INTERNATIONAL PHD CONTRACTS

LIST OF PROJECTS (13)

Application deadline: April 14, 2024

Link to the call

*The contracts are fully funded by **NeuroSchool** (nEURo*AMU, ANR-17-EURE-0029).*

1. **ASSAIANTE Christine (CRPN), RANJEVA Jean-Philippe (CRMBM):** Understanding the role of sensorimotor representation in dyslexia: neural basis and impact of comorbidity

State of art: The first attempt at integrating phonological and sensorimotor hypotheses of dyslexia in a unified framework yielded successful results in young adults with dyslexia, with sensorimotor impairment affecting phonemic and articulatory performances, as well as mental action representations (Marchetti et al., 2022; 2023). Interestingly, behavioural studies also highlighted an increased proportion of sensorimotor impairment in young adults with dyslexia (27%) compared to control readers (5%), further substantiating the link between deficits in phonemic representation and impaired articulatory and bodily actions internal representations, specific to the dyslexic subgroup with sensorimotor impairments.

Objectives: This PhD project aims to investigate the neural basis of the functional links between language and sensorimotor representations impairment in dyslexia. With a set of fMRI studies, this study will determine whether sensorimotor representation deficits are devoted to a particular sub-group of dyslexic adults (domain-specific, dependent of dyslexia) or devoted to more global sensorimotor impairments (domain-general, independent of dyslexia).

Expected results: We will investigate whether dyslexic deficits are underpinned by associated brain features in the networks devoted to internal representation of action and learning (i.e., fronto-parietal, cingulo-opercular, somato-motor and cerebellar-cortical networks), speech articulation (i.e., left posterior IFG, left anterior insula, left sensorimotor cortex, and right inferior cerebellum), skilled reading, including phonological processing (left fronto-temporo-parietal regions, planum temporale, and precentral gyrus) and visual-orthographic processing (left occipito-temporal regions), as well as the connection between the inferior parietal lobule and the visual word form area (VWFA), which was recently reported as a plausible marker for dyslexia. We propose a set of 3 MRI studies, using 7T ultra-high field (UHF) MRI, including structural and functional resting state investigations, along with two fMRI protocols of bodily and articulatory representations to unify sensorimotor and phonological hypotheses of dyslexia.

Feasibility: To address these questions, a comparative study of four groups is required: Dyslexic Adults (DA) without sensorimotor comorbidity; Dyslexic Adults with sensorimotor comorbidity (DAC); Skilled readers with sensorimotor deficit, called developmental coordination disorder (DCD); Skilled readers without sensorimotor deficit (SR), as controls. The total cohort will include 100 students (19 - 24 years), recruited from the Aix-Marseille university. The CNRS has agreed to promote this project. Ethical approval was obtained in December 2022 for a 5-year period (N°SI: 22.03910.000124). The first 7T MRI pilot acquisitions were performed in spring 2023, and the fMRI protocols were successfully tested. MRI acquisitions will benefit from previous funding of NeuroMarseille and ILSB that secure half of the project. Other funding applications are in progress.

Complementarity of the two co-supervisors: This PhD project results from an association between two scientists from NEUROMARSEILLE, specialized in cognitive neurosciences and neurodevelopmental deficits (Ch. Assaiante) and in magnetic resonance imaging and clinical expertise (JP. Ranjeva), located in the same place and used to collaborating.

Expected candidate profile: Ideally, candidates should have experience in 7T MRI acquisition, processing, analysis, and interpretation, along with proficiency in statistical analysis (MATLAB, Python, or R). Previous experience in designing and conducting experimental studies, especially with clinical populations, is necessary. Excellent interpersonal and communication skills are required. A solid understanding of cognitive theories linked to the project is desirable.

Laboratories and teams

1) CRPN, UMR 7077, AMU-CNRS

Centre Saint-Charles, Pole 3C, Case C, 3 Place Victor Hugo, 13331 Marseille Cedex 03

https://crpn.univ-amu.fr/fr (under construction)

Team: DéPHY

Team leaders: Isabelle DAUTRICHE et Nicolas CLAIDIERE

2) CRMBM UMR AMU CNRS 7339

27 boulevard Jean Moulin 13385 Marseille cedex 05

https://crmbm.univ-amu.fr/

Team: Exploration Système Nerveux Central

Team leader: Jean-Philippe RANJEVA

PhD supervisor

ASSAIANTE Christine, DR CNRS

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Currently supervised PhD student(s)

- Jade Mériaux (Co-supervision 50% with Pascale Colé CRPN).
- Pierre Olivier Morin (Co-supervision 50% with Angelo Arleo, Institut de la Vision, Paris)

Previously supervised PhD students

Supervision of 10 PhDs who have defended their work. 5 most recent students:

- Rebecca Marchetti (2018- 2022)
- Aurélie Fontan (2013- 2017)
- Catherine Agathos (2013- 2016)
- Fanny Barlaam (2009- 2013)
- Pierre-Yves Chabeauti (2009- 2012)

Publications of supervised PhD students

Rebecca Marchetti (2018- 2022) PhD in Neuroscience, AMU, Ministry of Research funding. *Exploration du couplage perception-action dans le déficit phonologique chez le jeune adulte dyslexique* (Co-supervised with Colé). 2 international publications as 1st author (PMID: 36831753 ; 34953794), a third submitted. Currently in 5th year of Medical Studies after being selected for direct entry into 3rd year.

Aurélie Fontan (2013- 2017) PhD in Neuroscience, AMU, funding from Fondation de France. *Construction du schéma corporel dans un cerveau en développement.* 2 international publications as 1st author and 3 as co-author (PMID: 36054951 ; 251973168 ; 29547764 ; 28314184 ; 26733535). Currently postdoctoral fellow at Umea University (Sweden).

Catherine Agathos (2013- 2016) PhD in Sport and human movement science, Université Paris Saclay, CIFRE funding, contract with ESSILOR. *Dépendance visuelle au cours du vieillissement: de la perception à la marche*. (Co-supervised with Brice Isableu). 2 international publications as 1st author (PMID: 28188853 ; 26122710), a 3rd one to be submitted. Currently post-doctoral fellow at the Smith-Kettlewell Eye Research Institute, San Francisco (USA).

Fanny Barlaam (2009- 2013) PhD in Neuroscience, AMU, Partial funding from Fondation Yves Cotrel. *Anticipation posturale et coordination bimanuelle chez les adolescents : étude EEG*. (Co-supervision with Christina Schmitz). 4 international publications as 1st author and 2 as co-author (PMID: 29617219; 27192604 ; 22771844 ; 22232581 ; 33428967 ; 24502900). Currently postdoctoral fellow at Université de Montréal (Canada).

Pierre-Yves Chabeauti (2009- 2012) PhD in Neuroscience, AMU, Funding from CNES/ Région PACA. *Adaptation des représentations internes de l'action à la microgravité.* 2 international publications as 1st author and 3 as co-author (PMID: 22796070 ; 20833048 ;23291457 ; 20705351 ; 28861024). Currently biology professor (*agrégé*).

PhD co-supervisor

RANJEVA Jean-Philippe (Professor)

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Current PhD students

- **PUNJABI Khushboo:** *Mesoscopic functional and structural connectivity underlying motor control:Linking large-scale networks at 3T and laminar connectivity at 7-Tesla MRI*
  co-supervision 50% with Jan-Patrick Stellmann (CRMBM)
  Started on September 2021. PhD defense expectation: May 2025
- **ROGER Coleen:** *Neural regulation of feeding. A translational approach from mice to humans*
  co-supervision 50% with Fu Yu (SBIC, Singapore)
  Started on January 2021. PhD defense expectation: September 2024
- **HOUIDEF Sabrina:** *In-vivo MRI study of the brainstem with ex-vivo histological correlation*
  co-supervision 30% with Patrice Peran (Tonic, Toulouse) and Germain ARRIBARRAT (Tonic Toulouse)
  Started on September 2021. PhD defense expectation: September 2024
- **COTINAT Maëva:** *Contribution of multimodal MRI studies of abnormalities in sodium homeostasis and brain connectivity organization for characterization and prediction of progression or recovery of lesions, impairments and activity limitations related to neurological pathologies*
  co-supervision 50% with Laurent Bensoussan (INT, Marseille)
  Started on October 2022. PhD defense expectation: October 2025
- **THOUVENOT Alexia:** *Impacts of 10-year progression of anatomo-functional damage on current cerebral functional connectivity in patients with Multiple Sclerosis*
  co-supervision 50% with Bertrand Audoin (CRMBM)
  Started on September 2022. (1 year break) PhD defense expectation: September 2026

Past supervised PhD students

Supervision of 11 PhDs who have defended their work.

