International Federation of Clinical Neurophysiology

THE FIRST IN-PERSON MEETING OF THE SPECIAL INTEREST GROUP

Functional Brain Connectivity as Revealed by EEG/MEG

Washington Marriott Wardman Park Hotel, Washington, USA
May 4th, 2018 at 12:00 - 1:00 (Park Tower 8228)

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International Federation of Clinical Neurophysiology

THE SPECIAL INTEREST GROUP
Functional Brain Connectivity as Revealed by EEG/MEG

OBJECTIVES OF THE WORKGROUP

Claudio Babiloni

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BACKGROUND

- *Neural Connectivity* as the activation of axonal connections between neural masses (Friston, 1994, 2013, Valdes Sosa et al., 2011,2015). Estimators:
  - Functional connectivity : mutual information, interdependence
  - Effective connectivity: biophysically based models to search for causality

- Functional magnetic resonance imaging (rs-fMRI) unveiled brain connectivity formed by interdependent neural masses (Damoiseaux et al., 2006)
  - Sensory; Attentional; Emotional coloring (i.e., salience); Executive (planning, execution, and control of behavior); and Resting state condition

- EEG and MEG techniques have an ideal millisecond time resolution to unveil frequency oscillatory code linking those neural masses in Clinical Neurophysiololgy (Mantini et al., 2007; Stam and Reijneveld, 2007; D’Amelio & Rossini, 2013)
  - Cortico-muscular
  - Cortico-cortical
  - Animal models for understanding basic neurophysiology across macro, meso, and microscales and back-translation

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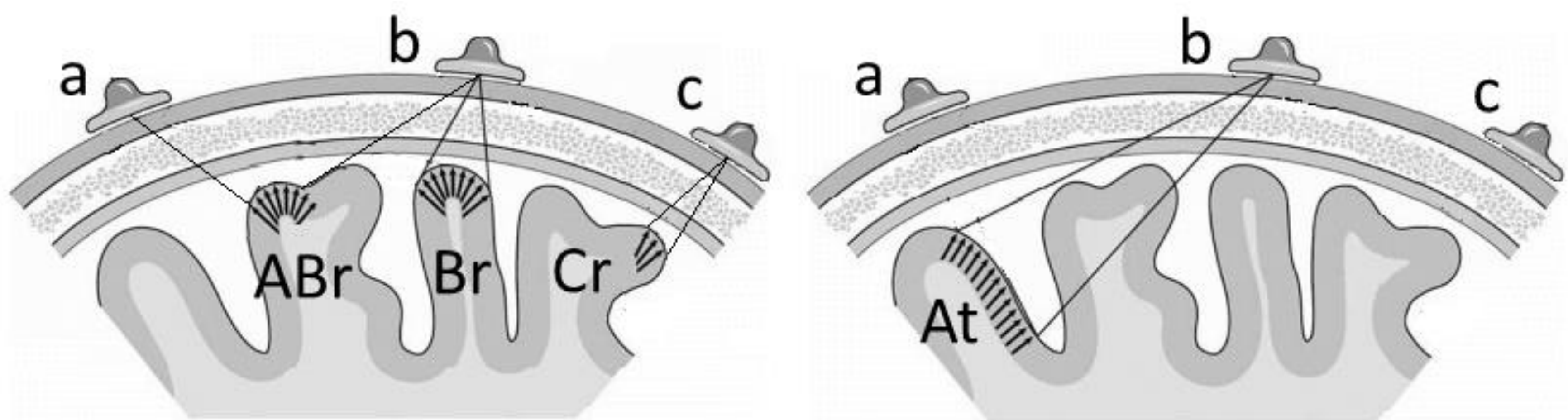
THE DRAGOON

- *Head volume conduction effect* spreading electric fields generated by brain sources can inflate (especially bivariate) measures of interdependence of scalp rsEEG rhythms (Blinowska, 2011, Nunez and Srinivasan, 2006)

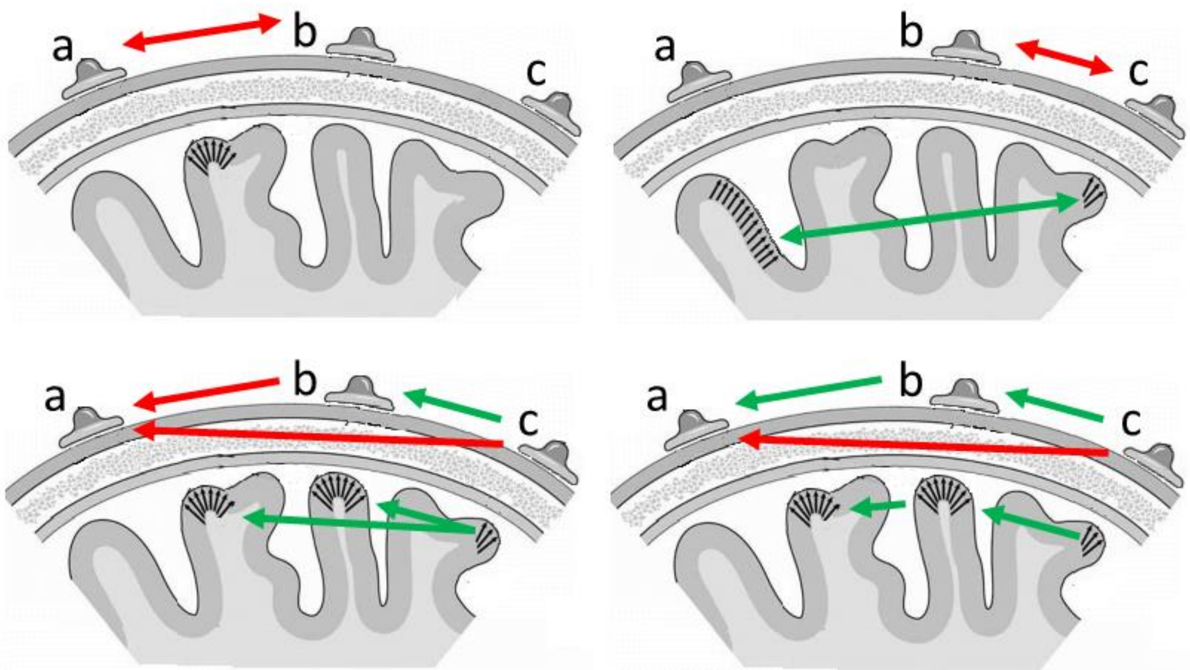


Legend. Three exploring scalp electrodes "a", "b", and "c" and four underlying cortical sources "At" (i.e., under the electrode "a" with a tangential orientation), "ABr" (i.e., halfway between the electrodes "a" and "b" with a radial orientation), "Br" (i.e., under the electrode "b" with a radial orientation), and "Cr" (i.e., under the electrode "c" with a radial orientation). In the model, the source "At" electric fields are volume conducted to the electrode "b". The source "ABr" electric fields are volume conducted to the electrodes "a" and "b". The source "Br" electric fields are volume conducted to the electrode "b". The source "Cr" electric fields are volume conducted to the electrode "c". In this model, the electrode "b" records electric fields generated by both the cortical tangential source "At" and the cortical radial sources "ABr" and "Br".

Electric fields generated from a cortical source decay to zero values at 10-12 centimeters of distance (Srinivasan et al., 2007).

THE DRAGOON

- *"Common drive"* and *"Cascade flow" effects* depend on physiological conduction of action potentials through axons from a brain neural mass to two (or more) cortical neural masses as EEG-MEG sources (Blinowska, 2011, Nunez and Srinivasan, 2006)



Legend. Due to the effect of "common drive", a coherent activation of the source "Cr" with the sources "Br" and ABr" may induce an interdependence of the rsEEG rhythms recorded at the electrodes "a" and "c" and those recorded at the electrodes "b" and "a". Such interdependence could be erroneously interpreted as a functional connectivity between the cortical sources "At" and "Cr" and between the cortical sources "Br" and "ABr", underlying those electrodes. A directional connectivity from the source "Cr" to "Br" and from "Br" to "ABr" (see nomenclature in the previous slide) is illustrated to show the difference between "direct" and "indirect" connection pathways. The green arrows indicate the interdependence of scalp EEG activity (not shown) that would correspond to the functional source connectivity, while red arrows indicate the interdependence of scalp EEG activity (not shown) that would not.

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THE CHALLENGES

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- What *Electrode Montage* and *spatial resolution* for EEG-MEG applications in Clinical Neurophysiology rhythms?
- *Sensors* or *sources*? Opportunities and limitation of topographical analysis of rsEEG rhythms at scalp sensors or sources.
- *Linear* or *nonlinear* measurements?
- *Topology* as global configuration of network nodes and their connectivity (e.g., *Graph theory* and beyond)? What dimensions? Controversies, limits, and opportunities.
- *Disease markers and/*or windows on *Human Neurophysiology*? Limits and opportunities.

SIG OBJECTIVES AND THE DRAGOON

- Enlarge the multidisciplinary discussion about the challenges to the study of EEG/MEG brain connectivity to experts of *Brain Biophysics*, *Computational Neuroscience*, *Clinical Neurophysiology*, *Translational Neurophysiology and Pharmacology*, and others.

- Pursue *consensus* about new *methodological standards* and research and clinical opportunities/limits of EEG/MEG brain connectivity.

- Promote *international scientific initiatives* to address main challenges (e.g., Electrode Montage/Spatial Resolution, Sensors vs. Sources, Linear vs. Nonlinear Measurements, Graph theory, clinical validation, etc.).

- Generate *position and white papers* on EEG/MEG brain connectivity and Clinical Neurophysiology.

National Institute of Neurological Disorders and Stroke

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THE SPECIAL INTEREST GROUP

Functional Brain Connectivity as Revealed by EEG/MEG

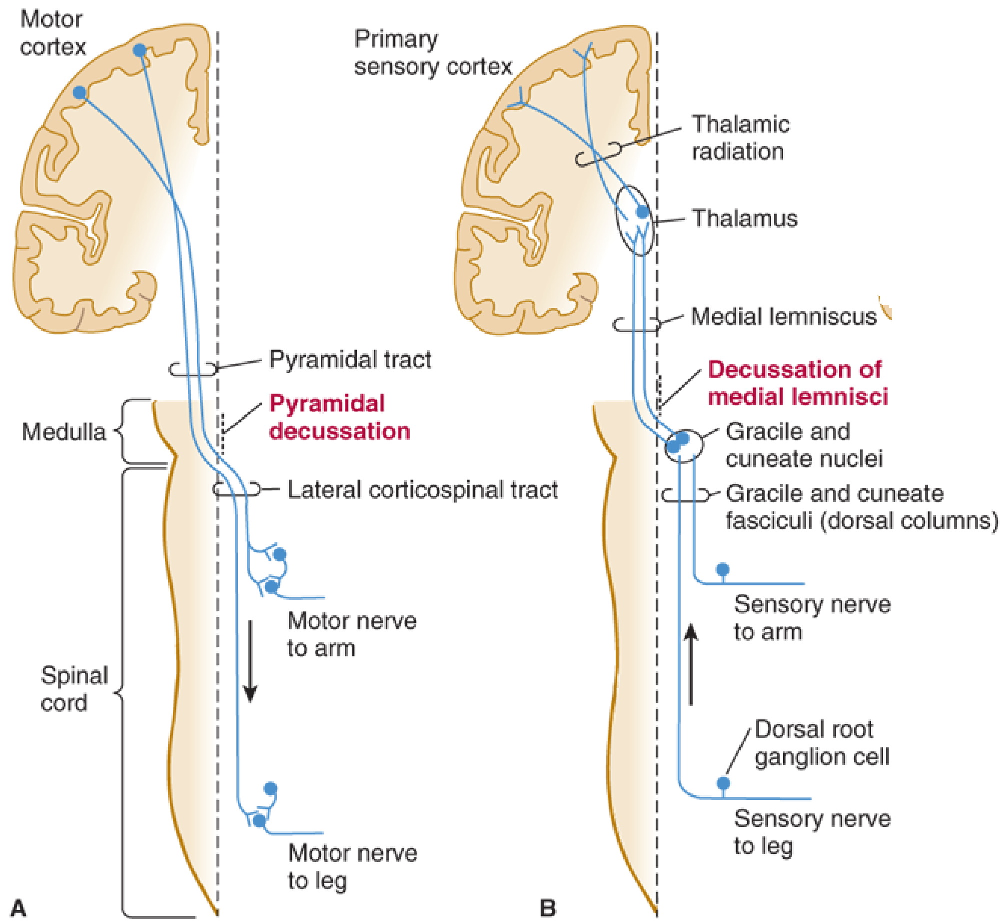
HUMAN FUNCTIONAL CORTICOMUSCULAR CONNECTIVITY IN CLINICAL NEUROPHYSIOLOGY: THE CHALLENGES

Mark Hallett

National Institute of Health, National Institute of Neurological Disorders and Stroke (NINDS), Bethesda, USA

BACKGROUND

- *Corticomuscular functional connectivity* is typically estimated by statistical interdependence (e.g. coherence) between EEG-MEG and EMG signals during isometric muscle contraction (Mima and Hallett, 1999; Schnitzler et al., 2009; Sharifi et al., 2017)
  - EEG-MEG signals reflect oscillatory activity of cortical neural masses
  - EMG signals reflect the enrollment of motorneurons activating skeletal muscle fibers



Source: Aaron L. Berkowitz: Clinical Neurology and Neuroanatomy: A Localization-Based Approach
www.neurology.mhmedical.com

Anatomical substrate of corticomuscular functional connectivity from the coherence between EEG-MEG signals over motor cortex and peripheral EMG signals from operating muscles mainly (but not totally) stems from the corticospinal pathway. A, Motor: the pyramidal pathway through the lateral corticospinal tract. Extrapyramidal pathways through basal ganglia, cerebellum, and motor thalamus may modulate activity in motor and premotor areas. B, Somatosensory: Ascending somatosensory pathways (re-afferent feedback) may contribute to EEG-MEG and EMG coherence as well. These pathways include medial lemniscal system that conducts information about discriminating touch and kinesthesis.

NORMAL CORTICOMUSCULAR CONNECTIVITY

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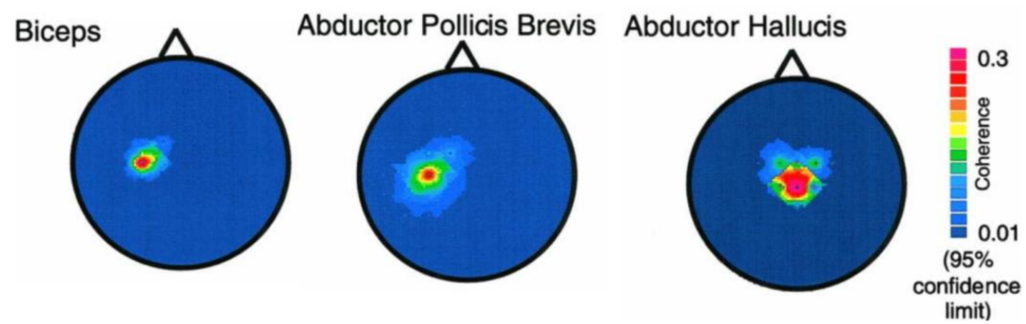
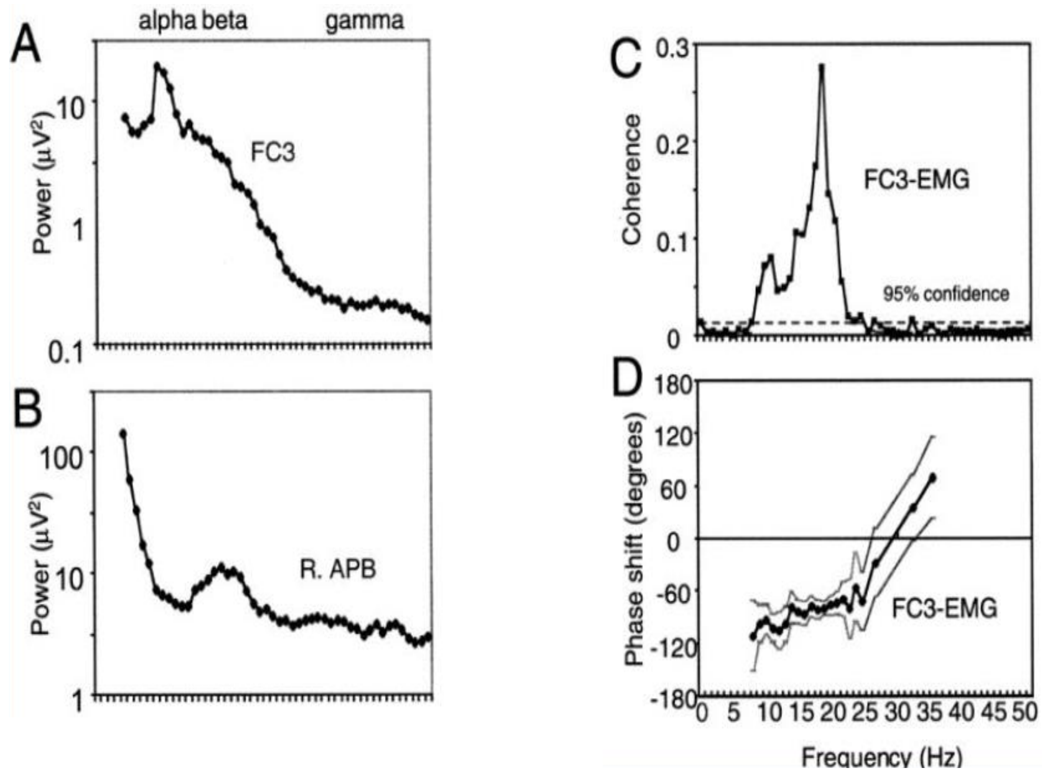
- *Laplacian estimation of source current density* from scalp EEG rhythms localized contralateral primary sensorimotor cortex as source of motor commands for motor neurons activating skeletal muscles during isometric muscle contraction (Mima and Hallett, 1999).
- *Rolandic sources of alpha, beta, and gamma rhythms* (10-50 Hz) were correlated with the force level of isometric muscle contractions in different ways (Mima et al., 1999, 2000).

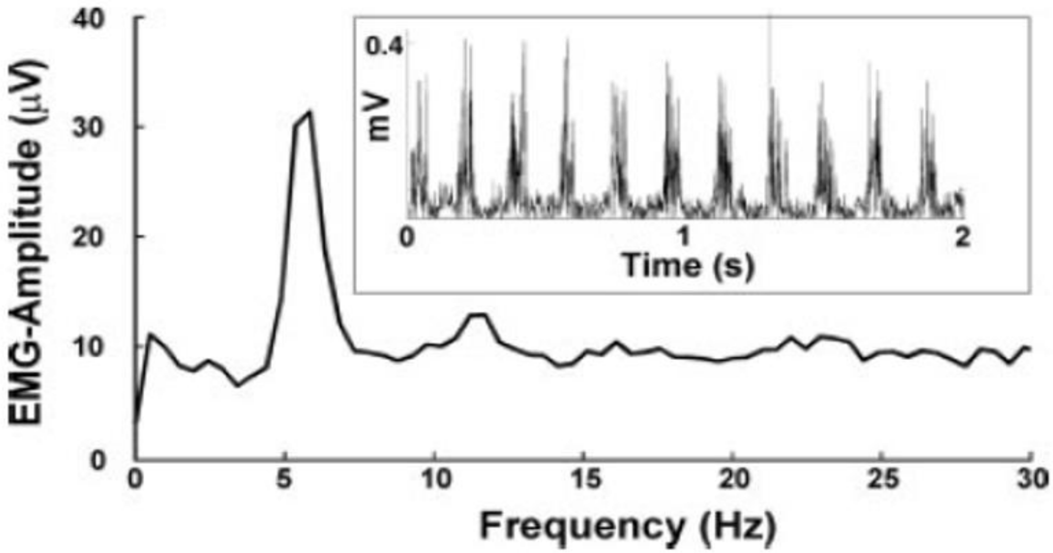


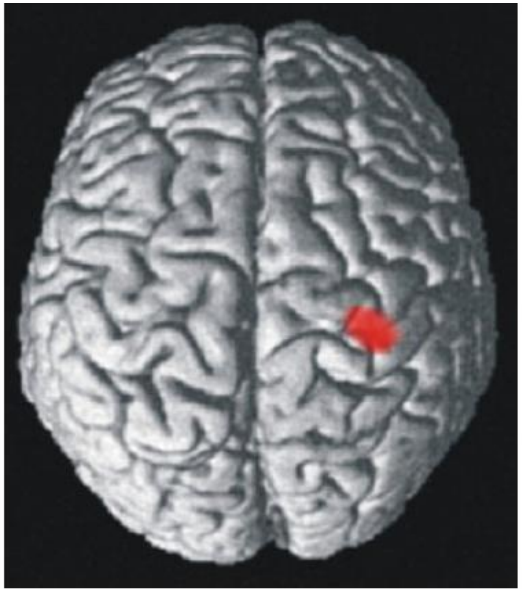


***Upper diagram**. Maps of spectral coherence (14-50 Hz) between Laplacian-transformed EEG rhythms and EMG activity recorded during isometric contractions of right biceps, abductor pollicis brevis (R. APB), and adductor hallucis (motorotopic organization is noted). **Middle and lower diagrams**. Power density spectra of EEG at FC3 scalp electrode (A) and EMG at R. APB contractions (B). Coherence spectra (C) and phase shift of those EEG (FC3)-EMG (R. APB) activities. Positive values of the phase shift suggest a directional information flow from EEG to EMG (e.g. motor command). Further details in Mima and Hallett, 1999.*

CORTICOMUSCULAR CONNECTIVITY AND ESSENTIAL TREMOR

- *Dynamic Imaging of Coherent Sources (DICS)* from MEG data localized brain motor areas showing a coupling of oscillatory activities underpinning the control of isometric muscle contraction in subjects with essential tremor (*Schnitzler et al., 2009*).
- These areas include contralateral primary motor, lateral premotor, and subcortical regions.

