MARIE SKLODOWSKA-CURIE ACTIONS

Co-funding of regional, national and international programmes (COFUND)

DOC2AMU PROJECT 2017 CALL FOR APPLICATIONS

PhD Project: Characterizing brain networks in real time across frequencies based on a combination of time frequency and source localization methods

1. DESCRIPTION OF THE PHD THESIS PROJECT

1.1 OBJECTIVES OF THE PROJECT BASED ON THE CURRENT STATE OF THE ART

Key concepts and acronyms

Magnetoencephalography (MEG): state-of-the art electrophysiological technique that records non-invasively the very small magnetic fields produced by brain signals, based on sensors in a supraconductive state. Application of advanced source localization methods make MEG an imaging tool with both high spatial and high temporal resolution.

Intracerebral EEG (sterotaxic EEG, SEEG): invasive method that consists in placing depth electrodes within the brain. This technique is routinely used during presurgical evaluation of epilepsy, and permits recording directly within brain structures, including deep regions such as hippocampus and amygdala.

Presurgical evaluation of epilepsy: patients with epilepsy that are not responding to pharmaceutical treatment can be evaluated for a surgical approach, where the brain region responsible for seizure is removed by resective surgery or neutralized by radiosurgery.

State of the art

It is now commonly accepted that the substrate of brain function is the activation of networks at different spatial and temporal scales (Nikolic *et al.*, 2013). Thus, cerebral activity relies on the dynamical interaction between brain areas at different spatial and temporal scales. The dysfunction of brain networks underlies several pathologies, one of the most common being epilepsy (Bartolomei *et al.*, 2010). Functional imaging techniques permit to map the regions involved in brain networks as well as their patterns of interaction, the most common methods being magnetic resonance imaging (fMRI) and electrophysiology techniques (electroencephalography, EEG and magnetoencephalography, MEG). The great advantage of electrophysiological tools is their ability to track neuronal activity at its temporal scale of activity, i.e. on the order of the millisecond (Sergent *et al.*, 2005). In particular this permits characterizing activity across different frequency range, from the classical low frequency bands (between 1 and 30 Hz), towards the gamma band (between 35 and 80 Hz) that have been shown to be a marker of regional neuronal activation, related to fMRI results (Lachaux *et al.*, 2007). Some recent work push the limit to very high frequencies, which are thought to be highly involved in memory processes and to be a marker of epileptic tissues (Urrestarazu *et al.*, 2007). An area of much interest is that of cross frequency interactions, that are believed to be a key player in brain network functioning (Canolty *et al.*, 2006; Florin and Baillet, 2015).

However, the difficulty of noninvasive electrophysiology tools is the fact that they rely on surface measurements. In order to be a full imaging method, they thus require solving a difficult inverse problem that projects the surface data towards the cortex (Baillet *et al.*, 2001). This results in the estimation of the time course of each brain region, a sort of 'virtual electrode', on which methods of analysis of brain networks can be performed (see Figure 1). The inverse problem is ill-posed, which requires the use of mathematical constraints that are not always physiologically justified. Many methods have been proposed to solve the inverse problem, but several other difficulties remain: (i) The sensitivity of methods to the signal to noise ratio, which is a key issue when studying spontaneous activity (ii) the 'source leakage' arising from the blurred reconstruction arising from the inverse problem methods, resulting in spurious correlations between brain regions (Brookes *et al.*, 2012) (iii) the mixture of transient and oscillatory activity that overlap in the frequency domain (Jmail *et al.*, 2011), with varying amplitudes resulting from the 1/f nature of electrophysiological signals (Dehghani *et al.*, 2010). So far, all these issues have been tackled mostly separately, with progress in inverse problem, wavelet analysis, orthogonalization methods, convex and non-convex optimization. However, a sensible strategy would be to combine all these approaches into a common multi-dimensional framework, that would take advantage of their added values while avoiding the pitfalls that have been attributed to the separate approaches.

The optimization of cross-frequency characterization of brain networks in low signal to noise conditions would be beneficial both to clinical practice and fundamental research. One particularly interesting application would be in the field of epilepsy, which is a disease of brain networks. For pharmacoresistant patients, the proposed solution is mostly based on surgery, consisting in removing a part of the brain. A new promising approach would be to help patients reshaping their brain networks based on neurofeedback (Kubik and Biedron, 2013). Within this approach, the synchrony of the pathological network, reconstructed thanks to the tools developed within this project, would be shown to the patient, who could thereby learn how to actively desynchronize such pathological activity. This technique has been used with electrodermal skin response (Micoulaud-Franchi *et al.*, 2014), with encouraging results, and is expected to be even more efficient when based on actual brain network activity.