Find below the five more recent students:

DONADIEU Maxime: *Magnetic Resonance Spectroscopy at high (3T) and ultra-high (7 Tesla) fields. Methodological developments and application to Multiple Sclerosis. PhD defense :12-21-2017. MD has published as first author 3*

international publications. (PMID: 29064346; 27059982; 26756662). Current position: tenure research fellow @ NIH Bethesda, USA.

MAAROUF Adil: *From inflammation to neurodegeneration: better understandings of MS physiopathology using MRI. Defended 01-06-2017. AD has published as first author 4 international publications* (PMID: 30786899; 27974643; 26453679; 23907269). Current position: Neurologist at APHM. Researcher in the CNS team of CRMBM.

WIRSICH Jonathan: *EEG-fMRI in partial epilepsies and neurodegenerative diseases.* Defended 11-02-2016. JW *has published as first author 4 international publications* **(**PMID: 2917085; 28842386 ; 27330970 ; 24910070). Current position: Tenure research engineer on the MRI research platform of Geneva University Hospital.

LECOCQ Angèle: *Perfusion and spectroscopic MR imaging for brain exploration in neurological diseases.* Defended 12-12-2014. AL *has published as first author 2 international publications* (PMID: 25431032; 24908199)*. Current position : Medical Physicist at Tourcoin.*

Optimisation des techniques non invasives d'IRM de perfusion cérébrale et d'imagerie spectroscopique par résonance magnétique pour l'exploration des pathologies cérébrales soutenue le 12/12/2014.

FAIVRE Anthony: *Functional connectivity in MS. Defended 07-11-2014. AF has published as first author 3 international publications.* (PMID:26838014; 26149402; 22307385). Current position: Professor of Neurology, St-Anne hospital Toulon.

2. **BECLIN Christophe (IBDM):** Role of micro-RNAs in the fate determination of neural progenitors during cortex development in the mouse brain

From embryonic stages E11 to E16, neural stem cells in the ventricular zone generate cortical neurons in the mouse brain. These neurons migrate radially to form distinct layers, each with specific functions and connectivity. Between E16 and birth, the same stem cells differentiate into glial cells. Thus, during embryogenesis, a unique pool of neural stem cells generates a wide variety of cell types. Despite extensive studies on gene expression and epigenetics, a comprehensive understanding of the molecular mechanisms governing the establishment of cell diversity in the cortex remains elusive.

Mi-RNAs are small non-coding RNAs that regulate gene expression by interacting with homologous mRNAs. Each mi-RNA can potentially regulate the expression of hundreds of targets, and conversely, a single mRNA is predicted to be targeted by numerous mi-RNAs. Thus, mi-RNAs can act as orchestrators in the development of organs as complex as the mammalian cortex. However, due to the specificity of their structure and mode of action, which makes their analysis experimentally challenging, mi-RNAs are often neglected in genetic screens.

Our team has been studying the role of mi-RNAs in the control of neurogenesis for several years. We have developed a strong expertise in this area. We have also developed several tools to study the expression and function of mi-RNAs in vivo. Recently, a post-doctoral fellow, using sophisticated approaches such as in-utero injection of dyes and FACS sorting, has generated a unique resource of RNA samples extracted from neural stem cells and intermediate progenitors of cortical neurons derived from E11 to E18 injected embryos. The current project aims to analyze these samples to identify mi-RNAs whose expression varies with the embryonic stage. The function of these mi-RNAs in regulating the fate of new neurons will then be investigated. The project will be carried out in several steps:

- Mi-RNAs sequencing of RNA samples using the sequencing machine (mini-Seq, Illumina) that we have recently purchased, using the original protocol set up by Surbhi, a PhD student funded by the NeuroSchool PhD program since 2020.

- These data will be bioinformatically analyzed to identify mi-RNAs differentially expressed between embryonic stages. The nature, the function, and the expression pattern of the predicted targets of these mi-RNAs will also be part of the analysis. Subsequently, we will be able to propose mi-RNA-mRNA interactions potentially determining the fate of cortical progenitor.

- To validate the role of these interactions, gain-of-function and loss-of-function plasmids (mostly for mi-RNAs, but also for mRNAs) will be electroporated in utero at the relevant embryonic stage. The phenotype and localization of the electroporated neurons will be analyzed using fluorescence microscopy.

The candidate must have a strong background in bioinformatics. Solid skills in molecular biology and cytology would be a plus. The candidate must be rigorous, have good communication skills, and be able to work in a team environment.

Laboratory and team

IBDM-CNRS - UMR7288

Case 907 campus de Luminy, 13288 Marseille cedex 09

http://www.ibdm.univ-mrs.fr

Team: Contrôle moléculaire de la neurogenèse (leader: Harold CREMER)

PhD supervisor

BECLIN Christophe (IR HC)

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Previously supervised PhD students

- Surbhi Surbhi
- Phillip Follert (2009-2012)

Publications of supervised PhD students

miR-200 family controls late steps of postnatal forebrain neurogenesis via Zeb2 inhibition. **Beclin** C, **Follert P**, Stappers E, Barral S, Coré N, de Chevigny A, Magnone V, Lebrigand K, Bissels U, Huylebroeck D, Bosio A, Barbry P, Seuntjens E, Cremer H. Sci Rep. 2016 Oct 21;6:35729.

MicroRNAs in brain development and function: a matter of flexibility and stability. **Follert P**, Cremer H, **Beclin C**. Front Mol Neurosci. 2014 Feb 7;7:5.

miR-7a regulation of Pax6 controls spatial origin of forebrain dopaminergic neurons. de Chevigny A, Coré N, **Follert P**, Gaudin M, Barbry P, **Beclin C**, Cremer H. Nat Neurosci. 2012 Jun 24;15(8):1120-6.

Dynamic expression of the pro-dopaminergic transcription factors Pax6 and Dlx2 during postnatal olfactory bulb neurogenesis. de Chevigny A, Core N, **Follert P**, Wild S, Bosio A, Yoshikawa K, Cremer H, **Beclin** C. Front Cell Neurosci. 2012 Feb 27;6:6.

3. **BERNARD-MARISSAL Nathalie (MMG), MARISSAL Thomas (INMED):** Oligodendrocytes: a key metabolic support for energy-voracious parvalbumin neurons?

State of the art: Key orchestrators of the hippocampal network activity and related behaviors, Parvalbumin-expressing interneurons (PV-INs) innervate a large number of target neurons and discharge at high frequency and action potentials propagate along their myelinated axon with high speed and reliability. To maintain their unique properties, PV-INs are energy-intensive, particularly during metabolically costly oscillations. We believe that oligodendrocytes (OLs) could maintain PV-IN properties and more broadly hippocampal function, not only through myelination, but also by providing a critical relay energy source in the form of lactate via the transporters MCT1/MCT2 under pathological conditions or at high energy expenditure. MCT1 enables the transfer of lactate both into OLs and into the extracellular space, from where lactate is then imported by MCT2 into the neuron. Importantly, deletion of one of these transporters affects hippocampal-related learning and memory processes. However, it was not investigated whether these observations specifically implicate PV-IN dysfunction.

Objectives: The main project objective will be to determine whether the coupling between OL and PV-IN through the lactate transporters MCT1 and MCT2 is key to PV-IN properties and hippocampal functions. Specific aims will be to test whether MCT1 and MCT2 impact: (1) PV-IN discharge and hippocampal network activity, (2) PV-IN myelination, as well as PV-IN and OL integrity? (3) hippocampal-dependent learning and memory function.

Methods: We will use a combination of cellular biology, immunohistochemistry, confocal and two-photon microscopy and behavioral testing in conditions where MCT1 or MCT2 are genetically or pharmacologically manipulated, using wild-type mice or models related to neuro-psychiatric diseases associated with PV-IN dysfunction.

Expected results: We believe this project will not only bring new insights about the mechanisms supporting the energetically costly role of PV-IN especially during the metabolically voracious processes of learning and memory, but also provide insightful information regarding their vulnerability to many genetic or environmental stressors in the context of neuropsychiatric pathologies.

Feasibility: All the necessary equipment and tools (e.g., biosafety level 2 room, behavioral and imaging facility, surgical room, drugs, vectors) are available, and techniques are routinely used in either of the two labs.

