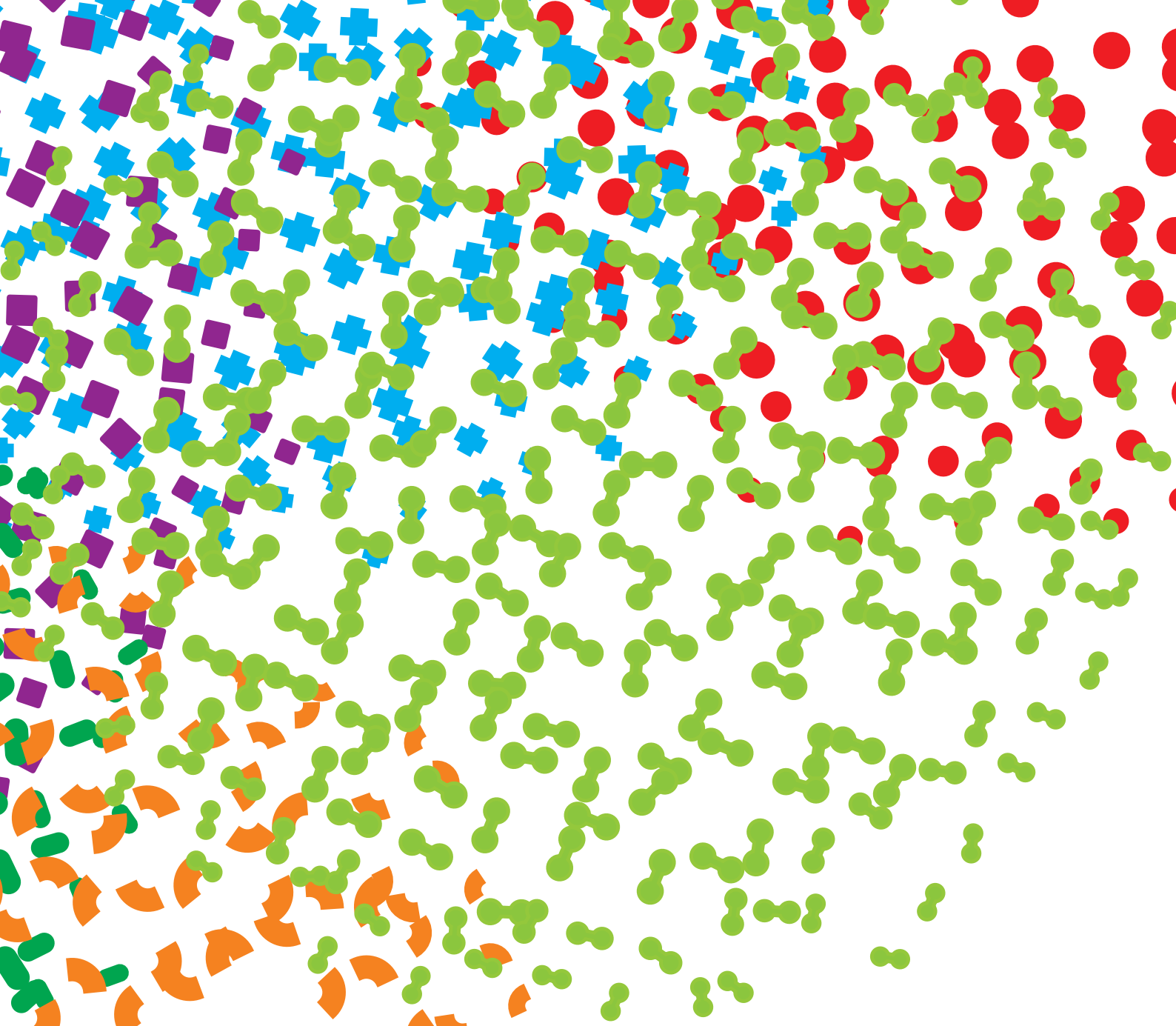


LabEx BRAIN

Activity report

2016/2017

INDEX

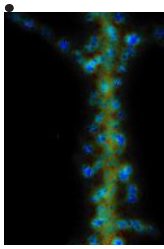
Overview

LabEx BRAIN is the Laboratory of Excellence (i.e. cluster of excellence) specialized in neuroscience in Bordeaux, headed by Daniel Choquet.

Thanks to the Investissement d'Avenir program, the LabEx BRAIN has obtained significant means to compete with its foreign counterparts and increase the international visibility of Bordeaux Neuroscience. The LabEx BRAIN project has received 20M€ of total funding until 2019. Its general ambition is to position our research community as a key player in the creation of new knowledge and the discovery of new treatments for neurodegenerative and psychiatric diseases at the European and global level. BRAIN also participates in the development of local employment with the emergence of start-ups, and is now becoming the reference for European training in neuroscience.

LabEx BRAIN's reputation and excellence allow for the accumulation of c.a. 10M€ of co-funds per year from various sources. This is a direct consequence of the considerable increase in the number of collaborative projects seeded by the LabEx. Indeed, the LabEx BRAIN supports about 10 new projects each year, 61 having been financially supported in total. Thanks to the core facility program, high-end technical equipment and qualified services are available to a variety of research disciplines, from molecular and cellular biology and cellular imaging up to animal and rodent behavior.

In order to connect basic research to societal issues, the transfer strategy developed within the LabEx BRAIN encourages the creation of new start-ups based on results and technologies emerging from BRAIN laboratories.



The **gradual work of including all Bordeaux Neurocampus teams within the LabEx BRAIN** community of excellence paid off in 2016 with the extension of the LabEx perimeter to all teams. This, along with the completion of the construction of the Broca building, resulted in a more united Bordeaux Neurocampus community.
A **common communication strategy** between Bordeaux Neurocampus and all the laboratories was conceived and implemented during 2016 to make 2017 "the year of the Neuroscience in Bordeaux", with events like the **international inaugural symposium**, gathering 25 of the world's leading neuroscientists, and **NeuroFrance 2017**, with more than 1,300 participants and 50 industrial exhibitors. Moreover, an in-depth communication study has been undergone to **homogenize the visual identities** of the institutes: the Bordeaux Neurocampus logo has been redesigned and serves as the basis for the logos of the laboratories.

Evolutions of LabEx BRAIN

2018

2017

30/11/2015

Re-election of LabEX BRAIN Director. Proposition of the Steering Committee:
to expand the LabEx BRAIN perimeter
To represent all laboratories at the steering committee

2016

Administration supervision committee

21/09/2016

LabEx BRAIN perimeter = **Bordeaux Neurocampus perimeter**

1st expansion of the call for projects:

- **One common evaluation procedure**
- Opening of a **non thematic axis**
- Possibility open to **all Bordeaux neurocampus researchers to apply**,
  - as partner for the thematic axes
  - as PI or partners to the non thematic axis

2015

Mid Term Evaluation

2/06/2015

2014

SAB

19/05/2014

2013

2nd expansion of the call for projects:

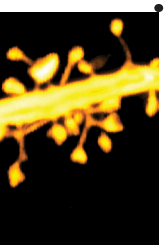
- Disappearance of the thematic axis
- **No distinction in the eligibility** critera between core and non core LabEx members

2012

2011

Launch

Initial perimeter restricted to A+ teams, except for:
- PhD extension Grant
- Symposium, Sabbatical Stay
- Facilities access



BRAIN also aims at developing major collaborations and large scale projects with other communities to further build its multidisciplinary actions. BRAIN maintains close relations with several other LabEx in Bordeaux, including the medical imaging community TRAIL, the clusters laser&optics Laphia and computation CPU. Strong links are built with international communities, based on existing collaborations, Associated International Laboratories (Optinutribrain nutrition et santé du cerveau, NutriNeuro and Université Laval (Québec), the signature of a Memorandum Of Understanding (MOU) with The Hotchkiss Brain Institute, Calgary, Canada and maintenance of close links with Bristol Neuroscience, the Neuroscience Department of the University of Bristol. The international influence of our community can also be measured by the immense success of the international call for applications for team leaders.

Research

Transversal projects ➔ (page 14)

From 2011 to 2018, LabEx BRAIN launched 5 calls for projects to deepen and expand Bordeaux Neurocampus collaborations. All projects involve partners from at least 2 different laboratories from Bordeaux Neurocampus. The evaluation criteria are based on the project significance, complementarity, multidisciplinary approach and innovation.

Clinical research projects ➔ (page 42)

2 calls were launched in 2015 and in 2017 to support transversal projects. It consists of financing clinical trials (physiological, pathophysiological, diagnostic or interventional therapeutic, industrial trials) in healthy or unhealthy subjects.

New team ➔ (page 45)

In 2014, LabEx BRAIN launched an international call for applications to set up a new team within the SANPSY unit.
The selected candidate received a competitive start-up package including running costs, equipments and salaries to set-up her team.

Core facilities ➔ (page 46)

10 core facilities are selected to be supported by the LabEx. The aim of this program is to offer high-end technical equipment and services to all Bordeaux Neurocampus teams at a reduced price. The IBISA labeling of 3 facilities testifies to the quality of this program.

Training

PhD Extension Grant ➔ (page 50)

The LabEx BRAIN offers students from Bordeaux a fellowship to complete their Ph.D thesis, immediately after a 3 year Ph.D, covering a period to finish their projects before leaving for a post-doc.

Bordeaux School of Neuroscience ➔ (page 61)

The LabEx BRAIN allowed the acquisition of all initial equipment for the creation of the Bordeaux School of Neuroscience.

Unique in Europe, the vocation of the Bordeaux School of Neuroscience is to offer the international/European Community a platform of high technological level, giving the opportunity to organize training for research in neuroscience based on experimental practice. The BSN has been selected by FENS/IBRO to be the major partner site of the Cajal Advanced Neuroscience Training Program.

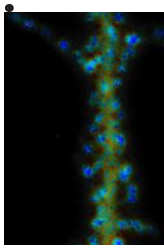
Dissemination

Applied research projects, Technological Transfer

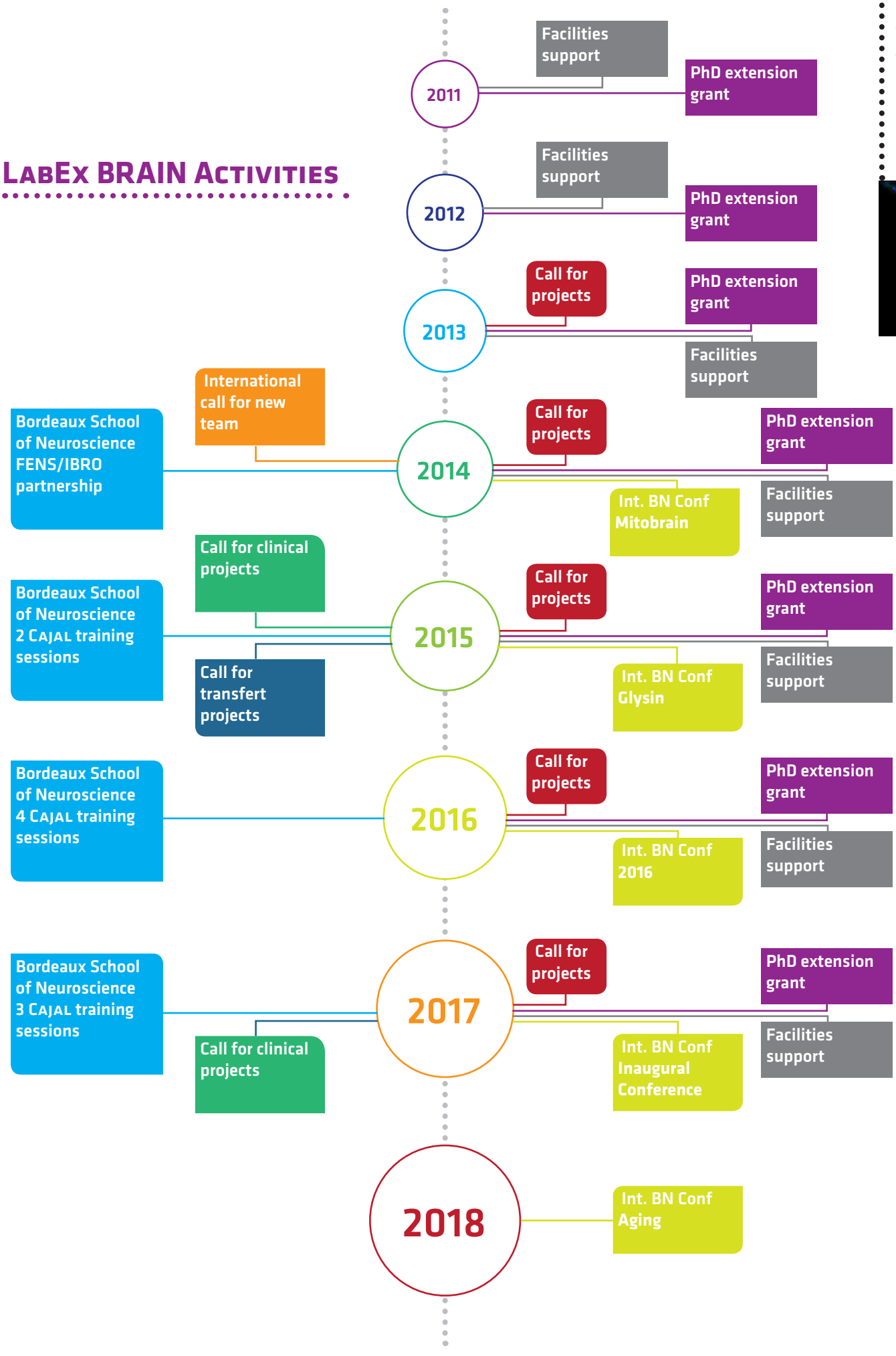
BRAIN launched a call in 2015 to support applied research projects with high potential economic impact. These projects include the discovery, development or optimization of innovative therapeutic or diagnostic products, as well as the promotion of research resources dedicated to the discovery of new therapies or diagnostic tools (in silico, cellular or animal screening methods).

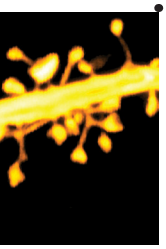
Knowledge transfer

The LabEx BRAIN supports symposiums organized in Bordeaux.
It is also implicated in popularization, such as conferences, debates, workshops for a general audience, in the context of "brain week" ("la semaine du cerveau") or the "science festival" ("la fête de la science")



LabEx BRAIN Activities





Related events

2011

2012

2013

2014

- Booth at FENS — Milan IT
- Inter-labex

2015

- Center of excellence BIND
- FHU Talisment
- Building of Broca

2016

- Booth at FENS — Copenhague DK
- Coordination EuBI training
- IBISA
- Groupe Leader International recruitement
- IdEx Bordeaux perpetuation

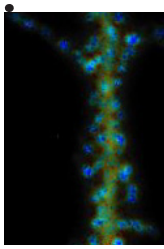
2017

- NeuroFrance
- Ecole universitaire de recherche
- Groupe Leader International recruitement

2018

- Booth at FENS — Berlin DE
- Groupe Leader International recruitement

2020



Highlight

Research

Increase in the number of collaborative projects

153 submitted and 61 projects supported

Attraction of a large amount of co-funds

>10M€ co-funds per year

International imaging excellence recognition

Selection of BIC within the European Infrastructure EuroBioImaging (EuBI)

Validation of the core facility program

3 IBISA certifications

Clinical excellence recognition

Certification (BIND) and the FHU (TALISMENT)

Training

International visibility

- The launch of the **Bordeaux School of Neuroscience**, in a partnership with FENS/IBRO
- The **EUR selection**
- Coordination of the EuBI Training working group

The large success of **PhD extension grant program**

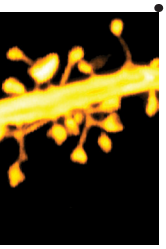
Dissemination

Technological transfer

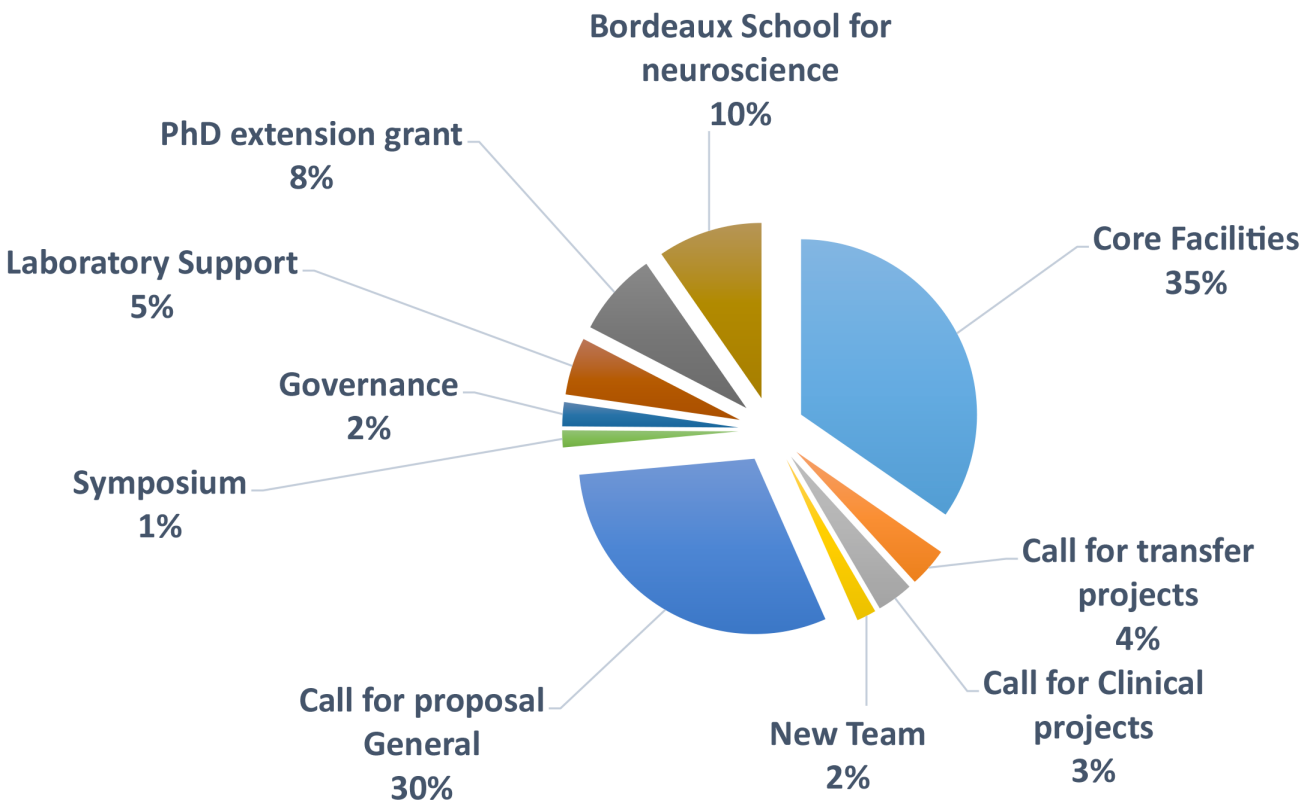
- 6 start-up will be hosted in Broca,
- 3 startups emanating directly from technology transfer from BRAIN labs

Success story

1 start-up raised 10M€ for clinical studies to develop a new treatment



Financial report



Research

- Scientific Projects
- New Team
- Core-Facilities

THEMATIC

MECHANISMS AND PATHOPHYSIOLOGICAL CONSEQUENCES OF THE DYNAMIC ORGANISATION OF SYNAPSES

Previous projects selected in 2013 to 2015

MEMBRANE DYNAMICS OF ASTROCYTIC GLUTAMATE TRANSPORTER AND ITS FUNCTIONAL IMPACT ON SYNAPTIC FUNCTIONS

Principal Investigator: Laurent Groc (IINS)	Partners: S. Oliet (NCM)

Murphy-Royal C, Dupuis JP, Varela JA, Panatier A, Pinson B, Baufreton J, Groc L*, Oliet SH*. Surface diffusion of astrocytic glutamate transporters shapes synaptic transmission. Nature Neurosci. 2015 Feb;18(2):219-26. *Equal contribution, co-corresponding.

MORPHO-FUNCTIONAL PLASTICITY OF THE TRIPARTITE SYNAPSE

Principal Investigator: Giovanni Marsicano (NCM)	Partners: V. Nägerl (IINS), S. Oliet (NMC)

ROLE OF NEURONAL AND ASTROGLIAL CB1 RECEPTORS IN MORPHO-FUNCTIONAL PLASTICITY OF THE TRIPARTITE SYNAPSE

Principal Investigator: Giovanni Marsicano (NCM)	Partners: V. Nagerl (IINS)

→ Publications

- Ruiz-Calvo A, et al. Pathway-Specific Control of Striatal Neuron Vulnerability by Corticostriatal Cannabinoid CB1 Receptors. Cereb Cortex. 2017 Oct 31:1-16.
- Busquets-Garcia A, et al. Representation-mediated Aversion as a Model to Study Psychotic-like States in Mice. Bio Protoc. 2017 Jun 20;7(12). pii: e2358
- Ruiz de Azua I, et al. Adipocyte cannabinoid receptor CB1 regulates energy homeostasis and alternatively activated macrophages. J Clin Invest. 2017 Nov 1;127(11):4148-4162.
- Piazza PV, Cota D, Marsicano G. The CB1 Receptor as the Cornerstone of Exostasis. Neuron. 2017 Mar 22;93(6):1252-1274.
- Busquets-Garcia A, et al. Pregnenolone blocks cannabinoid-induced acute psychotic-like states in mice. Mol Psychiatry. 2017 Nov;22(11):1594-1603.
- Hebert-Chatelain E, et al. A cannabinoid link between mitochondria and memory. Nature. 2016 Nov 24;539(7630):555-559.
- Busquets-Garcia A, et al. Peripheral and central CB1 cannabinoid receptors control stress-induced impairment of memory consolidation.Proc Natl Acad Sci U S A. 2016 Aug 30;113(35):9904-9.
- Colavita M, et al. Layer-specific potentiation of network GABAergic inhibition in the CA1 area of the hippocampus. Sci Rep. 2016 Jun 27;6:28454.
- Busquets Garcia A, et al. Cannabinoid receptor

type-1: breaking the dogmas. F1000Res. 2016 May 24;5. pii: F1000 Faculty Rev-990.
- Lutz B,, et al. The endocannabinoid system in guarding against fear, anxiety and stress. Nat Rev Neurosci. 2015 Dec;16(12):705-18.
- Soria-Gómez E, et al. CB1 Receptors Control the Expression of Aversive Memories. Neuron. 2015 Oct 21;88(2):306-13.
- Busquets-Garcia A, , et al. Dissecting the cannabinergic control of behavior: The where matters. Bioessays. 2015 Nov;37(11):1215-25.
- Oliveira da Cruz JF, et al. Astroglial type-1 cannabinoid receptor (CB1): A new player in the tripartite synapse. Neuroscience. 2016 May 26;323:35-42.
- Metna-Laurent M, Marsicano G. Rising stars: modulation of brain functions by astroglial type-1 cannabinoid receptors. Glia. 2015 Mar;63(3):353-64.

→ Co-funds

Funding agency: ANR
Name of the project: SUPERtri
Total amount: 536 720 €
Date and duration of the grant 01-04-2013 until 01-04-2016
Funding Agency : HFSP
Name of the Project : Mitochondrial G Protein signaling in astrocytes: a new player in the tripartite synapse
Total amount: 450.000 $
Date and duration of the grant 01-09-2014 until 31-10-2017

Additional grant obtained:
PhD fellowship from ENC, 09/2013 – 09/2016: Nanoscale imaging of the tripartite synapse in vivo
100 000 €
Equipe FRM (for Nägerl), starting 10/2016
400 000 €

New methods of aquisition and classification for high content screening of membrane receptor organization and dynamics using super-resolution microscopy

Principal Investigator: Jean-Baptiste Sibarita (IINS) | Partners: J.-P. Domenger (CPU)

→ Publications

- Beghin A, Kechkar A, Butler C, Levet F, Cabillic M, Rossier O, Giannone G, Galland R, Choquet D, Sibarita JB (2017) Localization-based super-resolution imaging meets high-content screening. Nat Methods 14:1184-1190.
- Single Molecule Localization Microscopy Symposium, Bordeaux (2015): Live super-resolution microscopy method meets high content screening approach, A. Beghin, A. Kechkar, C. Butler, D. Choquet, JB. Sibarita.

→ Co-funds

IdEx, program InterLabEx: 150 000€
LabEx CPU: 45 000€
Funding agencies
LabEx BRAIN, LabEx CPU, IdEx
Name of the project
SuperClass
Total amount
315 000€
Date of obtention and duration of the grant
2015, 2 years

Projects selected in 2016

Is the exosome secretion a new astrocyte-neuron communication pathway?

Principal Investigator: Alexandre Favereaux | Partners: A. Panatier (NCM)

→ Objectives of the project

Exosomes are small vesicles (50 – 200 nm) formed inside late endosomes that allow the transport and exchange of proteins, lipids and microRNAs between cells (Budnik et al., 2016). We investigate if exosome secretion is another pathway allowing astrocytes to support and regulate neurons during basal synaptic transmission and long-term synaptic potentiation (LTP). In addition, we will investigate if an alteration of this pathway participates to the development of Alzheimer's disease during which basal synaptic transmission and LTP are impaired.

Main results

We developped a specific tool to purify exosomes depending on their origin. To do that, we modified a well-known protein marker of exosomes, CD-63. We tagged this protein on its extra-vesicular loop with a peptide-tag and express it under the control of a cell-specific promoter. We are currently optimizing the expression of this molecular tool in neurons and astrocytes.In parallel, we established a robust HFS protocol to induce LTP in acute hippocampal brain slices.

Working plan to continue

First, we will optimize exosome isolation with magnetic beads covered with anti-tag antibodies.
Then we will analyse the protein and RNA content of these cell-specific exosomes with RNA-Seq and Mass spectrometry.
Finally, we will analyze the number and the content of astrocytic and neuronal exosomes in thecontext of LTP on acute hipocampal slices.

PCP SIGNALING CONTROL OF YOUNG NEURONS GROWTH: FROM NANOSCALE ANALYSIS TO DIRECTED MOTILITY

Principal Investigator: Mireille Montcouquio (NCM) | Partners: V. Studer (IINS)

Objectives of the project

Planar Cell Polarity (PCP) signaling comprises a number of transmembrane and cytosolic proteins acting together to modulate cytoskeleton dynamics, thus influencing cell shape and motility. Here, we want to identify the role and function of two PCP proteins during early phases of neuronal growth. We will address notably roles in cell adhesion, neuronal outgrowth, cytoskeleton motility and axonal guidance.

Main results

In 2017, we have hired 1 postdoc (S. Carvalho, Team Montcouquiol) to carry on the experiments. The results from Aim1 show almost opposite effects of the mutations of Gpsm2 and Vangl2 on neuronal outgrowth and actin dynamics, resulting in both cases in partial agenesis of the corpus callosum in the forebrain. Part of these results is now published; the other part is in preparation.

Working plan to continue

Regarding the evaluation of growth cone adhesion and axon guidance, we have used a patented micropatterning technique from V. Studer (LIMAP), combined with a biotin/avidin amplification system, to graft purified adhesion proteins on small dots surrounded by a cytophobic layer. We are validating the system with COS cells for the analysis of ligand/receptor interactions and will soon adapt it to study single molecule dynamics in primary neurons. We have modified our previously published microfluidic system for axonal guidance tests. It is now adapted to the multiwell format that we use for all our assays on cultured neurons. Preliminary axonal guidance experiments of dissociated hippocampal neurons in gradients of Slit1 are ongoing. After validation of a reliable guidance test we will start experiments on PCP protein mutants.

Published publications

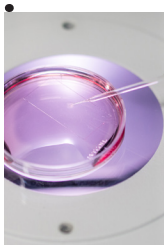
Defective Gpsm2/Gαi3 signalling disrupts stereocilia development and growth cone actin dynamics in Chudley-McCullough syndrome. Mauriac SA, Hien YE, Bird JE, Carvalho SD, Peyroutou R, Lee SC, Moreau MM, Blanc JM, Geyser A, Medina C, Thoumine O, Beer-Hammer S, Friedman TB, Rüttiger L, Forge A, Nürnberg B, Sans N, Montcouquiol M. Nat Commun. 2017 Apr 7;8:14907.

Publications in preparation

Steve Dos-Santos Carvalho, Esther Yeri Hien, Mikael Garcia, Ronan Peyroutou, Cedric Landmann, Nicolas Piguel, Deborah Anderson, Nathalie Sans, Olivier Thoumine, Mireille Montcouquiol. Vangl2 modulates neuronal outgrowth by controlling the interface between actin and N-cadherin.

Communications

- Organization of the Cajal course on Neuronal Trafficking and Cytoskeleton (C. Hoogenraad, O. Thoumine, and M. Souza). July 10-31 2016. Seminars by M. Montcouquiol and O. Thoumine.
- Seminar: Bordeaux Neurocampus Day, Bordeaux, April 2017.