Objectives

The objectives of this PhD project are two-fold:

- Develop a novel approach for characterizing brain networks across frequencies in real time on continuous data. This approach will combine in a single framework recent developments in source localization, time frequency and multivariate methods, in the context of high dimensional data. It will permit to handle difficult signal to noise ratio and to disentangle network activity across frequency bands. Results will be validated on simultaneous recordings of MEG and intracerebral recordings, which are extremely rare data that permit to give a 'ground truth' to which reconstructed surface data can be confronted.

- Apply the developed approach to a neurofeedback approach for curing epilepsy. The patients will be recruited in the clinical neurophysiological department of Timone hospital, a leading group in evaluation of epilepsy. Our hypothesis is that neurofeedback training will allow patients to reduce seizure frequency in their everyday life without the need of a heavy and costly surgical intervention.

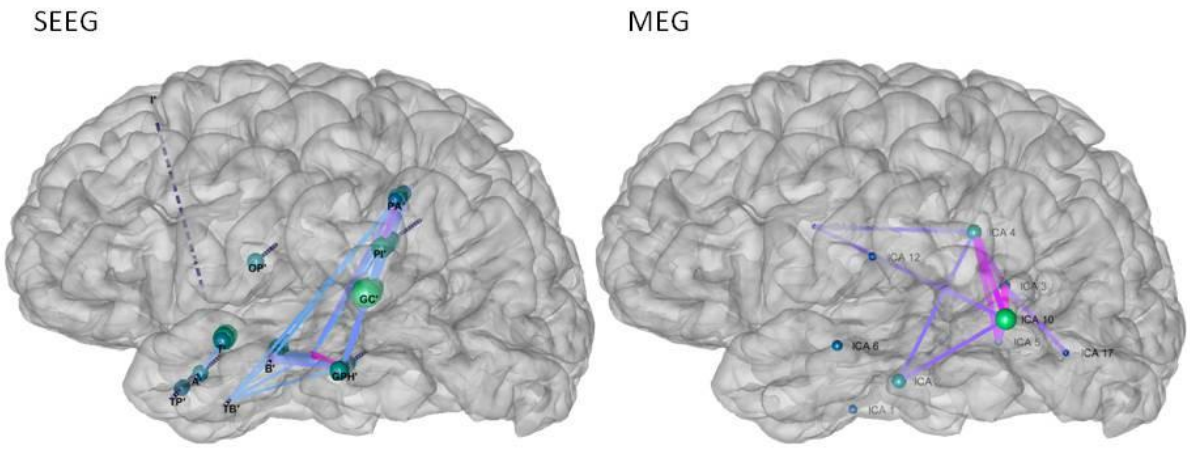

Figure 1: Graph of epileptic networks obtained offline on a patient with epilepsy (S Medina, in collab. Dynamap team /Clin Neurophys Dep. Timone Hospital). left: from intracerebral traces (right) from MEG signals obtained simultaneously. The goal of the proposed project is to extend the network characterization across frequencies (thanks to a unique combination of wavelet analysis multivariate methods and advanced source localization methods), and to apply it in real time in a neurofeedback paradigm.

1.2 METHODOLOGY

Task 1: Design the brain network estimation framework

The framework will consist in different modules that are inter-dependant. The first step will be to perform wavelet decomposition of the data at the sensor level, followed by a whitening procedure that allows compensating for the low amplitude of high frequency activity. We will use a technique that we introduced recently, based on empirical Bayesian estimation in the wavelet domain. The method will be first applied in the sensor space. The second will be independent component analysis, applied to the whitened data. Components that are not related to brain activity - as shown by their spatial characteristics - will be removed, leading to a reduced subspace containing large-band and denoised neuronal activity. Then the time courses for each brain regions and at each wavelet scale will be estimated based on a entropy framework (Lina *et al.*, 2014). The interaction within and between scales will be computed with two variations: phase locking and envelope correlations, in order to take into account putative different mechanisms of coupling. Finally, state of the art graph inference techniques will be employed (and adapted) to disentangle the brain networks involved across frequencies in a given period of time.

The method will be developed thanks to ultra-realistic simulations based on the virtual brain environment, developed within the Institut de Neuroscience des Systèmes by Viktor Jirsa's team. The deliverable of this task will be a software that estimates brain networks at different frequencies, either in offline processing or in real time.