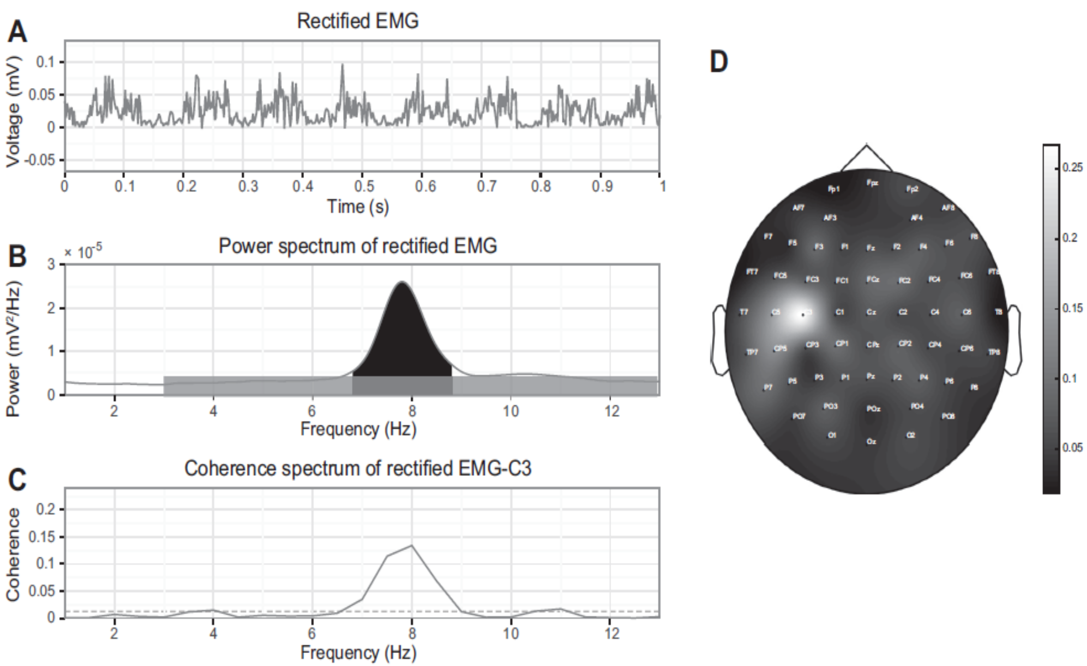


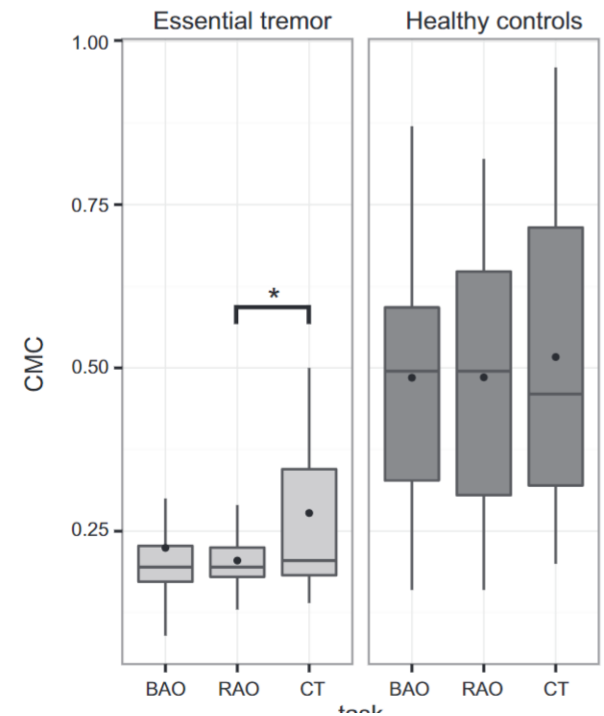


Upper left diagram. *EMG activity recorded during isometric contraction of forearm in a subject with essential tremor (several peaks in the EMG amplitude are noted).* ***Lower left diagram***. *Amplitude spectrum of that EMG activity (an amplitude peak at about 7 Hz is noted).* ***Right diagram.*** *Map of the coherence between cortical sources of MEG activity and EMG signals during that isometric muscle contraction (a significant cortical source in right primary sensorimotor cortex is noted). Further details in Schnitzler et al., 2009.*

CORTICOMUSCULAR CONNECTIVITY AND ESSENTIAL TREMOR

- *Laplacian estimation of source current density* from scalp EEG rhythms disclosed the minor role of contralateral primary sensorimotor cortex on corticomuscular connectivity underpinning essential involuntary tremor compared with voluntary tremor (*Sharifi et al., 2017*).

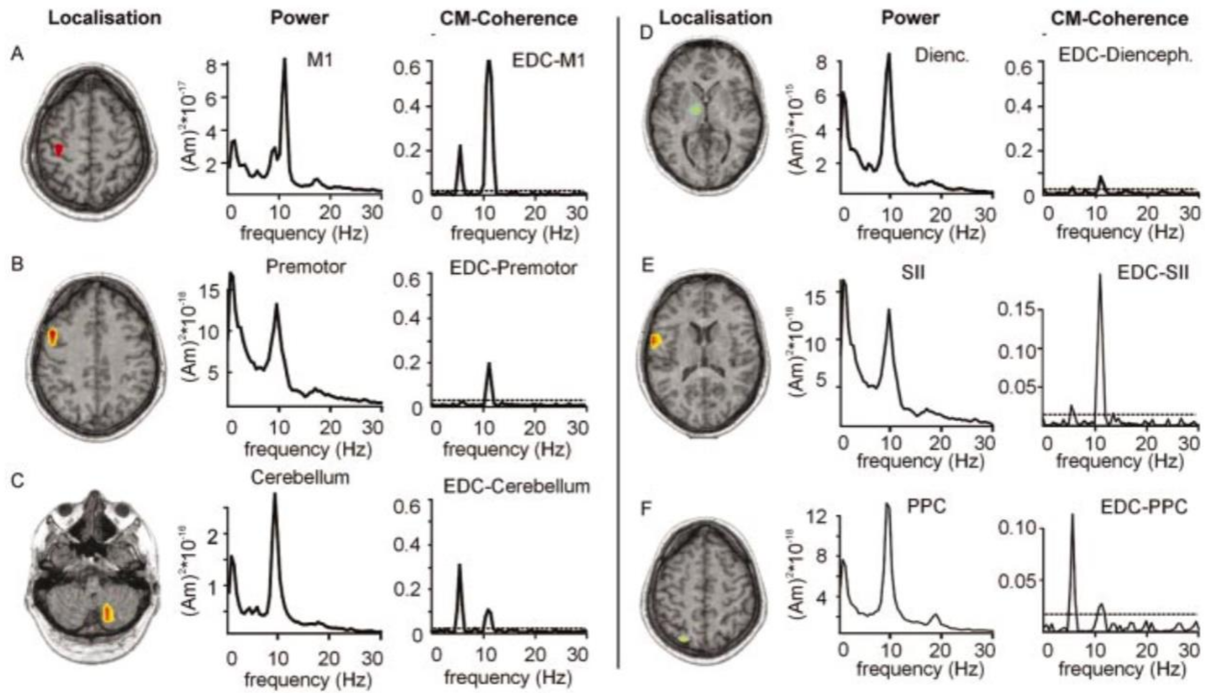




Left diagram. *In a patient with essential tremor, 1-s filtered and rectified EMG (right wrist) revealing the tremor pattern (A), power spectrum of 3 min of rectified EMG (B) and relative coherence spectrum between EEG (C3 electrode) and EMG (C), and map of corticomuscular coherence (CMC) around tremor frequency (6.8–8.8 Hz) by Laplacian derivation (D).* ***Right diagram.*** *Box plot of z-transformed CMC depicting the spread, mean (filled circle), and median (line) in healthy controls (who intentionally mimicked tremor) and patients with involuntary essential tremor during the following tasks: both arms outstretched (BAO), right arm outstretched (RAO), and a cognitive arithmetic task (CT). CMC was greater in controls than patients. Asterisk = statistical difference in the control group between RAO and CT (p<0.05). Further details in Sharifi et al., 2017.*

CORTICOMUSCULAR CONNECTIVITY AND PARKINSONIAN TREMOR

- *Dynamic Imaging of Coherent Sources (DICS)* from MEG data localized brain motor areas showing a coupling of oscillatory activities underpinning the control of isometric muscle contraction in parkinsonian patients with involuntary tremor (*Schnitzler et al., 2003*).
- These areas include contralateral primary motor, lateral premotor, and subcortical regions.



Localization, power spectra and spectra of cerebro-muscular coherence in a Parkinson's disease patient with right hand tremor. Source localization as revealed by DICS showed activity in contralateral M1 (A), PM (B), ipsilateral cerebellum (C), diencephalon (D),SII (E) and PPC (F). Note that the power spectra of all areas show a peak at double tremor frequency. Coherence between cortical and subcortical activity and the right extensor digitorum communis muscle (EDC) exhibits significant peaks at tremor frequency and, in some cases, stronger at double tremor frequency. Further details in Schnitzler et al., 2009.

SIG OBJECTIVES AND CORTICOMUSCULAR CONNECTIVITY

- Why is CMC difficult to record in some cases? What advantages/disadvantages in the use of EEG vs. MEG? What source estimation techniques?
- Rectified vs. unrectified EMG: advantages and disadvantages?
- How to disentangle sensory feedback from motor feedforward in CMC during isometric muscle contraction?
- Why better CMC readouts for postural muscle activity than kinetic movements? How to improve the use of CMC to study complex movements?
- What is the validity of CMC when estimated in subcortical regions in healthy controls and patients with movement disorders?

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Functional Brain Connectivity as Revealed by EEG/MEG

HUMAN FUNCTIONAL CORTICAL CONNECTIVITY FROM EEG-MEG DATA IN CLINICAL NEUROPHYSIOLOGY: THE CHALLENGES

Pedro Valdes Sosa

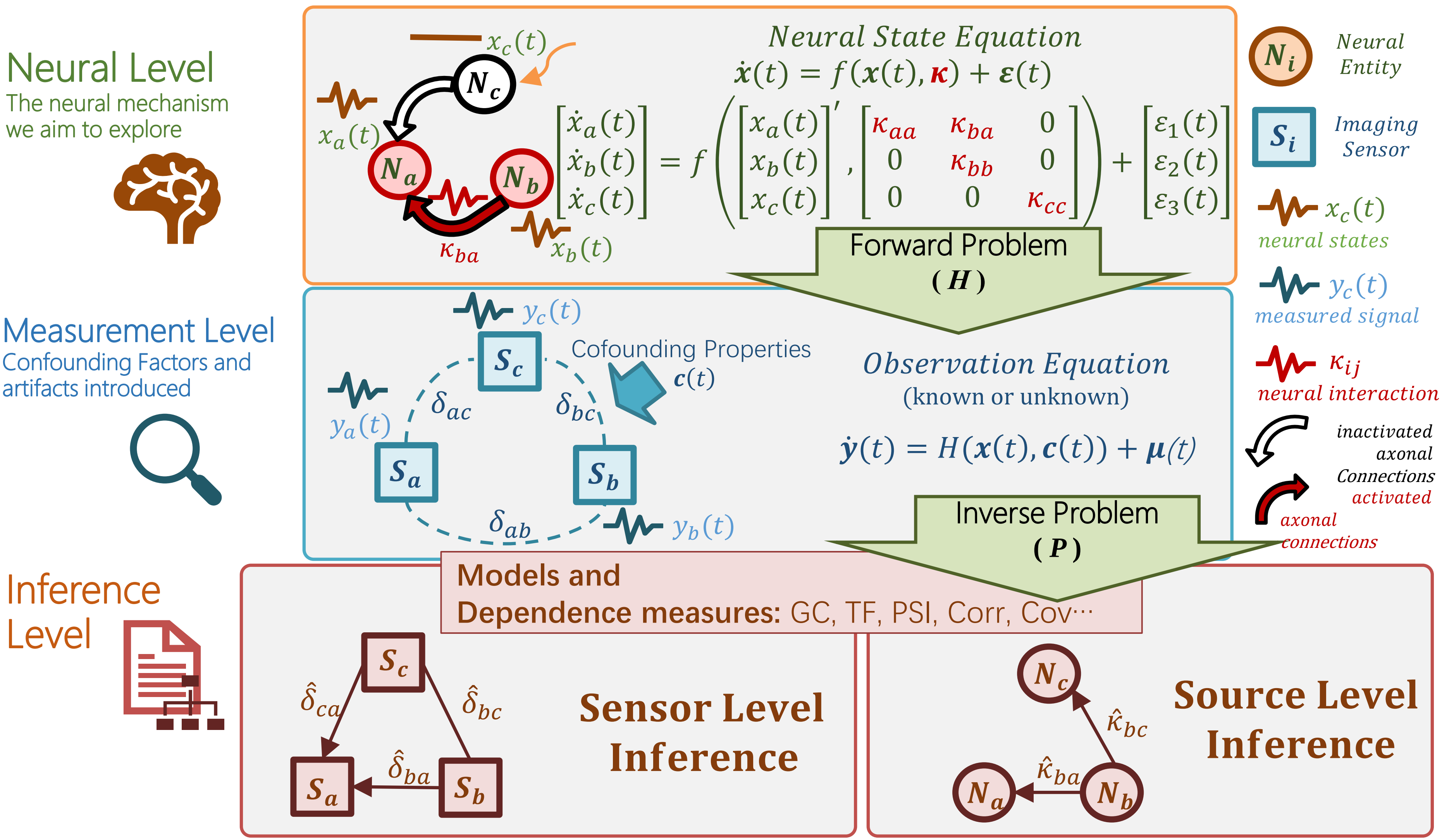
University of Electronic Science and Technology of China, UESTC Chengdu, China;

Cuban Neuroscience Center (CNEURO), Playa. La Habana, Cuba

There are many challenges to move forward in EEG-MEG functional connectivity (FC):

- There is confusion about ontological levels and definitions of functional connectivity.
- There are unsolved EEG-MEG specific biophysical challenges.
- There are challenges common to all causal inference.
- There is a lack of gold standards as reference true FC solutions in humans.

There is confusion about ontological levels and definitions of functional connectivity (FC). The real goal is NEURAL CONNECTIVITY (NC)



Dependency (δ) is not connectivity (κ)! Both are misleadingly called FC

Solution: define ontology with glossary. Ban term FC!

There are unsolved EEG-MEG specific Biophysical challenges

- How to eliminate the effects of volume conduction, common drive, and Cascade flow to estimate reliable NC?
- Sensor level dependency measures of EEG-MEG activity are not, in general, valid to infer underlying NC.
- Source connectivity estimation methods have several problems:
  - “leakage”, misspecification of NC.
  - Silent sources due to dendritic or neural spatial configuration at “close loop”.
  - Deep sources difficult to detect.
- No standard methods for quantifying NC estimation accuracy from real data.

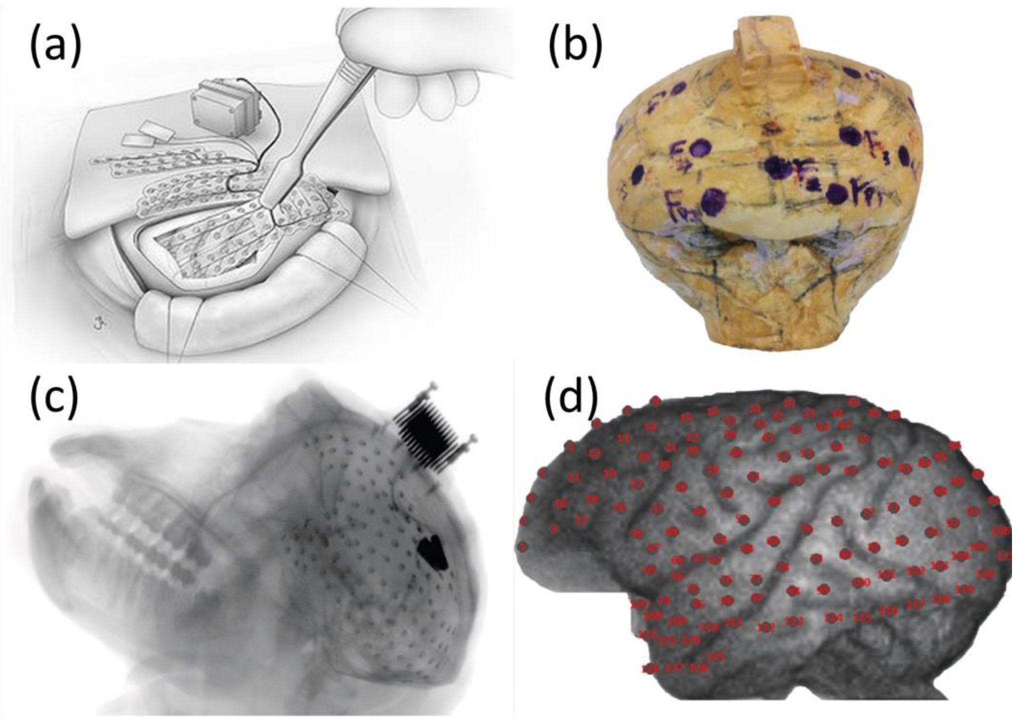
Solution: improve estimation methods for modelling source connectivity as a measure of NC.

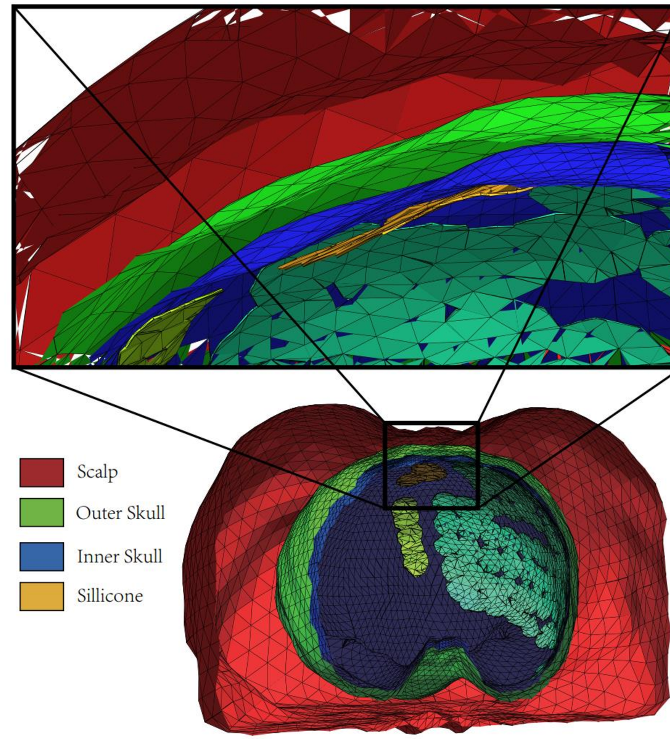
CORTICAL FUNCTIONAL CONNECTIVITY

- There are challenges common to all causal inference methods.
- Probabilistic dependency is not causal relation.
- Common drivers and other confounders are important factors to be taken into account.

