LIST OF PROJECTS (13)

INTERNATIONAL PHD SCHOLARSHIPS

FEBRUARY 2022

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PROJECT I1

Title : Search for factors explaining inter-individual variability in cognitive effort with advancing age

Supervisor : ALESCIO-LAUTIER Béatrice

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Co-supervisor : CHAMBON Caroline

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State of the art

Inter-individual variability exists at all ages and increases with time. While it is classically reduced to its minimum in scientific studies, we think that it can be a particularly interesting object of study and wish to focus here on the variability of "cognitive effort". Indeed, within the same age group, several individuals can provide a different "cognitive effort" in order to produce a good level of performance. Studying this variability across aging, in parallel with other variables (cognitive, physiological) could eventually allow us to better understand it and potentially intervene in subjects who will present a "cognitive effort" more important than the average and who would potentially be more sensitive to the negative effects of age on cognition.

Objectives

This study aims to describe the interindividual variability in working memory performance across aging, i.e., from 20 to 60 years old. It aims to explain it considering many factors: the memorization strategy selected, i.e., verbalization or mental imagery; performance in executive functions related to working memory, i.e., inhibition, flexibility and updating; the cognitive effort engaged during the task; and brain functional connectivity at rest.

Methods

EEG: connectivity during resting state; frequency analysis during the tasks; Measure of pupil dilation (eye-tracking); Cognitive evaluation: working memory and related executive functions (inhibition, flexibility and updating).

Expected results

At the end of this work, we believe that we will be able to identify a "profile of sensitivity to the effect of age" which will allow, in the future, to develop a prophylactic and not a curative approach to face the negative effects of age on cognitive functioning.

Feasibility

The project is at its starting point but it benefits from an authorization from the Committee for the Protection of Individuals (CPP) and from a funding to ensure the recruitment of subjects. We have the support of the members of the Computer Science Department and the Human Experimentation Department (data analysis; development of cognitive tasks...) of the Cognitive Neuroscience Laboratory. The experimental set-up is operational, and the cognitive tasks are already designed.

Expected candidate profil

The selected student should have previous experience (Master internship) in the field of human experimentation. He/she will be familiar with EEG data acquisition and treatment. He/she should be autonomous as he/she will be the only PhD student involved in this project. Notions of French would be appreciated to encourage interaction with the subjects.

SUPERVISED PHDS & PUBLICATIONS : ALESCIO-LAUTIER Béatrice

- **Previously supervised PhD students**

- MIMET Anaïs – 2017-2021
- DESHAYES Claire - 2016-2020
- CHAMBON caroline - 2004-2008
- PABAN Véronique – 1994-1998

- **Publications of previously supervised PHD students**

- A comprehensive approach to study the resting- state brain network related to creative potential (2021) Deshayes C, Paban V, Ferrer MH, Alescio-Lautier B, Chambon C
- Problem-solving training modifies cognitive functioning and related functional connectivity in healthy adults (2021) Alescio-Lautier B, Chambon C, Deshayes C, Anton JL, Escoffier G, Ferrer MH, Paban V
- Resting Brain Functional Networks and Trait Coping (2018) Paban V, Deshayes C, Ferrer MH, Weill A, Alescio-Lautier B
- Benefits of computer-based memory and attention training in healthy older adults (2014) Caroline Chambon, Cathy Herrera, Patricia Romaiguere , Véronique Paban, Béatrice Alescio -Lautier
- Positive effects of computer-based cognitive training in adults with mild cognitive impairment (2012) Herrera C, Chambon C, Michel BF, Paban V, Alescio-Lautier B
- Visual and visuospatial short-term memory in mild cognitive impairment and Alzheimer disease: role of attention (2007) Alescio-Lautier B, Michel BF, Herrera C, Elahmadi A, Chambon C, Touzet C, Paban V
- Paban V, Farioli F, Romier B, Chambon C, Alescio-lautier B. (2010). Gene expression profile in rat hippocampus with and without memory deficit. Neurobiol Learn Mem, 94(1):42-56
- Paban V, Chambon C, Manrique C, Touzet C, Alescio-lautier B. Epub 2009 (2011). Neurotrophic signaling molecules associated with cholinergic damage in young and aged rats. Environmental enrichment as potential therapeutic agent. Neurobiology of aging, 32(3):470-85
- Chambon C, Paban V, Manrique C, Alescio-lautier B. (2007). Behavioral and immunohistological effects of cholinergic damage in immunolesioned rats: Alteration of c-Fos and PSA-NCAM expression
- Alescio-lautier B, Michel B, Herrera C, Elhamadi A, Chambon C, Touzet C, Paban V. (2007) Visual and visuospatial short-term memory in mild cognitive impairment and Alzheimer disease: role of attention. Neuropsychologia, 45: 1948-1960
- Paban V, Jaffard M, Chambon C, Malafosse M, Alescio-lautier B. (2005) Time course of behavioral changes following basal forebrain cholinergic damage in rats: environmental enrichment as a therapeutic intervention
- Paban V, Chambon C, Jaffard M, Alescio-lautier B. (2005) Behavioral effects of basal forebrain cholinergic lesions in young adult and aging rats

SUPERVISED PHDS & PUBLICATIONS : CHAMBON Caroline

- **Previously supervised PhD students**

- DESHAYES Claire - 2017-2020

- **Publications of previously supervised PHD students**

- A comprehensive approach to study the resting-state brain network related to creative potential (2021) Deshayes C, Paban V, Ferrer MH, Alescio-Lautier B, Chambon C
- Problem-solving training modifies cognitive functioning and related functional connectivity in healthy adults (2021) Alescio-Lautier B, Chambon C, Deshayes C, Anton JL, Escoffier G, Ferrer MH, Paban V
- Resting Brain Functional Networks and Trait Coping (2018) Paban V, Deshayes C, Ferrer MH, Weill A, Alescio-Lautier B

PROJECT I2

Title : Plasma profiling as a novel biomarker for a rare neuromuscular disease

Supervisor : BARTOLI Marc

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Co-supervisor : GOROKHOVA Svetlana

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State of the art

LAMA2-related dystrophies are caused by a complete or partial deficiency of laminin-211. LAMA2-RD patents have mild to profound muscle weakness that can also be associated with central nervous system abnormalities, such as white matter changes and seizures. Disease biomarkers are critical to effectively detect and follow the potential changes in patients involved in therapeutic trials. Unfortunately, there are currently no validated biomarkers available for LAMA2-related dystrophies. A novel way to follow and diagnose various pathologies based on denaturation profiling of plasma using nanoDSF (Differential Scanning Fluorimetry) has recently been described for glioma by researchers of The INteractome Timone Platform (PINT) in the Institute of NeuroPhysiopathology (INP). Similar approaches have also shown reproducible disease-specific profiles in various other pathologies. It is therefore possible that the nanoDSF could detect plasma profile patterns specific to LAMA2-RD patients, thus identifying a novel minimally invasive way to diagnose and follow patients.

Objectives

The two objectives of our project are: 1. to test if denaturation profiling of plasma from patients can be used as a biomarker in LAMA2-RD disease population. 2. to explore the molecular processes leading to changes in plasma signature by analysing the extracellular environment of cultured cells from LAMA2-RD patients.

Methods

Frozen plasma samples from LAMA2-RD patients and from age-matched controls will be analysed by nanoDSF instrument at the The INteractome Timone Platform (PINT) in the Institute of NeuroPhysiopathology (INP), Aix-Marseille University. The denaturation profiles obtained from plasma samples from LAMA2-RD patients will be compared to that of control samples using advanced AI methods in order to detect the differences that could serve as non-invasive disease biomarkers. To further explore the identified differences in plasma signatures between LAMA2-RD patients and controls, the changes in the extracellular environment of patient-derived cell cultures will be analysed by nanoDSF instrument.

Expected results

We expect to observe differences between the patient and the control plasma profiles, thus helping to develop a non-invasive LAMA2-RD biomarker for future clinical studies. We also expect to see the effect of extracellular matrix changes typically present in LAMA2-RD patient-derived cell cultures on denaturing profiles of extracellular media. By controlling the different aspects of cell culture, we plan to identify the molecular changes that affect the denaturing profile.

Feasibility

Our “Translational Neuromyology” group in the Nerve and Muscle department of the Marseille Medical Genetics institute as well as our collaborators at The INteractome Timone Platform (PINT) in the Institute of NeuroPhysiopathology (INP) have all necessary equipment and infrastructure to accomplish the proposed research project.

Expected candidate profil

We are looking for a curious and motivated candidate with a solid fundamental background in molecular biology and biochemistry. Experience in cell culture would also be a plus.