- Seminar: 15th Meeting DRN Club (Club Développement des Réseaux Neuronaux), May 2017
- Dos Santos Carvalho S, Yeri E Y, Decroo M, Peyroutou R, Landmann C, Piguel N, Garcia M, Medina C, Henderson D, Sans N, Thoumine O, Montcouquiol M; Vangl2 affects neuronal ougrowth through a regulation of actin retrograde flow; Neurofrance 2017, Bordeaux, May 2017.
- Dos Santos Carvalho S, Yeri E Y, Decroo M, Peyroutou R, Landmann C, Piguel N, Garcia M, Medina C, Henderson D, Sans N, Thoumine O, Montcouquiol M; Vangl2 affects neuronal ougrowth through a regulation of actin retrograde flow; 5th International Symposium - Frontiers in Neurophotonics, Bordeaux, October 2017.

Identifying the Astrocytic Ca2+-signalling machinery governing synaptic plasticity

Principal Investigator: Stéphane Oliet (NCM)	Partners: V. Nägerl (IINS); F. Massa (NCM)

Objectives of the project

The objectives of the project are to identify the presence and functions of the IP3 receptor subtypes in astrocytes in the context of synaptic transmission and plasticity. Astrocytes release in a Ca2+-dependent manner active molecules known as gliotransmitters. This includes d-serine, an endogenous coagonist of NMDA receptors. The mechanism leading to the release of glia-derived D-serine, as well as other gliotransmitters, remains a subject of debate. The hypothesis we will test in this project is that several IP3R subtypes co-exist in astrocytes, generating distinct types of Ca2+ signals and subserving different functions.

Main results

The project started in 2017. We are currently developing tools to study astrocyte-neurons interactions under conditions where one sybtype of IP3R is genetically-ablated or pharmacologically inhibited. We are testing the consequences of such manipulations on Ca2 signaling and on the induction of NMDAR-dependent LTP in the hippocampus. Preliminary data indicate that blocking IP3R type 1 inhibit LTP induction, an effect that be rescue with exogenous D-serine. This result suggest that IP3R1, which was not suppose to be present nor functional in astrocytes, plays a role in D-serine release and the glial gating of NMDARs.

Working plan to continue

Once the tools developed, we will be able to test the role of each IP3R subtypes in gliotransmitter release. The genetic ablation will also provide the possibility to investigate the role of these astrocytic receptors during behavior. Through the ANR grant that was obtained in partnership with the lab of Pr Nagerl, we will also investigate the localization and distribution of the different IP3R subtypes in astrocytes using super-resolution mircoscopy. We will also study the distribution and dynamics of the endoplasmic reticulum (ER), the major source of intracellular Ca2+ in glial cells, at the vicinity of synaptic contacts.

Co-funds

- Additional grant obtained:

Funding agency: ANR
Name of the project: CASTRO
Total amount: 489 361,72 €
Date of obtention and duration of the grant
2017, Starting 2018, 4 years

- Talks:

Glial Biology: Functional Interactions Among Glia & Neurons, Gordon Research Conference, Ventura, USA March 5-10, 2017.
Astrocytic contributions to synaptic functions symposium, Mediterranean Neuroscience Society, 6th Conference, St-Julian, Malta, June 12-15, 2017.

- Seminars:

McGovern Institute for Brain Research, Peking University, Beijing, China, October 24, 2017
Faculté de Medecine Laënnec, Université de Lyon, November 23, 2017.

Projects selected in 2017

Optogenetic tuning of the synaptic excitation/inhibition balance though neurolgin phosphorylation

Principal Investigator: Mireille Montcouquiol (NCM)	Partners: O. Thoumine (IINS)

→ Objectives of the project

This project brings together two researchers from different Institutes, O. Thoumine (IINS), a biophysicist with strong knowledge of synaptogenic adhesion molecules, and F. Georges, an expert of in vivo electrophysiological recordings. The aim of the project is to examine the consequences of neuroligin (NLG) tyrosine phosphorylation on the excitation/inhibition balance, a crucial parameter of brain function in physio-pathological situations including autism spectrum disorders.

→ Main results

We use an optogenetic approach allowing the spatial and temporal control of NLG1 phosphorylation base on light-gated receptor tyrosine kinases (optoFGFR1). Using organotypic hippocampal slices combined to single cell electroporation of optoFGFR1, we have shown robust increases in dendritic spine number and evoked AMPA receptor mediated currents in CA1 neurons, upon light-induced NLG phosphorylation for 24 h with 470 nm light emitting diode (LED) arrays. These effects are specific for NLG1 since they are not observed in preparations from NLG1 KO mice.

→ Working plan to continue

Encouraged by our ex-vivo results, we will produce adenoviruses coding for optoFGFR1 with a TdTomato reporter. We will inject them in the mouse hippocampus, then stimulate NLG phosphorylation by light for several hours using a cannula bearing an optical fiber, and record excitatory field potentials in anesthetized animals. We expect a potentiation of excitatory synapses through the selective recruitment of AMPA receptors stimulated by NLG1 phosphorylation.

→ Additional grant obtained

Funding agency: ANR/FWF
Name of the project: SynThe Syn: Optical control of synaptic function via adhesion molecules.
Total amount: 325 k€
Date of obtention and duration of the grant: November 2017 (final decision pending January 2018), 3 years.

→ Publications in preparation

Letellier et al. Optogenetic control of excitatory synapse differentiation through the tyrosine phosphorylation of neuroligin-1.

→ Communications

O. Thoumine, invited conferences and seminars
1. The neuronal surfaceome in circuit formation, Anzola (Italy), July 10-11, 2017.
2. EMBO conference "Cell Biology of the Neuron", Fodele (Greece) May 7-10, 2017.
3. Institute for Science and Technology Austria, Vienna (Austria) March 31, 2017.
4. King's college (London), November 16, 2017.
M. Letellier (talk selected from abstracts)
5. Synapse formation, specification, and Elimination: from molecules to Circuits, Baeza (Spain) September 25-27, 2017.

Nanoscale imaging of synaptic molecules in braine slices

Principal Investigator: Jean-Baptiste Sibarita (IINS)	Partners: N. Sans (NCM)

Mechanisms underlying glycine compartmentalization in the extracellular space: identification and functional role

Principal Investigator: Laurent Groc (IINS)	Partners: S. Oliet (NCM), Castanon (Nutrineuro)

THEMATIC

INTEGRATIVE PHYSIOLOGY OF SYNAPSES AND NEURONAL NETWORKS

Previous projects selected in 2013 to 2015

PROGRAMMING SUPPORT FOR HYBRID SYSTEMS APPLICATIONS

Principal Investigator: Daniel Cattaert (INCIA) | Partners: G.Lemasson (NCM), D. Cattaert (INCIA)

Publications

Sieling F, Bédécarrats A, Simmers J, Prince AA, Nargeot R (2014). Differential roles of nonsynaptic and synaptic plasticity in operant reward learning-induced compulsive behavior. Curr. Biol. 24(9) :941-950.

Nargeot R., Bédécarrats A. (2017). Electrical synapses and learning-induced plasticity in motor rhythmogenesis. In "Nework functions and plasticity". Ed. J. Jing. Elsevier Academic Press, USA.

IMPACT OF PLANAR POLARITY ON SHAPING NEURONS AND SYNAPSES

Principal Investigator: Mireille Montcouquiol (NCM) | Partners: O. Thoumine (IINS)

Published publications

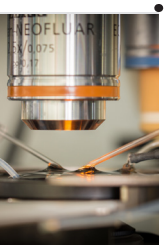
Defective Gpsm2/Gαi3 signalling disrupts stereocilia development and growth cone actin dynamics in Chudley-McCullough syndrome. Mauriac SA, Hien YE, Bird JE, Carvalho SD, Peyroutou R, Lee SC, Moreau MM, Blanc JM, Geyser A, Medina C, Thoumine O, Beer-Hammer S, Friedman TB, Rüttiger L, Forge A, Nürnberg B, Sans N, Montcouquiol M. Nat Commun. 2017 Apr 7;8:14907.

Publications in preparation

Steve Dos-Santos Carvalho, Esther Yeri Hien, Mikael Garcia, Ronan Peyroutou, Cedric Landmann, Nicolas Piguel, Deborah Anderson, Nathalie Sans, Olivier Thoumine, Mireille Montcouquiol. Vangl2 modulates neuronal outgrowth by controlling the interface between actin and N-cadherin.

Communications

- Organization of the Cajal course on Neuronal Trafficking and Cytoskeleton (C. Hoogenraad, O. Thoumine, and M. Souza). July 10-31 2016. Seminars by M. Montcouquiol and O. Thoumine.
- Seminar: Bordeaux Neurocampus Day, Bordeaux, April 2017.
- Seminar: 15th Meeting DRN Club (Club Développement des Réseaux Neuronaux), May 2017
- Dos Santos Carvalho S, Yeri E Y, Decroo M, Peyroutou R, Landmann C, Piguel N, Garcia M, Medina C, Henderson D, Sans N, Thoumine O, Montcouquiol M; Vangl2 affects neuronal ougrowth through a regulation of actin retrograde flow; Neurofrance 2017, Bordeaux, May 2017.
- Dos Santos Carvalho S, Yeri E Y, Decroo M, Peyroutou R, Landmann C, Piguel N, Garcia M, Medina C, Henderson D, Sans N, Thoumine O, Montcouquiol M; Vangl2 affects neuronal ougrowth through a regulation of actin retrograde flow; 5th Internaltional Symposium - Frontiers in Neurophotonics, Bordeaux, October 2017.



Unraveling the anatomical wiring diagram to understand the physiology and pathophysiology of the hippocampus and neocortex

Principal Investigator: Christophe Mulle (IINS) | Partners: A. Frick (NCM)

→ Publications

Viana da Silva, S., Haberl, M.G., Zhang, P., Bethge, P., Lemos, C., Gonçalves, N., Gorlewicz, A., Malezieux, M., Gonçalves, F.Q., Grosjean, N., Blanchet, C., Frick, A., Nägerl, U.V., Cunha, R.A., Mulle, C., 2016. Early synaptic deficits in the APP/PS1 mouse model of Alzheimer's disease involve neuronal adenosine A2A receptors. Nature Communications 7, 11915. doi:10.1038/ncomms11915.

Haberl, M.G., Viana da Silva, S., Guest, J.M., Ginger, M., Ghanem, A., Mulle, C., Oberlaender, M., Conzelmann, K.-K., Frick, A., 2015. An anterograde rabies virus vector for high-resolution large-scale reconstruction of 3D neuron morphology. Brain Struct Funct 220, 1369–1379. doi:10.1007/s00429-014-0730-z.

Role of planar polarity proteins in the cytoskeleton dynamics of dendritic spines

Principal Investigator: Nathalie Sans | Partners: G. Giannone (IINS)

→ Co-funds

Funding agency: ANR 2016
Name of the project NanoPlanSYN
Total amount : 545990 K€

Funding agency:
Project selected for phase II by ANR 2016
Name of the project NanoPlanSYN
Total amount requested 633 K€

Comparison of the plastic properties of adult-born and developmentally-born granule dentate neurons

Principal Investigator: Nora Abrous | Partners: C. Mulle (IINS)

Functional characterization of a dopaminergic projection to the bed nucleus of the stria terminalis during aversive learning

Principal Investigator: François Georges | Partners: C. Herry (NCM)

→ Publications

- Kaufling J., Girard D., Maitre M, Leste-Lasserre T., Georges F. Species-specific diversity in the anatomical and physiological organization of the BNST-VTA pathway. doi: 10.1111/ejn.13554
- Glangetas C*, Massi L*, Fois G.R. *, Jalabert M., Girard D., Diana M., Yonehara K., Roska B., Xu C., Lüthi A., Caille S. Georges F. NMDA-receptor-dependent plasticity in the bed nucleus of the stria terminalis triggers long-term anxiolysis. Nat Comm. 2017 Nat Commun. 2017 Feb 20;8:14456. doi: 10.1038/ncomms14456.
- Fois G.R. , Guillaumin, A., Ducrot, C., Doudnikoff, E., Girard, D., Bezard, E., Valjent E, Georges F. Origin and function of the dopaminergic innervation of the Juxta-capsular nucleus of the BNST. In preparation.

→ Co-funds

2017 ANR call. under evaluation

Neuronal circuits of contextual fear

Principal Investigator: Yann Humeau (IINS) | Partners: Cyril Herry (NCM)

Published publications

Zhang, C.L., Houbaert, X., Lepleux, M., Deshors, M., Normand, E., Gambino, F., Herzog, E., & Humeau, Y. (2014) Hippocampal projections to basolateral amygdala control contextual fear memory expression. Brain Structure and function, DOI: 10.1007/s00429-014-0882.

Publications in preparation

- Aincy M, Zhang C.L., Aime M., Houbaert X., Humeau Y., Herry C. Long range inhibitory prefrontal projections controls both PAG neuronal activity and fear behavior.
- Prefrontal-Periaqueductal Gray-Projecting Neurons Mediate Context Fear Discrimination.
- Rozeske RR, Jercog D, Karalis N, Chaudun F, Khoder S, Girard D, Winke N, Herry C.
- Neuron. 2018 Feb 21;97(4):898-910.e6. doi: 10.1016/j.neuron.2017.12.044. Epub 2018 Feb 3.

Modulation of synaptic calcium signaling by mitochondrial type 1 cannabinoid receptor

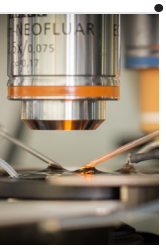
Principal Investigator:Sandrine Pouvreau (IINS) | Partners: F. Massa (NCM)

Publications

- Serrat R, Robin LM, Panatier A, Mulle C, Massa F, Pouvreau S, Marsicano G. Modulation of astroglial calcium signaling by mitochondrial type 1 cannabinoid receptor The international Astrocyte School 2017. Gliotransmission in health and disease. Bertinoro (FC) (Italy), 26th March-1April, 2017. Talk
- Serrat R, Robin LM, Panatier A, Mulle C, Massa F, Pouvreau S, Marsicano G. Modulation of astroglial calcium signaling by mitochondrial type 1 cannabinoid receptor Symposium on Metabolic and Redox Interactions between Neurons and Astrocytes in Health and Disease. Insternational Society for Neurochemistry. Salamanca (Spain), 28th June 2017. Poster presentation.
- Serrat R, Robin LM, Panatier A, Mulle C, Massa F, Pouvreau S, Marsicano G. Modulation of astroglial calcium signaling by mitochondrial type 1 cannabinoid receptor Gordon Research Conference on Cannabinoid Function in the CNS. Waterville Valley NH (United States) 20-25th August, 2017. Poster presentation.

Co-funds

An additional grant was obtained by the host laboratory of Federico Massa to continue the investigation of the role of mtCB1 in synaptic function and dysfunction
Funding agency: FRM
Name of the project : Role du recepteur mitochondrial aux canabinoides de type-1 (mtCB1) dans la schizophrenie et les symptomes psychotiques.
Total amount: 110 000 euros
Date of obtention and duration of the grant: 1 march 2016
Duration: 3 years.



Projects selected in 2016

Cellular mechanisms underlying hippocampal regulation of feeding behavior

Principal Investigator: Mario Carta (IINS)	Partners: G. Ferreira (Nutrineuro), A. Busquets-Garcia, (NCM)

Objectives of the project

It has been proposed that cortical areas, such as the hippocampus, may provide a «cognitive» control of food intake, through the activation of circuits and synaptic mechanisms similar to those involved in learning and memory processes. The main goal of this project is to elucidate the cellular and anatomical mechanisms underlying the implication of hippocampal circuits in the regulation of feeding behavior.

Main results

At first we aimed to directly test whether feeding behavior could be altered by controlling hippocampal activity. To inhibit the hippocampus we decided to activate parvalbumin (PV) GABAergic interneurons. To this end we injected cre-dependent excitatory Gq-DREADDs in the whole hippocampus of PV-cre mice and we monitored their activity and food consumption following the injection (i.p.) of the DREADDs activator CNO. We found that inhibition of the hippocampus leads to an increased food consumption during ad libitum food access, without altering the overall locomotion. These data support the hypothesis that hippocampus influences feeding behavior.

Working plan to continue

As future experiments, using pharmacogenetic and optogenetic viral tools, pharmacological inactivation, tracing approaches and slice electrophysiology we will investigate 1) which specific sub regions (DG, CA3 and CA1) or parts (dorsal, ventral) of the hippocampus are involved in controlling feeding behavior, 2) whether manipulation of other classes of hippocampal interneurons also modulate feeding, 3) finally, which are the downstream brain regions of the hippocampus involved in food intake.

Neuronal circuits of fear conditioned analgesia

Principal Investigator: Pascal Fossat (IINS)	Partners: C. Herry (NCM)

Objectives of the project

Aim 1 : Role of dedicated neuronal subpopulation of the vlPAG in Fear Conditioned Analgesia.

Aim 2 : Contribution of dedicated neuronal subpopulation in the vlPAG circuits.

Aim 3 : Role of dedicated neuronal subpopulation in descending control of pain.

Aim 4 : Deciphering cortical inputs that modulate PAG network during FCA.

Main results

- We developed a behavioural paradigm to elicit fear conditioned analgesia (FCA) in mice.
- We show that the optogenetic activation of somatostatin interneurons (SST-interneurons) specifically in the ventrolateral periaqueductal grey (vlPAG) suppresses FCA.
- We show that inhibition of SST-interneurons induces analgesia.
- Optogenetic manipulation of SST-interneurons modifies pain transmission.
- Optogenetic manipulation of SST-interneurons alters neuronal response to nociceptive inputs in the dorsal horn of the spinal cord.

Working plan to continue

- To identify brain regions and cell types targeting SST-interneurons in the context of FCA.
- Analyse vlPAG microcircuits involved in nociception and the role of SST-interneurons in the local microcircuit.
- To identify long-range circuits that allow SST-interneurons to control pain transmission in the dorsal horn of the spinal cord.

Publications in preparation

- vlPAG SST-interneurons control neuronal circuit involved in fear-induced analgesia. Winke N, Aby F, Jercog D, Landry M, Fossat P*, Herry C* and Valerio S*
- vlPAG SST-interneurons modulate nociceptive transmission through control of spinal nociceptive neurons. Aby F, Wincke N, Landry M, Herry C, Valerio S* and Fossat P*.

Communications

NeuroFrance : 2 posters :

■ Neural correlates of fear conditioned analgesia. Winke N, Jercog D, Aby F, Fossat P, Valerio S.*1, Herry C.*1

■ «SOM neurons of the ventro-lateral periqueductal grey modulate WDR neurons response to nociceptive inputs in the spinal cord».

Stéphane Valerio, Franck Aby, Nanci Winke, Jercog Daniel, Marc Landry, Cyril Herry, Pascal Fossat

Gordon Conference : 1 poster

■ Neural correlates of fear conditioned analgesia. Winke N, Jercog D, Aby F, Fossat P, Valerio S, Herry C.

Dopaminergic control of neuronal networks dynamics during goal-directed behaviors

Principal Investigator: Nicolas Mallet (IMN)	Partners: iF. Gambino (IINS)

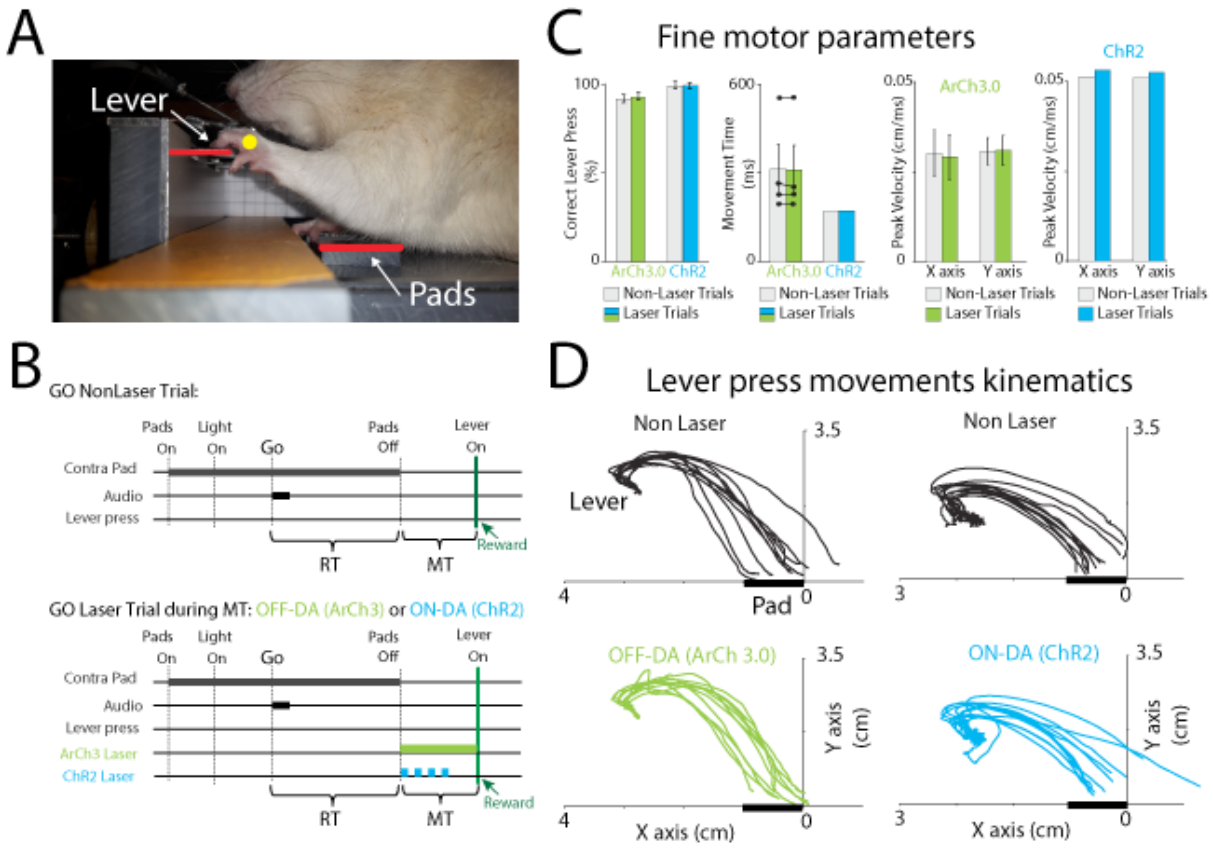
Objectives of the project

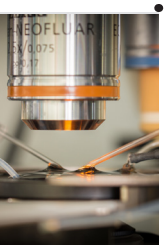
The dopamine is a key neurotransmitter in the brain but its cellular effect and contribution to motor behavior has not been defined precisely. Here, the objective of the project was to better understand the impact of dopamine on neuronal networks and its function during both behavioral learning and movement control. Both team (Mallet and Gambino) interacted to design relevant and similar behavioral task in rats (Mallet) or mice (Gambino).

Main results

We first developed and tested an optogenetic strategy to selectively manipulate (either excite: 'ON-DA' or inhibit 'OFF-DA') the release of dopamine in transgenic TH-Cre rats or mice. We then tested the behavioral effect of these brief (<300msec) optogenetic manipulations during fine movement control in rats trained to performed a skilled lever press task. Surprisingly, dopamine manipulation had no major impact on fine motor parameters or movement kinematics (see figure 1, team Mallet). Besides, we implemented

Figure 1: Effect of Dopamine manipulation on fine motor control, team Mallet.





the behavioral paradigm to test the learning of a motor task in mice (see figure 2, team Gambino).

→ Working plan to continue

These results go against the current thinking that dopamine is important for online movement control on a short time scale. Because the chronic loss of dopamine induce movement deficit such as Parkinson's disease, we are now planning to define the temporal window on which dopamine manipulation will impair motor control. Also, we will test whether dopamine neurotransmission is more important during the learning phase of a motor behavior or its maintenance in time rather than its pure execution (see figure 2).

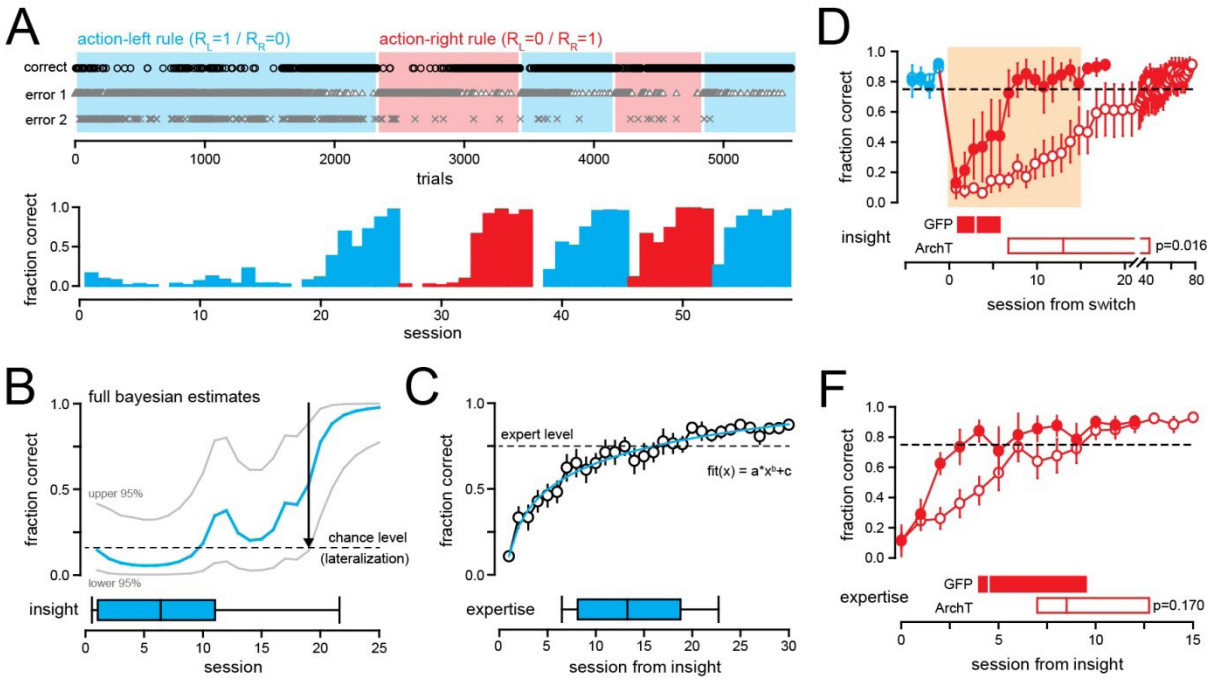
→ Additional grant obtained

(Frederic Gambino obtained an ERC starting grant (2016-2021)

→ Co-funds

Additional grant obtained: Funding agency ERC
Name of the project
Total amount 1 500 000€
Date of obtention and duration of the grant 2016-2021

Figure 2: Effect of Dopvamine manipulation on behavioral learning, team Gambino.



Exploring the vulnerability of the dopaminergic synaptic membrane to lipid manipulations: from molecular origin to behavioral consequences

Principal Investigator: Pierre Trifilieff (Nutrineuro)	Partners: E. Herzog (IINS)

→ Objectives of the project

This project aims at unraveling the molecular origin of the unique sensitivity of the dopaminergic neurotransmission to n-3 polyunsaturated fatty acid (PUFAs) variations. The goal is to establish the lipidome and proteome of the dopaminergic synapse compared to the glutamatergic one within the ventral striatum and assess whether selective PUFA manipulation at the dopaminergic synapse is sufficient to induce functional alterations in reward processing.

→ Main results

To date, we have managed to successfully sort fluorescently labeled dopaminergic and glutamatergic synaptosomes from the nucleus accumbens of mice and started establishing the relative proteomes of these synapses. We showed, using a transgenic approach, that a decrease in n-3 PUFA levels selectively in dopaminergic and dopaminoceptive neurons (pre- and postsynapse) is sufficient to induce deficits in motivation.

Working plan to continue

- Establish the proteome of dopaminergic synapses and compare protein composition between n-3 PUFA conditions.
- Optimize our synapse sorting approach to establish the lipidome of the dopaminergic and glutamatergic synapses.
- Assess the respective influence of PUFA alteration in pre- and postsynaptic compartments of the dopaminergic synapse on motivation.

Additional grant obtained

Funding agency: ANR
Name of the project: SynLip
Total amount: 300 000€
Date and duration: September 2016 – 4 years

Publications

Schreiner D, Savas JN, Herzog E, Brose N & de Wit J
Synapse biology in the 'circuit-age'-paths toward molecular connectomics.
Curr Opin Neurobiol, 2016, 42: 102–110

Publications in preparation

Véronique De-Smedt-Peyrusse, Laetitia Darriet, Pierre Trifilieff, Etienne Herzog, Maria Florencia Angelo.
Subcellular fractionation of brain tissue from small tissue explants.
Sous presse. ouvrage: Synaptosome methods and applications. Springer Protocols Neuromethods Series.

Communications

Communications orales:

- Herzog E. Frontiers in Neurophotonics. Bordeaux. France. October 2017.
  Exploring the molecular diversity of central synapses ex-vivo using a cell sorter.
- Herzog E. Université de Bonn. Bonn. Allemagne September 2017.
  Exploring the molecular diversity of central synapses in mice.
- Herzog E. NeuroFrance2017. Bordeaux. France. May 2017.
  Molecular analysis of selected central synapses in physiology and pathology in mice.
- Trifilieff P. Journées Francophones de Nutrition. Nantes. France. December 2017.
  Impact of n-3 PUFA deficiency on the brain reward system: relevance for mental health.
- Trifilieff P. Mini-symposium Circuit Development, Dynamics and Cognition. Bordeaux. France. December 2017.
  Modulation of dopamine transmission by membrane lipid composition: from receptor signaling to reward processing.
- Trifilieff P. French Neuroscience Meeting. Bordeaux. France. May 2017.
  Modulation of dopamine signaling by brain lipid composition: relevance for schizophrenia?
- Trifilieff P. Center for Addiction Research, Medical University of Vienna. Vienna. Austria. November 2016.
  Modulation of the reward system by lipids: relevance for psychiatric disorders.