Solution: Better causal inference methods and improved prior information

There is a lack of gold standards
Which might be possible with animal experiments





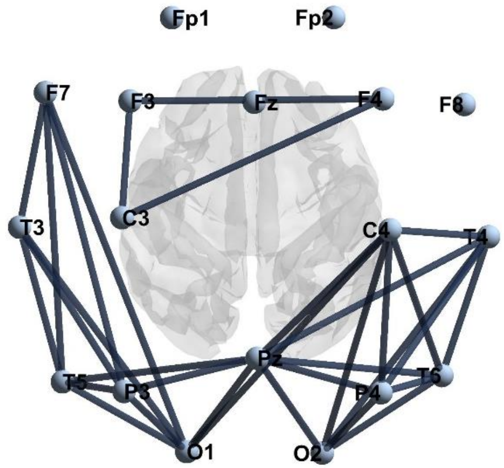
Macaque Simultaneous EEG/ECoG
www.neurotycho.org

A detailed forward head model was constructed

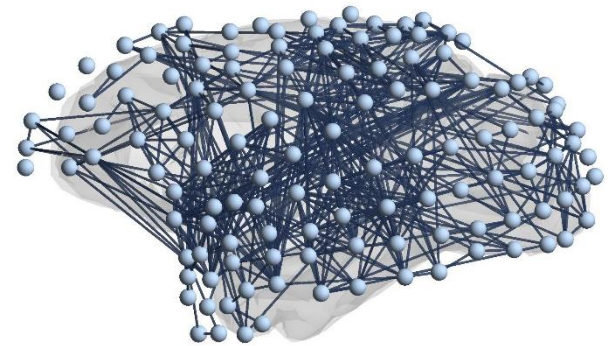
Preliminary results rule out simplistic conclusions. More data (and from human necessary)

$\hat{\delta}_{bc}$

Sensor level



EEG

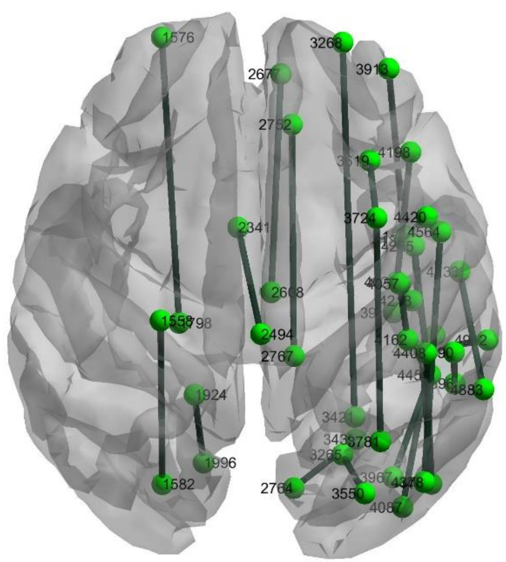


ECoG

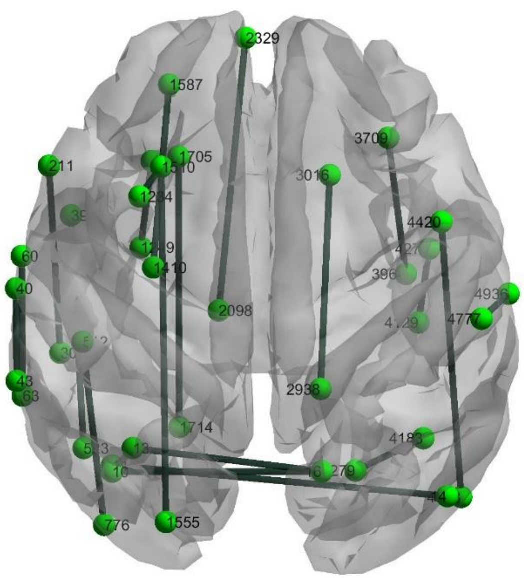
$\hat{\kappa}_{ba}$

Source level

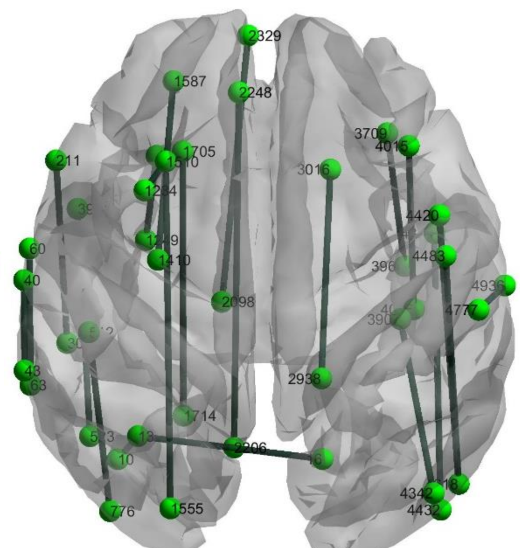
e-LORETA



From EEG



From ECoG



From ECoG+EEG

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Functional Brain Connectivity as Revealed by EEG/MEG

FUNCTIONAL SUBCORTICAL CONNECTIVITY IN ANIMAL MODELS FOR BACK-TRANSLATION: THE CHALLENGES

Mihály Hajós

Translational Neuropharmacology, Yale University School of Medicine, USA

Biomarkers CoE, Biogen, Cambridge, USA

Yale University
School of Medicine

ADVANCES IN ANIMAL MODELS

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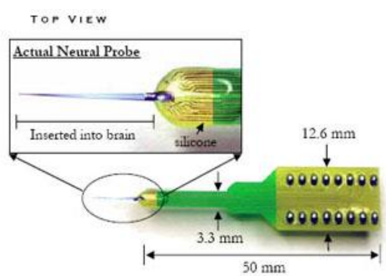
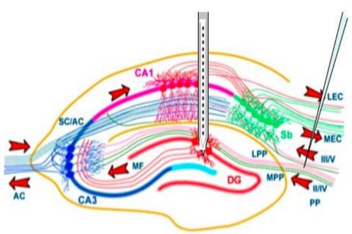
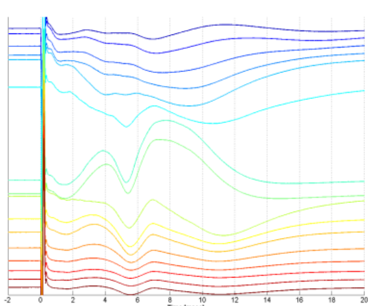
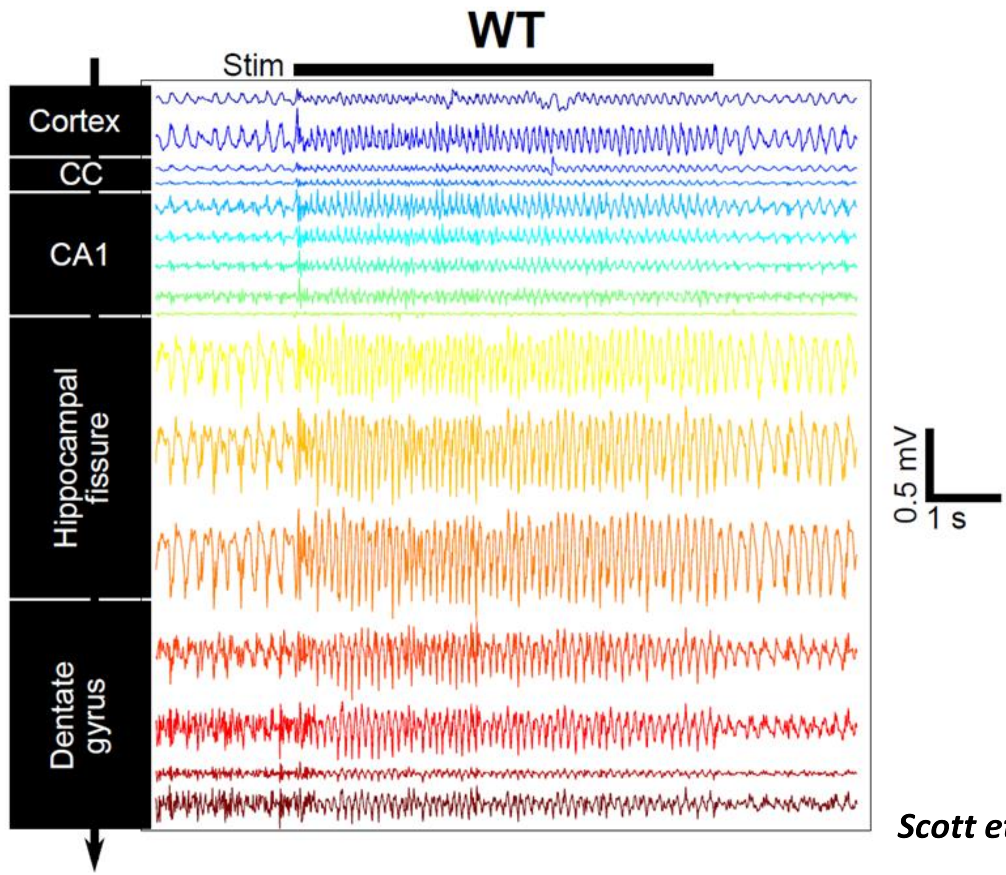
- **Methodological opportunities**:
  - ➢ Multiple, simultaneous cortical and subcortical recordings, including field, population spike, single/multi unit
- **Scientific opportunities:**
  - ➢ Addressing scientific questions, using genetic and pharmacological interventions









Scott et al., 2017

ANIMAL MODELS: TESTING CONNECTIVITY

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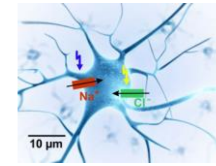
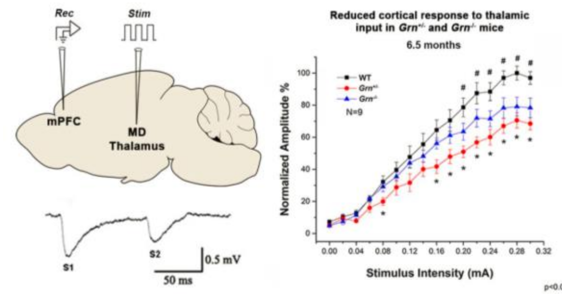
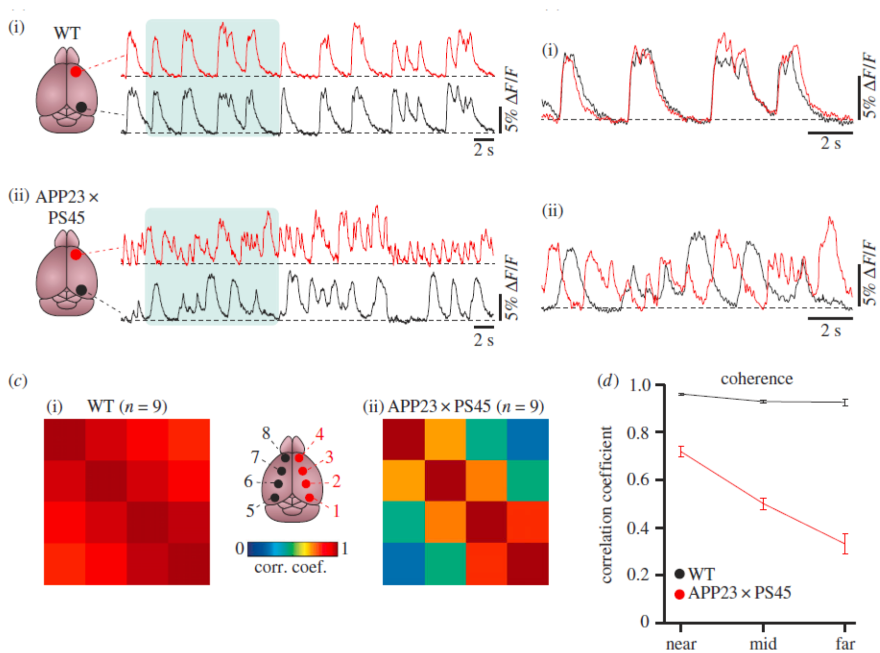
- Proving connectivity
  - ➢ Electric or optogenetic stimulation of pathways
  - ➢ Analysis of evoked responses
  - ➢ Orthodromic stimulation
- Simultaneous field recordings
  - ➢ Physiological or pathological correlations



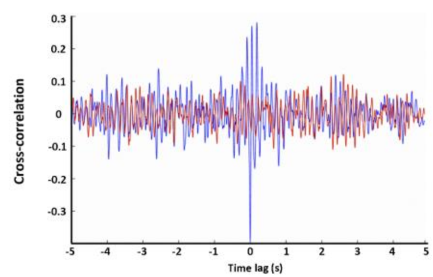


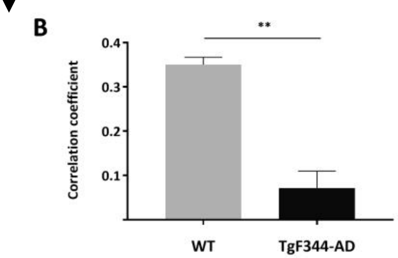
(Nagy et al., 2018)



Cortical coherence, *(Busche & Konnerth, 2016)*

Cross-correlation of cortical SWRs and hippocampal HVSs, ***(Stoiljkovic et al., 2018)***





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ANIMAL MODELS: GRANGER CAUSALITY

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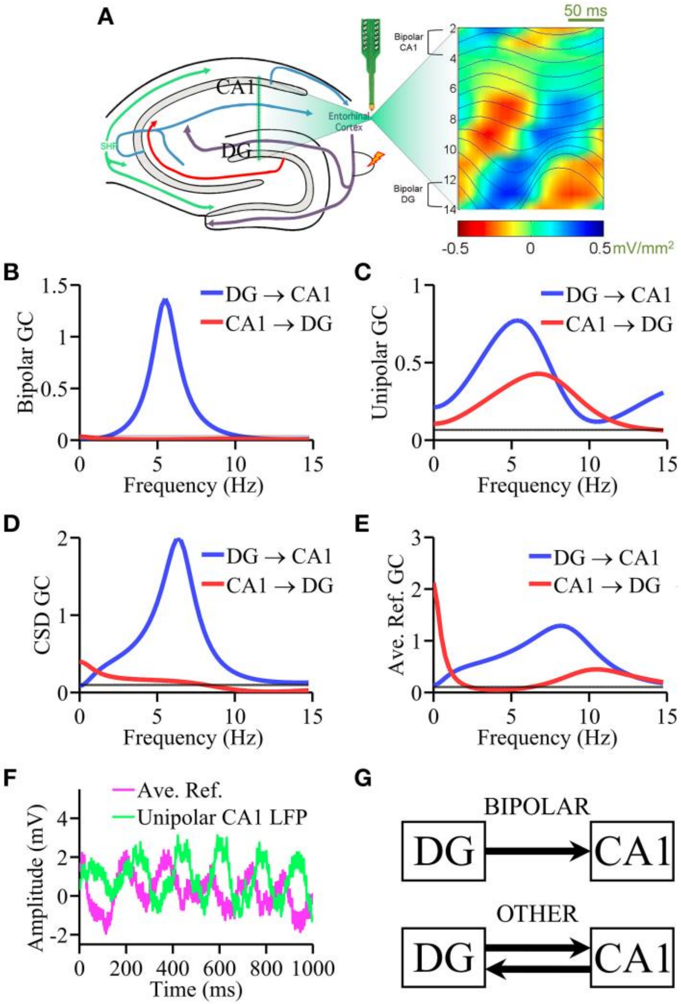
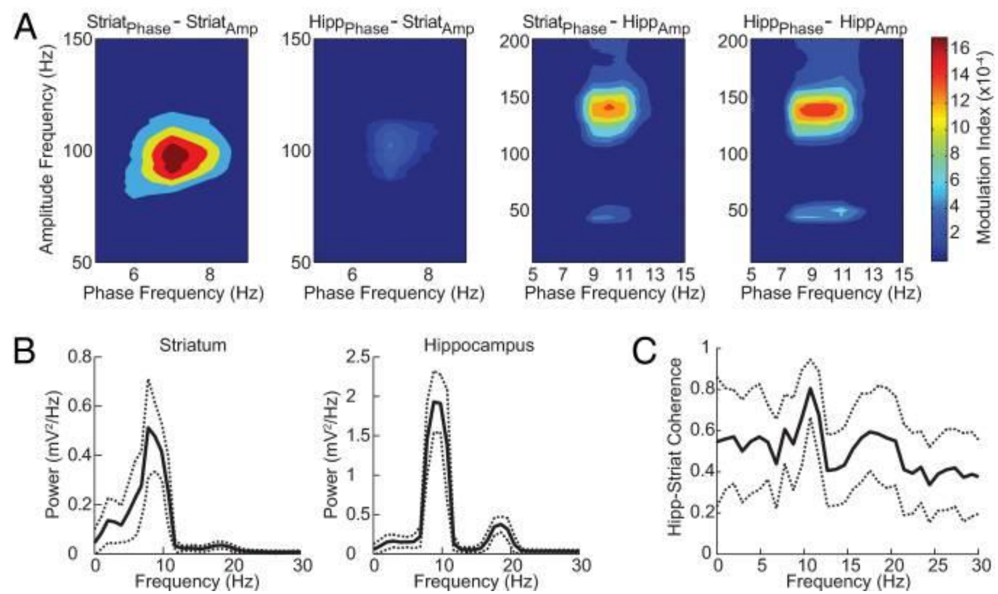
Bipolar Derivations



Trongnetrpunya et al., 2016

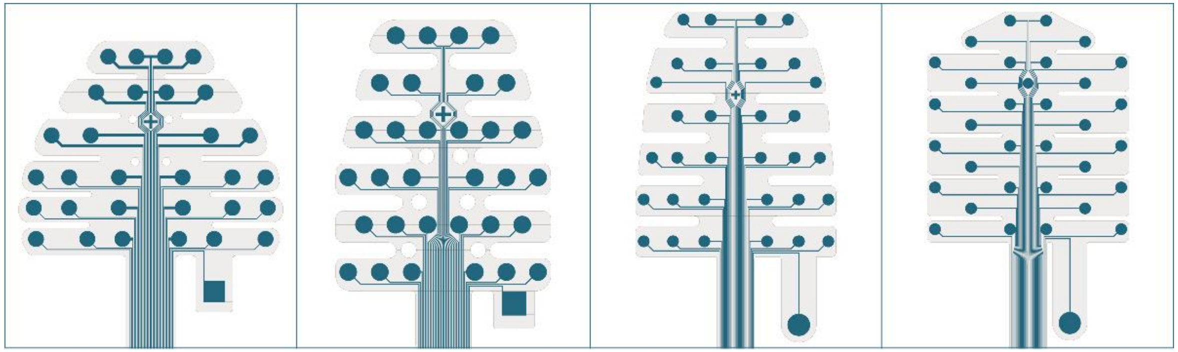
Phase-amplitude couplings between striatal and hippocampal oscillations



Tort et al., 2008

PRAGMATIC CHALLENGES AND SCIENTIFIC OPPORTUNITIES

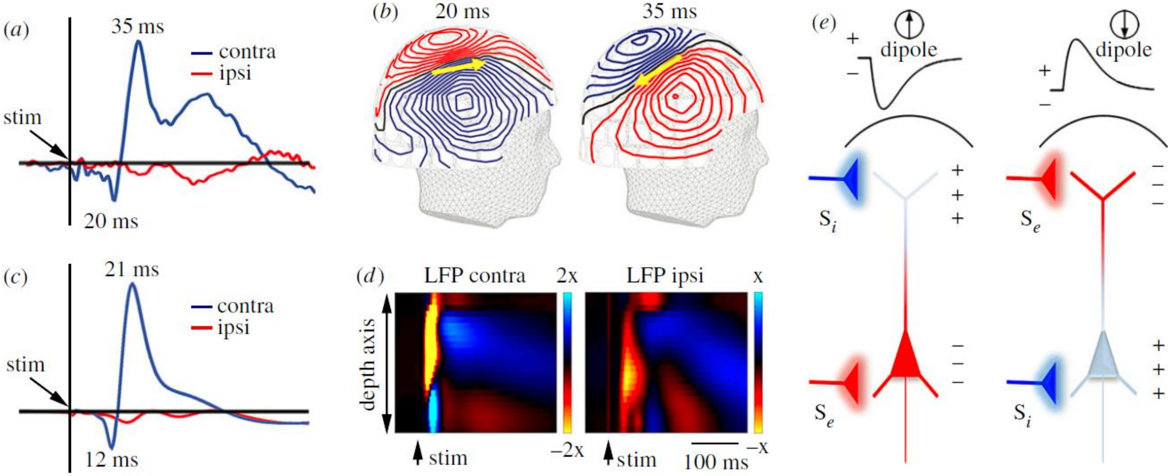
Rodent EEG or ECoG or LFP ?



Novel NeuroNexus probes

Combining LFP, CSD, anatomy, for developing cell-type specific non-invasive human imaging

Uhlirova H et al. Phil. Trans. R. Soc. 2016.