SUPERVISED PHDS & PUBLICATIONS : BARTOLI Marc

- **Currently supervised PHD students**

- Bénedicte Alary
- Benoit Drouillas (co-direction 50%)

- **Previously supervised PhD students**

- Océane Ballouhey 2018-2021
- Alexandra Salvi 2017-2021
- Juile Warnez 2015-2018
- André Maues de Paula 2011-2016
- Eugénie Dionnet 2012-2016
- Virgnie Kergourlay 2010-2014
- Florian Barthélémy 2009-2013

- **Publications of previously supervised PHD students (last 5 years)**

- Complete list : https://orcid.org/0000-0003-3339-9858

SUPERVISED PHDS & PUBLICATIONS : GOROKHOVA Svetlana

- **Currently supervised PHD students**

- Khaoula Rochdi (co-supervision with Abdelhamid Barakat and Martin Krahn)

- **Publications of previously supervised PHD students (last 5 years)**

- Khaoula Rochdi, Mathieu Cerino, Nathalie Da Silva, Valerie Delague, Aymane Bouzidi, Halima Nahili, Ghizlane Zouiri, Yamna Kriouile, Svetlana Gorokhova, Marc Bartoli, Rachid Saïle, Abdelhamid Barakat, Martin Krahn "Identification of novel mutations by targeted NGS in Moroccan families clinically diagnosed with a neuromuscular disorder" Clinica Chimica Acta 2022 524, 51-58
- Khaoula Rochdi, Mathieu Cerino, Nathalie Da Silva, Valerie Delague, Halima Nahili, Yamna Kriouile, Svetlana Gorokhova, Marc Bartoli, Rachid Saïle, Abdelhamid Barakat, Martin Krahn "First characterization of congenital myasthenic syndrome type 5 in North Africa" *Mol Biol Rep 2021 Sep 22. doi: 10.1007/s11033-021-06530-7*

PROJECT I3

Title : Emergent activity patterns in the developing brain

Supervisor : COSSART Rosa

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Co-supervisor : PLATEL Jean-Claude

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State of the art

Electrical activity plays a critical role in the developing brain and in the formation of the somatosensory topographical map. During their maturation, neurons exhibit successive patterns of neuronal activity, evolving from asynchronous sparse single-cell firing at low frequencies in embryo to correlated firing the first week after birth, reaching adult like activity patterns after the second postnatal week. We are particularly interested in the appearance and the cellular mechanisms of this first correlated activity occurring within the few days after birth. Results obtained with in vitro models showed that these correlated activities are mediated initially by electrical synapses. Moreover, it was demonstrated that clonally related neurons are preferentially coupled by electrical synapses, bringing the hypothesis of the role of the ontogenic origin on the construction of the neuronal network. It is also interesting to note that during the same time period several waves of neuronal death affect both pyramidal neurons and interneurons but the link with early neuronal network activity is not well established.

Objectives

Our general objective is to determine the cellular and network mechanisms underlying the formation of early networks and of topographic maps. We will first determine the in vivo pattern (in time and space) of recurrent neuronal activity during the first postnatal week. We will then determine if ontogeny drives the formation of this first neuronal network activity. We will finally determine the link between patterns of neuronal/network activity and neuronal death.

Methods

We have developed a unique multidisciplinary approach that combines in vitro and in vivo calcium imaging, electrophysiology, holographic photo-stimulation, neuroanatomy, data mining, mouse genetics (brainbow) and behavior during the first week after birth.

Expected candidate profil

We are looking for a motivated student with either a neurobiology background with a keen interest in computational neuroscience or a physics student with interest in neurobiology and experimentation.

SUPERVISED PHDS & PUBLICATIONS : COSSART Rosa

- **Currently supervised PhD students**

- Artem Vorobyev
- Marina Cretella

- **Previously supervised PhD students**

- Davide Cavalieri 2017-2021
- Thomas Tressard 2015-2019
- Claire Gouny 2014-2018

- **Publications of previously supervised PHD students (last 5 years)**

- CA1 pyramidal cell diversity is rooted in the time of neurogenesis.Cavalieri D, Angelova A, Islah A, Lopez C, Bocchio M, Bollmann Y, Baude A, Cossart R.Elife. 2021
- Hippocampal hub neurons maintain distinct connectivity throughout their lifetime.Bocchio M, Gouny C, Angulo-Garcia D, Toulat T, Tressard T, Quiroli E, Baude A, Cossart R.Nat Commun. 2020
- Assemblies of Perisomatic GABAergic Neurons in the Developing Barrel Cortex.Modol L, Bollmann Y, Tressard T, Baude A, Che A, Duan ZRS, Babij R, De Marco García NV, Cossart R.

SUPERVISED PHDS & PUBLICATIONS : PLATEL Jean-Claude

- **Currently supervised PhD students**

- Loizeau Mathieu

- **Previously supervised PhD students**

- Angelova Alexandra 2014-2018

- **Publications of previously supervised PHD students (last 5 years)**

- Neuronal integration in the adult mouse olfactory bulb is a non-selective addition process.Platel JC, Angelova A, Bugeon S, Wallace J, Ganay T, Chudotvorova I, Deloulme JC, Béclin C, Tiveron MC, Coré N, Murthy VN, Cremer H. Elife. 2019
- Characterization of perinatally born glutamatergic neurons of the mouse olfactory bulb based on NeuroD6 expression reveals their resistance to sensory deprivation.
  Angelova A, Platel JC, Béclin C, Cremer H, Coré N. J Comp Neurol. 2019 May

PROJECT I4

Title : Soluble TWEAK, a new biomarker of neuroinflammation during multiple sclerosis?

Supervisor : DESPLAT-JEGO Sophie

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State of the art

Multiple sclerosis (MS) is a chronic inflammatory demyelinating autoimmune disease of the central nervous system (CNS) affecting more than 3 million people worldwide. In its relapse-remitting form, phases of inflammation are intertwined with stable remission. Relapses are routinely evaluated by magnetic resonance imaging (MRI) of the CNS, but an easy-to-use serum biomarker for neuroinflammation would be useful to take care of, and follow up with, MS patients. TWEAK is a TNF family cytokine. It is produced by monocytes / macrophages in a membrane-bound form which can be cleaved to a soluble form (sTWEAK) and binds its receptor, Fn14. During MS, an overexpression of TWEAK is observed at the hub of inflammation. Our team has shown that: (a) inhibition of TWEAK reduces the severity of the disease and the number of infiltrating cells in the CNS in a mouse model of MS, (b) in vitro, the exposure of the blood-brain barrier (BBB) to TWEAK increases its permeability, and (c) the serum levels of sTWEAK are significantly elevated in relapsing MS patients during a pilot study. Thus, TWEAK is a potential biomarker for the early detection of the MS inflammatory phase. However, its origin and fate remain poorly characterized.

Objectives

To determine: (a) the origin of soluble TWEAK in the CNS (whether it crosses the BBB or is generated in situ through cleavage of membrane-bound TWEAK), (b) what causes variations in the measurement of serum sTWEAK in vivo (timing of the sample collection, the patient's demographic characteristics, or if TWEAK is bound or unbound, interfering with its quantification), and (c) if the serum level of TWEAK is a strong biomarker of MS inflammatory relapse.

Methods

We will study: (a) the transport in vitro of sTWEAK through a model of BBB and the modulation of TWEAK expression by microglia and infiltrating leucocytes, (b) diurnal variations and correlation of TWEAK serum levels with age, gender, sFn14 levels or TWEAK-binding autoantibodies detection, and (c) the longitudinal TWEAK serum levels during relapses and remissions in a cohort of MS patients also monitored by CNS MRI.
Cell cultures, experiments in C57Bl/6 mice, immunoanalysis, protein biochemistry, microscopy and molecular biology will be used especially.

Expected results

(a) a migration of TWEAK exists from the blood to the brain through the BBB, (b) optimal pre- and post-analytical conditions of sTWEAK quantification are established, and (c) high serum TWEAK levels are associated with inflammatory relapses of MS. This project will contribute to valuable new knowledge on this devastating neurological disease and has the potential to open new avenues for monitoring MS.

Feasibility

INP offers all means (state-of-the art technology facilities, internationally competitive research environment, continuous technical guidance and support) necessary for the project. The project has already received financial support. The Ethics Committee has recently approved the human participant portion of this project (collaboration with the Neurology and the Immunology teams of the University hospital).

Expected candidate profil

Excellent MSc degree in immunology, neuroscience, biochemistry or in a related field
- Dynamic, highly motivated, creative, and curious candidate
- Able to work both individually and as part of a team
- Knowledge of immunohistochemistry, protein biochemistry and molecular biology
- Previous experience in animal experiments is beneficial

PROJECT I5

Title : Large scale cortical interactions during comparison of visual and cognitive information in non-human primates

Supervisor : IBOS Guilhem

LABORATORY : INT CITY : Marseille COUNTRY : France

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LABORATORY WEBSITE : https://www.int.univ-amu.fr/spip.php?page=equipe&equipe=INVIBE&lang=en

Co-supervisor : MASSON Guillaume

LABORATORY : INT CITY : Marseille COUNTRY : France

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LABORATORY WEBSITE : https://www.int.univ-amu.fr/spip.php?page=equipe&equipe=INVIBE&lang=en

State of the art

Frédéric Chavane (head of the Neopto team in the Institut de Neurosciences de la Timone INT, Marseille France), would like to encourage applications for a Phd position with Dr Guilhem Ibos. Candidates should apply to the 2022 PhD scholarship for international students of Marseille's NeuroSchool.

The research group of Guilhem Ibos studies cortical mechanisms of cognitive control in non-human primates (NHP, macaque and marmoset monkeys). We specialize in training NHP to perform sets of cognitive tasks and recording/analyzing extra cellular neuronal activity in large populations of distributed cortical networks. Adapting our behavior to ever changing environment requires to constantly confront sensory representation and internally generated, goal-directed representations of our needs and expectations. For example, when looking for a friend in a crowd, we compare visual representation of each object (extracted within the hierarchy of visual areas) to internally generated representation of our friend. Such behavior engages a large set of cortical and sub cortical areas, and involves several cognitive processes such as working memory, selective attention and decision making. Our research group aims at understanding how different sources of information are integrated and compared in order to facilitate decision making processes. We recently proposed that a network of cortical areas, including parietal and prefrontal cortices, interact with sensory visual cortex when comparing what we are looking at (sensory information), to what we are looking for (working memory information)(1–4).

