LIST OF PROJECTS (4)

INTERNATIONAL CO-SUPERVISED PHD SCHOLARSHIPS

MARCH 2021

TABLE OF CONTENTS

PROJECT C1

Title : Role of long-range projecting GABAergic neurons on temporal lobe epilepsy pathology

Supervisor : CREPEL Valérie

LABORATORY : INMED CITY : Marseille COUNTRY : France

MAIL : valerie.crepel@inserm.fr PHONE : +33491828115

LABORATORY WEBSITE : http://www.inmed.fr/en/integrative-properties-of-plastic-neuronal-circuits-in-health-and-disease-en

Co-supervisor : QUAIRIAUX Charles

LABORATORY : NEUFO CITY : Genève COUNTRY : Suisse

MAIL : Charles.Quairiaux@unige.ch PHONE : +41(0)22 3795457

LABORATORY WEBSITE : https://www.unige.ch/medecine/neuf/en/research/grecherche/christoph-michel

Duration (workload distribution among the two laboratories)

Planned dates and duration of the work in the AMU lab : 50%

Planned dates and duration of the work in the partner lab : 50%

State of the art
Temporal Lobe Epilepsy (TLE) is the most prevalent type of epilepsy in adults. Patient must cope with the generation of recurrent epileptic seizures, as well as numerous invalidating psychiatric and cognitive deficits. Even though the damaged hippocampus is still considered as a key actor in those pathological features, it is now postulated that TLE rather involves a network of altered brain structures within the temporal lobe and beyond. Last, a high fraction of patients with TLE are intractable to classical pharmacological treatments or even to surgery. Therefore, it appears particularly important regarding public health to understand better the pathological mechanisms underlying TLE in order to identify the targets for novel treatments. Using TLE rodent models, we particularly focus on a rare subset of inhibitory hippocampal long-range projecting neurons (HLRP), which is quite resistant to cell loss. In non-epileptic conditions, those HLRP neurons orchestrate behavior-related rhythmic activity in the hippocampus, and its coupling with other brain areas. Interestingly, those processes are deeply altered in context of TLE. We hypothesize that an alteration of those long-range projecting inhibitory neurons might be critically involved in TLE pathology. A dysregulation of those inhibitory neurons, may not only participate to the generation and the propagation of seizure, but also could interfere with functions normally handled by the hippocampus and the temporal lobe.
Objectives
The proposed PhD project proposes to investigate how HLRP function is altered in TLE condition, and its impact on the generation and the propagation of pathological activity, the alteration of physiological rhythmic activity and the associated behavioral deficits.
Methods
Experimentation on mice, in vitro and in vivo electrophysiological recordings (patch-clamp, EEG and/or multitrode recordings), neuronal manipulation techniques (using optogenetic and/or chemogenetic approaches) and behavioral testing.
Expected results
That ambitious project aims at unravelling a key mechanism of TLE pathology, and ultimately identifying a target for novel therapy for that disease via existing collaborations (Biotechs, clinic).
Feasibility
Project has been designed for 3 years. Every tool necessary for the project is routinely used by one or the other hosting lab, and projects using similar methodologies were already conducted in the last years (Marissal et al., 2018; Sheybani et al., 2018; 2019). The prospective student will be closely monitored by Drs. Valérie Crépel and Thomas Marissal (Marseille) for the study at the cellular level (patch-clamp, specific neuronal manipulation, etc.), and by Dr. Charles Quairiaux (Geneva) for the experiments at the macroscopic level (in vivo local and large-scale neuronal recordings, etc.). Other team members with compatible expertise (histological analysis, electrophysiology, programming, etc.) will participate to the project when necessary.
Complementarity of the two laboratories
High. The two groups specifically study TLE, however they use distinct recording techniques at different biological scales (i.e. neuronal/local network aspects in Marseille, large-scale brain network levels in Geneva).
Expected candidate profil
Candidates should have strong background in cellular neurobiology and should be familiarized with mouse experimentation

SUPERVISED PHDS & PUBLICATIONS : CREPEL Valérie

- **Currently supervised PhD students**

- Lucas Goirand-Lopez
- Alexandre Vigier

- **Previously supervised PhD students**

- Claire Pléau, PhD – November 2019
- Shu Xian Ho, PhD – December 2018
- Angélique Peret, PhD – November 2014
- David Ouedraogo, PhD – September 2013
- Julien Artinian, PhD – December 2012
- Jérôme Epsztein, PhD – December 2005
- Patrice Congar, PhD – December 1998