Complementary between the 2 labs: This project will be supervised by 2 complementary PI (N. Bernard-Marissal, NBM, and T. Marissal, TM) in 2 labs in Marseille (MMG and INMED). NBM is expert in neuronal metabolism, neuronal-glial interaction as well as molecular biology and AAV vector design and will bring the genetic tools necessary for each project parts and supervise experiments related to aims 1 and 2. TM is expert in interneuron physiopathology, Ca2+ imaging and mouse behavior, he will supervise the experiments related to the aims 1 and 3.

Expected candidate profile: We are looking for a motivated, persevering, curious, team worker candidate. He/she must have basic knowledge in neuroscience and/or cell biology. Habilitation to work with mice as well as experience in cell culture and 2-photon imaging would be a plus.

Laboratory and team

Marseille Medical Genetics (U 1251)

Translational neuromyology team (leader: BARTOLI Marc)

Aix Marseille Université

Faculté de Médecine de la Timone

27 bd Jean Moulin- 13385 Marseille cedex 05

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PhD supervisor

BERNARD-MARISSAL Nathalie (CRCN, Inserm researcher)

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Previously supervised PhD students

- El-Bazzal Lara (direction: V.Delague)
- Rochat Cylia (direction: B. Schneider)
- Zheng Lu (direction: B.Schneider)

Publications of supervised PhD students

Lara El-Bazzal, Adeline Ghata, Clothilde Estève, Patrice Quintana, Nathalie Roeckel-Trévisiol, Nicolas Lenfant, Andre Mégarbané, Nicolas Lévy, Marc Bartoli, Yannick Poitelon, Pierre L. Roubertoux, Valérie Delague*, **Nathalie Bernard-Marissal***, Imbalance of Neuregulin1-ErbB2/3 signaling underlies altered myelin homeostasis in models of Charcot-Marie-Tooth disease type 4H, **BRAIN**, doi: 10.1093/brain/awac402

Cylia Rochat, **Nathalie Bernard-Marissal**, Sylvain Pradervand, Florence E. Perrin, Cedric Raoul, Patrick Aebischer, Bernard Laurent

Schneider, Expression of a miRNA targeting mutated SOD1 in astrocytes induces motoneuron plasticity and improves neuromuscular function in ALS mice, **Glia**. 2022

Zheng L, **Bernard-Marissal N**, Moullan N, D'Amico D, Auwerx J, Moore DJ, Knott G, Aebischer P, Schneider BL. Parkin functionally interacts with PGC-1α to preserve mitochondria and protect dopaminergic neurons, **Hum Mol Genet.** 2017 Jan 4

PhD co-supervisor

MARISSAL Thomas (CRCN, Inserm researcher)

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https://www.inmed.fr/

Team: Neuronal coding and plasticity in epilepsy (leader: CREPEL Valérie)

Previously supervised PhD students

- **Célanie Matringhen** (co-direction with C. Faivre-Sarrailh)
- **Lucas Goirand-Lopez** (director: V. Crepel 2020-2024)
- **Alexandre Vigier** (director: V. Crepel 2020-2024)
- **JC Vermoyal** (director: JB Manent 2019-2024)

Publications of supervised PhD students

Vigier A, Partouche N, Michel FJ, Crépel V, Marissal T. Substantial outcome improvement using a refined pilocarpine mouse model of temporal lobe epilepsy. Neurobiol Dis. 2021 Dec;161:105547. doi: 10.1016/j.nbd.2021.105547. Epub 2021. Nov 6. PMID: 34752924.

Goirand-Lopez L, Moulinier M, Vigier A, Boileau C, Carleton A, Muldoon SF, Crépel V, Marissal T. Kainate receptors modulate the microstructure of synchrony during dentate gyrus epileptiform activity. Neurobiol Dis. 2023 Sep;185:106260. doi: 10.1016/j.nbd.2023.106260. Epub 2023 Aug 11. PMID: 37573957.

Vermoyal JC, Hardy D, Goirand-Lopez L, Vinck A, Silvagnoli L, Fortoul A, Francis F, Cappello S, Bureau I, Represa A, Cardoso C, Watrin F, Marissal T, Manent JB. Grey matter heterotopia subtypes show specific morpho-electric signatures and network dynamics. Brain. 2023 Sep 19:awad318. doi: 10.1093/brain/awad318. Epub ahead of print. PMID: 37724593.

4. **BROCHIER Thomas & MEIRHAEGHE Nicolas (INT):** Neural decoding of motor cortex dynamics during learning of skilled arm movements

State of the art

A fundamental problem in modern neuroscience is to understand how the brain generates the rich repertoire of movements that humans and other animals exhibit. Decades of experimental work have highlighted the role of the motor cortex in issuing the high-level motor commands that are send down the spinal cord to activate muscles. Yet, the underlying "neural code", that is, the operation by which dynamic patterns of neural activity are transformed into the associated kinematic parameters is still not fully characterized. In particular, it remains unknown whether a "universal decoder" can be used to translate ongoing neural activity into features of movement across a wide range of behavioral contexts.

Objectives

This PhD project aims at exploring the relationship between motor cortical activity and upper-limb movements. One main objective is to investigate the role of neural activity *preceding* movement, also called preparatory activity, in determining the properties of the upcoming movement. We hypothesize that the contribution of preparatory activity to movement execution evolves with practice, as the motor cortex goes from being externally-driven to an autonomous movement generator.

Methods

To test this hypothesis, the successful candidate will have access to a rich behavioral and neural dataset collected in two macaque monkeys performing complex hand reaching movements. Movements were recorded in the context of an "unconstrained" motor learning task, thus providing a unique opportunity to characterize the properties of motor cortical activity over extensive practice periods and across a wide range of movements. The student will develop and test algorithms that will attempt to predict with high precision the instantaneous hand movement trajectories of the animals based on their ongoing neural activity. These algorithms will be guided by theoretical considerations, including the hypothesized role of preparatory activity in determining movement characteristics.

Expected results

The project will offer exciting prospects for the candidate to explore both basic and applied aspects of neuroscience research. From a *fundamental science* perspective, the project will provide important insights into the computational principles supporting the generation of complex movements. From an *applied sciences* perspective, the goals of the project are aligned with the growing interests in the neuro-engineering community to define robust decoding algorithms that could ultimately be used to drive neuro-prosthetics in paralyzed patients.

Feasibility

The dataset used in the project has already been collected (two monkeys) which minimizes the experimental risks/delays and will help expedite the publication process. Moreover, the student will be guided in their work by an expert in monkey electrophysiology and motor control (Thomas Brochier) and assisted by a senior postdoctoral fellow (Nicolas Meirhaeghe) in all aspects of the quantitative analyses.

Expected candidate profile

The ideal candidate should have an inclination for brain sciences and sufficient background in mathematics (linear algebra) and computer science to handle complex data (fluent in Python/Matlab). Interests or prior experience in dynamical systems, machine learning, and brain-computer interfaces would be a plus.

Laboratory and team

Institut de Neurosciences de la Timone (INT), UMR7289, CNRS Aix Marseille Univ

27 Bd Jean Moulin, 13005 Marseille

https://www.int.univ-amu.fr/

Cognitive Motor Control (CoMCo), team leaders: Bjorg Kilavik & Thomas Brochier

PhD supervisor

Thomas BROCHIER (CNRS DR2)

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Previously supervised PhD students

- Manuel Zaepffel 2010-2014
- Romain Trachel 2010-2014 (Cosupervised)
- Margaux Duret 2013-2018
- Lucio Condro 2019-2023

Publications of supervised PhD students

- Brochier T, Zehl L, Hao Y, Duret M, Sprenger J, Denker M, Grün S, Riehle A. Massively parallel recordings in macaque motor cortex during an instructed delayed reach-to-grasp task. Sci Data. 5:180055. 2018

- Trachel RE, Brochier TG, Clerc M. Brain-computer interaction for online enhancement of visuospatial attention performance. J Neural Eng. 15(4):046017. 2018
- Trachel R, Clerc M, Brochier T. Decoding covert shifts of attention induced by ambiguous visuospatial cues. Front Hum Neurosci., 9:358.2015
- Zaepffel M, Trachel R, Kilavik BE, Brochier T. Modulations of EEG Beta Power during Planning and Execution of Grasping Movements. PLoS One. 8:e60060, 2013.
- Zaepffel M, Brochier T. Planning of visually-guided reach-to-grasp movements: inference from reaction time and contingent negative variation (CNV). Psychophysiology, 49:17-30, 2012.

PhD co-supervisor

Nicolas MEIRHAEGHE (Postdoc)

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5. GESTREAU Christian & MENUET Clément (INMED): Cracking the neuronal code that generates the breathing rhythm

State of the art. Breathing is a vital physiological function, which has to be both robust, to maintain life, and plastic, to fit metabolic and behavioral demands. The command to breath is generated in the brainstem, by a complex network of neurons. At the core of this network lies a small group of neurons, called the preBötzinger Complex (preBötC), which generates the breathing rhythm. Despite the fundamental, vital property of the breathing rhythm, how preBötC neurons generate it remains unknown.

