# LIST OF PROJECTS (3)

## MD PHD SCHOLARSHIPS

## MARCH 2020

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# PROJECT M1

**Title** : Improving postural control by optimizing muscle proprioceptive information

**Supervisor** : BOREL Liliane (liliane.borel@univ-amu.fr - +33 (0)4 13 55 08 73)

**Laboratory** : Sensory and Cognitive Neuroscience Laboratory (LNSC, UMR 7260)

https://lnsc.fr/equipe/rehabilitation-sensorielle-et-cognitive

**Project**

**STATE OF THE ART :** Unilateral loss of vestibular information originating in the inner ear leads to perceptual (dizziness), oculomotor (nystagmus) and postural (loss of balance) symptoms. Vestibular compensation following this loss is a model of neuronal plasticity mainly based on sensory interactions and substitutions. Surprisingly, different individuals with apparently identical vestibular loss have different recovery processes. Some may recover fully, while others may retain balance difficulties. This phenomenon is of great scientific and clinical importance. What is the reason for this difference? This question is still unresolved. Our hypothesis is based on the idea that the alteration in postural stability is the result of an incorrect weighting of the different sensory information in the compensation process, more specifically related to poor proprioceptive feedback.

**OBJECTIVES** : In order to test this hypothesis, we propose a study whose aim is to test the effect of optimizing muscle proprioceptive information on postural control.

**METHODS** : Two methods will be used. The first is based on the application of mechanical noise to the tendons of the ankle muscles. In healthy subjects, we have shown that this type of stimulation leads to an improvement in postural control (Borel and Ribot-Ciscar, 2016). The second method consists of exercises to focus attention on illusory movements of the foot. Indeed, when the subject pays attention to the movements imposed on the ankle joint, this leads to sensitisation of the neuromuscular spindles (Ribot-Ciscar et al. 2009). The tests will be performed in patients with unilateral vestibular loss and in control subjects with no sensory impairment.

**EXPECTED RESULTS** : The expected results are an improvement in postural balance by increasing the weight of muscular proprioceptive information in balance, particularly in visually dependent patients who probably make little use of proprioceptive sensitivity. These results could be at the origin of a new rehabilitation method, appropriate not only after vestibular damage but also in all pathologies where the weighting of sensory information shows a deficit in the use of proprioceptive information.

**FEASABILTY :** Feasibility is attested by the expertise of the researchers involved in this study: Liliane Borel for vestibular compensation and sensory substitution and Edith Ribot-Ciscar for the proprioceptive modality. The study has begun. Thirty healthy subjects and thirty vestibulo-deficient patients will be included in this research.

**EXPECTED CANDIDATE PROFILE** : French-speaking physician (to interact well with patients). The candidate should have experience in ENT or Neurology.

## NAMES AND DATES OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Mathilde Bachelard-Serra. Thèse de Doctorat en Médecine (Aix-Marseille Université). Soutenue le 17 avril 2015
- Thierry Paillard. Thèse de Doctorat de l'Université de Provence. Soutenance le 17 décembre 2010

## PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Saj A, Bachelard-Serra M, Honoré J, Lavieille JP, Borel L. Body representation of vestibular-defective patients before and after unilateral vestibular neurotomy. JAMA otolaryngology. Head and Neck surgery (under preparation)

- Borel L, Bachelard-Serra M, Saj A, Lavieille JP, Honoré J Changes in body spatial representation after unilateral vestibular loss are modulated by the side of the lesion and the post-lesion delay. Cortex (under preparation)

- Paillard T, Chaubet V, Maitre J, Dumitrescu M, Borel L (2010) Disturbance of contralateral unipedal postural control after stimulated and voluntary contractions of the ipsilateral limb. Neurosci Res 68(4): 301-6

- Paillard T, Maitre J, Chaubet V, Borel L (2010) Stimulated and voluntary fatiguing contractions of quadriceps femoris differently disturb postural control. Neurosci Lett. 477(1): 48-51.

