UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI INFORMATICA

MVAR Analysis of iEEG Signals to Differentiate Conscious States

INF/01

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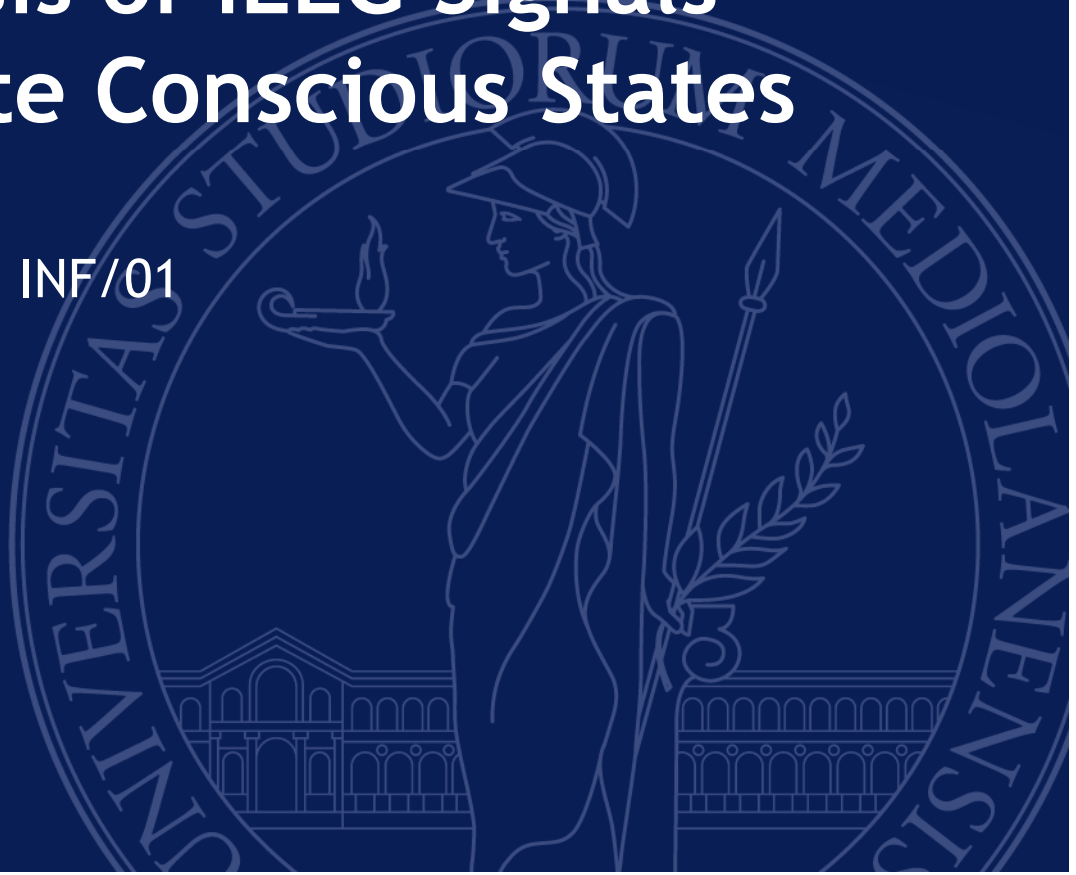


Brain Research

Brain Research is an interdisciplinary area with many different challenges, such as:

- Understanding the neurophysiological **connections between brain areas** (Connectome) and their functional meaning
- Revealing **mechanisms** that may define and recognize complex cognitive tasks

Novel computational tools are required!

Connectome and Connectivity

Human Connectome Project

Every connectome (brain wiring) displays unique structural and functional features that might explain differences in cognition and behavior

Connectivity and Consciousness

Main aim of the dissertation is to understand the neural signatures of consciousness investigating the connectome (**functional connectivity**)

Some connectivity models **from literature**:

- Antony et al., 2013 -> iEEG/epileptogenicity
- Schrouff et al., 2011 -> fMRI/consciousness
- Matsumoto et al., 2004 -> EcoG/human language
- Brovelli et al., 2004 -> monkey iEEG, fMRI/ behavioral studies

Connectivity and Consciousness

To the best of our knowledge, no study has yet investigated **functional connectivity** using **human iEEG data** that are the gold standard to analyze differences between signals in brain cortex
(with millisecond time resolution and centimeter spatial resolution)

Connectivity and Consciousness

Massimini et al., 2012:

By means of

transcranial magnetic stimulation (TMS) + intracranial single-pulse electrical stimulation and EEG recordings (intracranial EEG-iEEG)

Observed:

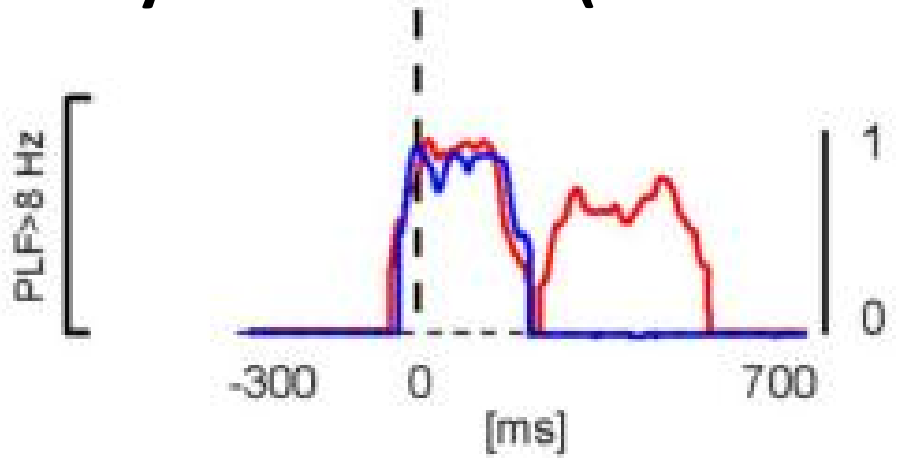
- **wakefulness** and REM (Rapid Eye Movement sleep) = **long-range patterns** of activation
- **NREM Sleep** (Non-Rapid Eye Movement sleep) and Midazolam-induced anesthesia = the **feature is lost**