Projects selected in 2017

Role of AMPA receptor mobility in hippocampal spatial coding and learning

Principal Investigator: Yann Humeau (IINS)	Partners: B. Bontempi (IMN)

Objectives of the project

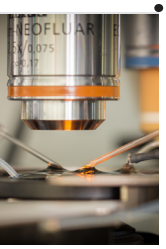
AMPA-MO aims at uncovering the fundamental mechanisms by which AMPAR mobility is involved in spatial memory consolidation. We are combining in vitro and in vivo approaches in order to examine the functional consequences of AMPAR immobilization onto synaptic and network activities in the dorsal hippocampus and the prefrontal corte.

Main results

We have obtained evidences that spatial memory consolidation is affected by AMPAR X-linking in the dHPC. We have setup an in vitro preparation that allows recording from sharp wave ripples activity, together with manipulations of synaptic plasticity and AMPAR X-linking. An automatized Y-maze is currently under construction.

Working plan to continue

We are starting in vivo recordings in both dHPC and mPFC to measure the frequency of SWRs in vivo in a behaving animal. In vitro experiments will now focus on the interaction between synaptic plasticity and SWRs frequency.



Additional grant obtained

An Equipe FRM (to YH) has reached the second round. An ERC grant to Daniel Choquet includes part of this objective. An ANR grant coorinated by DC will not be proposed to the second round although being selected.

Communications

YH did an internal IINS meeting on the AMPA-MO-CO progresses the 1st of March 2018. Two posters will be presented at the FENS meeting in July 2018 in Berlin.

THEMATIC

MOLECULAR BASIS OF THE TRANSITION TO ADDICTION

Previous projects selected in 2013 to 2015

IDENTIFYING THE CONTRIBUTION OF DISTINCT NEURONAL CIRCUITS IN THE ENCODING OF AFFECTIVE MEMORIES AFTER DRUG WITHDRAWAL

Principal Investigator: Martine Cador (INCIA)

→ Publication

Dejean C, Sitko M, Girardeau P, Bennabi A, Caillé S, Cador M, Boraud T, Le Moine C. Memories of Opiate Withdrawal Emotional States Correlate with Specific Gamma Oscillations in the Nucleus Accumbens. Neuropsychopharmacology. 2017 Jun ; 42(7) : 1558. doi: 10.1038/npp.2017.46.

→ Co-funds

Funding agency: FRM Innovative project

Name of the project: Neural networks and synchronization in addiction: development of multi-sites multi-unit recordings in behaving animals
Amount: 80 000 € for an IE in signal processing;
Date and duration of the grant: Nov 2013 for 2 years

Funding agency: FRM Physiopathology of Addiction
Name of the project: Affective memories in drug addiction: differentiation of context versus CS effects in the coding and retrieval of opiate withdrawal memory
Total amount: 220 000 €;
Date and duration of the grant: Jan 2015 for 3 years.

PSYCHOBEHAVIORAL CHARACTERIZATION OF ADDICTION

Principal Investigator: Daniela Cota (NCM) | Partners: P. Philip (SanPsy)

Aouizerate B, Gouzien C, Doumy O, Philip P, Semal C, Demany L, Piazza PV*, Cota D*. A new computer-based tool for the objective measurement of hedonic and motivational states in humans. BMC Psychology 2014, 2:23

→ Publication in preparation

Gouzien C, Delhaye D, Cherifi B, Tabarin A, Philip P, Piazza PV, Cota D, Aouizerate B. A new method of characterization of motivation for food in obesity. Relationships with the endocannabinoid system.

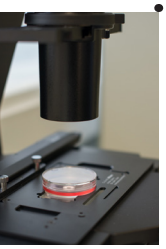
→ Co-funds

Funding agency: Fond Français Alimentation-Santé

Name of the project: A new method of characterization of pleasure for food in obesity. Relationships with the endocannabinoid system.

Total amount: 45000 €

Date and duration of the grant: August 2013 – Duration: 2 consecutive years (renewed for one additional year).



Characterization of molecular pathways in vulnerability to drug addiction

Principal Investigator: Jean-Michel Revest (NCM)

Publication:

- Devroye C, Cathala A, Haddjeri N, Rovera R, Vallée M, Drago F, Piazza PV, Spampinato U. Differential control of dopamine ascending pathways by serotonin2B receptor antagonists: New opportunities for the treatment of schizophrenia. Neuropharmacology. 2016; 109:59-68.
- Devroye C, Haddjeri N, Cathala A, Rovera R, Drago F, Piazza PV, Artigas F, Spampinato U. Opposite control of mesocortical and mesoaccumbal dopamine pathways by serotonin2B receptor blockade: Involvement of medial prefrontal cortex serotonin1A receptors. Neuropharmacology. 2017;119: 91-99.
- Devroye C, Cathala A, Piazza PV, Spampinato U. The central serotonin2B receptor as a new pharmacological target for the treatment of dopamine-related neuropsychiatric disorders: Rationale and current status of research. Pharmacol Ther. 2017 Jul 27. pii: S0163-7258(17)30194-8. doi: 10.1016/j.pharmthera.2017.07.014. [Epub ahead of print] Review.

Probing the role of dedicated valuation neuronal circuits in the development of pathological decision making in addicted individuals

Principal Investigator: Serge Ahmed (IMN)

Publication

- Vandaele Y, Cantin L, Serre F, Vouillac-Mendoza C & Ahmed SH (2016) Choosing under the influence: a drug-specific mechanism by which the setting controls drug choices in rats. Neuropsychopharmacology 41:646-57.
- Keramati M., Durand A., Girardeau P., Gutkin B.S. & Ahmed S.H. (2017) Cocaine addiction as a homeostatic reinforcement learning disorder. Psychological Review 124:130-153.

Publications in preparation

- Girardeau P, Navailles S, Durand A, Vouillac-Mendoza C, Guillem K & Ahmed SH (2017) Discovery of an unsuspected cause for persistent vulnerability to relapse despite complete extinction of cocaine craving. In preparation.
- Navailles S, Vandaele Y, Durand A, Guillem K & Ahmed SH (2017) Large-scale Fos mapping of preference for sweet reward over cocaine in rats. In preparation

Co-funds

Additional grant obtained:
Fondation pour la Recherche Médicale
Pathological decision-making in cocaine addiction: causal role of orbitofrontal neuronal activity
284 000 €
November 2014, 3 years.

Measures of motivational and hedonic states in rats

Principal Investigator: Martine Cador (INCIA)

Publication:

- Naneix F, Darlot F, Coutureau E, Cador M, Long-lasting deficits in hedonic and nucleus accumbens reactivity to sweet rewards by sugar overconsumption during adolescence, European Journal of Neuroscience, 43, 671-680, 2016.
- Naneix F, Darlot F, De Smedt-Peyrusse V, Pape JR, Coutureau E, Cador M. Protracted motivational dopamine-related deficits following adolescence sugar overconsumption. Neuropharmacology. 2018 Feb;129:16-25. doi: 10.1016/j.neuropharm.2017.11.021. Epub 2017 Nov 13

Co-funds:

Funding agency: FFAS (Fonds Francais Alimentatrion Santé).
Name of the project: Measures of motivational and hedonic states in rodents.
Amount:130 000 €;
Date and duration of the grant:
November 2012-november 2015.

Alteration in learning strategies associated with drug addiction

Principal Investigator: Véronique Deroche-Gamonet | Partners: V. David (INCIA)

→ Publication:

Martin-Garcia E., Courtin J., Renault P., Fiancette J-F., Wurtz H., Simonnet A., Levet F., Herry C., Deroche-Gamonet V. Frequency of cocaine self-administration influences drug seeking in the rat: optogenetic evidence for a role of the Prelimbic cortex. Neuropsychopharmacology, 2014, 39(10):2317-2330.

→ Publication in preparation:

Simonnet et al., Neuronal correlates of addiction-like behavior in rat.

→ Co-funds:

Funding agency: Eranet Neuron grant / ANR
Name of the project: COCADDICT
Total amount: 720 000 €
Date and duration of the grant: Starting 15 May 2014 (3 years)

Specifying the brain circuits involved in pathological incentive responses and the loss of control over drug taking during the development of addiction

Principal Investigator: Véronique Deroche-Gamonet | Partners: C. Herry (NCM)

→ Publication

Martin-Garcia E., Courtin J., Renault P., Fiancette J-F., Wurtz H., Simonnet A., Levet F., Herry C., Deroche-Gamonet V. Frequency of cocaine self-administration influences drug seeking in the rat: optogenetic evidence for a role of the Prelimbic cortex. Neuropsychopharmacology, 2014, 39(10):2317-2330.

→ Publication in preparation

Simonnet et al., Neuronal correlates of addiction-like behavior in rat.

→ Co-funds

Funding agency: Eranet Neuron grant / ANR
Name of the project: COCADDICT
Total amount: 720 000 €
Date and duration of the grant: Starting 15 May 2014 (3 years)
Funding agency: Idex Bordeaux
Name of the project: Bis-Canada - COCADDICT
Total amount: 24 000 €
Date and duration of the grant: Starting June 2014 (18 months)

Is stress-induced vulnerability to drug of abuse an astrocyte-dependent process

Principal Investigator: Aude Panatier (NCM) | Partners: P. V. Piazza, NCM ; F. Georges (IINS)

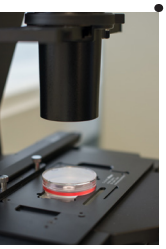
Projects selected in 2016

Are cannabinoid receptors on glutamatergic neurons involved in the imbalance between the motivational drives for feeding and running in restrictive anorexia?

Principal Investigator: Francis Chaouloff (NCM) | Partners: F. Georges (IMN)

→ Objectives of the project

The project, based on operant conditioning in mice, bears two aims. The first is to set up a behavioural and electrophysiological paradigm wherein the motivational conflict between the desires to eat and



to exercise is imbalanced in female adolescents, as in human restrictive anorexia. The second aim is to analyse whether the endocannabinoid system (ECS), and hence type-1 cannabinoid (CB1) receptors in glutamatergic neurones play a key role therein.

Main results

The project has began in November with the recruitment of a post-doc (Maria-Carmen MEDRANO). The goal is to analyse through in vitro electrophysiological means synaptic plasticity at ventral tegmental area (VTA) dopaminergic neurones in mice conditioned to work to get access either to a running wheel, to food pellets or to choose between either of these rewards. The host laboratory recently set up the appropriate protocols as to be able to do so.

Working plan to continue

Female (as opposed to male) adolescent mice housed individually (as opposed to collectively) might show a preferential choice for wheel-running over feeding, even under partial fasting conditions. In addition to synaptic plasticity at glutamate-dopamine synapses in the VTA (a key synapse in motivation processes), the host laboratory will examine through available conditional CB1 receptor mutants the role of the ECS in this model o f anorexia.

Publications in preparation:

Muguruza C et al. Endocannabinoids gate running motivation.

Communications

- Chaouloff F (oral). Addicted to running : is there a role for the endocannabinoid system ? NEUREX meeting, March 2017, Strasbourg
- Chaouloff F (oral). Run Forrest, run… but mind your CB1. NeuroCentre INSERM Symposium, April 2017, Bordeaux

Thematic

Transversal pathophysiology and innovative therapeutics for aging, memory and cognition

Previous projects selected in 2013 to 2015

Establishment of a biological resources collection

Principal Investigator: Erwan Bezard (IMN) | Partners: W.Meissner (IMN)

→ Publication

Laurens B, Constantinescu R, Freeman R, Gerhard A, Jellinger K, Jeromin A, Krismer F, Mollenhauer B, Schlossmacher MG, Shaw LM, Verbeek MM, Wenning GK, Winge K, Zhang J, Meissner WG. Fluid biomarkers in multiple system atrophy: a review of the MSA Biomarker Initiative. Neurobiol Dis 2015:80:29-41.

→ Co-funds

Funding agency: PHRC (French Health Ministry), PSP-France.
Name of the project: BIOAMS, BIOPARK, SYMPATH, A serum miRNAs signature as potential biomarker for MSA, Plasma exosomal IRS-1p312 as biomarker for MSA.
Total amount: 600 000 €
Date and duration of the grant: BIOAMS (2012-2015), BIOPARK 2013-2016), SYMPATH (2014-2018), MSA Coalition (2016-2017 and 2017-2018).

Functional contribution of newly born neurons to the formation of remote memories during normal aging

Principal Investigator: Bruno Bontempi (IMN) | Partners: N. Abrous (NCM)

→ Publication in preparation

Unraveling a new property of the cortex: the flexible expression of consolidated memories.
Bessières B, Nicole O, Bontempi B. Assessing recent and remote associative olfactory memory in rats using the social transmission of food preference paradigm. Nature Protocols, 2017, 12: 1415-1436.

→ Co-funds

Funding agency: ANR
Name of the project: MemoryTrack
Title: "Unraveling the dynamics of hippocampal-cortical interactions during the formation of recent and remote memories: behavioral, cellular, molecular and functional bases".
Total amount: 510 000 € (2 partner teams)
Date of obtention and duration of the grant: April 1, 2015, 60 months.

Early diagnosis and pleotherapy of Alzheimer Disease

Principal Investigator: Jean-Marc Orgogozo | Partners: P Philip, J-F Dartigues (SANPSY)

Translational study of the cerebral substrates involved in pathological fear recovery

Principal Investigator: Cyril Herry (NCM) | Partners: M. Bonnet (UMS CNRS 3428)

→ Published publication

■ Karalis et al., 4 Hz oscillations synchronize prefrontal-amygdala circuits during fear behavior. Nature Neuroscience, 2016, 19: 605-612.
■ Wurtz et al., Preventing long-lasting fear recovery using bilateral alternating sensory stimulation: a translational study. Neuroscience, in press.

→ Publication in preparation

Dejean C. et al., Prefrontal neuronal assemblies temporally control fear behavior. Under review at Nature.

Neuron-type specific cellular mechanisms underlying the organization of recent and remote memories in the normal and diseased brain

Principal Investigator: Andreas Frick (NCM) | Partners: B. Bontempi (IMN)

→ Co-funds

Additional grant obtained: ANR 2015 CortMem
Funding agency: ANR
Name of the project: Neuronal allocation mechanisms of recent and remote memories in the normal and pathological brain.
Total amount: 497 000 €
Date of obtention and duration of the grant: 01/10/2015 for 48 monthsIdex-University Bordeaux (2015-2017): 2 year postdoc fellowship for Dr. Isabel del Pino.

Contribution of the dentate gyrus to the ontogeny of learning and memory skills

Principal Investigator: Muriel Koehl (NCM) | Partners: F. Georges (IMN)

→ Publication in preparation

David J, Ladevèze E, Abrous DN and Koehl M. Different contributions of juvenile and adult neurogenesis to associative memory.
Lecordier S, Abrous DN and Koehl M. Ontogeny of associative memory in mice.

Pathophysiology and imaging biomarker of memory impairment in early multiple sclerosis – from animal model to patients

Principal Investigator: Thomas Tourdias (NCM) | Partners: B.Hiba (TRAIL)

→ Publication:

■ Accepted publications quoting the grant from the labex BRAIN:
• Thalamic alterations remote to infarct appear as focal iron accumulation and impact clinical outcome. Kuchcinski G, Munsch F, Lopes R, Bigourdan A, Su J, Sagnier S, Renou P, Pruvo JP, Rutt BK, Dousset V, Sibon I, Tourdias T. Brain. 2017 Jul 1;140(7):1932-1946. doi: 10.1093/brain/awx114
• Pattern separation performance is decreased in patients with early multiple sclerosis. Planche V, Ruet A, Charré-Morin J, Deloire M, Brochet B, Tourdias T. Brain Behav. 2017 Jun 21;7(8):e00739. doi: 10.1002/brb3.739. eCollection 2017 Aug

- Selective dentate gyrus disruption causes memory impairment at the early stage of experimental multiple sclerosis. Planche V, Panatier A, Hiba B, Ducourneau EG, Raffard G, Dubourdieu N, Maitre M, Lesté-Lasserre T, Brochet B, Dousset V, Desmedt A, Oliet SH, Tourdias T. Brain Behav Immun. 2017 Feb;60:240-254. doi: 10.1016/j.bbi.2016.11.010. Epub 2016 Nov 12.
- Hippocampal microstructural damage correlates with memory impairment in clinically isolated syndrome suggestive of multiple sclerosis. Planche V, Ruet A, Coupé P, Lamargue-Hamel D, Deloire M, Pereira B, Manjon JV, Munsch F, Moscufo N, Meier DS, Guttmann CR, Dousset V, Brochet B, Tourdias T. Mult Scler. 2017 Aug;23(9):1214-1224. doi: 10.1177/1352458516675750. Epub 2016 Oct 25.
- Cervical Spinal Cord DTI Is Improved by Reduced FOV with Specific Balance between the Number of Diffusion Gradient Directions and Averages. Crombe A, Alberti N, Hiba B, Uettwiller M, Dousset V, Tourdias T. AJNR Am J Neuroradiol. 2016 Jun 30.
- Regional hippocampal vulnerability in early multiple sclerosis: a dynamic pathological spreading from dentate gyrus to CA1. Vincent Planche, Ismail Koubyr, José E. Romero, José V. Manjon, Pierrick Coupé, Mathilde Deloire, Vincent Dousset, Bruno Brochet, Aurélie Ruet and Thomas Tourdias. Human Brain mapping.
- Deciphering the microstructure of hippocampal subfields with in vivo DTI and NODDI: applications to experimental multiple sclerosis. Amandine Crombe, Vincent Planche, Gerard Raffard, Julien Bourel, Nadège Dubourdieu, Aude Panatier, Hikaru Fukutomi, Vincent Dousset, Stephane Oliet, Bassem Hiba,Thomas Tourdias. Neuroimage.
- Preliminary evidence of the cerebellar role on cognitive performances in clinically isolated syndrome. Moroso A, Ruet A, Lamargue-Hamel D, Munsch F, Deloire M, Ouallet JC, Cubizolle S, Charré-Morin J, Saubusse A, Tourdias T, Dousset V, Brochet B. J Neurol Sci. 2018 Feb 15;385:1-6.

→ Co-funds

■ Additional grants obtained on this topic:

- Grant ARSEP foundation (Fondation pour l'aide à la recherche sur le sclérose en plaques) obtained in 2016: 76 K€.
- Grant the Labex TRAIL (Translational Advanced Imaging laboratory) obtained in 2016: 198 K€.

Projects selected in 2017

Multi-scale analysis of remodeling of brain extracellular space after traumatic brain injury: focus on astroglial mechanisms

Principal Investigator: Valentin Nägerl (IINS)	Partners: J. Badaut (INCIA) G. Marsicano (NCM)

→ Publications

This project has not yet started, it will start in January 2018.

THEMATIC

TRANSVERSAL PATHOPHYSIOLOGY AND INNOVATIVE THERAPEUTICS FOR SLEEP AND ATTENTION DISORDERS

Previous projects selected in 2013 to 2015

SLEEP, COGNITION AND ALZHEIMER

Principal Investigator: Pierre Philip (Sanpsy)

STUDY OF MIRNA EXPRESSION PATTERN AS DIAGNOSTIC AND PROGNOSTIC BIOMARKER IN AMYOTROPHIC LATERAL SCLEROSIS

Principal Investigator: Alexandre Favereaux (IINS)

Partners: G. Le Masson (NCM); A.-C.Wielanek-Bachelet (Centre référence SLA)

→ Additional grant obtained

A grant was submitted to the PEPS-IDEX-CNRS call, the project is entitled: "Analyse intégrative de données de grandes dimensions (miRNA et radiologique) appliquée à l'étude MIRSLA: Etude de l'expression des micro-ARN comme biomarqueur diagnostique et pronostique dans la Sclérose Latérale Amyotrophique (SLA).

DOES THE OREXIN SYSTEM CONTRIBUTE TO INDIVIDUAL DIFFERENCES IN SLEEP DEPRIVATION-INDUCED CHANGES IN NEUROBEHAVIORAL FUNCTION?

Principal Investigator: Pierre Philip (Sanpsy)

Partner: Sophie Layé (NutriNeuro)

→ Publication

Philip P., Nadjar A., Taillard J., Laye S., Chaufton C. Role of orexin in vulnerability to sleep deprivation in mice. Fundamental and Clinical Pharmacology, 2014, 28 (S1):9.

→ Communication

Philip P., Nadjar A., Taillard J., Laye S., Chaufton C. Role of orexin in vulnerability to sleep deprivation in mice. Congres de la Société physiologie stasbourg 2014.

→ Additional grant obtained

we obtained 200 mg of Almorexant from the Actelion company.

→ Working plan to continue

Both experiments need to be replicated in larger po-

pulation (animal and humans) to confirm these data. In human, we must complement these results with an objective assessment of excessive daytime sleepiness measure.
We are currently asking actelion to provide us more almorexant in order to launch a new study on animals with EEG recordings to confirm the objective sleep deprivation effect (time awake on the EEG) of the paradigm.

Exploring the brain extracellular space dynamics in physiology and pathology

Principal Investigator: : Laurent Groc

Partners: E. Bezard (IMN), L. Cognet (LAPHIA), M. Blanchard-Desce (LAPHIA)

→ Publications

- Godin AG, Varela JA, Gao Z, Danné N, Dupuis JP, Lounis B, Groc L, Cognet L. Single-nanotube tracking reveals the nanoscale organization of the extracellular space in the live brain. Nat Nanotechnol. 2017 Mar;12(3):238-243. (IF: 44).
- Gao Z, Varela JA, Groc L, Lounis B, Cognet L. Toward the suppression of cellular toxicity from single-walled carbon nanotubes. Biomater Sci. 2016 Feb;4(2):230-44. (IF: 4).
- Genin E, Gao Z, Varela JA, Daniel J, Bsaibess T, Gosse I, Groc L, Cognet L, Blanchard-Desce M. «Hyper-bright» near-infrared emitting fluorescent organic nanoparticles for single particle tracking. Adv Mater. 2014 Apr 9;26(14):2258-61, 2257. (IF: 20).

→ Co-funds

ANR NanoSpace, OH-Risk ANR Program (2015-2020), Partners: Cognet, Groc, Bezard.

Projects selected in 2016

Unraveling the implication of P2X4 purinoceptors in amyotrophic lateral sclerosis (ALS) pathogenesis

Principal Investigator: : Eric Boué-Grabot (IMN)

Partner: S. Bertrand (INCIA)

→ Objectives of the project

To unravel the potential role of P2X4 receptors during Amyotrophic Lateral Sclerosis (ALS) pathogenesis and to decrypt the mechanism of P2X4 upregulation in SOD1 motoneurons (MNs) by combining biochemical, electrophysiological and behavioral approaches using innovative double-transgenic mice carrying the human SOD1-G93A mutation and either lacking the endogenous P2X4 gene or expressing knockin non-internalized P2X4 gene.

→ Main results

- we generated SOD1-G93A /P2X4KO-/- and SOD-1G93A/P2X4mCherryINExc/Exc transgenic mice
- we showed that the ablation of P2X4 gene in SOD1 animal has a significant and positive impact on swimming performance and extends the survival of animals.
- we showed that mutated SOD1-G93A increases P2X4 surface trafficking and function in recombinant system as well as in peripheral macrophages from SOD1-G93A at pre-symptomatic phase suggesting that P2X4 may serve as a marker of ALS before the onset of symptoms.

→ Working plan to continue

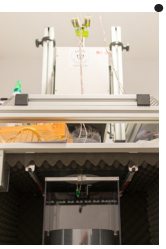
We now plan to determine the contribution of increased P2X4 in ALS-like disease by measuring body weight loss, locomotor scoring, swimming test and survival of SOD1-G93A/WT and SOD1-G93A/CMV-P2X4mCherryIN. We will determine the expression pattern and subcellular localization of P2X4 and inflammatory markers in the spinal cord and motor cortex of the transgenic mice: WT/WT, SOD1-G93A/WT, SOD1-G93A/P2X4KO and SOD1-G93A/P2X4mCherryIN during the time course of the sickness.

→ Publication in preparation and Communications

Implication of P2X4 purinoceptors in ALS pathogenesis. Bertin E , Martinez A, Fayoux A, Fernagut PO, Bertrand S and Boué-Grabot E. Poster presentation at the JR3 ARSLA 2017 Paris.

Projects selected in 2017

Understanding the pathophysiology of pain in Parkinson's disease



Principal Investigator: Hamid Benazzouz (IMN) | Partner: P. Fossat (IINS)

Objectives of the project

Pain is one of the major non-motor symptoms contributing to impaired quality of life of Parkinson's disease (PD) patients. However, its mechanism remains unknown.
Our project aimed to identify the pain phenotypes and the parallel changes in spinal integration of peripheral stimuli in a 6-hydroxydopamine (6-OHDA) rat model of PD induced by the lesion of dopamine neurons in the pars compacta of substantia nigra.

Main results

Our results show that dopamine depletion by 6-OHDA induced hypersensitivity to mechanical and thermal stimuli. These abnormal behaviors were paralleled by increased neuronal responses and hyperexcitability of wide dynamic range neurons of lamina V of the dorsal horn of spinal cord in response to electrical stimulations of the sciatic nerve in the 6-OHDA model as compared to sham rats.

Working plan to continue

The first part of the project has been achieved, now we are starting the following projects:

- Investigate the simultaneous changes in the neuronal activity of dorsal horn neurons (DHNs) of the spinal cord and the ventral posterolateral neurons (VPLNs) of the thalamus in response to peripheral stimulation.
- Investigate the involvement of L-type and T-type Ca2+ channels in the pathophysiology of pain and motor deficits in the context of PD. Cav1.3 and Cav3.2 KO in the subthalamic nucleus, DH of the spinal cord and VPL of the thalamus will be generated by local stereotaxic delivery of AAV viruses expressing the Cre recombinase.
- Different pharmacological strategies targeting the monoaminergic systems and the L- and T-types Ca2+ channels will be tested.

Publications in preparation

Charles K.A., Naudet F., Bouali-Benazzouz R., Landry M., De Deurwaerdère P., Fossat P., and Benazzouz A. Alteration of nociceptive integration in the spinal cord of a rat model of Parkinson's disease (submitted for publication).

Enhancing slow wave sleep to mitigate synucleinopathy and neurodegeneration in Parkinson's disease and multiple system atrophy models

Principal Investigator: Erwan Bezard (IMN) | Partner: A. Nadjar (Nutrineuro); P. Philip (Sanpsy)

Objectives of the project

SLOWSYN will characterize sleep architecture, structure and EEG density in two highly-relevant mouse models of PD and MSA in order to confirm pertinent EEG biomarkers in neurodegenerative diseases. SLOWSYN will validate sodium oxybate as a promising candidate to achieve disease modification in synucleinopathies by limiting α -syn accumulation. The project benefits from past collaborations between (i) E. Bezard and A. Nadjar on pathophysiology of PD, (ii) A. Nadjar and P. Philip on sleep recordings in mice (Labex grant 2012), (iii) and EXTRABRAIN Interlabex grant (LAPHIA – BRAIN : Cognet-Groc-Bezard-Blanchard).

Thematic

Blue sky program

Previous projects selected in 2013 to 2015

Deciphering the mechanism of central pain sensitization in vivo using innovative heat-shock local deletion of the L-type calcium channel Cav1.2 gene in the mouse lumbar bulge

Principal Investigator: Christel Baudet (IINS)	Partners: P. Fossat (INCIA), B. Quesson (CNRS UMS 3428,TRAIL) ; K. Petry (INSERM U1049) ; E. Dumont (Image Guided Therapy)

The impact of structural changes in axons on information transfer in CA3 neurons: a combined computational and nanoscale imaging study

Principal Investigator: Daniel Cattaert (INCIA)	Partner: P. Fossat (IINS)

→ Publication

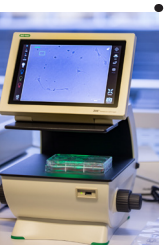
Ronan Chéreau, G. Ezequiel Saraceno, Julie Angibaud, Daniel Cattaert, U. Valentin Nägerl. (2017) Superresolution imaging reveals activity-dependent plasticity of axon morphology linked to changes in action potential conduction velocity. Proc Natl Acad Sci USA 114(6):1401-140.

Relative contribution of the hypothalamic proliferative and neuroinflammatory responses to the obese phenotype

Principal Investigator: Daniela Cota (NCM)	Partner: Nora Abrous (NCM) ; Sophie Layé (INRA)

→ Publication

Inhibiting Microglia Expansion Prevents Diet-Induced Hypothalamic and Peripheral Inflammation.
André C, Guzman-Quevedo O, Rey C, Rémus-Borel J, Clark S, Castellanos-Jankiewicz A, Ladeveze E, Leste-Lasserre T, Nadjar A, Abrous DN, Laye S, Cota D.
Diabetes. 2017 Apr;66(4):908-919. doi: 10.2337/db16-0586.
This manuscript was selected among the highlights by the French Society of Neuroendocrinology and it was the topic of an article in the INSERM magazine Science et Santé this year.