- **Publications of previously supervised PHD students**

- **Pléau C**, Peret A, Pearlstein E, Scalfati T, Marti G, Michel F, Crépel V. Dentate granule cells recruited in home environment display distinctive properties. Frontiers in Cellular Neuroscience, 2020.
- **Peret A**, Christie LA, **Ouedraogo** DW, Gorlewicz A, Epsztein J, Mulle C, Crépel V. Contribution of aberrant GluK2-containing kainate receptors to chronic seizures in temporal lobe epilepsy. Cell Rep. 2014 Jul 24;8(2):347-54.
- **Ouedraogo DW**, Lenck-Santini PP, Marti G, Robbe D, Crépel V, Epsztein J. Abnormal UP/DOWN Membrane Potential Dynamics Coupled with the Neocortical Slow Oscillation in Dentate Granule Cells during the Latent Phase of Temporal Lobe Epilepsy. eNeuro. 2016 May 31;3(3). pii: ENEURO.0017-16.2016.
- **Artinian J**, Peret A, Mircheva Y, Marti G, Crépel V. Impaired neuronal operation through aberrant intrinsic plasticity in epilepsy. Ann Neurol. 2015 Apr;77(4):592-606.
- Pinheiro PS, Lanore F, Veran J, **Artinian J**, Blanchet C, Crépel V, Perrais D, Mulle C. Selective block of postsynaptic kainate receptors reveals their function at hippocampal mossy fiber synapses. Cereb Cortex. 2013 Feb;23(2):323-31.
- **Artinian J**, Peret A, Marti G, Epsztein J, Crépel V. Synaptic kainate receptors in interplay with INaP shift the sparse firing of dentate granule cells to a sustained rhythmic mode in temporal lobe epilepsy. J Neurosci. 2011 Jul 27;31(30):10811-8.
- Goldin M, **Epsztein J**, Jorquera I, Represa A, Ben-Ari Y, Crépel V, Cossart R. Synaptic kainate receptors tune oriens-lacunosum moleculare interneurons to operate at theta frequency. J Neurosci. 2007 Sep 5;27(36):9560-72.
- **Epsztein J**, Milh M, Bihi RI, Jorquera I, Ben-Ari Y, Represa A, Crépel V. Ongoing epileptiform activity in the post-ischemic hippocampus is associated with a permanent shift of the excitatory-inhibitory synaptic balance in CA3 pyramidal neurons. J Neurosci. 2006 Jun 28;26(26):7082-92.

- **Epsztein J**, Represa A, Jorquera I, Ben-Ari Y, Crépel V. Recurrent mossy fibers establish aberrant kainate receptor-operated synapses on granule cells from epileptic rats. J Neurosci. 2005 Sep 7;25(36):8229-39.
- Crepel V, **Epsztein J**, Ben-Ari Y. Ischemia induces short- and long-term remodeling of synaptic activity in the hippocampus. J Cell Mol Med. 2003 Oct-Dec;7(4):401-7.
- Cossart R, **Epsztein J**, Tyzio R, Becq H, Hirsch J, Ben-Ari Y, Crépel V. Quantal release of glutamate generates pure kainate and mixed AMPA/kainate EPSCs in hippocampal neurons. Neuron. 2002 Jul 3;35(1):147-59.
- **Congar P**, Gaïarsa JL, Popovici T, Ben-Ari Y, Crépel V. Permanent reduction of seizure threshold in post-ischemic CA3 pyramidal neurons. J Neurophysiol. 2000 Apr;83(4):2040-6.
- Crépel V, **Congar P**, Anikstejn L, Gozlan H, Hammond C, Ben-Ari Y. Synaptic plasticity in ischemia: role of NMDA receptors. Prog Brain Res. 1998;116:273-85.
- **Congar P**, Leinekugel X, Ben-Ari Y, Crépel V. A long-lasting calcium-activated nonselective cationic current is generated by synaptic stimulation or exogenous activation of group I metabotropic glutamate receptors in CA1 pyramidal neurons. J Neurosci. 1997 Jul 15;17(14):5366-79

SUPERVISED PHDS & PUBLICATIONS : QUAIRIAUX Charles

- **Currently supervised PhD students**

- Selected PhDs: in animal epileptic models' studies, co-supervised with Dr. Charles Quairiaux: Guru Padmasola and Fabien Friscourt

- **Previously supervised PhD students**

- Selected PhD: in animal epileptic models' studies, co-supervised with Dr. Charles Quairiaux: Laurent Sheybani, 2016

- **Publications of previously supervised PHD students**

- Sheybani, L., Birot, G., Contestabile, A., Seeck, M., Kiss, J.Z., Schaller, K., Michel, C.M., and Quairiaux, C. (2018). Electrophysiological Evidence for the Development of a Self-Sustained Large-Scale Epileptic Network in the Kainate Mouse Model of Temporal Lobe Epilepsy. J. Neurosci. *38*, 3776–3791.
- Sheybani, L., van Mierlo, P., Birot, G., Michel, C.M., and Quairiaux, C. (2019). Large-Scale 3–5 Hz Oscillation Constrains the Expression of Neocortical Fast Ripples in a Mouse Model of Mesial Temporal Lobe Epilepsy. ENeuro *6*.
- Słowiński, P., Sheybani, L., Michel, C.M., Richardson, M.P., Quairiaux, C., Terry, J.R., and Goodfellow, M. (2019). Background EEG Connectivity Captures the Time-Course of Epileptogenesis in a Mouse Model of Epilepsy. ENeuro *6*, ENEURO.0059-19.2019.

