LIST OF PROJECTS (14)

INTERNATIONAL PHD SCHOLARSHIPS

MARCH 2021

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PROJECT I1

Title : Characterization of brain sequelae in experimental cerebral malaria

Supervisor : VIOLA Angèle

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Co-supervisor : PERLES-BARBACARU Teodora-Adriana

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State of the art

Cerebral malaria (CM) the most lethal complication in the course of *Plasmodium falciparum* infection leads to an encephalopathy and death in 15-20 % of the cases (mostly children under 5 years) as a consequence of brain oedema oedema (Penet et al, 2005, Seydel et al, 2015). Ten to twenty percent of survivors have gross neurological deficits at discharge (*eg* cortical blindness, paresis, hypotonia, ataxia, epilepsy…) and may have persisting sequelae (*eg* behavioural disorders, epilepsy, cognitive impairment, motor, sensory and language deficits…). Cerebral sequelae have received little attention although they have an impact on education and contribute to the human, social and economic burden of CM in endemic areas.

Objectives

Our purpose is to take advantage of an existing experimental model of CM with successful anti-malarial therapy to characterize short and long-term sequelae in terms of microstructure, neurometabolism and function. We will look for potential residual hypoperfusion and hypometabolism which are hallmarks of CM (Penet et al, 2005). We will also investigate the potential impact of CM on the structural and functional connectomes.

Methods

Two mouse strains susceptible to CM (CBA/J and C57BL/6) will be inoculated with the murine parasite *Plasmodium Berghei ANKA* and treated by the antimalarial drug chloroquine during 10 days from disease peak. They will be imaged using magnetic resonance imaging (MRI) and spectroscopy (MRS). Advanced MR methods for the study of brain microstructure, metabolism and function will be used, including diffusion tensor imaging (DTI) and resting-state (rs) fMRI for the study of the structural and functional connectomes. The brain of each mouse will be virtualized using the Virtual Brain (TVB, Dr Ch. Bernard, INS, Marseille). The in vivo MR protocol will be completed by behavioural tests (INS, Marseille), immunohistological investigations and quantitative NMR-based metabolomics of brain extracts.

Expected results

We expect that our MRI/MRS approach will permit the identification of alterations at the cell, tissue or network level that could be the substrates for persistent neurological deficits.

Feasibility

We have published the first MRI/MRS characterization of murine CM and identified the cause of death death (Penet et al, 2005).. We have recently developed a model of murine CM with survival on the C57BL/6 strain. We have already set up all the MRI/MRS methods and post-processing methods required for this project and have established the collaborations for the investigation of the connectome and the immunohistological analyses.

Expected candidate profil

We are looking for a highly motivated student with background in brain anatomy, neurometabolism and MRI. A hands-on experience with animal use in scientific procedures and MRI would be an advantage. A good working-knowledge of English would be appreciated.

SUPERVISED PHDS & PUBLICATIONS : VIOLA Angèle

- **Currently supervised PhD students**

- Anthony TESSIER (collaboration with the French Army, Ecole du Val de Grâce, confidential)

- **Previously supervised PhD students**

- Dr Brice MASI (Thesis defense December 2018)
- Dr Christophe LAIGLE (Thesis defense November 2008)
- Dr Marie-France PENET (Thesis defense December 2005)
- Dr Xavier COMBAZ (MD)
- Supervision of the MRI part of the Ph.D work of two Ph.D students in chemistry from January 2018 to November 2020 who were attached to CINaM (Centre Interdisciplinaire de Nanoscience de Marseille): Dr Ling DING and Dr Zhenbin LYU. Their supervisor at CINaM was Dr Ling PENG

- **Publications of previously supervised PHD students**

- Masi B, Perles-Barbacaru TA, Bernard M, Viola A. Clinical and Preclinical Imaging of Hepatosplenic Schistosomiasis. Trends Parasitol. 2020 Feb;36(2):206-226
- Masi B, Perles-Barbacaru TA, Laprie C, Dessein H, Bernard M, Dessein A, Viola A. In Vivo MRI Assessment of Hepatic and Splenic Disease in a Murine Model of Schistosomiasis. PLoS Negl Trop Dis. 2015 Sep 22;9(9):e0004036
- Laigle C, Confort-Gouny S, Le Fur Y, Cozzone PJ, Viola A.Deletion of TRAAK potassium channel affects brain metabolism and protects against ischemia. PLoS One. 2012;7(12):e53266
- Penet MF, Laigle C, Fur YL, Confort-Gouny S, Heurteaux C, Cozzone PJ, Viola A. In vivo characterization of brain morphometric and metabolic endophenotypes in three inbred strains of mice using magnetic resonance techniques.Behav Genet. 2006. 36(5):732-44
- Penet MF, Kober F, Confort-Gouny S, Le Fur Y, Dalmasso C, Coltel N, Liprandi A, Gulian JM, Grau GE, Cozzone PJ, Viola A. Magnetic resonance spectroscopy reveals an impaired brain metabolic profile in mice resistant to cerebral malaria infected with Plasmodium berghei ANKA. J Biol Chem. 2007;282(19):14505-14
- Penet MF, Viola A, Confort-Gouny S, Le Fur Y, Duhamel G, Kober F, Ibarrola D, Izquierdo M, Coltel N, Gharib B, Grau GE, Cozzone PJ. Imaging experimental cerebral malaria in vivo: significant role of ischemic brain edema. J Neurosci. 2005;25(32):7352-8

SUPERVISED PHDS & PUBLICATIONS : PERLES-BARBACARU Teodora-Adriana

- **Currently supervised PhD students**

- Anthony TESSIER (collaboration with the French Army, Ecole du Val de Grâce, confidential)

- **Previously supervised PhD students**

- Dr Brice MASI (Thesis defense December 2018)
- Dr Michel SARRAF (Thesis defense December 2019)
- Supervision of the MRI part of the Ph.D work of two Ph.D students in chemistry from January 2018 to November 2020 who were attached to CINaM (Centre Interdisciplinaire de Nanoscience de Marseille): Dr Ling DING and Dr Zhenbin LYU. Their supervisor at CINaM was Dr Ling PENG

- **Publications of previously supervised PHD students**

- Masi B, Perles-Barbacaru TA, Bernard M, Viola A. Clinical and Preclinical Imaging of Hepatosplenic Schistosomiasis. Trends Parasitol. 2020 Feb;36(2):206-226
- Masi B, Perles-Barbacaru TA, Laprie C, Dessein H, Bernard M, Dessein A, Viola A. In Vivo MRI Assessment of Hepatic and Splenic Disease in a Murine Model of Schistosomiasis. PLoS Negl Trop Dis. 2015 Sep 22;9(9):e0004036
- Sarraf M, Perles-Barbacaru AT, Nissou MF, van der Sanden B, Berger F, Lahrech H Rapid-Steady-State-T1 signal modeling during contrast agent extravasation: toward tumor blood volume quantification without requiring the arterial input function. Magn Reson Med. 2015 Mar;73(3):1005-14
- Perles-Barbacaru TA, Tropres I, Sarraf MG, Chechin D, Zaccaria A, Grand S, Le Bas JF, Berger F, Lahrech H. Technical Note: Clinical translation of the Rapid-Steady-State-T1 MRI method for direct cerebral blood volume quantification. Med Phys. 2015 Nov;42(11):6369-75

PROJECT I2

Title : Exploring the functional heterogeneity of striatal cholinergic interneurons in physiology and in Parkinson's disease: a microRNAs perspective

Supervisor : BEURRIER Corinne

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State of the art

Parkinson's disease (PD) is characterized by the progressive degeneration of dopaminergic neurons localized in the substantia nigra pars compacta (SNc). It is a complex multifactorial disorder involving the intricate interaction between aging, environmental and genetics factors. MicroRNAs (miRNAs) are considered as critical factors in gene regulation and last generation transcriptomic techniques have suggested that many miRNAs exhibit cell-specific expression patterns that can help to delineate different neuronal subsets and be therefore used as novel molecular markers in health and disease. Nonetheless, due to technical constraints intrinsic to their small size, the specific expression profile of miRNAs in different neuronal subtypes has not been thoroughly investigated. In this project, our objective is to develop an innovative toolkit to test whether specific miRNAs contribute to shape the functional heterogeneity of a neuronal population relevant to PD: the cholinergic interneurons of the striatum (CINs)

Objectives

The originality of this project lies in the combination of electrophysiology and molecular tools to (1) investigate how miRNAs shape CIN function in vivo both under physiological and PD conditions and (2) establish causal links between CIN functional properties and target miRNAs.

Methods

Patch-clamp recordings in striatal slices: we will perform patch-clamp recordings of CINs in striatal slices from transgenic mice in which CINs can easily be identified by YFP expression. The electrophysiological signatures of CINs (including modifications under pathological conditions) will be determined by analyzing key electrophysiological features (sag amplitude, rheobase, spiking frequency …).
Single-cell RT-qPCR: at the end of the recordings, the cytoplasm of each cell will be aspirated and the levels of specific miRNAs as well as their targets (synaptic receptors, voltage-gated channels) will be measured via single-cell RT-qPCR. Patch-qPCR would enable to establish correlations between electrophysiological properties and miRNA levels.
Cas9 technology: we will use Cas9 technology to establish causal links between CIN properties and target miRNAs. We will inactivate target miRNAs via Cas9 technology and assess the electrophysiological impact of such molecular manipulations on CIN properties.
Stereotaxic surgery: PD mouse model and Cas9 inactivation of specific miRNAs will be obtained by stereotaxic injection of 6-hydroxydopamine (in the SNc) and adeno-associated virus containing Cas9 tools (in the striatum)

Expected results

This project seeks to establish causal links between electrophysiological features and miRNAs in a neuronal population relevant to striatal function and dysfunction in PD, an important step for a better understanding of how molecular control sculpts neuronal function

Feasibility

The supervisor of this thesis, C Beurrier, has a long experience in CIN electrophysiology and PD mouse models. Molecular biology will be carried out in collaboration with E Gascon, an expert in miRNAs. All the tools and transgenic mice required for the completion of this project are available in our labs

Expected candidate profil

The candidate should be interested in a multi-level approach involving skills ranging from slice electrophysiology and molecular approach. No specific theoretical training is required but the applicant must be highly motivated to undertake a three-year research project

SUPERVISED PHDS & PUBLICATIONS : BEURRIER Corinne

- **Currently supervised PhD students**

- none

- **Previously supervised PhD students**

- Delphine Révy: defense on october 26th 2012
- Gwenaelle Laverne: defense on december 21th 2020

- **Publications of previously supervised PHD students**

- Beurrier C, Lopez S, Revy D, Selvam C, Goudet C, Lherondel M, Gubellini P, Kerkerian-LeGoff L, Acher F, Pin J-P, Amalric M. *The FASEB Journal*, 2009, 23(10):3619-3628
- Révy D, Jaouen F, Salin P, Melon C, Chabbert D, Tafi E, Concetta L, Langa F, Amalric M, Kerkerian-Le Goff L, Marie H, Beurrier C. *Neuropsychopharmacology,* 2014, 39(11): 2662-2672
- Ait Ouares K* Beurrier C*, Canepari M*, Laverne G*, Kuczewski N. *Eur J Neurosci*., 2019, 49(1):6-26. * equal contribution

PROJECT I3

Title : Mechanisms controlling Stem Cells in brain development and cancer: Non-coding RNAs as regulators of microRNA function

Supervisor : CORE Nathalie

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State of the art

In this project we will use mouse genetics to investigate a new class of long non-coding RNAs, so-called transcribed ultra-conserved elements (T-UCEs), in the control of neural stem cell (NSC) activation and proliferation. In particular we will focus on their role as regulators of microRNA function in the normal brain and in brain cancer.

