (8-12 Hz)





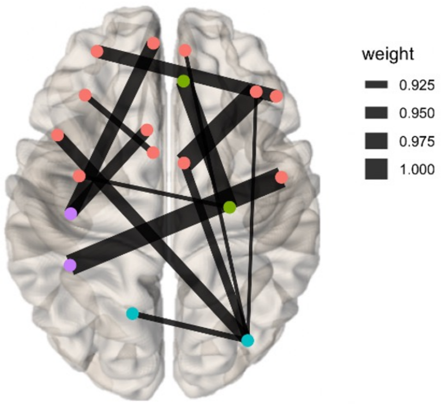


The beneficial effect seems to be due to the increase of the communication efficency of the network

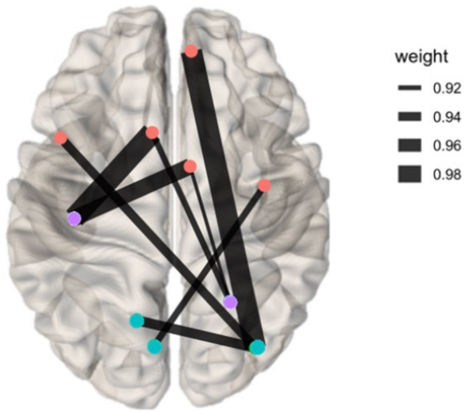
Migraine case study

EEG connectivity

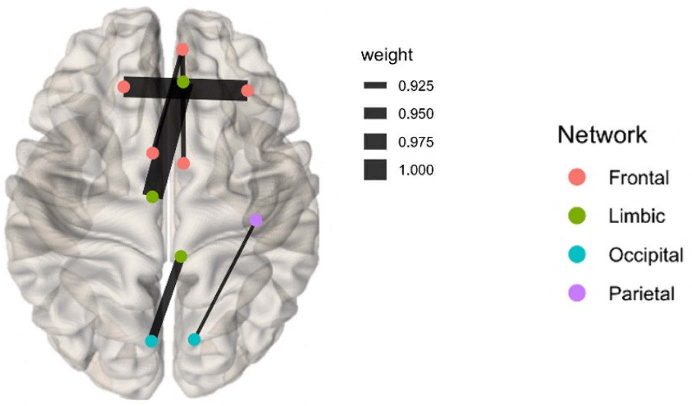
Differences in coherence between conditions greater than the 90th percentile of the distribution of the differences



T0-T2

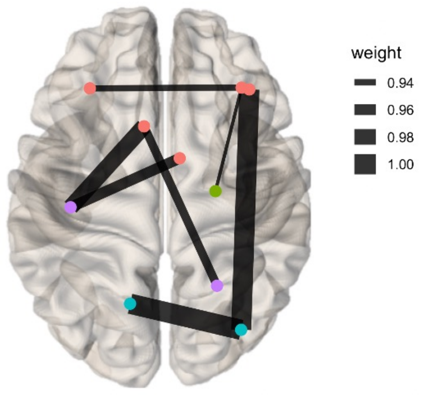


T1-T2

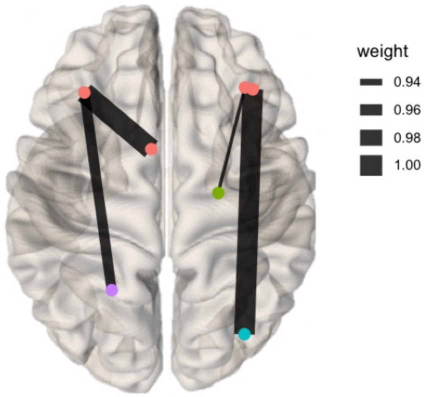


T0-T1

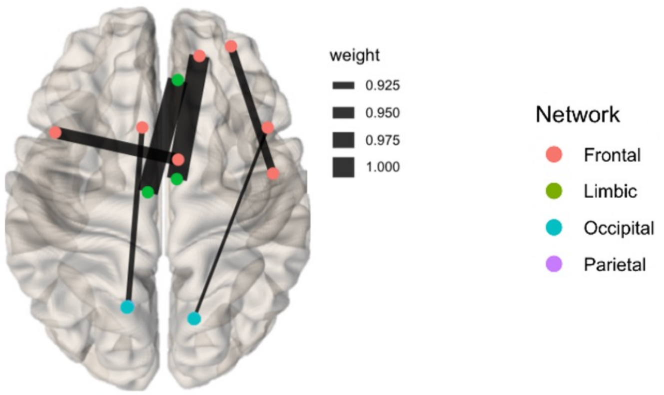
Theta band (4-7 Hz)



T0-T2



T1-T2



T0-T1

Alpha band (8-12 Hz)

The differences between T0 and T2 and T1 and T2 tend to be more intense, more numerous and for these differences the more intese links tend to connect the frontal and the occipital cortex confirming the role of the occipital cortex in migrine pain

Conclusions and future steps

- Complex networks and multiplex networks are excellent methods to analyze and compare multimodal data and to describe brain at different scales

- Network analysis in combination with machine learning techniques allow us to face different challenges in the field of neuroscience such as the early diagnosis of different neurological diseases.

- As to the evaluation of the GCA effects in migraine patients, we plan to carry out the same connectivity study used for EEG also for fNIRS data in order to have a comparison between two modalities.

- We are also considering to use the multiplex networks to study the mutual interaction between the electrical and hemodynamic signals as well as the mutual interaction among the different EEG frequency bands.

UNIBA team

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"M. Merlin"

Thank you for your attention