PROJECT C2

Title : KCC2 novel interaction with glycosphingolipids: functional relevance for developmental epilepsy

Supervisor : RIVERA Claudio

LABORATORY : INMED CITY : Marseille COUNTRY : France

MAIL : claudio.rivera@inserm.fr PHONE : +334.91.82.81.95

LABORATORY WEBSITE : http://www.inmed.fr/presentation-de-linmed

Co-supervisor : DI SCALA Coralie

LABORATORY : Neurosciences Center CITY : Helsinki COUNTRY : Finlande

MAIL : coralie.discala@helsinki.fi PHONE : +358503684369

LABORATORY WEBSITE : https://www2.helsinki.fi/en/hilife-neuroscience-center/news

Duration (workload distribution among the two laboratories)

Planned dates and duration of the work in the AMU lab
October 2021 - September 2022
October 2023 - Mach 2024

Planned dates and duration of the work in the partner lab
October 2022 - September 2023
April 2024 - September 2024

State of the art
Integrity of chloride homeostasis is animportant component of the healthy brain as highlighted by the increasing number of nervous diseases linked to its disturbance. Alteration of GABA signalling through dysfunction of thecation chloride co-transporters (KCC2) may play a key role in Temporal Lobe Epilepsy (TLE). This has led to make it a therapeutic relevant target and the development of KCC2 enhancing drugs for the use in pharmacorestitant TLE attractive for the pharmaceutical industry. However, it is still extremely challenging to target its pecifically and there is a current febrile search for efficient molecules. Although substantial progress has been made to identify the processes modulating KCC2 functionality the impact of its direct environment, namely membrane lipids, has beenunderstudied. Because glycosphingolipids (GSL -lipids highly express in brain) are known to be altered in epilepsy, this lack of interest for GSL, in link with KCC2 and TLE, is a considerable gap. In this context, we have identified a specific interaction between KCC2 and GSL who strongly modulates the activity of the transporter. Now we want to evaluate if a) this regulation is based on change in KCC2 stability and dynamics within the plasma membrane and b) what are the functional consequences for GABAergic communication
Objectives
The project aims to understand how GSL interaction with KCC2 modulates its functionality, its properties within the plasma membrane and GABA ergic signalling
Methods
STORM/PALM/confocalmicroscopy, ex vivoelectrophysiology,mass-spectrometry imaging (MSI), animal models of epilepsy, in vivotransfection
Expected results
The strategy will be to work with a mutated form of KCC2 not interacting with GSL and associated to epilepsy of infancy. This mutant will be expressed in mice brain by in vivotransfection approaches (non-viral and viral). BySTORM/PALM high resolution imaging, we will evaluate how this mutation modifies the membrane properties of KCC2 (stability and dynamic). We expect that this mutant will be less stabilized within the plasma membrane and less mobile than the wild-type. Then, the impact on GABAergic communication will be evaluate by electrophysiology (extracellular records on slices after injection of GABA agonist), and we think the mutation will contribute to render the GABA depolarizing (contrary to the wild-type KCC2 who sustains GABA hyperpolarization). In parallel we will evaluate on a TLE animal model how GSL are altered using MSI
Feasibility
The feasibility is excellent as we already have strong preliminary results that allowed this project to be supported by the prestigious Academy of Finland. The most important risk is technical as it is challenging to quantify GSL by MSI, but we will be support by HiLIPID platform at the University of Helsinki for this task
Complementarity of the two laboratories
Prof.Rivera is internationally recognized for his work on chloride homeostasis and TLE. He has all the equipment to quantify chloride alteration (electrophysiology, confocal microscopes, animal models) and a qualified team to support the PhD student. Dr. Di Scala is an expert in lipid-protein interactions. Her group possesses and have access to the equipment for lipid analysis and membrane protein dynamic (MSI, STORM/PALM microscopes) and the know-how to manipulate lipids and analyze data
Expected candidate profil
We are looking for a highly motivated and curious candidate. The candidate should have a master's degree in neurosciences with strong knowledge in lipid biochemistry. Technical skills in microscopy will be an advantage.

SUPERVISED PHDS & PUBLICATIONS : RIVERA Claudio

- **Currently supervised PhD students**

- Marine Tessier
- Amina Rezzag
- Liilia Andriichuk
- Marta Saez-Garcia

- **Previously supervised PhD students**

- Judith Thomas-Crusells (2004)
- Hong Li (2008)
- Anastasia Ludwig (2008)
- Anastasia Shulga (2011)
- Nazim Kourdougli (2015)
- Olaya Llano (2015)
- Ana Cathia Magalhães (2016)
- Mikhail Yuryev (2017)
- Emmanuelle Goubert (2017)