Neurogenesis, the generation of neurons from NSCs, is a temporally and quantitatively highly balanced process. First, neural stem cells divide symmetrically to amplify the stem cell pool precisely to the needed size. Then, sufficient NSCs are activated and enter into proliferation, while a subset of NSCs is maintained quiescent. These will be used later during postnatal stages and for adult neurogenesis. Once activated NSCs are sufficiently amplified they have to become post-mitotic and differentiate. It is evident that this succession of complex events has to be tightly regulated, as even small alterations can have severe consequences for development or lead to brain cancer. For example, glioblastoma, the most devastating type of brain tumor, starts with mutations and subsequent molecular deregulations in postnatal and adult neural stem cells

Objectives

The precision of the neurogenic process in the normal situation, and its safeguarding against defects, is stunning and poses several important questions. For example, what controls which neural stem cells remain silent and which enter proliferation? How do proliferating cells count their divisions before becoming post-mitotic? In this PhD project we address these questions, thereby focusing on the regulatory role of non-coding RNAs, a molecule class that is highly versatile and therefore ideally suited for the precise control of cellular processes. Moreover, numerous studies have highlighted their contribution in carcinogenesis. In particular, we will focus on the ultraconserved RNA T-UCstem1. We found that this non-coding RNA plays a key role in neurogenesis by favoring proliferation of progenitors at the expense of neuron production. Importantly, this regulatory function is mediated by interacting with the microRNAs miR-9-3p and miR-9-5p, two important regulators that control regulators of stem cells state like the Notch pathway, the REST/CoREST system or the orphan nuclear receptor TLX (Pascale, Béclin et al, 2020)

Methods

The candidate will manipulate T-UCstem1 and miR-9 expression and activity in vivo in the mouse brain and study the consequences. Importantly, an in vivo clonal analysis system to study NSCs proliferation will be developed based on the Brainbow labeling system. Experimental design will also include a wide spectrum of state-of-the-art techniques, particularly mouse transgenesis, CRISPR/CAS9 technology, single cell sequencing, in vivo brain electroporation, immunofluorescence and biphoton/confocal microscopy. Finally, the role of T-UCstem1/miR-9 interactions will be studied in a new model of glioblastoma development

Expected candidate profil

The candidate must hold a Master's degree in biological science and have a basic knowledge of genetics, cellular and molecular biology. Knowledge in neurodevelopment and skills in confocal microscopy will be helpful. He/she should be able to apply animal (mouse) experimentation procedures

SUPERVISED PHDS & PUBLICATIONS : CORE Nathalie

- **Currently supervised PhD students**

- none

- **Previously supervised PhD students**

- Alexandra Angelova 2014-2018

- **Publications of previously supervised PHD students**

- Platel JC, Angelova A, Bugeon S, Wallace J, Ganay T, Chudotvorova I, Deloulme JC, Béclin C, Tiveron MC, Coré N, Murthy VN, Cremer H (2019). eLife 2019;8:e44830
- Angelova, A, Platel, JC, Béclin, C, Cremer, H and Coré, N. (2019). J Comp Neurol, 527, 1245-1260
- Angelova A, Tiveron MC, Cremer H, Beclin C. (2018). J Exp Neurosci.;12:1179069518755670

PROJECT I4

Title : Effect of cannabis on sex-and pathway- specific developmental trajectories in the mesocorticolimbic network

Supervisor : MANZONI Olivier

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State of the art
Adolescence is a period of profound morphological and neurodevelopmental maturation in the mesocorticolimbic network (MCN), an ensemble of intricately connected structures involved in cognition, emotion, reward and social behaviors. The most connected structures of the MCN are the nucleus accumbens (NAc) and the prefrontal cortex (PFC). Although the NAC and the PFC are implicated in numerous neuropsychiatric disorders, the global view of their circuits in physio-pathological conditions is missing. Notably, the acute and long-term effects of adolescent consumption of cannabis remain largely unknown
Objectives
1/ Understanding how meso-corticolimbic microcircuits are shaped in a sex-dependent manner to give rise to harmonious emotional behaviors and cognitive functions. 2/ Discovering how peri-adolescent exposure to cannabis' main active molecules (cannabidiol CBD and Tetrahydrocannabinol THC) perturbate developmental trajectories in the MCN
Methods
Based on our large expertise we will apply a multidisciplinary approach to draw a functional portrait of disambiguated synapses onto D1 and D2 expressing principal neurons in the NAc and PFC (GABAergic medium spiny and Glutamatergic pyramidal neurons respectively). We will combine ex vivo optogenetic and electrophysiological methods; quantitative tridimensional neuroanatomy and whole brain light-sheet microscopy; ex-vivo 2photon microscopy and in-vivo large-scale neuronal circuit dynamic imaging in freely behaving animals (Inscopix) to correlate neural activity with naturalistic behaviors across the emotional and cognitive domains. Animals of both sexes will be compared and we will investigate how exposure to THC or CBD during a selected window of adolescence delays maturation of the PFC and NAC and how the disruption alters how these areas process information when the animals are adults.
Expected results
The project will shed light on the developmental trajectory of the MCN and allow deciphering the circuit level foundation of the effects of cannabis on the adolescent brain
Feasibility
All the equipment and expertise necessary to the project are already available in the laboratory and at INMED
Expected candidate profil
The candidate should have a good sense of humor, a strong work ethic and be passionate about science. Prior knowledge of electrophysiology and/or imaging and/or behavioral experiments in rodents are all big plus. More info on our team here: tinyurl.com/bk7rw7kn

SUPERVISED PHDS & PUBLICATIONS : MANZONI Olivier

- **Currently supervised PhD students**

- Pauline Guily (thesis defense in June 2021, NIH funding)
- Gabriele Giua (thesis defense in October 2022, ANR funding)

- **Previously supervised PhD students**

In the past 8 years :

- Axel Bernabeu (17 Décembre 2020)
- Marion Deroche (22 March 2019)
- Anissa Bara (7 December 2017)
- Aurore Thomazeau (15 June 2012)

- **Publications of previously supervised PHD students**

- Sex-specific maturational trajectory of endocannabinoid plasticity in the rat prefrontal cortex
  Axel Bernabeu, Anissa Bara, Antonia Manduca, Milene Borsoi, Olivier Lassalle, Anne-Laure Pelissier-Alicot, Olivier JJ Manzoni bioRxiv 2020.10.09.332965
- Cell-Type- and Endocannabinoid-Specific Synapse Connectivity in the Adult Nucleus Accumbens Core. Deroche MA, Lassalle O, Castell L, Valjent E, Manzoni OJ. J Neurosci. 2020 Jan 29;40(5):1028-1041.
- Sex Differences in the Behavioral and Synaptic Consequences of a Single in vivo Exposure to theSynthetic Cannabimimetic WIN55,212-2 at Puberty and Adulthood.
  Borsoi M, Manduca A, Bara A, Lassalle O, Pelissier-Alicot AL, Manzoni OJ. Front Behav Neurosci. 2019 Mar 5;13:23.
- Sex-dependent effects of in utero cannabinoid exposure on cortical function.
  Bara A, Manduca A, Bernabeu A, Borsoi M, Serviado M, Lassalle O, Murphy M, Wager-Miller J, Mackie K, Pelissier-Alicot AL, Trezza V, Manzoni OJ. Elife. 2018 Sep 11;7:e36234
- Amplification of mGlu5-Endocannabinoid Signaling Rescues Behavioral and Synaptic Deficits in a Mouse Model of Adolescent and Adult Dietary Polyunsaturated Fatty Acid Imbalance.
  Manduca A, Bara A, Larrieu T, Lassalle O, Joffre C, Layé S, Manzoni OJ. J Neurosci. 2017 Jul 19;37(29):6851-6868.
- Endocannabinoid LTD in Accumbal D1 Neurons Mediates Reward-Seeking Behavior.
  Bilbao A, Neuhofer D, Sepers M, Wei SP, Eisenhardt M, Hertle S, Lassalle O, Ramos-Uriarte A, Puente N, Lerner R, Thomazeau A, Grandes P, Lutz B, Manzoni OJ, Spanagel R. iScience. 2020 Mar 27;23(3):100951. doi: 10.1016/j.isci.2020.100951
- Nutritional n-3 PUFA Deficiency Abolishes Endocannabinoid Gating of Hippocampal Long-Term Potentiation.

Thomazeau A, Bosch-Bouju C, Manzoni O, Layé S. Cereb Cortex. 2017 Apr 1;27(4):2571-2579

- Prefrontal deficits in a murine model overexpressing the down syndrome candidate gene dyrk1a. Thomazeau A, Lassalle O, Iafrati J, Souchet B, Guedj F, Janel N, Chavis P, Delabar J, Manzoni OJ. J Neurosci. 2014 Jan 22;34(4):1138-47
- The serine hydrolase ABHD6 controls the accumulation and efficacy of 2-AG at cannabinoid receptors. Marrs WR, Blankman JL, Horne EA, Thomazeau A, Lin YH, Coy J, Bodor AL, Muccioli GG, Hu SS, Woodruff G, Fung S, Lafourcade M, Alexander JP, Long JZ, Li W, Xu C, Möller T, Mackie K, Manzoni OJ, Cravatt BF, Stella N. Nat Neurosci. 2010 Aug;13(8):951-7

PROJECT I5

Title : Microtubules wear and repair: a new mechanism for neuronal polarity?

Supervisor : LETERRIER Christophe

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Co-supervisor : THERY Manuel

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LABORATORY WEBSITE : http://www.cytomorpholab.com/

State of the art : microtubule-based transport in neuronsand self-repair

Information flow in the brain depends on the extraordinary shape and exquisite compartmentation of neurons. How neurons establish, maintain and adapt this complex architecture relies on the neuronal cytoskeleton (1). Microtubule networks allow for long-range transport of cellular components toward the dendrites and axon-despite decades of studies, the rules governing this directed transport are still unclear (2). Here, we want to focus on a new phenomenon recently described by the Cytomorpho lab (M. Théry, CEA, Paris): microtubule damage and self-repair within the assembled lattice. In vitro and in cells, mechanical stress results in the loss of tubulin from the microtubule lattice and the appearance of defects, which are repaired by the incorporation of new tubulin monomers (3,4). Moreover, motor proteins induce such lattice wear, with heavy traffic resulting in more defects and more repair (5). This led us to propose that a cycle of motor trafficking, lattice wear, and repair inducing motor recruitment, could underlie cellular polarization in migrating cells (6) and axonal specification in neurons (7).

Project : a role for microtubule self-repair in shaping neurons

In this project, we want to explore the existence and role of such a microtubule “wear and repair” cycle in neurons, thanks to our ongoing collaboration with the Théry lab (5). They recently developed a robust method to visualize microtubule self-repair based on micro-injection of fluorescent tubulin. The first aim of the project will be to visualize the microtubule network and repair sites in non-neuronal cells at the nanoscale, by leveraging our expertise in multicolor single-molecule localization microscopy (8,9). The second aim will be to implement the micro-injection method to map microtubule repair localization and dynamics in cultured neurons. Finally, we will determine the functional role of wear and repair: we want to test if a positive feedback between motor recruitment, microtubule wear and network self-repair can induce preferential trafficking between the cell body and the axon, allowing to establish and maintain neuronal polarity.

Why us, why you

This project will benefit from a close collaboration between the NeuroCyto team and the Théry lab, as well as from the development of a dedicated super-resolution microscopy center of excellence at the INP imaging facility. We are looking for a candidate interested in delicate cellular work, quantitative biology and advanced microscopy techniques to tackle this ambitious project.

