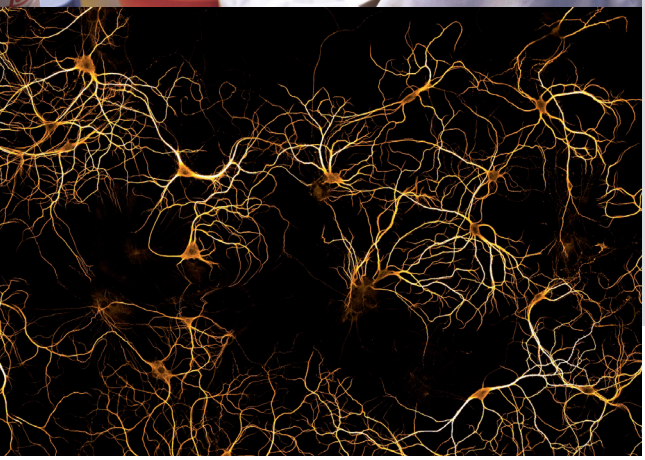
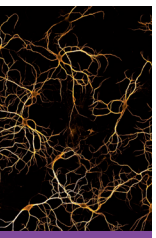


LabEx BRAIN
Report

2014-2015

INDEX



THE LABEX BRAIN *(Bordeaux Region Aquitaine Initiative for Neuroscience)* is a project from the first wave of the "Investissement d'Avenir" national programme selected by an international jury. It runs until 2019 and received a total funding of 20 M€. The aim of the "Investissement d'Avenir" programme is to build an integrated high-level policy in research, training, dissemination and technology transfer, with the final objective of developing the economical impact of research results. Hence, BRAIN general ambition is to place our research community as recognized worldly in Neuroscience and leaders at the European level, being key actors in the creation of new knowledge, discovery of new treatments for neurodegenerative and psychiatric diseases, participate to the development of local employment, with the emergence of start-ups, and being the benchmark for European neuroscience training.

The general **scientific objective** of BRAIN is to put together a multidisciplinary consortium of scientists, featuring world renowned leaders, in order to meet the most important challenges facing neuroscience research. With this aim, BRAIN is built on the diverse and complementary expertise of its teams and partners, in fields ranging from high resolution imaging and cell biology of the neuron to animal and human behaviour through the physiology of neural networks and mechanisms of neuro-degenerative and behavioural disorders.
The totality of Bordeaux neuroscience community is united within the Bordeaux Neurocampus federal organization. Bordeaux Neurocampus and BRAIN work hand in hand to promote neuroscience research in Bordeaux. In 2015, the perimeter of BRAIN has been extended to Bordeaux Neurocampus. BRAIN also aims at developing and structuring major collaborations and large scale projects with other communities to further build its multidisciplinary actions. BRAIN has favored links with several other Labex, including the medical imaging community TRAIL, the clusters laser&optics-Laphia and computation-CPU.

BRAIN helps to

- Reinforce **innovative and transversal projects**, by stimulating intra-Bordeaux Neurocampus collaborations, inter-LabEx programmes, and by facilitating access to high-end common core facilities,
- **Increase European visibility and training**, with the creation of the Bordeaux School of Neuroscience and the European certification of the BIC,
- **Promote technology transfer** with a dedicated programme and closed interactions with venture capital

Highlights of the period 2011-2015

- The launch of the Bordeaux School of Neuroscience, in a partnership with FENS/IBRO
- The large success of PhD Extension Grant Program, that allows to publish in high Impact Factor journals
- Increase in the number of collaborative projects (60 collaborative projects submitted to LabEx calls)
- Increase in the number of papers published in journals of high Impact Factor
- Attraction of a large amount of co-funds (Total 61 M€)
- Regular interactions with venture capital, one project coached
- IBISA certification of 3 core facilities, validating the core facility support program
- Coordination of the EuBI working group «training», which aims to coordinate all the European Imaging Trainings
- Selection of the Bordeaux Imaging Center within the European Infrastructure EuroBioImaging (EuBI)
- Certification of the Center of Excellence in Neurodegenerative Diseases (BIND) and the FHU (TALISMENT)

Operating processes

Governance

The form of governance of BRAIN reflects the overall objective of the partners involved, i.e. to collaborate constructively with efficient and transparent processes, and in keeping with a longer term strategy.