- Paillard T, Margnes E, Maitre J, Chaubet V, François Y, Jully JL, Gonzalez G, Borel L (2009) Electrical stimulation superimposed onto voluntary muscular contraction reduces deterioration of both postural control and quadriceps femoris muscle strength. Neuroscience 165 (4): 1471-5

# PROJECT M2

**Title** : Understanding brain network disruption in subjective cognitive decline using Electroencephalography

**Supervisor** : PABAN Véronique (veronique.paban@univ-amu.fr) - +33 (0)6 31 78 82 25)

**Laboratory** : Sensory and Cognitive Neuroscience Laboratory (LNSC, UMR 7260)

https://lnsc.fr/

**Project**

**STATE OF THE ART :** Older adults with subjective cognitive decline (SCD) are increasingly viewed as being at risk for nonnormative cognitive decline and eventual progression to Alzheimer's disease (AD) dementia. SCD refers to a self-perception of progressive deterioration of cognitive abilities independently of the objective performance on neuropsychological tests. It has been proposed that SCD be considered stage 3 of preclinical AD, which is described as the stage in which the first changes in cognition emerge, before mild cognitive impairment (MCI) can be detected. During AD progression, various Electroencephalography (EEG) changes have been identified. However, the network alterations at rest (in the absence of any specific stimulus) and during cognitive tasks for the very early stages of AD remain elusive. To tackle this problem, we aim using a very recent method called "EEG source connectivity" to detect alterations in SCD brain networks compared to age-matched healthy subjects. This method conceptually represents a breakthrough in network neuroscience, since high spatiotemporal resolution networks can be directly identified at the level of cortical regions. In this project, we will explore and quantify alterations in dynamic functional connectivity in SCD patients at rest and during tasks. Such analysis is essential to better understand SCD's brain networks and develop rehabilitation therapies based on real-time modulation of brain activity, such as neurofeedback.

**OBJECTIVES** : The specific objectives of the proposed project are i) explore, for the first time, the network disruptions in SCD as compared to healthy subjects at rest and during cognitive tasks; ii) quantify these network disruptions to develop EEG-based neuromarkers of SCD; and iii) enable the development of protocols of rehabilitation by neurofeedback training, guided by the network-based analysis.

**METHODS** : Eighty subjects will be recruited: 40 patients with SCD and 40 age-matched healthy elderly subjects. All participants will be evaluated using a battery of cognitive tasks and questionnaires which will be analyzed using Structural Equation Modeling. Dense-EEG (64 channels) will be recorded under "active" conditions (cognitive tasks) and during resting-state. EEG data will be analyzed using the EEG source connectivity method. The reconstructed functional networks will be characterized and quantified using graph theory-based metrics analysis.

**EXPECTED RESULTS :** Results will contribute to better understand SCD's brain networks. The developed network-based neuromarkers will be derived from EEG recordings performed during protocols that will reduce patients' efforts (resting state), or while activating key target large-scale brain networks (cognitive task). These data are necessary for the development of rehabilitation therapies based on neurofeedback, in which knowledge is required on both the EEG frequency bands to train and the brain regions to target.

**FEASABILITY :** EEG and neurofeedback material are available. Financial support exists for subjects' compensation fees. Our lab has expertise in EEG data analysis and cognitive evaluation.

**EXPECTED CANDIDATE PROFILE :** The candidate will have to take in charge the subjects. Take care of the cognitive testing and ensure EEG and Neurofeedback experiences. Also, the subject will have to be able to speak French.

## NAMES AND DATES OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- A. Kabbara (2016-2018)
- N. Sambuchi (2010-2014)
- C. Chambon (2006-2009)

## PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :


- Detecting dynamic changes in modular organization of spontaneous brain activity: A preliminary study. Kabbara A, **Paban V**., Hassan M. IEEE. 2019. In press
- Subjective cognitive impairment and Alzheimer's disease: a two year follow up of 51 subjects during two years. Sambuchi N, Muraccioli I, Alescio-Lautier B, **Paban** V, Sambuc R, Jouve É, Geda YE, Petersen RK, Michel BF. Geriatr Psychol Neuropsychiatr Vieil. 2015 Dec;13(4):462-71.
- In Alzheimer's disease, the clinical expression of behavioral and psychological signs and symptoms is early and specific of neuropathological stages. Michel BF, Luciani V, Geda YE, Sambuchi N, **Paban** V, Azorin JM. Encephale. 2010 Sep;36(4):314-25
- Benefits of computer-based memory and attention training in healthy older adults. Chambon C, Herrera C, Romaiguere P, **Paban V**, Alescio-Lautier B. Psychol Aging. 2014 Sep; 29(3):731-43.