Objectives & expected results

The goal of the project is to test how prefrontal, parietal and visual cortical areas interact during comparative decision making. Two macaques are already trained, data acquisition will start during spring 2022. The selected student will fully participate to data acquisition (single and multiple point electrodes in behaving monkeys), analysis (spiking pattern dynamics) and modeling (attention/decision decoding). As a starting point, she/he will focus on data analysis. In parallel, she/he will develop her/his own research project in an approach fostering independence and creative thinking.

Expected candidate profil

Candidates should:

(a) have notions of cognitive neurosciences and show record of highest grades. Experience in animal research in general and with NHP in particular will be a plus but is not mandatory.

(b) have a solid experience in programming (Matlab, Python), statistics and data analysis. (c) be able to collaborate with other students/post docs.

She/he will integrate the NeuroSchool PhD Program of Aix-Marseille Université which organizes postgraduate studies in Neurosciences with theoretical courses and soft skills. Starting date is Fall 2022. For administrative reasons, applications must be addressed to Dr Chavane via the Neuroschool website, but candidates must contact Guilhem Ibos (guilhem.ibos@univ-amu.fr) who will supervise the project.

Reference list

1. *G. Ibos, D. J. Freedman, Sequential sensory and decision processing in posterior parietal cortex. Elife. 6 (2017), doi:10.7554/eLife.23743.*
2. *G. Ibos, D. J. Freedman, Interaction between Spatial and Feature Attention in Posterior Parietal Cortex. Neuron. 91, 931–943 (2016).*
3. *G. Ibos, D. J. Freedman, Dynamic Integration of Task-Relevant Visual Features in Posterior Parietal Cortex. Neuron. 83, 1468–80 (2014).*
4. *D. J. Freedman, G. Ibos, An Integrative Framework for Sensory, Motor, and Cognitive Functions of the Posterior Parietal Cortex. Neuron. 97, 1219–1234 (2018).*

SUPERVISED PHDS & PUBLICATIONS : IBOS Guilhem

- **Currently supervised PhD students**

- Alexis Monnet-Aimard

SUPERVISED PHDS & PUBLICATIONS : CHAVANE Frédéric

- **Currently supervised PhD students**

- Salvatore Giancani (co-supervised, start 2021)
- Isabelle Racicot (co-supervised, start 2019)
- Florent Missey (co-supervised 2018)

Previously supervised PhD students

- G. Benvenuti (09-15)
- Q Montardy (08-12)
- A Reynaud (05-10) S Chemla (06-10)
- F. Matonti (09-13)
- L. Hoffart (05-10)

- **Selected publications of previously supervised PHD students (last 5 years)**

Selected (last 5 years)

Bourbousson M, Racicot I, Muslimov E, Behaghel T, Blaize K, Bourdet A, Chemla S, Hugot E, Jahn W, Roux S, Vanzetta I, Weber P, Sauvage J-F, Chavane F, Ferrari M. 2020. Imaging multiple cortical areas with high spatio-temporal resolution using innovative wide-field imaging system. *NeuroPhotonics*. doi.org/10.1117/12.2556793

Racicot I, Muslimov E, Degiovanni X, Baurberg J, Blaize K, Sauvage J-F, Ferrari M, Chavane F. 2021. Optical system with a curved detector for wide-field high-resolution cortical imaging at meso-scale. *Opt Instrum Sci Technology Appl Ii* 6. doi:10.1117/12.2597067

Hahn G, Ponce-Alvarez A, Monier C, Benvenuti G, Kumar A, Chavane F, Deco G, Frégnac Y. 2017. Spontaneous cortical activity is transiently poised close to criticality. *PLoS Computational Biology* **13**:e1005543. doi:10.1371/journal.pcbi.1005543

Chemla S, Reynaud A, Volo M di, Zerlaut Y, Perrinet L, Destexhe A, Chavane F. 2019. Suppressive Traveling Waves Shape Representations of Illusory Motion in Primary Visual Cortex of Awake Primate. *Journal of Neuroscience* **39**:4282– 4298. doi:10.1523/jneurosci.2792-18.2019

Chemla S, Muller L, Reynaud A, Takerkart S, Destexhe A, Chavane F. 2017. Improving voltage-sensitive dye imaging: with a little help from computational approaches. *Neurophotonics* **4**:031215. doi:10.1117/1.nph.4.3.031215

PROJECT I6

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

Supervisor : KAVOUNOUDIAS Anne

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

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. 2018). 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 and structural remodeling of the brain networks following sensory training using fMRI and diffusion-weighted-imaging data.

Methods

Proprioceptive training will consist of repeated vibratory stimulation applied daily for two consecutive weeks on 40 participants over 65 years of age and 25 younger control. Before and immediately after the training, all the participants will undergo a psychophysical test and an MRI session.

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 restoration of the lateralization of brain activations toward the contralateral side in older participants, similarly to that evidenced in young adults. As interhemispheric lateralization was found to correlate with better discrimination perception, we hypothesize that older participants should gain in perceptual and motor capabilities after the training. In addition, the structural changes within the corpus callosum and the sensorimotor tracts connecting the two primary sensorimotor cortex will be estimated before and after the training. Structural markers predicting the level of proprioceptive function recovery will be explored.

Feasibility

The protocol has been already approved by the ethical committee (CPP oust II- ° IDRCB (ANSM) : 2018-A02607-48). The project will be supported by two main grants: Carnot Cognition (20 k€) and ACI Fed3C (10 k€). The development of required equipment will be provided by an ANR grant (PhantomPain project, ANR- ASTRID 2021-2024).

Expected candidate profil

The candidate will have a background in neurophysiology, statistics and programming skills (Matlab, python). They will also have a keen interest for clinical perspectives and a desire to interact with patients. Knowledge in the steps of fMRI or diffusion MRI analysis would be appreciated.

SUPERVISED PHDS & PUBLICATIONS : KAVOUNOUDIAS Anne

• **Currently supervised PhD students**

- Raphaëlle SCHLIENGER

• **Previously supervised PhD students**

- Caroline BLANCHARD (2009-2013)
- Marie CHANCEL (2013-2016)
- Caroline LANDELLE (2015-2019)
- Jeanne CARON-GUYON (2016-2020)
-

• **Publications of previously supervised PHD students**

- [NAZARIAN B, CARON-GUYON J]co, ANTON JL, SEIN J, CATZ N & **KAVOUNOUDIAS A** (2022) A new Patterned Air-Flow device to reveal the network for tactile motion coding using fMRI J Neurosci Methods 365:109397 https://doi.org/10.1016/j.jneumeth.2021.109397
- C LANDELLE, O LUNGU, S VAHDAT, **A KAVOUNOUDIAS**, V MARCHAND-PAUVERT, B DE LEENER, & J DOYON – (2021) Investigating the human spinal sensorimotor pathways through functional magnetic resonance imaging- NeuroImage 245:118684 https://doi.org/10.1016/j.neuroimage.2021.118684
- C Landelle, J Danna, B Nazarian, L Pruvost, M Amberg, F Giraux, R Kronland-Martinet, S Ystad, M Aramaki, **Kavounoudias A*** - (2021) Hearing the touch: Impact of sonification in the haptic perception of artificial textures and its modulation with aging. *Scientific Reports* 4;11(1):5124. doi: 10.1038/s41598-021-84581-3
- 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* 20: 180-185 DOI: 10.1016/j.cophys.2021.01.016
- 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 functional MRI data acquired at rest and during exposure to tactile or muscle proprioceptive stimulation in healthy young and older volunteers. *Data in brief* 31:105939. 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 Cortex* 2020 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. *Neuropsychologia* 119:45-58
- Landelle C, El Amadi , **Kavounoudias A** (2018) Age-related impairment of hand movement perception based on muscle proprioception and touch. *Neuroscience* 381: 91-104

- Chancel M, **A Kavounoudias**, Guerraz M (2017) What's left of the mirror illusion when the mirror is no longer seen? Bilateral integration of proprioceptive afferents! *Neuroscience* 362: 118-126
- Chancel M., Blanchard C., Guerraz M, Montagnini A, **Kavounoudias A** (2016) Optimal visuo-tactile integration for perception of self-hand movement. *J Neurophysiol* 116(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 Res 234 (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. *PlosOne* 10(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 Res* 233 (Issue: 5): 1463-70.
- Brun C, Metral M, Chancel M, **Kavounoudias A**, Luyat M, Guerraz M. (2015) Passive or simulated displacement of one arm, but not mirror vision, modulates involuntary displacements of the other. *Neuroscience* 285: 343-355
- Blanchard C, Roll R, Roll JP & **Kavounoudias A** (2013) Differential contributions of vision, touch and muscle proprioception to the coding of hand movements. *PlosOne* 8 **:** 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 I7

Title : Fronto-parietal and cortico-striatal neuronal interactions underlying interceptive movements in macaques (In2CoSt)

Supervisor : KILAVIK Bjørg Elisabeth

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State of the art

In natural conditions, many animals, and in particular non-human primates (NHPs) perform interceptive movements with the upper limbs to catch small prey. These movements must take into account the visual context and be rapid and accurate, even though the relevant information is typically highly variable (prey speed, size, position and trajectory…). These behaviors therefore necessitate coordination between different brain structures, including the fronto-parietal cortical network and sub-cortical areas.
Anatomically, the cortex is organized in layers. Superficial layers receive the majority of bottom-up sensory cortical and thalamic inputs and mainly project to local and distant cortices. Deep layers receive inputs of cortical origins and mainly project to sub-cortical regions including the striatum, thalamus and spinal cord. However, the intra- and inter-areal cortical and sub-cortical dynamics underlying interceptive movements are poorly understood.