A possible marker of consciousness

Pigorini et al., 2015:

The electrical perturbation

- in **conscious** state is followed by a **time variant signal** behavior: activation, silencing, **reactivation**.
- in **unconscious** state the silencing stage is **not followed by reactivation (=down state)**



NREM Sleep -> NREM
wakefulness -> WAKE

Aims of the Thesis

1. **Evaluate** brain **network changes** during different levels of consciousness
2. **Classify** WAKE/NREM **states**
3. **Assess parameters** that correlate with the level of consciousness
4. **Investigate** the role of the **reactivation phenomenon**
5. **Analyze** the functional meaning of the adoption of **re-reference styles**

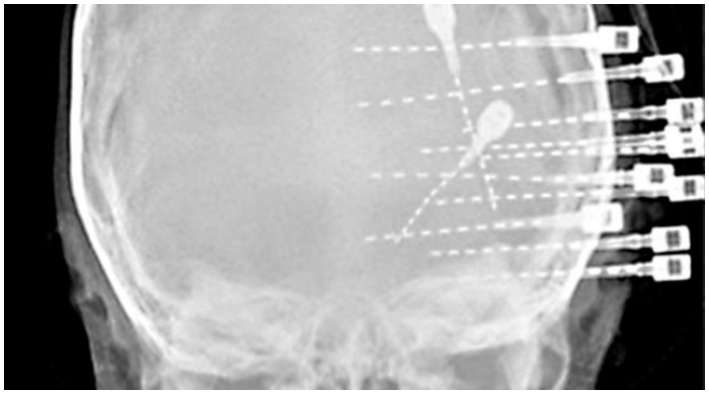
Dataset

iEEG: intracranial EEG signals

- Five subjects
- 8 channels/subjetc
- 29 stimulation session
- Epochs 800 ms long (for each session)

wakefulness (**WAKE**)

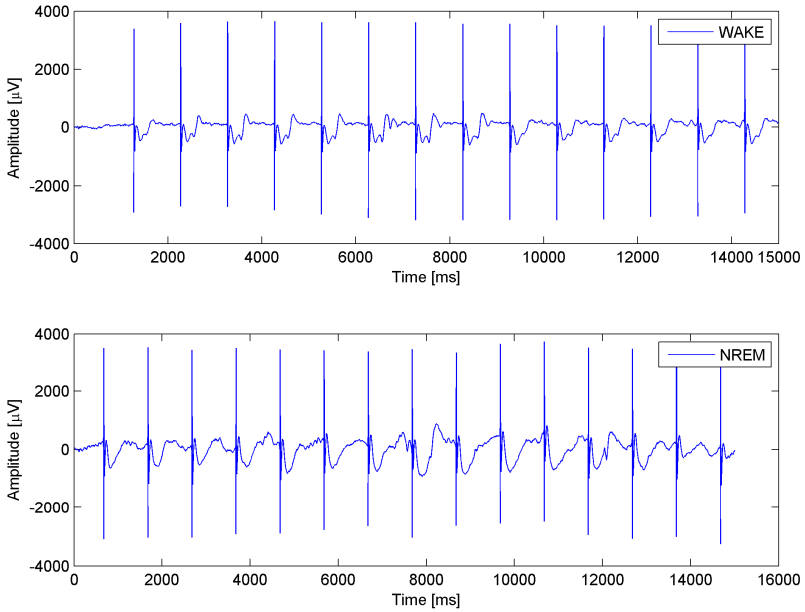
NREM Sleep, stage 3 (**NREM**)



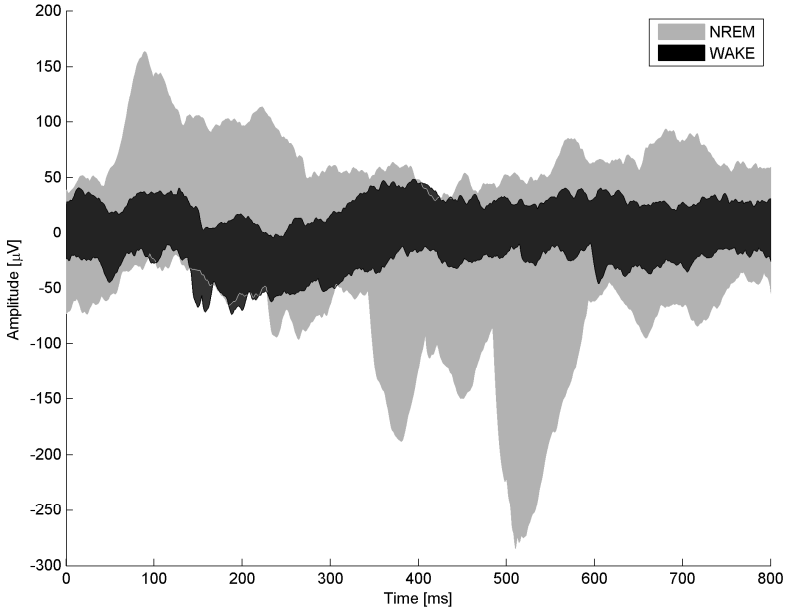
REF: Deepak Lachhwani, MD, and Jorgé Gonzalez-Martinez, MD, PhD

Dataset

iEEG: intracranial EEG signals



16 representative seconds of a raw iEEG signal



Minimum and maximum values of the signal in every epoch over time

Methods

Type of Analysis	Methods	Main Aims
Connectivity	Directed Transfer Function (DTF)	• Analyze the functional meaning of the adoption of re-reference styles • Evaluate brain network changes linked to the consciousness
Considering two frequency bands: Delta and Gamma	Adaptive DTF (Time Varying) (ADTF) + Statistical Analysis (ANOVA/MANOVA)	• Investigate the role of the reactivation phenomenon (down-state) • Evaluate brain network changes linked to the levels of consciousness
Feature Extraction (FE)	Standard Deviation *vs* Wavelet coefficients + ANN classification.	• Classify WAKE/NREM Sleep states