Current theories, based on work *in vitro*, state that a subgroup of excitatory preBötC neurons generates subthreshold oscillations, which can lead to an excitation build-up among all preBötC neurons. The emergence of actual inspiratory bursts would depend on the level of network excitability and inputs from other brainstem respiratory neurons. However, to test these theories, one must be able to record concomitantly the electrical activity of multiple preBötC neurons, in an integrated preparation that preserves a fully functioning brainstem, while manipulating the level of network excitability or the activity of other respiratory neurons. This is now achievable thanks to recent developments in all-optical recordings and manipulations of neuronal activity.

This project aims at cracking the code of the preBötC, discovering how it generates the breathing rhythm, an unresolved mystery since the discovery of the preBötC 30 years ago.

Objectives.
1. SPECIFICITY. We will identify and characterize the subthreshold oscillations in subgroups of preBötC neurons that generate the breathing rhythm.
2. ROBUSTNESS. We will test if these subthreshold oscillations persist, as rhythm keepers, in conditions of low network excitability leading to apnea.
3. PLASTICITY. We will determine if the subthreshold oscillations are regulated by inputs from other respiratory neurons that modulate the breathing rhythm.

Methods. The activity of preBötC neurons will be measured by 2-photon voltage imaging, on rat Working Heart-Brainstem Preparations that generate a physiological breathing command. Combinations of transgenic rats and viruses will be used to express genetically encoded voltage indicators in subgroups of preBötC neurons. The preBötC network excitability will be modulated pharmacologically, and inputs from other respiratory neurons will be modulated by optogenetics.

Expected results. We expect that a subgroup of glutamatergic preBötC neurons would display subthreshold membrane voltage oscillations at high frequency and in phase with each other *via* synaptic coupling. These oscillations would persist as the only activity in the preBötC in conditions of low network excitability. External

inputs would determine which up-states of these oscillations lead to inspiratory bursts to modulate the breathing rhythm.

Feasibility. This project has received approval from our institutional ethics committee. All equipment and reagents necessary are present and functional in the host laboratory, including the 2-photon voltage imaging set-up (Karthala AODscope). Preliminary proof-of-concept experiments have been performed.

Expected candidate profile. We are looking for a highly motivated candidate, with strong interest in neuronal networks and technological development, and if possible a previous experience in rodent surgery, electrophysiology, and/or signal processing.

Laboratory and team

Institut de Neurobiologie de la Méditerranée (Inmed), UMR1249 INSERM Aix-Marseille University

Parc scientifique de Luminy, 163 avenue de Luminy, BP13 – 13273 Marseille cedex 09, France

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Team: Perinatal imprintings and neurodevelopmental disorders

Team leader: Françoise Muscatelli

PhD supervisor

Christian GESTREAU (Professor, Aix-Marseille University)

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Previously supervised PhD students

- Ambre Linossier (currently)
- Stéphanie Le Guen, 01/09/1998-08/11/2000
- Fabrice Roda, 01/09/2000-17/12/2002
- Stéphane Besnard, 15/09/2006-05/07/2008
- Clément Menuet, 01/09/2009-28/09/2011
- Hanan Khemiri, 01/09/2010-13/10/2013
- Kofi-Kermit Horton, 15/12/2014-26/06/2018
- Victor Bergé-Laval, 01/02/2018-15/07/2022

Publications of supervised PhD students

Le Guen S: 10.1002/cne.1140 ; 10.1002/1096-9861(20001113)427:2<285::aid-cne9>3.0.co;2-t ; 10.1046/j.1460-9568.2003.02678.x

Roda F: 10.1002/cne.10974 ; 10.1152/jn.00347.2001

Besnard S: 10.1007/s11325-007-0107-0 ; 10.1007/s11325-010-0466-9 ; 10.1016/j.resp.2008.12.004

Menuet C: 10.1152/ajpregu.00474.2015 ; 10.1371/journal.pone.0025770 ; 10.1016/j.nbd.2012.01.012 ; 10.1016/j.resp.2011.06.030 ; 10.1016/j.celrep.2012.09.013 ; 10.1523/JNEUROSCI.5261-09.2010

Khemiri H: 10.1152/ajpregu.00474.2015 ; 10.1016/j.resp.2012.05.027 ; 10.1007/s11325-010-0466-9 ; 10.1016/j.resp.2016.06.002

Horton KK: 10.3389/fphys.2018.00785

Bergé-Laval V: 10.3390/s21165594 ; 10.3390/ijms21145120 ; 10.1109/EMBC48229.2022.9871144

PhD co-supervisor

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Previously supervised PhD students

- Julie Buron, 01/10/2019-30/09/2023
- Ambre Linossier (currently)

Publications of supervised PhD students

Buron J, Linossier A, Gestreau C, Schaller F, Tyzio R, Felix MS, Matarazzo V, Thoby-Brisson M, Muscatelli F, Menuet C. *The oxytocin-modulated brain circuit that synchronizes heart rate with breathing*. **BioRxiv** 2023 Sep 27:2023.09.26.559512, **under revision in Nature Neuroscience** ;

- Dridi H, Liu X, Yuan Q, Reiken S, Mohamad Y, Apostolou P, Buron J, Sicard P, Matecki S, Thireau J, Menuet C, Lacampagne A, Marks AR. *Role of defective calcium regulation in cardiorespiratory dysfunction in Huntington's disease*. **Journal of Clinical Investigation Insight** 2020 Oct 2;5(19):e140614.

6. **JIRSA Viktor & DEPANNEMAECKER Damien (INS):** Multiscale Models to Link Cellular Mechanisms of Dopamine Neuromodulation to whole-brain Dynamics

Neuromodulation is characterized by changes in the biophysical properties of single neurons that orchestrate shifts in whole-brain activity and function [1] not solely at individual neurons' level but through the complex dynamics of mesoscopic neural ensembles. The comprehension of this multiscale mapping stands as a pivotal endeavor, especially concerning diseases such as Parkinson's and psychiatric disorders, where it holds significant implications.

Quantitative models that bridge microscale neuronal neuromodulation with systems-level brain function underscore gaps in knowledge and offer avenues for integrating theoretical and experimental work. Efforts to develop models accounting for population-level activity modulated by single-neuron properties rely on key methods such as mean-field reduction. This approach describes the state of a large population using the first moments of the population variable’s distributions.

At the *Institut de Neurosciences de Systemes* (INS), this methodology has been applied [2] to theoretically elucidate the effects of the extracellular potassium concentration at the population activity emerging from ionic mechanisms that operate at the single-cell level [3]. It offers a mathematical framework for analyzing large-scale neuronal activity, focusing on aggregate properties rather than individual neuron dynamics.

Similarly, our PhD project aims to develop a theoretical framework integrating large-scale modeling with biophysical detail, focusing on distilling predictive data from biophysically detailed models to capture essential features relevant to neuromodulation effects. The initial phase involves constructing a data-driven biophysical model at the cellular level, incorporating dynamics related to neuromodulation, particularly variations in local dopamine concentration. Subsequently, this single-cell model will inform large neural network simulations, followed by mean-field reduction to a neural mass model. This dimensionally reduced neural mass model will serve as a foundation for building whole-brain models that can be validated with clinical data (see figure 1).

At the end of this project, we expect to have developed and characterized the dynamics of multiscale models accounting for the neuromodulation of localized dopamine at the cellular, population, and whole-brain levels. By deepening our understanding of neuromodulatory dynamics, these models play an essential role in understanding neurological conditions. These models hold the potential to be used for personalized brain model as it has been previously developed at the INS for epilepsy [4], [5] and advance nosology refinement, facilitating early detection and accurate personalized treatments of neurological disorders such as Parkinson's disease.

Under Viktor Jirsa's supervision and Damien Depannemaecker's co-supervision at INS, the project benefits from extensive experience in multiscale modeling, experimental data collection, and collaborative efforts, ensuring its feasibility.

The ideal candidate would possess an interdisciplinary background in physics with programming experience and a keen interest in neuroscience or a neuroscience background with strong programming and mathematical analysis skills. Prior experience with cellular biophysical mechanisms, single-cell modeling, spiking neural networks, dynamical systems, and derivation of mean-field models would be advantageous.