Objectives & methods

In a first part, we will study the behavior of macaque monkeys trained in an interception task. We will study eye-hand coordination, and the influence of manipulating the parameters of the task (e.g. speed, visibility or position of the target) and consequently the predictability of the time and location of interception on the performance.
The implication of and interaction between fronto-parietal areas might vary with such parameters but also with the level of learning. Subsequently, we will therefore record neuronal activity simultaneously from the different layers of premotor and parietal cortical areas involved in visuomotor integration with chronic 3D arrays. At the same time we will record the sensorimotor striatum, which receives input from these cortical regions and is involved in movement planning and control. Neuronal spiking activity and local field potentials (LFPs) will be analyzed to determine the interactions across cortical layers together with the inter-areal cortico-cortical and cortico-striatal communication.

Expected results

As striatum has been implicated in shaping skills and habits and in the perception of time, we expect a change in the interactions between cortex and the striatum during the manipulation of task parameters and as the animal becomes an expert. These results should permit an increased understanding of how neuronal activity is integrated in cortico-subcortical networks in order to adapt behavior in unpredictable conditions.

Feasibility & environment

This PhD project is part of a broader, recently initiated scientific focus of the team aimed at studying interceptive movements across multiple scales in cortico-subcortical networks, with complementary experimental approaches in human participants and patients, and in NHPs. The student will share setup and data analysis techniques with a PhD student and a senior post-doc (Dr. Simon Nougaret; co-supervisor; expert in basal ganglia electrophysiology) working on another project. Neuronal connectivity analyses will be done in collaboration with Dr. Brovelli (INT) and Dr. Battaglia (INS).

Expected candidate profil

A background in biology, neuroscience or engineering is optimal. The project will combine experimental work (training and recording from NHPs) and data analysis (matlab/python), providing an excellent opportunity to gain a solid experience in integrative neurosciences.

SUPERVISED PHDS & PUBLICATIONS : KILAVIK Bjørg Elisabeth

- **Currently supervised PhD students**

- Laura Lopez Galdo (start 2021)

- **Previously supervised PhD students**

- Joachim Confais (2008-2013)

- **Publications of previously supervised PHD students**

- Kilavik BE, Roux S, Ponce-Alvarez A, **Confais** J, Grün S, Riehle A (2009) Long-term modifications in motor cortical dynamics induced by intensive practice. J Neurosci 29: 12653-12663. doi: 10.1523/JNEUROSCI.1554-09.2009
- Kilavik BE, **Confais J**, Ponce-Alvarez A, Diesmann M, Riehle A (2010) Evoked potentials in motor cortical local field potentials reflect task timing and behavioral performance. J Neurophysiol 104: 2338-2351. doi: 10.1152/jn.00250.2010
- Kilavik BE, Ponce-Alvarez A, Trachel R, **Confais J**, Takerkart S, Riehle A (2012) Context-related frequency modulations of macaque motor cortical LFP beta oscillations. Cereb Cortex 22: 2148-2159. doi: 10.1093/cercor/bhr299
- **Confais J**, Kilavik BE, Ponce-Alvarez A, Riehle A (2012) On the anticipatory pre-cue activity in motor cortex. J Neurosci 32: 15359-68. doi: 10.1523/JNEUROSCI.1768-12.2012
- Kilavik BE, **Confais J**, Riehle A (2014) Signs of timing in motor cortex during movement preparation and cue anticipation. Adv Exp Med Biol 829: 121-142. doi: 10.1007/978-1-4939-1782-2_7
- **Confais J**, Malfait N, Brochier T, Riehle A, Kilavik BE (2020) Is there an Intrinsic Relationship between LFP Beta Oscillation Amplitude and Firing Rate of Individual Neurons in Macaque Motor Cortex? Cereb Cor Comm tgaa017. doi: 10.1093/texcom/tgaa017

PROJECT I8

Title : Deregulation of Tau/tubulin Interaction through AT8 epitope as an early event for Tau aggregation and neurotoxicity

Supervisor : KOVACIC Hervé

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State of the art

Intracellular plaques containing B-amyloid protein and neurofibrillary tangles consisting of accumulation of hyperphosphorylated Tau (P-Tau) are the hallmarks of Alzheimer's disease (AD). Tau is involved in axonal microtubules (MTs) stability for synaptic function. In AD, MTs depolymerizes and P-Tau aggregates into pathological threads that appears many years before the onset of clinical symptoms. Despite the progress of the last years, the binding mode of Tau to tubulin and MTs as well as the structural and functional impact of specific phosphorylations are not completely understood particularly for the epitope AT8 (S202; T205; S208).

Objectives

The general objective of the project is to demonstrate that the third phosphorylation site on AT8 epitope at S208 is necessary for tau-tau-mediated neurodegeneration through molecular and cellular approaches.

Methods

We will used recombinant HTau40, and combination of mutants on amino-acid 202, 205 and 208. All Tau mutants will be phosphorylated by brain mice extracts or specific kinases in vitro and characterized by Mass Spectroscopy and Nuclear Magnetic Resonance. In vitro study on the different mutant and their interaction with microtubules will be carried out by biophysical approaches at molecular level (turbidimetry, Differential Scanning Fluorimetry, Isothermal Titration Calorimetry, Site Directed Spin Labeling combined with Electron Paramagnetic Resonance). P-Tau oligomers with the different mutants will be characterized by Analytical UltraCentrifugation and Dynamic Light Scattering. The P-tau oligomers made in vitro will be test in cellular context using HEK293 biosensor cells and cultured rat neurons. Finally, we will also analyse in neurons the effects of these Tau mutants on the axonal, dendritic differentiation, spinogenesis and synaptogenesis and the consequences of Tau mutants effects on the synaptic function.

Expected results

We expect to highlight the role of Tau hyperphosphorylation in a relation with structure activity study from molecule to cells. More precisely, we expect to evidence the pathological role of the misunderstood phosphorylation of Tau on S208 in AT8 epitope by demonstrating that tau should be phosphorylated not only on S202 and T205 but also on the third phosphorylation site S208. We hypothesize that this latter phosphorylation induces Tau restructuration and conformational changes that lead to its wrong binding on tubulin, MTs depolymerisation and its self-assembly in pathological oligomers. Our finding will open the way to use the Tau/tubulin interaction as a potential target for therapy intervention.

Feasibility

The project is financially supported by the ANR MAgnetau. All mutants for Tau AT8 phosphorylation modifications and characterization of Tau phosphorylation by brain mice has been already performed thanks to the ANR consortium. Work on cells and neurons will be conducted in collaboration with Dr Lotfi Ferhat from the team 1 of INP.

SUPERVISED PHDS & PUBLICATIONS : KOVACIC Hervé

• **Currently supervised PhD students**

- BENSSOUINA Fatima zahra (3eme année) 50%
- HEDNA Rayane (2eme année) 50%

• **Previously supervised PhD students**

- DE BESSA Tiphany soutenue 2018 Cotut. Brésil (USP)
- CHOCRY Mathieu soutenue 2017
- MOUSSLIM Mohamed soutenue 2014
- DAHAN Laetitia soutenue 2009
- SADOK Amine soutenue 2009

• **Publications of previously supervised PHD students (13 avec les étudiants mentionnés)**