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Multivariate AutoRegressive model

Multivariate AutoRegressive model (MVAR):

- Pattern from a unique model estimated on the whole **set of signals**
- **Reciprocal interactions** are taken into account
- Allows to recognize the **direction** of signals propagation
- Allows to derive **time/frequency** domain **images** by using model coefficients and their **spectral properties**

Multivariate AutoRegressive model

$$y(t) = -\sum_{k=1}^{p} A(k)y(t-k) + u(t)$$

Where

$\mathrm{y(t)} = [\mathrm{y_1(t)}, \mathrm{y_2(t)}, \ldots, \mathrm{y_N(t)}]^{\mathrm{T}}$

data vector in time

A(1), A(2), … A(p) = NxN matrices of the model coefficients

p = model order

k = lag

$\mathrm{u(t)}$ = independent white noise

Connectivity Estimator: DTF

Directed Transfer Function (DTF) :

- Frequency domain estimator of **cross interactions** based on the MVAR model
- Uses **spectral density**
- Defined by the elements of the transfer matrix H(f)= $\left|H_{ij}(f)\right|^2$
- H(f) is the inverse of the frequency-transformed coefficients matrix, A(f) (Fourier Transform)

Connectivity Estimator: DTF

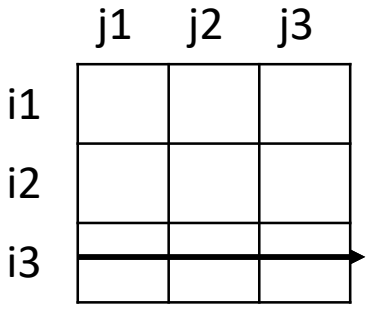
DTF is expressed by the normalized formula:

$$D_{ij}(f) = \frac{|H_{ij}(f)|^2}{\sum_{j=1}^{N} |H_{ij}(f)|^2} \qquad \sum_{j=1}^{N} D_{ij}(f) = 1$$

Where

$H_{ij}(f)$ is the Transfer Matrix

N is the number of channels



It describes the directional flow from channel j (source) to i (sink) with values [0, 1]

Connectivity Estimator: ADTF

- The adaptive DTF (ADTF), a time-varying multivariate method, has been developed for the estimation of rapidly changing connectivity influences

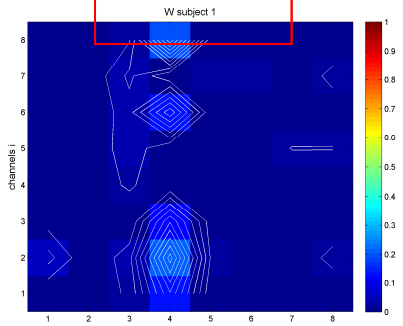
- It provides a 4D matrix

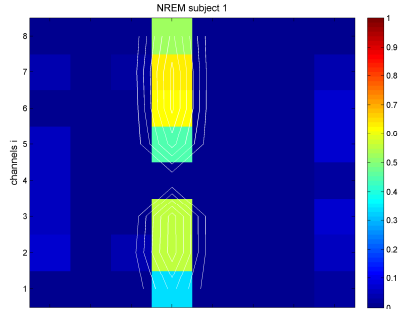
$$D_{ij}(f,t) = \frac{\left|H_{ij}(f,t)\right|^2}{\sum_{j=1}^{N}\left|H_{ij}(f,t)\right|^2}$$

DTF Results

WAKE **NREM**

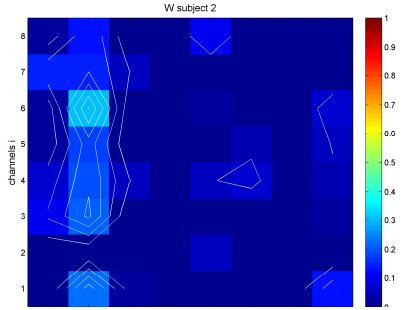
 # 1

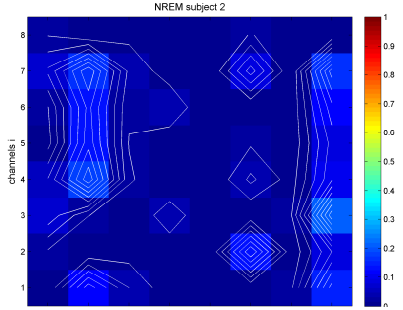




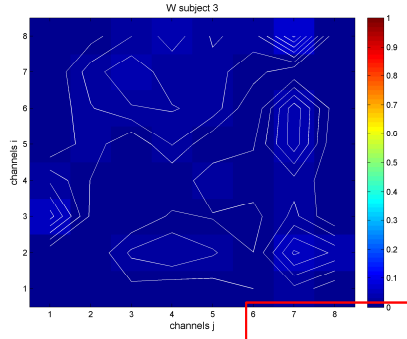
Information flow: from j to i

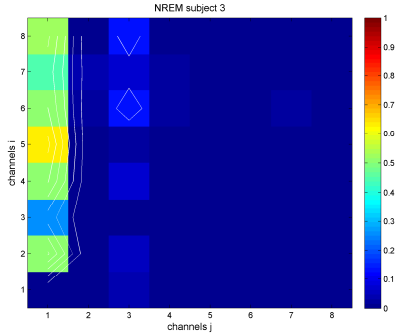
 # 2





 # 3





DTF values: NREM>WAKE

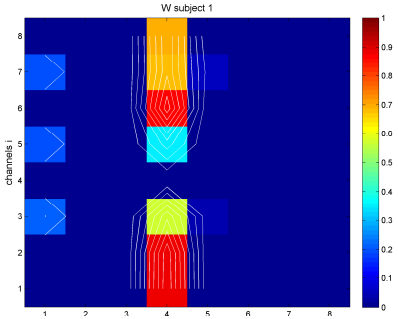
$p < 0.05$

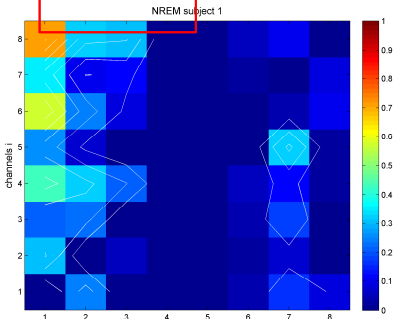
Averaged values in Gamma Frequency band (30-100 Hz)