Keywords: dopamine neuromodulation, multiscale modeling, computational neuroscience, computational psychiatric, whole-brain models. personalized medicine

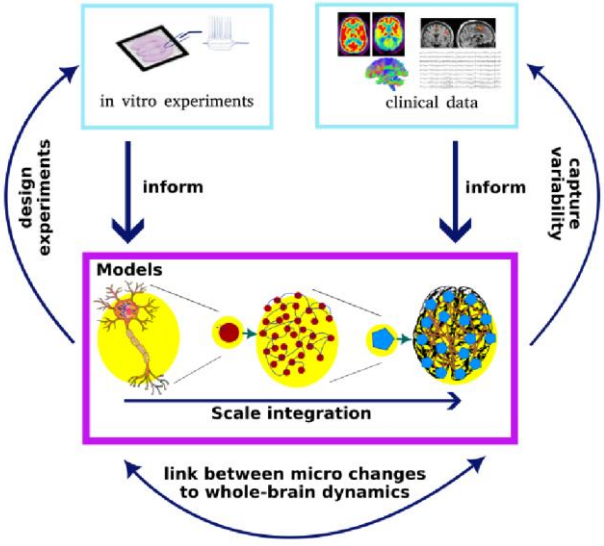

Figure 1:

Project workflow overview. Data-driven model building and scale integration: the models are constrained by the data at the cellular level and whole-brain level. The models integrate over scale thanks to methods such as mean-field derivation, once built it enables the study of the effect at the whole-brain level of changes at the local microscopic level. Thus, this modeling framework brings an understanding of how local actions through stimulation or pharmacological intervention lead to dynamical changes noticeable at the whole-brain level. The strength of this approach is the ability to keep the biophysical interpretation of biophysical parameters over the scales.

[1] Hansen, J.Y., Shafiei, G., Markello, R.D. et al. Mapping neurotransmitter systems to the structural and functional organization of the human neocortex. Nat Neurosci 25, 1569–1581 (2022). https://doi.org/10.1038/s41593-022-01186-3

[2] Damien Depannemaecker, Anton Ivanov, et al.. A unified physiological framework of transitions between seizures, sustained ictal activity and depolarization block at the single neuron level. Journal of Computational Neuroscience, 50(1):33–49, January 2022. ISSN 1573-6873. doi 10.1007/s10827-022-00811-1.

[3] Abhirup Bandyopadhyay, Giovanni Rabuffo, et al. Mean-field approximation of network of biophysical neurons driven by conductance-based ion exchange. Nov. 2021. doi: 10.1101/2021.10.29.466427.

[4] Huifang E. Wang, Marmaduke Woodman, et al. Delineating epileptogenic networks using brain imaging data and personalized modeling in drug-resistant epilepsy. Science Translational Medicine, 15, 1 2023. ISSN 1946-6234. doi: 10.1126/scitranslmed.abp8982.

[5] Viktor Jirsa, Huifang Wang, et al. Personalised virtual brain models in epilepsy. The Lancet Neurology, 3 2023. ISSN 14744422. doi:10.1016/S1474-4422(23)00008-X.

Laboratory and team

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Publications of supervised PhD students

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7. **MANENT Jean-Bernard (INMED):** Multimodal profiling of epilepsy onset and progression in preclinical models of cortical malformations

State of the art

Brain malformations are a major cause of drug-resistant epilepsy in children and adolescents. Studying the pathophysiological mechanisms that lead to these epilepsies is challenging because malformations are typically diagnosed only after the first seizure. In addition, it is impossible to directly study the pathological changes that occur in the brains of patients and contribute to the onset and progression of epilepsy. Preclinical models are therefore essential for a better understanding of the disease, its onset and progression, and ultimately for improved therapy.

This project will combine electrophysiology to study brain activity and transcriptomics to measure gene expression changes in preclinical models of brain malformations. By correlating epilepsy-associated electrophysiological properties of anatomically identified brain regions with their underlying, spatially resolved, molecular changes, the project aims to 1) gain new insights into the onset and progression of epilepsy and 2) precisely delineate key pathophysiological mechanisms underlying circuit alterations in cortical malformations.

Methods

in vivo and in vitro electrophysiology; transcriptomics; in vivo genetic manipulations to induce MCDs (in utero electroporation); in vivo stereotactic injection of viral vectors to express candidate genes; histology

Expected results

Identification of circuit and molecular changes detectable at different stages of disease progression that may serve as biomarkers or predictors of epilepsy outcome and as potential targets for therapy (some will be tested).

Feasibility

3 murine models with cortical malformations; equipped in vivo setups for head-fixed and freely moving recordings; in-house in vivo imaging facility; project authorization for animal research; ongoing local and international collaborations, including with human epileptologists and geneticists

Expected candidate profile

Prior experience with rodent handling and surgeries; in vivo recordings including electrode preparation and stereotactic implantation; histology and microscopy; data analysis; prior experience with bioinformatics and transcriptomics is a plus

Bibliography

Petit, Jalabert et al Ann Neurol 2014; Sahu et al Epilepsia 2019; Plantier et al Cereb Cortex 2019; Hardy, Buhler, Suchkov et al Neurobiol Dis 2023; Vermoyal, Hardy et al Brain 2023 ; Roig-Puiggros et al bioRxiv 2024

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- F Martineau (PhD defense 2017)
- L Petit (PhD defense 2014)

Publications of supervised PhD students

- Vermoyal JC, Hardy D, Goirand-Lopez L, Vinck A, Silvagnoli L, Fortoul A, Francis F, Cappello S, Bureau I, Represa A, Cardoso C, Watrin F, Marissal T, Manent JB. Grey matter heterotopia subtypes show specific morpho-electric signatures and network dynamics. Brain. 2023 Sep 19.
- Sahu S, Buhler E, Vermoyal JC, Watrin F, Represa A, Manent JB. Spontaneous epileptiform activity in a rat model of bilateral subcortical band heterotopia. Epilepsia. 2019 Feb;60(2):337-348.

- Plantier V, Watrin F, Buhler E, Martineau FS, Sahu S, Manent JB, Bureau I, Represa A. Direct and Collateral Alterations of Functional Cortical Circuits in a Rat Model of Subcortical Band Heterotopia. Cereb Cortex. 2018 Dec 7.
- Martineau FS, Sahu S, Plantier V, Buhler E, Schaller F, Fournier L, Chazal G, Kawasaki H, Represa A, Watrin F, Manent JB. Correct Laminar Positioning in the Neocortex Influences Proper Dendritic and Synaptic Development. Cereb Cortex. 2018 Aug 1;28(8):2976-2990
- Martineau FS, Fournier L, Buhler E, Watrin F, Sargolini F, Manent JB, Poucet BRepresa A. Spared cognitive and behavioral functions prior to epilepsy onset in a rat model of subcortical band heteropia. Brain Res. 2019 Jan 25. pii:S0006-8993(19)30052-6.
- Petit LF, Jalabert M, Buhler E, Malvache A, Peret A, Chauvin Y, Watrin F, Represa A, Manent JB. Normotopic cortex is the major contributor to epilepsy in experimental double cortex. Ann Neurol. 2014 Sep;76(3):428-42.

8. **MASSON Guillaume & CAZETTES Fanny (INT):** Identifying the distributed neural circuit for strategy selection

- **State of the art**

The brain has the remarkable ability to imagine different solutions to a problem and to rapidly switch between them to adapt to new situations. Such properties are essential for flexible behaviors but remain poorly understood. In mice, a premotor region called the secondary motor cortex (M2) can hold information about multiple decision strategies simultaneously. This "reservoir" of decision strategy could, in theory, provide a simple but powerful mechanism for flexibility, where new strategies are selected on the fly from the reservoir without the need to learn new computations. Nonetheless, whether the brain uses this solution is still controversial because experimental evidence of neural circuits performing such computations is sparse. Identifying the circuit underlying strategy selection is thus a timely challenge that will advance our understanding of distributed temporal information processing in the brain.

- **Objectives**

We will determine how a wide net of cortical and subcortical regions involved in sensory-motor transformation interact to support decision selection.

- **Methods**

Experiments: We will address our questions using mice in the context of foraging, a fundamental survival behavior shared among all animals, involving the search for resources in dynamic environments. Specifically, we will leverage a foraging task in virtual reality for head-fixed mice developed in the lab and use videography to monitor facial and body movements. During the behavior, we will record simultaneously large neuronal ensembles (hundreds of neurons) simultaneously in multiple brain region using next-generation Neuropixels probes. We will target M2 and connected areas known for their roles in rule and action selection. This includes sensory (somatosensory cortex and thalamus), frontal (orbitofrontal and anterior cingulate cortices) and motor (primary motor, dorsal striatum) areas. Analysis & models: We will dissect the computational properties of each region using multivariate regression and determine when information about task and decision variables first emerges. In collaboration with theoreticians, we will develop data-driven multi-regions recurrent neural network models that recapitulate activity propagation and make predictions about interactions between brain regions during strategy selection.