CHALLENGES AND OPPORTUNITIES

- What are the analogue oscillators in humans and rodent?
- Nomenclature of traditional EEG signals (e.g. theta in rodents and humans) corresponding ERP values (P50/N100)
- Disease markers in transgenic animals – back translation of pathophysiological endophenotypes
- Linear or nonlinear signals processing
- Application of computational neuroscience

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Functional Brain Connectivity as Revealed by EEG/MEG

GENERAL DISCUSSION

All SIG Members

Washington Marriott Wardman Park Hotel, Washington, USA
May 4th, 2018 at 12:00 - 1:00

EBERHARD KARLS UNIVERSITÄT TÜBINGEN

International Federation of Clinical Neurophysiology

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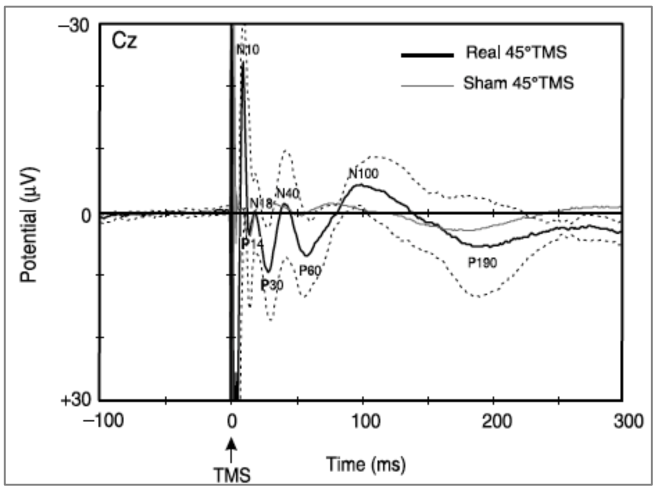
Functional Brain Connectivity as Revealed by EEG/MEG

EFFECTIVE CONNECTIVITY AS REVEALED BY TMS-EVOKED EEG POTENTIALS

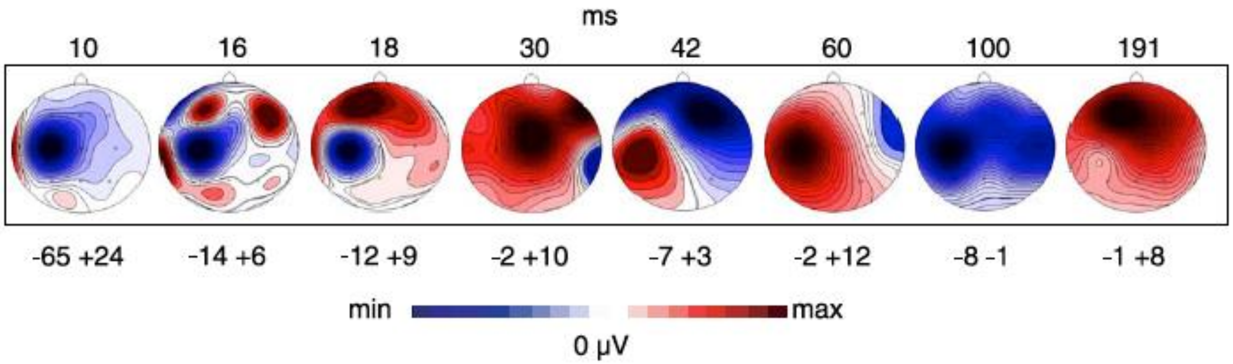
Ulf Ziemann

Department of Neurology & Stroke, and Hertie-Institute for Clinical Brain Research, University of Tübingen, Germany

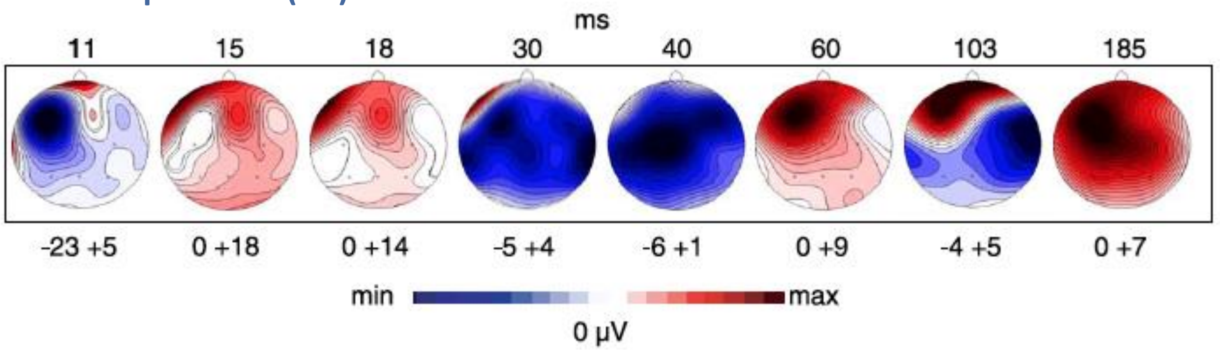
TMS-EEG: Introduction



Posterior-anterior (PA) direction of induced current in motor cortex



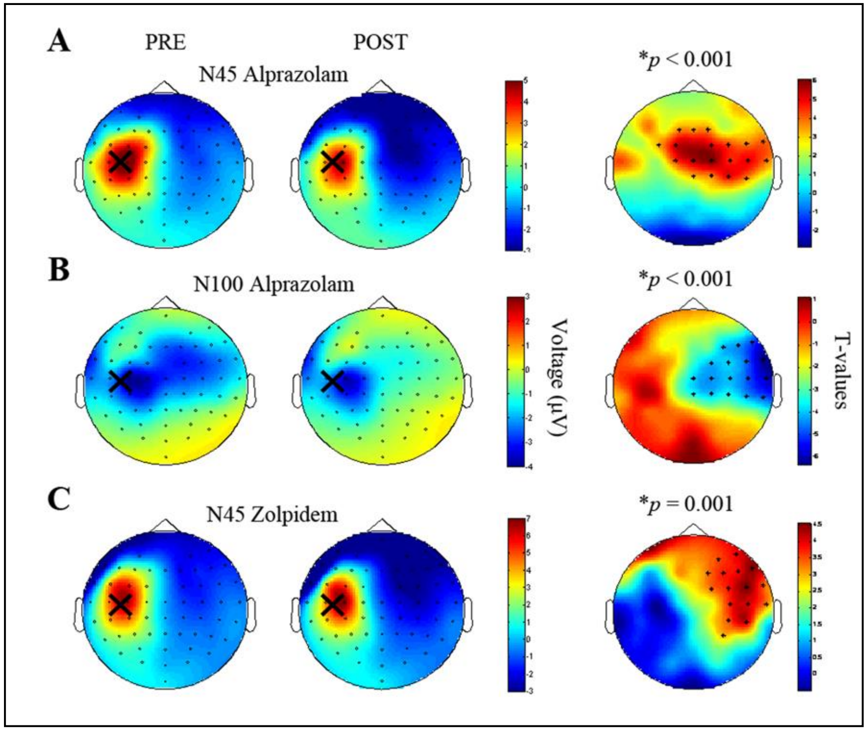
Anterior-posterior (AP) direction of induced current in motor cortex



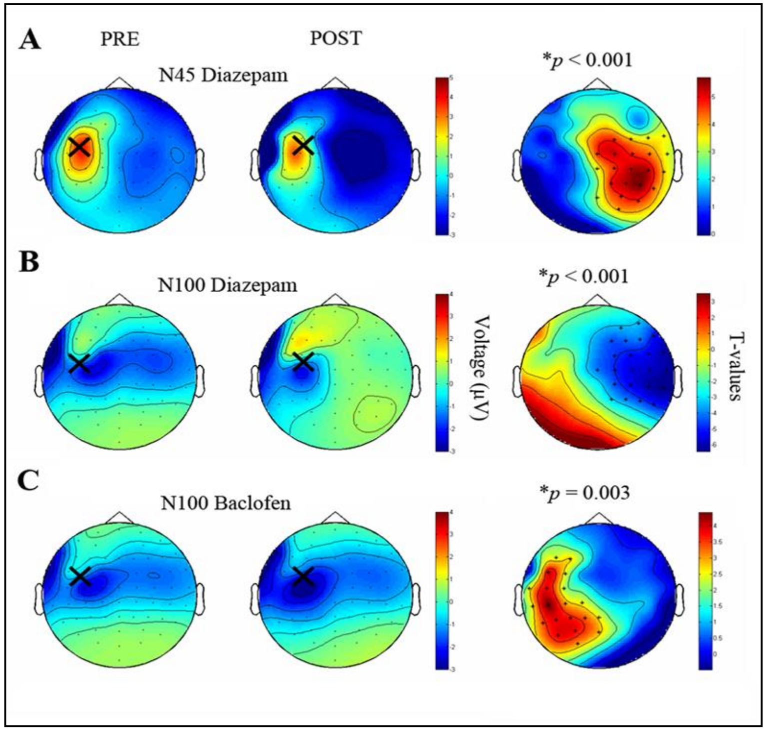
Bonato et al. (2006) Clin Neurophysiol 117:1699-1707

Pharmaco-TMS-EEG: Drug effects on TEPs

EXP1: Topoplots of N45/N100 changes



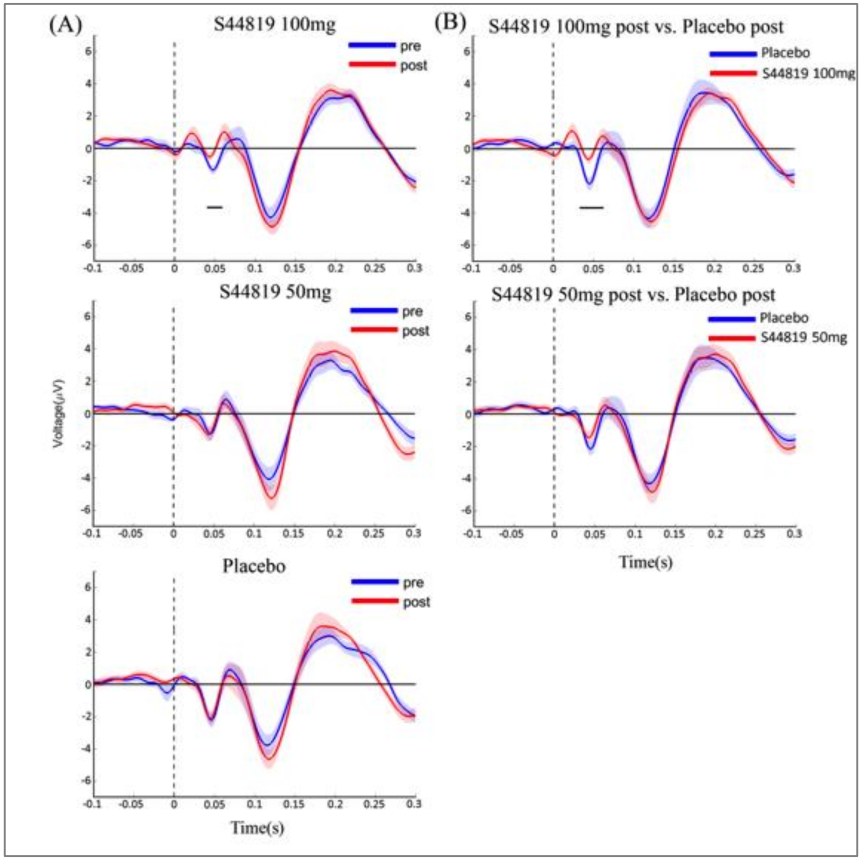
EXP2: Topoplots of N45/N100 changes

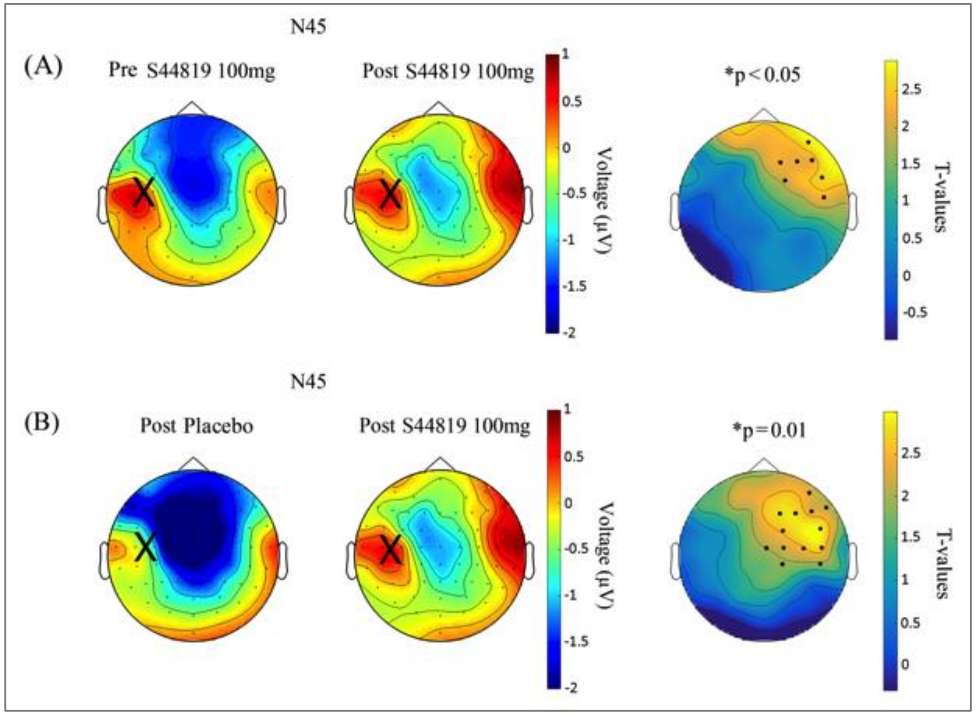


Premoli et al. (2014) J Neurosci 34, 5603–5612

EFFECTIVE CONNECTIVITY AND TMS-EEG

Pharmaco-TMS-EEG: Drug effects on TEPs





Darmani et al. (2016) J Neurosci 36:12312-20

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Functional Brain Connectivity as Revealed by EEG/MEG

HUMAN FUNCTIONAL CORTICO-SUBCORTICAL CONNECTIVITY IN BASAL GANGLIA DISORDERS

Alfons Schnitzler

Department of Neurology, Center for Movement Disorders and Neuromodulation, University Düsseldorf Heinrich-Heine, Germany

CORTICO-SUBCORTICAL CONNECTIVITY IN BASAL GANGLIA DISORDERS

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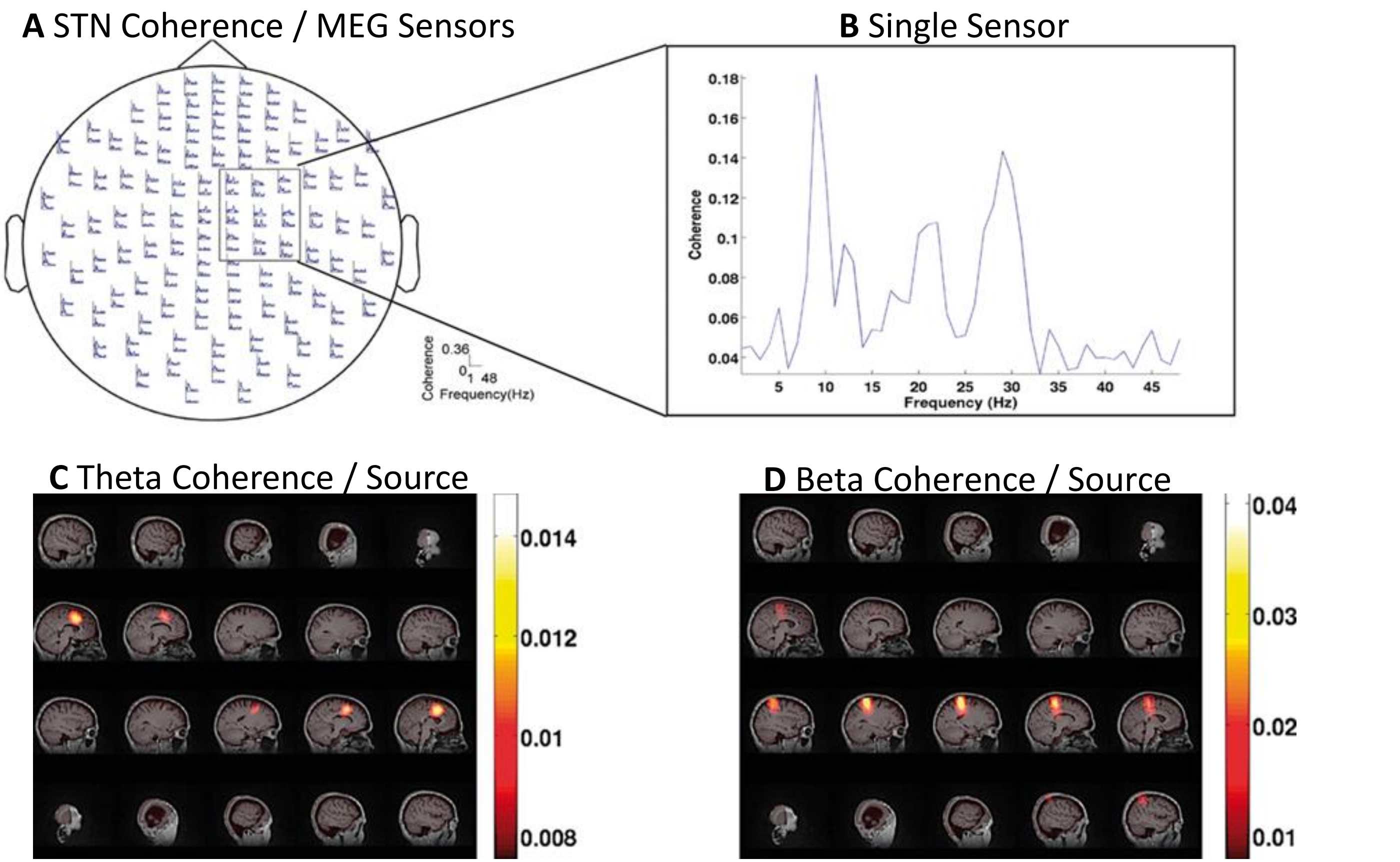
HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

- *Combined LFP-MEG recording in patients undergoing deep brain surgery: a promising approach to study **frequency-specific functional connectivity** between distinct basal ganglia targets (e.g. STN subterritories) and cortical/cerebellar regions.*



Coherence of local field potentials from the subthalamic nucleus with MEG. Shown here analysis from right electrode, bipolar reference from contacts 0 versus 1 (LFP R01) ***(A) Sensor plot*** *with spectogram of each MEG channel; x-axis = coherence; y-axis = frequency;* ***(B) Scaled-up diagram of central single sensor*** *ipsilateral to STN electrode; (C and D) STN-coherent sources on sagittal MRI. Colour scale = coherence.* ***(C) STN-coherent theta source****; (****D) STN-coherent beta source****. Beta is coherent to sensorimotor cortices, whereas theta-coupling is evident to the anterior cingulate cortex. Further details in Wojtecki, Hirschmann, Elben, Boschheidgen, Trenado, Vesper, Schnitzler. Oscillatory coupling of the subthalamic nucleus in obsessive compulsive disorder. Brain 2017.*

CORTICO-SUBCORTICAL CONNECTIVITY IN BASAL GANGLIA DISORDERS

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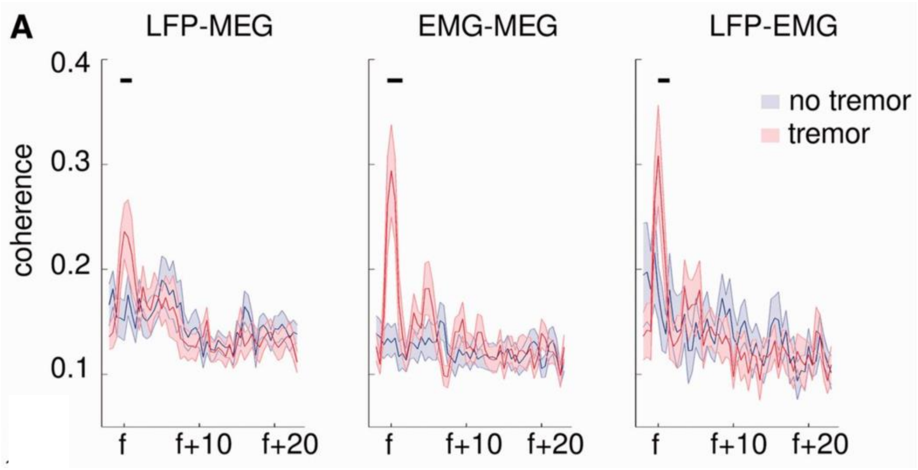
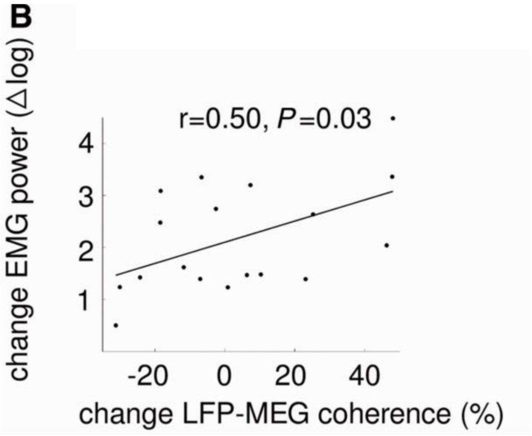
- *Combined LFP-MEG recording in patients undergoing deep brain surgery: a promising approach to study **symptom-related functional connectivity** between distinct basal ganglia targets (e.g. STN) and cortical/cerebellar regions.*





***Subthalamic nucleus, cortical motor areas and muscle synchronized during tremor**. **(A)** Plots show mean LFP-MEG, EMG-MEG and LFP-EMG coherence in the presence (red) and absence of tremor (blue). Spectra were aligned to individual tremor frequency (f) before averaging. Coherence with MEG was averaged over the sensors of interest. Black, horizontal bars indicate significant differences ($P < 0.05$; $n = 18$). Shaded areas indicate standard error of the mean. **(B)** Changes in LFP-MEG coherence are plotted against changes in EMG power. The line indicates the best linear fit. Values were averaged over the tremor frequency and its first harmonic. Further details in: Hirschmann, Hartmann, Butz, Hoogenboom, Özkurt, Elben, Vesper, Wojtecki, Schnitzler . A direct relationship between oscillatory subthalamic nucleus–cortex coupling and rest tremor in Parkinson’s disease. Brain 2013.*