- → **The steering committee:** is representing the research laboratories of BRAIN. It meets every two months to discuss growth strategy and to decide on general guidelines.
- → **The executive committee:** is composed of three deputy directors in charge of technology transfer, training and clinical relationships alongside the Neurocampus project coordinator. It handles BRAIN management on a daily basis through the project manager.
- → **The external scientific committee:** is composed of highly qualified international scientists. It meets every two years, convened by the director, to discuss the Cluster's global policy for the forthcoming years and appraise the annual scientific program.
- → After four years of operation, as stipulated in the LabEx charter, the direction of LabEx has been renewed. Daniel Choquet was unanimously re-elected as Director of the Steering Committee for 4 more years. Moreover, the steering committee has been enlarged and one seat has been added for Nutrineuro.

Principles of the calls for proposals

The LabEx BRAIN launches calls for proposals for scientific projects (transversal, transfer and clinical projects), PhD extension grant, symposium, etc... The general principles are aimed at favouring a rapid, efficient and transparent process.

Launching of the call for proposal: The criteria are discussed by the steering committee. The call text is then largely diffused through the LabEx and Bordeaux Neurocampus websites as well as the newsletter.

Evaluation and selection process: In order to favour risky and early stage projects, we proceed to an internal evaluation of the proposals. Each grant is independently evaluated by the steering committee members and then discussed for final selection in plenary session, taking every step to reduce the impact of potential conflicts of interest. The projects are evaluated on significance, multidisciplinary approach and innovation. The projects submitted to the call for clinical proposals were first sent to external referees before committee evaluation.

Monitoring systems: We analyse every other year the impact of the selected project on additional grants obtained, publications published and in progress. For core facilities, we evaluate the service given to the community, the degree of opening, the number of users and the overall operation of the facility analysing the description of the service offer and price list, personnel list, total budget outcomes and total incomes. We also ask for a report on the symposium activity, reporting the number of participant and speakers, from Bordeaux, vs French vs international laboratories.

Main activities of BRAIN

→ Research

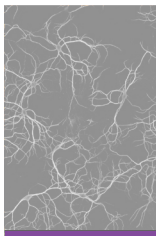
Call for proposals

Transversal projects

From 2011 to 2015, the LabEx BRAIN launched 3 calls for proposal, in order to deepen and enlarge intra Bordeaux Neurocampus collaborations. All the scientific topics aiming at improving our knowledge in neuroscience were progressively eligible to these open calls for proposal. Nevertheless, the LabEx BRAIN scientific areas of excellence remained priorities.

The partnership was progressively opened to all Bordeaux Neurocampus members, but the collaborative aspect remained a primordial criterion as all the projects should involve partners from at least 2 different institutes (or research units) of Bordeaux Neurocampus.

The evaluation criteria are based on significance, complementarity, multidisciplinary approach, and innovation.



Applied research projects

Brain opened a call in 2015 to support applied research projects whose potential economic impact is high. These projects include the discovery, development or optimization of innovative therapeutic or diagnostic products, together with the promotion of research resources dedicated to the discovery of new therapies or diagnosis tools (screening methods, for instance, in silico, cellular or animal models).

Clinical research projects

A call was dedicated in 2015 to support transversal or innovative translational research, from results obtained by a Bordeaux Neurocampus team (basic, pre-clinical or clinical). It consists in funding trials (whether physiological, pathophysiological, diagnostic or therapeutic interventional, out industrial trials) in healthy or unhealthy subjects.

Details page 12

New team

In 2014 the LabEx launched an international call for candidate to set up a new team within the SANPSY Unit. The applicant expertise and professional background expected was included a PhD or MD-PhD plus a Post Doc experience, experience as principal Investigator in National and/or international Grants, teaching expertise in neuroscience and sleep research. The candidate should develop a translational approach with basic teams working on animals and epidemiological projects (i.e. I Share) to implement the new team in the SANPSY Unit.
The team leader was selected after an external referee evaluation and audition with the local selection committee. The selected candidate received support to setup her research grant in the form of an advantageous start-up package including post-doc salaries as well as equipment and running costs funding.

Details page 52

Core facilities

10 core facilities have been selected to be supported by the LabEx after an internal audit, according to their utilisation rate and the excellence of the service offer. Our goal is to propose high-end technical equipment and service to all the Bordeaux Neurocampus teams with a reduced price.
This programme had a strong impact on the quality of the service offer and the transparency of the facilities organisation. The IBISA labelling of 3 of our facilities testify the pertinence of this programme.