- **Expected results**

Results from this work will reveal how information is transformed across brain regions during the foraging decision. One specific prediction is that, while M2 encodes distributed information about multiple decision strategies, downstream motor regions (e.g. the striatum, M1), primarily represents the decision reflected

behaviorally, which can be linearly decoded from M2 activity. Such a mechanism would concur with the hypothesis that M2 acts as a high-dimensional reservoir of decision strategy that are flexibly routed downstream. Our data-driven modelling approach will allow an unprecedented characterization of inter-areal communications, perhaps identifying changes in cortical dynamics as a general principle of flexibility.

- **Feasibility**

The project is ambitious but highly feasible. The equipment (behavioral and recording set-ups) are in place and running at INT, with animals performing the task. A semi-automated pipeline for processing behavior and electrophysiology data is currently being developed. The training time required for each animal is relatively short (3 to 6 weeks). Therefore, we envision that the first 1.5 year will be dedicated to data collection and processing, and the second 1.5 year will be dedicated to analysis, modeling and paper writing. The project will be co-supervised by two researchers working in the same team at the Timone Neuroscience Institute: Fanny Cazettes (CRCN) and Guillaume Masson (DR1, HdR). The project is based on Fanny Cazettes' scientific CNRS project and objectives, which has obtained a start-up funding from the Simons Foundation (NYC) in 2022.

- **Expected candidate profile**

The candidate is expected to have: (1) a solid scientific background in mathematics, physics or engineering, (2) coding proficiency (Python preferably), (3) a strong interest for systems neuroscience and (4) be willing to work with animal models.

Laboratory and team

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Currently supervised PhD students

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- Sina KLING (1st year, M Szinte)
- Uriel LASCOMBES (1st year, M Szinte)
- Alexis MONNET-AYMARD (4th year, G Ibos)

Previously supervised PhD students

10 students since 2002 including:

- Vanessa CARNEIRO (2023)
- Emmanuel BONNET (2023)
- Kiana MANSOUR-POUR (2019)
- Kartheek MEDATHATI (2016)

Publications of supervised PhD students

Over the last 2 years:

Carneiro Morita V, Souto D, **Masson GS** & Montagnini A (2024) *Journal of Vision* (in revision)

Bonnet E, **Masson GS** & Desantis A (2022) *Consciousness and Cognition* 104:103378

Barthelemy FV, Fleuriet J, Perrinet LU & **Masson GS** (2022) *eNeuro* ENEURO.0374-21.2022

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9. **MOYON Sarah (INP):** Role of oligodendroglial cells in Alzheimer's Disease pathology

State of art

Alzheimer's Disease (AD), by its exceptional prominence in people aged 75 and above, represents a major public health issue worldwide (Hebert et al., 2013). Unfortunately, compared to other neurodegenerative diseases, the failure rate in clinical trials of AD drugs in one of the highest (Cummings et al., 2014). One explanation could be that we still do not completely understand disease onset and progression. Past studies have mainly been focused on the repercussions of amyloid plaque and neurofibrillary tangles accumulation around and within neuronal cells only. Recently, new evidence, on human post-mortem tissues and AD murine models, have highlighted **the importance to extend our research to glial cells, such as oligodendroglial cells.**

Objectives

If many data support an oligodendroglial contribution in AD pathology, how oligodendroglial cell lineage could have a causal role in AD onset and progression is still largely unknown. We will test **whether age-related dysregulation of oligodendroglial functions could result in** defective neuro-oligodendroglial communication, thereby impacting neuronal function, inducing **early neurodegeneration and disease onset in AD models.**

Methods

1/ Test whether oligodendroglial aging directly induces early cognitive deficits in an AD mouse model. By taking advantage of the *Tet1cKO* mouseline (Moyon et al., 2021), presenting an aging-like phenotype restricted to the oligodendroglial cell lineage, we will functionally characterize the oligodendroglial contribution to cognitive deficits onset in an AD mouse model (5xFAD) (Oakley et al., 2006).

2/ Which pathways are dysregulated in aging-like oligodendroglial cells in an AD mouse model? Using spatial transcriptomic analysis, we will identify neuronal-oligodendroglial communication pathways dysregulated in aging-like oligodendroglial cells in an AD model.

3/ Test whether ablation of specific neuro-oligodendroglial pathways in oligodendroglial cells can impact neuronal function and/or survival, hence accelerate AD onset in a mouse model. We will validate their functional roles during neuronal activity *in vitro* and during learning and memory abilities *in vivo*.

Expected results

This project will better characterize the molecular and phenotypic mechanisms underlying oligodendroglial dysfunction in AD. It should determine how oligodendroglial aging could directly affect their support to neurons, inducing neurodegeneration and accelerating disease onset.

Feasibility

We have the scientific expertise on oligodendroglial lineage, aging biology, and AD pathology. Collaborators at the INP also complement our tools and knowledge on AD. Sequencing expertise is available at the MMG (Dr. V. DELAGUE). The mouse models are breeding in our animal facility. Behavioral tests are being set up and optimized. Co-culture models are set-up in the lab.

Expected candidate profile

The ideal candidate should have a master (or equivalent) in cell biology or neurosciences, an interest in glial cells, aging, and in neurodegenerative diseases.

Required skills: Mouse handling, team player, motivation, organization skills, communication skills.

Appreciated skills: cell culture, histology, microscopy and/or live-imaging, animal behavior, electrophysiology, bioinformatics.

Laboratory and team

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- Andrew T. MCKENZIE (with Pr. Bin ZHANG), 2014-2017

Publications of supervised PhD students

- Moyon S*,#, Ma D*, **Huynh JL**, Coutts D, Zhao C, Casaccia P, Franklin R#. Efficient remyelination in adult murine spinal cord requires DNA methylation. *eNeuro*. 2017;4(2).
  Moyon S*, **Huynh JL***, Yoo S, Dutta D, Zhang F, Ma D, Yoo S, Lawrence R, Wegner M, John G, Emery B, Lubetzki C, Franklin R, Fan G, Zhu J, Dupree J and Casaccia P. Functional characterization of DNA methylation in the oligodendrocyte lineage. *Cell Reports.* 2016;15(4):748-60.
- **McKenzie AT***, Moyon S*, Wang M, Katsyv I, Song WM, Zhou X, Dammer EB, Duong DM, Aaker J, Zhao Y, Zhu J, Lah JJ, Seyfried NT, Levey AI, Katsel P, Haroutunian V, Schadt EE, Popko B, Casaccia P, Zhang B. Multiscale network modeling oligodendrocytes reveals molecular components of myelin dysregulation in Alzheimer's Disease. *Mol. Neurodegener.* 2017;12(1):82.

**Authors contributed equally to the work. #Corresponding authors.*

10. **NIVET Emmanuel (INP):** Human iPSC-based modeling platforms to study the consequences of astrocytic reactivity in Alzheimer's disease: from molecular investigations to candidate validation

State of art: Synapse loss and reactive gliosis are amongst the best correlates of early memory deficits in Alzheimer's disease (AD) patients. Abeta and Tau pathology affects neurons, but also induce cell non-autonomous responses in astrocytes that are increasingly recognized as drivers of the disease. Several studies revealed that modulation of astrocyte reactivity can alleviate AD symptoms in mouse models and also prevent from astrocytic changes related to neuronal support, suggesting a critical role for both astrocytes and inflammation in AD initiation/progression. Therefore, research on AD should move beyond the neuronal focus and include astrocyte-based disease mechanisms at the earliest stages of the disease. This prompts the need to study whether and how some specific molecular changes related to astrocyte reactivity could lead to alterations impacting the neuron-astrocyte crosstalk and ultimately leading to AD pathology. This could pave the way for therapeutic applications targeting the astrocytes.

Objectives: The overall objective is to demonstrate that astrocytes are at the core of molecular underpinnings in AD, specifically through pathogenic feedback loops in which astrocytic reactivity may be involved in early neuronal deficits in AD. The first task will be to determine the cellular and functional consequences of modulations targeting a selection of astrocytic proteins involved in astrogliosis and possibly at play in AD. In a second task, we will determine the consequences of those astrocytic manipulations on AD pathological marks in human neurons.