Thermosensitive nanoparticules as a carrier of bioactive peptide against pain sensitization

Principal Investigator: Marc Landry

Partners: V. Heroguez (UMR CNRS 562) ; K. Petry (INSERM U1049)

→ Co-funds

Additional grant obtained: Funding agency: InCA
Name of the project : Les microARNs: une cible thérapeutique innovante pour les patients cancéreux souffrant de douleurs sévères Total amount: 301 600 €
Date and duration of the grant: 10/08/2015, 36 mois.

Determining the mode of binding of PSD-95 tandem PDZ domains

Principal Investigator: Matthieu Sainlos

Partner: C. Mackereth (IECB)

→ Publication

Rimbault, C., Maruthi, K., Breillat, C., Genuer, C., Crespillo, S., Gauthereau, I., Antoine, S., Thibault, C., Wong, F., Grillo-Bosch, D., Claverol, S., Poujol, C., Choquet, D., Mackereth, C. & Sainlos, M. Engineering selective competitors targeting PSD-95 PDZ domains. Manuscript in preparation.

→ Co-funds

Additional grant obtained: ANR blanche 2013
Funding agency: ANR
Name of the project: CheMoPPI
Total amount: 434 747 €
Date and duration of the grant:
01/10/2013-30/09/2016 (36 months)

Nanoparticles as a carrier of bioactive peptide against pain sensitization

Principal Investigator: Marc Landry

Partner: V.Heroguez (AMADEUS)

→ Co-funds

Additional grant obtained: Funding agency: InCA
Name of the project : Les microARNs: une cible thérapeutique innovante pour les patients cancéreux souffrant de douleurs sévères Total amount: 301 600 €
Date and duration of the grant: 10/08/2015, 36 mois
Date and duration of the grant:
01/10/2013-30/09/2016 (36 months).

Projects selected in 2017

Role of the pro-opio-melanocortin (POMC)-mesolimbic neurocircuit in the development of diet-induced obesity

Principal Investigator: Daniela Cota

Partner: X. Fioramanti (Nutrineuro)

→ Publication

I have no major activity to report for the MesoPOM project as this project just started in September and we just now secured the post-doc that will work on the project by performing electrophysiology.

Interplay between scribble and the phosphoinositide metabolism controls the AIS structure and the axonal excitability

Principal Investigator: Mireille Montcouquiol (NCM)	Partner: A. Brachet (IINS)

→ Objectives of the project

In this project, build up on preliminary data obtained in the group of M. Montcouquiol and on the expertise of A. Brachet on the AIS, we are testing the hypothesis that the original accumulation of Scrib observed at the AIS could influence the recruitment of phosphoinositides (PIP) or phosphoinositides proteins (PIPE), and regulate neuronal excitability. To address this, we are implementing a project combining genetics, biochemical, cutting-edge imaging (super-resolution, optogenetics) and electrophysiology methods.

→ Main results

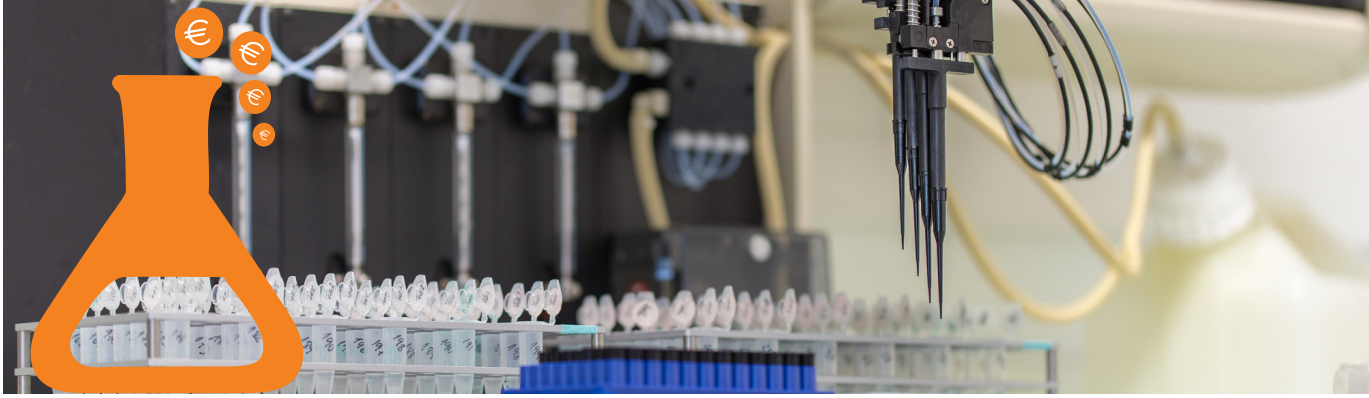
Since September 2017 we have ordered tools required for the experiments planned in Aim1 & 2 of our project. We also hired as of December 2017 an Assistant engineer trained in cell biology and biochemistry. We have started immunocytochemistry for PIP labelling in neurons while establishing the protocols for PIP screening on cell lysates. Notably, we did transfections in HEK cell lines followed by western blotting to adjust the conditions for the cell extracts we will use in the PIP screening (transfection of scrib constructs but also transfection of known protein domains exhibiting strong binding with different PIP to be used as positive controls).

→ Working plan to continue

In the coming months we will: (i) start PIP screening on strips with our lysates of either transfected cells and eventually brain lysates; (ii) validate the positive immunocytochemistry on neurons using the inhibitors of the PIP pathway (in vitro), (iii) validate (or not) the 4 identified PIPE found in our Y2H screen. Once this is achieved, we will move to (iv) the characterization of the interplay between scrib disruption (mouse KO and ShRNA) and PIP perturbations (optogenetic, drugs) on axonal initial segment organization and function (by imaging and electrophysiology experiments).

Regulation of membrane trafficking by Rnd2 in newborn neurons of the adult hippocampus

Principal Investigator: Emilie Pacary (NCM)	Partner: D. Perrais (IINS)



APPLIED AND TRANSFER RESEARCH PROJECTS

Preclinical development of AEF0117, the first of a new pharmacological class: the C3-17,NMPDs (Non Metabolized Pregnenolone Derivatives)

Principal Investigator: Pier-Vincenzo Piazza

The objective of this project was to complete the regulatory preclinical development of a NCE AEF0117 that is the first clinical candidate of a new pharmacological class the C3-17,NMPDs (Non Metabolized Pregnenolone Derivatives), which are able to specifically inhibit only part of the signaling pathways activated by the CB1 receptors. AEF0117 is being developed as a therapy of cannabis use disorders (CUD) for which there are no available pharmacological therapeutic tools.

All the experiments planned in the grant have been completed and show that AEF0117 has very good absorption, distribution, metabolism and toxicity (ADMET) characteristics. After oral administration AF0117 is well absorbed (>72%), it is stable (half-life> 20h in dogs); it does not interact with the major metabolic enzymes and is excreted intact at 90% through the gastrointestinal tract. Finally, it has not toxic effect up to 3000 times the active dose.

The final step of this project was the submission of an Investigative New Drug (IND) application to the FDA. The IND has been obtained in November 2016. Phase one clinical studies have now been successfully completed and trial in cannabis abusers are planned to start in October 2018. This project obtained in 2016 a NIDA grant that has been obtained in collaboration with Prof. Margaret Haney (Columbia University, US). This is a three years grant of 3.3M$ in direct costs that has covered the costs of the phase I trials and will cover part of the costs of the first study in cannabis abusers that will be performed in Prof. Haney laboratory.

Single molecule pull-down platform to dissect protein-protein interactions in neurobiology

Principal Investigator: Vincent Studer

→ Objectives of the project

The main objective of this project is to build a commercial instrument able to perform single-molecule pull-down of fluorescently tagged proteins from a cell extract in a simple and automated fashion. To reach this goal, we will apply single-molecule, TIRF and FRAP imaging modalities and develop quantitative analysis software in order to extract statistical information of the composition and stoichiometry of individual protein complexes.

→ Main results

During the first year of the project we managed to

- Pattern the bait protein at precise locations with a controlled density.
- Define a protocol to specifically target the bait protein with dedicated anchors.
- Develop a dedicated software able to analyze multicolor single molecule fluorescence, colocalization and photobleaching steps (quantification).

→ During the second year of the project

- We optimized our multilayer protein coating to elicit specific recognition between purified adhesion proteins on the patterned substrate and the recombinant counter receptors expressed in living cultured cells (N-Cadherins, SynCam, Neurexin/Neuroligin complexes).
- We managed to perform reproducible FRAP (Fluorescence Recovery After Photobleaching) on GFP tagged receptors accumulated at the micropatterns, providing a way to quantify ligand-receptor interaction rates.
- Alveole our industrial partner commercialized a fluid handling robot based on our prototype.

→ Working plan to continue

- We will establish a bank of interaction rates characterizing various synaptic adhesion complexes. These results are expected to be published within a year.
- Increase the throughput of the system (software and liquid handling).

CLINICAL RESEARCH PROJECTS

The sleepless brain: neuroimaging support for a differential diagnosis of insomnia

Principal Investigator: Ellemarije Altena (Sanpsy)	Partners: M. Joliot, (GIN), E. Sanz (Argita, GIN), P. Philip, (Sanpsy)

→ Publications

- Altena E, Daviaux Y, Sanz-Arigita EJ, Bonhomme E, De Sevin E, Micoulaud-Franchi J-A, Bioulac S, Philip P. How sleep problems contribute to simulator sickness: preliminary results from a realistic driving scenario. Journal of Sleep Research (in press).
- Altena E, Chen I, Daviaux Y, Ivers H, Philip P, Morin CM. How hyperarousal and sleep reactivity are represented in different adult age groups: results from a large cohort study on insomnia. Brain Sciences 7: doi: 10.3390/brainsci7040041, 2017.
- Altena E, Micoulaud-Franchi J-A, Geoffroy P-A, Sanz-Arigita EJ, Bioulac S, Philip P. The bidirectional relation between sleep and emotional reactivity: from disruption to recovery. Behavioral Neuroscience 130: 335-350, 2016.
- Bioulac S, Sagaspe P, Micoulaud Franchi J-A, Altena E, Taillard J, Benard A, Bouvard M-P, Fabrigoule C, Philip P. Objective level of alertness and inhibitory control predict highway driving impairment in adults with ADHD. Journal of Attention Disorders (in press).

Use of an innovative and easy-to-use tool based on the perception of visual food stimuli for assessing hedonic and motivational states in major depression. Relationships with peripheral endocannabinoids

Principal Investigator: Bruno Aouizerate (NCM)	Partner: P. Philip (Sanpsy)

Identification of the cerebral networks mediating pathological fear behavior in PostTraumatic Stress Disorder patients and in rodents: a translational study

Principal Investigator: Vincent Dousset (NCM)	Partner: C.Herry (NCM), M. Bonnet (IBIO/NCM)

Neurocognitive impact of adolescent obesity

Principal Investigator: Guillaume Ferreira (NCM)	Partner: P. Barrat (CHU), G. Catheline et S. Chanraux (INCIA)

→ Publications

Additional grant obtained: ANR international with Mexico
Funding agency: ANR-CONACyT

Name of the project: OBETEEN
Total amount: 275 k€ in France (same amount in Mexico for the Mexican partners)
Date of obtention and duration of the grant: 01/10/2015 – 3 years (end of 2018)

Study of miRNA expression pattern in patient's samples as diagnostic and prognostic biomarker in Amyotrophic Lateral Sclerosis

Principal Investigator: Gwendal Le Masson (NCM)	Partners: A. Favereaux (IINS), A.C. Wielanek-Bachelet (CHU)

Near infrared spectroscopy for assessing freezing of gait in Parkinson's disease

Principal Investigator: Wassilios Meissner (IMN)	Partners: B. Mazoyer (GIN), N. Tzourio-Mazoyer (GIN), G. Perchey(GIN)

→ Co-funds

Funding agency: FRC
Name of the project: Cognition and motor behaviour networks assessed with near infrared spectroscopy

Total amount: 200000€ for acquisition of the NIRS system necessary for conducting the study
Date and duration of the grant: 2015.

Projects selected in 2017

In vivo involvement of the cholinergic and dopaminergic systems in the pathophysiology of apathy

Principal Investigator: : Joachim Mazere (INCIA)	Partners: G. Catheline (INCIA), Fernandez (INCIA), Mayo (INCIA)

→ Objectives of the project

To provide a better characterization of the cholinergic and dopaminergic functioning in apathy as a syndrome. We will use a positron emission tomography molecular imaging of the dopaminergic (DA) and cholinergic (ACh) pathways in apathetic and unapathetic patients 3 months after stroke, without overlapping depression, complemented by a functional network analysis using functional Magnetic Resonance Imaging.

→ Main results

Setting up of the study in progress. Implementation meetings with clinical research direction of Bordeaux University Hospital planned for the beginning of the year 2018.
Objective: to start the first inclusions before the end of the year 2018.

→ Working plan to continue

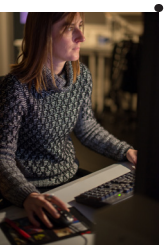
To compare the integrity of ACh and DA pathways in apathetic (n = 15) and unapathetic (n = 15) patients 3 months after stroke.
To assess whether modifications of ACh and DA activities can be linked (1) with the clinical expression of apathy (2) with alterations in the functional organization of the resting brain (functionnal MRI) (3) with specific local changes in white matter microstructure (structural MRI).

Effectiveness of neurofeedback on cognitive performance and daytime alertness in controlled sleep restricted healthy subject

Principal Investigator: : Jean-Arthur Micoulaud-Franchi (Sanpsy)	Partners: F. Lotte (INRIA)

→ Objectives of the project

The objectives are to demonstrate that neurofeedback targeting activities in the EEG theta / beta spectral bands will teach the subject to desynchronize brain activities in order to restore the daytime



alertness level (evaluated objectively with sleep latencies measures and subjectively with standardized sleepiness scale) and the cognitive performance (evaluated with a sustained-attention and vigilance tasks) in a context of repeated mild sleep restriction.

→ Main results

May 2017: approval of the protocol by the CPP and CNIL notification

- Jun 2017: finalization of the neurofeedback solution
- July 2017: first test of the neurofeedback solution
- September 2017: beginning of the protocol with participants with repeated mild sleep restriction.

→ Published publications

On assessing neurofeedback effects: should double-blind replace neurophysiological mechanisms? Fovet T, Micoulaud-Franchi JA; Vialatte FB; Lotte F; Daudet C; Batail JM; Mattout J; Wood G; Jardri R; Enriquez-Geppert S; Ros T. Brain. 2017 Oct 1;140(10):e63.

→ Publication submitted

- Manuscript Number: NSC-17-493R2 / How to improve clinical neurofeedback using a human-factor-centred standpoint: A short review of the insights provided by the literature on brain-computer interface; C Jeunet; F Lotte; JM Batail; P Pierre; JA Micoulaud Franchi; Neuroscience.
- Manuscript Number: ENCEP-D-17-00163JA / Neurofeedback research: a fertile ground for psychiatry? JA Micoulaud Franchi; JM Batail; S Bioulac; F Cabestaing; C Daudet; D Drapier; M Fouillien; T Fovet; A Hakoun; R Jardri; C Jeunet; F Lotte; E Maby; J Mattout; T Medani; J Mladenovic; L Perronet; L Pillette; T Ros; F Vialatte; Encéphale.

→ Communications

- 1-2 Juin 2017 / 13ème édition de la réunion annuelle du GREPACO (Groupe de Réflexion en Psychopathologie Cognitive) « Nouvelles perspectives d'interventions en psychopathologie cognitive » Le neurofeedback : une remédiation cognitive centrée sur l'apprentissage psychophysiologique.
- 24 janvier 2018 Congrés de l'Encéphale, Pour la mise en place de recommandations françaises de bonne pratique pour l'utilisation du neurofeedback en psychiatrie.

Team installation Dr. Ellemarije Altena

Publications since 2014

Altena E, et al. How sleep problems contribute to simulator sickness: preliminary results from a realistic driving scenario. Journal of Sleep Research (in press).

Altena E, et al. How hyperarousal and sleep reactivity are represented in different adult age groups: results from a large cohort study on insomnia. Brain Sciences 7: doi: 10.3390/brainsci7040041, 2017.

Altena E, et al. The bidirectional relation between sleep and emotional reactivity: from disruption to recovery. Behavioral Neuroscience 130: 335-350, 2016.

Bioulac S, et al. Objective level of alertness and inhibitory control predict highway driving impairment in adults with ADHD. Journal of Attention Disorders (in press).

Ye Z, et al. Predicting beneficial effects of atomoxetine and citalopram on response inhibition in Parkinson's disease with clinical and neuroimaging measures. Human Brain Mapping 37: 1026-1037, 2016.

Ye Z, et al. Improving impulsivity in Parkinson's disease by atomoxetine. Biological Psychiatry, 77: 740-748, 2015.

Raaphorst J, et al. Prefrontal involvement related to cognitive impairment in progressive muscular atrophy. Neurology, 83: 818-825, 2014.

Ye Z, et al. Selective serotonin reuptake inhibition modulates impulsivity in Parkinson's disease. Brain, 137: 1145-1155, 2014.

Stoffers D, et al. The caudate; a key node in the neuronal network disbalance of insomnia? Brain, 137: 610-620, 2014.

Publications submitted

Bioulac S, et al. Virtual remediation versus Methylphenidate to improve distractibility in ADHD children: A controlled randomized proof of concept study.

Altena E, et al. Goal neglect in Parkinson's disease.

Patel R, et al. Restoring executive systems in Parkinson's disease with noradrenergic and serotonergic reuptake inhibition.

Philip P, et al. Effects of Hypoglossal Nerve Stimulation on Sleep Architecture and Objective Level of Alertness in OSA Patients: a preliminary study.

Wink AM, et al. Functional brain network centrality is related to APOE genotype in cognitively normal elderly.

Philip P, et al. Specific insomnia symptoms and self-efficacy explain CPAP compliance in a French population of OSAS patients.

Costanzo EY, et al. Distinct relationship between degree of language lateralization and degree of handedness in right- and nonright-handed healthy individuals.

Publications in preparation

Daviaux Y, et al. Stress reactions measured per event through electrodermal activity: results from a realistic driving simulator scenario.

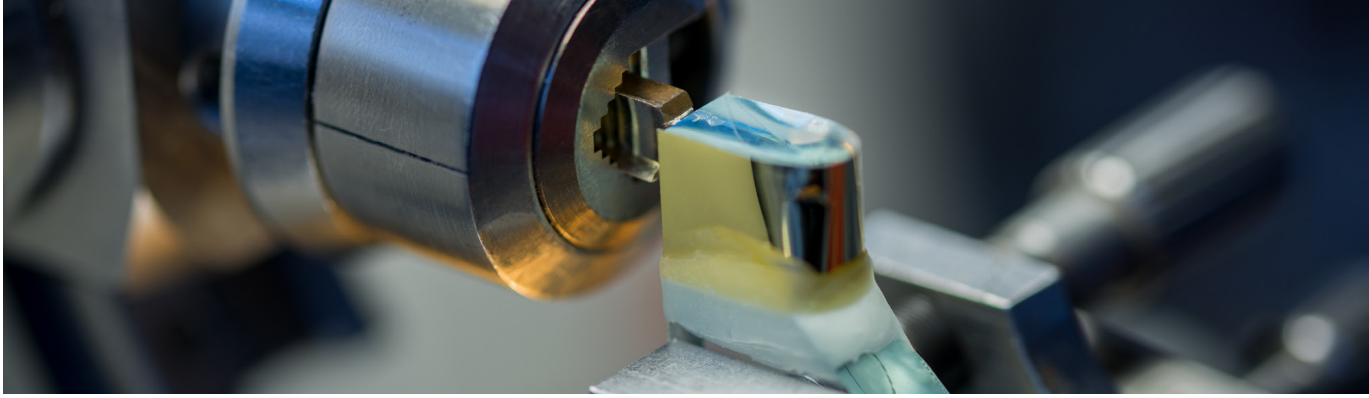
Sanz-Arigita EJ, et al. Resting state connectivity changes after emotional stimuli in insomnia.

Altena E, Det al. How insomnia patients are differentially affected by emotional stimuli: an fMRI study.

Altena E, et al. Sympathetic nervous system reactivity in insomnia.

Morin C, et al. Insomnia and Risk of Traffic Accidents: A 5-year Follow Up Cohort Study.

Sanz-Arigita EJ, et al. Alterations of resting state functional networks in Alzheimer's disease risk.



Core facility staff

94 core facility staff

- 3 microdissection
- 3 primate
- 3 transcriptome
- 3 vectorologie
- 4 biochimie
- 4 PAM
- 5 génotypage
- 14 biocell
- 14 neuropsychopharmacologie
- 17 animalerie magendie
- 24 BIC

58 permanent

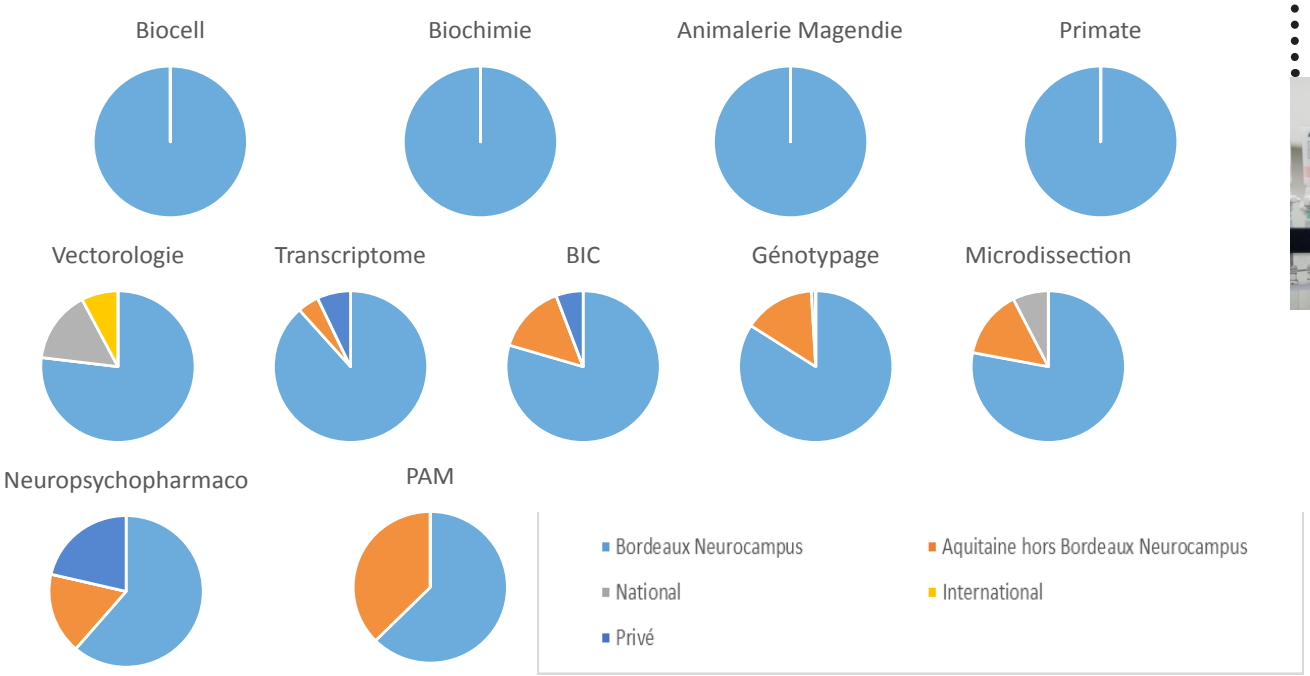
36 non-permanent

9 funded by BRAIN

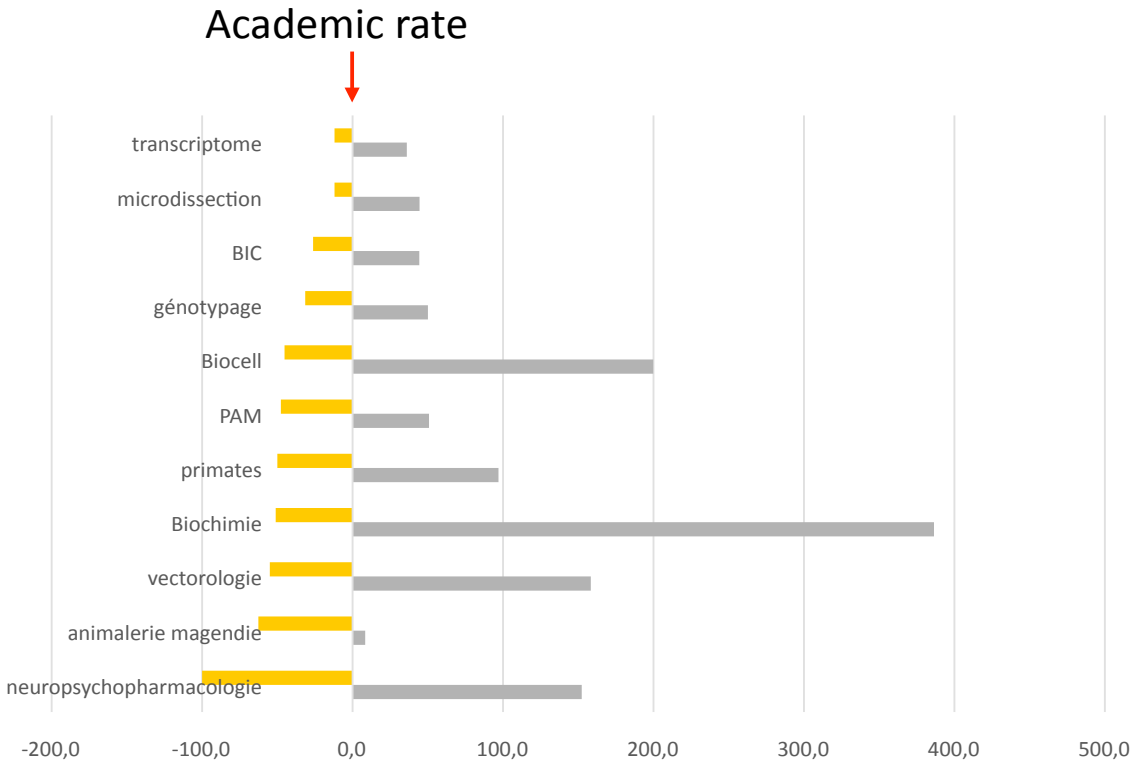
Average working time on the platform is **70%**

5% at 100%

FACILITY USERS

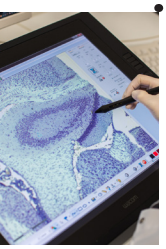


FACILITY COST REDUCTION FOR ALL BORDEAUX NEUROCAMPUS USERS



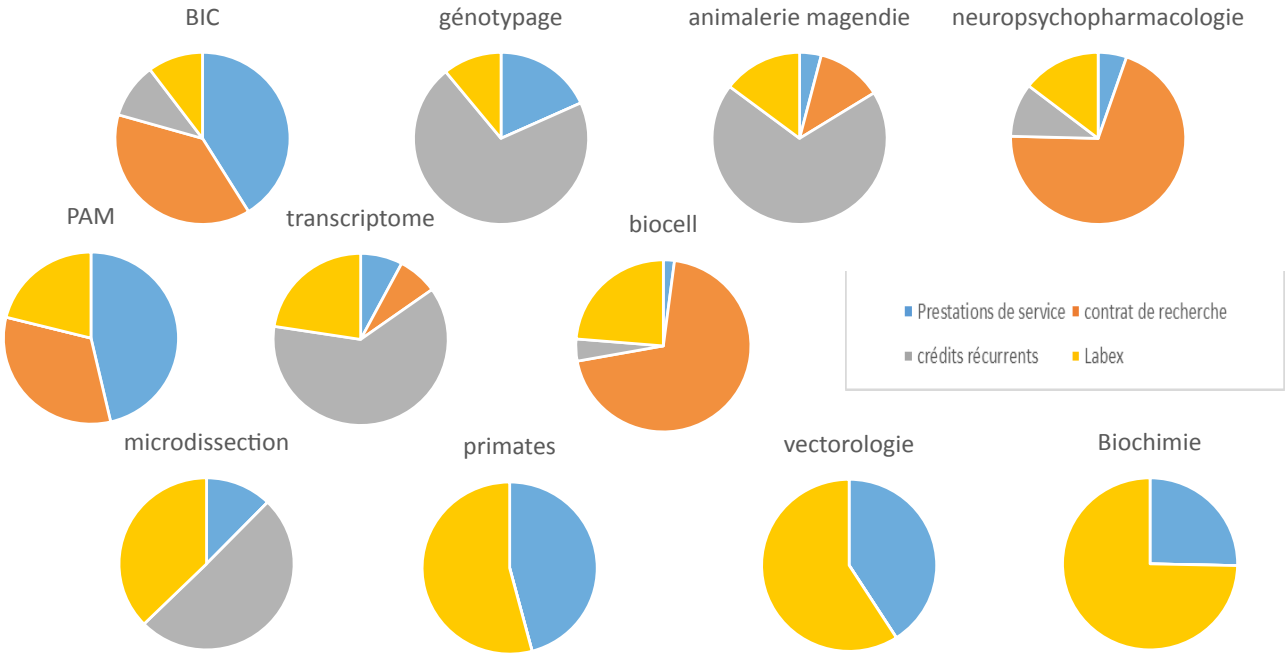
Average reduction Bordeaux Neurocampus

Average increase Private

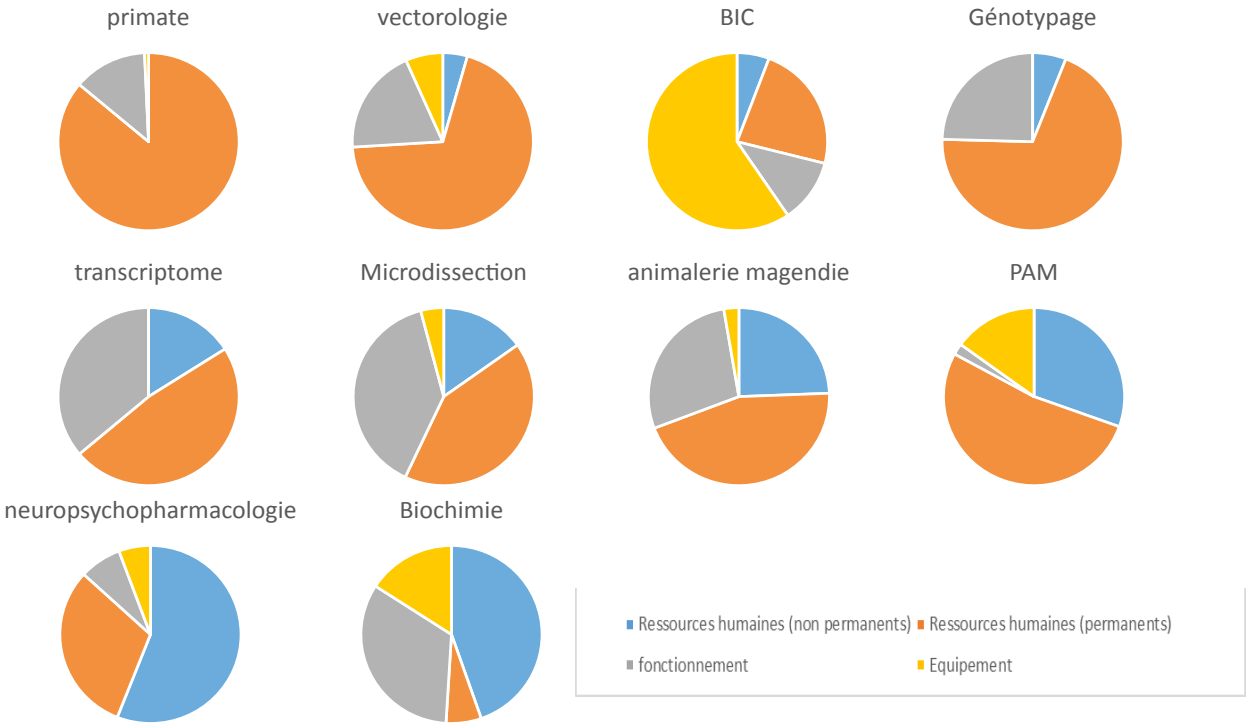


Budget

Incomes



Outcomes



Training

- PhD Extension Grants
- Bordeaux School of Neuroscience

2012

Nanoscale functional organization of branched F-actin networks and N-cadherin adhesion during dendritic spine motility

Laureate name: Anael Chaezau	Supervisor name: Grégory Giannone

- Mehidi A., Rossier O., Chazeau A., Binamé F., Remorino A., Coppey M., Karatas Z., Sibarita J.B., Moreau V., Giannone G. (2017). Fast activation cycles of Rac1 at the lamellipodium tip trigger membrane protrusion. bioRchiv, doi: https://doi.org/10.1101/130849.
- Chazeau A. and Giannone G. (2016) Organization and dynamics of the actin cytoskeleton during dendritic spine morphological remodeling. Cellular and Molecular Life Science, 73, 3053-73.
- Chazeau A., Garcia M., Czöndör K., Perrais D., Tessier B., Giannone G., Thoumine O. (2015) A mechanical coupling between trans-synaptic N-cadherin adhesions and the actin flow stabilizes dendritic spines. Mol Biol Cell, 26, 859-73.
- Chazeau A., Mehidi A., Nair D., Gautier J., Leduc C., Chamma I., Kage F., Kechkar A., Thoumine O., Rottner K., Choquet D., Gautreau A., Sibarita J.B., Giannone G. (2014) Nanoscale segregation of branched F-actin nucleation and elongation factors determines dendritic spine protrusions. EMBO J, 33, 2745-2764.