DTF Results

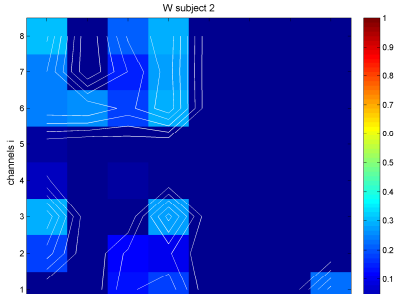
WAKE **NREM**

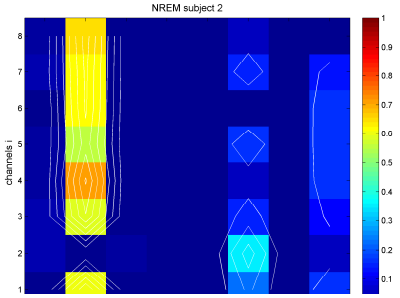
 # 1





 # 2





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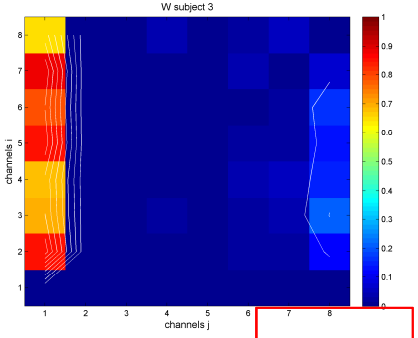
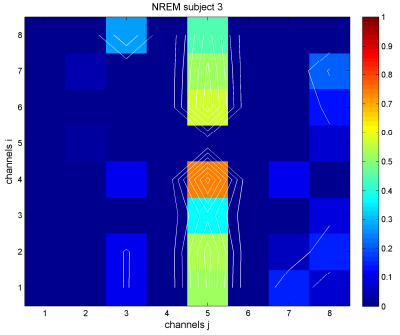




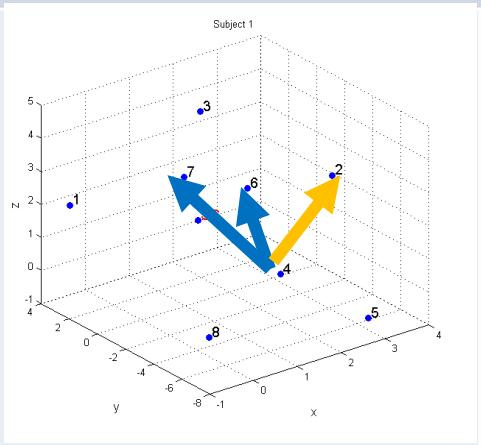
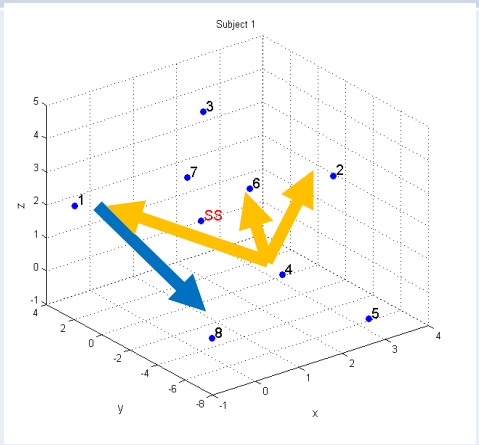
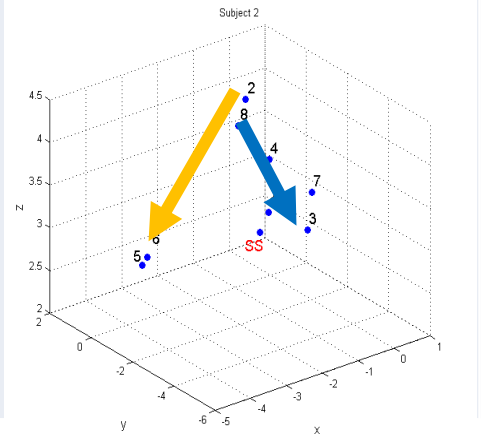
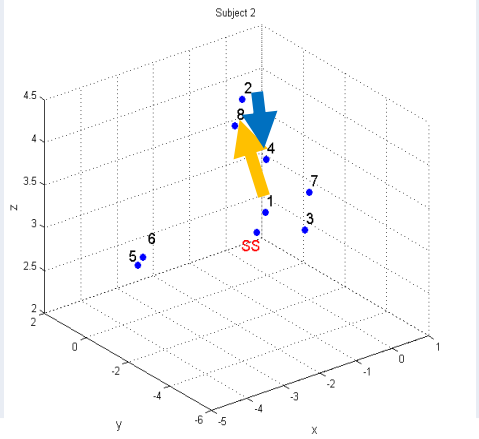
Information flow: from j to i

DTF values: WAKE>NREM

Averaged values in Delta Frequency band (0.4 - 5 Hz)

$p < 0.05$

DTF Results

Connections in Gamma Band	Connections in Delta Band
# 1	
	
# 2	
	

WAKE

NREM

DTF Results

DTF analysis :