Task 2: Validate method on simultaneous depth and surface recordings

Our team has setup up a strategy for recording simultaneously depth (intracerebral EEG, performed during presurgical evaluation of epilepsy) and surface activity (EEG and magnetoencephalography). These unique recordings allow validating the results obtained from surface recording with a "ground truth" measured directly within the brain. Thus, we will compare the networks obtained non-invasively with that reconstructed on

intracerebral recordings, using the same methodology by without the need for solving an inverse problem. The framework will be applied both in an offline manner, and in an emulated real time manner.

We will use a population of 20 patients, recorded in the MEG centre of Marseille. The protocol for recording the simultaneous data has already obtained acceptance from the local ethical committee (CCPRB). The deliverable of this task will be a validated framework for estimating brain networks across frequencies in real time and offline.

Task 3: Apply the method in the context of neurofeedback for epilepsy

We will implement the method, validated in the previous tasks, in a neurofeedback paradigm. The system will be trained on each patient's brain signals (EEG and MEG) obtained clinically during non-invasive evaluation of epilepsy. The regions and frequency involved in the epileptic discharges will be identified in a patient specific manner. Then, in a series of 5 neurofeedback sessions, the level of synchrony within the patient's own epileptic network will be presented to the patient. We will use software for real -time methods that have already been developed and that are compatible with the amplifiers used in the MEG center (either OpenVIbe or the real-time modules of the Fieldtrip toolbox).

The patient will be asked to lower the level of synchrony, as was performed previously at the Timone hospital using skin galvanic response. The temporal evolution of synchrony across each session will be assessed. our hypothesis is that patients will be able to learn how to decrease synchrony in an internal manner, thus reducing the need for surgery. This should be particularly interesting for patients that are difficult to operated due to the location of their epileptogenic tissues, which could lead to postsurgical deficits.

1.3 WORK PLAN

Gantt Chart

year	**1**				**2**				**3**			
month	**1**	4	7	10	**13**	16	19	22	**25**	28	31	34
Task 1 Design	M	X	X	X	X	D1						
Task 2 Validate				X	M	X	D2					
Task 3 Neurofeedback						X	X	X	X	X	W	D3

Deliverables

D1 Software that estimates brain networks at different frequencies. Publication 1 : a novel method of estimation

D2 Validation on simultaneous recordings. Publication 2: validation of multi frequency brain network estimations based on a ground truth

D3: Application to neurofeedback . Publication 3: added value of neurofeedback in clinical care of epilepsy patients.

M: Stays of the candidate in Montreal laboratory, under joint supervision of C Grova and JM Lina.

W: Write thesis; finalise publications

1.4 SUPERVISORS AND RESEARCH GROUPS DESCRIPTION

The dynamical brain mapping (Dynamap) team (head C Bénar): This team is within the Institut de Neuroscience des Systèmes (head V Jirsa) The principal objective of the Dynamap group is to design and optimize signal processing methods for multimodal functional investigation of human cerebral activity (pathological and physiological). Our interests are structured into two research axes: (i) Fusion of recordings from multimodal non-invasive techniques (ii) Confrontation of non-invasive results with depth EEG. Our research is in strong collaboration with the other teams of the laboratory, as well as the Clinical Neurophysiology department and the Stereotactic and Functional Neurosurgery department of the Timone hospital, Marseille (AP-HM).

The magnetoencephalography center is part of the Institut de Neurosciences des systèmes, and is hosted within the clinical neurophysiology department of the Timone hospital (Assistance Publique - Hôpitaux de MArseille, AP-HM). It is an open platform for users from the neuroscience community, and is part of the collaborative Convergence projet Institute language, communication and brain (ILCB). It also takes part in the presurgical evaluation of patients with epilepsy, though the involvement in a day hospital, in link with AP-HM.

Institut de recherche mathématique The "Institut de Mathématiques de Marseille" (I2M, UMR 7373) is a joint research unit Aix-Marseille Université/CNRS/Centrale Marseille. It hosts around 130 teacher-researchers, 30 CNRS researchers, 15 technical and administrative staff, 60 PhD students and 20 postdocs. The I2M arose from the fusion, on janvier 1, 2014, of the LATP (Laboratoire d'Analyse, Topologie et Probabilités) and the IML (Institut de Mathématiques de Luminy).

Other funds: A pre-prosal was submitted to the call from Agence Nationale de la Recherche, "projet de recherche collaborative-internationale" (PRCI). A full proposal will be submitted in April 2017. This proposal includes the Canadian partner (concordia university). This grant will permit funding travels, as well as recruit other members (postdocs). To be noted: the current PhD project as proposed is feasible even without this grant. In particular, all the equipment, infrastructures, support of permanent engineers are already in place.