Alterations of dendritic electrogenesis in layer 5B pyramidal neurons in a mouse model of Fragile X Syndrome

Laureate name: Audrey Bonnan	Supervisor name: Andreas Frick

- Maria Szlapczynska*, Audrey Bonnan*, Melanie Ginger and Andreas Frick. Plasticity and Pathology of Dendritic Intrinsic Excitability. Horizons in Neuroscience Research. 14, (Nova Publishers) (2014).
- Yu Zhang*, Audrey Bonnan*, Guillaume Bony*, Isabelle Ferezou, Susanne Pietropaolo, Melanie Ginger, Nathalie Sans, Jean Rossier, Ben Oostra, Gwen LeMasson and Andreas Frick. Dendritic channelopathies contribute to neocortical and sensory hyperexcitability in Fmr1(-/y) mice. Nature Neuroscience (2014).
- Audrey Bonnan*, Yu Zhang*, Alexis Fedorchak*, Richard Kramer, Andreas Frick. Optical control of dendritic excitability with an ion channel photoswitch. In preparation.

Nanoscale functional organization of branched F-actin networks and N-cadherin adhesion during dendritic spine motility

Laureate name: Laurent Ladepeche	Supervisor name: Laurent Groc

- Ladepeche L.#, Dupuis J.P.#, Seth H., Bard L., Varela J., Mikasova L., Bouchet D., Rogemond V., Honnorat J., Hanse E. and Groc L. Surface dynamics of GluN2B-NMDA receptors controls LTP of maturing glutamatergic synapses, EMBO J. 2014 ; in press. doi:10.1002/embj.201386356.

#Equal contribution

- Ladepeche L., Dupuis J.P., Bouchet D., Dounikoff E., Yang L., Campagne Y., Grea H., Bezard E., Hosy E. and Groc L. Single molecule imaging evidence of the functional crosstalk between surface NMDA and dopamine D1 receptors, PNAS 2013 ; 110(44):18005-10.

- Ladepeche L., Yang L., Bouchet D. and Groc L. Regulation of dopamine D1 receptor dynamics within the postsynaptic density of hippocampal glutamate synapses, PloS ONE 2013 ; 8(9): e74512. doi:10.1371/journal.pone.0074512.

- Ladepeche L., Dupuis J.P. and Groc L. Surface trafficking of NMDA receptors: gathering from a partner to another, Semin. Cell. Dev. Biol. 2013 ; pii: S1084-9521(13)00110-9. doi: 10.1016/j.semcdb.2013.10.005.

→ Publication in preparation:

- Papouin T., Ladepeche L., Yao A., Langlais V., Dulong J., Sacchi S., Mothet J.P., Pollegioni L., Paoletti P., Groc L. and Oliet S.H.R. Co-agonist availability controls NMDA receptor composition at synapses.

- Potier M., Georges F., Brayda-Bruno L., Ladepeche L., Mikasova L., Lamothe V., Bonnet C., Groc L., Marighetto A. Temporal memory requires surface trafficking of hippocampal NMDA receptors.

- Lesept F., Chevilley A., Ladepeche L., Jezequel J., Macrez R., Bertrand T., Hommet Y., Maubert E., Cobo S., Galea P., Groc L. and Vivien D. The extracellular Serine protease tissue plasminogen activator (tPA) promotes the dynamic of neuronal extrasynaptic NMDA receptors and subsequent signaling through direct NTD-GluN1 (Lys178) coupling.

Cannabinoid type 1 receptor (CB1) deletion in discrete hypothalamic nuclei: its role in energy and glucose homeostasis

Laureate name: Pierre Cardinal	Supervisor name: Daniela Cota

- Cardinal P, Bellocchio L, Clark S, Cannich A, Klugmann M, Lutz B, Marsicano G, Cota D. Hypothalamic CB1 Cannabinoid Receptors Regulate Energy Balance in Mice. Endocrinology, 2012 Sep;153(9):4136-43.

- Bermudez-Silva FJ, Cardinal P, Cota D. The Role of the Endocannabinoid System in the Neuroendocrine Regulation of Energy Balance. J Psychopharmacol 2012 Jan; 26(1):114-24. (revue)

- Dubreucq S, Matias I, Cardinal P, Häring M, Lutz B, Marsicano G, Chaouloff F. Genetic Dissection of the Role of Cannabinoid Type-1 Receptors in the Emotional Consequences of Repeated Social Stress in Mice. Neuropsychopharmacology 2012 July; 37(8):1885-900.

- Bellocchio L, Soria-Gomez E, Quarta C, Metna-Laurent M, Cardinal P, Binder E, Cannich A, Delamarre ■ A, Häring M, Martín-Fontecha M, Vega D, Bartsch D, Monory K, Lutz B, Chaouloff F, Guzman M, Pagotto U, Cota D, Marsicano G. Activation of the sympathetic nervous system mediates hypophagic and anxiety-like effects of CB1 receptor blockade. PNAS, 2013, March 9;110(12):4786-91.

- Bosier B, Bellocchio L, Metna-Laurent M, Soria-Gomez E, Matias I, Cannich A, Maitre M, Verrier D, Leste-Lasserre T, Cardinal P, Mendizabal-Zubiaga J, Canduela MJ, Reguero L, Chaouloff F, Hermans E, Grandes P, Cota D, Marsicano G. Critical role of astroglial CB1 cannabinoid receptors in the regulation of leptin-mediated functions. Mol Metab. 2013 Aug 9;2(4):393-404.

- Cardinal P, André C, Quarta C, Bellocchio L, Clark S, Elie M, Leste-Lasserre T, Maitre M, Gonzales D, Cannich A, Pagotto U, Marsicano G, Cota D. CB1

cannabinoid receptor in SF1-expressing neurons of the ventromedial hypothalamus determines metabolic responses to diet and leptin. Mol Metab. 2014 Aug 1;3(7):705-16.

- Cardinal P, Bellocchio L, Guzmán-Quevedo O, André C, Clark S, Elie M, Leste-Lasserre T, Gonzales D, Cannich A, Marsicano G, Cota D. Cannabinoid type 1 (CB1) receptors on Sim1-expressing neurons regulate energy expenditure in male mice. Endocrinology. 2015 Feb;156(2):411-8. Adipocyte cannabinoid receptor CB1 regulates energy homeostasis and alternatively activated macrophages.

- Ruiz de Azua I, Mancini G, Srivastava RK, Rey AA, Cardinal P, Tedesco L, Zingaretti CM, Sassmann A, Quarta C, Schwitter C, Conrad A, Wettschureck N, Vemuri VK, Makriyannis A, Hartwig J, Mendez-Lago M, Bindila L, Monory K, Giordano A, Cinti S, Marsicano G, Offermanns S, Nisoli E, Pagotto U, Cota D, Lutz B. J Clin Invest. 2017 Nov 1;127(11):4148-4162. doi: 10.1172/JCI83626. Epub 2017 Oct 16.

→ Communications:

- Cardinal, P, Bellocchio L, Clark S, Elie M, Marsicano G, Cota D." The role of CB1 located in the ventromedial nucleus in energy and glucose homeostasis." TOS meeting in Orlando (USA), October 2011.
- Cardinal, P, Bellocchio L, Clark S, Elie M, Marsicano G, Cota D." The role of CB1 located in the ventromedial nucleus in energy and glucose homeostasis." Neurocentre Magendie Symposium in Bordeaux (France), December 2011.
- Cardinal, P, Bellocchio L, Clark S, Elie M, Marsicano G, Cota D." The role of CB1 located in the ventromedial nucleus in energy and glucose homeostasis." European Congress of Obesity in Lyon (France), May 2012.

Dietary omega-3 deficiency and emotional behaviors: role of hypothalamic-pituitary-adrenal axis

Laureate name: Thomas Larrieu	Supervisor name: Sophie Layé

- Manduca A, Bara A, Larrieu T, Lassalle O, Joffre C, Layé S, Manzoni OJ. Amplification of mGlu5-Endocannabinoid Signaling Rescues Behavioral and Synaptic Deficits in a Mouse Model of Adolescent and Adult Dietary Polyunsaturated Fatty Acid Imbalance. J Neurosci. 2017 Jul 19;37(29):6851-6868. doi: 10.1523/JNEUROSCI.3516-16.2017. Epub 2017 Jun 19.

- Bosch-Bouju C, Larrieu T, Linders L, Manzoni OJ, Layé S. Endocannabinoid-Mediated Plasticity in Nucleus Accumbens Controls Vulnerability to Anxiety after Social Defeat Stress. Cell Rep. 2016 Aug 2;16(5):1237-1242. doi: 10.1016/j.celrep.2016.06.082. Epub 2016 Jul 21.

- Larrieu T, Hilal ML, De Smedt-Peyrusse V, Sans N, Layé S.Nutritional Omega-3 Deficiency Alters Glucocorticoid Receptor-Signaling Pathway and Neuronal Morphology in Regionally Distinct Brain Structures Associated with Emotional Deficits. Neural Plast. 2016;2016:8574830. doi: 10.1155/2016/ 8574830. Epub 2015 Dec 30.

- Delpech JC, Thomazeau A, Madore C, Bosch-Bouju C, Larrieu T, Lacabanne C, Remus-Borel J, Aubert A, Joffre C, Nadjar A, Layé S.Dietary n-3 PUFAs Deficiency Increases Vulnerability to Inflammation-Induced Spatial Memory Impairment. Neuropsychopharmacology. 2015 Nov;40(12):2774-87. doi: 10.1038/npp.2015.127. Epub 2015 May 7.

- Larrieu T, Hilal ML, Fourrier C, De Smedt-Peyrusse V, Sans N, Capuron L, Layé S.Nutritional omega-3 modulates neuronal morphology in the prefrontal cortex along with depression-related behaviour through corticosterone secretion. Transl Psychiatry. 2014 Sep 9;4:e437. doi: 10.1038/tp.2014.77.

Activity-dependent regulation of AMPA-type glutamate receptors trafficking by auxiliary proteins interaction with PSD-95

Laureate name: Anne-Sophie Hafner	Supervisor name: Daniel Choquet

Hafner, A.S., Penn, A.C., Grillo-Bosch, D., Retailleau, N., Poujol, C., Philippat, A., Coussen, F., Sainlos, M., Opazo, P., and Choquet, D. (2015). Lengthening of the Stargazin Cytoplasmic Tail Increases Synaptic Transmission by Promoting Interaction to Deeper Domains of PSD-95. Neuron 86, 475-489.

Adolescence, a period of vulnerability to the effects of obesity on memory : a focus on hippocampus and amygdala

Laureate name: Chloé Boitard	Supervisor name: Guillaume Ferreira

- Boitard C, Etchamendi N, Sauvant J, Aubert A, Tronel S, Marighetto A, Layé S & Ferreira G (2012). Juvenile, but not adult, exposure to high-fat diet impairs relational memory and hippocampal neurogenesis in mice. Hippocampus, 22: 2095 –2100.
- Boitard C, Cavaroc A, Sauvant J, Aubert A, Castanon N, Layé S & Ferreira G (2014). Impairment of hippocampal-dependent memory induced by juvenile high-fat diet intake is associated with enhanced hippocampal inflammation in rats. Brain, Behavior and Immunity, 40: 9-17.
- Boitard C, Maroun M, Tantot F, Cavaroc A, Sauvant J, Marchand A, Layé S, Capuron L, Darnaudery M, Castanon N, Coutureau E, Vouimba RM & Ferreira G (2015). Juvenile obesity exacerbates emotional memory and amygdala plasticity through glucocorticoids. The Journal of Neuroscience, 35(9):4092– 4103.
- Boitard C, Parkes SL, Cavaroc A, Tantot F, Castanon N, Layé S, Tronel S, Pacheco-Lopez G, Coutureau E & Ferreira G (2016) Switching adolescent high-fat diet to adult control diet restores neurocognitive alterations. Frontiers in Behavioral Neuroscience, 10: 225.
- Tantot F, Parkes SL, Marchand AR, Boitard C, Naneix F, Layé S, Trifilieff P, Coutureau E and Ferreira G (2017). The effect of high-fat diet consumption on appetitive instrumental behavior in rats. Appetite, 108: 203-211.
- Naneix F, Tantot F, Glangetas C, Kaufling J, Janthakhin Y, Boitard C, De Smedt-Peyrusse V, Pape JR, Vancassel S, Trifilieff P, Georges F, Coutureau E & Ferreira G (2017). Impact of early consumption of high-fat diet on the mesolimbic dopaminergic system. eNeuro, 4(3).

Neuromodulation by ATP P2X receptors of excitatory synapses

Laureate name: Johan-Till Pougnet	Supervisor name: Eric Boue-Grabot

- Pougnet J-T, Compans B, Martinez A, Choquet D, Hosy E, and Boué-Grabot E. (2016) P2X-mediated AMPA receptor internalization and synaptic depression is controlled by two CamKII phosphorylation sites on GluA1 in hippocampal neurons » Scientific Reports, 6, 31836. http://doi.org/10.1038/srep31836.
- Pougnet J-T, Toulmé E, Martinez A, Choquet D, Hosy E, and Boué-Grabot E. (2014) ATP P2X receptors down-regulate AMPA receptor trafficking and postsynaptic efficacy in hippocampal neurons. Neuron 83(2):417-430. doi: 10.1016/j.neuron.2014.06.005.

And a recent review on the topic (LabEx is alos aknowledged):

- Boué-Grabot E and Pankratov Y (2017) Modulation of central synapses by astrocyte-released ATP and postsynaptic P2X receptors. Neural Plasticity 2017:9454275. doi: 10.1155/2017/9454275. Epub 2017 Aug 6.

Role of prefrontal parvalbumin interneurons in the expression of conditioned fear behaviour

Laureate name: Julien Courtin	Supervisor name: Cyril Herry

- Courtin, J., Chaudun, F., Rozeske, R.R., Karalis, N., Gonzalez-Campo, C., Wurtz, H., Abdi, A., Baufreton, J., Bienvenu, T.C.M., and Herry, C. (2014). Prefrontal parvalbumin interneurons shape neuronal activity to drive fear expression. Nature, 505: 92-96. IF: 38.597.
- Karalis, N., Dejean, C., Chaudun, F., Khoder, S., Rozeske, R.R., Wurtz, H., Bagur, S., Benchenane, K., Sirota, A., Courtin, J., and Herry, C. (2014). 4 Hz Oscillations synchronize prefrontal-amygdala circuits during fear behavior Nature Neuroscience, 19:605-612. IF: 16.095 Prefrontal neuronal assemblies temporally control fear behaviour.
- Dejean C, Courtin J, Karalis N, Chaudun F, Wurtz H, Bienvenu TC, Herry C. Nature. 2016 Jul 21;535(7612):420-4. Epub 2016 Jul 13.

Alterations in neocortical circuits are a crucial feature of cognitive defects in Fragile X Syndrome

Laureate name: Matthias Haberl	Supervisor name: Andreas Frick

- Valerio Zerbi, Giovanna D. Ielacqua, Marija Markicevic, Matthias Georg Haberl, Mark H. Ellisman, Arjun A-Bhaskaran, Andreas Frick, Markus Rudin and Nicole Wenderoth (2018) Dysfunctional Autism Risk Genes Cause Circuit-Specific Connectivity Deficits With Distinct Developmental Trajectories. Cerebral Cortex, in press.
- Aloisi,E., Le Corf, K., Dupuis, J., Zhang, P., Ginger, M., Labrousse, V., Spatuzza, M., Haberl, MG., Costa, LT., Shigemoto, R., Thappe Theoder, A., Drago, F., Piazza, PV., Mulle, C., Groc, L., Ciranna, L., Catania, MV., and Frick, A. (2017) Altered surface mGluR5 dynamics provoke synaptic NMDAR dysfunction and cognitive defects in Fmr1 knockout mice. Nature Communications. 2017 Oct 24;8(1):1103. doi: 10.1038/s41467-017-01191-2.
- Haberl, M., Ginger, M., Frick, A. (2017) Dual anterograde and retrograde viral tracing of reciprocal connectivity. Methods Mol Biol. 1538:321-340.
- Silvia Viana da Silva, Matthias Haberl, Philipp Bethge, Cristina Lemos, Nelio Gonçalves, Adam Gorlewicz, Francisco Q. Goncalves, Noelle Grosjean, Christophe Blanchet, Andreas Frick, U. Valentin Nägerl, Rodrigo A. Cunha, Christophe Mulle. Early synaptic deficits in the APP/PS1 mouse model of Alzheimer's disease involve neuronal adenosine A2A receptors. (2016). Early synaptic deficits in the APP/PS1 mouse model of Alzheimer's disease involve neuronal adenosine A2A receptors. Nature communications 7, 11915. http://doi.org/10.1038/ncomms11915.

- Haberl, M. G., Zerbi, V., Veltien, A., Ginger, M., Heerschap, A., and Frick A. (2015). Structural-functional connectivity deficits of neocortical circuits in the Fmr1-/y mouse model of autism. Science Advances, 1(10), e1500775–e1500775. doi:10.1126/sciadv.1500775.
- Haberl, M.*, Viana da Silva, S.*, Guest, M., Ghanem, A., Ginger, M., Mulle, C., Oberlaender, M., Conzelmann, K.K., Frick, A. (2015) An anterograde rabies virus vector for high-resolution large-scale reconstruction of 3D neuron morphology. Brain Structure and Function. 220(3):1369-79. doi: 10.1007/s00429-014-0730-z.
- Ginger, M., Haberl, M., Conzelmann, K.-K., Schwarz, M.K., Frick, A. (2013) Revealing the secrets of neuronal circuits with recombinant rabies virus technology. Frontiers in Neural Circuits. doi: 10.3389/fncir.2013.00002.

Development of novel micro-patterned substrates for axonal growth and synaptogenesis

Laureate name: Mikael Garcia	Supervisor name: Olivier Thoumine

- Garcia M, Leduc C, Lagardère M, Argento A, Sibarita JB, Thoumine O (2015). Two-tiered coupling between flowing actin and immobilized N-cadherin/catenin complexes in growth cones. Proc Natl Acad Sci USA 112(22):6997-7002.
- Chazeau* A, Garcia* M, Czöndör* K, Perrais P, Tessier B, Giannone G, Thoumine O (2015). A mechanical coupling between N-cadherin adhesions and the F-actin flow stabilizes dendritic spines. Mol Biol Cell 26(5):859-73.

(*) equally contributing first authors

Role of the endocannabinoid system in morphological plasticity probed by two-photon excitation STED microscopy

Laureate name: Philipp Bethge	Supervisor name: Valentin Nägerl

Springer Book: Nanoscale Imaging of Synapses: New Concepts and Opportunities. U. Valentin Nägerl and Antoine Triller (Eds.) Chapter 11: Two-photon STED microscopy.

Analysis of synaptic plasticity in CA3 pyramidal cells in vivo

Laureate name: Stefano Zucca	Supervisor name: Christophe Mulle

- Zucca, S., Griguoli, M., Malezieux, M., Grosjean, N., Carta, M., Mulle, C., 2017. Control of Spike Transfer at Hippocampal Mossy Fiber Synapses In Vivoby GABA Aand GABA BReceptor-Mediated Inhibition. Journal of Neuroscience 37, 587–598. doi:10.1523/JNEUROSCI.2057-16.2016.
- Griguoli M, Betterton R, Zucca S, Mulle C. Cholinergic modulation of neuronal oscillation and hippocampal CA3 circuits using in vivo recordings and optogenetics. (en préparation).

2014

Pacemaker properties of identified neurons triggering compulsive behavior in Aplysia: an analysis using combined electrophysiology and functional magnetic resonance imaging at single-cell resolution

Laureate name: Alexis Bédécarrats	Supervisor name: Romuald Nargeot

Pavel Svehlaa, Alexis Bédécarrats, Caroline Jahna, Romuald Nargeot, Luisa Ciobanua (2017). Intracellular manganese enhanced MRI signals reflect the frequency of action potentials in Aplysia neurons. J. Neurosci. Meth. (in press).

Nargeot R., Bédécarrats A. (2017). Associative learning in invertebrates. In "Oxford Handbook of Invertebrate Neurobiology". Ed. J.H. Byrne. Oxford University Press, USA.

The following articles are still in preparation:

Bédécarrats A, Castro J, Lade Q, Cattaert D, Simmers J, Nargeot R. Role for a non-linear interaction between organellar and transmembrane calcium dynamics in the generation of feeding behavior in Aplysia.

Bédécarrats A, Castro J, Lade Q, Cattaert D, Simmers J, Nargeot R. Ionic mechanisms of pacemaker properties and plateau potential in neurons of the decision-making network for feeding behavior in Aplysia

Regulations of BNST neurons by the medial prefrontal cortex and the ventral subiculum

Laureate name: Christelle Glangetas	Supervisor name: François Georges

- Glangetas C, Fois G.R., Jalabert M., Lecca S., Valentinova K., Meye F.J., Diana M., Faure P., Mameli M., Caille S., Georges F. Ventral Subiculum Stimulation Promotes Persistent Hyperactivity of Dopamine Neurons and Facilitates Behavioral Effects of Cocaine. Cell Reports. 2015 ; 13(10), 2287-2296. IF : 8.358.
- Glangetas C, Georges F. Pharmacology of the Bed Nucleus of the Stria Terminalis. Current Pharmacology Reports 2017 2 (6), 262-270.
- Glangetas C*, Massi L*, Fois G.R. *, Jalabert M., Girard D., Diana M., Yonehara K., Roska B., Xu C., Lüthi A., Caille S. Georges F. NMDA-receptor-dependent plasticity in the bed nucleus of the stria terminalis triggers long-term anxiolysis. Nat Comm. 2017 Nat Commun. 2017 Feb 20;8:14456. doi: 10.1038/ncomms14456.

Altered mGlu5 receptor surface dynamics are linked to abnormal NMDA receptor function and plasticity in Fragile X Syndrome

Laureate name: Elisabetta Alosi	Supervisor name: Andreas Frick

- Aloisi E., Le Corf K., Zhang P., Labrousse V., Dupuis J.P., Haberl M.G., Costa L., Ginger M., Shigemoto R., Tappe-Theoder A., Drago F., Piazza P.V., Mulle C., Groc L., Ciranna L., Catania M.V. and Frick A. Altered surface dynamics of mGlu5 receptor lead to synaptic NMDA receptor dysfunction and cognitive defects in the mouse model of Fragile X Syndrome. Submitted.
- Carreno, M.I., Aloisi E., Deschaud, C., Subashi, E., Morales Navas, M., Pietropaolo S., Ginger, M., Frick, A. and Xavier, L. Pharmacological rescue of novelty-induced behavioural disturbances in a mouse model of FXS. In preparation.
- Spatuzza M., D'Antoni S., Aloisi E., Bonaccorso C.M., Molinaro G., Battaglia G., Musumeci S., Maurin T., Bardoni B., Shigemoto R., Nicoletti F., Catania M.V. Metabotropic Glutamate subtype 5 receptors are increased at synapses and do not undergo agonist-induced internalization in the Fmr1 KO mouse model of Fragile X Syndrome. In preparation.

Compressive Fluorescence Microscopy for Biological Imaging and Super Resolution Microscopy

Laureate name: Makhlad Chahid	Supervisor name: Vincent Studer

A publication is in preparation in collaboration with Jean Barbier (EPFL):

Approximate Message Passing for compressive fluorescence microscopy.

Visualisation and Perturbation of the spatio-temporal dynamics of endocytosis

Laureate name: Morgane Rosendale	Supervisor name: David Perrais

- Perrais, D., and Rosendale, M. (2017). [Endocytosis in dendrites: a local tool to regulate synaptic transmission]. Med. Sci. MS 33, 942–945.
- Rosendale, M., and Perrais, D. (2017). Imaging in focus: Imaging the dynamics of endocytosis. Int. J. Biochem. Cell Biol. 93, 41–45.
- Rosendale, M., Jullié, D., Choquet, D., and Perrais, D. (2017). Spatial and Temporal Regulation of Receptor Endocytosis in Neuronal Dendrites Revealed by Imaging of Single Vesicle Formation. Cell Rep. 18, 1840–1847.
- Cauvin, C., Rosendale, M., Gupta-Rossi, N., Rocancourt, M., Larraufie, P., Salomon, R., Perrais, D., and Echard, A. (2016). Rab35 GTPase Triggers Switch-like Recruitment of the Lowe Syndrome Lipid Phosphatase OCRL on Newborn Endosomes. Curr. Biol. 26, 120–128.
- Shen, Y., Rosendale, M., Campbell, R.E., and Perrais, D. (2014). pHuji, a pH-sensitive red fluorescent protein for imaging of exo- and endocytosis. J. Cell Biol. 207, 419–432.

Dynamin requires multimeric interactions with SH3 domain containing proteins for efficient endocytosis. Morgane Rosendale, Thi Nhu Ngoc Van, Dolors Grillo-Bosch, Isabel Gauthereau, Daniel Choquet, Matthieu Sainlos and David Perrais. In préparation.