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Functional Brain Connectivity as Revealed by EEG/MEG

COMPARING EEG SOURCE ACTIVITY AND CONNECTIVITY IN THE NEUROPHYSIOLOGICAL MODELS OF DEMENTIAS

Claudio Babiloni

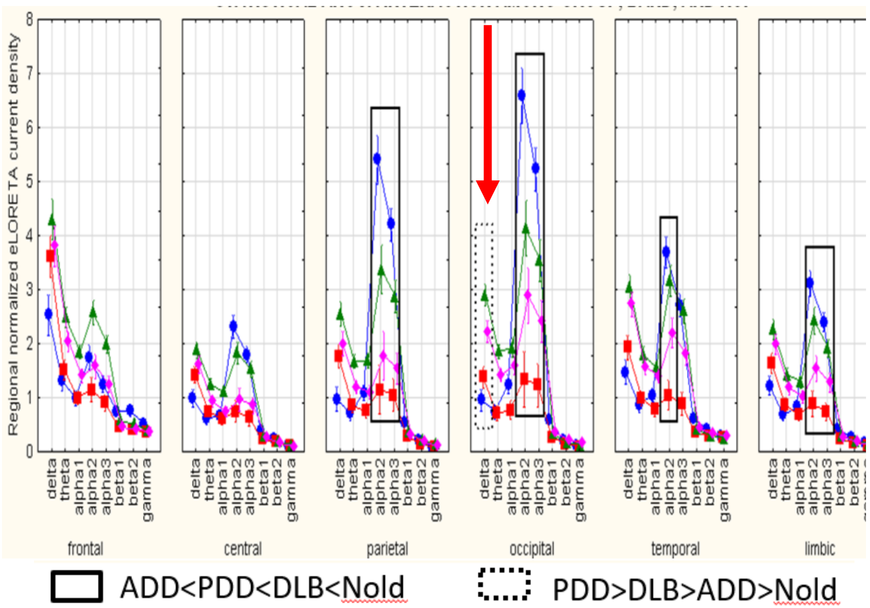
Department of Physiology and Pharmacology "V. Erspamer", Sapienza University of Rome, Italy

COMPARING EEG SOURCE ACTIVITY AND CONNECTIVITY

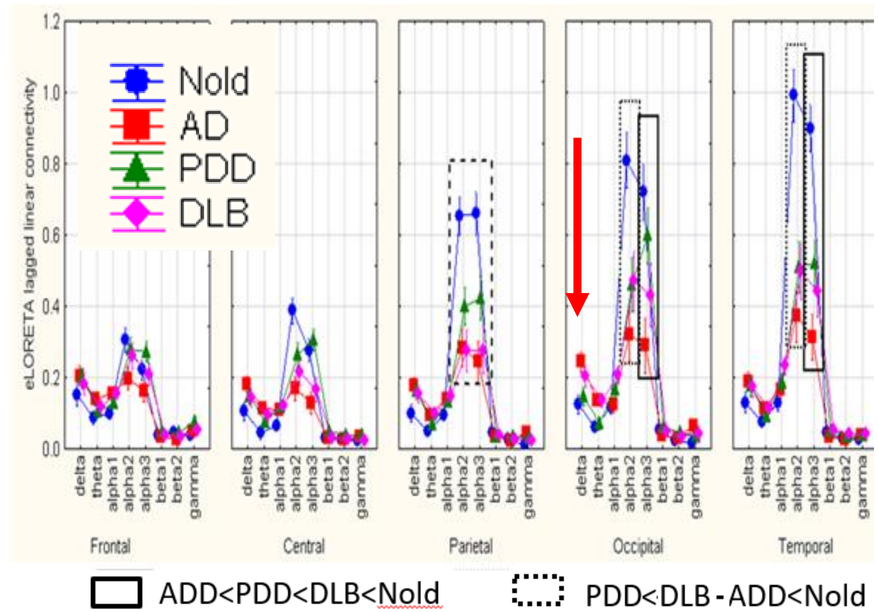
SAPIENZA UNIVERSITÀ DI ROMA

International Federation of Clinical Neurophysiology

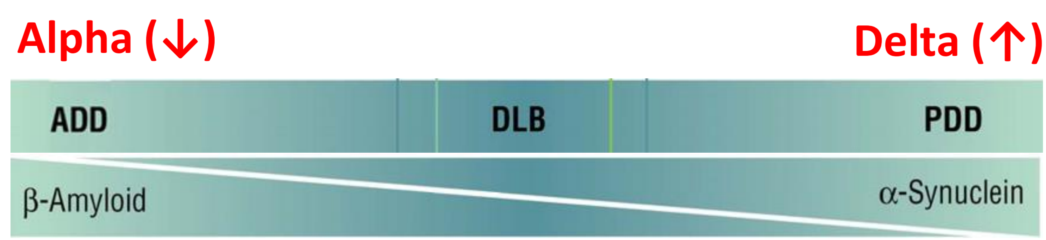
(eLORETA) source activity differs among groups in both delta and alpha rhythms



Intrahemispherical source connectivity differs among groups only in alpha rhythms



Of note, abnormal posterior delta source activity but not connectivity is greater in Parkinson disease dementia (PDD) than Alzheimer's disease dementia (ADD) while Lewy body dementia (LBD) is halfway



Babiloni et al., 2017 Neurobiol Aging,

Babiloni et al., 2018 Neurobiol Aging.

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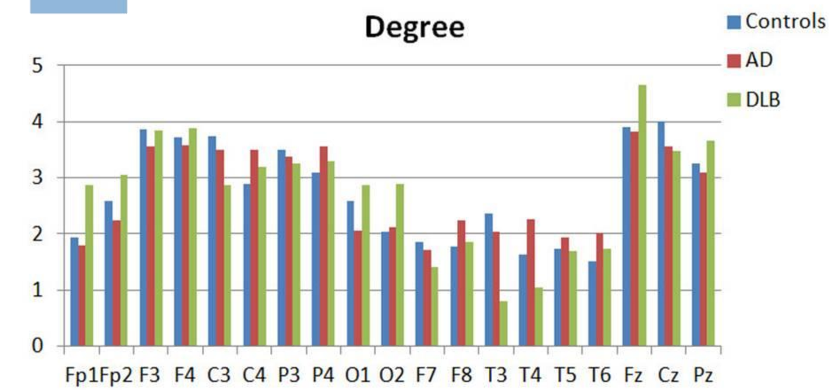
DYNAMIC GRAPH THEORY ANALYSIS IN PATIENTS WITH DEMENTIA WITH LEWY BODIES AND ALZHEIMER'S DISEASE

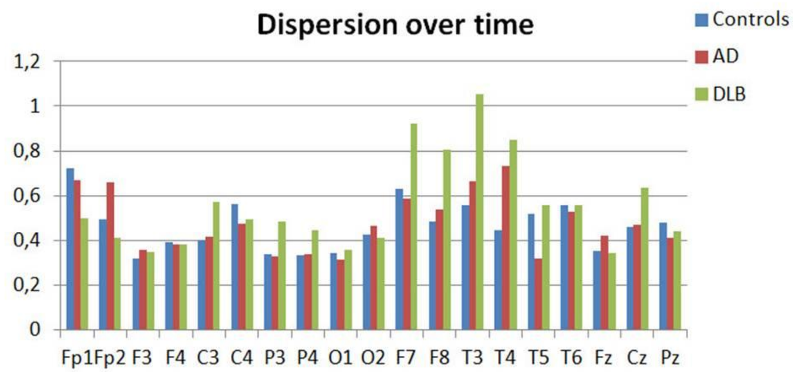
Raffaella Franciotti and Laura Bonanni

University of Chieti "D'Annunzio",
Chieti, Italy

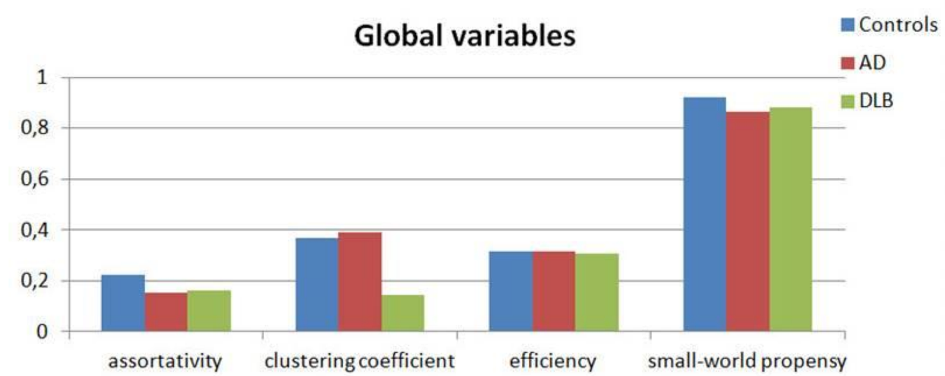
DYNAMIC GRAPH THEORY ANALYSIS

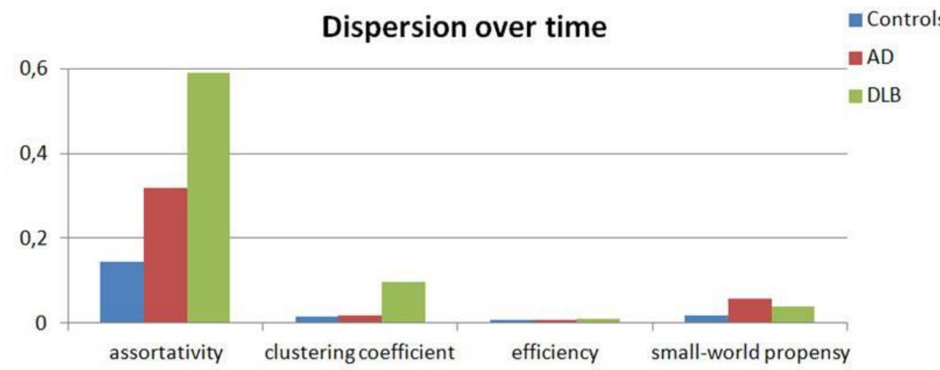
International Federation of Clinical Neurophysiology





Number of links (degree) of each node and their variation over time for control, Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) groups.





Global variables and their variation over time for control, AD and DLB groups.

The number of connections between nodes (degree), measure of segregation (clustering coefficient) and resilience (assortativity) had larger variations over time in DLB patients than in control and in AD group.
Possible link with fluctuationg cognition in DLB.

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Functional Brain Connectivity as Revealed by EEG/MEG

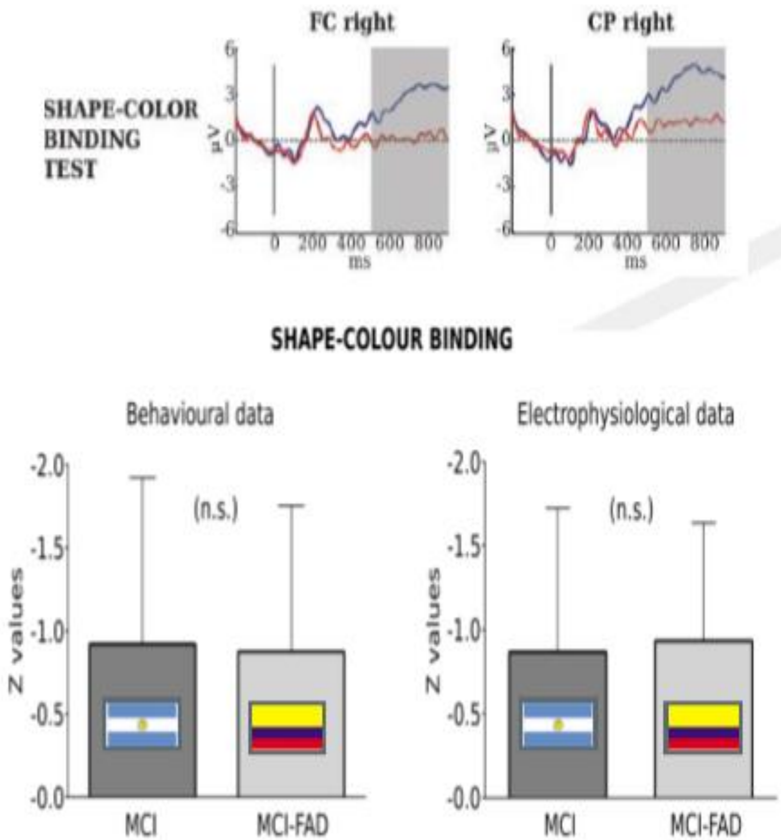
EEG SOURCE CONNECTIVITY IN ALZHEIMER'S DISEASE

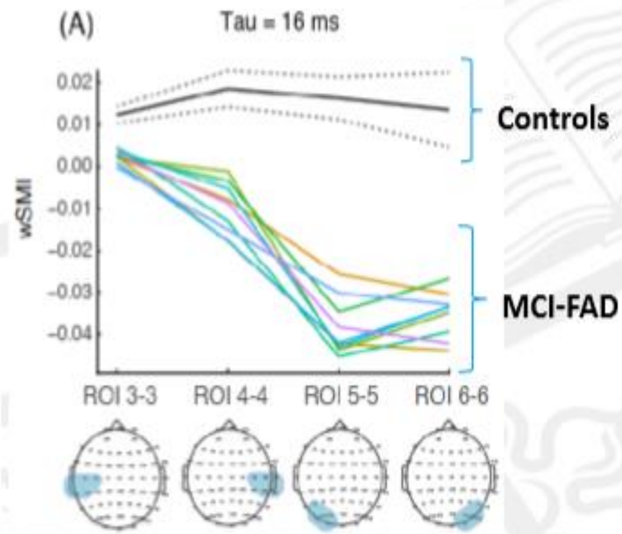
Mario Parra Rodriguez

Heriot-Watt University,

Edinburgh, UK

EEG-based markers for assessment of AD





Pietto et al., 2016

Parra et al., 2017

STM Binding impairments in the prodromal stages (MCI) of familial and sporadic AD are indistinguishable both behaviourally and electrophysiologically.

Brain connectivity analysis (wSMI) yielded 100% accuracy detecting AD risk.

Remark

Combining behavioural and EEG data recorded during performance on cognitive markers can yield affordable biomarkers for AD.

LEADERS IN IDEAS AND SOLUTIONS

HERIOT WATT UNIVERSITY NEUROPHYSIOLOGY LAB

https://www.neurophysiologylab.hw.ac.uk/

UNIVERSIDAD COMPLUTENSE MADRID

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Functional Brain Connectivity as Revealed by EEG/MEG

WHOLE-BRAIN MEG CONNECTIVITY IN DEMENTIA

Ricardo Bruña

Complutense University of Madrid,
Madrid, Spain

WHOLE BRAIN CONNECTIVITY

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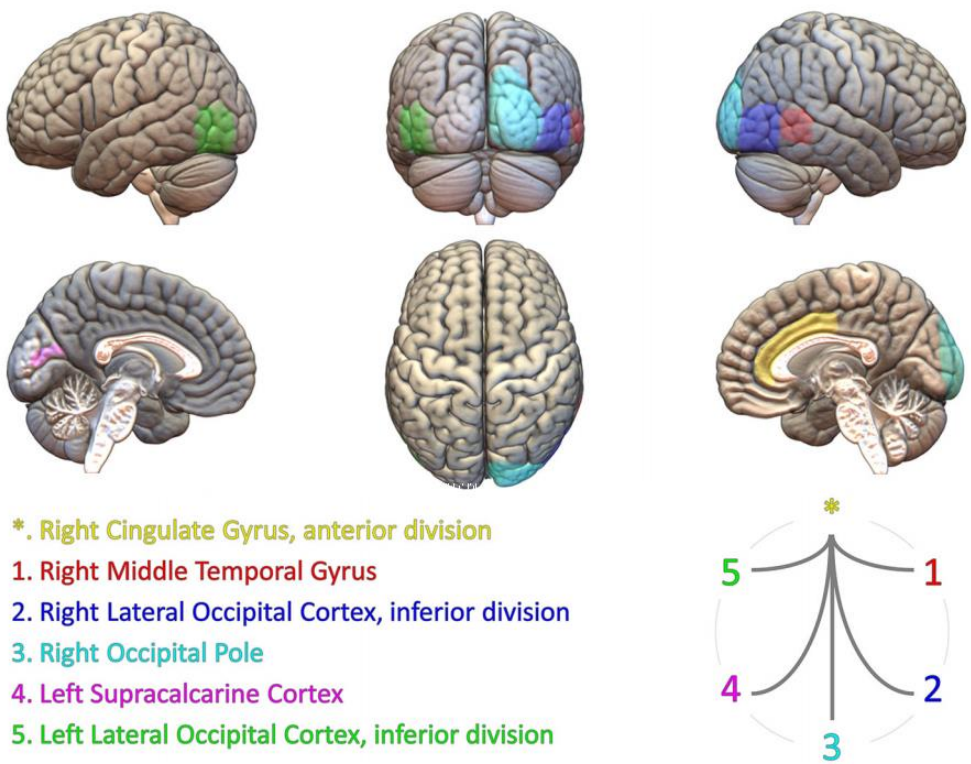
- *EEG/MEG whole-brain connectivity* have proven useful to tell apart prodromical stages of dementia (López et al. 2014, López-Sanz et al. 2017, Nakamura et al. 2018)
- Source space must be parcellated in ~70 areas
- Connectivity metrics must be fast enough

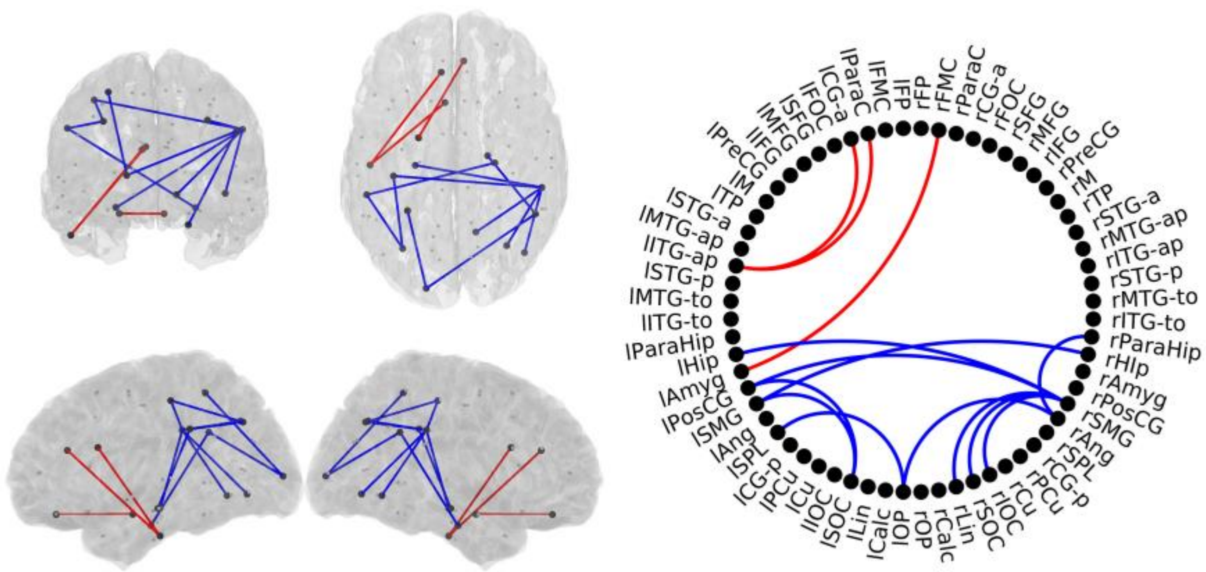


Differences between progresive and not progressive MCI patients 6 months to 2 years before progression in alpha band (PLV)

WHOLE BRAIN CONNECTIVITY

Open questions:

- Anatomical or functional atlas? Population or subject-dependent?
- How to better combine EEG and MEG?
- How to combine the different sources in each ROI?
- What is the best source reconstruction method (MNE, beamformer, LORETA)?