ts

- Pagano A, Breuzard G, Parat F, Tchoghandjian A, Figarella-Branger D, De Bessa TC, Garrouste F, Douence A, Barbier P, Kovacic H. Tau Regulates Glioblastoma Progression, 3D Cell Organization, Growth and Migration via the PI3K-AKT Axis. Cancers (Basel). 2021 Nov 19;13(22):5818. doi: 10.3390/cancer
- Soubéran A, Cappaï J, Chocry M, Nuccio C, Raujol J, Colin C, Lafitte D, Kovacic H, Quillien V, Baeza-Kallee N, Rougon G, Figarella-Branger D, Tchoghandjian A. Inhibitor of Apoptosis Proteins Determines Glioblastoma Stem- Like Cell Fate in an Oxygen-Dependent Manner. Stem Cells. 2019 Jun;37(6):731-742. doi: 10.1002/stem.2997. Epub 2019 Mar 28. PMID: 30920104.
- De Bessa TC, Pagano A, Moretti AIS, Oliveira PVS, Mendonça SA, Kovacic H, Laurindo FRM. Subverted regulation of Nox1 NADPH oxidase-dependent oxidant generation by protein disulfide isomerase A1 in colon carcinoma cells with overactivated KRas. Cell Death Dis. 2019 Feb 13;10(2):143. doi: 10.1038/s41419-019-1402-y. PMID: 30760703; PMCID: PMC6374413.
- Chocry M, Leloup L, Kovacic H. Correction: Reversion of resistance to oxaliplatin by inhibition of p38 MAPK in colorectal cancer cell lines: involvement of the calpain / Nox1 pathway. Oncotarget. 2018 Jun 1;9(42):26978-26979. doi: 10.18632/oncotarget.25605. Erratum for: Oncotarget. 2017 Oct 10;8(61):103710-103730. PMID: 29928496; PMCID: PMC6003572.
- Chocry M, Leloup L, Kovacic H. Reversion of resistance to oxaliplatin by inhibition of p38 MAPK in colorectal cancer cell lines: involvement of the calpain / Nox1 pathway. Oncotarget. 2017 Oct 10;8(61):103710-103730. doi: 10.18632/oncotarget.21780.
- Ben Sghaier M, Pagano A, Mousslim M, Ammari Y, Kovacic H, Luis J. Rutin inhibits proliferation, attenuates superoxide production and decreases adhesion and migration of human cancerous cells. Biomed Pharmacother. 2016 Dec;84:1972-1978. doi: 10.1016/j.biopha.2016.11.001. Epub 2016 Nov 6. PMID: 27829548.
- Mousslim M, Pagano A, Andreotti N, Garrouste F, Thuault S, Peyrot V, Parat F, Luis J, Culcasi M, Thétiot-Laurent S, Pietri S, Sabatier JM, Kovacic H. Peptide screen identifies a new NADPH oxidase inhibitor: impact

on cell migration and invasion. Eur J Pharmacol. 2017 Jan 5;794:162-172. doi: 10.1016/j.ejphar.2016.10.011. Epub 2016 Oct 12. PMID: 27743884.

- Ben Sghaier M, Mousslim M, Pagano A, Ammari Y, Luis J, Kovacic H. β-eudesmol, a sesquiterpene from Teucrium ramosissimum, inhibits superoxide production, proliferation, adhesion and migration of human tumor cell. Environ Toxicol Pharmacol. 2016 Sep;46:227-233. doi: 10.1016/j.etap.2016.07.019. Epub 2016 Jul 30. PMID: 27497729.
- Pescatore LA, Bonatto D, Forti FL, Sadok A, Kovacic H, Laurindo FR. Protein disulfide isomerase is required for platelet-derived growth factor-induced vascular smooth muscle cell migration, Nox1 NADPH oxidase expression, and RhoGTPase activation. J Biol Chem. 2012 Aug 24;287(35):29290-300. doi: 10.1074/jbc.M112.394551. Epub 2012 Jul 6. PMID: 22773830; PMCID: PMC3436193.
- Dahan L, Sadok A, Formento JL, Seitz JF, Kovacic H. Modulation of cellular redox state underlies antagonism between oxaliplatin and cetuximab in human colorectal cancer cell lines. Br J Pharmacol. 2009 Sep;158(2):610-20. doi: 10.1111/j.1476-5381.2009.00341.x. PMID: 19732064; PMCID: PMC2757701.
- Sadok A, Pierres A, Dahan L, Prévôt C, Lehmann M, Kovacic H. NADPH oxidase 1 controls the persistence of directed cell migration by a Rho-dependent switch of alpha2/alpha3 integrins. Mol Cell Biol. 2009 Jul;29(14):3915-28. doi: 10.1128/MCB.01199-08. Epub 2009 May 18. PMID: 19451223; PMCID: PMC2704751.
- de Carvalho DD, Sadok A, Bourgarel-Rey V, Gattacceca F, Penel C, Lehmann M, Kovacic H. Nox1 downstream of 12-lipoxygenase controls cell proliferation but not cell spreading of colon cancer cells. Int J Cancer. 2008 Apr 15;122(8):1757-64. doi: 10.1002/ijc.23300. PMID: 18076063.
- Sadok A, Bourgarel-Rey V, Gattacceca F, Penel C, Lehmann M, Kovacic H. Nox1-dependent superoxide production controls colon adenocarcinoma cell migration. Biochim Biophys Acta. 2008 Jan;1783(1):23-33. doi: 10.1016/j.bbamcr.2007.10.010. Epub 2007 Oct 30. PMID: 18023288.

PROJECT I9

Title : Neurobehavioral adaptations to perinatal adversity: maternal neglect and cannabis

Supervisor : MANZONI Olivier

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State of the art

During the perinatal period the developmental sequence is influenced, by maternal factors and environmental stimuli that can impair neuronal networks activity and structure with lasting neurobehavioral consequences. The impact of environmental factors and the mechanisms by which they promote progressive cognitive and emotional dysfunction remain largely unknown. Specifically, how cortical areas and behavior adapt to pathological maternal environment is poorly understood. We will employ a longitudinal multidisciplinary strategy combining an ethologically inspired behavioral analysis method, deep learning, optogenetics and electrophysiology to tease out in adult mice of both sexes specific neuronal and behavioral adaptations in response to maternal neglect and maternal consumption of cannabis.

Objectives

Discovering how maternal neglect or consumption of cannabis perturbates in a sex-dependent manner 3D body language and microcircuits in two neuronal hubs of the social brain, the prefrontal cortex (PFC) and the insular cortex (IC).

Methods

We propose a multi-scale (from dendrites to behavior) study of neuronal structural and functions in two validated pathological neurodevelopment models. First, to recapitulate parental neglect, we use a naturalistic model of limited bedding and nesting material (PND 2-9). This ecologically advantageous protocol has a large translational potential to human with minimal external intervention. Second, cannabis is the most commonly consumed/abused illegal drug by pregnant women and gestating mouse will be exposed to cannabis' main active molecules (CBD and/or THC, G5-20). To investigate how prenatal stress alters the behavioral grammar and identify underlying cellular mechanisms two methods will be combined. 1/ To discover how perinatal adversity changes the behavioral grammar of the progeny, we will use Live Mouse Tracker (LMT), an ethologically inspired behavioral analysis method using deep learning to identify body language in groups of freely interacting mouse. LMT allows repeated long-term recordings, behavior we will be tracked at adolescence and adulthood in animals of both sexes. 2/ in parallel to LMT, we will determine how perinatal adversity reprograms the architecture and the synaptic rules of cortical networks implicated in cognition and intellectual functions. Thus, IC and PFC circuits will be interrogated with in/ex-vivo electrophysiological experiments in optogenetically-disambiguated synapses. We will elucidate how perinatal stress impacts the tridimensional structure of IC and PFC neurons, with 3D quantitative morphometry of spines/dendrites' architecture. Changes in intrinsic excitability and elemental forms of synaptic learning will be systematically audited to shed new lights on how in-utero drugs transform neuronal and synaptic performances as previously described repertoire.

Expected results

We will decipher mouse body language and establish an unbiassed framework for portraying the consequences of maternal environment on behavior of the progeny and decipher the circuit level foundation of the behavioral deficits. This thesis project will enable rigorous exploration of joint dependencies, at the synaptic, circuit and behavioral levels.

Feasibility

All the equipment and expertise necessary to the project is already available in the laboratory and at INMED.

Expected candidate profil

Having a good sense of humor, a strong work ethic, being passionate about science, knowledge of electrophysiology and/or imaging, rodent behavior and Python coding are big plus.
Team info: tinyurl.com/bk7rw7kn

SUPERVISED PHDS & PUBLICATIONS : MANZONI Olivier

- **Currently supervised PhD students**

- Gabriele Giua (thesis ends in December 2022, financement ANR)

- **Previously supervised PhD students**

- Pauline Guily (financement NIH)
- Axel Bernabeu (financement AP-HM)
- Marion Deroche (financement Ecole Doctorale AMU)
- Anissa Bara (financement ANR)
- Aurore Thomazeau (financement Ecole Doctorale Bordeaux)
- Mathieu Lafourcade (financement Ecole Doctorale Bordeaux)
- Lenka Mikasova
- Laetitia Kahn (financement Ecole Doctorale Montpellier)
- David Robbe (financement Ecole Doctorale Montpellier)

- **Publications of previously supervised PHD students**

- Sex-specific divergent maturational trajectories in the postnatal rat basolateral amygdala Pauline Guily, Olivier Lassalle, Pascale Chavis, Olivier JJ Manzoni. 2022, iScience in press.
- 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; doi: https://doi.org/10.1101/2020.10.09.332965
- 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. Epub 2020 Feb 28.
- 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. doi: 10.1523/JNEUROSCI.1100-19.2019. Epub 2019 Dec 12
- Sex Differences in the Behavioral and Synaptic Consequences of a Single *in vivo* Exposure to the Synthetic 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. doi: 10.3389/fnbeh.2019.00023. eCollection 2019.