Molecular mecanisms for synaptic segregation of kainate receptors at hippocampal mossy fiber synapse

Laureate name: Sabine Fièvre	Supervisor name: Christophe Mulle

- Carta, M., Fievre, S., Gorlewicz, A., & Mulle, C. (2014). Kainate receptors in the hippocampus. European Journal of Neuroscience.
- Piguel, N. H., Fievre, S., Blanc, J.-M., Carta, M., Moreau, M. M., Moutin, E., et al. (2014). Scribble1/AP2 Complex Coordinates NMDA Receptor Endocytic Recycling. Cell Reports.
- Fièvre, S., Carta, M., Chamma, I., Labrousse, V., Thoumine, O., Mulle, C., 2016. Molecular determinants for the strictly compartmentalized expression of kainate receptors in CA3 pyramidal cells. Nature Communications 7, 12738. doi:10.1038/ncomms12738.

and postsynaptic P2X receptors. Neural Plasticity 2017:9454275. doi: 10.1155/2017/9454275. Epub 2017 Aug 6.

NMDA receptor subcellular location and memory functions are altered in the APP/PS1 mouse model of Alzheimer's disease

Laureate name: Senka Hadzibegovic	Supervisor name: Bruno Bontempi

- O. Nicole*, S. Hadzibegovic*, J. Gajda, B. Bontempi, T. Bem, P. Meyrand. Soluble amyloid beta oligomers block the learning-induced increase in hippocampal sharp wave-ripple rate and impair spatial memory formation. Scientific Reports 2016; 6, 22728; doi: 10.1038/srep22728. * Equal contribution.
- Hadzibegovic Senka. Behavioral, molecular and electrophysiological characterization of the learning and memory deficits induced in mouse models of Alzheimer's disease. PhD thesis, University of Bordeaux, September 10, 2015, 202 p. (http://www.bordeaux-neurocampus.fr/fr/formation-doctorale/theses-2015/s-hadzibegovic.html).
- S. Hadzibegovic, B. Bontempi, O. Nicole. NMDAR subcellular location and memory functions are altered in the APPswe/PS1dE9 mouse model of Alzheimer's disease. In preparation.
- O. Moustié, S. Hadzibegovic, F. El gaamouch, B. Bontempi, T. Freret, E. Maubert, K.Brodji, A. Buisson, O. Nicole. Accumulation of amyloid β oligormers in the post-synaptic compartment as an early marker of cognitive deficits in transgenic mouse model of Alzheimer's disease. In preparation.

The role of mitochondrial cannabinoid receptor type 1 in the brain

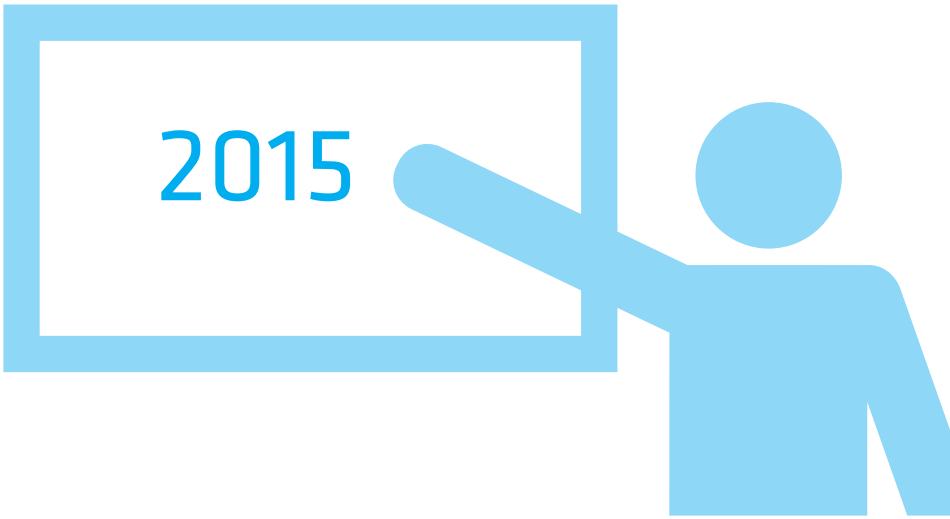
Laureate name: Tifany Desprez	Supervisor name: Giovanni Marsicano

Dissecting the cannabinergic control of behavior: The where matters. 2015. Busquets-Garcia A, Desprez T, Metna-Laurent M, Bellocchio L, Marsicano G, Soria-Gomez. BioEssays. 37(11), 1215-1225. Impact factor 4.73.

Olfactory habituation in fasted mice. Bio-protocol. 2014. Desprez T, Marsicano G, Soria-Gomez E#. Published on-line in www.bio-protocol.org.

A Cannabinoid Link Between Mitochondria and Memory. Etienne Hebert-Chatelain*, Tifany Desprez*, Román Serrat*, et al., in préparation.

CB1 receptors in the substantia nigra mediate the motor impairment induced by cannabinoids. Desprez T, et al., In preparation.



Unravelling the functional dynamics of cortical GluN2-containing NMDA receptors during systems-level memory consolidation

Laureate name: Benjamin Bessieres	Supervisor name: Olivier Nicole

- Bessières B, Giacinti A, Nicole O, Bontempi B. Assessing recent and remote associative olfactory memory in rats using the social transmission of food preference paradigm.
- Bessières B, Dupuis J, Hambucken A, Groc L, Bontempi B, Nicole O. Surface dynamics of cortical GluN2B-containing NMDA receptors drives stabilization and forgetting of long-lasting associative memory. in preparation.

Development and application of FN3 domain-derived stabilizers of PDZ domain-mediated interactions by directed evolution

Laureate name: Charlotte Rimbault	Supervisor name: Matthieu Sainlos

- Rimbault, C., Maruthi, K., Breillat, C., Genuer, C., Crespillo, S., Gauthereau, I., Antoine, S., Thibault, C., Wong, F., Grillo-Bosch, D., Claverol, S., Poujol, C., Choquet, D., Mackereth, C. & Sainlos, M. Engineering selective competitors targeting PSD-95 PDZ domains. Manuscript in preparation.
- Rimbault, C., Breillat, C., Compans, B., Toulme, E., Mascalchi, P., Fernandez Monreal, M., Gauthereau, I., Genuer, C., Antoine, S., Hosy, E., Poujol, C., Choquet, D. & Sainlos, M. Highly specific binders for imaging endogenous PSD-95. Manuscript in preparation.

Thalamocortical control of goal-directed behaviors in Rats

Laureate name: Fabien Alcaraz	Supervisor name: Etienne Coutureau & Mathieu Wolff

- Alcaraz F., Courtand G., Marchand A.R., Coutureau E., Wolff M. (2016) Parallel inputs from the mediodorsal thalamus to the prefrontal cortex in the Rat, European Journal of Neuroscience, 44:1972-86.
- Alcaraz F, Fresno V, Marchand AR, Kremer EJ, Coutureau E, Wolff M Thalamocortical and corticothalamic pathways differentially contribute to goal-directed behaviors in the rat, eLife, under revision.

Identification of exocytosis proteins involved in postsynaptic trafficking

Laureate name: Julia Krapivkina	Supervisor name: David Perrais

VAMP4 control constitutive recycling in neuronal dendrites.

Krapivkina J, Jullié D, Petersen J, Retailleau N, Choquet D & Perrais D.n preparation.

Non-canonical action of psychotomimetic molecules on NMDA receptor trafficking

Laureate name: Julie Jezequel	Supervisor name: Laurent Groc & Pr. Constantine-Paton

J.JEZEQUEL, E.Johansson, H.Gréa, V.Rogemond, B. Kellermeyer, N.Hamadani, E. LeGuen, C.Rabu, E.Mathias, J.Varela, D.Bouchet, R.H. Yolken, R.Tamouza, J.Dalmau, J.Honnorat, M.Leboyer, and L.Groc. Heterogeneity of human anti-NMDA receptor antibodies: nanoscale disorganization of synaptic receptors by autoantibodies from schizophrenic patients. En soumission (Neuron). In preparation.

Reduced GABA uptake by astrocytes is responsible for pathological tonic inhibition in the external globus pallidus in experimental Parkinsonism

Laureate name: Marine Chazalon	Supervisor name: Jérome Baufreton

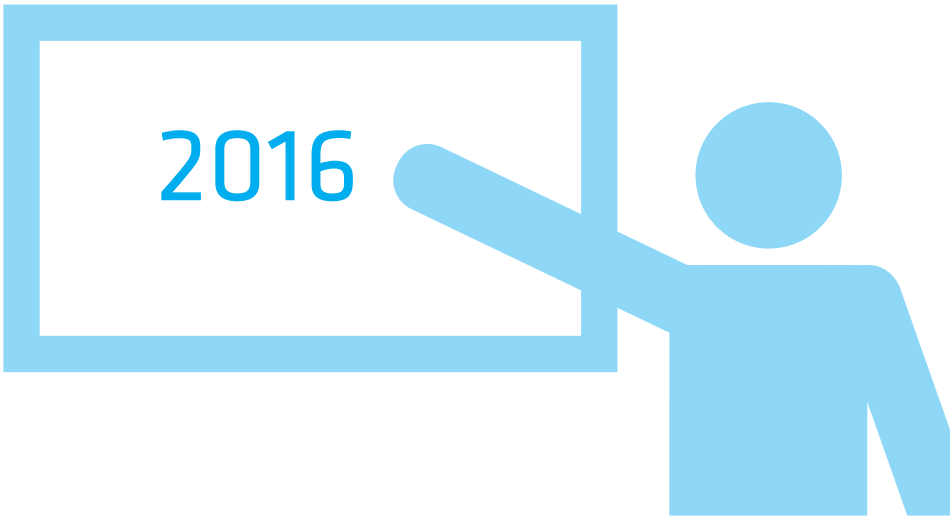
- Du Z, Chazalon M, Bestaven E, Leste-Lasserre T, Baufreton J, Cazalets JR, Cho YH, Garret M. Early GABAergic transmission defects in the external globus pallidus and rest/activity rhythm alteration in a mouse model of Huntington's disease. (2016) Neuroscience: 329:363-79.
- Chazalon M, Morin S, Martinez A, Cristóvão-Ferreira S, Vaz S, Sebastiao A, Paredes-Rodriguez E, Panatier A, Boué-Grabot E, Miguelez C and Baufreton J. GAT-3 dysfunction generates tonic inhibition in external globus pallidus neurons in Parkinsonian rodents. In revision (Cell Reports).
- Garret M, Du Z, Chazalon M, Cho YH, Baufreton J. Alteration of GABAergic neurotransmission in Huntington's disease. (2016). Submitted (CNS Neuroscience & Therapeutics).
- Baufreton J, Milekovic T, Li Q†, McGuire S, Martin Moraud E, Porras G, Sun S, Ko W, Chazalon M, Morin S, Normand E, Farjot G, Milet A, Pype J, Pioli E, Courtine G, Bessière B and Bezard E. Inhaling xenon ameliorates L-DOPA-induced dyskinesia in Parkinson's disease through normalizing maladaptive corticostriatal plasticity. Submitted (Brain).

Synaptic vesicle mobility and turnover at VGLUT1 excitatory axons in mice

Laureate name: Xiaomin Zhang	Supervisor name: Etienne Herzog

molecular characterization of VGLUT1 contribution to excitatory transmission in rodents.
X M Zhang et al in preparation.

In vivo imaging of VGLUT1mEOS2 labeled synaptic vesicle super-pool in mice.
X M Zhang et al in preparation.



Imaging and quantification of single molecules in thick biological samples with adaptive optics

Laureate name: Corey Butler | Supervisor name: Jean-Baptiste Sibarita

Project Objectives

This project aimed to apply the spectrally-resolved single molecule tracking microscope I developed during my PhD to neuroscience applications. More specifically, the primary objective was to collaborate with Laurent Groc's group to perform simultaneous multicolor, multi-receptor tracking in live dissociated neuron cultures.

Main Results

Working in close collaboration with Ezequiel Saraceno (Laurent Groc's group, IINS), we have succeeded to routinely track multiple membrane receptors tagged with quantum dots of different colors in dissociated hippocampal neuron cultures. Furthermore -- and beyond the initial scope of the project -- we have extended the capabilities of the microscope for compatibility with live brain slice imaging, and to that end we have performed the first proof of principle experiments of spectrally-resolved single particle tracking in organotypic brain slices using a dual-collection objective configuration. Apart from these neuroscience applications, two collaborations with external laboratories were initiated, expanding applications of the system to live and fixed bacteria imaging as well as material science.

Working Plan to Continue

With the proof of concept nearly complete, Ezequiel Saraceno will continue to perform spectral single particle tracking experiments in primary neuron cultures and organotypic slices. He will focus on using the system to answer questions regarding the interaction and organization of several membrane-bound proteins.

Published Publications

Localization-based super-resolution imaging meets high-content screening. Anne Beghin, Adel Kechkar, Corey Butler, Florian Levet, Marine Cabillic, Olivier Rossier, Gregory Giannone, Rémi Galland, Daniel Choquet & Jean-Baptiste Sibarita. Nature Methods December 2017.

Publications in Preparation

- Spectrally-Resolved Simultaneous 3-Dimensional Multi-Receptor Tracking. Corey Butler, G Ezequiel Saraceno, Julien Dupuis, Remi Galland, Laurent Groc, Vincent Studer, Jean-Baptiste Sibarita. In Preparation for submission in early 2018.

- A super-resolution platform for correlative single molecule and STED microscopy. V. V. G. Krishna Inavalli, Martin O. Lenz, Corey Butler, Julie Angibaud, Benjamin Compans, Florian Levet, Jan Tønnesen, Olivier Rossier, Gregory Giannone, Olivier Thoumine, Eric Hosy, Daniel Choquet, Jean-Baptiste Sibarita*, U. Valentin Nägerl*. In preparation for submission to Nature Methods in January 2018.

Collaborations

Bacterial cell wall nanoimaging by autoblinking microscopy. Kevin Floch, Françoise Lacroix, Liliana Barbieri, Remi Galland, Corey Butler, Jean-Baptiste Sibarita, Dominique Bourgeois*, Joanna Timmins*. Submitted Nature Communications December 2017.

Communications

- Poster Presentation. Multicolor 3D Single Particle Tracking Using Spectrally Displaced Localization. Biophysical Society Meeting, New Orleans, Louisiana, USA. February 2017.
- Oral Presentation. Multicolor 3D Single Particle Tracking Using Spectrally Displaced Localization. Focus on Microscopy, Bordeaux, France. 12 April, 2017.
- Oral Presentation. Spectrally-Resolved Simultvvaneous 3-Dimensional Multi-Receptor Tracking. Frontiers in Neuroscience, Bordeaux, France. 15 October, 2017.

C low threshold mechanoreceptors a key for the nociceptive circuitry

Laureate name: Charline Kambrun	Supervisor name: Yves Le Feuvre

Project Objectives

The neuronal networks processing CLTMR triggered information are not yet identified, and the functional repercussions of their recruitment on sensory-nociceptive integration remains poorly understood. We took advantage of the C-LTMRs restricted expression of TAFA4 to inquire into the contribution of these neurons in the control of nociceptive information transmission.

Main Results

Here, we demonstrate that the C-LTMR derived TAFA4 chemokine, through presynaptic mechanisms, induces a reinforcement of inhibitory synaptic transmission within spinal networks, which consequently depresses local excitatory synapses and impairs synaptic transmission from high threshold C-fibers. In Complete Freund's Adjuvant (CFA) inflamed animals, TAFA4 decreases the neuronal response recorded in vivo following noxious stimulus, and alleviates mechanical pain, both effects being blocked by antagonists of GABAergic transmission. Furthermore, TAFA4 promotes microglial retraction in CFA inflamed animals, together with an increase in the number of inhibitory synapses on lamina IIi somata.

Working Plan to Continue

Confirm that an injection of TAFA4 induces a displacement of inhibitory synapses, first by using electron microscopy which will allowing us to quantify inhibitory synapses on neuronal somata, on glomeruli and on neuronal fibers. To assess microglial mobility in presence of TAFA4 we will use STED microscopy on spinal cord slices and measure glial retraction.

Publications in Preparation

The C-LTMR derived chemokine TAFA4 reverses mechanical allodynia through activation of GABAergic transmission and microglial process retraction.
Kambrun C, Roca-Lapirot O, Salio C, Landry M, Moqrich A, Le Feuvre Y
In revision, Cell Report

Communications

Oral communication
Pain relief through activation of spinal GABAergic neurons by the C-LTMR derived chemokine TAFA4.
Kambrun C, Roca-Lapirot O, Salio C, Landry M, Moqrich A, Le Feuvre Y.
NeuroFrance 2017 (Bordeaux), 17th May 2017.
Poster
Activation of spinal dorsal horn inhibitory networks by the C-LTMR derived chemokine TAFA4
Kambrun C, Roca-Lapirot O, Salio C, Landry M, Moqrich A, Le Feuvre Y.
NeuroFrance 2017 (Bordeaux), 17, 18,19th May 2017.

Modulation of nociceptive response by group I Metabotropic Glutamate Receptors and L-type calcium channels in spinal cord: Electrophysiological approach in vivo

Laureate name: Houda Radwani	Supervisor name: Pascal Fossat

Project Objectives

The dorsal horn of the spinal cord is a crucial site for pain transmission and modulation. Dorsal horn neurons express group I metabotropic glutamate receptors (group I mGluRs) that exert a complex role in nociceptive transmission. In particular, group I mGluRs promote the activation of L-type calcium channels, voltage-gated channels involved in short- and long-term sensitization to pain. In this study, we analyzed the role of group I mGluRs in spinal nociceptive transmission and the possible cooperation between these receptors and L-type calcium channels in the pathophysiology of pain transmission in the dorsal horn of the spinal cord.

Main Results

We demonstrate that the activation of group I mGluRs induces allodynia and L-type calcium channel-dependent increase in nociceptive field potentials following sciatic nerve stimulation. Surprisingly,

in a model of persistent inflammation induced by complete Freund's adjuvant, the activation of group I mGluRs induced an analgesia and a decrease in nociceptive field potentials. Among the group I mGluRs, mGluR1 promotes the activation of L-type calcium channels and increased nociceptive transmission while mGluR5 induces the opposite through the inhibitory network. These results suggest a functional switch exists in pathological conditions that can change the action of group I mGluR agonists into possible analgesic molecules, thereby suggesting new therapeutic perspectives to treat persistent pain in inflammatory settings.

Working Plan to Continue

My professional project is to become ''lecturer'' in the university. Prior to this, I would like to pursue with Post-Doctorate position to acquire more scientific maturity, learn new techniques, create collaboration, develop my skills, expand my professional network, and also to publish mu publications.

Published Publications

- Radwani. H, Cattaert. D, Favereaux. A, Dobremez. E, Lopez-gonzalez. M, Eiríksdóttir. E, Langel. Ü, Errami. M, Landry. M, Fossat. P: ''Cav1.2 and Cav1.3 L - type calcium channels independently control short- and long-term sensitization to pain''. (J Physiol. 2016).
- Roca-Lapirot O, Radwani H, Aby F, Nagy F, Landry M and Fossat P, ''Calcium signaling through L-type calcium channels: role in pathophysiology of spinal nociceptive transmission'' (British Journal of Pharmacology. 2017).
- Radwani H, Roca-Lapirot O, Aby F, Lopez-gonzalez M, Benazzouz R, Errami M, Favereaux A, Landry M, Fossat P, ''Group I metabotropic glutamate receptors plasticity after peripheral inflammation alters nociceptive transmission in the dorsal horn of the spinal cord in adult rat. (Molecular pain. 2017).

The Planar Cell Polarity pathway regulates the balance between Pattern Completion and Pattern Separation

Laureate name: Benjamin Robert	Supervisor name: Nathalie Sans

Project Objectives

Vangl2 is a conserved transmembrane protein and one of the most upstream core planar cell polarity (PCP) proteins, which is involved in coordinating tissue growth in different developmental contexts.
The objective of this project was to understand the role of vangl2 signaling at a cellular, physiological and behavioural level, on the establishment, maturation and function of a well-defined synaptic circuit in the hippocampus.

Main Results

We found that Vangl2 is enriched in the dentate gyrus (DG)/CA3 network of the adult hippocampus, a structure intimately associated with memory processes. We thus postulated that Vangl2 modulates cognitive functions dependent on this network. To discriminate the embryonic from the postnatal role of vangl2, we generated conditional mutant (cKO) mice using a CaMKIIα promoter. The loss of vangl2 in these transgenic mice did not alter the acquisition of the spatial memory but the reorganization of spatial information and the computational information transmitted by the DG were affected. Notably, Vangl2 cKO mice were impaired in a Morris watermaze 'pattern completion' task, requiring rebuilding a spatial map using partial cues, and performed better than controls in a fear conditioning 'pattern separation' task, where mice have to distinguish two similar contexts. Using a viral approach, we further demonstrate that the specific loss of vangl2 in the DG leads to a similar phenotype. Our own results suggest that Vangl2 tunes DG/CA3 network maturation, thus affecting an optimal balance between 'pattern completion' and 'pattern separation' processes required for memory function.

Working Plan to Continue

The next step is to combine behavioural and in vivo electrophysiological approaches to assess hippocampal function after manipulating the expression of Vangl2 in specific hippocampal neuronal populations in the adult mouse. We expect to clarify the role of Vangl2-dependent signaling and function in the hippocampal circuit, and more generally to pave the way for a better understanding of the importance of PCPs in adult neuronal microcircuits.

Publications in Preparation

- Dos-Santos Carvalho S*, Quiedeville A*, Moreau MM*, Stockton J, Al-Abed S, Decroo M, Peyroutou R, Robert BJA, Racca C, Marighetto A, Sans N, Montcouquiol M. Vangl2 controls the morphofunctional development of the DG-CA3 network of the hippocampus.

- Robert BJA et al., and Marighetto A, Sans N, Montcouquiol M. Vangl2 fine-tunes hippocampus-dependent context discrimination and spatial completion.

Communications

- Robert B, Moreau M, Carvalho S, Decroo M, Brayda-Bruno L, Guette C, Desmedt A, Henderson D, Marighetto A, Montcouquiol M and Sans N 'Planar Cell Polarity signalling controls hippocampus-dependent cognitive processes' à la 15e Journée Scientifique de l'École Doctorale Sciences de la Vie et de la Santé Palais des Congrès – Arcachon, France, April 2015.
- Robert B, Moreau M, Carvalho S, Decroo M, Brayda-Bruno L, Guette C, Desmedt A, Henderson D, Marighetto A, Montcouquiol M and Sans N. Planar Cell Polarity signaling controls hippocampus-dependent cognitive processes' Journée Bordeaux Neurocampus/BRAIN 2015, France, May 2015.
- Moreau M, Pietropaolo S, Ezan J, Robert RJA, Medina C, Crusio W, Montcouquiol M & Sans N. Scribble1 controls social interest and preference for social novelty through ERK signaling. 12e Colloque de la Société des Neurosciences, Montpellier, mai 2015.
- Robert B, Moreau M, Carta M, Fievre S, Carvalho S, Decroo M, Brayda-Bruno L, Guette C, Desmedt A, Henderson D, Mulle C, Marighetto A, Montcouquiol M and Sans N. Planar Cell Polarity signaling controls hippocampus-dependent cognitive processes. 12e Colloque de la Société des Neurosciences, Montpellier, mai 2015.
- Robert B, Moreau M, Carta M, Fievre S, Carvalho S, Decroo M, Brayda-Bruno L, Guette C, Desmedt A, Henderson D, Mulle C, Marighetto A, Montcouquiol M and Sans N. Vangl2 in right amount required for a balanced memory ?. Symposium du Neurocentre Magendie, Decembre 2015, Bordeaux.
- Robert B, Moreau M, Carta M, Carvalho S, Quiedeville A, Peyroutou R, Atchama B, Decroo M, Barthet G, Brayda-Bruno L, Guette C, Desmedt A, Henderson D, Mulle C, Marighetto A, Montcouquiol M and Sans N. The Planar Cell pathway regulates the balance between Pattern Completion and Pattern separation' GDR NeuroMem, Lacanau, France, May 2016.
- Robert B, Moreau M, Carta M, Carvalho S, Quiedeville A, Peyroutou R, Atchama B, Decroo M, Barthet G, Brayda-Bruno L, Guette C, Desmedt A, Henderson D, Mulle C, Marighetto A, Montcouquiol M and Sans N. The Planar Cell pathway regulates the balance between Pattern Completion and Pattern separation' Bordeaux Neurocampus day, Bordeaux, France, Juin 2016.
- Robert B, Moreau M, Carta M, Carvalho S, Quiedeville A, Peyroutou R, Barthet G, Garret M, Fievre S, Atchama B, Brayda-Bruno L, Guette C, Racca C, Median C, Henderson D, Desmedt A, Mulle C, Marighetto A, Montcouquiol M and Sans N 'The Planar Cell pathway regulates the balance between Pattern Completion and Pattern separation' 46th annual meeting of Society for Neuroscience, San Diego, CA, U.S.A., 2016.
- Robert B, Carvalho S, Quiedeville A, Moreau M, Carta M, Peyroutou R, Atchama B, Decroo M, Fievre S, Barthet G, Brayda-Bruno L, Guette C, Medina C, Desmedt A, Henderson D, Mulle C, Marighetto A, Montcouquiol M and Sans N. The Planar Cell Polarity pathway regulates the balance between Pattern Completion and Pattern Separation. Neurofrance 2017, 13e Colloque de la Société des Neurosciences, Bordeaux, Mai 2017.

How neuroscientists and journalists deal with uncertainty: replication validity of biomedical findings covered by mass media

Laureate name: Estelle Dumas-Mallet

Supervisor name: Thomas Boraud and François Gonon

Project Objectives

During my PhD, we showed that newspapers preferentially cover initial positive biomedical studies. These studies are often invalidated by subsequent studies and journalists scarcely mentioned it. Hence, the results echoed in the press are mostly false or exaggerated. This project is aimed at exploring how three classes of actors, journalists, neuroscientists and patients and family, perceive and deal with the uncertainty inherent to initial findings.

Main Results

I have mainly been working on the first class of actors, the journalists. I have exploited the data of the 21 interviews of science journalists (18 French and 3 British). The results show that journalists still rely on press releases and publications in prestigious scientific journals. They consider them to be valid sources of trustworthy information. They do not question the peer-review system. For them, it guaranties the validity of the published results. Moreover, most of them do not seem to grasp how scientific knowledge is produced: they do not know that most initial findings are contradicted by subsequent studies. Surprisingly, journalists with a scientific background (some of them had a PhD in science) are not more cautious with initial findings. Finally, all of them agree that they should always mention when results have been invalidated but they reckon they would have a hard time to convince their editors to do so.

Working Plan to Continue

I am planning on tackling questions regarding the medialization of science. Medialization postulates an increased coupling between science and the medias. Using the database we have built, I will explore the influence of geographical localization (i.e. where the scientific study was done) on journalist' selection and its consequences on subsequent citation rate. I will also interview neuroscientists who have or not interacted with journalists.

Published Publications

Dumas-Mallet, E., Smith, A., Boraud, T., & Gonon, F. (2018). Scientific uncertainty in the press: how newspapers describe initial biomedical findings. Science Communication. In press.

Communications

12th January 2018: "Why biomedical findings echoed in the press are often invalidated? Uncertainty in science and in the press. Invited to give a presentation for the seminar series "Recherche et pratique en Santé Publique" ISPED-Bordeaux.

Survival and maturation of new neurons in the adult hippocampus: exploration of the key role played by Rnd2

Laureate name: Thomas Kerloch | Supervisor name: Emilie Pacary

Project Objectives

The main objective of my PhD is to understand the role of the RhoGTPase Rnd2 in the regulation of adult hippocampal neurogenesis. RhoGTPase family members are well known regulators of the actin cytoskeleton dynamics as well as embryonic neurogenesis, but very little is known about their role in the adult process. By implementing a strategy of loss of function we have studied the impact of Rnd2 deletion on the successive steps of adult hippocampal neurogenesis.

Main Results

So far we have been able to show that Rnd2 is critical for the survival, migration and the morphological maturation of adult-born hippocampal neurons (dendrites and cell body). Recently we tried to determine whether the increased death observed after Rnd2 deletion results from the mispositionning and/or aberrant morphology of newborn neurons or is independent. For this we deleted Rnd2 when new neurons had migrated and developed their dendritic arborization. In this paradigm new neurons positioning and morphology were not affected but their survival was still decreased demonstrating that Rnd2 controls directly the survival of adult-born neurons and regulates their migration and maturation through independent pathways. The impact on the survival was not observed when Rnd2 was deleted 8 weeks after neuronal birth, indicating that Rnd2 is important for the survival of adult-born neurons during a defined period.

Working Plan to Continue

To further understand the mechanisms underlying Rnd2 action in adult hippocampal neurogenesis we are currently studying the implication of RhoA which has been described to regulate survival of newborn hippocampal neurons, and Akt which is involved in their migration and morphological maturation. In parallel we are studying the impact of Rnd2 deletion in newborn neurons generated in the hippocampus of mice, at P0. By pursuing these analyses we will be able to better understand the role of Rnd2 in the development of new hippocampal neurons.

Publications in Preparation

- T. Kerloch, A. Goron, F. Farrugia, M. Maitre, H. Doat, T. Leste-Lasserre, F. Guillemot, D.N. Abrous, E. Pacary. The atypical RhoGTPase Rnd2 is critical for the survival and maturation of adult-born neurons in the hippocampus.
- T. Kerloch, S. Clavreul, A. Goron, D.N. Abrous, E. Pacary. Dentate granule neurons generated during embryogenesis and perinatally display distinct morphological features compared to adult-born neurons.

Communications

Oral communication

T. Kerloch, A. Goron, F. Guillemot, D.N. Abrous, E. Pacary. «The RhoGTPase Rnd2 is critical for the survival and maturation of newly generated neurons in the adult hippocampus». Hottopics of the Neurocentre Magendie (8th March 2017), Bordeaux, France.