# PROJECT M3

**Title** : Blood-based biomarkers for traumatic brain injury

**Supervisor** : RIVERA Claudio (claudio.rivera@inserm.fr - +33 (0)4 91 82 81 13

**Co supervisor** : PELLEGRINO Christophe (christophe.pellegrino@univ-amu.fr - +33 (0)6 03 67 45 13)

**Laboratory** : Mediterranean Institute of Neurobiology (INMED, UMR 1249)

http://www.inmed.fr/

**Project**

**STATE OF THE ART :** Traumatic brain injury (TBI) is a major public health problem. It is amongst the leading causes of mortality in young people, and many survivors of TBI suffer from persistent disabilities. As a result, there remains an unmet clinical need for the development of more robust diagnostic and prognostic indicators of TBI. Biomarkers can be any quantifiable product serving as a marker of physiopathological state of a subject at a certain time point or disease state *(Strathmann.F et al, 2018)*. They can indicate health, pathology, or response to treatment, including unwanted side effects. Blood biomarkers are valuable tools for elucidating complex cellular and molecular mechanisms underlying traumatic brain injury. Profiling distinct classes of biomarkers could aid in the identification and characterization of initial injury and secondary pathological processes *(Battista. A et al, 2015)*. Biomarkers, to assess neurological involvement, should be objective, inexpensive, easily accessible, noninvasive tools to monitor the course of infection and identify those at risk for neurological damage. While cerebrospinal fluid (CSF) is thought to be closest to the neuropathology, it is an invasive procedure, and like blood, will have a complex protein profile comprised of different cell types. Exosomes are 30–150 nm microvesicles formed in late endosomes and collected as multivesicular bodies prior to fusion with the plasma membrane. They are shed from various cells under normal as well as pathological conditions into the surrounding milieu including plasma, urine, saliva and inflammatory tissues. The cellular cargo packaged into exosomes can be significantly altered depending on the physiological state of the parent cell including immune activation *(Sun.B et al, 2018)*. Most cells in the (CNS) nervous system including neurons, astrocytes, oligodendrocytes and microglia shed exosomes (Review *Gupta.A et al, 2014)*. These extracellular vesicles are secreted by neural cells under normal and pathological conditions and have been isolated from the CSF, adult human brain and recently plasma. Exosomes can reflect the host cell proteins and nucleic acids at the time of secretion, and can be taken up by recipient cells thereby altering their function and setting off a cascade of events that alter homeostasis *(lynn.P et al, 2018)*. Exosomes can diffuse across the blood brain barrier (BBB) into the periphery and be captured by antibodies directed against the cell surface proteins embedded in the vesicle membrane. This strategy has been used to isolate neuron-derived exosomes (NDE) *(Mustapic.M et al, 2017)*. In this project, our goal is to identify and characterize the diagnostic and prognostic performance of blood biomarkers that reflect specific pathogenic mechanisms including neuroinflammation, oxidative damage, and neuroregeneration, and to use circulating neuronal derived exosomes as a new source of biomarkers.

Our approach combines a biochemical study by analysis of candidate proteins by western blot and an RNAseq analysis to target on a large scale the constitution of circulating cerebral exosomes. Thus, the expected results will be to confirm a specific isolation method of neuronal derived exosomes combined with rapid detection of proteins (western blot, proteomics) or miRNA (Q-PCR), and to go through a first validation step for candidate biomarkers useful for the early detection of post-traumatic disorders (primary screening, first hours) and for the evaluation of the disease (severity, functional consequences) also for early assessment of response to therapeutic agents. The feasibility of the project is good, the murine model of trauma is used routinely in the team, the institute is fully equipped to conduct all of the studies and the staff of the team trained in all the approaches necessary to the success of this project. The first two years of the project, our student learnt the needed technology and abilities that allowed us to detect some of our candidate markers of interest in biological samples. In the third year we will try to characterize the fluctuation of those candidates in TBI context.

## RIVERA / NAMES AND DATES OF THE CURRENTLY SUPERVISED PHD STUDENTS :

- Marine TESSIER 3rd year
- Amina REZZAG LEBZA 2nd year

## RIVERA / NAMES AND DATES OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Mike Yuryev (2018)
- Emmanuelle Goubert (2017)
- Nazim Kourdougli (2015)
- laya Llano (2015)
- Judith Thomas-Crusells (2004)
- Hong Li (2008)
- Anastasia Ludwig (2008)
- Anastasia Shulga (2010)

## RIVERA / PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :


- Thomas-Crusells, J., Vieira, A., Saarma, M., Rivera, C. A novel method for monitoring cell surface membrane trafficking on hippocampal acute slice preparation. (2003) J.Neurosci. Methods 125:159-166.
- Li, H, Tornberg, J., Kaila, K., Airaksinen, M. Rivera, C. (2002). Patterns of cation-chloride cotransporter expression during embryonic rodent CNS development Eur. J. Neurosci. 16: 2358-2370.
- Ludwig, A., Li, H., Saarma, M., Kaila, K., Rivera, C. (2003). Developmental up-regulation of KCC2 in the absence of GABAergic and glutamatergic transmission. Eur. J. Neurosci. 18: 3199-3206.