- 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. doi: 10.7554/eLife.36234.
- Amplification of $mGlu_5$-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. doi: 10.1523/JNEUROSCI.3516-16.2017. Epub 2017 Jun 19.
- 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. doi: 10.1093/cercor/bhw052.
- Endocannabinoids Mediate Muscarinic Acetylcholine Receptor-Dependent Long-Term Depression in the Adult Medial Prefrontal Cortex. Martin HG, Bernabeu A, Lassalle O, Bouille C, Beurrier C, Pelissier-Alicot AL, Manzoni OJ. Front Cell Neurosci. 2015 Dec 1;9:457. doi: 10.3389/fncel.2015.00457. eCollection 2015.
- 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. doi: 10.1523/JNEUROSCI.2852-13.2014.
- Prefrontal synaptic markers of cocaine addiction-like behavior in rats. Kasanetz F, Lafourcade M, Deroche-Gamonet V, Revest JM, Berson N, Balado E, Fiancette JF, Renault P, Piazza PV, Manzoni OJ. Mol Psychiatry. 2013 Jun;18(6):729-37. doi: 10.1038/mp.2012.59. Epub 2012 May 15. PMID: 22584869
- Polymodal activation of the endocannabinoid system in the extended amygdala. Puente N, Cui Y, Lassalle O, Lafourcade M, Georges F, Venance L, Grandes P, Manzoni OJ. Nat Neurosci. 2011 Nov 6;14(12):1542-7. doi: 10.1038/nn.2974. PMID: 22057189
- Nutritional omega-3 deficiency abolishes endocannabinoid-mediated neuronal functions. Lafourcade M, Larrieu T, Mato S, Duffaud A, Sepers M, Matias I, De Smedt-Peyrusse V, Labrousse VF, Bretillon L, Matute C, Rodríguez-Puertas R, Layé S, Manzoni OJ. Nat Neurosci. 2011 Mar;14(3):345-50. doi: 10.1038/nn.2736. Epub 2011 Jan 30.
- Transition to addiction is associated with a persistent impairment in synaptic plasticity. Kasanetz F, Deroche-Gamonet V, Berson N, Balado E, Lafourcade M, Manzoni O, Piazza PV. Science. 2010 Jun 25;328(5986):1709-12. doi: 10.1126/science.1187801.
- Localization and function of the cannabinoid CB1 receptor in the anterolateral bed nucleus of the stria terminalis. Puente N, Elezgarai I, Lafourcade M, Reguero L, Marsicano G, Georges F, Manzoni OJ, Grandes P. PLoS One. 2010 Jan 25;5(1):e8869. doi: 10.1371/journal.pone.0008869
- Altered surface trafficking of presynaptic cannabinoid type 1 receptor in and out synaptic terminals parallels receptor desensitization. Mikasova L, Groc L, Choquet D, Manzoni OJ. Proc Natl Acad Sci U S A. 2008 Nov 25;105(47):18596-601. doi: 10.1073/pnas.0805959105. Epub 2008 Nov 17
- Molecular components and functions of the endocannabinoid system in mouse prefrontal cortex. Lafourcade M, Elezgarai I, Mato S, Bakiri Y, Grandes P, Manzoni OJ. PLoS One. 2007 Aug 8;2(8):e709. doi: 10.1371/journal.pone.0000709.
- Role of the cyclic-AMP/PKA cascade and of P/Q-type Ca++ channels in endocannabinoid-mediated long-term depression in the nucleus accumbens. Mato S, Lafourcade M, Robbe D, Bakiri Y, Manzoni OJ. Neuropharmacology. 2008 Jan;54(1):87-94. doi: 10.1016/j.neuropharm.2007.04.014. Epub 2007 May 5.
- Presynaptic homeostatic plasticity rescues long-term depression after chronic Delta 9-tetrahydrocannabinol exposure. Mato S, Robbe D, Puente N, Grandes P, Manzoni OJ. J Neurosci. 2005 Dec 14;25(50):11619-27. doi: 10.1523/JNEUROSCI.2294-05.2005.
- Repeated morphine treatment alters polysialylated neural cell adhesion molecule, glutamate decarboxylase-67 expression and cell proliferation in the adult rat hippocampus. Kahn L, Alonso G, Normand E, Manzoni OJ. Eur J Neurosci. 2005 Jan;21(2):493-500. doi: 10.1111/j.1460-9568.2005.03883.x.

- A single in-vivo exposure to delta 9THC blocks endocannabinoid-mediated synaptic plasticity. Mato S, Chevaleyre V, Robbe D, Pazos A, Castillo PE, Manzoni OJ. Nat Neurosci. 2004 Jun;7(6):585-6. doi: 10.1038/nn1251. Epub 2004 May 16
- Exogenous and endogenous cannabinoids control synaptic transmission in mice nucleus accumbens. Robbe D, Alonso G, Manzoni OJ. Ann N Y Acad Sci. 2003 Nov;1003:212-25. doi: 10.1196/annals.1300.013
- Metabotropic glutamate receptor 2/3-dependent long-term depression in the nucleus accumbens is blocked in morphine withdrawn mice. Robbe D, Bockaert J, Manzoni OJ. Eur J Neurosci. 2002 Dec;16(11):2231-5. doi: 10.1046/j.1460-9568.2002.02273.x.
- Endogenous cannabinoids mediate long-term synaptic depression in the nucleus accumbens. Robbe D, Kopf M, Remaury A, Bockaert J, Manzoni OJ. Proc Natl Acad Sci U S A. 2002 Jun 11;99(12):8384-8. doi: 10.1073/pnas.122149199.
- Role of p/q-Ca2+ channels in metabotropic glutamate receptor 2/3-dependent presynaptic long-term depression at nucleus accumbens synapses. Robbe D, Alonso G, Chaumont S, Bockaert J, Manzoni OJ. J Neurosci. 2002 Jun 1;22(11):4346-56. doi: 10.1523/JNEUROSCI.22-11-04346.2002.
- Group 2 metabotropic glutamate receptors induced long term depression in mouse striatal slices. Kahn L, Alonso G, Robbe D, Bockaert J, Manzoni OJ. Neurosci Lett. 2001 Dec 28;316(3):178-82. doi: 10.1016/s0304-3940(01)02397-7.
- Localization and mechanisms of action of cannabinoid receptors at the glutamatergic synapses of the mouse nucleus accumbens. Robbe D, Alonso G, Duchamp F, Bockaert J, Manzoni OJ. J Neurosci. 2001 Jan 1;21(1):109-16. doi: 10.1523/JNEUROSCI.21-01-00109.2001. PMID: 11150326 Free PMC article.

PROJECT I10

Title : Neural dynamics constraining audio-motor coupling during speech and music processing

Supervisor : MORILLON Benjamin

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State of the art

Cognitive processes need time to unfold. During perceptual decision-making tasks, each of the different processing stages leading to a decision impose a temporal delay, which is overall reflected by reaction times. The natural dynamics of different cognitive processes has started to be established, with visual perception (VanRullen, Tics 2016), spatial attention (Fiebelkorn and Kastner, Tics 2019) and central inferential (Wyart et al., Neuron 2012) processes having each their own temporal constraints (from few tens to few hundreds of milliseconds).
What temporal constraints govern auditory perception is unknown. The two main auditory stimuli –speech and music– naturally unfold at different rates –5 and 2 Hz, respectively– and these rates were recently suggested to reflect internal temporal constraints of the dorsal auditory pathways (Assaneo et al., Sci. Adv. 2019; Zalta et al., Nat. Commun. 2020). However, why these temporal constraints differ between these two auditory domains is unknown.

Objectives

To investigate the neural dynamics at play in and the temporal constraints governing the dorsal auditory pathways –the cortical tracks linking auditory and motor regions– during auditory perception of speech and music.

Methods

The candidate will adapt a behavioral paradigm that manipulates the rate at which speech and music unfolds (see Giroud et al., bioRxiv 2021). Stereotactic electroencephalography (SEEG) and magnetoencephalography (MEG) will be recorded and analyzed with spectral decomposition, connectivity analyses and modeling approaches. Relation between stimulus characteristics, brain dynamics and behavioral outcome will be thoroughly investigated.

Expected results

Different sub-regions of the motor cortex may impose different temporal constraints during auditory perception of structured sequences (such as speech and music). Alternatively, the differential contribution of the two hemispheres during speech and music perception might lead to different rates of occurrence.

Feasibility

Feasibility of SEEG and MEG studies is ensured by the excellent infrastructures offered at our System Neurosciences Institute.

Expected candidate profil

Programming skills in Python (or Matlab); good notions of English; interest in clinical neurophysiology (SEEG); highly motivated; willing to perform collaborative work.

SUPERVISED PHDS & PUBLICATIONS : MORILLON Benjamin

- **Currently supervised PhD students**

- Paul-Lalande Robert
- Akanksha Gupta
- Arnaud Zalta, w. PhD defense planned for sept. 2022

- **Previously supervised PhD students**

- Jérémy Giroud (2017-2021)

- **Publications of previously supervised PHD students**

- Giroud J, Lerousseau JP, Pellegrino F, Morillon B, 2021. The channel capacity of multilevel linguistic features constrains speech comprehension. *bioRxiv.*
- Zalta A, Petkoski S, Morillon B, 2020. Natural rhythms of periodic temporal attention, *Nature Communications*, 11:1051
- Giroud J, Trébuchon A, Schön D, Marquis P, Liégeois-Chauvel C, Poeppel D, Morillon B, 2020. Asymmetric sampling in human auditory cortex reveals spectral processing hierarchy, *PloS Biology*, 18(3): e3000207
- Zalta A, Hou J-C, Thonnat M, Bartolomei F, Morillon B*, McGonigal A* (*co-senior authors) 2020. Neural correlates of rhythmic rocking in prefrontal seizures *Neurophysiologie Clinique*, 50(5): 331-338

PROJECT I11

Title : Studying TAGLN3 as a new regulatory target to control neuroinflammation in astrocytes: implications and applications in Alzheimer's disease

Supervisor : NIVET Emmanuel

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State of the art

Alzheimer's disease (AD) is a neurodegenerative disease accounting for the majority of all cases of dementia for which no efficient treatment exists. Elucidating the earliest brain molecular events that progressively predispose to sporadic forms of Alzheimer's disease (sAD) remains a great challenge. Mounting evidence indicate that dysregulation of inflammatory responses can, on the long run, impact brain function, thereby facilitating the onset and progression of neurodegeneration in sAD. We recently unraveled a novel Apolipoprotein E (APOE)-TAGLN3 axis that controls the NF-kB pathway in astrocytes. Based on our recent data, we hypothesize that alterations of TAGLN3 expression in astrocytes, either as a consequence of ageing and/or genetic traits, can generate a "hostile" pro-inflammatory environment for neuronal cells.