Differences between healthy controls and
subjective cognitive decline elders in alpha band (PLV)

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Functional Brain Connectivity as Revealed by EEG/MEG

HYPER- AND HYPO-SYNCHRONIZATION OF MEG ACTIVITY IN CORRELATION WITH CSF PHOSPHO-TAU BIOMARKER IN ALZHEIMER'S DISEASE

Fernando Maestu

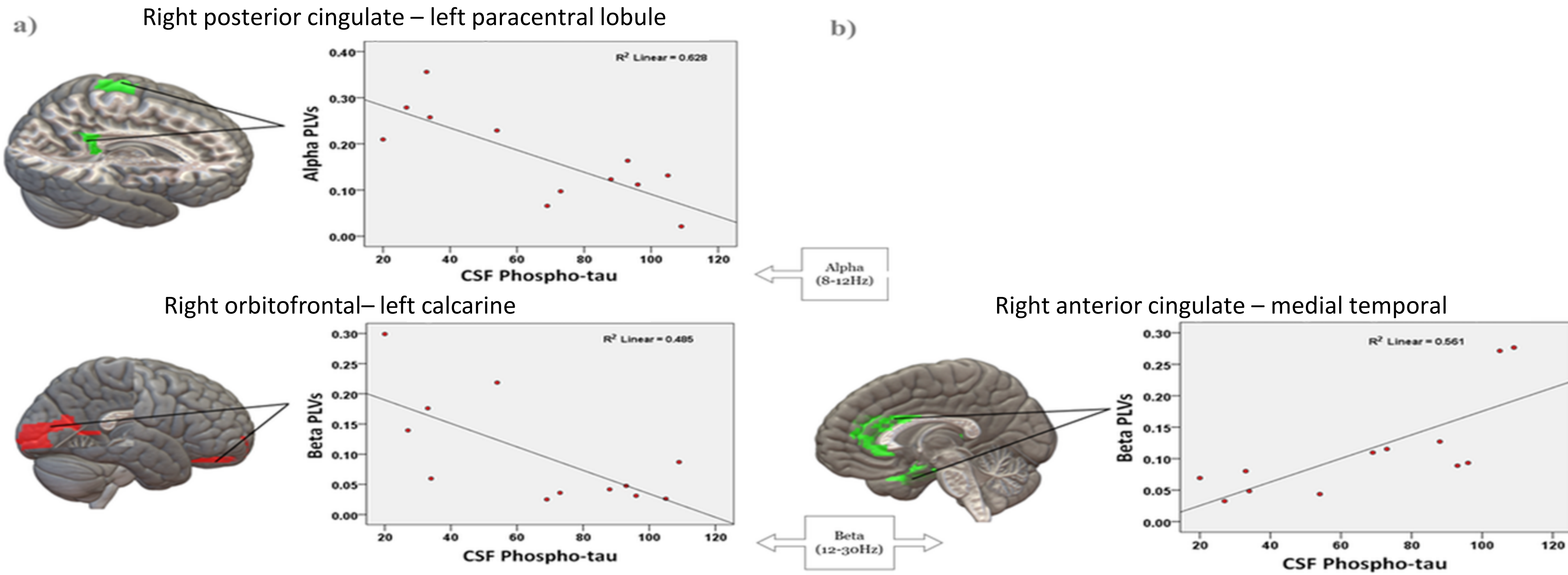
University of Madrid,
Madrid, Spain

MEG CONNECTIVITY AND TAU-CSF

CTB center for biomedical technology

International Federation of Clinical Neurophysiology

The phase-locking value (PLV) algorithm measured functional connectivity between all pairs of regions (88 X 88) for each frequency band (Lachaux et al., 1999). PLV assumes that the difference of phases between two phase-locked systems must be nonuniform.



Hyposynchronization Hypersynchronization

Patients with mild cognitive impairment (MCI) showed abnormal increased (hypersynchronization) or decreased (desynchronization) connectivity in limbic structures (anterior/posterior cingulate cortex, orbitofrontal cortex, and medial temporal areas) at alpha and beta frequency bands.

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Functional Brain Connectivity as Revealed by EEG/MEG

EEG CONNECTIVITY FOR LOCALIZATION OF EPILEPTIC FOCI/NETWORKS

Margitta Seeck

University of Genève,
Genève, Switzerland

EFFECTIVE CONNECTIVITY ANALYSIS WITH HIGH-DENSITY EEG

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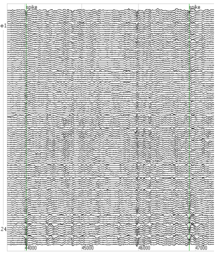
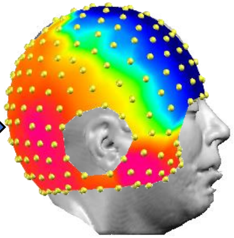
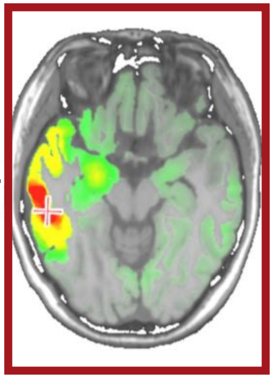
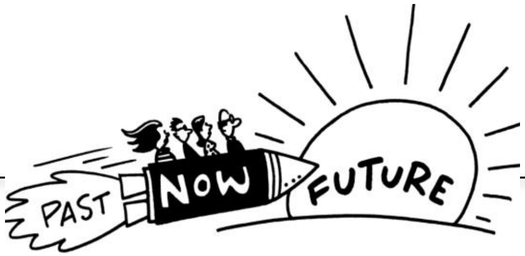
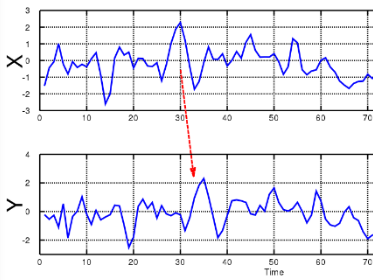


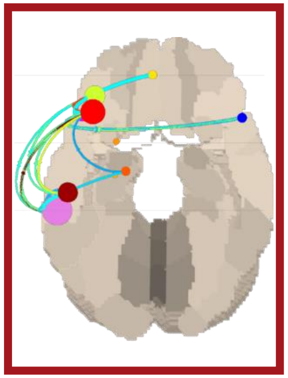




High density EEG
Electric Source imaging
Source activity







CONNECTIVITY
between cortical sources
(Granger causality)

ICTAL LOCALIZATION IS BETTER USING ESI AND CONNECTIVITY

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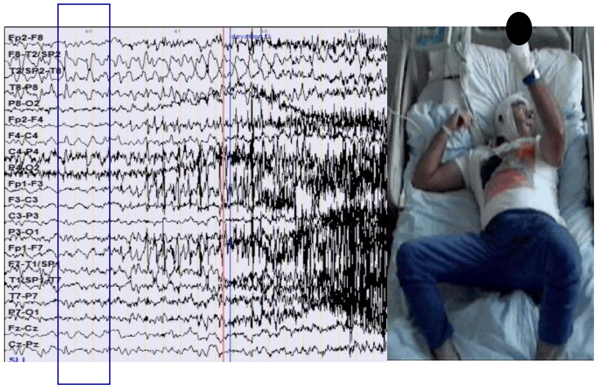

Clinical video-EEG (27-32 electrodes): 111 seizures/27 pts post-OP Sz-free

EEG window 2 sec
Determination of frequency band of interest, FOI (band of maximal global field power using the Fast Fourier Transform (FFT) → power and connectivity values of the FOI in 82 ROIs

(green) < 10mm

(red) > 10mm

Staljanssens et al. Neuroimage Clin 2017

Pat. \ Sz.	ESI power 1	2	3	4	5	6	7	8	9	10	11	12	% = 0	% ≤ 10
1	10	10	10	10	10	38	10	-	-	-	-	-	0	86
2	36	36	48	36	48	0	36	-	-	-	-	-	14	14
3	5	15	5	5	-	-	-	-	-	-	-	-	0	75
4	17	0	0	32	0	-	-	-	-	-	-	-	60	60
5	0	0	0	0	-	-	-	-	-	-	-	-	100	100
6	9	9	9	74	50	50	50	-	-	-	-	-	0	43
7	49	67	20	-	-	-	-	-	-	-	-	-	0	0
8	72	0	89	71	72	0	-	-	-	-	-	-	33	33
9	33	-	-	-	-	-	-	-	-	-	-	-	0	0
10	49	17	0	17	-	-	-	-	-	-	-	-	25	25
11	0	17	17	17	0	0	-	-	-	-	-	-	50	50
12	63	0	13	0	0	0	13	13	-	-	-	-	50	50
13	78	-	-	-	-	-	-	-	-	-	-	-	0	0
14	55	13	13	13	-	-	-	-	-	-	-		0	0
14	20	20	31	-	-	-	-	-	-	-	-	-	0	0
16	0	0	0	0	-	-	-	-	-	-	-	-	100	100
17	78	19	73	-	-	-	-	-	-	-	-	-	0	0
18	0	0	16	-	-	-	-	-	-	-	-	-	67	67
19	23	-	-	-	-	-	-	-	-	-	-	-	0	0
20	39	39	29	0	39	0	13	29	52	39	75	39	17	17
21	0	47	-	-	-	-	-	-	-	-	-	-	50	50
22	0	6	36	36	20	53	20	20	0	-	-	-	22	33
23	0	23	0	-	-	-	-	-	-	-	-	-	67	67
24	0	-	-	-	-	-	-	-	-	-	-	-	100	100
25	40	-	-	-	-	-	-	-	-	-	-	-	0	0
26	0	-	-	-	-	-	-	-	-	-	-	-	100	100
27	0	-	-	-	-	-	-	-	-	-	-	-	100	100

Pat. \ Sz.	ESI+CONNECTIVITY 1	2	3	4	5	6	7	8	9	10	11	12	% = 0	% ≤ 10
1	10	10	10	10	10	10	10	-	-	-	-	-	0	100
2	0	0	0	0	0	48	0	-	-	-	-	-	86	86
3	5	5	5	5	-	-	-	-	-	-	-	-	0	100
4	0	0	0	0	0	-	-	-	-	-	-	-	100	100
5	0	0	0	0	-	-	-	-	-	-	-	-	100	100
6	9	9	9	9	9	9	9	-	-	-	-	-	0	100
7	0	0	0	-	-	-	-	-	-	-	-	-	100	100
8	0	0	81	35	0	0	-	-	-	-	-	-	67	67
9	0	-	-	-	-	-	-	-	-	-	-	-	100	100
10	0	17	0	17	-	-	-	-	-	-	-	-	50	50
11	0	0	0	0	0	0	-	-	-	-	-	-	100	100
12	0	12	13	0	0	0	0	0	-	-	-	-	75	75
13	0	-	-	-	-	-	-	-	-	-	-	-	100	100
14	0	0	0	0	-	-	-	-	-	-	-	-	100	100
14	5	0	0	-	-	-	-	-	-	-	-	-	100	100
16	0	0	0	0	-	-	-	-	-	-	-	-	100	100
17	10	0	0	-	-	-	-	-	-	-	-	-	67	100
18	0	0	0	-	-	-	-	-	-	-	-	-	100	100
19	0	-	-	-	-	-	-	-	-	-	-	-	100	100
20	0	0	0	0	0	0	0	0	0	0	0	0	100	100
21	0	0	-	-	-	-	-	-	-	-	-	-	100	100
22	0	6	6	0	6	6	0	0	6	-	-	-	44	100
23	0	0	0	-	-	-	-	-	-	-	-	-	100	100
24	0	-	-	-	-	-	-	-	-	-	-	-	100	100
25	0	-	-	-	-	-	-	-	-	-	-	-	100	100
26	0	-	-	-	-	-	-	-	-	-	-	-	100	100
27	0	-	-	-	-	-	-	-	-	-	-	-	100	100

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BRAIN NETWORK CONNECTIVITY ANALYSIS WITH HIGH-DENSITY EEG

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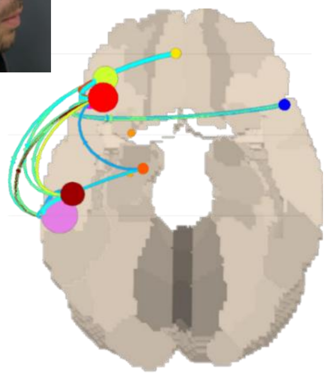
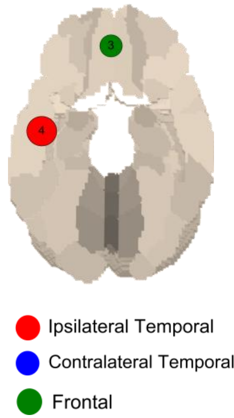
During spikes

LTLE

N=8

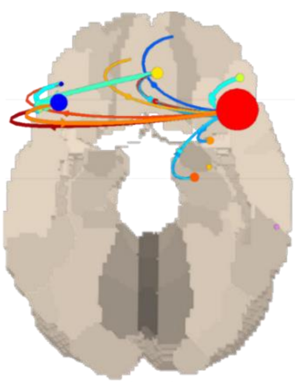


Cognitive Deficits LTLE

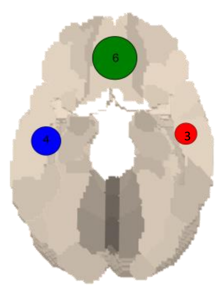


RTLE

N=8

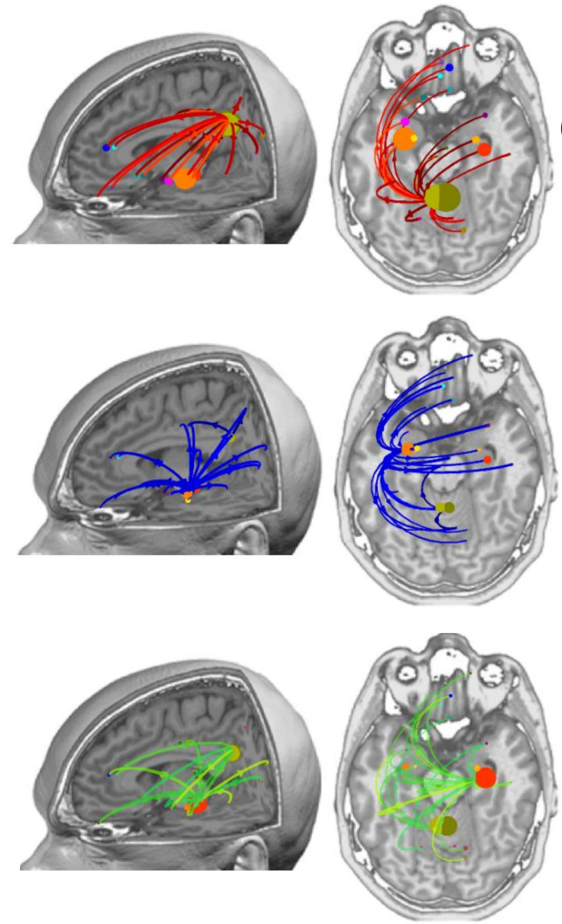


Cognitive Deficits RTLE



Coito et al, *Epilepsia 2015*

Between spikes



Control

N=20

LTLE

N=20

RTLE

N=20

Coito et al, *Epilepsia 2016*

Universitätsklinikum Erlangen

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Functional Brain Connectivity as Revealed by EEG/MEG

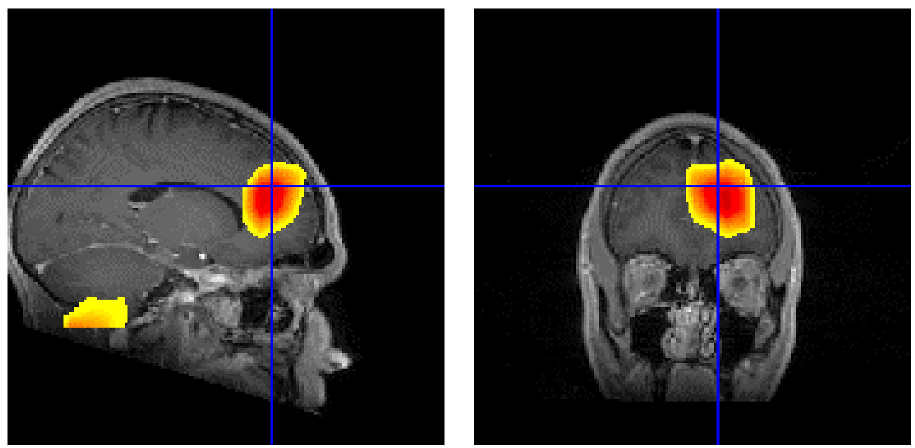
EEG/MEG CONNECTIVITY FOR LOCALIZATION OF EPILEPTIC FOCI/NETWORKS

Stefan Rampp

Department of Neurology, University of Erlangen,
Erlangen, Germany

EPILEPTIC FOCUS LOCALIZATION

- *EEG/MEG connectivity* for localization of epileptic foci/networks for planning of epilepsy surgery and invasive recordings (Elisevich et al., 2011; Jin et al., 2013; Wu et al., 2014;Krishnan et al., 2015, …)
- Complementary or alternative marker in patients without (clear) interictal/ictal findings
- Potential for automation



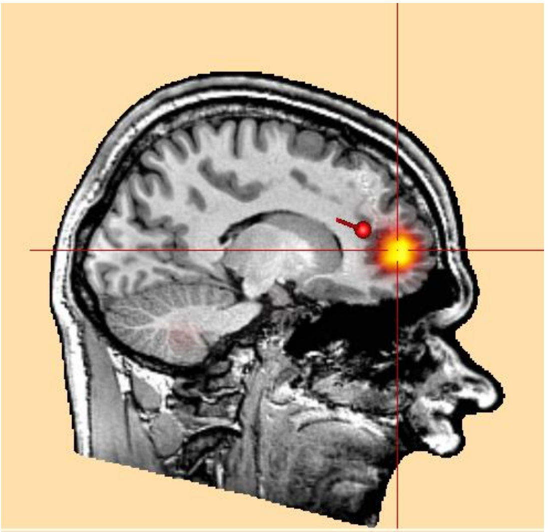
Gamma band imaginary coherence, all-to-all within a grid of cortical nodes.

EPILEPTIC FOCUS LOCALIZATION

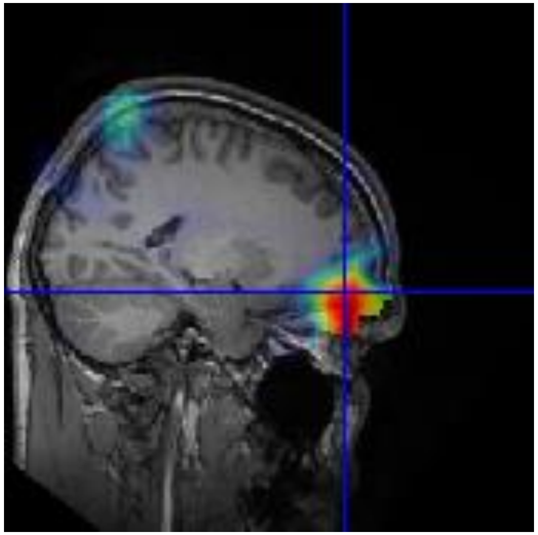
Open questions:

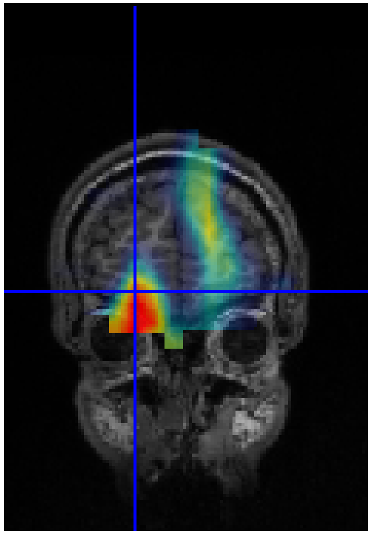
- Connectivity and graph analysis methods: Differences between methods? Optimal method?
- Frequency bands?
- EEG +- MEG? Recording durations?
- Neurophysiology: Relation to spikes and seizures
- Validation: Gold standard? Resection? Invasive EEG?

Spikes



Delta band imaginary coherence, , all-to-all within a grid of cortical nodes.





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THE SPECIAL INTEREST GROUP

Functional Brain Connectivity as Revealed by EEG/MEG

EEG SOURCE CONNECTIVITY IN SCHIZOPHRENIA

Giorgio di Lorenzo

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EEG SOURCE CONNECTIVITY IN SCHIZOPHRENIA

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rs
an Neuroscience

ORIGINAL RESEARCH
published: 05 May 2015
doi: 10.3389/fnhum.2015.00234

Altered resting-state EEG source functional connectivity in schizophrenia: the effect of illness duration

Giorgio Di Lorenzo[1,2], Andrea Daverio[1,2,3], Fabiola Ferrentino[2,3], Emiliano Santarnecchi[4,5], Fabio Ciabattini[1,2,3], Leonardo Monaco[1,2], Giulia Lisi[2,3], Ylenia Barone[2,3], Cherubino Di Lorenzo[6], Cinzia Niolu[2,3], Stefano Seri[7] and Alberto Siracusano[1,2,3]*

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Despite the increasing body of evidence supporting the hypothesis of schizophrenia as a disconnection syndrome, studies of resting-state EEG Source Functional Connectivity (EEG-SFC) in people affected by schizophrenia are sparse. The aim of the present study was to investigate resting-state EEG-SFC in 77 stable, medicated patients with schizophrenia (SCZ) compared to 78 healthy volunteers (HV). In order to study the effect of illness duration, SCZ were divided in those with a short duration of disease (SDD; $n = 25$) and those with a long duration of disease (LDD; $n = 52$). Resting-state EEG recordings in eyes closed condition were analyzed and lagged phase synchronization (LPS) indices were calculated for each ROI pair in the source-space EEG data. In delta and theta bands, SCZ had greater EEG-SFC than HV; a higher theta band connectivity in frontal regions was observed in LDD compared with SDD. In the alpha band, SCZ showed lower frontal EEG-SFC compared with HV whereas no differences were found between LDD and SDD. In the beta1 band, SCZ had greater EEG-SFC compared with HVs and in the beta2 band, LDD presented lower frontal and parieto-temporal EEG-SFC compared with HV. In the gamma band, SDD had greater connectivity values compared with LDD and HV. This study suggests that resting state brain network connectivity is abnormally organized in schizophrenia, with different patterns for the different EEG frequency components and that EEG can be a powerful tool to further elucidate the complexity of such disordered connectivity.