REFERENCES

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Brookes M J, Woolrich M W and Barnes G R 2012 Measuring functional connectivity in MEG: a multivariate approach insensitive to linear source leakage *Neuroimage* **63** 910-20

Canolty R T, Edwards E, Dalal S S, Soltani M, Nagarajan S S, Kirsch H E, Berger M S, Barbaro N M and Knight R T 2006 High gamma power is phase-locked to theta oscillations in human neocortex *Science* **313** 1626-8

Dehghani N, Bedard C, Cash S S, Halgren E and Destexhe A 2010 Comparative power spectral analysis of simultaneous elecroencephalographic and magnetoencephalographic recordings in humans suggests non-resistive extracellular media *J Comput Neurosci* **29** 405-21

Florin E and Baillet S 2015 The brain's resting-state activity is shaped by synchronized cross-frequency coupling of neural oscillations *Neuroimage* **111** 26-35

Jmail N, Gavaret M, Wendling F, Kachouri A, Hamadi G, Badier J-M and Bénar C-G 2011 A comparison of methods for separation of transient and oscillatory signals in EEG *Journal of neuroscience methods* **199** 273-89

Kubik A and Biedron A 2013 Neurofeedback therapy in patients with acute and chronic pain syndromes--literature review and own experience *Przegl Lek* **70** 440-2

Lachaux J P, Fonlupt P, Kahane P, Minotti L, Hoffmann D, Bertrand O and Baciu M 2007 Relationship between task-related gamma oscillations and BOLD signal: new insights from combined fMRI and intracranial EEG *Hum Brain Mapp* **28** 1368-75

Lina J M, Chowdhury R, Lemay E, Kobayashi E and Grova C 2014 Wavelet-based localization of oscillatory sources from magnetoencephalography data *IEEE Trans Biomed Eng* **61** 2350-64

Micoulaud-Franchi J A, Kotwas I, Lanteaume L, Berthet C, Bastien M, Vion-Dury J, McGonigal A and Bartolomei F 2014 Skin conductance biofeedback training in adults with drug-resistant temporal lobe epilepsy and stress-triggered seizures: a proof-of-concept study *Epilepsy Behav* **41** 244-50

Nikolic D, Fries P and Singer W 2013 Gamma oscillations: precise temporal coordination without a metronome *Trends Cogn Sci* **17** 54-5

Sergent C, Baillet S and Dehaene S 2005 Timing of the brain events underlying access to consciousness during the attentional blink *Nat Neurosci* **8** 1391-400

Urrestarazu E, Chander R, Dubeau F and Gotman J 2007 Interictal high-frequency oscillations (100-500 Hz) in the intracerebral EEG of epileptic patients *Brain* **130** 2354-66

2. 3I DIMENSIONS AND OTHER ASPECTS OF THE PROJECT

2.1 INTERDISCIPLINARY DIMENSION

Christian Bénar was trained in biomedical engineering. His research interest is application of brain mapping methods (fMRI, EEG, MEG), in order to characterize the spatio-temporal dynamics of networks in cognition and

disease. One key project of his team is simultaneous recordings of surface (EEG, MEG) and depth (SEEG) signals. Another project is the development and translation of signal processing tools to clinicians, though the Anywave software. He is affiliated to the doctoral school "life science" of Aix-Marseille university.

The role of Christian Benar's team in the project will be to provide the expertise on brain signal acquisition and analysis in a clinical context, as well as setting up the acquisition of signals on patients (simultaneous MEG and SEEG recordings, real time processing of EEG, MEG and SEEG). Collaborations will be set up within the Institut de Neuroscience des Systèmes in order to use the Virtual Brain environment (hosted and developped at INS) for setting up ultra-realistic simulations.

Bruno Torrésani is a mathematician. His research interests concern mathematical signal processing, with emphasis on harmonic analysis and probability based approaches, and applications to various domains, including audio signal processing, neuroscience signals and molecular biology. Bruno Torrésani is affiliated to the "Ecole doctorale en mathématiques et informatique" of AMU.

The role of Bruno Torrésani will be to provide expertise and guidance on development of new methods for characterizing brain networks based on advanced signal processing methods, in particular wavelet analysis and time-frequency analysis, high dimensional statistical modelling and multivariate methods (independent component analysis, non-negative matrix factorization).