Methods: The project will involve the use of human iPSC-derived astrocyte cultures, neuron-astrocytes co-cultures (*e.g.* microfluidic-based), as well as cerebral organoids enriched for astrocytes. From those models, we will use genetic manipulations in astrocytes specifically (*e.g.* using CRISPR-Cas9 based strategies) and perform a battery of evaluations on both astrocytes and neurons including for instance transcriptomic (*e.g.* RNAseq) and proteomic analyses, immunostainings combined with imaging (*e.g.* synaptic markers), as well as functional assays (*e.g.* ca^{2+} imaging, MEAs, axonal transport using live-cell imaging).

Expected results: We expect to identify at least one candidate protein that is involved in astrocyte reactivity and from which its experimental modulation in human astrocytes is able to reduce or delay AD-related pathological marks in human neurons.

Feasibility: Our team has strong expertise with hiPSC-based disease modeling and the proposed models are already implemented. We also have experience with CRISPR-Cas9 based genetic manipulation in hiPSCs. We will also take advantage of our previous work that led to the identification of TAGLN3 as a new candidate of interest that will be included in this project, along with other candidate proteins. Moreover, we have the necessary expertise and equipment to perform the different analyses included in the project either in our lab or through a network of collaborators. Last, the running costs for this project are already secured.

Expected candidate profile: The candidate is expected to have a solid background in the field of Neuroscience and a strong interest for neurodegenerative diseases. First-hand experience with cell culture (hiPSC) and genetic modifications (CRISPR) would be a strong plus. Among the many soft skills we are expecting from the candidate, the most important will be Teamwork, Analytical and critical thinking, Autonomy, Flexibility and adaptability, Communicative, Co-operation.

Laboratory and team

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Publications of supervised PhD students

Arnaud L, Benech P, Greetham L, Stephan D, Jimenez A, Jullien N, García-González L, Tsvetkov P.O, Devred F, Sancho-Martinez I, Izpisua Belmonte JC, Baranger K, Rivera S, Nivet E. APOE4 drives inflammation in human astrocytes via TAGLN3 repression and NF-κB activation. ***Cell Reports.*** 2022 Aug 16;40(7):111200. doi: 10.1016/j.celrep.2022.111200.

Arnst N, Belio-Mairal P, García-González L, Arnaud L, Greetham L, Nivet E, Rivera S, Dityatev A. Deficiency in MT5-MMP supports branching of human iPSCs-derived neurons and reduces expression of GLAST/S100 in iPSCs-derived astrocytes. ***Cells***. 2021 Jul 6;10(7):1705. doi: 10.3390/cells10071705.

11. **OUAGAZZAL Abdel-Mouttalib (CRPN)**: Cortico-pallidal circuits and motor functions: optogenetic, fiber photometry and behavioral studies in normal and Parkinsonian mice

The basal ganglia (BG) are a set of interconnected subcortical nuclei involved in voluntary motor control and are target of many neurodegenerative disorders, including Parkinson's disease (PD). The external segment of the globus pallidus (GPe) has long been regarded as a simple relay within the BG, connecting the striatum and the subthalamic nucleus in the indirect pathway. In the past years, a diversity of GABAergic cell type and anatomical connectivity of GPe were uncovered suggesting that it may rather act as an integrative hub for shaping motor and non-motor aspects of behavior. More recently, direct projections from the neocortex to GPe were uncovered indicating that these nuclei provides an entry for cortical information to the BG. Despite surge of interest over the past years, our understanding of the functional significance of the cellular diversity and anatomical connectivity of GPe remains largely incomplete.

The aim of this project is to specify the nature of the functional relationship between the cortex and GPe in normal conditions and pathological states associated with PD. Using optogenetic approach, we recently showed that reduced neuronal activity of the GPe is a key mechanism contributing to motor deficits of PD (Di Bisceglie Caballero et al., 2023, Int. J. Mol. Sci. 24, 7935). In the present flow up project, we will use our mouse models of PD and multidisciplinary approach combining original optogenetic tools with calcium imaging and behavioral techniques to selectively manipulate cortico-pallidal projections and GPe neurons and clarify their contribution to motor deficits. Transgenic mice (FoxP2-cre and Parvalbumin (PV)-cre) will be used to specifically target FoxP2-expressing and PV-expressing neurons, which represent two distinct populations of GPe projection neurons. Dual-color optogenetic studies with blue and red lights will be used to manipulate conjointly the activity of cortical projections and GPe output neurons and determine when and how cortical control of GPe takes place. Photometric calcium recordings will be conducted in parallel to monitor changes of postsynaptic cortico-pallidal transmission. As well as enhancing our understanding of the pathophysiological mechanisms of PD, this project will also provide new grounds that may guide development of more effective and well-tailored DBS treatments.

This project will be conducted in the team "Cognition and Pathophysiology of Basal Ganglia" headed by Drs. AM. Ouagazzal & P. Gubellini. The research team has broad-based expertise that spans neuropharmacology, biochemistry, optogenetic, behavioral genetics and patch-clamp electrophysiology. During his (her) PhD work, the student will acquire strong expertise in behavioral analysis (battery of test for cognitive, emotional and motor functions) optogenetic and fiber photometry. He/she will also acquire immunofluorescence techniques to map protein expression and brain circuitry. The student will benefit from a rich scientific

and technical environment, in the CRPN, that will let him develop his/her researcher potential and communication skills.

Skills: knowledge in optogenetic or fiber photometry, immunochemistry, Matlab or python programming.

Laboratory and team

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Publications of supervised PhD students

Di Bisceglie Caballero S, Ces A, Liberge M, Ambroggi F, Amalric M, Ouagazzal AM. (2023). Optogenetic Globus Pallidus Stimulation Improves Motor Deficits in 6-Hydroxydopamine-Lesioned Mouse Model of Parkinson's Disease. Int. J. Mol. Sci. 24, 7935.

Sikora J, Di Bisceglie Caballero S, Reiss D, Kieffer BL, Paoletti P, Jacob PY, Ouagazzal AM. (2022). Zn2+ inhibits spatial memory and hippocampal place cell representation through high-affinity binding to the NMDA receptor GluN2A subunit. iScience, 25:105355.

Sikora J, Ouagazzal AM. (2021). Synaptic Zinc: An Emerging Player in Parkinson's Disease. Int J Mol Sci. 22(9):4724.

Sikora J, Kieffer BL, Paoletti P, Ouagazzal AM. (2020). Synaptic zinc contributes to motor and cognitive deficits in 6-hydroxydopamine mouse models of Parkinson's disease. Neurobiol Dis. 134:104681. DOI: 10.1016/j.nbd.2019.104681

12. **PAPANDREOU Marie-Jeanne (INP):** Axonal zoning: interplay between presynapses and the periodic actin-spectrin scaffold

State of the art

Axons grow and maintain extended and complex arborizations thanks to a specialized organization of the axonal cytoskeleton, with numerous branches contacting downstream cells via presynaptic boutons. Within the last decade, our knowledge of this unique architecture has been transformed by the discovery of a submembrane periodic scaffold made of actin and spectrin lining the axon shaft[1], and by the delineation of distinct actin nanostructures within presynapses, where this scaffold is absent[2]. Yet the patterning of presynaptic boutons along the shaft, and how the periodic scaffold is rearranged to allow for the formation or disappearance of a bouton, remains unknown.

Objectives

We want to understand how the axon is patterned between scaffold-lined shaft segments and scaffold-free presynapses, and if the actin-spectrin scaffold itself has a role in regulating the presence of presynaptic boutons. We hypothesize that this is linked to an insulating role of the submembrane scaffold which restricts endocytosis (as we showed recently[4]) and exocytosis along the axon. We will this elucidate the dynamic relationship between the scaffold, endo/exocytosis, and presynapse formation during neuronal development in cultured hippocampal neurons.

Methods

We have built a recognized expertise of using super-resolution microscopy to dissect the nano-architecture of the axonal cytoskeleton[3]. We are now developing new approaches to visualize the 190 nm-periodic scaffold in living neurons, adding a dynamic dimension to our understanding of its organization and roles. We have also developed ways to visualize endocytosis and exocytosis along the axon, distinguishing shaft segments and presynapses, as well as correlative methods to link endo/exocytosis sites to the nanoscale architecture of the cytoskeleton. These advanced methods will be used to visualize the transformation of the actin-spectrin scaffold during presynapse formation and the emergence of the synaptic vesicle exo/endocytic cycle, in control and perturbed conditions where the scaffold is disassembled or over-stabilized.

Expected results

We expect to obtain crucial insights on the cell-autonomous mechanism of axonal compartmentation and synaptic plasticity, revealing a new physiological role for the periodic actin-spectrin scaffold in this process.