Objectives

This project will build on our recent discovery, highlighting TAGLN3 as a lead target candidate underlying a risk for sAD as a consequence of astrocytic immune dysfunctions. Thus, we will: aim#1) investigate how TAGLN3 regulates inflammation in astrocytes; #2) study the cellular and functional consequences of astrocytic TAGLN3 downregulation on neurons using in vitro models; #3) validate astrocytic TAGLN3 as a therapeutic target using in vivo models.

Methods

Aim#1. We will use genetic systems allowing fine modulations of endogenous TAGLN3 in human iPSC-astrocytes (e.g. dCas9-VPR and -KRAB). Astrocytes will be analysed by RNAseq to generate a transcriptomic view of the reactive cell states under TAGLN3 modulations. We will also determine the sequence of TAGLN3 responsible for its immunomodulatory function by transfecting TAGLN3 mutants.
Aim#2. We will use hiPSC-derived astrocytes-neurons co-cultures using microfluidics to evaluate how the experimental modulation of TAGLN3 in astrocytes impacts the neurons. We will also use iPSC-derived brain organoids. Imaging and biochemial analyses will be performed to assess parameters related to synaptogenesis, neuronal demise, inflammation and Aβ pathology.
Aim#3. We will generate and characterize a novel mouse model to evaluate whether Tagln3 loss-of-function, in astrocytes specifically, can predispose the brain for neurodegeneration under inflammatory situations. In parallel, the therapeutic potential of Tagln3 activation in astrocytes will be evaluated in AD mouse models using in vivo gene transfer.

Expected results

- Demonstrate that TAGLN3 modulations in astrocytes can predispose neurons to neurodegeneration through inflammatory dysfunctions.
- Validate astrocytic TAGLN3 as a potent new therapeutic target.

Feasibility

The host team is specialized in hiPSC-derived models, also has good experience with animal studies and has already developed unique tools to study TAGLN3. The host team is supported by a 4-year ANR research grant to work on TAGLN3.

Expected candidate profil

- Laboratory skills: cell culture (human iPS cells and their differentiation into neural derivatives 2D and 3D); mouse handling (brain injections, behavioral studies); Bioinformatics (RNAseq analyses); Imaging/Microscopy (e.g. confocal microscopy); biochemistry and molecular biology (e.g. ELISA, Western Blot). - Good theoretical background in neuroscience/neuropathology.

SUPERVISED PHDS & PUBLICATIONS : **NIVET Emmanuel**

- **Currently supervised PhD students**

- Pedro Belio-Mairal (acting as co-director. Lead PhD supervisor: Santiago Rivera)

- **Previously supervised PhD students**

- Laurie Arnaud (co-director. Director: Santiago Rivera) 08/2017 – 09/2021

- **Publications of previously 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. The Alzheimer's disease risk factor APOE4 drives pro- inflammation in human astrocytes via HDAC-dependent repression of TAGLN3. BioRxiv2021.04.16.440108. doi: https://doi.org/10.1101/2021.04.16.440108

Please, note that this paper (preprint) is under revision for *Cell Reports*

- Arnst N, Belio-Mairal P, García-González L, **Arnaud L**, Greetham L, Nivet E, Rivera S, DityatevA. 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.

PROJECT I12

Title : Combination between an injectable drug-loaded hydrogel and endurance training in rats with cerebral ischemia

Supervisor : RIVERA Claudio

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Co-supervisor : LAURIN Jérôme

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State of the art

A primary problem in stroke rehabilitation is the early closure of post-traumatic plasticity window, limiting recovery. The long-term cognitive deficits should be reduced by combining innovative pharmacological local treatments with physical exercise during this window (first 2 weeks in rats with stroke). Local treatment should be early administered when exercise is not yet possible for stroke patients because of early symptoms.
a) Local delivery of plasticity window reopening (PRW) agents. The use of synthetic hydrogel (biomaterials) to deliver therapeutic compound is now a promising strategy by controlling the progressive diffusion over days after a single injection, only in the targeted area (striatum). However, the effectiveness of injectable drug-loaded hydrogels remains unclear following stroke.
b) Endurance training after stroke. Training benefits on brain functions are associated with the release of neurotrophic/angiogenic factors promoting synaptic plasticity, neuronal survival and angiogenesis and GABAergic changes, potentially facilitating cognitive recovery. However, the most effective type of exercise promoting both these brain processes and cognition remains unclear.

Objectives

The purpose of this interdisciplinary project (neurosciences/exercise physiology and chemistry) is to improve cognitive functions after cerebral ischemia by using the combination of a novel biocompatible thermosensitive hydrogel (ICR) for PRW with clinically relevant post-stroke trainings in male and female middle-aged rats

Methods

Experimental protocols are approved by the Animal Care Committees of Marseille n°14.
a) Hydrogel. To determine the effectiveness of this new hydrogel for delivering Apelin (= higher effectiveness on neuronal excitotoxicity than other promising drugs from our in vitro preliminary results), it will be compared to the classical delivery systems (repeated intraperitoneal or intravenous injections). The hydrogel-apelin will be injected in the striatum within the first 24h to prevent lesion spreading over days when exercise is not possible.
b) Training. Ten individualized treadmill sessions perform in a clinically relevant manner for improving applications in humans.
c) Measurements at 2 weeks: Infarct volume, neurotrophins/GABAergic activity in the ipsi- and contralesional cortex and hippocampus and behavioral tests.

Expected results

Endurance+hydrogel combination might i) reduce the lesion area, ii) accentuate cognitive recovery, iii) promote suitable levels of neurotrophins in both injured and spared brain areas and iv) restore the chloride homeostasis, strongly disturbed after stroke and involved in cognitive deficits.

Feasibility

Researchers have the skills required for tMCAO surgery as well as molecular and behavioral procedures. Preliminary results on hydrogel brain injection were already performed by this team. Risk assessment: The in vivo hydrogel degradation and Apelin release might be slightly different than in vitro. Nevertheless, hydrogel degradation is easily controllable through polymers concentration. As each exercise intensity is individualized, it should be feasible for all rats.

Expected candidate profil

i) Surgery skills and rodent handling for behavioral tests. ii) Different molecular and cellular measurements. iii) Good level in statistics and English language. iv) Background in chemistry and polymer biomaterials would be welcome.

SUPERVISED PHDS & PUBLICATIONS : RIVERA Claudio

• **Currently supervised PhD students**

- Amandine CONSUMI

• **Previously supervised PhD students**

- Marine TESSIER - 2021
- Emmanuelle GOUBERT - 2017
- Nazim KOURDOUGLI - 2015

• **Publications of previously supervised PHD students**

- Bumetanide Prevents Brain Trauma-Induced Depressive-Like Behavior. Goubert E, Altvater M, Rovira MN, Khalilov I, Mazzarino M, Sebastiani A, Schaefer MKE, **Rivera C**, Pellegrino C.Front Mol Neurosci. 2019 Feb 5;12:12. doi: 10.3389/fnmol.2019.00012
- Protective Role of Low Ethanol Administration Following Ischemic Stroke via Recovery of KCC2 and p75NTR Expression. Khirug S, Soni S, Saez Garcia M, Tessier M, Zhou L, Kulesskaya N, Rauvala H, Lindholm D, Ludwig A, Molinari F, **Rivera C**.Mol Neurobiol. 2021 Mar;58(3):1145-1161. doi: 10.1007/s12035-020-02176-x
- Depolarizing γ-aminobutyric acid contributes to glutamatergic network rewiring in epilepsy. Kourdougli N, Pellegrino C, Renko JM, Khirug S, Chazal G, Kukko-Lukjanov TK, Lauri SE, Gaiarsa JL, Zhou L, Peret A, Castrén E, Tuominen RK, Crépel V, **Rivera C**.Ann Neurol. 2017 Feb;81(2):251-265. doi: 10.1002/ana.24870
- Pro-Brain-Derived Neurotrophic Factor (proBDNF)-Mediated p75NTR Activation Promotes Depolarizing Actions of GABA and Increases Susceptibility to Epileptic Seizures. Riffault B, Kourdougli N, Dumon C, Ferrand N, Buhler E, Schaller F, Chambon C, **Rivera C**, Gaiarsa JL, Porcher C.Cereb Cortex. 2018 Feb 1;28(2):510-527. doi: 10.1093/cercor/bhw385
- Detrimental effect of post Status Epilepticus treatment with ROCK inhibitor Y-27632 in a pilocarpine model of temporal lobe epilepsy. Kourdougli N, Varpula S, Chazal G, **Rivera C**.Front Cell Neurosci. 2015 Oct 23;9:413. doi: 10.3389/fncel.2015.00413