References

1. Leterrier, C. A Pictorial History of the Neuronal Cytoskeleton. J Neurosci41, 11–27 (2021)
2. Leterrier, C., Dubey, P. & Roy, S. The nano-architecture of the axonal cytoskeleton. Nat Rev Neurosci 18, 713–726 (2017).
3. Schaedel, L. et al. Microtubules self-repair in response to mechanical stress. Nat Mater 14, 1156–1163 (2015).
4. Aumeier, C. et al. Self-repair promotes microtubule rescue. Nat Cell Biol 18, 1054–1064 (2016).
5.Triclin, S. et al. Self-repair protects microtubules from destruction by molecular motors. Nat Mater 1–9 (2021).
6. Théry, M. & Blanchoin, L. Microtubule self-repair. Curr Opin Cell Biol 68, 144–154 (2021).
7. Leterrier, C. The Axon Initial Segment: An Updated Viewpoint. J Neurosci 38, 2135–2145 (2018).
8. Jimenez, A., Friedl, K. & Leterrier, C. About samples, giving examples: optimized procedures for Single Molecule Localization Microscopy. Methods 174, 100–114 (2020).
9. Jacquemet, G., Carisey, A. F., Hamidi, H., Henriques, R. & Leterrier, C. The cell biologist’s guide to super-resolution microscopy. J Cell Sci 133, jcs240713 (2020)

SUPERVISED PHDS & PUBLICATIONS : LETERRIER Christophe

- **Currently supervised PhD students**

- Dominic Bingham -codirection MJ Papandréou, NeuroSchool 2018-2021
- Florian Wernert -codirection MJ Papandréou, ED 2019-2022
- Karoline Friedl -codirection MJ Papandréou, CIFRE 2019-2022

- **Previously supervised PhD students**

- none

- **Publications of previously supervised PHD students**

- Jimenez A, Friedl K, Leterrier C. About samples, giving examples: optimized procedures for Single Molecule Localization Microscopy. Methods,2020 Mar 1;174:100–14
- Ganguly A, Wernert F, Phan S, Boassa D, Das U, Sharma R, Caillol G, Han X, Yates JR, Ellisman MH, Leterrier C, Roy S.Mechanistic Determinants of Slow Axonal Transport and Presynaptic Targeting of Clathrin Packets.bioRxiv,2020;2020.02.20.958140

SUPERVISED PHDS & PUBLICATIONS : THERY Manuel

- **Currently supervised PhD students**

- Alexandre Schaeffer
- Adrian Candelas
- Juliana Geay
- Khansa Saadalah

- **Previously supervised PhD students**

- Thomas Bessy(Sept 2019)
- Stefan Biedzinski(Nov 2018)
- Fabrice Senger (Jan 2017)
- Laura Schaedel (Jul 2016)
- Mithila Burute(2016)
- Amandine Pitaval(Feb2016)

- **Publications of previously supervised PHD students**

- Bessy T, Souquet B, Vianay B., Schaeffer A, Jaffredo T, Larghero J, Blanchoin L, Brunet S, Faivre L*, Théry M*. Hematopoietic progenitors polarize in contact with bone marrow stromal cells by engaging CXCR4 receptors.bioRxiv, 2020 (under review at Journal of Cell Biology)

- Biedzinski S, Agsu G, Vianay B, Delord, Blanchoin L, Larghero J, Faivre L, Théry M*, Brunet S*. Microtubules control nuclear shape and gene expression during early stages ofhematopoietic differentiation. EMBO Journal, 39:e103957, 2020
- Toro-Nahuelpan M, Zagoriy I, Senger F, Blanchoin L, Thery M, Mahamid J. Tailoring cryo-electron microscopy grids by photo-micropatterning for in-cell structural studies.Nature Methods,17(1):50-54, 2020
- Senger F, Pitaval A, Ennomani H, Kurzawa L, Blanchoin L*, Théry M*. Spatial integration of mechanical forces by α-actinin establishes actin network symmetry.Journal of Cell Science, 14;132(22), 2019.
- Schaedel L, Triclin S, Chrétien D, Abrieu A, Aumeier C, Gaillard J, Blanchoin L*, Théry M*, John K*. Lattice defects induce microtubule self-renewal.Nature Physics, 15:830–838, 2019.
- Aumeier C, Schaedel L, Gaillard J, John K, BlanchoinL* and Théry M*. Self-repair promotes microtubule rescue.Nature Cell Biology, 18(10):1054-64, 2016.
- Schaedel L, John K, Gaillard J, Nachury MV, Blanchoin L*, Théry M*. Microtubules self-repair in response to mechanical stress. Nature Materials, 14, 1156–1163, 2015
- Burute M, Prioux M, Blin G, Truchet S, Letort G, Tseng Q, Bessy T, Lowell S, Young J, Filhol O, Théry M. Polarity Reversal by Centrosome Repositioning Primes Cell Scattering during Epithelial-to-Mesenchymal Transition.Developmental Cell, 40 (2): 168-84, 2017
- Pitaval A, Senger F, Letort G, Guyon L, Sillibourne J* and Théry M*. Microtubule stabilization drives 3D centrosome migration to initiate primary ciliogenesis.The Journal of Cell Biology, 216(11):3713-3728, 2017

PROJECT I6

Title : Mechanisms of action of MT5-MMP in the control of neuroinflammation in Alzheimer's disease

Supervisor : RIVERA Santiago

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State of the art
We found that protease MT5-MMP (MT5 thereafter) promotes amyloidosis and neuroinflammation, while its deficiency prevents the former as well as LTP and cognitive deficits in the 5xFAD mouse model of Alzheimer's disease (AD). Moreover, the knockout (KO) of MT5 reduces neuroinflammation in mixed neuron/astrocyte cultures from 5xFAD and in induced pluripotent stem cell (iPS)-derived astrocytes from AD patients. Additional preliminary data from our group suggest that MT5 may control early neuroinflammatory processes in the brain through interplay with key inflammatory mediators (i.e., IL-1b). Based on the above, we hypothesize that MT5 contributes to inflammatory pathways to promote amyloidogenesis and synaptic dysfunction, which set the basis of pre-symptomatic dysregulation in AD
Objectives
To test this hypothesis, the objectives are as follows: 1. To identify mechanisms by which MT5 promotes inflammatory responses in AD, in particular in concert with IL-1b. 2. To study the impact of MT5 modulation on the pathological outcome in cultures of neurons and astrocytes from mice and AD patients. 3. To study the impact of MT5 modulation on the pathological outcome in vivo in a mouse model of AD
Methods
Models: Cell cultures: a) primary cultures of neurones/astrocyte from WT, MT5KO, 5xFAD and 5xFAD/MT5KO mice; b) iPS-derived neurons and astrocytes from AD patients; c) 5xFAD mice for in vivo studies. All recapitulate the principal marks of the pathology **Techniques** :MT5 activity will be modulated by: a) transducing cells and mice with AAVs coding for mutated variants of MT5; b) chemical drugs. After MT5 modulation, we will analyse the inflammatory status as well as the metabolism of amyloid precursor protein, tau dysregulation and synaptic deficits, using biochemistry (WB, immunoprecipitation, ELISA), molecular and cell biology (qPCR, mutagenesis, immunocytochemistry), advanced microscopy (SIM, High content screening), electrophysiology (whole cell patch clamp), anatomopathology and mouse behaviour
Expected results
Discover new pathways involving MT5 contribution to early AD neuroinflammation that may ultimately trigger/contribute to pathology Validate MT5 as new target in a pre-clinical murine and human context
Feasibility
All the state of the art techniques/equipment are available: AD mice, primary neural cell cultures and genetically modified iPSs using CRISPR/Cas9, AAVs constructs, qPCR, advanced microscopy, patch-clamp and behavioural tests
Expected candidate profil
The candidate should be -Highly motivated, hard working and well organized person with knowledge or keen to learn some of the techniques mentioned above, and who can work independently as well as in a group. - Capable of conceptual thinking, with a good theoretical background in neuroscience/neuropathology

SUPERVISED PHDS & PUBLICATIONS : RIVERA Santiago

- **Currently supervised PhD students**

- Dominika Pilat (thesis defense by the end of 2021) - is co-surpervised with Dr.Kévin Baranger
- Laurie Arnaud (thesis defense in September 2021) - co-supervised with Dr. Emmanuel Nivet
- Pedro Belio Mairal (2nd year) - co-supervised with Dr. Emmanuel Nivet

- **Previously supervised PhD students**

- Laura Garcia-Gonzalez 2016-2020
- Jean-Michel PAUMIER 2015-2018
- Nathalie Py 2011-2014
- Adlane Ould-yahoui 2007-2011
- Crystel Ogier 2002-2005
- Jérôme Jourquin 1999-20

- **Publications of previously supervised PHD students**

- **García-González L,** Jean-Paumier JM, Louis L, Pilat D, Bernard A, Stephan D, Jullien N, Checler F, Nivet N, Khrestchatisky M, Baranger K and Rivera S. MT5-MMP controls APP and b-CTF/C99 metabolism through proteolytic-dependent and -independent mechanisms relevant for Alzheimer's disease. (submitted). bioRxiv : 2020.09.01.258665; doi : https://doi.org/10.1101/2020.09.01.258665.
- **García-González L,** Baranger K and Rivera S. MT-MMPs in Neurodegenerative disorders. Front Aging Neurosci 2019 doi: 10.3389/fnagi.2019.00244. eCollection 2019.
- Rivera S**, García-González** L, Khrestchatisky M and Baranger K. Metalloproteinases and their tissue inhibitors in Alzheimer's disease and other neurodegenerative disorders. Cell. Mol. Life Sci. 2019 76: 3051. https://doi.org/10.1007/s00018-019-03172-8,
- **Paumier JM, Py NA, García-González L,** Bernard A, Stephan D, Louis L, Checler F, Khrestchatisky M, Baranger K, Rivera S. Proamyloidogenic effects of membrane type 1 matrix metalloproteinase involve MMP-2 and BACE-1 activities, and the modulation of APP trafficking. FASEB J. 2019 Feb;33(2):2910-2927. doi: 10.1096/fj.201801076R. Epub 2018 Oct 17.
- Girard SD, Virard I, Lacassagne E, **Paumier JM,** Lahlou H, Jabes F, Molino Y, Stephan D, Baranger K, Belghazi M, Deveze A, Khrestchatisky M, Nivet E, Roman FS, Féron F. From Blood to Lesioned Brain: An In Vitro Study on Migration Mechanisms of Human Nasal Olfactory Stem Cells. Stem Cells Int. 2017;2017:1478606. doi: 10.1155/2017/1478606.
- Baranger K, Bonnet AE, Girard SD, **Paumier JM, García-González L,** Elmanaa W, Bernard A, Charrat E, Stephan D, Bauer C, Moschke K, Lichtenthaler SF, Roman FS, Checler F, Khrestchatisky M, Rivera S. MT5-MMP Promotes Alzheimer's Pathogenesis in the Frontal Cortex of 5xFAD Mice and APP Trafficking in vitro. Front Mol Neurosci. 2017 Jan 10;9:163. doi: 10.3389/fnmol.2016.00163. eCollection 2016.