Keywords: schizophrenia, psychosis, brain oscillations, disconnectivity, synchronization, excitatory/inhibitory dysfunction, neural plasticity, brain network

OPEN ACCESS

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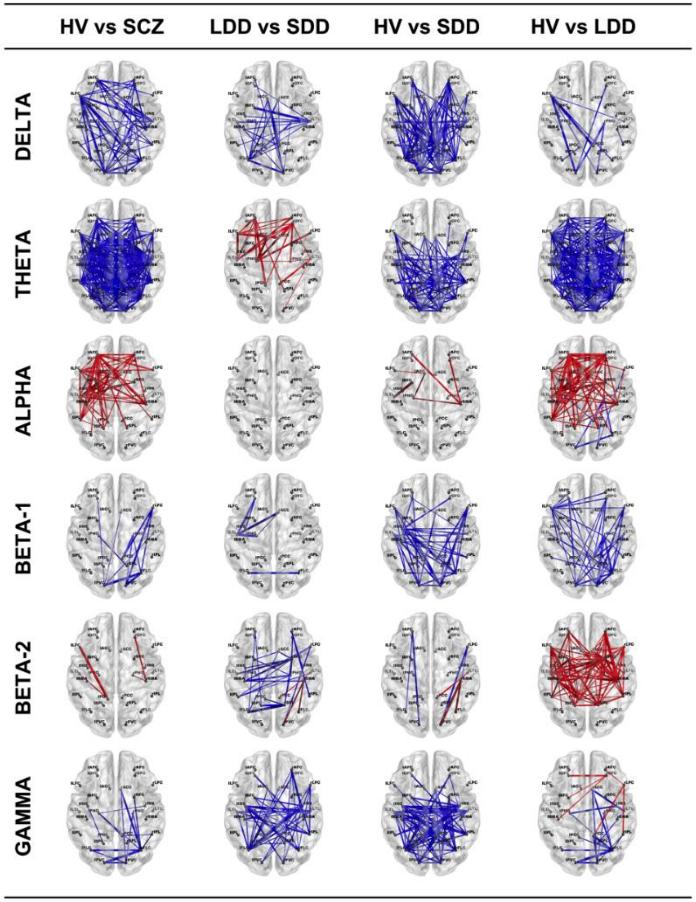
Introduction

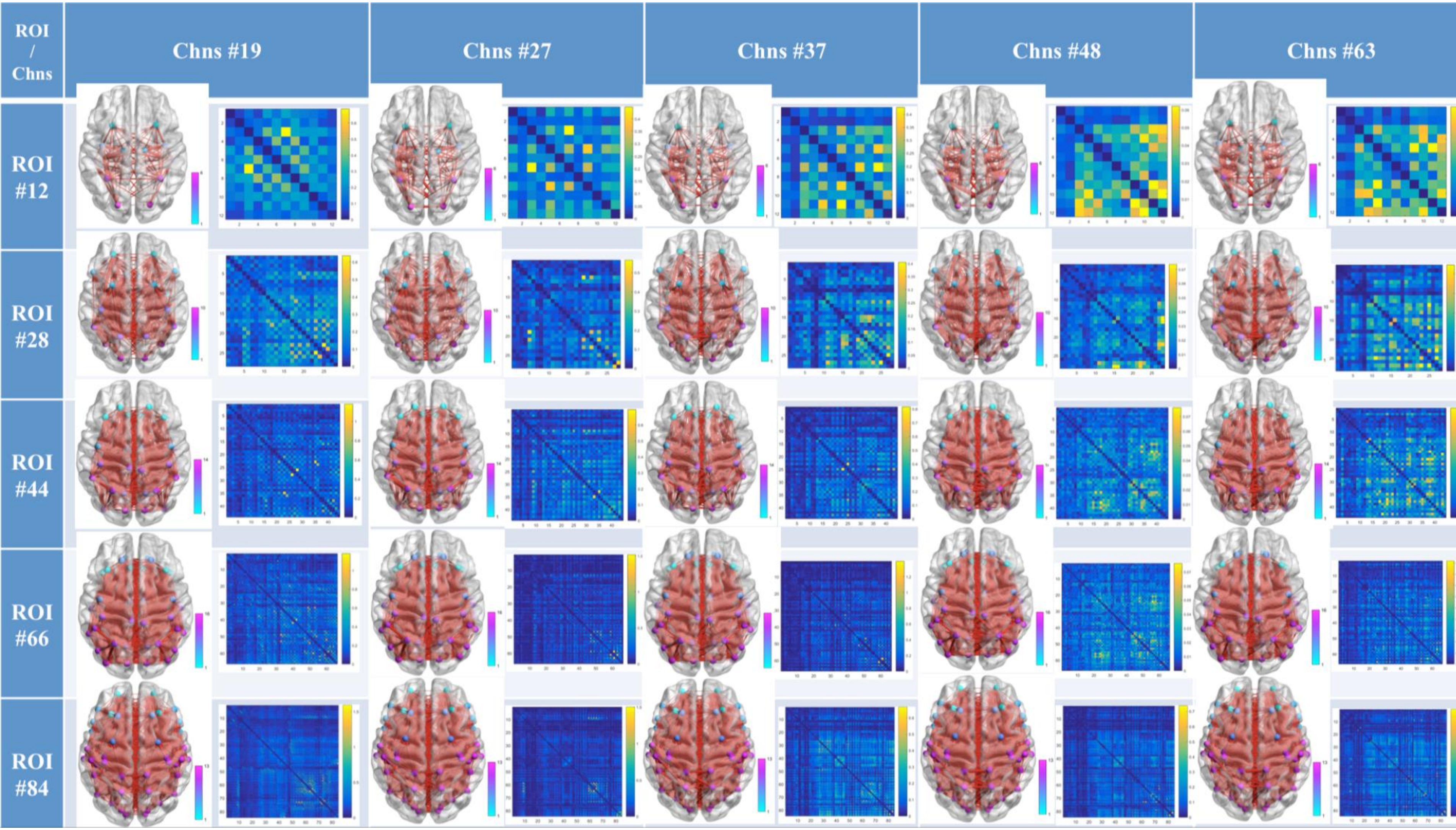
Disordered brain connectivity at cortical level, generally defined as failure of effective functional integration within and between brain areas, has been proposed as a *core* deficit of schizophrenia.



Di Lorenzo *et al*., Front Hum Neurosci 2015

Influence of channel and ROI numbers on EEG source connectivity strength

- An example of resting state EEG Lagged Linear Connectivity Alpha 1 in healthy controls –



Giorgio Di Lorenzo & Endrit Pashaj, 2017

Laboratory of Psychophysiology, Department of Systems Medicine, University of Rome Tor Vergata

UNIVERSITÀ DEGLI STUDI DI MILANO

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Functional Brain Connectivity as Revealed by EEG/MEG

EEG SOURCE CONNECTIVITY IN VEGETATIVE STATE

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Department of Biomedical and Clinical Sciences "L. Sacco",
University of Milan, Milan, Italy

EEG SOURCE CONNECTIVITY IN VEGETATIVE STATE

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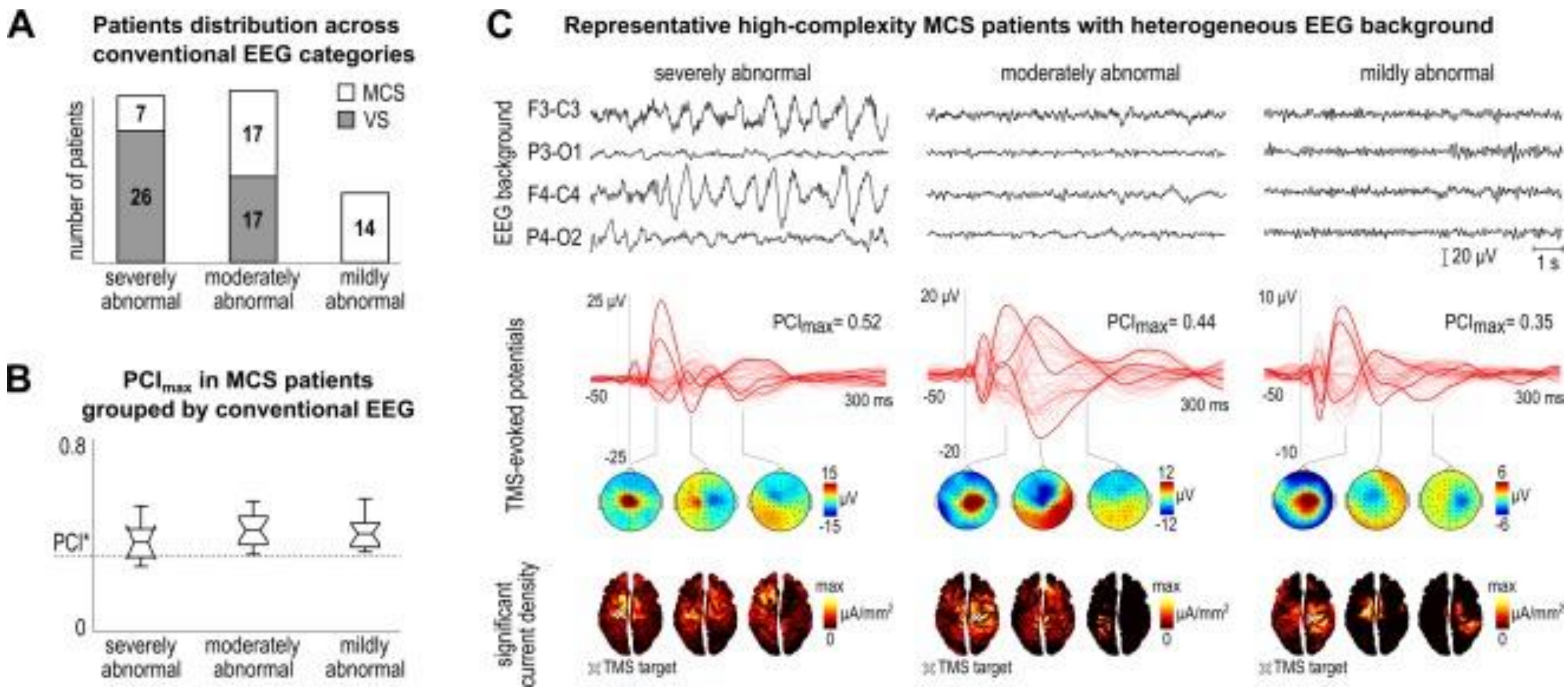

(A) Distribution of vegetative state (VS) and minimally conscious state (MCS) patients across conventional electroencephalographic (EEG) categories (i.e., severely abnormal, moderately abnormal, and mildly abnormal). The number of patients in each EEG category is explicitly indicated within the bars for VS and MCS patients. (B) Boxplot of the maximum individual Perturbational Complexity Index values (PCI_{max}) computed in MCS patients as a function of conventional EEG category. The dashed horizontal line highlights the optimal cutoff (PCI*) obtained from the benchmark population. (C) The first row shows 10-second continuous EEG recordings from 4 bipolar channels (F3-C3, P3-O1, F4-C4, P4-O2) in 3 representative MCS patients with PCI_{max} higher than PCI* (from left to right: Patients 19, 10, and 25), and respectively with a severely abnormal (left), a moderately abnormal (center), and a mildly abnormal (right) background. The second row shows the corresponding average transcranial magnetic stimulation (TMS)-evoked potentials (all channels superimposed, with 3 illustrative channels highlighted in bold) together with the PCI_{max} values. Three voltage scalp topographies (third row) and significant current density cortical maps (fourth row) are shown at selected time points for each patient. A white cross on the cortical map indicates the stimulation target. [Color figure can be viewed at wileyonlinelibrary.com]

Casarotto *et al.*, Ann Neurol. 2016

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Functional Brain Connectivity as Revealed by EEG/MEG

MULTIVARIATE FUNCTIONAL CONNECTIVITY FOR MACHINE LEARNING APPLICATIONS

Ernesto Pereda

University of Laguna,
Tenerife, Spain

CONNECTIVITY FOR MACHINE LEARNING

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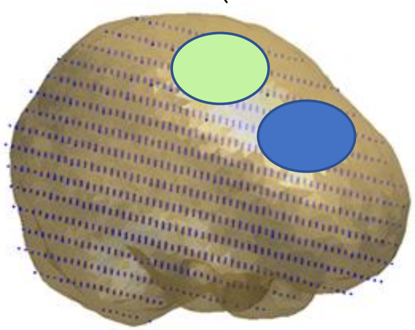
From the M/EEG sensors to the connectivity matrix in the souce domain:

1. Individual MRIs coregistered with M/EEG sensor positions
2. Leadfield calculation
3. LCMV beamformer
4. ~ 10^3 sources -> *NxN* ROIs connectivity matrix

$$\begin{pmatrix} s_1 \\ \vdots \\ s_{1500+} \end{pmatrix} \rightarrow \begin{pmatrix} ROI_1 & \cdots & ROI_N \\ \vdots & \ddots & \vdots \\ ROI_N & \cdots & ROI_N \end{pmatrix}$$

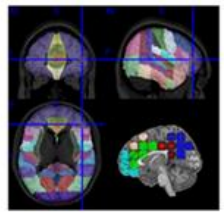


OPEN ISSUES:

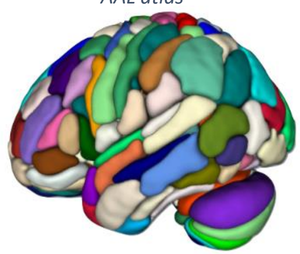
- How to define the ROIs?
- **How to go from the sources to the connectivity matrix?**
- **Which strategy (anatomical or adaptive) is best for classification using ML algorithms?**

Typical options: anatomic atlases

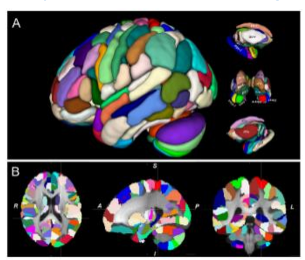
H-O atlas



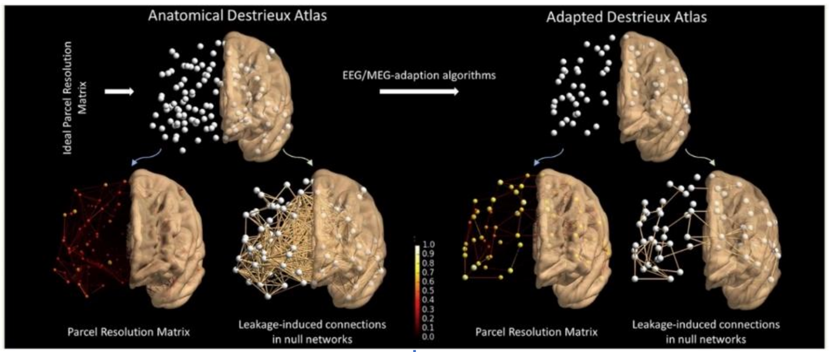
AAL atlas

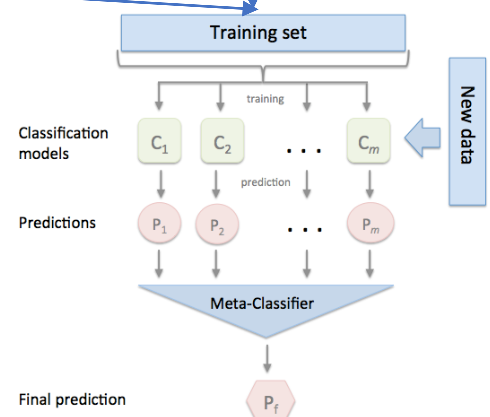


Brainnetome atlas
http://atlas.brainnetome.org/



More recent: Adaptive parcellations, to minimize source leakage between adjacent ROIs





Ernesto Pereda and colleagues

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Functional Brain Connectivity as Revealed by EEG/MEG

THE FUNCTIONAL CONNECTIVITY BETWEEN HOMOLOGOUS REGIONS IN MULTIPLE SCLEROSIS

Franca Tecchio

Let's - Laboratory of Electrophysiology for Translational neuroScience, ISTC- CNR
UCSC & Gemelli Hospital, Rome

FUNCTIONALLY HOMOLOGOUS AREAS

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tips

- Identification of regions exploiting their dynamics, investigated at rest (see **A**)
  - **M1** as the region expressing activity synchronous with the muscle during a handgrip
  - **S1** as maximally responding at around 20 ms to the median nerve stimulation at wrist
- Via the neuromodulation of bilateral **S1** (non-invasive brain stimulation, NIBS; “Fatigue Relief in Multiple Sclerosis, FaReMuS) in fatigued people with multiple sclerosis, the sensorimotor rebalances resulted in re-establishing a more physiological **M1**-**M1** resting functional connectivity (see **B**)

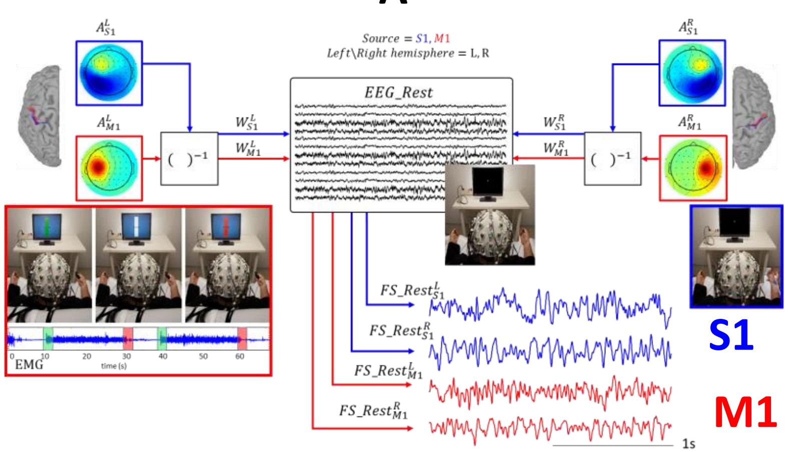
caveat

- *Symmetric* NIBS, *Asymmetric* effects dependent on local neuronal state

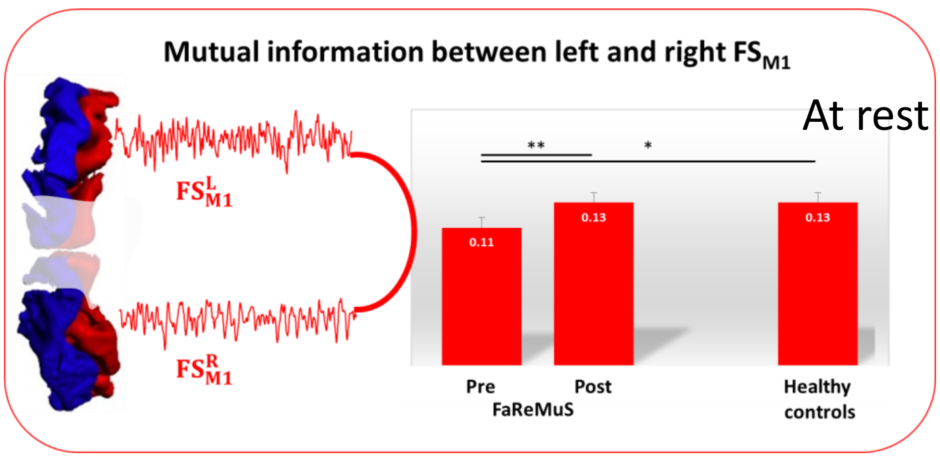
challenge

- Need to integrate functional connectivity & local excitability
  - Identification of symptom-related impairments (S1-M1 connectivity impairment, S1 too few excitable)

A



B



Tecchio et al J Neurol 2014, Cancelli et al MultScler 2017, Porcaro et al submitted

UCL

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Functional Brain Connectivity as Revealed by EEG/MEG