SUPERVISED PHDS & PUBLICATIONS : LAURIN Jérôme

• Currently supervised PhD students

- Nicolas HUGUES until December 2022

• Previously supervised PhD students

- Annabelle CONSTANS 2019
- Caroline PIN-BARRE 2017

• Publications of previously supervised PHD students

- **HUGUES N, PIN-BARRE** C, PELLEGRINO C, RIVERA C, BERTON E, LAURIN J. Time-dependent cortical plasticity during moderate-intensity continuous training versus high-intensity interval training in rats. Cerebral Cortex. (2022) doi: 10.1093/cercor/bhab451. (IF année de publication: 5.357).
- **HUGUES N**, PELLEGRINO C, RIVERA C, BERTON E, **PIN-BARRE C**, LAURIN J. Is High-Intensity Interval Training Suitable to Promote Neuroplasticity and Cognitive Functions after Stroke? Int J Mol Sci. (2021) Mar 16;22(6):3003. doi: 10.3390/ijms22063003. (IF année de publication: 5.93)
- **PIN-BARRE C; HUGUES N; CONSTANS A**; BERTON E; PELLEGRINO C; LAURIN J. Effects of Different High-Intensity Interval Training Regimens on Endurance and Neuroplasticity After Cerebral Ischemia. Stroke (2021); 52:00–00. DOI: 10.1161/STROKEAHA.120.031873. (IF année de publication: 7.9)
- TORRE MM, LANGEARD A, **HUGUES N**, LAURIN J, TEMPRADO JJ. Comparison of Three Physical—Cognitive Training Programs in Healthy Older Adults: A Study Protocol for a Monocentric Randomized Trial. Brain Sciences (2021); 11(1), 66. (IF année de publication: 3.332)
- **CONSTANS A, PIN-BARRE C**, MOLINARI F, TEMPRADO JJ, BRIOCHE T, PELLEGRINO C, LAURIN J. High-intensity interval training is superior to moderate intensity training on aerobic capacity in rats: Impact on hippocampal plasticity markers. Behavioural Brain Research 398 (2021) 112977. (IF année de publication: 3.10)
- PERTICI V, **PIN-BARRE C**, RIVERA C, PELLEGRINO C, LAURIN J, GIGMES D, TRIMAILLE T. Degradable and Injectable Hydrogel for Drug Delivery in Soft Tissues. Biomacromolecules. (2019). Doi: 10.1021/acs.biomac.8b01242. (IF année de publication: 5.738)
- **PIN-BARRE C**, PELLEGRINO C, LAURIN F, LAURIN J. Cerebral Ischemia Changed the Effect of Metabosensitive Muscle Afferents on Somatic Reflex Without Affecting Thalamic Activity. Frontiers in Physiology (2018). 29;9:638. (IF année de publication: 4,134)
- **PIN-BARRE C, CONSTANS A**, BRISSWALTER J, PELLEGRINO C, LAURIN J. Effects of High- Versus Moderate-Intensity Training on Neuroplasticity and Functional Recovery After Focal Ischemia. Stroke (2017). 117.017962. (IF année de publication: 6,032)
- **CONSTANS A*, PIN-BARRE C*,** TEMPRADO J.J, DECHERCHI P, LAURIN J. Influence of Aerobic Training and Combinations of Interventions on Cognition and Neuroplasticity after Stroke. Frontiers in Aging Neuroscience (2016). 48(6):1033-43. Review. (IF année de publication: 4,348). * first authors
- LAURIN J, **PIN-BARRE C**, BERNARD G, DOUSSET E, DECHERCHI P. Functional and Neuromuscular Changes after Anterior Cruciate Ligament Rupture in Rats. Medicine and Science in Sports and Exercise (2016). 48(6):1033-43. (IF année de publication: 4,14)

- **PIN-BARRE C**, LAURIN J. Physical Exercise as a Diagnostic, Rehabilitation, and Preventive Tool: Influence on Neuroplasticity and Motor Recovery after Stroke. Neural Plasticity (2015). 2015:608581. Review. (IF année de publication: 3,582)
- **PIN-BARRE C**, LAURIN J, FELIX MS, PERTICI V, KOBER F, MARQUESTE T, MATARAZZO V, MUSCATELLI-BOSSY F, TEMPRADO JJ, BRISSWALTER J, DECHERCHI P. Acute Neuromuscular Adaptation at the Spinal Level Following Middle Cerebral Artery Occlusion-Reperfusion in the Rat. PLOS one (2014). Volume 9, Issue 2, e89953 (IF année de publication: 3,73)
- PERTICI V*, **PIN-BARRE C*,** FELIX MS, LAURIN J, BRISSWALTER J, DECHERCHI P. A new method to assess weight-bearing distribution after central nervous system lesions in rats. Behavioural Brain Research (2014). 78– 84 (IF année de publication: 3,417). * first authors

PROJECT I13

Title : Investigating the role of striatum in learning and motivation processes of skilled behavior

Supervisor : ROBBE David

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LABORATORY WEBSITE : https://www.inmed.fr/en/en-avenir-dynamiques-neuronales-et-fonctions-des-ganglions-de-la-base

Co-supervisor : FINO Elodie

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LABORATORY WEBSITE : https://www.inmed.fr/en/en-avenir-dynamiques-neuronales-et-fonctions-des-ganglions-de-la-base

State of the art

Motor skills are essential for survival as they consist into refining and automatizing sequences of basic behaviors. Such skills range from learning how to approach a prey for animals to, for humans, using tools, riding a bicycle or playing an instrument. The dorsal striatum and its multiple cortical inputs is central in the development of skilled behaviors, with potentially different contributions. On one hand, the dorsal striatum is considered the locus of action selection and of the storage of motor skills through long-term plasticity of cortico-striatal connections. On the other hand, functional studies have suggested a role of the dorsal striatum and its targets in controlling the vigor of goal-directed motor sequences. Deciphering the contribution of striatal mechanisms responsible for vigor control and/or learning/remembering of motor skills will not only further the understanding of the behavioral function of the dorsal striatum but might provide valuable insight in regard of several prominent brain disorders at the interface between movement and motivation (Parkinson disease, OCD, addiction).

Objectives

1) Dissect the contribution of motivation and memory formation in the development of a motor skill
2) Characterize how the two components are encoded in corticostriatal circuits activity.
3) Examine how local (GABAergic microcircuits) or extrinsic (cortical and dopaminergic inputs) modulation affects motor skill learning and performance

Methods

1) The project is based on the accelerating rotarod training, a well-described behavioral task to probe motor skill learning. Mice have to walk/run on a rotating rod with increasing speed. Modulation of either the motivation of the mice or difficulty in motor learning will be tested by introducing rewards/punishments, or random or faster speeds.
2) In vivo two-photon calcium imaging will be performed to monitor dorsal striatum activity in animals trained with different behavioral conditions.
3) Chemogenetic manipulation of local GABAergic or dopaminergic circuits (DREADDs system) will be coupled to rotarod training and two-photon imaging.

Expected results

1) A quantitative understanding of motivational and motor memory contributions to skill formation
2) To associate specific striatal activity with the two different components
3) Evaluate the contribution of local and extrinsic modulation to motor skill learning and its neural implementation.

Feasibility

The project is designed with a simple behavioral task and the techniques are already implemented in the lab, ensuring first results in a short period of time. Ethical authorizations for the different protocols have been already validated so experiments can be started immediately. The team has ongoing grants and excellent track record to secure fundings.

Expected candidate profil

We are seeking candidates with a strong interest in integrative neuroscience approaches and animal behavior. Programming skills or previous experience in two-photon calcium imaging will be a bonus.

SUPERVISED PHDS & PUBLICATIONS : ROBBE David

- **Currently supervised PhD students**

- Thomas Morvan (3rd year, with DR)

- **Previously supervised PhD students**

- Nagham Badreddine (2017-2020, with EF)
- Mostafa Safaie (2016-2019, with DR)
- Laetitia Lalla (2014-2017, with DR)
- Carola Sales Carbonell (2012-2016, with DR)

- **Publications of previously supervised PHD students**

- Badreddine N, Z. G., Appaix F, Becq G, Tremblay N, Saudou F, Achard S and Fino E. Spatiotemporal reorganization of corticostriatal networks encode motor skill learning. In revision in Cell Reports.
- Safaie M, Jurado-Parras MT, Sarno S, Louis J, Karoutchi C, Petit LF, Pasquet MO, Eloy C and Robbe D. (2020) Turning the body into a clock: accurate timing is facilitated by simple stereotyped interactions with the environment. Current Biology
- Sales-Carbonell C, Taouli W, Khalki L, Pasquet M, Petit F, Moreau T, Rueda-Orozco PE and Robbe D. (2018) No discrete start/stop signals in the dorsal striatum of mice performing a learned action. Current Biology, 28(19): 3044:3055.
- Lalla L, Rueda Orozco PE, Jurado-Parras MT, Brovelli A and Robbe D. (2017) Local or not local: investigating the nature of striatal theta oscillations in behaving rats. eNeuro
- Sales Carbonell C, Rueda Orozco PE, Soria-Gomez, Buzsaki G, Marsicano G and Robbe D (2013) Striatal GABAergic and cortical glutamatergic neurons mediate contrasting effects of cannabinoids on cortical network synchrony. Proc Natl Acad Sci USA