- Baranger K, Marchalant Y, Bonnet AE, Crouzin N, Carrete A, **Paumier JM, Py NA**, Bernard A, Bauer C, Charrat E, Moschke K, Seiki M, Vignes M, Lichtenthaler SF, Checler F, Khrestchatisky M, Rivera S. MT5-MMP is a new pro-amyloidogenic proteinase that promotes amyloid pathology and cognitive decline in a transgenic mouse model of Alzheimer's disease. Cell Mol Life Sci. 2016 Jan;73(1):217-36. doi: 10.1007/s00018-015-1992-1. Epub 2015 Jul 23.
- **Py NA,** Bonnet AE, Bernard A, Marchalant Y, Charrat E, Checler F, Khrestchatisky M, Baranger K, Rivera S. Differential spatio-temporal regulation of MMPs in the 5xFAD mouse model of Alzheimer's disease: evidence for a pro-amyloidogenic role of MT1-MMP. Front Aging Neurosci. 2014 Sep 18;6:247. doi: 10.3389/fnagi.2014.00247. eCollection 2014.
- **Ould-Yahoui** A, Sbai O, Baranger K, Bernard A, Gueye Y, Charrat E, Clément B, Gigmes D, Dive V, Girard SD, Féron F, Khrestchatisky M, Rivera S. Role of matrix metalloproteinases in migration and neurotrophic properties of nasal olfactory stem and ensheathing cells. Cell Transplant. 2013;22(6):993-1010. doi: 10.3727/096368912X657468.
- Gueye Y, Ferhat L, Sbai O, Bianco J, **Ould-Yahoui A**, Bernard A, Charrat E, Chauvin JP, Risso JJ, Féron F, Rivera S, Khrestchatisky M. Trafficking and secretion of matrix metalloproteinase-2 in olfactory ensheathing glial cells: A role in cell migration? Glia. 2011 May;59(5):750-70. doi: 10.1002/glia.21146.
- Banasr S, Sbai O, Ould-Yahoui A, Gueye Y, Sakly M, Abdelmelek H. Ligation induced matrix-metalloproteinase-9 activity in peripheral frog nervous system. Arch Ital Biol. 2010 Dec;148(4):397-403. doi: 10.4449/aib.v148i4.1133.
- Sbai O, **Ould-Yahoui A**, Ferhat L, Gueye Y, Bernard A, Charrat E, Mehanna A, Risso JJ, Chauvin JP, Fenouillet E, Rivera S, Khrestchatisky M. Differential vesicular distribution and trafficking of MMP-2, MMP-9, and their inhibitors in astrocytes. Glia. 2010 Feb;58(3):344-66. doi: 10.1002/glia.20927.
- **Ould-yahoui A,** Tremblay E, Sbai O, Ferhat L, Bernard A, Charrat E, Gueye Y, Lim NH, Brew K, Risso JJ, Dive V, Khrestchatisky M, Rivera S. A new role for TIMP-1 in modulating neurite outgrowth and morphology of cortical neurons. PLoS One. 2009 Dec 14;4(12):e8289. doi: 10.1371/journal.pone.0008289.
- Sbai O, Ferhat L, Bernard A, Gueye Y, **Ould-Yahoui A**, Thiolloy S, Charrat E, Charton G, Tremblay E, Risso JJ, Chauvin JP, Arsanto JP, Rivera S, Khrestchatisky M. Vesicular trafficking and secretion of matrix metalloproteinases-2, -9 and tissue inhibitor of metalloproteinases-1 in neuronal cells. Mol Cell Neurosci. 2008 Dec;39(4):549-68. doi: 10.1016/j.mcn.2008.08.004.
- **Ogier C,** Bernard A, Chollet AM, LE Diguardher T, Hanessian S, Charton G, Khrestchatisky M, Rivera S. Matrix metalloproteinase-2 (MMP-2) regulates astrocyte motility in connection with the actin cytoskeleton and integrins. Glia. 2006 Sep;54(4):272-84.
- Chaillan FA, Rivera S, Marchetti E, **Jourquin J,** Werb Z, Soloway PD, Khrestchatisky M, Roman FS. Involvement of tissue inhibition of metalloproteinases-1 in learning and memory in mice.Behav Brain Res. 2006 Oct 16;173(2):191-8. Epub 2006 Jul 24.
- **Jourquin J,** Tremblay E, Bernard A, Charton G, Chaillan FA, Marchetti E, Roman FS, Soloway PD, Dive V, Yiotakis A, Khrestchatisky M, Rivera S. Tissue inhibitor of metalloproteinases-1 (TIMP-1) modulates neuronal death, axonal plasticity, and learning and memory. Eur J Neurosci. 2005 Nov;22(10):2569-78.
- **Ogier C,** Creidy R, Boucraut J, Soloway PD, Khrestchatisky M, Rivera S. Astrocyte reactivity to Fas activation is attenuated in TIMP-1 deficient mice, an in vitro study. BMC Neurosci. 2005 Nov 29;6:68.
- Rivera S, **Jourquin J, Ogier C**, Bernard A, Charton G, Tremblay E, Khrestchatisky M. The MMP/TIMP system in the nervous system. Med Sci (Paris). 2004 Jan;20(1):55-60

- Rivera S, **Jourquin J, Ogier C**, Bernard A, Charton G, Tremblay E, Khrestchatisky M. The MMP/TIMP system in the nervous system. Med Sci (Paris). 2004 Jan;20(1):55-60.
- Khrestchatisky M, **Jourquin J, Ogier C,** Charton G, Bernard A, Tremblay E, Rivera S. Matrix metalloproteinases and their inhibitors, modulators of neuro-immune interactions and of pathophysiological processes in the nervous system. J Soc Biol. 2003;197(2):133-44.
- **Jourquin J,** Tremblay E, Décanis N, Charton G, Hanessian S, Chollet AM, Le Diguardher T, Khrestchatisky M, Rivera S. Neuronal activity-dependent increase of net matrix metalloproteinase activity is associated with MMP-9 neurotoxicity after kainate. Eur J Neurosci. 2003 Sep;18(6):1507-17.
- Rivera S, **Ogier C, Jourquin J**, Timsit S, Szklarczyk AW, Miller K, Gearing AJ, Kaczmarek L, Khrestchatisky M. Gelatinase B and TIMP-1 are regulated in a cell- and time-dependent manner in association with neuronal death and glial reactivity after global forebrain ischemia. Eur J Neurosci. 2002 Jan;15(1):19-32

PROJECT I7

Title : Control of attention in children: Interaction of voluntary and involuntary attention

Supervisor : BIDET-CAULET Aurélie

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State of the art
The successful control of attention is based on a balance between two important aspects of attention: voluntary attention that allows to focus on goal-relevant information and the involuntary capture of attention by task-irrelevant but potentially important events outside the current focus of attention (e.g., fire alarm). Attention can be regarded as the bottleneck of acquiring knowledge about the world. It is thus of utmost importance to understand attention and its development in order to understand and improve the acquisition of cognitive, social, and emotional knowledge and skills. However, the developmental pathway of the underlying mechanisms and of the interaction between involuntary and voluntary attention are widely unclear. Even less is known on the role of arousal – mediated by the Locus Coeruleus Norepinephrine (LC-NE) system – on the balance between voluntary and involuntary attention
Objectives
The main aim of the present project is to characterize the typical developmental trajectory of attention control. More specifically, we will dissociate the developmental trajectories of involuntary and voluntary auditory attention and characterize the influence of arousal on these attention processes, from early childhood to adulthood (4 to 25 year-old).
Methods
Newly developed innovative and well-established paradigms, adapted to the needs of children will be used, such as the Competitive Attention test and the oddball paradigms (e.g., Hoyer et al 2021; Wetzel et al 2006 2007 2009 2016). A combination of complementary psychophysiological measures (behavior, pupil dilation, skin conductance, heart rate, micro-saccades and EEG) will enable to link the maturation of brain markers of voluntary and involuntary attention with the activation of the LC-NE system, providing a comprehensive view of the neural mechanisms related to the development of attention control
Expected results
To characterize (1) the development of behavioral, physiological and brain markers of voluntary, involuntary attention, and their interaction, from childhood to adulthood; (2) the influence of arousal mediated by the LC-NE on these markers.
Feasibility
Feasibility of studies is ensured by the excellent infrastructures offered at our System Neurosciences Institute and by a strong international collaboration with Pr N. Wetzel, expert in the development of attention in children using EEG and pupil dilation, in Germany
Expected candidate profil
The PhD candidate will be involved in protocol design, data collection and analysis. He/she is expected to have a strong interest in cognitive development, experience in programming and to be fluent enough in French to interact with kids

SUPERVISED PHDS & PUBLICATIONS : BIDET-CAULET Aurélie

- **Currently supervised PhD students**

- SEROPIAN Lou (ED NSCO Lyon, co-direction)
- GINZBURG Jérémie (ED NSCO Lyon, co-direction)

- **Previously supervised PhD students**

- THILLAY Alix (2011-2015)
- ELSHAFEI Hesham (2014-2018)
- NICOLAS Judith (2015-2019)
- HOYER Roxane (2016-2020)
- MASSON Rémy (2017-2020)
- BLAIN Salomé (2017-2020)

- **Publications of previously supervised PHD students**

- R. S. Hoyer, H. Elshafei, J. Hemmerlin, R. Bouet, A. Bidet-Caulet. Why are children so distractible? Development of attention and motor control from childhood to adulthood. 2021. *Child Development. In press.* doi: https://doi.org/10.1101/747527
- Masson R, Demarquay G, Meunier D, Lévêque Y, Hannoun S, Bidet-Caulet A, Caclin A. Is Migraine Associated to Brain Anatomical Alterations? New Data and Coordinate-Based Meta-analysis. 2021. *Brain Topogr. In press.* doi: 10.1007/s10548-021-00824-6.
- Nicolas J, Bidet-Caulet A, Pélisson D. Reactive saccade adaptation boosts orienting of visuospatial attention. 2020. *Sci Rep,* 10(1):13430. doi: 10.1038/s41598-020-70120-z.
- ElShafei HA, Fornoni L, Masson R, Bertrand O, Bidet-Caulet A. Age-related modulations of alpha and gamma brain activities underlying anticipation and distraction. 2020. *PLoS One*, 15(3):e0229334. doi: 10.1371/journal.pone.0229334.
- ElShafei HA, Fornoni L, Masson R, Bertrand O, Bidet-Caulet A. What's in Your Gamma? Activation of the Ventral Fronto-Parietal Attentional Network in Response to Distracting Sounds. 2020. *Cereb Cortex*, 30(2):696-707. doi: 10.1093/cercor/bhz119.
- Lévêque Y, Masson R, Fornoni L, Moulin A, Bidet-Caulet A, Caclin A, Demarquay G. 2020. Self-perceived attention difficulties are associated with sensory hypersensitivity in migraine. *Rev Neurol (Paris),* S0035-3787(20)30463-X. doi: 10.1016/j.neurol.2020.01.360. Online ahead of print.
- Masson R, Lévêque Y, Demarquay G, ElShafei H, Fornoni L, Lecaignard F, Morlet D, Bidet-Caulet A*, Caclin A*. Auditory attention alterations in migraine: A behavioral and MEG/EEG study. 2020. *Clin Neurophysiol*, 131(8):1933-1946. doi: 10.1016/j.clinph.2020.05.024. Online ahead of print.
- Nicolas J, Bidet-Caulet A, Pélisson D. Inducing oculomotor plasticity to disclose the functional link between voluntary saccades and endogenous attention deployed perifoveally. 2019. *Sci Rep*, 9(1):17770. doi: 10.1038/s41598-019-54256-1.
- Masson R, Bidet-Caulet A. Fronto-central P3a to distracting sounds: An index of their arousing properties. 2019. *Neuroimage*, 15;185:164-180. doi: 10.1016/j.neuroimage.2018.10.041. Epub 2018 Oct 15.