- helped to **localize** sinks, sources, and locations of the **major players** of the network (Brodman and parietal area)
- the information flow swapped direction only in Delta: is this the **re-elaboration role of brain during night?**
- Interesting findings: **higher DTF values** are observable: i) in WAKE for DELTA frequencies and ii) in NREM for GAMMA frequencies (opposite then expected)

Methods

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Re-referencing style: Results

Referential montage: every single intracranial channel was referenced to a single channel placed into the white matter (electrically inactive)

- Bipolar re-referencing (**BP**)=subtraction of the signal from the adjacent contact
- Common Average (**MA**)=the mean value of every voltage from all channels is subtracted
- Closest white (**CW**)= referenced to the closest white-matter electrodes (Arnulfo et al., 2015)

Re-referencing style: Results

subject	min	max	threshold	main	source	sink
1	0	0,210214	0,199703	0,210214	4	2
2	0	0,301177	0,286118	0,301177	2	6
3	0	0,071934	0,068337	0,071934	7	8
4	0	0,190279	0,180765	0,190279	5	7
5	0	0,214859	0,204116	0,214859	5	7

BP montage

subject	Min	Max	threshold	main	source	sink
1	0	0,173092	0,164437	0,173092	4	1
2	0	0,279753	0,265766	0,279753	6	7
3	0	0,366743	0,348406	0,366743	1	7
4	0	0,363329	0,345463	0,363329	6	4
5	0	0,26004	0,247038	0,26004	5	7
				0,251454	5	8

CW montage

subject	min	max	threshold	main	source	sink
1	0	0,468768	0,445329	0,468768	4	7
2	0	0,298803	0,283863	0,298803	8	7
3	0	0,500054	0,475051	0,500054	1	3
4	0	0,381167	0,362109	0,381167	5	1
5	0	0,380565	0,361536	0,380565	2	4
				0,37959	4	2

MA montage threshold : 95°percentile

Re-referencing method deeply influences the result

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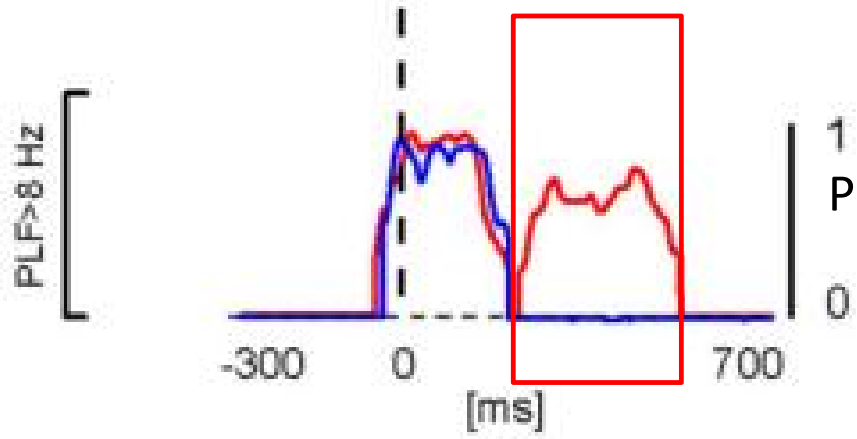
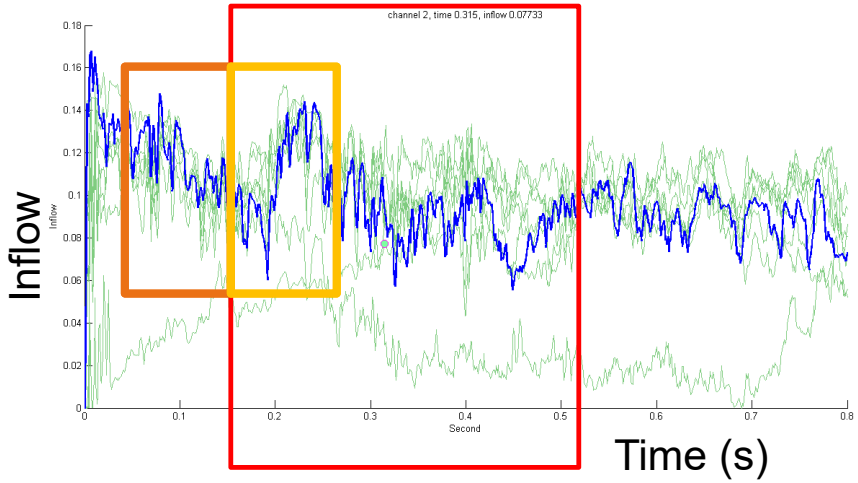
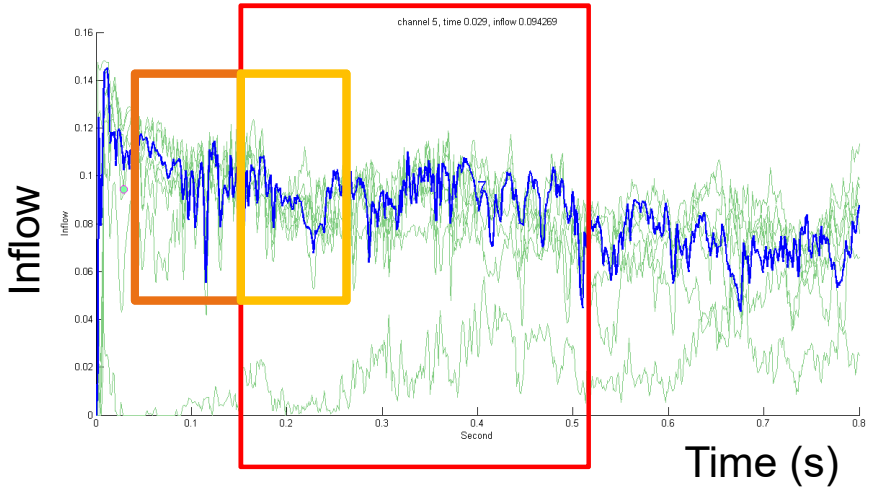
ADTF Results