- **Publications of previously supervised PHD students**

- KesafS,KhirugS,DinhE,GarciaMS,SoniS,OravE,DelpireE,TairaT,LauriSE,*RiveraC(2020)TheKainateReceptorSubunitGluK2InteractsWithKCC2toPromoteMaturationofDendriticSpines.FrontCellNeurosci14:252.
- GoubertE,AltvaterM,RoviraMN,KhalilovI,MazzarinoM,SebastianiA,SchaeferMKE,*RiveraC,PellegrinoC.(2019)BumetanidePreventsBrainTrauma-InducedDepressive-LikeBehavior.FrontMolNeurosci12:12.
- YuryevM, Andriichuk L, LeiweM, JokinenV, CarabalonaA and *RiveraC(2018)In vivo two-photon imaging of the embryonic cortex reveals spontaneous ketamine-sensitive calcium activity. . Sci Rep. 8:16059
- Kourdougli N, Pellegrino C, Khirug S, Renko JM, Vaha M, Chazal G, Gaiarsa JL, Tuominen R, Crépel V, *Rivera C.(2017) Glutamatergic network rewiring is triggered by depolarising GABA in epilepsy.
- Riffault B., Kourdougli N.,Dumon C., Chambon C., Ferrand N., Rivera C.,Gaiarsa J.L., and Porcher C. (2016) Pro-Brain-Derived Neurotrophic Factor (proBDNF)-mediated p75NTRactivation promotes depolarizing GABA and increases susceptibility to epileptic seizures. Cerebral Cortex
- Yuryev M, Almeida Ferreira MP, Balasubramanian V, Correia A, Mäkilä E, Jokinen V, Andriichuk L, Kemell ML, Salonen J, HirvonenJT, Almeida Santos H. & *Rivera C.(2016) Active Diffusion of Nanoparticles of Maternal Origin Within the Embryonic Brain Aug, Nanomedicine
- Magalhães AC, *Rivera C.(2016) NKCC1-Deficiency Results in Abnormal Proliferation of Neural Progenitor Cells of the Lateral Ganglionic Eminence.Front Cell Neurosci.
- 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.

- 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.
- Saarikangas J, Kourdougli N, Senju Y, Chazal G, Segerstråle M, Minkeviciene R, KuurneJ, Mattila P, Garrett L, Hölter S M, Becker L, Racz I, Hans W, Klopstock T, Wurst W, Zimmer A, Fuchs H, Gailus-Durner V, Hrabě de Angelis M, von Ossowski L, Taira T, Lappalainen P, *Rivera C and Hotulainen P. (2015) Dendritic Spines Are Initiated by MIM-Induced Membrane Bending. Developmental Cell
- Magalhães AC, *Rivera C(2014) Superior performance of decloaking chamber-based heat-induced epitope retrieval method improves the quantification of Olig2 cells in paraffin-embedded section of embryonic mousebrain. J Neurosci Methods
- Pallud J, Le Van Quyen M, 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
- Kislin M, Mugantseva E, Molotkov D, Kulesskaya N, Khirug S, Kirilkin I, Pryazhnikov E, Kolikova J, Toptunov D, Yuryev M, Giniatullin R, Voikar V, Rivera C, Rauvala H, Khiroug L. (2014) Flat-floored air-lifted platform: a new method for combining behavior with microscopy or electrophysiology on awake freely moving rodents. J Vis Exp.
- 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.
- Ning L, Tian L, Smirnov S, Vihinen H, Llano O, Vick K, Davis RL, Rivera C., Gahmberg CG. (2012) Interactions between ICAM-5 and β1 integrins regulate neuronal synapse formation. J Cell Sci.
- Shulga A, Magalhães A, Autio H, di Lieto A, Nykjær A, Arumäe U, Castrén C and *Rivera C. (2012) The loop diuretic bumetanide blocks posttraumatic p75NTR upregulation and rescues injured neurons. J. Neurosci.
- Shulga, A.,Blaesse, A., Tanhuanpää, K., Saarma, M. and *Rivera C.(2009) Thyroxin regulates BDNF expression to promote survival of injured neuronsMol Cell Neurosci.
- Uvarov P, Ludwig A, Markkanen M, Soni S, Hübner CA, Rivera C, Airaksinen MS. (2009) Coexpressionand heteromerization of two neuronal K-Cl cotransporter isoforms in neonatal brain. J Biol Chem.
- Hotulainen P, Llano O, Smirnov S, Tanhuanpää K, Faix J, *Rivera C,Lappalainen P. (2009) Defining mechanisms of actin polymerization and depolymerizationduring dendritic spine morphogenesis. J Cell Biol.
- Rivera, C,Nothwang, HG, Llano, O, Ludwig, A(2009) KCC2 a synchronizing factor in synaptic maturation J. Physiol. Sci.
- Shulga A, Thomas-Crusells J, Sigl T, Blaesse A, Mestres P, Meyer M, Yan Q, Kaila K, Saarma M, Rivera C, Giehl KM.(2008) Posttramatic GABA(A)-mediated [Ca2+]I increase us essential for the induction od brain-derived neurotrohic factor -dependent survical of mature central neurons. J Neurosci.
- Li H, Khirug S, Cai C, 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.
- 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.
- Thomas-Crusells J, Vieira A, Saarma M, RiveraC.(2003) A novel method for monitoring surface membrane trafficking on hippocampal acute slice preparation. J Neurosci Methods

SUPERVISED PHDS & PUBLICATIONS : DI SCALA Coralie

- **Currently supervised PhD students**

- Marta Saez-Garcia

PROJECT C3

Title : Emotional stress and vestibular compensation: influence of serotonergic neural networks on the restoration of vestibular functions in a mouse model of vestibular pathology

Supervisor : THIGILET Brahim

LABORATORY : LNC CITY : Marseille COUNTRY : France

MAIL : brahim.tighilet@univ-amu.fr PHONE : +33 413550881

LABORATORY WEBSITE : https://lnc.univ-amu.fr/

Co-supervisor : WANG Liping

LABORATORY : BCBDI CITY : Shenzen COUNTRY : Chine

MAIL : lp.wang@siat.ac.cn PHONE : 0086-755-86134099

LABORATORY WEBSITE : http://wanglab.siat.ac.cn/wanglab_en/index.php

Duration (workload distribution among the two laboratories)