- Nicolas J, Bompas A, Bouet R, Sillan O, Koun E, Urquizar C, Bidet-Caulet A, Pélisson D. Saccadic Adaptation Boosts Ongoing Gamma Activity in a Subsequent Visuoattentional Task. 2019. Cereb Cortex. 14;29(9):3606-3617. doi: 10.1093/cercor/bhy241.
- ElShafei HA, Bouet R, Bertrand O, Bidet-Caulet A. Two Sides of the Same Coin: Distinct Sub-Bands in the α Rhythm Reflect Facilitation and Suppression Mechanisms during Auditory Anticipatory Attention. 2018. *eNeuro*, 5(4):ENEURO.0141-18.2018. doi: 10.1523/ENEURO.0141-18.2018.
- Kovarski K, Thillay A, Houy-Durand E, Roux S, Bidet-Caulet A, Bonnet-Brilhault F, Batty M. Brief Report: Early VEPs to Pattern-Reversal in Adolescents and Adults with Autism. 2016. *J Autism Dev Disord,* 46(10):3377-86.
- Thillay A, Lemaire M, Roux S, Houy-Durand E, Barthélémy C, Knight RT, Bidet-Caulet A, Bonnet-Brilhault F. Atypical Brain Mechanisms of Prediction According to Uncertainty in Autism. 2016. *Front Neurosci,* 10:317.
- Thillay A, Roux S, Gissot V, Carteau-Martin I, Knight RT, Bonnet-Brilhault F, Bidet-Caulet A. 2015. Sustained attention and prediction: distinct brain maturation trajectories during adolescence. *Front Hum Neurosci,* 9:519

PROJECT I8

Title : Rhythm for interpersonal verbal coordination

Supervisor : SCHON Daniele

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Project

Communication and verbal coordination often go along with a largely automatic process of 'interactive alignment'. This implies that two individuals simultaneously align their neural dynamics at different linguistic levels by imitating each other's choices of speech rate, prosodic contour, meanings, etc. Multi-level alignment, by optimizing turn-taking and coordination behaviors, improves communication.
However, most studies focus on production or comprehension of individuals, thus on the nature of the mental processes used by the isolated individual. Because in communication the action of producing or comprehending depends on the integrated behavior of two or more individuals, moving towards a joint-action approach to the study of communication is highly relevant.
This approach reposes on the active inference theoretical framework. More precisely, "actors" must be able to predict others' actions and integrate predictions in a joint-action model. Thus, in a successful verbal interaction, it is essential to be able to predict the partner's verbal actions in advance.
Because, music-making requires a high flexibility in interpersonal coordination at multiple timescales and across different sensory modalities, we hypothesize that, by enhancing the precision and flexibility of temporal predictions and adaptations, music training/stimulation will facilitate verbal coordination at different linguistic levels via more efficient neural entrainment.
The aim of this project is to study the extent to which music making affects interpersonal verbal coordination, as well as to advance our understanding of the underlying neural mechanisms in normal and pathological conditions. Firstly, we will quantify with behavioral and neural measures the interpersonal coordination during musical and verbal exchange. Secondly, we will assess whether and how temporally constrained interaction, such as musical rhythmic performance, modifies coordination metrics in verbal interaction. At the first aim we will collect behavioural and EEG data on individuals performing different interactive rhythmic and verbal tasks while controlling the difficulty level of the coordination. This will allow to bridge interactive musical and verbal behaviors quantified via objective measures and to relate these to specific spatio-temporal neural dynamics. At the second aim we will assess the hypothesis of a positive effect of intensive music training as well as of a short musical rhythmic-like interaction on the interpersonal verbal coordination abilities in children and prelingually deaf children with cochlear implants.

Objectives

This project has the goal of bridging musical and verbal conversational dynamics and of assessing the effect of synchronous joint activity (music) on interpersonal verbal coordination via neural entrainment. Assessing conversational skills in children is challenging but of utmost importance because these abilities are not yet fully developed. Moreover, the project is relevant to a translational research program to adjust conversational developmental trajectories in children with a cochlear implant. Most of the tasks have already been developed and we also master the different analytical pipelines. Moreover, we have a privileged access to the clinical population in Marseille and Lyon as well as an ethical approval for the experiments.

Expected candidate profil

The expected candidate will have a strong interest in language and music cognition, in particular under a dynamical system perspective. Solid skills in data analysis are also required as the will to learn French

SUPERVISED PHDS & PUBLICATIONS : SCHON Daniele

- **Currently supervised PhD students**

- Jacques Pesnot (defending June 2021), Isaïh Mohamed (co-supervision)
- Joan Belo (co-supervision at Inria)

- **Previously supervised PhD students**

- Hidalgo Céline 2015-2018
- Intartaglia Bastien (2013-2017)
- Cason Nia 2010-2013
- François Clément 2007-2011
- Trost Wiebke (co-supervisor) 2010-2014

- **Publications of previously supervised PHD students**

- Lerousseau, J. P., & **Schön**, D. (under review). Musical expertise is associated with improved neural statistical learning. bioRxiv.
- Hidalgo, C., Zécri, A., Pesnot-Lerousseau, J., Truy, E., Roman, S., Falk, S., ... & **Schön**, D. (2020). Rhythmic Abilities of Children With Hearing Loss. *Ear and Hearing*.
- Lerousseau, J. P., Trébuchon, A., Morillon, B., & **Schön**, D. (under review). Persistent neural entrainment in the human cortex is frequency selective. *bioRxiv*, 834226.
- Pesnot Lerousseau, J., Hidalgo, C., & **Schön**, D. (2020). Musical Training for Auditory Rehabilitation in Hearing Loss. *Journal of Clinical Medicine,* 9(4), 1058.
- Hidalgo, C., Pesnot-Lerousseau, J., Marquis, P., Roman, S., & **Schön**, D. (2019). Rhythmic Training Improves Temporal Anticipation and Adaptation Abilities in Children With Hearing Loss During Verbal Interaction. *Journal of Speech, Language, and Hearing Research*, 1-14.
- Cason, N., Marmursztejn, M., D'Imperio, M., & **Schön**, D. (2019). Rhythmic Abilities Correlate with L2 Prosody Imitation Abilities in Typologically Different Languages. *Language and speech*, https://doi.org/10.1177/0023830919826334.
- Intartaglia, B., White-Schwoch, T., Kraus, N., & **Schön**, D. (2017). Music training enhances the automatic neural processing of foreign speech sounds. Scientific reports, 7(1), 12631.
- Intartaglia, B., White-Schwoch, T., Meunier, C., Roman, S., Kraus, N., & **Schön**, D. (2016). Native language shapes automatic neural processing of speech. Neuropsychologia, 89, 57-65.
- Lévêque Y, **Schön** D (2015) Modulation of the motor cortex during singing-voice perception. *Neuropsychologia*, 70:58-63.
- Cason N, Astesano C, **Schön** D (2015) Bridging music and speech rhythm: rhythmic priming and audio-motor training affect speech perception, *Acta Psychologica,* 155:43-50.
- François C, Jaillet F, Takerkart S, & **Schön** D (2014). Faster Sound Stream Segmentation in Musicians than in Nonmusicians. *PloS one*, *9*(7), e101340.
- Trost W, Frühholz S, **Schön** D, Labbé C, Pichon S, Grandjean D, & Vuilleumier P (2014). Getting the beat: Entrainment of brain activity by musical rhythm and pleasantness. *NeuroImage*, 103, 55-64.
- Cason N, Hidalgo C, Roman S, Isoard F, **Schön** D (2014) Rhythmic priming enhances speech production abilities: evidence from prelingually deaf children, *Neuropsychology*

- François C, **Schön** D (2014) Neural sensitivity to statistical regularities as a fundamental biological process that underlies auditory learning: the role of musical practice. *Hear Res*. 308:122-8.
- Lévêque, Y., & **Schön**, D. (2013). Listening to the Human Voice Alters Sensorimotor Brain Rhythms. *PloS one*, *8*(11), e80659.
- Lévêque Y, Muggleton N, Stewart L, **Schön** D (2013) Involvement of the larynx motor area in singing-voice perception: a TMS study. *Front Psychol*., 4:418.
- François C, Chobert J, Besson M, **Schön** D. (2013). Music Training for the Development of Speech Segmentation. *Cerebral Cortex*, 9, 2038-43.
- Cason N, **Schön** D. (2012). Rhythmic priming enhances the phonological processing of speech. *Neuropsychologia*, 50, 2652-8.
- François C, Tillmann B, **Schön** D. (2012). Cognitive and methodological considerations on the effects of musical expertise on speech segmentation. *Ann N Y Acad Sci*. 1252:108-15.
- Lévêque Y, Giovanni A, **Schön** D. (2011). Pitch-Matching in Poor Singers: Human Model Advantage. *J Voice*. 26(3), 293-8
- **Schön** D, François C. (2011) Musical expertise and statistical learning of musical and linguistic structures. *Front Psychol*., 152-167
- Chobert J, Marie C, François C, **Schön** D, Besson M. (2011) Enhanced passive and active processing of syllables in musician children. *J Cogn Neurosci*., 23, 3874-87
- François C, **Schön** D (2011) Musical expertise boosts implicit learning of both musical and linguistic structures, *Cerebral Cortex.* 21, 2357-65
- François C, **Schön** D (2010) Learning of musical and linguistic structures: comparing event-related potentials and behavior. *Neuroreport*, 21, 928-32

PROJECT I9

Title : Understanding the role of microRNAs in midbrain dopaminergic neuron activity using combined patch-clamp/transcriptomics

Supervisor : GOAILLARD Jean-Marc

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State of the art
While any neuronal type displays a distinctive and stable electrical phenotype, most of the ion channels underlying neuronal activity display highly variable expression levels in a same neuronal population. Our recent work has demonstrated that ion channels in midbrain dopaminergic (DA) neurons are co-expressed in functional modules, such that their expression levels are correlated (Tapia et al., 2018, Sci. Rep.). We believe these correlations play a central role in the stability of neuronal activity. We hypothesize that microRNAs (miRNAs), as powerful regulators of mRNA expression, play a central role in this modular expression of ion channels
Objectives
The objective of this project is to identify the miRNAs involved in the co-regulation of expression of ion channels. In particular, we will start this project by performing a partial screening of the miRNAs expressed in midbrain DA neurons using qPCR on fluorescence-sorted samples of DA neurons. Then we will use combined patch-clamp/transcriptomics to determine how the expression of 30-35 identified miRNAs varies from cell to cell, and whether these variations correlate with the variations in expression of ion channel mRNAs (already identified in a previous study, Tapia et al., 2018, Sci. Rep.). We will use chronic pharmacological treatments and ion channel transgenic mice (available in the team) to define whether the variations in expression of miRNAs and mRNAs are influenced by variations in activity. Ion channel co-expression appears as a central mechanism to maintain neuronal activity, and miRNAs might represent the missing link bridging the gap between activity changes and genetic expression of ion channels.
Methods
Electrophysiology on acute slices (patch-clamp, current-clamp and voltage-clamp), single-neuron transcriptomics (microfluidic qPCR), multivariate analysis (PCA, LDA, clustering, topological information data analysis).
Expected results
We expect to identify the main miRNAs that are involved in ion channel co-expression patterns in mibdrain DA neurons
Feasibility
All the methods and technical resources necessary for the implementation of this project are already used in routine in the SANE team (combined patch-clamp/transcriptomics on acute slices in particular). The application of this strategy to microRNAs and their relationship to neuronal activity does not represent a particular challenge
Expected candidate profil
A candidate with a solid background in neuroscience and/or biophysics would be appreciated.

SUPERVISED PHDS & PUBLICATIONS : GOAILLARD Jean-Marc

- **Currently supervised PhD students**

- none

- **Previously supervised PhD students**

- A. Haddjeri-Hopkins (defended 11/12/2019)
- E. Moubarak (defended 10/12/2018)
- M. Dufour (defended 15/12/2014)

- **Publications of previously supervised PHD students**

- Haddjeri-Hopkins A, Tapia M, Ramirez-Franco J, Tell F, Marquèze-Pouey B, Amalric M and Goaillard JM (*BiorXiv, in review at Journal of Neuroscience*)
- Goaillard JM, Moubarak E, Tapia M and Tell F (2020). Frontiers in cellular Neuroscience, 13, 570
- Moubarak E, Engel D, Dufour MA, Tapia M, Tell F and Goaillard JM (2019). Journal of Neuroscience, 39(26): 5044-5063.
- Tapia M, Baudot P, Formisano-Tréziny C, Dufour MA, Temporal S, Lasserre M, Marquèze-Pouey B, Gabert J, Kobayashi K and Goaillard JM (2018). Scientific Reports, 8(1): 13637.
- Goaillard JM and Dufour MA (2014). eLife, 3:e02615.
- Mlayah-Bellalouna S, Dufour M, Mabrouk K, Mejdoub H, Carlier E, Othmane H, Tarbe M, Goaillard JM, Gigmes D, Seagar M, El Ayeb M, Debanne D and Srairi-Abid N (2014). Toxicon, 92C:14-23.
- Dufour MA, Woodhouse A, Amendola J and Goaillard JM (2014). eLife, 20th Oct 2014.
- Dufour MA, Woodhouse A and Goaillard JM (2014). Journal of Neuroscience Research, 92(8): 981-99

PROJECT I10

Title : Mesoscopic functional and structural connectivity underlying motor control: Linking large-scale networks at 3T and laminar connectivity at 7-Tesla MRI