2.2 INTERSECTORAL DIMENSION:

The intersectoral partner will be the Clinical Neurophysiology department of the Timone Hospital (AP-HM), headed by Fabrice Bartolomei. This department will provide access to patients, though a protocol that will be submitted to the relevant ethical committee through AP-HM, and will bring expertise on the interpretation of clinical data.

The project will help improving the care of patients with difficult cases of epilepsy by developing a new technology (neurofeedback based on advanced characterization of brain networks). It therefore fits perfectly in the Stratégie Régionale d'innovation "Santé " under the guideline "améliorer la prise en charge des patients et le dépistage précoce (prévention, aide au diagnostic et développement de nouvelles technologies médicales)".

We expect that the technological developments set up during this project will give rise to a system that can be transferred to industry though patents and software.

The candidate will be hosted within the magnetoencephalography center, a part if the Institut de Neurosciences des Systèmes located within the clinical neurophysiology department of Timone hospital. This constitutes a unique environment for development of applied mathematics methods while being in a "real life" situation. As a consequence, interactions with clinicians will happen in an everyday basis.

2.2 INTERNATIONAL DIMENSION:

The project will happen in collaboration with Christophe Grova (Concordia University) and Jean-Marc Lina (Ecole de Technologie supérieure, Montréal), who are both affiliated to the Centre de Recherche Mathématiques from Université de Montréal. These researchers are experts in source localisation methods applied to brain signals, and in particular in the combination of wavelet analysis and advanced source localisation. The candidate will benefit from their expertise, though short stays in Montreal. More funding will

be sought in order to set in place bilateral exchanges of researchers. Bruno Torrésani is currently staying 6 month at the CRM in collaboration with Jean-Marc Lina, which is participating to strengthening links between AMU and CRM. The current project will help continuing this process.

3. RECENT PUBLICATIONS

From C Bénar

Roehri N, Lina JM, Mosher JC, Bartolomei F, Benar CG. Time-Frequency Strategies for Increasing High-Frequency Oscillation Detectability in Intracerebral EEG. IEEE Trans Biomed Eng. 2016 Dec;63(12):2595-2606.

Jmail N, Gavaret M, Bartolomei F, Chauvel P, Badier JM, Bénar CG. Comparison of Brain Networks During Interictal Oscillations and Spikes on Magnetoencephalography and Intracerebral EEG. Brain Topogr. 2016 Sep;29(5):752-65.

Colombet B, Woodman M, Badier JM, Bénar CG. AnyWave: a cross-platform and modular software for visualizing and processing electrophysiological signals. J Neurosci Methods. 2015 Mar 15;242:118-26.

Dubarry AS, Badier JM, Trébuchon-Da Fonseca A, Gavaret M, Carron R, Bartolomei F, Liégeois-Chauvel C, Régis J, Chauvel P, Alario FX, Bénar CG. Simultaneous recording of MEG, EEG and intracerebral EEG during visual stimulation: from feasibility to single-trial analysis. Neuroimage. 2014 Oct 1;99:548-58.

Malinowska U, Badier JM, Gavaret M, Bartolomei F, Chauvel P, Bénar CG. Interictal networks in magnetoencephalography. Hum Brain Mapp. 2014 Jun;35(6):2789-805.

From B Torrésani

H. Omer and B. Torrésani Time-frequency and time-scale analysis of deformed stationary processes, with application to non-stationary sound modeling, Applied and Computational Harmonic Analysis in press

J. Spinnato, M.-C. Roubaud, M. Perrin, E. Maby, J. Mattout, B. Burle and B. Torrésani Analyse discriminante matricielle descriptive. Application a l'étude de signaux EEG Journées de statistique de la SFDS, Juin 2015, Lille, France , (2015).

J. Spinnato, M.C. Roubaud, B. Burle, B. Torrésani. Detecting single-trial EEG evoked potential using a wavelet domain linear mixed model: application to error potentials classification. J Neural Eng. 2015 Jun;12(3):036013.

J. Spinnato, M.-C. Roubaud, B. Torrésani and B. Burle Finding EEG space-time-scale localized features using matrix-based penalized discriminant analysis Proceedings of ICASSP, IEEE Conference on Acoustics, Speech and Signal Processing, Florence (Italy), (2014).

B. Ricaud, G. Stempfel, B. Torrésani, C. Wiesmeyr, H. Lachambre, D. Onchis An optimally concentrated Gabor transform for localized time-frequency components Advances in Computational Mathematics 40:3 (2014), pp. 683-702.