Planned dates and duration of the work in the AMU lab : 2021-09 to 2023-03

Planned dates and duration of the work in the partner lab : 2023-03 to 2024-09

State of the art

Vestibular pathologies result in postural, oculomotor, cognitive and perceptive disorders, which a context-dependent kinetic of compensation, through a process known as vestibular compensation (Lacour and Demanze 2014). In particular, stress is a key factor in vestibular compensation, since recovery prognoses is poor in patients with high levels of stress (Saman et al., 2012; Tjernström et al., 2018). Serotonin is a crucial neurotransmitter in stress control (Chaouloff, 1999; Puglisi-Allegra and Andolina, 2015), yet it is still insufficiently taken into account in the understanding of vestibular recovery. Indeed, the vestibular nuclei (VN) receive serotoninergic projections from the dorsal raphe nucleus (DRN) (Halberstadt and Balaban, 2007), whilst VN neurons express 5-hydroxytryptamine (5-HT) 1A, 5-HT1B and 5-HT2 receptors (Balaban, 2016; Smith and Darlington, 1994). Peripheral vestibular lesions induce an increase in serotonin in the median vestibular nuclei (Zhang et al., 2015). Here, we hypothesize that serotonin projections from the DRN to the VN could play a role in vestibular compensation mechanisms.

Objectives

This project aims first at mapping the projections from the DRN to the VN, and then at investigating the modulatory influences of this serotoninergic pathway on the recovery kinetics following vestibular injury

Methods

The implementation of the project will consist in: 1/ Verify the influence of stress on the vestibular compensation following a vestibular lesion in a mouse model. A behavioral and pharmacological approach will highlight the negative effect of stress on functional recovery kinetics. A histological approach by immunohistochemistry analysis of the brains will reveal the consequences of stress on the mechanisms of compensation, such as neuronal excitability in VN. 2/ Mapping DRN-VN projections via viral tracings, then recording their responses in-vivo using calcium imaging (fiber photometry). Controlling DRN-VN pathways at different post-lesional stages, in genetically engineered mice (PET-cre lines), by using chemogenetic tools allowing to excite or inhibit of serotonergic pathway. 3/ To counteract the effects of stress on recovery, using the same neural manipulation techniques but on stressed mice

Expected results

Understanding of the NRD-NV axis on post-injury recovery. This project will allow the PhD student to acquire training in cutting edge techniques such as chemogenetics and calcium imaging, in an emerging thematic focusing on the impact of emotions on post-injury plasticity

Feasibility

The project is built to be feasible in three years, between two laboratories where the techniques presented are routine: behavioral pharmacology and immunohistochemistry at the LNSC, viral mapping, chemogenetics and calcium imaging at the BCBDI. Finally, Dr. Montardy will act as a bridge between the two laboratories, helping the student to smoothly perform his work

Complementarity of the two laboratories

This thesis project is based on the complementary expertise of the LNSC (UMR7260), specialist in normal and pathological vestibular pathophysiology, as well as the underlying mechanisms of plasticity (Rastoldo et al., 2020; Marouane et al., 2020); and of the BCBDI, specialist in the functional study of subcortical networks of emotions (Zhou et al., 2019; Montardy et al., 2020). Finally, as previously mentioned (Feasibility), the techniques used in the two laboratories are perfectly complementary.

Expected candidate profil

The candidate should be motivated by in-vivo animal model experimentation, behavior and neurophysiology. In this context, a certificate of training in animal experimentation is desirable. It is essential that the candidate be autonomous, adaptable and ready for mobility, since he will have to alternate work in two laboratories: one in France, one in China