Supervisor : MALFAIT Nicole

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State of the art
The cortex is a massively recurrent network, characterized by feedforward and feedback connections between brain areas as well as lateral connections within an area. Movement control and adaptation recruit extended neural networks, encompassing cortico-basal ganglia and cortico-cerebellar loops. These loops are largely conceived as parallel circuits that process motivational, cognitive, and sensorimotor information separately. However, whether and how these functionally distinct loops interact remains unclear. Motor control tasks and 3T MRI allow studying connectivity, interaction and plasticity of these loops on a whole brain level in vivo. Through invasive neurophysiological techniques, it has been shown that feedforward, horizontal and feedback responses generally activate separate cortical layers. Ultra-high spatial resolution 7-Tesla MRI allows now non-invasive, in vivo sub-millimetre mesoscale (cortical columns and layers) imaging, thus providing a new opportunity to investigate functional and structural connectivity at a finer level than previously possible in humans.
Twofold objectives
(i) Build upon invasive anatomical and electrophysiological studies, we explore large-scale loops in a functional MRI (fMRI)-based task at 3T. We will investigate the modifications related to our task between basal ganglia (BG), cerebellum (Cb) and the primary motor cortex (M1) via distinct thalamic nuclei. Second, we focus on BG and Cb links to the supplementary area (SMA) and the pre-motor cortex (PM), respectively, for which layer-specific projections to M1 have also been described. (ii) While tremendously promising, ultra-high field imaging at the mesoscale remains challenging by means of optimal sequence selection and post-processing. Here, we aim to establish, implement and analyse such techniques in a state-of-the-art fMRI motor control experiment. We hypothesize to identify distinctive mesoscale connections within and between M1, PM and SMA that are linked to connectivity shift of the major control loops analysed at 3T.
Methods
We designed a predictive motor timing task (interception of a moving target using a joystick) in which participants have (under different trial conditions) to update their motor command based on distinct error signals (motivational, cognitive, and sensorimotor) assumed to be processed through distinct anatomo-functional tracks. 3T and 7T MRI will be used to acquire fMRI during rest and task execution, as well as ultra-high-resolution anatomical images (MP2RAGE, DWI) for 30 healthy volunteers. Whole brain connectivity analyses will be conducted on the 3T fMRI data. 7T fMRI analyses will focus on cortical interconnections (between M1, SMA and PM) and thalamic inputs to M1. Volunteers will also undergo EEG/MEG recordings outside of this PhD project.
Twofold expected results
(i) Offer new insight into the cortico-basal ganglia-cerebellar network dynamics at work in movement control and adaptation, both on the large-scale level and the mesoscale level, and more importantly their interaction. (ii) Establish optimized functional and diffusion sequences for mesoscale analyses, develop a suitable post processing pipeline and provide a representative data set for tuning of processing and analysis techniques.
Feasibility
Funding for data acquisition is already available, as well as ethical authorisations. The behavioural task and the MRI sequences are currently piloted on the new 7T MRI system before the fellow arrival. The CRMBM-CEMEREM has internationally recognized expertise in the most advanced neuroimaging technologies. The INT conducts multiscale and multimodal research on the neural processes underlying movement control and adaptation.
Expected candidate profil
Proficiency in programming (e.g. Python, R or Matlab) is required. Candidates with background in Neuroscience, Engineering or Computational Science are all welcome.

SUPERVISED PHDS & PUBLICATIONS : MALFAIT Nicole

- **Currently supervised PhD students**

- Antoine SCHWEY (2019 -)

- **Previously supervised PhD students**

- Amirhossein JAHANI (2016-2020)
- Julie ALAYRANGUES (2015-2018)
- Flavie TORRECILLOS (2012-2016)

- **Publications of previously supervised PHD students**

- **Jahani A, Schwey A**, Bernier PM, Malfait N. Spatially Distinct Beta-Band Activities Reflect Implicit Sensorimotor Adaptation and Explicit Re-aiming Strategy The Journal of Neuroscience 40:2498-2509.
- **Alayrangues J, Torrecillos F, Jahani A,** Malfait N (2019) Error-related modulations of the sensorimotor post-movement and foreperiod beta-band activities arise from distinct neural substrates and do not reflect efferent signal processing. Neuroimage 184:10-24.
- **Torrecillos F, Alayrangues J,** Kilavik BE, Malfait N (2015) Distinct Modulations in Sensorimotor Postmovement and Foreperiod β-Band Activities Related to Error Salience Processing and Sensorimotor Adaptation. The Journal of Neuroscience 35:12753-65.
- **Torrecillos F.,** Albouy P, Brochier T, Malfait N. (2014) Does the processing of sensory and reward-prediction errors involve common neural resources? Evidence from a frontocentral negative potential modulated by movement execution errors. The Journal of Neuroscience 34:4845-56.

SUPERVISED PHDS & PUBLICATIONS : STELLMANN Jan-Patrick

- **Currently supervised PhD students**

- Arzu Ceylan Has (Hamburg)

PROJECT I11

Title : Choral singing at school: effects on the neuro-cognitive development of 7 to 10 years old children

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State of the art

While many studies examined the influence of instrumental training on language processing, and more generally on executive functions1, less studies focussed on the impact of singing. Recent results with pre-school children showed that musical and singing abilities are associated to enhanced working memory capacity and phonetic abilities2. However, the causal influence of singing practice on linguistic, cognitive and social skills has not yet been demonstrated

Objectives

This longitudinal project (Randomized Control Trial) over 2 years aims at testing for the impact of choral singing every morning at school for 20 min on the neuro-cognitive development of 7-10 years old children. Control groups will be involved in creative writing (also every morning for 20 min) or in no training. Training aspects are organized by the Vocal Art National Center (VANC, Musicatreize) and an association for writers, “La Marelle”.

Methods

A total of 120 children (CE1 and CE2) will be tested using standard psychometric tests (duration 2 h) and a subset of children will also be tested using MEG and EEG (1h). We aim to record both MEG and EEG data simultaneously in Mismatch Negativity and oddball protocols, using harmonic sounds (HC) and syllables (Syll.) to directly compare the size of the effects on the components of interest (ERP/ERF) and Mismatch Negativity/Mismatch Fields, the localization of the generators and connectivity metrics at the neural networks level. To our knowledge such an attempt has never been conducted in children

Expected results

After training, “singing” children will outperform children in the writing or no training groups in musicality and phonological awareness tests, reading, short-term and working memory, attention, and social attitudes2,3,4. Conversely, children in the creative writing group will outperform children in the singing group in lexical and semantic fluency, visuo-motor precision, and creative behaviour (story-telling and drawing). In the MMN and oddball experiments, “singing” children will show a specific maturation of the auditory system with enhanced MMN/MMF and ERP/ERF to both HC and syll. and stronger coupling between MMN and brain oscillations in the theta frequency band5.

Feasibility

we have a unique opportunity to test these children as this project is implemented by the VANC since 2019. We are currently conducting a pilot study (sept. 2020-May 2021) testing 80 children with M2, M1 and orthophonists students to test for the feasibility of the project and for simultaneous MEG/EEG recordings

Expected candidate profil

Master in cognitive neuroscience, psychology or linguistics. Expected to learn MEG and EEG processing with our collaborators at the MEG Center

1Besson, M., Dittinger, E. & Barbaroux, M. (2018). Topics in Cog. Psych., 118, 273-; 2Christiner & Reiterer, 2018. Brain Sci. 2018, 8, 169-; 3Dewaele & Wei, 2012. Internat. Jal Multilingualism 9(4). 352–366; 4Strait et al. Behav. Brain Funct. 2011 ; 5Bishop et al, 2010. Jal Neurosc., 30(46):

SUPERVISED PHDS & PUBLICATIONS : BESSON Mireille

- **Currently supervised PhD students**

- none

- **Previously supervised PhD students**

- 18 PhD students
- In the past 3 years: Barbaroux Mylène (PhD Defence, December 2019); Dittinger Eva (PhD defence, December 2018)

- **Publications of previously supervised PHD students**

- Dittinger E, Korka, B. & Besson M. Evidence for enhanced long-term memory in professional musicians and its contribution to novel word learning. *Journal of Cognitive Neuroscience*, *in press*.
- Barbaroux M., Norena A. Rasamimanana M., Castet E. & Besson M. From psychoacoustics to brain waves: a longitudinal approach to novel word learning". *Journal of Cognitive Neuroscience*, *in press*.
- Dittinger E, Valizadeh SA, Jäncke L, Besson M, Elmer S. (2019). Testing the Influence of Music Training on Novel Word Learning across the Lifespan Using a Cross-Sectional Approach in Children, Young Adults and Older Adults. *Brain and Language. https://doi.org/10.1016/j.bandl.2019.104678.*
- Barbaroux, M., Dittinger, E. & Besson, M. (2019). Music training with Démos Program positively influences cognitive functions in children from low socio-economic backgrounds. *PLoSONE;* 14(5):e0216874.https://doi.org/10.1371/journal.pone.0216874.
- Dittinger, E., D'império M. & Besson, M. (2018). Enhanced neural and behavioral processing of a non-native phonemic contrast in professional musicians. *Eur. J. Neurosci. pp.1-13.*
- Dittinger E, Valizadeh SA, Jäncke L, Besson M, Elmer S. (2017). Increased functional connectivity in the ventral and dorsal streams during retrieval of novel words in professional musicians. *Hum Brain Mapp.* 2017;00:000–000. https://doi.org/10.1002/hbm.23877)
- Dittinger, E., Chobert, J., Ziegler, J. & Besson, M. (2017). Fast Brain Plasticity during Word Learning in Musically-Trained Children. *Front. Hum. Neurosci.* 11:233. doi: 10.3389/fnhum.2017.00233
- Dittinger, E., Barbaroux, M., D'império M., Jäncke, L., Elmer, S & Besson, M. (2016). Professional music training and novel word learning: from faster semantic encoding to longer-lasting word representations. *Journal of Cognitive Neuroscience.* 28:10, pp. 1584–1602. doi:10.1162/jocn_a_00997

PROJECT I12

Title : Deciphering the mechanisms of painful and painless Nav1.9 channelopathies

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State of the art

Chronic pain is a global problem affecting up to 20% of the world's population and has a significant economic, social and personal cost to the society. More than half of patients with chronic pain do not obtain sufficient pain relief with current systemic analgesics (Finnerup et al., 2010). Recent research has provided valuable insights into the critical role of the voltage gated Nav1.9 channel (gene name Scn11a) in inflammatory and neuropathic pain pathways both in mice and humans (Dib-Hajj et al., 2015). The critical role of Nav1.9 in nociception, along with its absence in the central nervous system and cardiac tissue, suggest it is a valid target for novel analgesic drugs.
Activation of Nav1.9 channels gives rise to a persistent, non-inactivating Na+ current operating at relatively negative membrane potentials. Acting as a subthreshold channel Nav1.9 contributes to setting the membrane potential, amplifying sensory subthreshold depolarization, and thereby generating pain messages. About 20 mutations have been reported for SCN11A in humans, most of them lead to gain of function of Nav1.9 channels. However, these mutations cause either painful conditions (familial episodic pain and painful small fiber neuropathy) (Leipold et al., 2015; Baker and Nassar, 2020) or a complete insensitivity to pain (CIP) (Leipold et al., 2013; King et al., 2017). How gain of function of 'pain transmitting' Nav1.9 channels leads to either painless or painful phenotype is currently unknown. How excitability of peripheral nociceptive fibers depends on Nav1.9 properties and ion channel complement? Could we restore normal firing patterns of nociceptors by fine-tuning Nav1.9 mutant properties by using gating-modifier molecules?

Objectives

To decipher the link between the biophysical properties of Nav1.9 mutants (L396P and L811P; R222H and V1184A), those of co-expressed nociceptor spike-generating channels and corresponding painful (episodic pain) or painless (CIP) phenotypes. Testing in house gating modifier drugs to restore normal functioning of mutant channels.