Pigorini et al, 2015

~150 ms :~500 ms





Time-Varying Inflows

ADTF Results

4D matrix -> Descriptive Feature

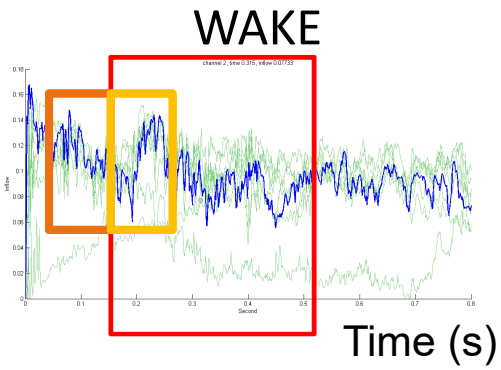
1. 4D.matrix(time, sink, source, frequency)
2. 3D.matrix(time, sink, source): **mean over frequency**
3. 2D.matrix(time, sink): **influence of all sources** in every sink
4. A **descriptive feature** (ADTF mean value over time) for every sink

ADTF Results

Experiments designed considering **4 INPUT groups of 40 elements each** (all patients and all electrodes pooled).

ADTF values were extracted from the windows :

1. **BEFORE** the down-state in **WAKE**
2. **AFTER** the down-state in **WAKE**
3. **BEFORE** the down-state in **NREM**
4. **AFTER** the down-state in **NREM**



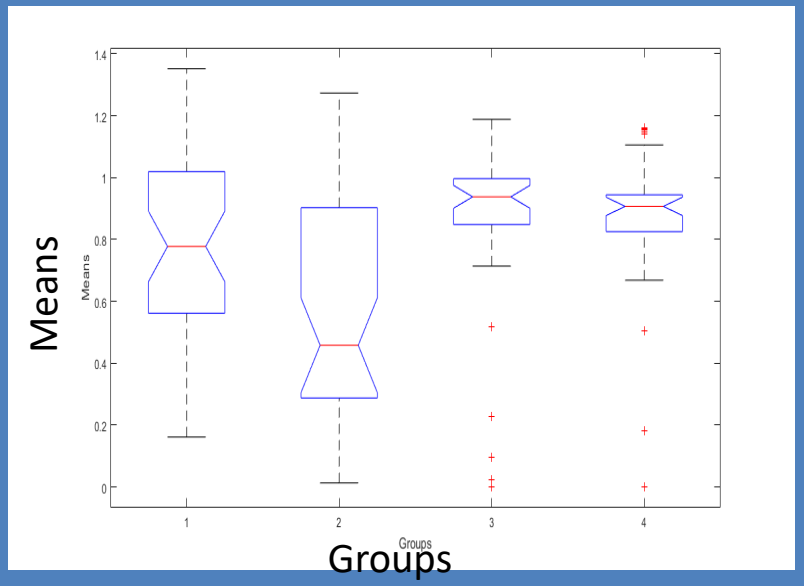
ADTF Results

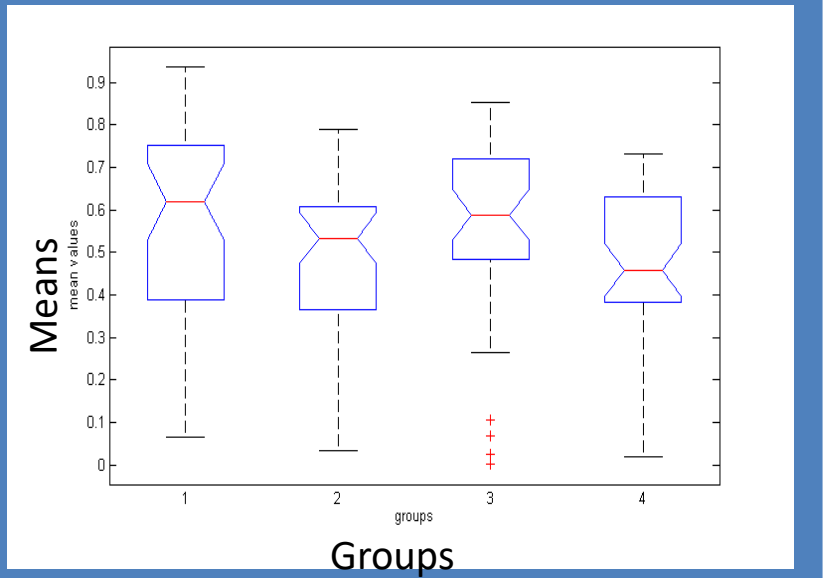
Analysis of variance (ANOVA):

- **Pairwise comparison** of the groups mean
- The two-way ANOVA that compares the mean differences between groups that have been split in **two independent variables** A,B
- Variable A (rows): feature for each observation; Variable B (columns): conditions (WAKE/NREM, BEFORE/AFTER)

ADTF Results

BOXPLOT





Delta Band

Gamma Band

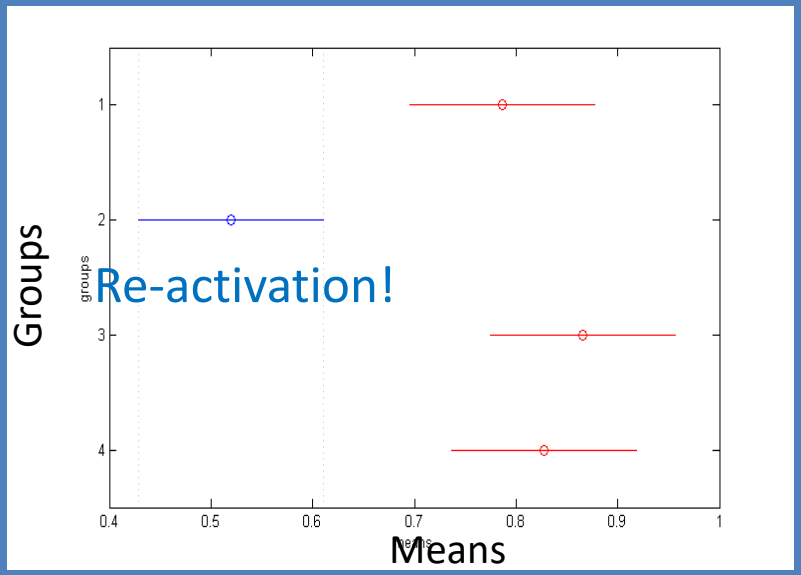
4 Groups: 1) Before/WAKE condition; 2) After/WAKE condition;
3) Before/NREM condition ; 4) After/NREM condition