Poster

T. Kerloch, A. Goron, F. Guillemot, D.N. Abrous, E. Pacary. «The RhoGTPase Rnd2 is critical for the survival and maturation of newly generated neurons in the adult hippocampus». NeuroFrance International Meeting (17-19th May 2017), Bordeaux, France.

Role of the prefontal cortex in mediating passive and active fear behaviours

Laureate name: Suzanna Khoder	Supervisor name: Cyril Herry

Project Objectives

The main objectives of my project were: (i) to develop a behavioural model in which a single conditioned stimulus can elicit, depending on the context, a freezing or avoidance response, (ii) to evaluate the contribution of dorsal medial prefrontal cortex (dmPFC) neurons to freezing/avoidance using single-unit recordings in behaving animals and (iii) to provide causal relationships between changes in dmPFC activity and freezing/avoidance behaviours.

Main Results

We developed a task in which mice could freeze or avoid as a function of the context and we identified two groups of mice: the first group exhibited avoidance and freezing (Good learners), while the second group displayed freezing but no avoidance to an auditory conditioned stimulus (Bad learners). We also recorded the activity of dmPFC neurons during behaviour and we stimulated the dorsolateral and lateral periaqueductal gray dl/lPAG (a structure mediating active fear responses) to identify antidromic spikes from dmPFC-recorded neurons. Our data indicate that dmPFC neurons activated during avoidance project to the dlPAG. Optogenetic light activation of dmPFC-dl/lPAG pathway enhanced avoidance in Bad learners suggesting that this pathway is sufficient for avoidance behaviour.

Working Plan to Continue

During the 4th year of this thesis, we will optogenetically inhibit dmPFC-dl/lPAG projecting neurons to address the necessity of the dmPFC-dl/lPAG pathway in avoidance. We will also identify the cellular type of dl/lPAG neurons target by dmPFC inputs.

Published Publications

Karalis*, N., Dejean*, C., Chaudun*, F., Khoder, S., Rozeske, R., R., Wurtz, H., Bagur, S., Benchenane, K., Sirota, A., Courtin, J., and Herry, C. (2016) 4-Hz oscillations synchronize prefrontal–amygdala circuits during fear behavior. Nature Neuroscience 19, 605-612 (*co first authors).

Publications in Preparation

Robert R.,R., Jercog, D., Karalis, N., Khoder, S., Chaudun, F., Girard D., Winke N., Esposito ms., Arber S., Tovote P., Lüthi, A., and Herry, C. Prefrontal-periaqueductal gray projecting neurons encode context fear discrimination. Neuron (Accepted in Neuron).

Communications

- 10th Federation of European Neurosciences Societies, Copenhagen, Denmark. Poster Title: Prefrontal neuronal circuitry involved in passive and active fear behaviours.
- Gordon Research Conference on Amygdala function in emotion, cognition and disease, Stonehill College, Easton, MA, USA (august 2017) Poster Title: Prefrontal neuronal circuitry involved in passive and active fear behaviours.

Molecular mechanisms of kindlin mediated integrin activation and cell adhesion

Laureate name: Thomas Orré	Supervisor name: Olivier Rossier

Project Objectives

Determine if integrin immobilization (activation) depends on kindlin.
Determine the molecular behavior of kindlin in integrin adhesion sites at the single molecule level.
Determine the molecular basis of the single molecule behavior of kindlin.
Correlate the single molecule behavior of kindlin to its functions in integrin activation.

Main Results

We found that integrin immobilization depended on the interaction with kindlin, and reciprocally, kindlin immobilization in focal adhesion depended on the interaction with integrins. Kindlin displayed lateral free diffusion along the plasma membrane outside and inside integrin adhesion sites, whereas talin is mostly localized inside integrin adhesion sites, where it is immobile, and that the the PH domain of kindlin-2

is crucial for its recruitment and free-diffusion at the plasma membrane. Using kindlin-1/kindlin-2 double KO cells, we demonstrated that kindlin-2 membrane recruitment and diffusion are crucial for cell spreading and favor adhesion formation. This suggests that kindlin uses a different route than talin to reach integrins and trigger their activation, providing a possible molecular basis for their complementarity during integrin activation.

Working Plan to Continue

Quantify how the duration of integrin immobilization depends on the interaction with kindlin using sptPALM. Determine the effect of kindlin membrane diffusion on integrin immobilisation by sptPALM, and on integrin adhesion site formation/stability by timelapse fluorescence microscopy. Determine the axial (z) position of kindlin in integrin adhesion sites in a superresolutive manner using the DONALD and SAIM microscopy techniques.

Publications in Preparation

- Using single protein tracking to study cell migration. Thomas Orré*, Amine Mehidi*, Sophie Massou, Olivier Rossier, Grégory Giannone. Submitted to Methods in Molecular Biology. *: co-first authors.
- Linking kindlin molecular behaviour to its function in focal adhesions. Thomas Orré, Zeynep Karatas, Birgit Kastberger, Marina Theodosiou, Reinhard Fässler, Bernhard Wehrle-Haller, Olivier Rossier*, Grégory Giannone* (in preparation). *: co-last authors.

Communications

- Kindlin-2 membrane diffusion is crucial to integrin activation. Focus on Microscopy 2017, Bordeaux.
- Deciphering integrin activation using single particle tracking. Doctoral School Day, 2016, Arcachon, France.
- Deciphering integrin activation using single particle tracking. Imaging the cell 2015, Bordeaux, France.
- Inserm worskshop 237: New developments in superresolution optic microscopy: revealing the ultrastructure and the dynamic of molecular complexes at the cellular and tissue level.

Role of the brain-gut axis in early stress-induced emotional vulnerability

Laureate name: Marion Rincel	Supervisor name: Muriel Darnaudery

Project Objectives

The etiology of psychiatric disorders is not fully understood, but there are strong evidences that childhood adverse experience is a major risk factor. In rodents, early-life stress produces lasting emotional alterations and gastrointestinal dysfunctions such as gut dysbiosis and increased gut barrier permeability. In the last decade, there has been a huge interest in the field of gut -brain communication as regards mental disorders and especially the regulation of emotions. The aim of my PhD was to unravel the role of gut permeability and dysbiosis in the neurobehavioral effects of early-life stress.

Main Results

First, we investigated the intrinsic role of gut permeability in the regulation of behavior but also on gut microbiota composition. We report that restoration of gut barrier function attenuates some of the behavioral alterations associated with maternal separation and that chronic gut leakiness in naive adult transgenic mice recapitulates the effects of maternal separation. Finally, we examined the effects of multifactorial early-life adversity on behavior, gut leakiness in naive adult transgenic mice recapitulates the effects of maternal separation.
Second, we developed a mouse model of early-adversity that more closely reproduces what happens in humans in order to examine the effects of multifactorial early-life adversity on behavior, gut function and microbiota composition in males and females. At adulthood, offspring exposed to early adversity displayed sex-specific behavioral (social behavior deficits in males and hyper anxiety in females) and intestinal phenotypes.

Working Plan to Continue

For my post-doc, I aim to get expertised in immunology in order to pursue my research in neuroscience in the field of immunopsychiatry. To this end, I need to publish my results in high-impact, multidisciplinary journals. The LabEx PhD extension grant allows me to stay in the lab for a short-term postdoctoral fellows-

hip in order to finalize and submit 3 articles in preparation. Moreover, this fellowship provides ideal conditions to apply for several grants including the Human Frontier Science Program (HFSP) for Cross-Disciplinary Fellowships while contacting potential host labs.

Published Publications

- Rincel M, Lépinay AL, Janthakhin Y, Soudain G, Yvon S, Da Silva S, Joffre C, Aubert A, Séré A, Layé S, Theodorou V, Ferreira G, Darnaudéry M. Maternal high-fat diet and early-life stress differentially modulate spine density and dendritic morphology in the medial prefrontal cortex of juvenile and adult rats. Brain Struct Funct 2017 Oct 11.
- Janthakhin Y*, Rincel M*, Costa AM, Darnaudéry M* and Ferreira G*. Maternal high-fat diet leads to hippocampal and amygdala dendritic remodeling in adult male offspring. Psychoneuroendocrinology 2017 83, 49–57. *contributed equally.
- Romaní-Pérez M*, Lépinay AL*, Alonso L, Rincel M, Xia L, Fanet H, Caillé S, Cador M, Layé S, Vancassel S and Darnaudéry M. Impact of perinatal exposure to high-fat diet and stress on response to nutritional challenge, food-motivated behaviour and mesolimbic dopamine function. Int J Obes 2017 41,502-509. *contributed equally.
- Rincel M*, Lépinay AL*, Delage P, Fioramonti J, Théodorou VS, Layé S and Darnaudéry M. Maternal high-fat diet prevents developmental programming by early-life stress. Transl Psychiatry 2016; 6: e966. *contributed equally.
- Rincel M, Lépinay AL, Gabory A, Théodorou V, Koehl M, Daugé V, Maccari S and Darnaudéry M. [Early life stressful experiences and neuropsychiatric vulnerability: evidences from human and animal models]. Med Sci (Paris) 2016; 32: 93–99.

Publications in Preparation

- Rincel M*, Olier M*, Minni A, Monchaux de Oliveira C, Matime Y, Gaultier E, Grit I, Helbling JC, Costa AM, Lépinay AL, Heil SDS, Yvon S, Moisan MP, Layé S, Ferrier L, Parnet P, Theodorou V* and Darnaudéry M* Early restoration of gut barrier function abrogates the long-term neurobehavioral effects of early-life stress in rats.
- Rincel M*, Xia L*, Thomas J, Lainé J, Monchaux de Oliveira C, Gros L, Beyris A, Helbling JC, Bacquié V, Capuron L, Moisan MP, Theodorou V, Turner J, Ferrier L* and Darnaudéry M*. Gut-specific overexpression of the myosin light chain kinase impairs emotional behavior, neuroendocrine response to stress and brain expression of stress-related genes in a sex-dependent manner.
- Rincel M, Aubert P, Chevalier J, Grohard PA, Basso L, Monchaux de Oliveira C, Lévy E, Chevalier G, Leboyer M, Eberl G, Layé S, Capuron L, Vergnolle N, Neunlist M, Boudin H, Lepage P and Darnaudéry M. Sex-specific behavioral alterations are associated with gut dysbiosis in mice exposed to multifactorial early-life adversity.

Communications

Oral communication

- Role of gut leakiness in early-life-stress-induced behavioral and neuroendocrine alterations. 42nd congress of the french Society of Neuroendocrinology, Dijon, France, September 18-21, 2017.
- Early restoration of gut barrier function abrogates the long-term neurobehavioral effects of early-life stress in rats. 47th annual meeting of the International Society of Psychoneuroendocrinology, Zurich, Switzerland, September 7-9, 2017.
- Role of the gut-brain axis in early stress-induced emotional vulnerability. Lab meeting in A. Macpherson's lab, Bern, Switzerland, August 2017 (invited).
- Gender specific behavioral alterations are associated with gut dysbiosis in mice exposed to multifactorial early-life adversity. Annual meeting of the french Society of Neurogastroenterology, Nantes (France), June 22-23, 2017. Best oral communication award.
- Role of gut leakiness in the regulation of behavior. Annual meeting of Bordeaux Doctoral School, Talence, France, April 12, 2017. Best oral communication award.
- Early-life adversity, psychiatric vulnerability and gut microbiota: a focus on sex differences in mice. 3rd SF-DOHaD seminar, Paris, France, December 1-2, 2016.
- Microbiota and the brain, and beyond. NutriNeurO monthly seminar, Bordeaux, France, November 21, 2016.
- Maternal high-fat diet prevents the decrease in basilar spine density in the medial prefrontal cortex of pups exposed to chronic maternal separation. 2nd SF-DOHaD seminar, Nantes, France, November 6-7, 2014. Best oral communication award.

Poster

- Rincel M, Aubert P, Chevalier J, Grohard PA, Basso L, Monchaux de Oliveira C, Lévy E, Chevalier G, Leboyer M, Eberl G, Vergnolle N, Neunlist M, Layé, Capuron, Boudin H, Lepage P and Darnaudéry M. Gender specific behavioral alterations are associated with gut dysbiosis in mice exposed to multifactorial early-life adversity. Submitted at the 30th European College of Neuropsychopharmacology congress, Paris, France, September 2-5, 2017.
- Rincel M, Xia L, Monchaux de Oliveira C, Thomas J, Bacquié V, Gros L, Dinca A, Barnett Burns S, Matime Y, Turner J, Capuron L, Théodorou V, Ferrier L and Darnaudéry M. Chronic gut leakiness induces gender-specific neurobehavioral alterations in transgenic CA-MLCK mice. Abstract accepted at Neurogastro 2017, Cork, Ireland, August 24-26, 2017.

- Darnaudéry M, Rincel M, Minni A, Olier M, Monchaux de Oliveira C, Matime Y, Thomas J, Gaultier E, Grit I, Costa AM, Lepinay AL, Layé S, Ferrier L, Parnet P and Théodorou V. Pharmacological inhibition of gut leakiness prevents the long-term effects of early-life stress in rats. Submitted at the 30th European College of Neuropsychopharmacology congress, Paris, France, September 2-5, 2017.
- Rincel M, Aubert P, Chevalier J, Grohard PA, Basso L, Monchaux de Oliveira C, Lévy E, Chevalier G, Leboyer M, Eberl G, Vergnolle N, Neunlist M, Layé S, Capuron L, Boudin H, Lepage P and Darnaudéry M. Sex differences in behavior and gut microbiota in mice exposed to early-life stress. NeuroFrance 2017, Bordeaux, France, May 17-19, 2017.
- Rincel M, Inczefi O, Minni A, Bacquie V, Lepinay AL, Xia L, Gaultier E, Turner JR, Layé S, Ferrier L and Darnaudéry M. Genetic and environmental alterations of the epithelial barrier function trigger HPA axis dysfunction and behavioral impairments in rodents. 2nd Federation of Neurogastroenterology and Motility Meeting, San Francisco, USA, August 25-28, 2016.
- Darnaudéry M., Rincel M, Lépinay AL, Delage P, Fioramonti J, Théodorou VS and Layé S Maternal high-fat diet prevents developmental programming by early life stress, 46th Annual ISPNE Conference, Miami, USA, September 8-11, 2016.
- Rincel M, Janthakhin Y, Nicolas V, Costa AM, Layé S, Darnaudéry M and Ferreira G. Impact of a perinatal high-fat diet on amygdala function in rats. Annual meeting of Bordeaux Neurocampus, Talence, France, June 7, 2016. Best poster prize.
- Rincel M, Janthakhin Y, Nicolas V, Costa AM, Layé S, Darnaudéry M and Ferreira G. Impact of a perinatal high-fat diet on amygdala function in rats. 5th GDR Neuromem seminar, Lacanau, France, May 17-20 2016.
- Rincel M, Lépinay AL, Xia L, Aubert A, Séré A, Théodorou V, Layé S and Darnaudéry M. Maternal high fat diet prevents the loss of spines in the prefrontal cortex and visceral hyperpermeability in pups exposed to maternal separation. Annual meeting of Bordeaux Doctoral School, Arcachon, France, April 6, 2016. Best poster prize.
- Rincel M, Lépinay AL, Xia L, Aubert A, Séré A, Théodorou V, Layé S and Darnaudéry M. Maternal high fat diet prevents the loss of spines in the prefrontal cortex and visceral hyperpermeability in pups exposed to maternal separation. 12th French Society for Neuroscience seminar, Montpellier, France, May 19-22, 2015.
- Romani-Pérez M, Lépinay AL, Alonso L, Rincel M, Xia L, Fanet H, Caillé S, Cador M, Layé S, Vancassel S and Darnaudéry M. Maternal high fat diet and early life stress induce metabolic disturbances and enhance motivation for palatable food in offspring. 12th French Society for Neuroscience seminar, Montpellier, France, May 19-22, 2015.
- Darnaudéry M, Minni AM, Xia L, Rincel M, Lepinay AL, Ferrier L, Layé S and Théodorou V. Attenuation of gut leakiness in stressed neonates prevents HPA axis dysfunction and behavioral impairments produced by maternal separation. 12th French Society for Neuroscience seminar, Montpellier, France, May 19-22, 2015.
- Rincel M, Lépinay AL, Delage P, Fioramonti J, Theodorou V, Guesnet P, Acar N, Layé S and Darnaudéry M. Perinatal high fat exposure through maternal diet protects against the adverse effects of early life stress. 3rd Chevreul Lipids & Brain seminar, Paris, France, March 16-18, 2015.
- Lépinay A, Delage P, Rincel M, Layé S, Darnaudéry M. Maternal high fat consumption protects offspring against neurobiological and emotional alterations induced by maternal separation. 9th FENS forum of neuroscience, Milan, Italy, July 5-9, 2014.

Role of astroglial type-1 cannabinoid receptor in long-term memory and synaptic physiology

Laureate name: Laurie Robin	Supervisor name: Giovanni Marsicano

→ Project Objectives

This thesis work aims at studying the endogenous role of astroglial type - 1 cannabinoid receptors (CB1) in memory processes and the mechanisms using a combination of tools such as behavior, in vitro and in vivo electrophysiology and calcium imaging in astrocytes.

→ Main Results

We found that GFAP - CB1 - KO (Mice carrying a specific deletion of CB1 in astrocytes) have strong memory impairment as compared to their control littermates as well as NMDAR - dependent long term pot entiation impairment both in vivo and in vitro . D - serine is one of the most important gliotransmitter at

synaptic levels and is necessary for proper NMDARs activity. By recording NMDAR field - potentials and infusing D - serine in the bath, we found that the co - agonist binding site of the NMDAR is less saturated in GFAP - CB1 - KO as compared to controls, meaning that D - serine availability at the synapse is decreased in the mutant mice. Interestingly, systemic or intra - hippocampal injections of D - serine after the acquisition rescued the phenotype of the GFAP - CB1 - KO in the memory task.

Working Plan to Continue

Calcium activity is known to be an essential mechanism for the rele ase of D - serine and synaptic plasticity. I will keep perform ing Bi - photon analysis in slices to record calcium activity in the astrocytes of the CA1 region of the hippocampus of GFAP - CB1 - WT and GFAP - CB1 - KO in basal conditions or after stimulati on with a CB1 agonist (WIN - 55212) to provide fine - tuned mapping of CB1 impact on astroglial calcium signaling.

Published Publications

- Mario Martin - Fernandez, Stephanie Jamison, Laurie M. Robin , Zhe Zhao, Eduardo D. Martin, Juan Aguilar, Michael A. Benneywor th, Giovanni Marsicano, Alfonso Araque. . Synapse - specific astrocytes gating of amygdale - related behavior. Nature neuroscience 20 :1540 – 154.

- Hebert - Chatelain E, Desprez T, Serrat R, Bellocchio L, Soria - Gomez E, Busquets - Garcia A, Pagano Zottola AC, Dela marre A, Cannich A, Vincent P, M. Robin LM , Terral G, García - Fernández M - D, Colavita M, Mazier W, Drago F, Puente N, Reguero L, Elezgarai I, Dupuy J - W, Cota D, Lopez - Rodriguez M - L, Barreda - Gómez G, Massa F, Grandes P, Bénard G * , Marsicano G * . A Cannabinoid Link Between Mitochondria and Memory. Nature 539 (7630):555 - 559.

- Oliveira da Cruz JF*, Robin LM *, Drago F, Marsicano G, Metna - Laurent M. Astroglial type - 1 cannabinoid receptor (CB1): a new player in the tripartite synapse. Neuroscience . 323: 35 - 42.

Communications

Oral communication

- Astroglial CB1 receptors determine synaptic D - serine availability to enable recognition memory. (Salamanca, June 2017). International Symposium on Metabolic and redox interactions between neurons and astrocytes in health and disease.
- Role of hippocampal astroglial cannabinoid type - 1 receptors in memory and synaptic plasticity. (Bertinoro, April 2014) International astrocytes school.

Poster

- International conferences
  - L.M Robin , J. F. Oliveira Da Cruz, V. C. Langlais, M. Metna - Laurent , A.Busquets - Garcia , E. Soria - Gomez , T. Papouin , B. Bosier , F. Drago, A. Van Eeckaut, I. Smolders , F. Georges , A. Panatier , S. H. R. Oliet , G. Marsicano. Astroglial CB1 receptors control memory via D - serine (2016) Society for Neurosciences (San Diego, USA).
  - Laurie M. Robin , José F. Oliveira da Cruz, Valentin C. Langlais, Arnau Busquets - Garcia, Edgar Soria - Gomez, Filippo Drago, Aude Panatier, Franç ois GeorgeS, Mathilde Metna - Laurent, Stéphane Oliet, Giovanni Marsicano. Astroglial Type - 1 cannabinoid receptors (CB1R) are necessary for long - term object recognition memory. (2015) Cannabinoid conference 2015 (Sestri - Levante, Italy).
- National conferences
  - Robin LM ., Langlais V. Metna - Laurent M., Busquets - Garcia A., Papouin T., Leste - Lasserre T., Oliet S.H.R., Marsicano G. Astroglial CB 1 receptors control long - term memory formation and NMDAR - dependent synaptic plasticity (2015) Neurocampus conference, the q uadripartite synapse.
  - Robin LM ., Langlais V. Metna - Laurent M., Busquets - Garcia A., Papouin T., Leste - Lasserre T., Oliet S.H.R., Marsicano G. Astroglial CB 1 receptors control long - term memory formation and NMDAR - dependen t synaptic plasticity (2014). LabeX day.
  - Robin LM ., Langlais V. Metna - Laurent M., Busquets - Garcia A., Papouin T., Leste - Lasserre T., Oliet S.H.R., Marsicano G. Astroglial CB1 receptors control object recognition memory (2014) Neurocampus day.
  - Metna - Lauren t M.*, Robin LM *., Langlais V., Busquets - Garcia A., Papouin T., Leste - Lasserre T., Oliet S.H.R., Marsicano G. Astroglial CB1 receptors control object recognition memory (2012). Annual Neurocenter Magendie meeting.

Bordeaux School of Neurosciences

Cajal Course in 2016 and 2017

2016

Neuronal Cell Biology – Cytoskeleton and Trafficking (NCB-CT)

11 – 30 July 2016

Course directors:

Casper Hoogenraad
Utrecht University, Utrecht – The Netherlands
Monica M Sousa – University of Porto - Portugal

On-site chair:

Olivier Thoumine – University of Bordeaux – France

Nutrition and Brain Functions (NBF)

19 September – 7 October 2016

Course directors:

Richard P Bazinet – Toronto University, Toronto – Canada

On-site chair:

Sophie Layé – University of Bordeaux – France

Hippocampus from Circuits to Cognition (HCC)

10 - 29 October 2016

Course directors:

Jozsef Csicsvari – Institute of Science and Technology, Klosterneuburg - Austria
Charan Ranganath – UC Davis Center for Neuroscience, University of California – US

On-site chair:

Christophe Mulle – University of Bordeaux – France
Mario Carta – University of Bordeaux – France

CAJAL-ISN course - Glial Cells in Health and Disease (GCHD)

28 November - 10 December 2016

Course directors:

Ismael Galve Roperh – Complutense University, Madrid - Spain
Frank Kirchhoff – Saarland University, Homburg – Germany
Serge Nataf – University of Lyon 1 – France

On-site chair:

Stéphane Oliet – University of Bordeaux – France

2017

Advanced Techniques for Synapse Biology

July 3 -21, 2017

Course directors:

Monica Di Luca – University of Milan
Fabrizio Gardoni – University of Milan (Co-director)
Nathalie Sans – University of Bordeaux (On-site chair)

Connectomics: from Micro- to Meso- and Macro-Scales

October 2 -21, 2017

Course directors:

Andreas Frick – University of Bordeaux, France
Laurent Petit – University of Bordeaux, France
Olaf Sporns – Indiana University, USA

Ion channels in the brain in health and disease

September 4 -22, 2017

Course directors:

Florian Lesage – University of Sophia Antipolis, France
Teresa Giraldez – University of La Laguna, Spain
Eric Hosy – University of Bordeaux, France (On-site chair)

Annexes

NCM: The Neurocentre Magendie

STEPHANE OLIET

Neural Circuits of Anxiety

ANNA BEYELER

A leading hypothesis posits that anxiety disorders are caused by dysfunctions of neural circuits controlling the level of anxiety and/or circuits encoding emotional valence. However these hypotheses remain untested, and the brain circuit dysfunctions present in anxiety disorders remain unknown.

Our research program aims at identifying cellular, synaptic and molecular alterations in animal models of anxiety disorders within the circuits of the insular cortex (insula), which has been identified by human imaging as a key structure involved in anxiety disorders. We also envision to develop strategies to restore those dysfunctions, with the long term goal to translate our fundamental findings to clinical trials.

Neurogenesis and pathophysiology

NORA ABROUS

Our team is interested in elucidating the physiological significance of adult neurogenesis (ANg) in memory and emotion. We have demonstrated a causal relationship between ANg & memory, the existence of a complex reciprocal relationship between ANg & spatial learning and revealed that ANg plays a pivotal role in the development of pathological aging and in the appearance of anxiety-like behavior. We have also shown that inter&individual differences in neurogenesis potential result from early deleterious life events: prenatal stress decreases neurogenesis for the entire life. Abrous' lab research also highlights that optimizing neurogenesis can be used for the development of new therapeutic tools for memory and stress related pathologies.

Energy balance and obesity

DANIELA COTA

Our research activity focuses on understanding how caloric overload is decoded so to impact behavior and metabolism. To this goal, we study the role of hypothalamic circuits in the detection and integration of nutrient-related signals informing the brain about fuel use and availability and the involvement of these circuits in the pathophysiology of obesity and type 2 diabetes.

Cortical plasticity

ANDREAS FRICK

Our research topic is focused on the structure, function and dynamic regulation of cortical circuits in various conditions such as learning, development and disease. We investigate ion channel function in the different neuronal compartment to predict/analyse the coding properties of cortical neurons alone or in cell assembly. Using genetic models, we revealed the implication of ion channel dysfunctions in the hypersensitivity in response to sensory stimuli associated to neocortical hyperexcitability, features of fragile X syndrome and autism. We also study the anatomical connectivity of neocortical circuits and showed that its alterations named as a «connectopathy,» cause functional defects that may explain mental retardation states.

Fear circuits and neuronal mechanisms

CYRIL HERRY

Our research is focused on the identification of the neuronal circuits and mechanisms mediating aversive associative learning. Using a combination of state of the art, behavioral, single unit and local field potential recrodings, optogenetic and anatomical tracing we aim to decipher the specific neuronal elements, circuits and mechanisms involved in the control of fear behavior and to understand how alteration sin such circuits promotes the development of pathological fear behavior.

Physiopathology of declarative memory

ALINE MARIGHETTO

Our team aims at characterizing the neurobiological basis of addiction and molecular basis of traumatic memories. By applying a translational research, our work is dedicated to offer and develop new treatment Our aim is to identify psychobiological bases of declarative memory (DM) alterations occurring in aging and post-traumatic stress disorder (PTSD). We have developed specific behavioral models of age- and PTSD-related memory alterations in the mouse. Using these models, we search correlates of the cognitive changes at the system, cellular and molecular levels of brain activities. To establish causality links between neurobiological and cognitive changes, we then combine interventional approaches with pharmacological tools/optogenetics to our behavioral testing.

Endocannabinoids and Neuroadaptation

GIOVANNI MARSCIANO

Our team aims at uncovering the functions of the endocannabinoid system in the brain as well as the cannabinoids regulation of behavior and psychotic disorders. By using conditional mutagenesis, we are currently dissecting the roles of cannabinoid receptors type-1 (CB1) in different cellular and subcellular localizations towards a better understanding of the general rules governing behavior such as memory, locomotor activity and olfaction. In particular, the impact of CB1 receptors on mitochondrial and bioenergetic functions and their role in behavior are at the focus of our most recent research.

Planar polarity and plasticity

MIREILLE MONTCOUQUIOL & NATHALIE SANS

Our group is interested in elucidating the role of the mammalian planar cell polarity (PCP) in the developing and adult nervous system. We study how defects in PCP genes cause developmental delays, sensory defects, sociability impairements and memory imbalances, typical of Autism spectrum disorder and other communication disorders. To this goal, we explore the impact of PCP protein complexes (i.e. Vangl2-Scrib1 and mPins/Gai) on neuronal development and synaptic functions and characterise PCP protein complexes and downstream targets. In parallel, we use the inner ear as a model to address the role and mechanisms of PCP signalling and identify novel molecular actors of PCP pathway.

Neuron-glia interactions

STEPHANE OLIET

Our aim is to understand the biological bases of glia-neurons interactions in healthy and diseased nervous system (Alzheimer disease, multiple sclerosis, addiction...). We showed the contribution of astrocyte to synaptic functions by establishing the role of D-serine, a gliotransmitter released by astrocytes, in gating synaptic NMDA receptors and the long-term plasticity they mediate. We are also interested in analyzing fine morphological plasticity of astroglial cells as well as monitoring membrane trafficking of key proteins at the surface of astrocytes.

Psychobiology of drug addiction

VÉRONIQUE DEROCHE-GAMONET

Our goal is to help improve the understanding of the psychobiological mechanisms of cocaine and tobacco addiction, so that eventually effective therapeutic solutions can be developed.