Methods

The successful candidate will use unique complementary approaches, including recording of recombinant mutant channels using patch clamp, numerical simulations of virtual 'mutated' nociceptors, and ex vivo and in vivo analysis of Nav1.9 mutant knock-in mouse line by CRISPR editing. DRG neuron excitability, single sensory nerve fiber activity using skin-nerve preparation and painful or painless behaviors will be investigated in these CRISPR/Cas9 genome-edited knock-in mouse lines.

Expected results

The study will provide valuable insight into the underlying pathophysiological mechanisms of the symptoms seen in patients who have Nav1.9 mutations. First, it will clarify the electrophysiological parameters reflecting pathological hyper- and hypo-sensitivity of primary afferents with Nav1.9 mutants. We hypothesize that the Nav1.9 window current component (activation/inactivation-gating overlap), responsible for sustained depolarization, is different in painful and painless phenotype. Depending on its amplitude and persistence, the generated window current may promote hyper or hypo-excitability by interfering with channels responsible for action potential generation and propagation in sensory ending. Second, CRISPR/Cas9 animals will be used to validate the effect of Nav1.9 variants, to characterize the pathogeny of the variants and ultimately to provide ways of correcting molecular defects of pain perception by using gating modifier molecules. Altogether, modelling pain disorders will provide new and fundamental insight into Nav1.9 channelopathies that may be useful in future studies evaluating possible treatments of neuropathic pain

Feasibility
The team has all necessary equipment and infrastructure, and long-term expertise and excellent technical staff, to accomplish the proposed research project. The experimental approaches, including many mutant mouse models, are already established in the lab and available from the start of the project. The team has strong financial support and has built a permanent partnership with the Pitié-Salpêtrière Hospital
Expected candidate profil
In addition to solid knowledge in pain signaling mechanisms, gene-editing technologies and neurophysiology, the candidate is expected to have experience in computer modeling. Clinical knowledge and experience in pain management will be appreciated.
References
Baker MD, Nassar MA. Painful and painless mutations of SCN9A and SCN11A voltage-gated sodium channels. Pflugers Arch. 2020 Jul;472(7):865-880. Dib-Hajj SD, Black JA, Waxman SG. NaV1.9: a sodium channel linked to human pain. Nature Rev Neurosci. 2015 Sep;16(9):511-9. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 2010 Sep;150(3):573-581. Leipold E, Hanson-Kahn A, Frick M, Gong P, Bernstein JA, Voigt M, Katona I, Oliver Goral R, Altmüller J, Nürnberg P, Weis J, Hübner CA, Heinemann SH, Kurth I. Cold-aggravated pain in humans caused by a hyperactive NaV1.9 channel mutant. Nat Commun. 2015 Dec 8;6:10049. Leipold E, Liebmann L, Korenke GC, Heinrich T, Giesselmann S, Baets J, Ebbinghaus M, Goral RO, Stödberg T, Hennings JC, Bergmann M, Altmüller J, Thiele H, Wetzel A, Nürnberg P, Timmerman V, De Jonghe P, Blum R, Schaible HG, Weis J, Heinemann SH, Hübner CA, Kurth I. A de novo gain-of-function mutation in SCN11A causes loss of pain perception. Nat Genet. 2013 Nov;45(11):1399-404. King MK, Leipold E, Goehringer JM, Kurth I, Challman TD. Pain insensitivity: distal S6-segment mutations in NaV1.9 emerge as critical hotspot. Neurogenetics. 2017 Jul;18(3):179-181.

SUPERVISED PHDS & PUBLICATIONS : DELMAS Patrick

- **Currently supervised PhD students**

- none

- **Previously supervised PhD students**

- Bertrand Coste (2004-2007)
- Aurélie Giamarchi (2006-2009)
- Jizhe Hao (2007-2011)
- Muriel Amsalem (2010-2014) Co-direction
- Caroline Bonnet (2013-2017)

- **Publications of previously supervised PHD students**

- Bonnet C, Delmas P. (2020). Activation of Nav1.9 channels by nitric oxide causes medication-overused headache. Med Sci (Paris) (1):16-19.
- Bonnet C, Hao J, Osorio N, Donnet A, Penalba V, Ruel J, Delmas P. (2019). Maladaptive activation of Nav1.9 channels by nitric oxide causes triptan-induced medication overuse headache. Nature Commun. 10(1):4253.
- Amsalem M, Poilbout C, Ferracci G, Delmas P, Padilla F. (2018). Membrane cholesterol depletion as a trigger of Nav1.9 channel-mediated inflammatory pain. EMBO J. 37(8):e97349.
- Lolignier S, Eschalier A, Bonnet C, Delmas P, Busserolles J. (2016). Le canal Nav1.9 - Protéine clé pour la perception du froid et cible thérapeutique potentielle contre la douleur [The Nav1.9 channel is crucial for sensing noxious cold]. Med Sci (Paris). (2):162-5.
- Lolignier S, Bonnet C, Gaudioso C, Noël J, Ruel J, Amsalem M, Ferrier J, Rodat-Despoix L, Bouvier V, Aissouni Y, Prival L, Chapuy E, Padilla F, Eschalier A, Delmas P, Busserolles J. (2015). The Nav1.9 channel is a key determinant of cold pain sensation and cold allodynia. Cell Rep. 11(7):1067-78.
- Hao J, Bonnet C, Amsalem M, Ruel J, Delmas P. (2015). Transduction and encoding sensory information by skin mechanoreceptors. Pflugers Arch. 467(1):109-19.
- Delfini MC, Mantilleri A, Gaillard S, Hao J, Reynders A, Malapert P, Alonso S, François A, Barrere C, Seal R, Landry M, Eschallier A, Alloui A, Bourinet E, Delmas P, Le Feuvre Y, Moqrich A. (2013). TAFA4, a chemokine-like protein, modulates injury-induced mechanical and chemical pain hypersensitivity in mice. Cell Rep. 5(2):378-88.
- Hao J, Padilla F, Dandonneau M, Lavebratt C, Lesage F, Noël J, Delmas P. (2013). Kv1.1 channels act as mechanical brake in the senses of touch and pain. Neuron, 77(5):899-914.
- Abbas N, Gaudioso-Tyzra C, Bonnet C, Gabriac M, Amsalem M, Lonigro A, Padilla F, Crest M, Martin-Eauclaire MF, Delmas P. (2013). The scorpion toxin Amm VIII induces pain hypersensitivity through gain-of-function of TTX-sensitive Na^+ channels. Pain. 154(8):1204-15.
- Hao J, Ruel J, Coste B, Roudaut Y, Crest M, Delmas P. (2013). Piezo-electrically driven mechanical stimulation of sensory neurons. Methods Mol Biol. 998:159-70.
- Rodat-Despoix L, Hao J, Dandonneau M, Delmas P. (2013). Shear stress-induced Ca^{2+} mobilization in MDCK cells is ATP dependent, no matter the primary cilium. Cell Calcium. 53(5-6):327-37.
- Roudaut Y, Lonigro A, Coste B, Hao J, Delmas P, Crest M. (2012). Touch sense: functional organization and molecular determinants of mechanosensitive receptors. Channels (Austin). 6(4):234-45.
- Gaudioso C, Hao J, Martin-Eauclaire MF, Gabriac M, Delmas P. (2012). Menthol pain relief through cumulative inactivation of voltage-gated sodium channels. Pain 153(2):473-484.
- Lolignier S, Amsalem M, Maingret F, Padilla F, Gabriac M, Chapuy E, Eschalier A, Delmas P, Busserolles J. (2011). Nav1.9 channel contributes to mechanical and heat pain hypersensitivity induced by subacute and chronic inflammation. PLoS One. 6(8):e23083.
- Hao J, Delmas P. Recording of mechanosensitive currents using piezoelectrically driven mechanostimulator. Nature Protoc. 6(7):979-90.
- Delmas P, Hao J, Rodat-Despoix L. (2011). Molecular mechanisms of mechanotransduction in mammalian sensory neurons. Nature Rev Neurosci. 12(3):139-53.
- Hao J, Delmas P. (2010). Multiple desensitization mechanisms of mechanotransducer channels shape firing of mechanosensory neurons. J Neurosci. 30(40):13384-95.
- Giamarchi A, Feng S, Rodat-Despoix L, Xu Y, Bubenshchikova E, Newby LJ, Hao J, Gaudioso C, Crest M, Lupas AN, Honoré E, Williamson MP, Obara T, Ong AC, Delmas P. (2010). A polycystin-2 (TRPP2) dimerization domain essential for the function of heteromeric polycystin complexes. EMBO J. 29(7):1176-91.

- Maingret F, Coste B, Hao J, Giamarchi A, Allen D, Crest M, Litchfield DW, Adelman JP, Delmas P (2008). Neurotransmitter modulation of small-conductance Ca^{2+}-activated K^{+} channels by regulation of Ca^{2+} gating. Neuron. 59(3):439-49.
- Raoux M, Rodat-Despoix L, Azorin N, Giamarchi A, Hao J, Maingret F, Crest M, Coste B, Delmas P. (2007) Mechanosensor Channels in Mammalian Somatosensory Neurons. Sensors (Basel).,7(9):1667-1682.
- Maingret F, Coste B, Padilla F, Clerc N, Crest M, Korogod SM, Delmas P. (2008). Inflammatory mediators increase Nav1.9 current and excitability in nociceptors through a coincident detection mechanism. J Gen Physiol. 131(3):211-25.
- Coste B, Crest M, Delmas P. (2007). Pharmacological dissection and distribution of NaN/Nav1.9, T-type Ca^{2+} currents, and mechanically activated cation currents in different populations of DRG neurons. J Gen Physiol. 129(1):57-77.
- Delmas P, Coste B, Gamper N, Shapiro MS. (2005). Phosphoinositide lipid second messengers: new paradigms for calcium channel modulation. Neuron. 47(2):179-82.
- Delmas P, Padilla F, Osorio N, Coste B, Raoux M, Crest M. (2004). Polycystins, calcium signaling, and human diseases. Biochem Biophys Res Commun. 322(4):1374-83.
- Delmas P, Nauli SM, Li X, Coste B, Osorio N, Crest M, Brown DA, Zhou J. (2004). Gating of the polycystin ion channel signaling complex in neurons and kidney cells. FASEB J. 18(6):740-2.
- Coste B, Osorio N, Padilla F, Crest M, Delmas P. (2004). Gating and modulation of presumptive NaV1.9 channels in enteric and spinal sensory neurons. Mol Cell Neurosci. 26(1):123-34.
- Delmas P, Coste B. (2003). Na^{+} channel Nav1.9: in search of a gating mechanism. Trends Neurosci. 26(2):55-7

PROJECT I13

Title : Restoring proprioception in the elderly : psychophysical and MRI approaches

Supervisor : KAVOUNOUDIAS Anne

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State of the art
All the sensory systems deteriorate progressively with age, leading to an impairment of perceptive and motor functions. In particular, we recently showed that muscle proprioception, vision and touch are both functionally affected after 65 years old, with a more pronounced alteration for muscle proprioception (Chancel et al 2018; Landelle et al. 018). Interestingly, the proprioceptive impairment seems to be related to a decrease in inter-hemispheric balance at the cortical level, as evidenced in a functional magnetic resonance imaging (fMRI) study (Landelle et al. 2020)
Objectives
In line with our previous work, this project aims to: 1) Investigate the age-related alteration of the inter-hemispheric structural connectivity between the two sensorimotor cortices, and correlate this possible alteration with the degree of inter-hemispheric functional loss 2) Test whether a training protocol based on the reinforcement of proprioceptive feedback is likely to compensate or reinforce kinesthetic information processing, 3) Determine possible functional remodelling of the brain networks following sensory training using fMRI and possible changes in neurometabolites concentration (GABA, Glutamate) by magnetic resonance spectroscopy
Methods
Proprioceptive training will consist of repeated vibratory stimulation applied daily for two consecutive weeks on 25 participants over 65 years of age, and 25 younger control. Before and immediately after the training, all the participants will undergoan MRI session. A spectroscopy sequence centered on the two primary sensorimotor cortices will also be acquired. Theb rain's structural connectivity will be investigate dusing atractography approach based on diffusion-weighted-imaging data already acquired. Psychophysical and motor tests will be carried out.
Expected results
The proprioceptive training applied unilaterally on one hand should restore the inter-hemispheric balance of the sensorimotor cortices in older participants. We expect a lateralization of brain activations toward the contralateral side in older participants, similarly to that evidenced in young adults. As inter hemispheric lateralization was found to correlate with better discrimination perception, we hypothesize that older participants should gain in perceptual and motor capabilities after the training. Finally, changes in the relative concentration of GABA and Glutamate within the sensorimotor corticesare also expected
Feasibility
Stimulation device compatible with MRI scanner have already been developed and tested. DWI images already acquired could be first analyzed, while waiting for additional financial support (grant proposal under submission)
Expected candidate profil
The candidate will have a background in neurophysiology, statistics and programming skills (Matlab). They will also have a keen interest for clinical perspectives and a desire to interact with patients. Knowledge of fMRI would be appreciated.