SUPERVISED PHDS & PUBLICATIONS : THIGILET Brahim

- **Currently supervised PhD students**

- Guillaume Rastoldo
- Nada El Mahmoudi
- Emna Marouane

- **Previously supervised PhD students**

- Dutheil Sophie 2012

- **Publications of previously supervised PHD students**

- Rastoldo G, El Mahmoudi N, Marouane E, Pericat D, Watabe I, Toneto A, López-Juárez A, Chabbert C, Tighilet B. Adult and endemic neurogenesis in the vestibular nuclei after unilateral vestibular neurectomy. Prog Neurobiol. 2021 Jan;196:101899. doi: 10.1016/j.pneurobio.2020.101899. Epub 2020 Aug 26
- Tighilet B, Rastoldo G, Chabbert C. Le cerveau adulte produit de nouveaux neurones pour restaurer l'équilibre après une perte vestibulaire [The adult brain produces new neurons to restore balance after vestibular loss]. Med Sci (Paris). 2020 Jun-Jul;36(6-7):581-591. French. doi: 10.1051/medsci/2020112. Epub 2020 Jul 2. PMID: 32614308
- Rastoldo G, Marouane E, El Mahmoudi N,Péricat D, Bourdet A, Timon-David E, Dumas O, Chabbert C, Tighilet B. Quantitative Evaluation of a New Posturo-Locomotor Phenotype in a Rodent Model of Acute Unilateral Vestibulopathy. Front Neurol. 2020 Jun 5;11:505. doi: 10.3389/fneur.2020.00505. Erratum in: Front Neurol. 2020 Oct 26;11:614242. PMID: 32582016; PMCID: PMC7291375.
- Marouane E, Rastoldo G, El Mahmoudi N, Péricat D, Chabbert C, Artzner V, Tighilet B. Identification of New Biomarkers of Posturo-Locomotor Instability in a Rodent Model of Vestibular Pathology. Front Neurol. 2020 May 29;11:470. doi: 10.3389/fneur.2020.00470. PMID: 32547480; PMCID: PMC7273747
- Tighilet B, Péricat D, Frelat A, Cazals Y, Rastoldo G, Boyer F, Dumas O, Chabbert C. Adjustment of the dynamic weight distribution as a sensitive parameter for diagnosis of postural alteration in a rodent model of vestibular deficit. PLoS One. 2017 Nov 7;12(11):e0187472. doi: 10.1371/journal.pone.0187472. PMID: 29112981; PMCID: PMC5675415.
- Dutheil S, Watabe I, Sadlaoud K, Tonetto A, Tighilet B. BDNF Signaling Promotes Vestibular Compensation by Increasing Neurogenesis and Remodeling the Expression of Potassium-Chloride Cotransporter KCC2 and GABAA Receptor in the Vestibular Nuclei. J Neurosci. 2016 Jun 8;36(23):6199-212. doi: 10.1523/JNEUROSCI.0945-16.2016. PMID: 27277799; PMCID: PMC6604891.
- Dutheil S, Escoffier G, Gharbi A, Watabe I, Tighilet B. GABA(A) receptor agonist and antagonist alter vestibular compensation and different steps of reactive neurogenesis in deafferented vestibular nuclei of

- adult cats. J Neurosci. 2013 Sep 25;33(39):15555-66. doi: 10.1523/JNEUROSCI.5691-12.2013. PMID: 24068822; PMCID: PMC6618455.
- Dutheil S, Lacour M, Tighilet B. Neurogenic potential of the vestibular nuclei and behaviouralrecovery time course in the adult cat are governed by the nature of the vestibular damage. PLoS One. 2011;6(8):e22262. doi: 10.1371/journal.pone.0022262. Epub 2011 Aug 11. PMID: 21853029; PMCID: PMC3154899.
- Dutheil S, Brezun JM, Leonard J, Lacour M, Tighilet B. Neurogenesis and astrogenesis contribution to recovery of vestibular functions in the adult cat following unilateral vestibular neurectomy: cellular and behavioral evidence. Neuroscience. 2009 Dec 29;164(4):1444-56. doi: 10.1016/j.neuroscience.2009.09.048. Epub 2009 Sep 25. PMID: 19782724.
- Lacour M, Dutheil S, Tighilet B, Lopez C, Borel L. Tell me your vestibular deficit, and i'll tell you how you'll compensate. Ann N Y Acad Sci. 2009 May;1164:268-78. doi: 10.1111/j.1749-6632.2008.03731.x. PMID: 19645911.Dutheil S, Lacour M, Tighilet B. Une nouvelle zone de neurogenèse fonctionnelle: les noyaux vestibulaires du tronc cérébral [Discovering a new functional neurogenic zone: the vestibular nuclei of the brainstem]. Med Sci (Paris). 2011 Jun-Jul;27(6-7):605-13. French. doi: 10.1051/medsci/2011276012. Epub 2011 Jul 1. PMID: 21718644

SUPERVISED PHDS & PUBLICATIONS : WANG Liping

- **Currently supervised PhD students**

- Nan Liu
- Shanping Chen
- Kang Huang
- Peilei Shen
- Xue Liu
- Huiying Tan
- Shaohua Ma
- Jinling Zhong
- Xulin Li

- **Previously supervised PhD students**

- Pengfei Wei –07/2014
- Chen Zhong –01/2018
- Zheng Zhou –01/2019
- Xuemei Liu–07/2019
- Xianglian Jia –01/2020

- **Publications of previously supervised PHD students**

- Wei PF, HeW, Zhou Y,WangLP*. Performance of motor imagery brain-computer interface based on anodal transcranial direct current stimulation modulation. IEEE Transactions on Neural Systems and Rehabilitation Engineering. 2013; 21(3):404-15