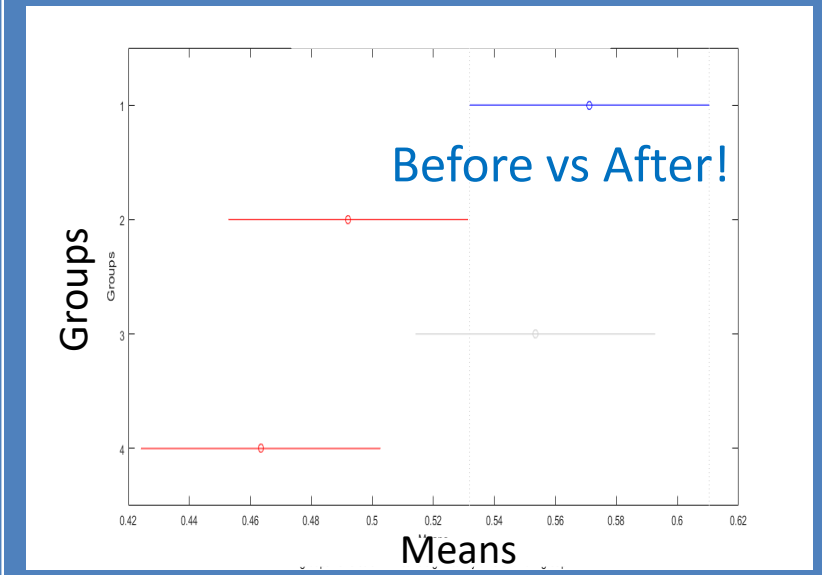
Condition effect: $p < 0.01$
Inter-patients variability: $p < 0.01$

Condition effect: $p < 0.01$
Inter-patients variability: $p < 0.01$

ADTF Results

MULTI-COMPARISON BETWEEN GROUPS





Delta Band	Gamma Band

4 Groups: 1) Before/WAKE condition; 2) After/WAKE condition;
3) Before/NREM condition; 4) After/NREM condition

Group 2 differs from all (p <0,0001)	**Group 1 differs from Group 2 (p =0,0477)** **Group 1 differs from Group 4 (p =0,0028)** **Group 3 differs from Group 4 (p=0.0178)**

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ADTF Results

ADTF/ANOVA analysis confirms:

- A different behaviour in WAKE with respect to NREM during slow oscillations (DELTA band) and after the downstate

- Interestingly, changes into the network do not occur only in Delta, but also in Gamma Band (the result is not reported in literature):

  Even if the re-activation is peculiar of slow waves, a different behaviour, during time, is detectable also in Gamma band

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Feature Extraction: Aim

Connectivity Analysis :

- Identified different network behaviors in the two states
- Measured the information flows
- Revealed the direction of information according to the role of some brain areas

Feature Extraction method:

To examine **how signals vary** according to the conscious conditions, we extracted a set of **features** and we identified the one that allows **to differentiate** WAKE vs NREM

Feature Extraction: Method

1. Channels selection criteria: the ones with maximum absolute difference between the two conditions
2. Features extraction :
   - coefficients from Wavelet decomposition (Ca, Cd6)
   - STD values
3. Classification:
   - Artificial Neural Network (MPL).
   - ROC (Receiver Operating Characteristic) to evaluate the performance of the classifier.

Feature Extraction: Results

wavelet

	Performance (%)		
Features	Accuracy	Specificity	Sensitivity
STD	82,84±13,14	70,87±33,81	87,51±16,30
Ca	95,71±9,65	92,5±16,87	100±0,00
Cd6	92,85±10,11	88±17,35	96,67±10,53
Ca+STD	98,57±4,52	96,67±10,53	100±0,00
Cd6+STD	98,57±4,52	97,5±7,91	100±0,00
Ca+Cd6	98,57±4,52	96,67±10,53	100±0,00

ANN classification: Average and standard deviation evaluated on the test set, computed over 10 runs (Sensitivity: the true recognition of wakefulness).

	AUC
STD	0,9389±0,063
Ca	0,9986±0,003
Cd6	0,9967±0,006
Ca+STD	0,9960±0,012
Cd6+STD	0,9998+0,001
Ca+Cd6	0,9934±0,018

Average and standard deviation of AUC of the NN outputs computed over 10 runs

	t	p-value
Ca vs STD	3.143	0.006
Cd6 vs STD	3.042	0.007
Ca+STD vs STD	2.957	0.008
Cd6+STD vs STD	3.126	0.006
Ca+Cd6 vs STD	2.725	0.014

t test

Rutigliano et al.,2018

Feature Extraction: Results

- Found of **composition of features** that is able to recognize WAKE or NREM states with very good discrimination performances **using one single iEEG electrode**

- Evaluation of anatomical regions capable of differentiating the two conditions

Conclusions

Because of the iEEG **technique's limitations**, the **variability** of the results, that depends on the *inter*-patients variability and on the methods used (both **re-reference and analysis**), a satisfying **understanding** of brain connectivity and the ability to distinguish states **of consciousness** and unconsciousness **is still a work in progress.**

Conclusions

This work offers **a first experimental approach** toward **distinction and characterization** of **WAKE/NREM** states using a human dataset that provides excellent spatial and temporal resolution