The originality of our experimental strategy lies in taking into account individual vulnerabilities, largely ignored in psychopharmacology. Indeed, all users are not at risk for addiction and drug use is not sufficient to induce an addiction. Moreover, regarding tobacco, clinical data indicate that the expression of addiction, hence the underlying psychobiological mechanisms, can differ from one smoker to another.

In studying the psychobiological mechanisms of cocaine and nicotine (the main addictive compound of tobacco) addiction, we apply methods of experimental psychology and psychopharmacology that we combine with complementary techniques for neurobiological exploration; from molecular level to functional connectivity.

Physiopathology and therapeutic approaches of stress-related diseases

JEAN-MICHEL REVEST

Our team aims at characterizing the neurobiological basis of addiction and molecular basis of traumatic memories. By applying a translational research, our work is dedicated to offer and develop new treatment for addiction. We successfully revealed neurobiological substrates involved in the transition to cocaine addiction. We recently demonstrated that pregnenolone can protect the brain from cannabis intoxication, that serves as a ground for clinical research.

Innovative techniques: neurosteroids biochemistry, In vivo HPLC-microdialysis, model of addiction, rodent behavioral testing.

IINS:
Interdisciplinary Institute for Neuroscience

DANIEL CHOQUET

Dynamics of Synapse Organization and Function

DANIEL CHOQUET

Our team pursues a transdisciplinary approach, to study the interplay between the dynamics of the molecular components and the synaptic transmission. Based on advanced imaging techniques, we study AMPA receptors and its molecular partners. We obtained breakthrough data on nano-scale organization, dynamics and interaction of synaptic proteins and membrane trafficking, Our efforts are focused on the understanding of the synaptic components dynamics involved in higher cognitive functions and pathologies, such as Alzheimer disease.

Computational and Systems Neuroscience

FREDERIC GAMBINO

Neocortical function and plasticity underlie the remarkable adaptive skills of mammals. Among different projects, our team is studying how the prefrontal cortex computes and adapts its strategies through experience and learning to optimally select the sequence of actions that is expected to produce the most beneficial outcome. We developed an entirely in vivo multidisciplinary approach combining electrophysiology and functional imaging (intrinsic and voltage-sensitive dyes imaging), multiphoton laser-scanning microscopy, gene transfer and optogenetic during behavior in head-fixed and freely-moving mice.

Spatio-temporal and mechanical control of motile structures

GREGORY GIANNONE

Our goal is to decipher at the molecular level the spatiotemporal and mechanical mechanisms which control the architecture and dynamics of motile structures. First in the context of cell migration by studying integrin-based adhesion sites and the actin-based lamellipodium. Second in the context of neuronal structural plasticity by studying the actin cytoskeleton in axons and dendritic spines. Exploration of these new dimensions requires an innovative and multidisciplinary approach combining cell biology, biophysics, biomechanics and advanced optical microscopy techniques including super-resolution microscopy, single protein tracking and quantitative image analysis.

Development and Adaptation of Neuronal Circuits

LAURENT GROC

A great challenge for our comprehension of brain development is to identify how biological signals (glutamate, monoamine, immune system, hormones) control the maturation of neuronal connections and brain circuit assemblies in healthy conditions as well as in psychotic disorders. In particular, we showed that the adaptation of developing excitatory synapses mainly depend on the dynamics of surface postsynaptic receptor, including the NMDA and AMPA receptor. Our team will combine cutting edge high resolution imaging and classical electrophysiological approaches to detect and decrypt the impact of auto-antibodies from psychotic patients.

Synapse in Cognition

YANN HUMEAU

Our main objective is to understand the link between synapse and cognition by manipulating synaptic function in behaving mice. The synaptic analysis is performed in vivo and ex vivo using "state of the art" imaging, electrophysiological and biochemical techniques. We are deciphering the role of certain forms of synaptic plasticity in given behavioral adaptations. At the behavioral level, we are interested by cognitive modalities such as learning, consolidation, flexibility, perseveration and use of deliberative and procedural strategies.

Central Mechanisms of Pain sensitization

MARC LANDRY

The aim of our project is to shed light on basic mechanisms responsible for cellular and network dysfunctions in the dorsal spinal cord in rodent models of neuropathic pain. We investigate the role of excitation/inhibition balance and microRNA-based regulatory mechanisms influencing nociceptive transmission and plasticity leading to chronic pain. We are developing in-vivo-based high intensity focused ultrasound (HIFU), a non-invasive approach to deliver antinociceptive drugs that represents a potentially efficient intervention for chronic pain with limited side-effects. This innovative technique will allow the study the functional role of GABAB dimers and L-type channel properties of spinal neurons in chronic pain conditions.

Synaptic Circuits of Memory

CHRISTOPHE MULLE

The research carried out in our group ambitions to link cell biological mechanisms to synaptic function and dysfunction in vivo. We explore the molecular mechanisms governing synapse specification and plasticity in a given neuron. We address how presynaptic and postsynaptic parameters integrate to determine proper network function and how synaptic plasticity modifies network activity and contribute to memory in control conditions and in Alzheimer's disease. We develop new methods for investigating the connectivity and function of local circuits in vivo contributing to memory.

Synaptic Plasticity and Superresolution Microscopy

VALENTIN NÄGERL

Our group objective is to better understand higher brain function and disorders through innovative and advanced technological developments. To this end, we are applying novel superresolution microscopy approaches (STED microscopy), giving us a much more complete and refined view of the dynamic behavior and plasticity of neuronal synapses and their interactions with glia cells inside living brain slices. This approach is complemented by a combination of 2-photon imaging and patch-clamp electrophysiology to address the underlying synaptic mechanisms of plasticity in the mammalian brain.

Olfaction and Memory

LISA ROUX

The ability to store and retrieve associations between specific sensory stimuli and behaviorally relevant information is a vital memory function: it allows the organism to adapt its behavior based on prior experience. Olfaction is a central sensory modality in rodents as it supports an array of crucial behaviors such as predator avoidance, feeding, reproduction, maternal behavior and social interactions. Most odor stimuli acquire behavioral significance upon learning and experience. The goal of our team is to identify the network mechanisms underlying the formation of olfactory memory traces across distributed brain regions. More generally, we aim at understanding how sensory information is routed and processed in the brain to integrate lasting memories.

Quantitative Imaging of the Cell

JEAN-BAPTISTE SIBARITA

Our team aims at developing novel imaging techniques to decipher protein organization and dynamics at high spatial and temporal resolutions. More precisely, four main research areas are dedicating to develop: 1) Novel instruments for super-resolution microscopy of living samples, 2) Analytical tools for object segmentation, tracking and visualization, 3) High Content Screening Microscopy to quantify the dynamics of active proteins within the living cells, using super-resolution microscopy and 4) Bioengineering for micropatterning and microfluidics to control cell geometry and their local chemical environment.

Cell Adhesion Molecules in Synapse Assembly

OLIVIER THOUMINE

Our team aims at characterizing the molecular mechanisms of synapse formation, with a focus on the function of cell adhesion molecules including neurexins and neuroligins. We are studying the membrane dynamics and nanoscale organization of these adhesion molecules at synapses, and their contribution to the recruitment of scaffolding proteins and glutamate receptors, by combining single molecule detection and computer simulations. We are also characterizing a neuroligin-1 phosphotyrosine signaling mechanism regulating the differential assembly of excitatory versus inhibitory synapses, by using a combination of electrophysiology and optogenetic approaches. Finally, we are investigating the trafficking and function of neurexins and neuroligins harboring genetic mutations identified in autism spectrum disorders.

IMN: Neurodegeneratives Diseases Institute

ERWAN BEZARD

Pathological decision-making in addiction

SERGE AHMED

Our research aims at identifying the psychological and neurobiological determinants of the different stages of addiction, drug choices and preferences in order to develop/improve strategies to prevent relapse. To successfully tackle these goals, we compare drug- versus nondrug-preferring rats to elucidate the psychological and neurobiological substrates underlying the abnormal preference for the drug. Our efforts are also concentrated in investigating the long-term preventive effects of a cue exposure procedure against relapse to reveal the brain regions that play a critical role in interoception, behavioral inhibition and motivation.

Mnemosyne : mnemonic synergy

FREDERIC ALEXANDRE

Mnemosyne is a research team in computer science, developing models of neural networks with the aim to study synergies between different kinds of learning with an impact in Neuroscience and in Machine Learning. To better understand the prediction of values, we model the amygdala, the temporal cortical lobe, the hippocampus and the medial prefrontal cortex. In Machine Learning, these models can be checked against hierarchical classifiers and associative memories, respectively developing semantic and episodic memories. We also study loops connecting the basal ganglia and the prefrontal cortex to understand goal-directed as well as habitual behaviors. In Machine Learning, such models refer to decision making in model-based and model-free reinforcement learning and to sequence learning.

Dopamine and Neuronal Assemblies

JEROME BAUFRETON & FRANÇOIS GEORGES

Our laboratory examines the functions of the « extended basal ganglia network », a neuronal network composed of interconnected limbic and motor nuclei. We aim at characterizing this network at the synaptic level, focusing on how synaptic transmission and plasticity are controlled by dopamine. Our research will provide new understandings of physiological functions (voluntary movements, associative learning...) and of dopamine-associated disorders (Parkinson's disease, addiction...).

Pathophysiology Of Parkinsonian Syndromes

ERWAN BEZARD

Our translational research is dedicated to uncovering the pathophysiology of Parkinson's disease and works towards development of therapeutic solutions. Our team is best known for its work on L-DOPA-induced dyskinesia (LID), serious motor complications associated to the chronic dopamine replacement therapy. Recently, we work on a collaborative project using innovative nanotechnology as a new means of imaging living systems and of delivering therapy.

Dynamics of neuronal and vascular networks underlying memory processing

BRUNO BONTEMPI

Our team aims at elucidating the spatio-temporal evolution of memory traces and their underliing cerebral support in healthy and diseased conditions. We have made an important breakthrough in identifying early tagging of cortical networks as a prerequisite for the formation of enduring associative memory. Currently, our research goals are threfold. First, understanding the functional contributions of NMDA receptor subtypes to the formation and retrieval of remote memories. Second, deciphering the roles of neuronal and vascular networks in memory stabilization. And last, determine to what extent neuro-vascular networks are altered in the event of memory dysfunction, whether associated with normal aging and hypertension, or with more severe pathological conditions such as Alzheimer's disease.

Physiology and pathophysiology of executive functions


THOMAS BORAUD & PIERRE BURBAUD

Our objective is to unravel the neural mechanisms underlying cognitive and motor executive functions. Our main interests are the physiology of the planning, decision making, learning processes and their pathophysiological aspects such as dystonia and obsessive-compulsive disorder. We adopted a phylogenetic approach that drive us to address the question in a broad variety of vertebrates such as salamander, rodents, primates (both human and non-human) and songbirds in order to unravel the emerging complexity of the system studied along the evolution tree. We based our research on system level theoretical models validated by experimental data. Our experimental procedures range from optogenetic approaches coupled with single cell electrophysiology in anaesthetized animals to multiple electrode recording in awake and behaving primates. We also conduct several clinical studies in the fields of dystonia, OCD and Parkinson's disease.

Neurochemistry, deep brain stimulation and Parkinson's disease

ABDELHAMID BENAZZOUZ

Our research project aims to better understand the pathophysiology of Parkinson's disease in order to improve the existing therapeutic approaches and to develop new therapies for the disease. Currently, we especially focus our work on the role of monoaminergic systems (noradrenaline, dopamine, serotonin) in the pathophysiology and therapy of Parkinson's disease. The team is acknowledged for its neurochemical and electrophysiological inputs unraveling the mechanisms of action of the deep brain stimulation of the subthalamic nucleus and L-DOPA medication in animal models of Parkinson's disease.

Neurofunctional imaging group (GIN)

NATHALIE TZOURIO-MAZOYER

Our multidisciplinary team brings together scientists from different backgrounds: mathematics and instrumentation in medical imaging, nuclear medicine, signal processing, psychiatry and cognitive neuroscience, dealing with databasing structural and functional brain images, socio-demographic, behavioural, genetic, and clinical data from cohorts of individuals to understand how the brain architecture relates to cognition, and to differentiate healthy from neuropathological conditions. Our efforts are currently organized around three main themes: population neuroimaging, neuroimaging of hemispheric specialization and cerebral connectivity.

INCIA: Aquitaine Institute for Cognitive and Integrative Neuroscience

JEAN-RENE CAZALETS

Brain molecular imaging

JEROME BADAUT

Our translational research is to decode the pathophysiological mechanisms after acute brain injuries (traumatic brain injury and stroke) in order to identify new biomarkers in neuroimaging and therapeutic targets. We focus on the changes in interactions between cells in the neurovascular unit formed in part by the endothelium, smooth muscle layer, astrocyte and neuron. Dysfunctions in the neurovascular unit are contributing to alterations of the blood-brain barrier properties and cerebral blood flow. For this work, we are using a vertical-integrated approach from the molecule such as the glycoproteins of the extracellular matrix to the behavior outcomes and non-invasive neuroimaging (MRI with diffusion tensor imaging, perfusion weighted imaging...).

Motor Control & Cognition

ARNAUD BADETS

The main goal of our team is to understand the link between motor control, motor learning and higher cognitive functions in healthy and pathological conditions. We explore the human capacity to plan different actions and form decisions from an abstract level (e.g number processing) to more concrete situation (e.g the ability to use tools). We also seek to understand the impact of mental effort and consecutive mental fatigue on these activities. These studies are performed in healthy subjects but also in different populations like Parkinson patients, individuals with neurodevelopmental disorders like developmental coordination disorder or specific learning disorders (dyslexia or dyscalculia). We are also interested in psychiatric diseases like obsessive compulsive disorders in which patients exhibit decision-making dysfunctions.

Memory interacting Networks under Drugs and Stress (MINDS)

DANIEL BERACOCHEA & VINCENT DAVID

Our research is interested in the interactions between emotions and cognitive processes in normal conditions and pathological states (short and long-stress, aging, disease, addiction...). Our main project aims at characterizing the neuronal substrates underlying the positive and negative emotion-memory interaction in normal young adult mice. We also study how the emotional impact on memory is altered by aging or in pathological states such as in Alzheimer's disease, chronic alcohol and diencephalic dementia, to possibly restore the impaired memory functions.

Coordination and Plasticity of spinal Generators (CPGs)

SANDRINE BERTRAND

Our project aims to study mammalian spinal neural networks involved in motor functions. On one hand, we investigate the cellular and synaptic mechanisms, which allow the various neuronal networks, engaged in locomotion and respiration as well as in non-rhythmic (such as posture) motor activities to operate independently or together as they necessarily do during normal behavior. Second, we explore the plastic capabilities of the ventral spinal cord that contains the neural circuitry responsible for posture and locomotion under both physiological and pathological conditions. To this end, we investigate the activity-dependent plasticity of synapses onto lumbar motoneurons during normal development and following spinal cord injury.

Development of spinal motor networks, DMSN

PASCAL BRANCHEREAU

The objective of our team is to understand the mechanisms involved in the function of mammal spinal motor networks from its embryonic development to its pathological conditions, such as amyotrophic lateral sclerosis, ALS. In particular, we focus our efforts on: 1) deciphering the role of GABAergic interneuron in the genesis of spontaneous activity at early developmental stages and 2) identifying cellular and molecular mechanisms involved in the early motor deficits observed in spinal motoneurons from ALS mouse models.

Addicteam

MARTINE CADOR

Our research investigates the behavioural and neurobiological processes involved in addiction to different drugs (nicotine, cocaine, opiate, alcohol) but also to natural rewards (foods,..) focussing on both adolescent and adult rodents (rats, mice) populations. Using behavioral models of taking, seeking, relapse..in relation to cognitive, motivational, learning functions or dysfunctions, we study more specifically plasticity at different levels (neurone, brain pathways,brain networks) of the mesorticolimbic system (VTA, N. Accumbens, Amygdala, Prefrontal cortex, BNST..)

Neurobiology of Behavior

Yoon CHO

Our team aims at dissecting at the molecular, cellular, synaptic, and network levels, the neural bases of cognitive functions and behaviors in normal and pathological conditions. Special emphasis is placed on multilevel analysis of social behaviors combining genetic, molecular, cellular, and biochemical approaches, as well as in vivo electrophysiological recordings in freely behaving or head-restrained mice.

STRESS, Searching Targets to Regulate Stress Systems

ANGELO CONTARINO

Our team develops two different lines of research. Using clinically-relevant rodent models, our main objective is to understand the brain mechanisms underlying behavioral disorders and vulnerability to stress induced by drugs of abuse. Notably, we contributed to highlight a key role for the stress-responsive corticotropin-releasing factor (CRF) system in the behavioral and brain alterations induced by drugs of abuse. Besides, we use transgenic Drosophila models to understand the role of neuropeptides in physiology and behavior.

Decision and Adaptation

ETIENNE COUTUREAU

Our team studies basic cognitive representations and operations which allow animals to adapt their actions according to their predicted consequences. Our approach stands at the interface of cognitive and experimental psychology, integrative and developmental neuroscience, and clinical neuroscience. We use specific behavioural and associative learning tasks in rodents (rats, mice), as well as techniques from functional neuroanatomy, neurochemistry and computational neuroscience, to model the role of prefrontal brain regions and circuits in the emergence of executive functions.

Auditory perception

LAURENT DEMANY

We work on auditory perception and memory with the tools of psychophysics. Our recent researches concern 1) harmonic fusion, that corresponds to the perception of a single sound when we are presented with a sum of simultaneous pure tones one octave apart;2) auditory divided attention, that investigates the capability of the auditory system to discriminate two simultaneous streams, 3) discrimination of enhancement phenomena in auditory perception, 4) the perceptual salience of a sound as a function of the shape of its amplitude envelope, 5) echoic memory in children and adults with autism spectrum disorders.

Bordeaux PET Research center

PHILIPPE FERNANDEZ

The PET research unit is a center dedicated to the molecular imaging with positron emitter tracers. Our expertise is triple: 1) Participating to multicentric clinical trials promoted by academic structures (hospital, university) or industrial partners, 2) Developing and conducting clinical trials in oncology and neurology fields with commercial tracers or tracers without market authorization (in situ synthesis), 3) Developing and validating new radiopharmaceuticals (synthesis of specific peptides in collaboration with ISM-UMR 5255 directed by Dr Eric Fouquet, or aptamers in collaboration with ARNA laboratory-INSERM U869 directed by Dr Jean-Jacques Toulmé, development of new methods for fast synthesis of tracers radiolabeled with gallium 68).

Hybrid Sensorimotor Performance (HYBRID)

AYMAR de RUGY

Our team uses hybrid systems, mixing biological control with artificial devices, in order to (i) increase our understanding of the fundamental mechanisms of sensorimotor control and (ii) exploit this knowledge to restore and optimize movement, such as in prothesis control.

Nuroimaging and human cognition

IGOR SIBON, JOEL SWENDSEN

The principal objective of our team is to combine advanced neuroimaging techniques and state-of-the-art mobile assessments of daily life behaviors, emotions and cognitive processes in order to understand the etiology and pathophysiology of CNS disorders. MRI allows for the characterization of neural networks involved in cognitive and emotional processes and their dysfunction, assessing the structural and functional integrity both of brain regions and the connections between regions of the brain network. Recent studies have also demonstrated the contribution of jointly using MRI and PET techniques, an approach which opens numerous new opportunities to identify structural and functional brain dysfunction and neuropathological tissue damage. The coupling of imaging data with that acquired through mobile technologies, including cellular telephones and actigraphy, provides highly novel information concerning the daily life correlates of brain markers as well as new perspectives for treatment strategies.

Organization and adaptability of motor systems (OASM)

MURIEL THOBY-BRISSON

Our overall research objective is to decipher the neuronal basis of the short- and long-term functional plasticity of motor systems. Using different animal models, we are investigating properties of several neural networks involved in generating organized motor activities (respiration, locomotion, posture, feeding) in the context of development, modulation, network interactions and plasticity. The principal experimental goal of our work is to causally link cellular, synaptic and neural network physiology to particular aspects of adaptive behaviour.

PSYCHONEUROIMMUNOLOGY AND NUTRITION: EXPERIMENTAL AND CLINICAL APPROACHES

LUCILE CAPURON & SOPHIE LAYE

The aim of our research is to understand the role of nutrition in neuropsychiatric disorders. We study how unbalanced diet influences mood and well-being and contribute to major depression or neurodevelopmental diseases (autism, schizophrenia). Using translational approaches, we study how metabolic disorders and lipid nutrition contribute to depression, focusing on neuroinflammatory processes, gut to brain relationship (microbiota) and brain glucose metabolism. Also, we study the mechanisms of n-3 polyunsaturated fatty acid levels on brain remodeling, neuroimmune responses and emotional/motivational behavior. We focus on neurodelopment, using several nutritional, early life psychological and immunogene stress and transgenic mice model.

NUTRITION, MEMORY AND GLUCOCORTICOIDS

MARIE-PIERRE MOISAN & GUILLAUME FERREIRA

The objective of our team, in a perspective of healthy brain aging, is to better understand how unbalanced diets alter memory processes, and how specific micronutrients (vitamins, polyphenol) prevent memory decline in elderly. At the mechanistic level, the impact of nutritional status on glucocorticoid regulation is specifically studied knowing that glucocorticoids are critical for memory processes,and in metabolic response to nutrition.

Genetics and Physiology of Hearing, INSERM U1120 –EA 3665 (UB)

Deciphering and rescuing hair cell auditory synaptopathies

Didier DULON

Our main objectives are to characterize the molecular mechanisms by which auditory hair cells control transmitter release at their ribbon synapses, in normal and pathological conditions. Our project investigates the role of otoferlin (in which mutaions lead to nonsyndromic hearing loss DFNB9) and its interaction with proteins defective in the Usher Syndrome (USH), the most frequent cause of deaf-blindness in humans, with 10 different USH genes identified so far. The final goals of our research aim to: 1) allow a better understanding of auditory synaptic failures (synaptopathies) occurring during genetic defects (DFNB9, USH) but also during sound trauma, aging and tinnitus; 2) help in designing future gene-therapy strategies to rescue hair cell synaptic defects; 3) help in refining new strategies to design more efficient cochlear prosthetic implants.

SANPSY (Sleep, Addiction and Neuropsychiatry)

PIERRE PHILIP

Phenomenology and determinants of appetitive behaviours, (addiction and psychiatry)

MARC AURIACOMBE

Our research focuses on the commonalities of addictive behaviors whether substance related (tobacco, alcohol, cannabis, heroin, cocaine and other drugs) or non-substance related (gambling, internet, food ...). Our goal is to contribute to the understanding and characterization of the phenomenology of addictive behavior and its determinants in Humans. We use a multidisciplinary approach drawing on the research paradigms of clinical neurobiology, epidemiology, psychology and sociology. We have developed a human model of addiction, in which the intensity of craving was shown as a predictor of later use and relapse after exposure to stimuli (The cues-craving-use model).aim to: 1) allow a better understanding of auditory synaptic failures (synaptopathies) occurring during genetic defects (DFNB9, USH) but also during sound trauma, aging and tinnitus; 2) help in designing future gene-therapy strategies to rescue hair cell synaptic defects; 3) help in refining new strategies to design more efficient cochlear prosthetic implants.

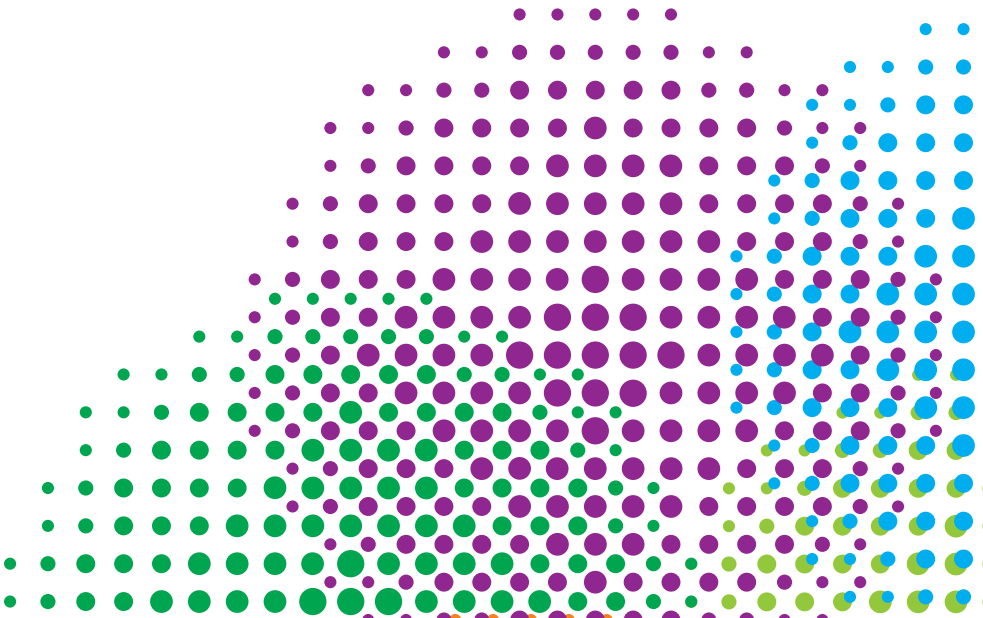
Credits

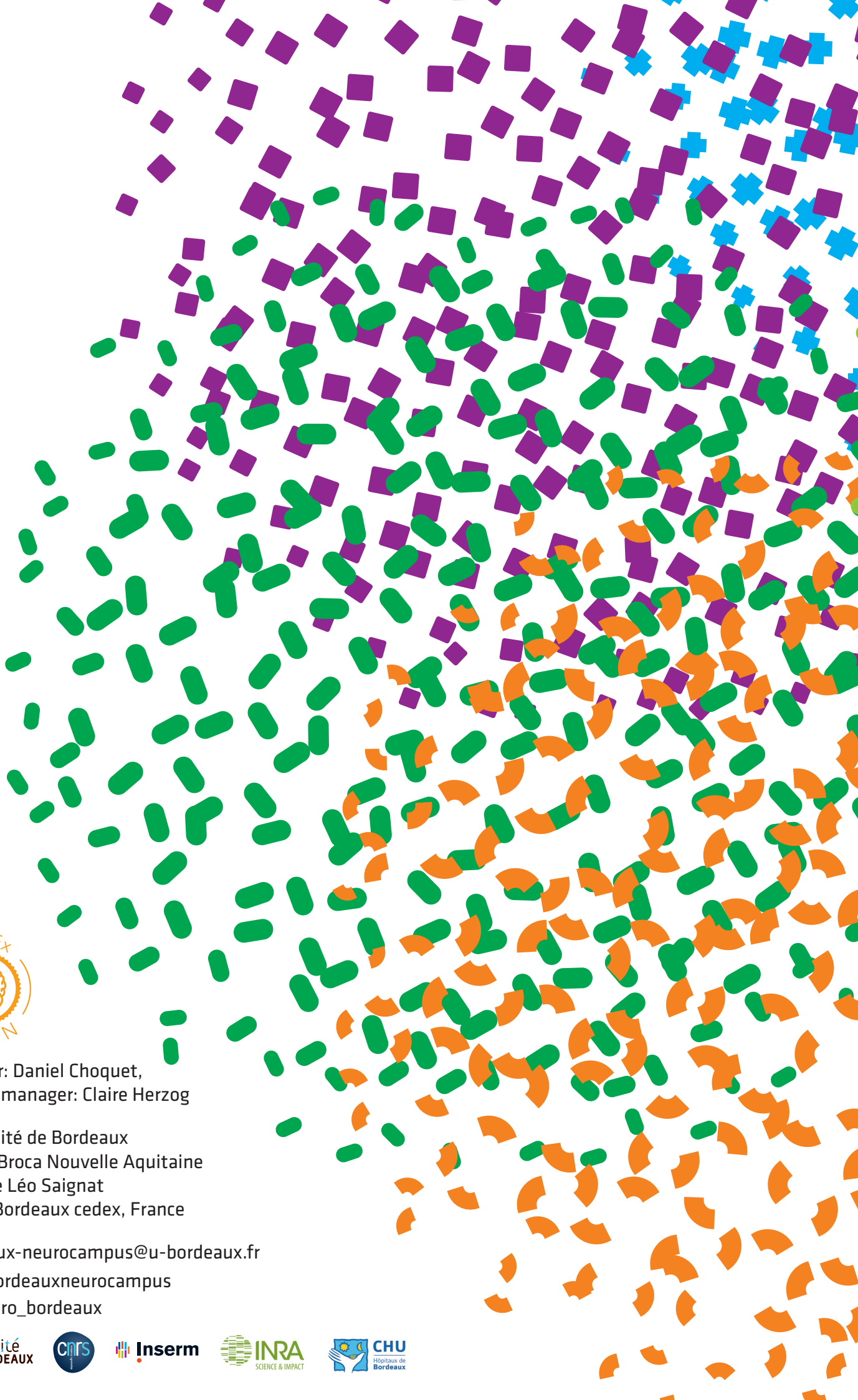
■ **Publication director:** Claire HERZOG

■ **Layout and printing:** Patrick CARTRON, graphic designer, University of Bordeaux & Printing services, University of Bordeaux (Carreire)

■ **Photography Library:** Sharpen

■ **Pictograms :** The noun project





Director: Daniel Choquet,
Project manager: Claire Herzog

Université de Bordeaux
Centre Broca Nouvelle Aquitaine
146, rue Léo Saignat
33076 Bordeaux cedex, France

bordeaux-neurocampus@u-bordeaux.fr
@Bordeauxneurocampus
Neuro_bordeaux