A NEW PERSPECTIVE FOR FUNCTIONAL BRAIN CONNECTIVITY: ELECTRICAL IMPEDANCE TOMOGRAPHY

David Holder

Department of Medical Physics,
University College London, UK

CONNECTIVITY AND ELECTRICAL IMPEDANCE

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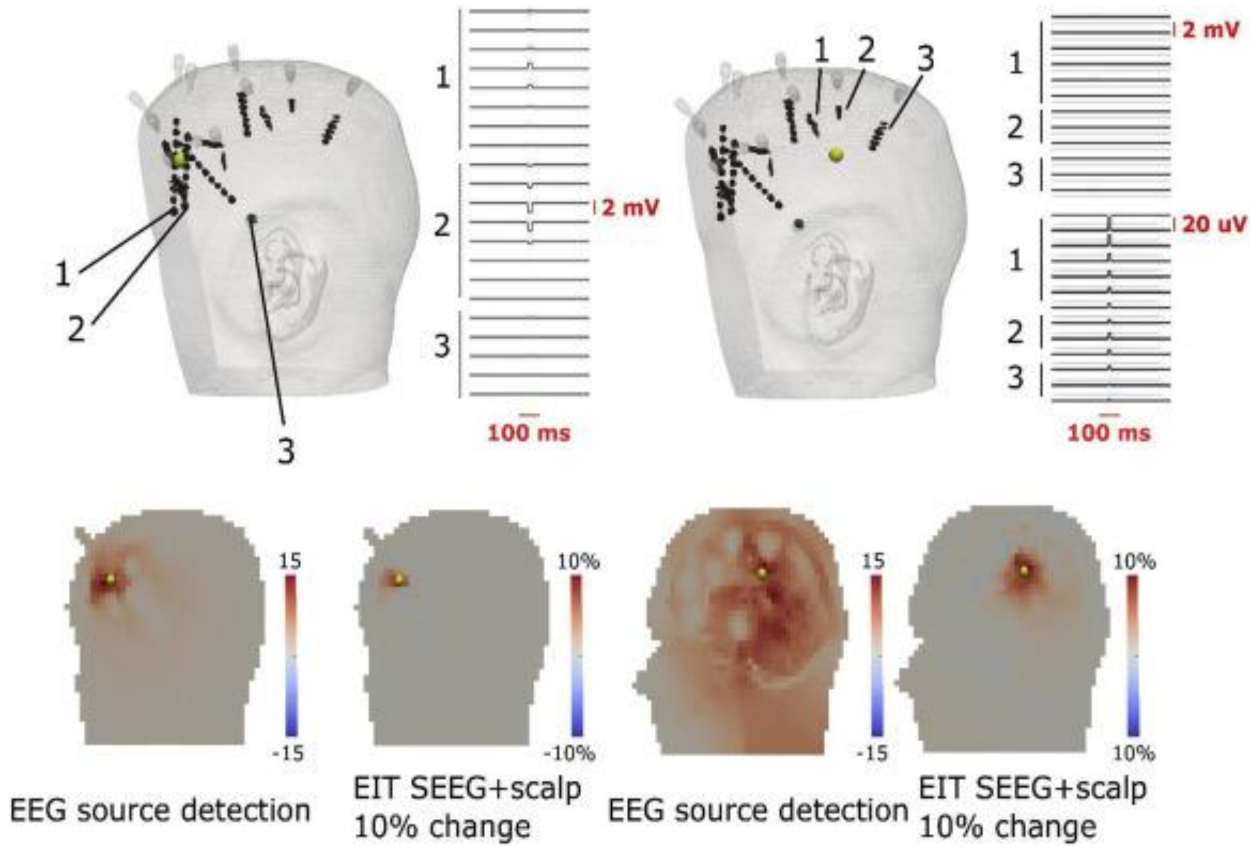

Detection accuracy with three methods: the model of clinical spike detection (top, SEEG on respective contacts presented as horizontal lines), the reconstruction with the EEG inverse source (the source as corrected current density, t-score based noise correction) and the best protocol for Electrical Impedance Tomography (EIT; Depth + Scalp protocol, described as conductivity change in %, t-score based noise correction) (bottom). The real location of the source is shown as a yellow sphere. Visual detection of a dipole spike shows that sources close to the contact (~7 mm distance, left panel) produced spikes above the threshold (the highest amplitude was ~1.5 mV) and the spike amplitude changes with respect to the distance and orientation. A more distant source still within SEEG coverage (~18 mm distance, right panel) produced a significantly lower voltage (~16 µV) on the closest SEEG contact, below the detection threshold of 250 µV. In this case, the perturbation was not successfully localised with inverse source modelling but was located within 5 mm using EIT.

Witkowska-Wrobel *et al.*, NeuroImage. 2018

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Functional Brain Connectivity as Revealed by EEG/MEG

SMALL-WORLD BIOMARKERS FROM EEG SOURCES IN ALZHEIMER'S DISEASE

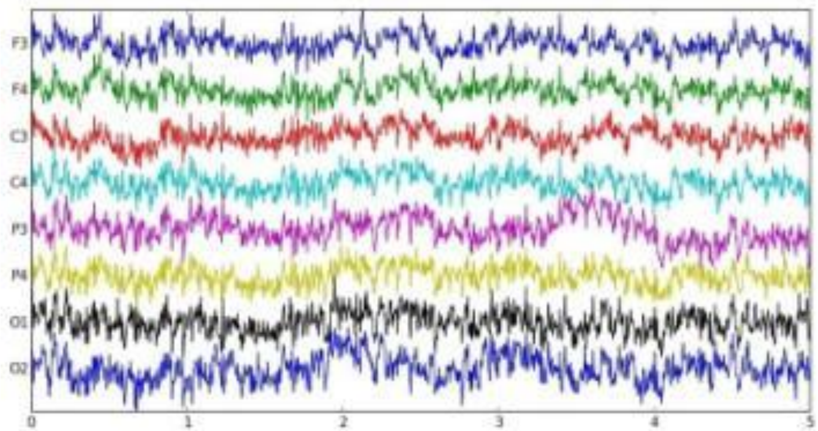
Francesca Miraglia

BCLab Brain Connectivity Laboratory for cognitive neuroscience
IRCCS San Raffaele Pisana of Rome, Italy

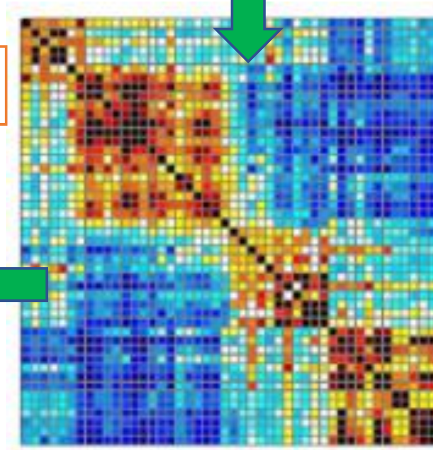
GRAPH ANALYSES FLOWCHART

Undirected and weighted network based on **eLORETA connectivity** between Regions Of Interest (ROIs). The **nodes** of the network are **ROIs,** the **edges** of the network are weighted by the **Lagged Linear Connectivity values**.

From **EEG DATA ANALYSIS AND ARTIFACTS REMOVAL**



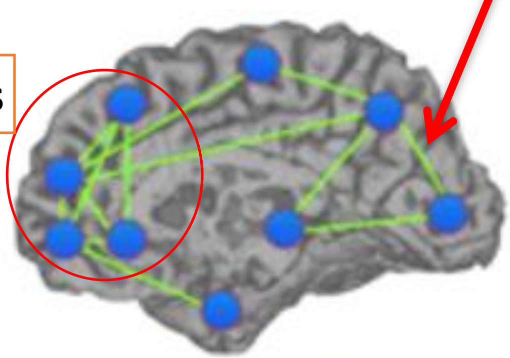
Compute **CORTICAL SOURCES OF EEG RHYTMS**



Obtaine **CONNECTION MATRIX**

WEIGHTED EDGES WITH LAGGED LINEAR CONNECTIVITY

NETWORKS' NODES : ROIs



NETWORK, COMPLEXITY

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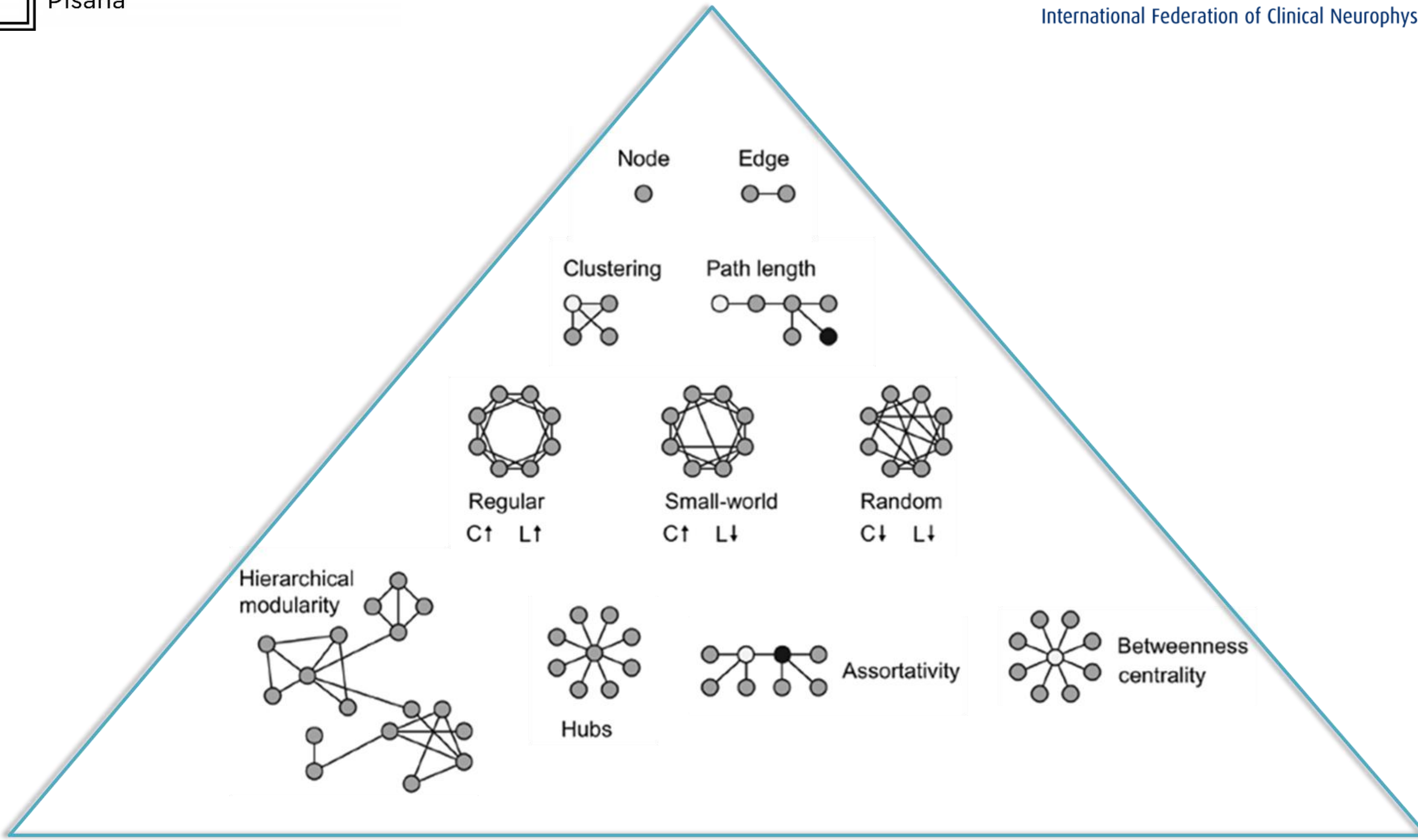

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NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Complex network measures of brain connectivity: Uses and interpretations

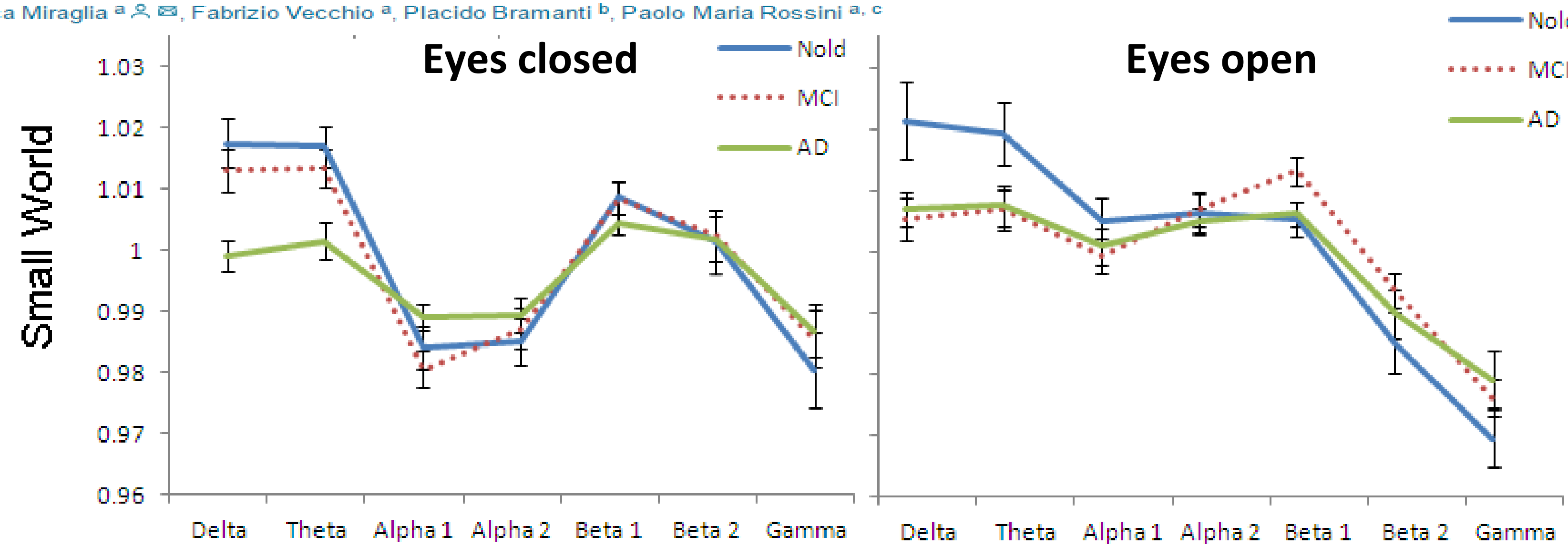
Mikail Rubinov [a,b,c], Olaf Sporns [d,*]

ELSEVIER
Clinical Neurophysiology
Volume 127, Issue 2, February 2016, Pages 1261-1268

90 Subjects: - 30 **AD** (MMSE 22.3) - 30 **MCI** (MMSE 26.8) - **30** normal people Nold (MMSE 28.9)

EEG characteristics in "eyes-open" versus "eyes-closed" conditions: Small-world network architecture in healthy aging and age-related brain degeneration

Francesca Miraglia [a], Fabrizio Vecchio [a], Placido Bramanti [b], Paolo Maria Rossini [a, c]



In **Eyes Closed condition,** at low frequencies (**delta e theta bands**), **MCI** group presented network's architecture **similar to Nold**, while in **Eyes Open condition, MCI** small worldness **is superimposable to AD** ones. **Pathological changes of delta and theta oscillation** are mainly reported in **association with memory deficits** (involved in some cognitive functions such as declarative memory and **attentional control processes**). **The cognitive impairment of MCI** is probably **causing small world architecture alteration**, and the **effect seen on the EO reactivity** could lead to the **absence of the brain's ability to react** as rapidly and **efficiently as normally when the brain is** visually **connected to the external environment**.

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Functional Brain Connectivity as Revealed by EEG/MEG

GRAPH-VARIATE SIGNAL ANALYSIS FOR TRANSIENT EEG ACTIVITY

Javier Escudero

University of Edinburgh,
Edinburgh, UK

GRAPH-VARIATE SIGNAL ANALYSIS FOR TRANSIENT EEG ACTIVITY

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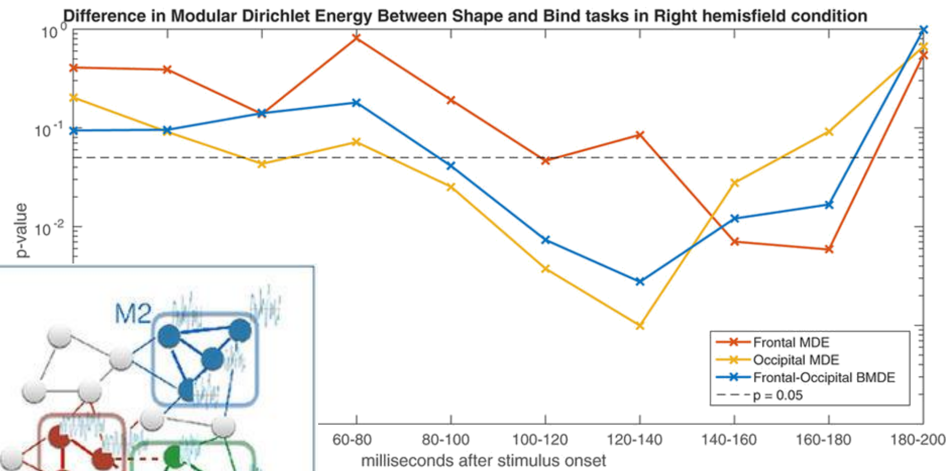
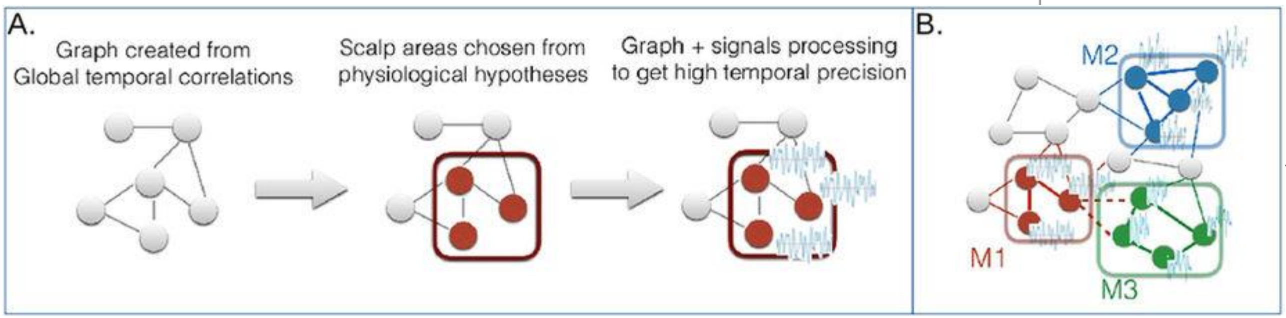
- *Graph-Variate Signal Analysis* is new methodology to exploit the longer-term, more stable functional connectivity of EEG signals towards the analysis of transient, event-related activity.
- The methodology has recently been introduced by Smith *et al.*, 2017 in a visual short-term memory binding task and it is being further refined in Smith *et al.*, submitted.
- It allows fusing connectivity information with transient amplitudes resulting in temporally precise information about the dynamics of brain activity and connectivity.





***Bottom Left diagram**. (A) Outline of the main principles of the methodology. Circles represent electrodes and lines are the connections computed for the long-term connectivity. (B) Example of modules for the Modular Dirichlet Energy (MDE). A set of electrodes are grouped together in modules (M1, M2, M3) within the network. The coloured nodes and edges are the ones belonging to a specific module and interactions between modules are computed. **Upper Right diagram.** The p-values for shape only vs. shape-colour binding tasks reflecting interactions between occipital (yellow) and frontal regions (red) alongside the Between-Region dependencies (blue) calculated at a time resolution of 20 ms.*

University of Basel

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Functional Brain Connectivity as Revealed by EEG/MEG

REPRODUCIBILITY OF FUNCTIONAL CONNECTIVITY AND GRAPH MEASURES FROM HIGH RESOLUTION EEG

Peter Fuhr

Department of Neurology, University of Basel,
Basel, Switzerland

University of Basel

REPRODUCIBILITY OF FUNCTIONAL CONNECTIVITY

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The inter-subject-variability using the coefficient of variation (CoV) and long-term test-retest-reliability (TRT) using the intra-class correlation coefficient (ICC) was tested in 44 healthy subjects with 35 having a follow-up at years 1 and 2. Functional connectivity from high resolution EEG was estimated from 256-channel-EEG by the phase-lag-index (PLI) and weighted PLI (wPLI) during an eyes-closed resting state condition. Reproducibility of FC and graph measures was good.

Table 1. Inter-subject variability of global PLI and wPLI at baseline by frequency band expressed by the coefficient of variation (CoV; CI: confidence interval estimated from bootstrapping).

		theta	alpha1	alpha2	beta
PLI		**0.12**	**0.23**	**0.28**	**0.15**
	95% CI	0.08–0.20	0.17–0.31	0.21–0.38	0.12–0.17
wPLI		**0.25**	**0.44**	**0.55**	**0.29**
	95% CI	0.14–0.41	0.33–0.56	0.39–0.76	0.25–0.33

doi:10.1371/journal.pone.0108648.t001

Hardmeier M, Hatz F, Bousleiman H, Schindler C, Stam CJ, et al. (2014) Reproducibility of Functional Connectivity and Graph Measures Based on the Phase Lag Index (PLI) and Weighted Phase Lag Index (wPLI) Derived from High Resolution EEG. PLoS ONE 9(10): e108648. doi:10.1371/journal.pone.0108648

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Functional Brain Connectivity as Revealed by EEG/MEG

CLOSING REMARKS

Fabrizio Vecchio

IRCCS San Raffaele Pisana of Rome, Italy