- Lu Yi#, Zhong Cheng#, Wang Lulu, Wei Pengfei, He Wei, Huang Kang, Zhang Yi, Zhan Yang, Feng Guoping, Wang Liping*, Optogenetic dissection of ictal propagation in the hippocampal–entorhinal cortex structures. Nature Communications, 2016:7:10962. Zhong C, Ke DN, Wang LL, Lu Y*, Wang LP*, Bioactiveinterpenetrating polymer networks for improving the electrode/neural-tissue interface. Electrochemistry Communications, 2017:79:59-62.
- Li L#, Feng XL#, Zhou Z#, Zhang HQ, Shi QQ, Lei ZG, Shen PL, Yang QN, Zhao BH, Chen SR, Li L, Zhang YL, Wen PJ, Lu ZH, Li X, Xu FQ, Wang LP*.Stress accelerates defensive responses to looming in mice and involves a locus coeruleus -superior colliculus projection. Current Biology. 2018, 28(6):859-871.
- Zhou CR#, Zhou Z#, Han YS, Lei ZG, Li L, Montardy Q, Xu FQ & Wang LP.Activation of parvalbumin interneurons in anterior cingulate cortex impairs observational fear learning.Science Bulletin.2018,63(12):771-778.Montardy Quentin#, Zheng Zhou#, Zhuogui Lei#, Xuemei Liu#, Pengyu Zeng, Chen Chen, Yuanming Liu, Sanz-Leon Panla, Kang Huang, Liping Wang. Characterization of VTA glutamatergic neural population responses to aversive and rewarding conditioning in freely behaving mice. Science Bulletin(2019).64, 16:1167-1178.
- Xuemei Liu#,Chen Chen#, Yuanming Liu#, Zhijie Wang, Kang Huang, Feng Wang*, Liping Wang*.Gentle handling attenuates innate defensive responses to visual threats, Frontiers in Behavioral Neuroscience (2018) 12:239.
- Zheng Zhou #, Xuemei Liu#, Shanping Chen, Zhijian Zhang, Yuanming Liu, Quentin
- Montardy,Yongqiang Tang, Pengfei Wei, Nan Liu, Lei Li, Ru Song, Juan Lai, Xiaobin He, Chen chen, Guoqiang Bi, Guoping Feng, Fuqiang Xu * & Liping Wang *. A VTA GABA neural circuit mediates a visually evoked innate defensive responses. Neuron (2019) 103-1-16
- Xianglian Jia#, Xin-an Liu#, Yan Shi, Shiqi Yao, Xin Zhong, Ye Tian, Qing Tian, Zuxin Chen*, Liping Wang*.Profiling of key brain nuclei involved in CNS control of stress and glucose homeostasis.Biochemical and Biophysical Research Communications.2020, 521(2):441-448
- Xianglian Jia, Yueyan Hu, Xing Yang, Taian Liu, Yan Huang, Pengfei Wei, Yongmei Hao & Liping Wang.Stress affects the oscillation of blood glucose levels in rodents.Biological Rhythm Research.1-10,2019

PROJECT C4

Title : Adaptive plasticity of interactive somatosensory and motor cortical networks underlying recovery of forelimb skills following cortical ministroke in rats

Supervisor : XERRI Christian

LABORATORY : LNC CITY : Marseille COUNTRY : France

MAIL : christian.xerri@univ-amu.fr PHONE : +33413550955

LABORATORY WEBSITE : https://lnc.univ-amu.fr/

Co-supervisor : DANCAUSE Numa

LABORATORY : CITY : Montréal COUNTRY : Canada

MAIL : numa.dancause@umontreal.ca PHONE : 1-514-343-6317

LABORATORY WEBSITE : http://www.numadancause.com/index.php/fr/

Duration (workload distribution among the two laboratories)

Planned dates and duration of the work in the AMU lab : 18 months starting before December 2021

Planned dates and duration of the work in the partner lab : 18 months starting before July 2023

State of the art
Sensory contribution to the recovery of movement is currently neglected in thevast majority of stroke studies which mainly focus on the motor component of movements and most often assess deficits and recovery of movement execution that do not require a fine somatosensory feedback. Therefore, there is a need to evaluate the contribution of somatosensory function to the recovery of motor skills and to provide a neural basis to the optimization of somatosensory feedback in the rehabilitation procedures following stroke.It is well established that cortical map remodeling is a substrate of adaptive changes in the post-stroke recovery of skilled movement. A way of searching for the neural underpinning of thisrecovery is to track postlesion changes taking place in a global interactive network that includes motor and somatosensory cortical areas which have so far been investigated independently of each other in the animal stroke studies
Objectives
We will investigate the postlesion remodeling of sensory and motor somatotopic maps in parallel with the spontaneous recovery of impaired somatosensory-guided distal movementsfollowinga ministroketargeting the forelimb areas in S1 or M1 in rats. In addition, we will search for the effects of a rehabilitative training procedure on the time course of both cortical changes and behavioral recovery
Methods
In a rat model of cortical stroke, we will use a combination of micro-electrode array covering somatosensory and motor areaand cortical mapping techniques complemented by voltage-sensitive-dye (VSD) imaging as well asbehavioral assessment of deficits and recovery of fine sensorimotor skills(manual dexterity, fine locomotor adjustments). A forced-locomotion carrousel will be used as a rehabilitativesensorimotortraining procedure.In addition, we will use GABA-mediated (muscimol) cortical inactivation to explore thecausalrelation between cortical changes and behavioral recovery
Expected results
Following stroke inthe forepaw area in S1, we expect both a reinforcement of thalamocortical tactile inputs converging to M1 on the ipsilesional sideand a motor map remodelingas the functional recovery develops. Reciprocally, a lesion targeting M1 is expected to remodel theS1 forepaw map through an increased contributionof somatosensory feedback in the recovery of sensorimotor abilities. Moreover, we hypothesize that reinforcing sensorimotor experience as a rehabilitative training willimprove and shorten the functionalrecovery through adaptive changesin sensorimotor cortical networks
Feasibility
All the technical skills (electrophysiological, VSD imaging, behavioral methods...) required to carry out this project successfully are well mastered by the collaborative teams, each having its own expertise
Complementarity of the two laboratories
Bothpartner teams have a strong experience in stroke-induced cortical plasticity, cortical mapping and behavioral assessmentof sensorimotor recovery. The team in Montreal has had a focus on themotor cortexplasticityand currently uses the chronic implantation of electrode arrays, whereas the team in Marseille on somatosensory cortex plasticityand uses both electrophysiological mapping and VSD imaging. Therefore, this collaboration is a unique opportunity to explore the postlesion adaptive remodeling of sensorimotor cortical networks bysharing scientific expertise and transferring technical skills
Expected candidate profil
The PhD candidate will acquire or improve skills in electrophysiological cortical mapping (motor and somatosensory), VSD imaging and behavioral assessment in rats