From the Montreal team

Chowdhury RA, Merlet I, Birot G, Kobayashi E, Nica A, Biraben A, Wendling F, Lina JM, Albera L, Grova C. Complex patterns of spatially extended generators of epileptic activity: Comparison of source localization methods cMEM and 4-ExSo-MUSIC on high resolution EEG and MEG data. Neuroimage. 2016 Dec;143:175-195.

Lee K, Lina JM, Gotman J, Grova C. SPARK: Sparsity-based analysis of reliable k-hubness and overlapping network structure in brain functional connectivity. Neuroimage. 2016 Jul 1;134:434-49.

Chowdhury RA, Zerouali Y, Hedrich T, Heers M, Kobayashi E, Lina JM, Grova C. MEG-EEG Information Fusion and Electromagnetic Source Imaging: From Theory to Clinical Application in Epilepsy. Brain Topogr. 2015 Nov;28(6):785-812.

Lina JM, Chowdhury R, Lemay E, Kobayashi E, Grova C. Wavelet-based localization of oscillatory sources from magnetoencephalography data. IEEE Trans Biomed Eng. 2014

4. EXPECTED PROFILE OF THE CANDIDATE

The candidate is expected to have initial training in engineering, applied mathematics, physics or signal processing. He/she should have interest in the development application of advanced signal processing methods to brain mapping in a clinical context. Programming skills in Matlab or Python are required, as well as academic knowledge on signal processing algorithms, including wavelet and multivariate statistics. Knowledge on inverse problem, as well as signal acquisition including real time acquisition and processing would be an added value to the profile.

5. SUPERVISORS' PROFILES

Christian Bénar was initially trained at Ecole Supérieure d'Electricité (Supélec), from 1991 to 1994. Then, he worked at a software developper for a EEG software company (Stellate Systems, Montreal). He came back to the academics in 1998, for a master in biomedical engineering transferred to PhD in 2001, under supervision of Jean Gotman. After two postdoctoral stays at Inserm in Marseille and INRIA in Sophia Antipolis, he was hired accepted as an Inserm researcher in 2006. Since 2012, he is the head of the Dynamical Brain Mapping team of the Institute de Neurosciences des systèmes. Since 2014, he is also the scientific head of the magnetoencephalography center of Marseille.

Christian Bénar's current supervision

As principal supervisor (in co supervision with F Bartolomei)

Nicolas Roehri start 05/01/15 (expected end dec 2017)
Stanislas Lagarde start 01/10/2015
Francesca Pizzo start 13/10/16

as co-supervisor: I Lambert start 2014

Christian Bénar's previous supervision

Nawel Jmail 2009-2012, publications J Neurosci Meth 2011, Brain topogr 2016, Phys Meas in press; actuellement maître assistante à l'ESCS (Sfax, Tunisie), chercheur miracl / INS

as co-supervisor:

J Wirsich 2013-2016 (superviseur principal M Guye), publications Neuroimage 2014, 2016; currently postdoc at Beckmann Institute, Illinois

AS Dubarry 2013-2016 (superviseur principal X Alario), publications Neuroimage 2014, Psych Science in press; now holding a permanent Research Engineer position at CNRS

J Krieg 2012-2016 (superviseur principal L Maillard), publications Cortex 2014, Neuroimage under review; currently working at CRAN Nancy.

B Torrésani received a PhD degree in theoretical physics at Université de Provence (Marseille) in 1986, and the habilitation degree at Université de la Méditerranée (Marseille) in 1993. He held a *Chargé de Recherches* position at CNRS from 1989 du 1998, and is now a Professor at Université d'Aix-Marseille, in the *Département de Mathématiques* and *Institut de Mathématiques de Marseille*, In the *Signal-Image* team. He has been the director of *Laboratoire d'Analyse, Topologie et Probabilités* (2012-13) and *Institut de Mathématiques de Marseille* (2014-15).

B. Torrésani's current supervision :

Adrien Meynard (single supervisor, start september 2016)

Bruno Torrésani's recent supervision:

Juliette Spinnato (principal supervisor, co-supervisor B. Burle), 2012-16, publications, *J Neural Eng.*, IEEE ICASSP 2015, *SFDS* 2014, 2016

Harold Omer (single supervisor), 2012-16, publications Applied and Computational Harmonic Analysis, in press, SAMPTA 2013

Ichrak Toumi (co-supervisor, principal supervisor S. Caldarelli), 2012-15, publications Analytical Chemistry 2013, Progress in NMR Spectroscopy 2014