SUPERVISED PHDS & PUBLICATIONS : KAVOUNOUDIAS Anne

- **Currently supervised PhD students**

- Raphaëlle SCHLIENGER

- **Previously supervised PhD students**

- Caroline BLANCHARD
- Marie CHANCEL
- Caroline LANDELLE
- Jeanne CARON-GUYON

- **Publications of previously supervised PHD students**

- C LANDELLE,J DANNA,B NAZARIAN,L PRUVOST,M AMBERG,F GIRAUX,R KRONLAND-MARTINET,SYSTAD,MARAMAKI,KAVOUNOUDIASA*-(2021)Hearing the touch: Impact of sonification in the haptic perception of artificial textures and its modulation with aging. Scientific Reports(in press)
- LANDELLE C, CHANCEL M, BLANCHARD C,GUERRAZ M , KAVOUNOUDIAS A* (2021)Contribution of muscle proprioception to limb movement perception and proprioceptive decline with aging Current Opinion in Physiology(in press)
- Landelle C,Anton JL, Nazarian B, Sein J, Gharbi A, Félician O, Kavounoudias A*(2020) -Functional brain changes in the elderly for the perception of hand movements: a greater impairment in proprioception than touch NeuroImage Jun 17: 117056.
- LANDELLE C,SEIN J,ANTON JL,NAZARIAN B,FÉLICIAN O,KAVOUNOUDIAS A(2020) The aging brain: a set of 2Supervisors who obtained a fellowship in 2020(Ecole Doctoralor NeuroSchool PhD program) cannot apply. Reminder:a maximum of 3 full-time PhD studentsper HDR is accepted. functional MRI data acquired at rest and during exposure to tactile or muscle proprioceptive stimulation in healthy young and older volunteers. Data in brief31:105939. doi: 10.1016/j.dib.2020.105939
- 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 Cortex2020 Jun 4:bhaa118. doi: 10.1093/cercor/bhaa118
- ACKERLEY R,CHANCEL M,AIMONETTI JM,RIBOT-CISCAR E,KAVOUNOUDIAS A(2019) Seeing your foot move changes muscle proprioceptive feedback. eNeuro.0341-18.2019; DOI: https://doi.org/10.1523/ENEURO.0341-18.2019[IF = 3.46
- CHANCEL M,LANDELLE C,BLANCHARD C,FELICIAN O,GUERRAZ M,KAVOUNOUDIAS A(2018) Hand movement illusions show changes in sensory reliance and preservation of multisensory integration with age for kinaesthesia. Neuropsychologia119:45-58
- LANDELLE C,EL AMADI ,KAVOUNOUDIAS A(2018)Age-related impairment of hand movement perception based on muscle proprioception and touch. Neuroscience381: 91-104
- CHANCEL M,AKAVOUNOUDIAS,GUERRAZ M(2017) What's left of the mirror illusion when the mirror is no longer seen? Bilateral integration of proprioceptive afferents! Neuroscience362: 118-126
- CHANCEL M.,BLANCHARD C.,GUERRAZ M,MONTAGNINI A,KAVOUNOUDIAS A.(2016)Optimal visuo-tactile integration for perception of self-hand movement. J Neurophysiol116(3):1522-1535. doi: 10.1152/jn.00883.2015

- CHANCEL M,BRUN C,ROULIN JL,KAVOUNOUDIAS A,GUERRAZ M(2016)Kinesthetic mirror illusions: Does the mirror matter?Exp Brain Res234 (6): 1459-1468
- KANEKO F,BLANCHARD C,LEBAR N,NAZARIAN B,KAVOUNOUDIAS A&ROMAIGUÈRE P(2015) Brain regions associated to a kinesthetic illusion evoked by watching a video of one's own moving hand.PlosOne10(8): e0131970. doi:10.1371/journal.pone.0131970
- METRAL M,CHANCEL M,BRUN C,LUYAT M,KAVOUNOUDIAS A,MICHEL GUERRAZ(2015)Kinaesthetic mirror illusion and spatial congruence. Exp Brain Res233(Issue:5):1463-70.
- BRUN C,METRAL M,CHANCEL M,KAVOUNOUDIAS A,LUYATM,GUERRAZM.(2015) Passive or simulated displacement of one arm, but not mirror vision, modulates involuntary displacements of the other. Neuroscience285: 343-355
- BLANCHARD C,ROLL R,ROLL JP& KAVOUNOUDIASA(2013) Differentialcontributions of vision, touch and muscle proprioception to the coding of hand movements.PlosOne8:4-e62475;DOI:10.1371/journal.pone.0062475
- BLANCHARD C,ROLL R,ROLL JP& KAVOUNOUDIAS A(2011) combined contribution of tactile and proprioceptive feedback to hand movement perception. Brain Res 1382: 219-229

PROJECT I14

Title : *Molecular mechanism of zinc-induced aggregation in neurodegenerative disease*

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State of the art
Most neurodegenerative diseases are characterized by the presence of aggregation-prone proteins associated with the pathology. For instance, amyloid-β and tau are found aggregated in Alzheimer's disease (AD), α-synuclein in Parkinson disease, TDP-43, FUS and SOD1 in Amyotrophic Lateral Sclerosis (ALS). Even though these proteins signoficantly differ in their structures and functions, they share common features. For instance, most of them are known to bind zinc ions. While zinc might not be the causative agent of neurodegenerative diseases, it was shown to bind to these proteins and favor their aggregation. Recently, we have identified three zinc binding sites in tau and two zinc binding sites in TDP-43. However, the role of these sites in zinc-induced aggregation is not clearly elucidated.
Objectives
The objective of this project is to demonstrate the direct implication of zinc in the pathogenesis of neurodegenerative diseases by (1) Determining the role of each zinc-binding site on Tau and TDP-43 aggregation (in vitro and in cell); (2) Showing the presence of zinc ions in aggregates of Tau and TDP-43 using cell and animal models of AD and ALS.
Methods
To achieve these objectives, we will use different in vitro and in vivo approaches. In the frame of the first objective, a set of TDP-43 and Tau mutants as well as their fragments will be purified using standard biochemical approaches. Then, the interaction of these mutants proteins with zinc will be studied using biophysical methods such as Isothermal Titration Calorimetry (ITC), Differential scanning Calorimetry and fluorimetry (DSC and nanoDSF). Finally, zinc-induced aggregation of these mutants will be investigated both in vitro and in cells using turbidimetry, ThT-assays, dynamic light scattering (DLS) as well as TEM fluorescent microscopy. To achieve the second objective, TDP-43 and Tau aggregates from brains of ALS and AD animal models will be purified to measure the content of metal ions, in particular zinc, using flame atomic absorption spectrometric (FAAS) analysis.
Expected results
We plan to determine zinc-binding sites and amino acids that are responsible for zinc-induced aggregation of TDP-43 and Tau. By mutating these amino acids, we expect to significantly reduce zinc-induced aggregation of TDP-43. Moreover, we expect to find zinc in TDP-43 and Tau aggregates extracted from the brain of ALS animal models. This will demonstrate the direct implication of zinc in the pathogenesis of neurodegenerative disease and reveal zinc-binding sites as potential drug targets for ALS and AD therapy.
Feasibility
Institute of NeuroPhysiopathology and collaborators have all necessary equipment and infrastructure to accomplish proposed research project. Moreover, a similar project focused on zinc-induced aggregation of tau has been previosly successfully carried out in our laboratory be a PhD student.
Expected candidate profil
We are looking for a motivated candidate with a solid fundamental background and who is willing to acquire complementary expertise in *in vitro*, in cell and *in vivo* approaches.

SUPERVISED PHDS & PUBLICATIONS : DEVRED François

- **Currently supervised PhD students**

- Dahbia Yatoui (co direction P.O. Tsvetkov, Tunisie 2019-22)

- **Previously supervised PhD students**

- Romain La Rocca (2017-2020)
- Andrei Roman (2014-2017)
- Roqyia Nouar (2009-2013)

- **Publications of previously supervised PHD students**

- Philipp O. Tsvetkov, **Romain La Rocca**, Soazig Malesinski, François Devred. Characterization of Microtubule-associated proteins and tubulin interactions by isothermal titration calorimetry. Microcalorimetry of Biological Molecules: Methods and Protocols, Methods in Molecular Biology, (chap. 12) vol. 1964, 2019
- **Andrei Roman**, François Devred*, **Romain La Rocca,** Cyrille Garnier, Deborah Byrne, Evgeni Yu. Zernii, Vincent Peyrot, Philipp O. Tsvetkov. Zinc-dependent reversible self-assembly of tau. J Mol Biol 2018
- Philipp O. Tsvetkov, **Andrei Roman**, Viktoriia E. Baksheeva, Aliya A. Nazipova, Marina P. Shevelyova, Vasiliy I. Vladimirov, Michelle F. Buyanova, Dmitry V. Zinchenko, Andrey A. Zamyatnin Jr., François Devred, Andrey V. Golovin, Sergei E. Permyakov, Evgeni Yu. Zernii. Functional status of neuronal calcium sensor-1 is modulated by zinc binding. Frontiers in Molecular Neuroscience. 2018
- Philipp O. Tsvetkov, Emeline Tabouret, **Andrei Roman**, Sylvie Romain, Céline Bequet, Olga Ishimbaeva, Stéphane Honoré, Dominique Figarella-Branger, Olivier Chinot, Francois Devred Differential Scanning Calorimetry of plasma in glioblastoma: toward a new prognostic / monitoring tool. Oncotarget. 2018
- Cyrille Garnier, Francois Devred, Deborah Byrne, Rémy Puppo, **Andrei Roman**, Soazig Malesinski, Andrey Golovin, Régine Lebrun, Natalia Ninkina, Philipp O. Tsvetkov, Zinc binding to RNA recognition motif of TDP-43 induces the formation of amyloid-like aggregates. Scientific Reports 2017
- **Roqiya Nouar**, Gilles Breuzard, Sonia Bastonero, Svetlana Gorokhova, Pascale Barbier, François Devred, Hervé Kovacic, Vincent Peyrot. Direct evidence for the interaction of stathmin with the length and the plus-end of microtubules in cells. FASEB J. 2016
- **Andrei Roman**, Francois Devred, Alexander A. Makarov Aslan A. Kubatiev, Vincent Peyrot, Philipp O. Tsvetkov. Sequential binding of calcium ions to B-repeat domain of SdrD from Staphylococcus aureus. Canadian Journal of Microbiology 2016
- Gilles Breuzard, Pierre Hubert, **Roqiya Nouar**, Tiffany De Bessa, François Devred, Pascale Barbier, James Sturgis, and Vincent Peyrot. “Molecular Mechanisms of Tau Binding to Microtubule and its Role in Microtubule Dynamics in Live Cells.” J Cell Sci, 2013
- **Roqiya Nouar**, François Devred, Gilles Breuzard, and Vincent Peyrot. " FRET and FRAP imaging: approaches to characterise tau and stathmin interactions with microtubules in cells.” Biol Cell. 2013