SUPERVISED PHDS & PUBLICATIONS : XERRI Christian

- **Currently supervised PhD students**

- Noformal PhD direction currently, but co-supervisionof Justine Facchini's doctoral research with Yoh'i Zennou-Azogui (director)

- **Previously supervised PhD students**

- 2011-2015 Sandie THOMATY (codirection withJ-M. Jean-Michel Brezun)
- 2014-2017 Julien CORBO (codirection withNicolasCatz)
- 2016-2020 Jeanne CARON-GUYON (codirection with NicolasCatz until2018, then I handed over to Anne Kavounoudias, as a fRMI project was included in the doctoral research).

- **Publications of previously supervised PHD students**

- ZENNOU-AZOGUI Y, XERRI C(2016) Hypergravity experience within a critical period impacts on the THOMATY S, PEZARD L, XERRI C, BREZUN J-M (2017) Acute granulocyte macrophage-colony stimulating factor treatment modulates neuroinflammatory processes and promotes tactile recovery after spinal cord injury. **Neuroscience**, 349: 144-164.
- CORBO J, ZENNOU-AZOGU Y, XERRI C, CATZ N (2017) Cortical merging in S1 as a substrate for tactile input grouping. **ENeuro**; doi: 10.1523/ENEURO.0342-17.
- CARON-GUYON J, CORBO J, ZENNOU-AZOGUI Y, XERRI C, KAVOUNOUDIAS A, CATZ N (2020) Heteromodal motion coding in the associative parietal cortex in rats. **Cerebral Cortex**, 30: 5372-5386; doi: 10.1093/cercor/bhaa118.
- FACCHINI F, RASTOLDO G, PERICAT D, XERRI C, TIGHILET B, ZENNOU-AZOGUI Y (2021). Unilateral vestibular neurectomy induces a remodeling of somatosensory cortical maps. **Prog Neurobiol**. PRONEU-D-20-00395 (sous-presse)**.**

SUPERVISED PHDS & PUBLICATIONS : DANCAUSE Numa

- **Currently supervised PhD students**

- Youstina Mikai
- Ian Moreau
- Boris Touvykine

- **Previously supervised PhD students**

- Meghan Watson (2012/05 – 2015/09)
- Sandrine Côté (2014/09 – 2020/08)

- **Publications of previously supervised PHD students**

- Moreau-Debord I, Serrano E, Quessy S, Dancause N. Rapid and bihemispheric reorganization of neuronal activity in premotor cortex after brain injury. (Submitted to J Neurosci).
- Jeffers MS, Touvykine B, Ripley A, Lahey G, Carter A, Dancause N, Corbett D.Poststroke impairment and recovery are predicted by task-specific regionalization of injury. J Neurosci.2020 Jul 29;40(31):6082-6097.
- LaferriereS, BonizzatoM, Côté SL, DancauseN,LajoieG. Learning to evoke complex motor outputs with spatiotemporal neurostimulation using a hierarchical and adaptive optimization algorithm. IEEE Trans Neural Syst Rehabil Eng.2020 Apr 13.
- Touvykine M, Elgbeili G, Quessy S, Dancause N.Interhemispheric modulations of motor outputs by the rostral and caudal forelimb areas in the rat. (J Neurophysiol. 2020 Apr 1;123(4):1355-1368)
- Côté SL,Quessy S, Dancause N. Modulatory effects of the supplementary motor area (SMA) on primary motor cortex outputs and comparison to those of the dorsal and ventral premotor cortex. J. Neurophysiol. 2020 Jan 1;123(1):407-419.
- Côté SL,Hamadjida A, Quessy S, DancauseN. Contrasting modulatory effects from the contralateral dorsal and ventral premotor cortex on primary motor cortex outputs. J Neurosci. 2017 May 23. pii: 0462-17.
- Quessy S, Côté S,Hamadjida A, Deffeyes J, Dancause N.Ipsi and interhemispheric interactions of the ventral premotor cortex (PMv) with the primary motor cortex (M1) in cebus apella. Cerebral Cortex. 2016 Oct;26(10):3905-20.
- Watson M, SawanM, Dancause N. The Duration of Motor Responses Evoked with Intracortical Microstimulationin Rats Is Primarily Modulated by Stimulus Amplitude and Train Duration. PLoS One.2016 Jul 21;11(7):e0159441.
- Watson M, Dancause N, Sawan M. Intracortical Microstimulation Parameters Dictate the Amplitude and Latency of Evoked Responses.Brain Stimul.2016 Mar-Apr;9(2):276-84.10.Watson M,Dancause N, Sawan M. Efficient Microstimulation of the Brain: A Parametric Approach. Conf Proc IEEE Eng Med Biol Soc. 2015 Aug; 2015:2155-8.