Conclusions

We proved the following combination of **methods, analysis and statistics to be valid and useful:**

- the downstate presence and the re-activation phenomenon was revealed by means of computational techniques (ADTF + ANOVA)
- wavelet coefficients are valid parameters able to differentiate the states

Conclusions

The DTF analysis, interesting findings:

- the information flow swapped direction only in Delta: can this explain the **re-elaboration role** of brain during night for memory consolidation?
- **higher DTF values** are observable: i) in WAKE for DELTA frequencies and ii) in NREM for GAMMA frequencies (opposite then expected)
- **re-referencing style** produces different connectivity results: it deeply **influences any following analysis**

Conclusions

ADTF/ANOVA analysis interesting findings:,:

- **Confirmed the presence of re-activation** effect only in WAKE and during slow oscillations (DELTA)
- Revealed **interesting changes** in the network, according to the downstate time, **not only during Delta, but also in Gamma frequency in both NREM and WAKE states.**

Thank you for the attention

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Future works

- **Further investigaton on the temporal slices** used in ADTF analysis
- **Enhance data robustness**: increasing the number of i) subjects and ii) channels
- Play with other **conditions** (time series lenght, frequency ranges..)
- **Detect the down state point** by means of computational techniques (e.g. feature extraction)
- **Confirm** the presence of the re-activaton and downstate **phenomena also in the case of other re-refencing syles** (e.g. CW)

Tools

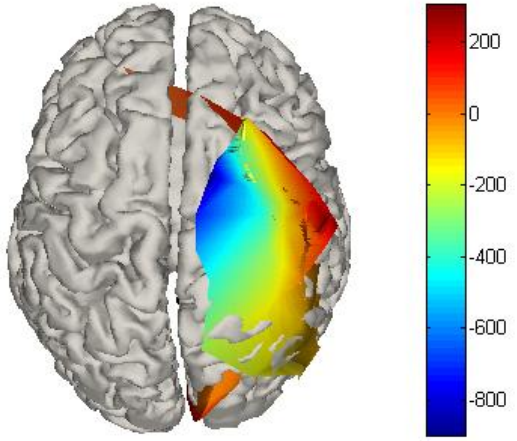
Type of Analysis	Tools
Connectivity	Data extraction and Preprocessing: **Ad hoc Matlab script** DTF/ADTF values calculation: **eConnectome toolbox** He et al, 2011 Visualization, analysis, statistics: **Ad hoc Matlab script**
Feature Extraction (FE)	Std and Wavelet analysis: **Ad hoc Matlab script** Neural network classification: **NN pattern recogniton Matlab's tool**

Limitations

SPES-iEEG analysis, and EEG analysis in general, suffer from the following limitations:

1. the data type
2. the experimental protocol
3. the preprocessing step
4. non-stationarity of signals
5. high *inter*-patient variability

Dataset: limitations



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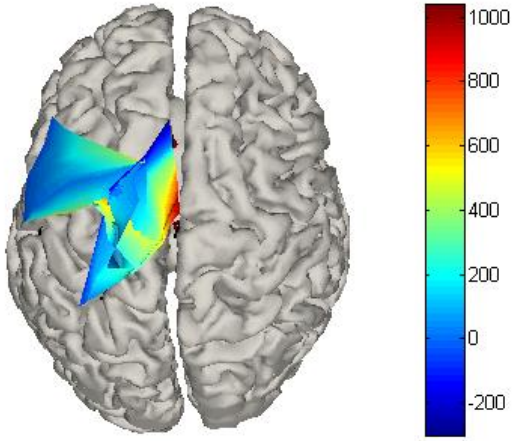

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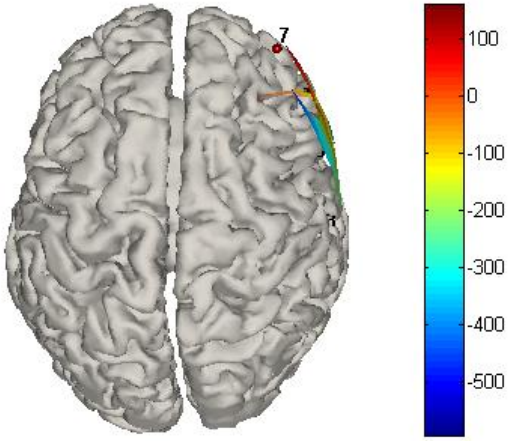

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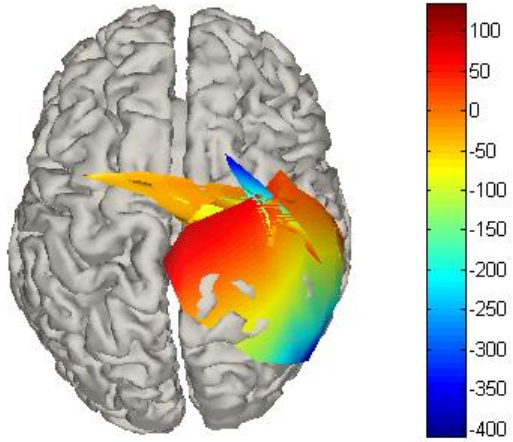

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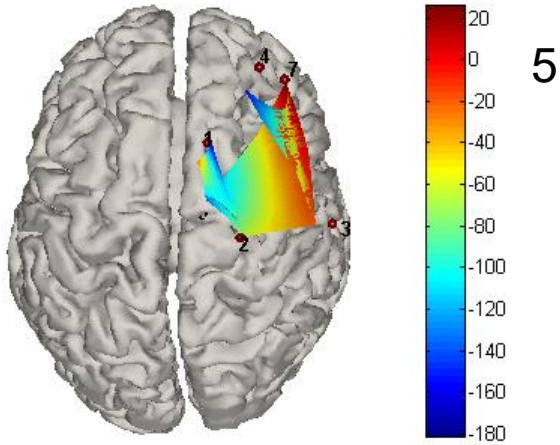

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Dataset: limitations