Feasibility

The team is currently composed of 11 people including strong technical support (2 technicians, 1 engineer). Key methods for this project are currently developed thanks to works of post-doctoral fellows funded by ANR and FRM, which will be able to help the PhD student start their project.

Expected candidate profile

We are looking for a motivated candidate with experience on some of the following: advanced microscopy, live-cell imaging, quantitative biology, working with cultured neurons. Don't hesitate to contact marie-jeanne.papandreou@univ-amu.fr if you have any question or want to know more.

1. Papandréou & Leterrier. Mol Cell Neurosci, 2018 Sep;91:151-159. 10.1016/j.mcn.2018.05.003

2. Bingham et al. J Cell Biol, 2023; 222(10):e202208110. 10.1083/jcb.202208110

3. Leterrier et al. Nature Rev Neurosci, 2017; 18(12):713-726. 10.1038/nrn.2017.129

4. Wernert et al. bioRxiv, 2023 Dec 19. 10.1101/2023.12.19.572337

Laboratory and team

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Team: NeuroCyto: The neuronal cytoskeleton in health and disease

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PhD supervisor

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Currently supervised PhD student(s)

Sofia Tumminia (10/2021-09/2024)

Previously supervised PhD students

Florian Wernert (10/2019-02/2024)

Dominic Bingham (10/2018-07/2022)

Publications of supervised PhD students

Wernert F, Moparthi SB, Lainé J, Moulay G, Boroni-Rueda F, Pelletier F, Jullien N, Benkhelifa-Ziyat S, Papandreou MJ, Leterrier C*, Vassilopoulos S*. (co-last author) The actin-spectrin submembrane scaffold restricts endocytosis along proximal axons.

bioRxiv, 2023 Dec 19. (in revision)

ingham D, Jakobs CE, Wernert F, Boroni-Rueda F, Jullien N, Schentarra EM, Friedl K, Da Costa Moura J, van Bommel DM, Caillol G, Ogawa Y, Papandréou MJ*, Leterrier C*. (co-corresponding authors) Presynapses contain distinct actin nanostructures.

Journal of Cell Biology, 2023; 222(10):e202208110.

Ganguly A, Sharma R, Boyer NP, Wernert F, Phan S, Boassa D, Parra L, Das U, Caillol G, Han X, Yates JR, Ellisman MH, Leterrier C, Roy S. Clathrin packets move in slow axonal transport and deliver functional payloads to synapses.

Neuron, 2021 Sep 15;109(18):2884-2901.e7.

13. **WANAVERBECQ Nicolas & TROUSLARD Jérôme (INT):** Are spinal Cerebrospinal Fluid contacting neurons novel interoceptors involved in the modulation of supraspinal autonomic centers?

- **State of art**

Around the medullo-spinal central canal of most vertebrates, cerebrospinal fluid contacting neurons (CSF-cNs) are present. They exhibit a unique morphology with a single dendrite that project through the ependymal cell layer and ends in a protrusion bathed by the CSF. Their axons extend to the ventral region and form large bilateral fiber bundles, but in mammals little is known about the neuronal network they are inserted in. Further they selectively express "Polycystic Kidney Disease 2-like 1" channels (PKD2L1; members of the TRP superfamily) with properties of multimodal sensory receptors (temperature, pressure pH, osmolarity). Finally, they are thought to sense circulating bioactive molecules (hormones, neurotransmitters, cytokines, protons...) within the CSF.

Due to their localization, morphology, and physiological properties, CSF-cNs are suggested to act as sensory neurons and we hypothesize they represent novel actors of the interoceptive system to inform the CNS about its inner state.

- **Objectives**

Our recent results support this hypothesis and indicate that CSF-cNs send ascending projection to cholinergic neurons of the Dorsal Motor Nucleus of the *Vagus* nerve (DMV) a source of the parasympathetic innervation to several organs. The objective of the *PhD* project will be to characterize anatomical and functional CSF-cN connectivity within the DMV, test whether they are in turn modulated by supraspinal descending projection and understand at the behavioral level how CSF-cN contribution is integrated with other synaptic neuromodulatory systems to regulate physiological parameters.

- **Methods**

Tracing experiments in transgenic mouse lines combined with stereotactic viral-based injections will be performed with a focus on the above-mentioned circuits. Resolving CSF-cN connectivity maps by state-of-the-art conventional (confocal) and non-conventional (3D microscopy) imaging techniques with classical histology and whole tissue clearing. Testing the functional integration of the identified connectivity patterns with *in vitro* electrophysiology combined to optogenetics and behavioral tests.

- **Expected results**

Elucidating ascending and descending CSF-cN connectivity maps and the functional consequence on neuronal activity. Based on the results, we will demonstrate for the first time in mammals that CSF-cNs represent a novel actor of autonomous

system informing the CNS about its inner state to trigger responses according to the individual needs (arousal, vigilance, attention, motivation, etc.).

- **Feasibility**

The SpiCCI team has all human resources, financial support, technical expertise and the required animal models/viral constructs to successfully conduct the proposed project. SpiCCI benefits from INT technical facilities.

- **Expected candidate profile**

- Highly motivated, implicated, and curious student with a background in cell biology and/or neuroscience. Capable of teamwork and adaptability. English speaking - Laboratory experience (histology and microscopy), proficient in basic IT. Capability in coding (Python, Matlab, Javascript) - The student will be enrolled in a caring environment and supervision and is expected to fully commit to his research and *PhD* project.

Laboratory and team

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Team: Spinal Cord & CSF Interface (SpiCCI)

Team leader: Nicolas WANAVERBECQ

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Currently supervised PhD student(s)

- L LEBLOND (2022, Inter-ED), Supervisor: M Evin (50%), Co-Supervisor: N Wanaverbecq (50%)
- E CROZAT (2021, ED62), Supervisor: N Wanaverbecq (100%)
- E BLASCO (2020, ANR MotoNeuroMod, ED62), Supervisor: N Wanaverbecq (100%)

Previously supervised PhD students

- 2019-2023: P RIONDEL (ED62), Supervisor: N Wanaverbecq (50%), Co-Supervisor: R Seddik (50%)
- 2015-2019: N JURČIĆ (Contrat du Programme Doctoral ICN ,A*Midex, ED62), Supervisor: J Trouslard (50%), Co- Supervisor: N Wanaverbecq (50%)
- 2010-2014: A ORTS DEL'IMMAGINE (Contrat de l'Ecole Doctorale ED62, AMU), Supervisor: J Trouslard (50%), Co- Supervisor: N Wanaverbecq (50%)

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Publications of past and current supervised PhD students

Bold: PhD Supervisor ***Bold italic*:** PhD Co-Supervisor

Edith BLASCO

1) Gerstmann K, *Jurčić N*, Blasco E, Kunz S, de Almeida Sassi F, **Wanaverbecq N**, Zampieri N (2022) Curr Biol. 6;32(11):2442-2453

Priscille RIONDEL

1) Riondel R, Jurčić N, Trouslard J, **Wanaverbecq N** & ***Seddik R*** (2022) bioRxiv 2022.12.14. 520067;doi:https://doi.org/10.1101/ 2022.12.14.520067 - Under revision at J. Neurosci.

Nina JURČIĆ

1) Gerstmann K, Jurčić N, Blasco E, Kunz S, de Almeida Sassi F, **Wanaverbecq N**, Zampieri N (2022) Curr Biol. 6;32(11):2442-2453

2) Jurčić N, Michelle C, **Trouslard J**, ***Wanaverbecq N***, Kastner A (2021). Eur J Neurosci. 54(3):4781-4803.

3) Jurčić N, Er-Raoui G, Airault C, **Trouslard J**, ***Wanaverbecq N***, Seddik R (2019). J. Physiol 597(2): 631-651.

Adeline ORTS-DEL'IMMAGINE

1) Orts-Del'Immagine A, **Trouslard J,** Airault C, Hugnot JP, Cordier B, Doan T, Kastner A, ***Wanaverbecq N*** (2017) Neuroscience 20(343): 39-54.

2) Orts-Del'Immagine A, Seddik R, Tell F, Airault C, Er-Raoui G, Najimi M, **Trouslard J**, ***Wanaverbecq N*** (2016) Neuropharmacology. 101: 549-65.

3) Orts-Del'Immagine A, Kastner A, Tillement V, Tardivel C, **Trouslard J**, ***Wanaverbecq N*** (2014) PLoS One 9(2): e87748.

4) Orts-Del'immagine A, ***Wanaverbecq N***, Tardivel C, Tillement V, Dallaporta M, **Trouslard J** (2012) J. Physiol. 15;590(16): 3719-41.