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- Khirug S, Huttu K, Ludwig A, Smirnov S, Voipio J, Rivera C, Kaila K, Khiroug L. (2005). Distinct properties of functional KCC2 expression in immature mouse hippocampal neurons in culture and in acute slices. Eur J Neurosci. 21:899-904.
- Cai C, Li H, Rivera C, Keinanen K. (2005) Interaction between SAP97 and PSD-95, two Maguk proteins involved in synaptic trafficking of AMPA receptors. J Biol Chem. 281(7):4267-73
- Uvarov P, Ludwig A, Markkanen M, Rivera C, Airaksinen MS. (2007) Upregulation of the neuron- specific K+/Cl- cotransporter expression by transcription factor early growth response 4.
- J Neurosci. 26:13463-73.
- Uvarov P, Ludwig A, Markkanen M, Pruunsild P, Kaila K, Delpire E, Timmusk T, Rivera C, Airaksinen MS.(2007) A Novel N-terminal Isoform of the Neuron-Specific K-Cl cotransporter KCC2. J Biol Chem. 282:30570
- Li H, Khirug S, Cai S, Ludwig A, Blaesse P, Kolikova J, Afzalov R, Coleman SK, Lauri S, Airaksinen MS, Keinänen K, Khiroug L, Saarma M, Kaila K, Rivera C. (2007) KCC2 interacts with the dendritic cytoskeleton to promote spine development. Neuron 56:1019-33
- Cai C, Li H, Kangasniemi A, Pihlajamaa T, Von Ossowski L, Kerkelä K, Schulz S, Rivera C, Keinänen K. (2008) Somatostatin receptor subtype 1 is a postsynaptic density-95/discs large/zona occludens-1 ligand for synapse-associated protein 97 and a potential regulator of growth cone dynamics. Neuroscience 157:833-43
- Shulga A, Thomas-Crusells J, Sigl T, Blaesse A, Mestres P, Meyer M, Yan Q, Kaila K, Saarma M, Rivera C, Giehl KM. (2008) Posttraumatic GABA(A)-mediated [Ca2+]i increase is essential for the induction of brain-derived neurotrophic factor-dependent survival of mature central neurons. J Neurosci. 28:6996-7005
- Hotulainen P, Llano O, Smirnov S, Tanhuanpää K, Faix J, Rivera C, Lappalainen P. (2009) Defining mechanisms of actin polymerization and depolymerization during dendritic spine morphogenesis. J Cell Biol. 185:323-39.
- Uvarov P, Ludwig A, Markkanen M, Soni S, Hübner CA, Rivera C, Airaksinen MS. (2009) Coexpression and heteromerization of two neuronal K-Cl cotransporter isoforms in neonatal brain. J Biol Chem. 284:13696-704.
- Shulga, A., Blaesse, A., Tanhuanpää, K., Saarma, M. and Rivera C. (2009) Thyroxin regulates BDNF expression to promote survival of injured neurons Mol Cell Neurosci. 42:408-18.
- Ludwig A, Uvarov P, Soni S, Thomas-Crusells J, Airaksinen M and Rivera C. (2011) Egr4 mediates BDNF induction of KCC2 transcription. J. Neurosci. 31(2):644-9.

- Ludwig A, Uvarov P, Pellegrino C, Thomas-Crusells J, Schuchmann S, Saarma M, Airaksinen MS, Rivera C. (2011) Neurturin evokes MAPK-dependent upregulation of Egr4 and KCC2 in developing neurons. Neural Plast. 2011:1-8.
- Shulga A, Magalhães A, Autio H, di Lieto A, Nykjær A, Arumäe U, Castrén C and Rivera C. (2012) GABAA-mediated [CA2+]i increase uprgulates P75NTR to trigger BDNF dependency in axotomized mature central neurosn. J. Neurosci. 35:1757-70.
- Shulga A, Rivera C. (2013) Interplay between thyroxin, BDNF and GABA in injured neurons.Neuroscience. 239:241-52.
- Markkanen M, Karhunen T, Llano O, Ludwig A, Rivera C, Uvarov P, Airaksinen MS. (2014) Distribution of neuronal KCC2a and KCC2b isoforms in mouse CNS. J Comp Neurol. 522: 1897-1914
- Pallud J, Le Van Quyen M1, Bielle F, Pellegrino C, Varlet P, Cresto N, Baulac M, Duyckaerts C, Kourdougli N, Chazal G, Devaux B, Rivera C, Miles R, Capelle L, Huberfeld G (2014) Cortical GABAergic excitation contributes to epileptic activities around human glioma. Science Trans. Med. 6: 244-89.
- Saarikangas J, Kourdougli N, Senju Y, Chazal G, Segerstråle M, Minkeviciene R, Kuurne J, Mattila P,Garrett L,Hölter S M, Becker L, Racz I, Hans W, Klopstock T, Wurst W, Zimmer A, Fuchs
- Llano, O., Smirnov, S., Golubtsov, A., Soni, S., Guillemin, I., Hotulainen, P., Medina, I., Nothwang, HG., Rivera, C. and Ludwig, A. (2015) KCC2 regulates actin dynamics in dendritic spines via interaction with βPix. J. Cell Biol. 209: 671-686.
- Kourdougli N, Varpula S, Chazal G, Rivera C. (2015) Detrimental effect of post Status Epilepticus treatment with ROCK inhibitor Y-27632 in a pilocarpine model of temporal lobe epilepsy. Front Cell Neurosci. 9:413.
- Markkanen M, Ludwig A, Khirug S, Pryazhnikov E, Soni S, Khiroug L, Delpire E, Rivera C, Airaksinen MS, Uvarov P. (2017) Implications of the N-terminal heterogeneity for the neuronal K-Cl cotransporter KCC2 function. Brain Res. 1675: 87-101
- Friedel P, Ludwig A, Pellegrino C, Agez M, Jawhari A, Rivera C, Medina I. (2017) A Novel View on the Role of Intracellular Tails in Surface Delivery of the Potassium-Chloride Cotransporter KCC2. eNeuro. 4(4).
- Ludwig A, Rivera C, Uvarov P. (2017) A noninvasive optical approach for assessing chloride extrusion activity of the K-Cl cotransporter KCC2 in neuronal cells. BMC Neurosci. 18: 23.
- Goubert E, Mircheva Y, Lasorsa FM, Melon C, Profilo E, Sutera J, Becq H, Palmieri F, Palmieri L, Aniksztejn L, Molinari F.Front Cell Neurosci. 2017 May 31;11:149. doi: 10.3389/fncel.2017.00149. eCollection 2017.
- Kourdougli N, Pellegrino C, Renko JM, Khirug S, Chazal G, Kukko-Lukjanov TK, Lauri SE, Gaiarsa JL, Zhou L, Peret A, Castrén E, Tuominen RK, Crépel V, Rivera C.Ann Neurol. 2017 Feb;81(2):251-265. doi: 10.1002/ana.24870.
- Goubert E, Altvater M, Rovira MN, Khalilov I, Mazzarino M, Sebastiani A, Schaefer MKE, Rivera C, Pellegrino C.Front Mol Neurosci. 2019 Feb 5;12:12. doi: 10.3389/fnmol.2019.00012. eCollection 2019

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- DiScala C, Tessier M, Sapet C, Poulhes F, Sicard F, Zelphati O & Pellegrino C. Journal of Neuroscience Methods 311 (2019) 295–306

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**PELLEGRINO / NAMES AND DATES OF THE CURRENTLY SUPERVISED PHD STUDENTS :**

- Marine TESSIER 3rd year
- Amina REZZAG LEBZA 2nd year

**PELLEGRINO / NAMES AND DATES OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :**

- GOUBERT Emmanuelle (defense 2017)

**PELLEGRINO / PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :**

- DiScala C, Tessier M, Sapet C, Poulhes F, Sicard F, Zelphati O & Pellegrino C. Journal of Neuroscience Methods 311 (2019) 295–306.
- Goubert E, Mircheva Y, Lasorsa FM, Melon C, Profilo E, Sutera J, Becq H, Palmieri F, Palmieri L, Anikstejn L, Molinari F.Front Cell Neurosci. 2017 May 31;11:149. doi: 10.3389/fncel.2017.00149. eCollection 2017.
- Goubert E, Altvater M, Rovira MN, Khalilov I, Mazzarino M, Sebastiani A, Schaefer MKE, Rivera C, Pellegrino C.Front Mol Neurosci. 2019 Feb 5;12:12. doi: 10.3389/fnmol.2019.00012. eCollection 2019
- Blauwblomme T, Dossi E, Pellegrino C, Goubert E, Iglesias BG, Sainte-Rose C, Rouach N, Nabbout R, Huberfeld G.Ann Neurol. 2019 Feb;85(2):204-217. doi: 10.1002/ana.25403. Epub 2019 Jan 17.