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Training

PhD extention grants

The LabEx BRAIN offers to students from Bordeaux a fellowship to complete their Ph.D.thesis, either before or after the defence. The fellowship aims at funding either a fourth year of Ph.D. or up to one year immediately after a 3 year Ph.D., covering up a period to finish projects before leaving for a post-doc.

Details page 58

Bordeaux School of Neuroscience

The Bordeaux School of Neuroscience proposes a dedicated training laboratory fully equipped for modern neuroscience research with complementary access to high level core facilities for specialized technical aspects. It also offers all the logistics for the administrative and technical organization of courses. The Bordeaux School of Neuroscience offers its services (provide the infrastructure, the logistics, the administrative as well as technical support) to international teams of neuroscientists for the organization of training activities year-round. All the courses are open to international scientists.
The LabEx BRAIN strongly supports the Bordeaux School of Neuroscience (1.7M€for the equipment and initial running costs).

Details page 86

→ Dissemination

Knowledge transfer

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

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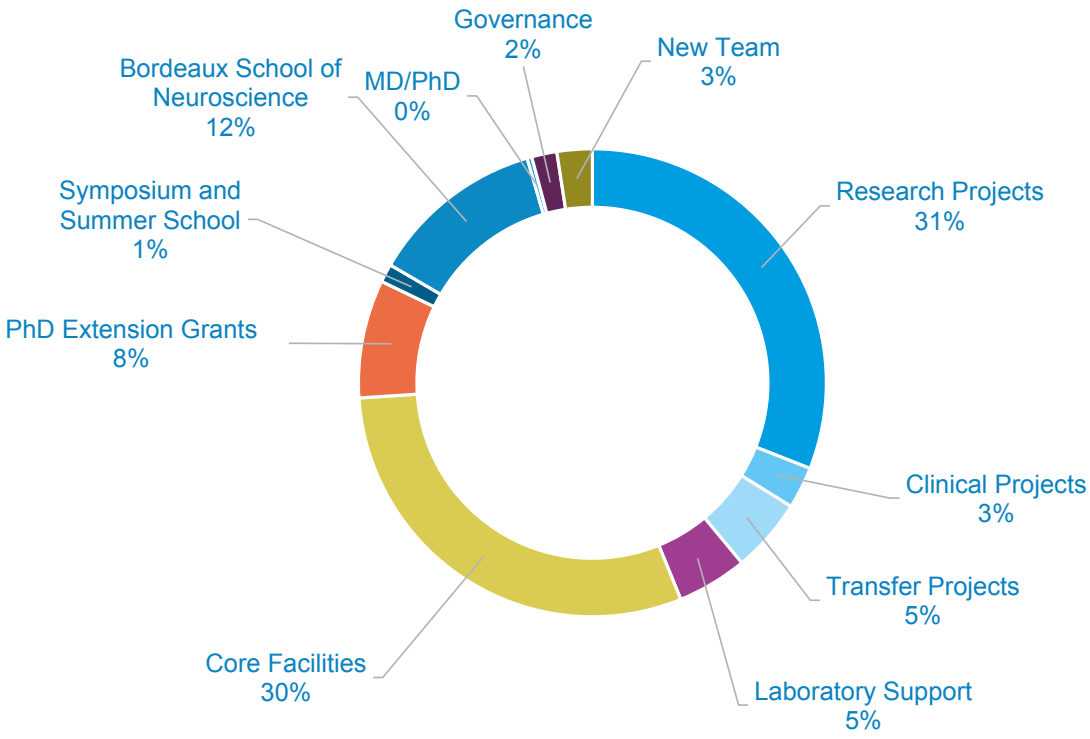
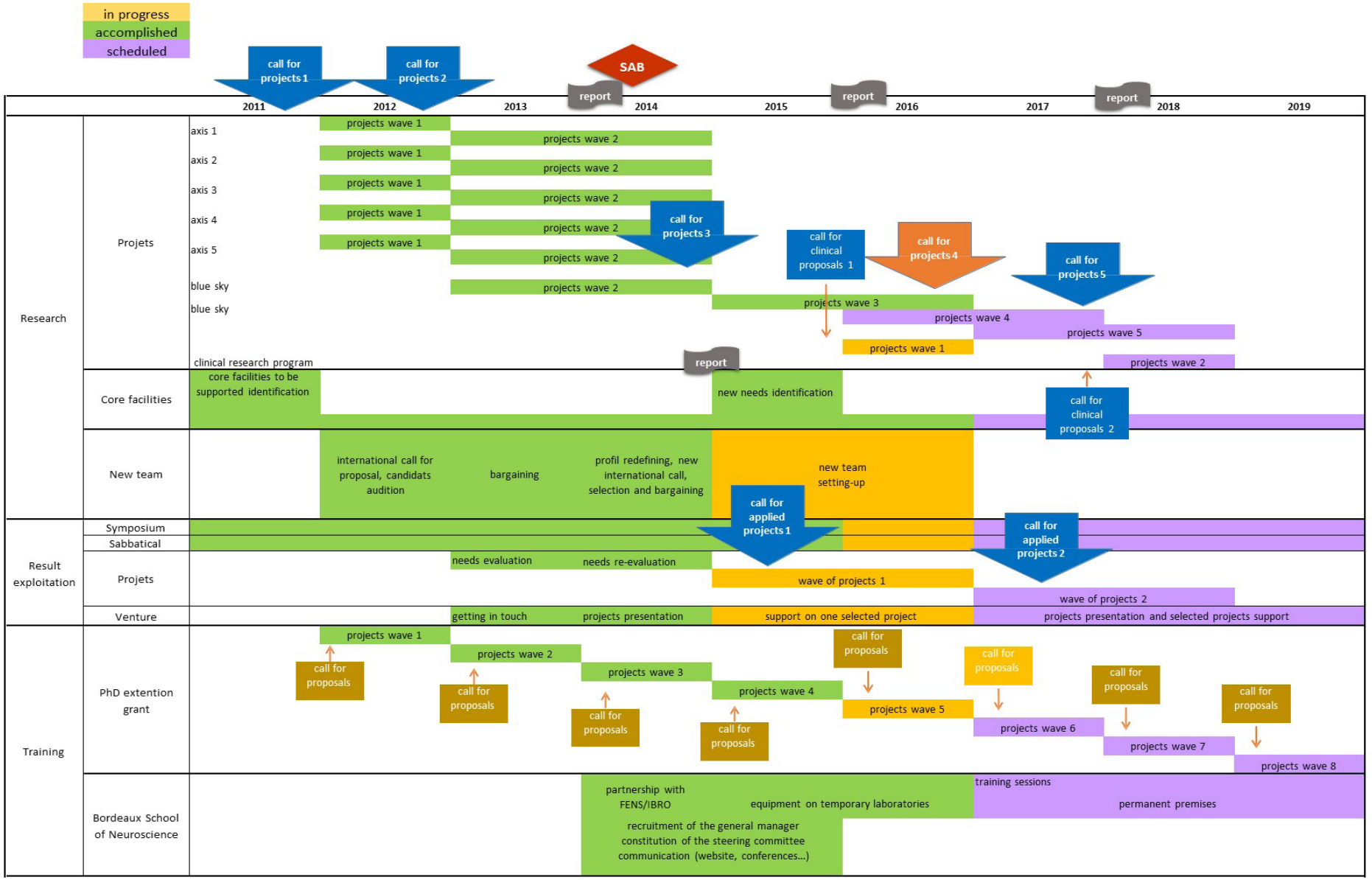
BRAIN Budget

Our resources are dedicated to **increase the attractiveness** of Bordeaux for outstanding external scientists and students, the **excellence** of the research, and the **exploitation and dissemination** of the results produced by the BRAIN teams.

During the first 4 years of the LabEx, the expenses were spread out as described in the pie-chart below.





Global view of accomplished and scheduled actions

For the coming years, the LabEx will continue to develop its high added value activities on translational research and technology transfer. The LabEx will also run its annual activities : PhD extension grants, core facility support, international conferences , visiting professors , etc ...

→ Cofunds and Bordeaux Neurocampus strategy

The impact of the LabEx BRAIN in terms of general strategy to attract new funds was to bring a comprehensive strategy at the Bordeaux Neurocampus level. Therefore, we observe that the laboratories redefined their own strategy by taking into account the overall strategy of the site.

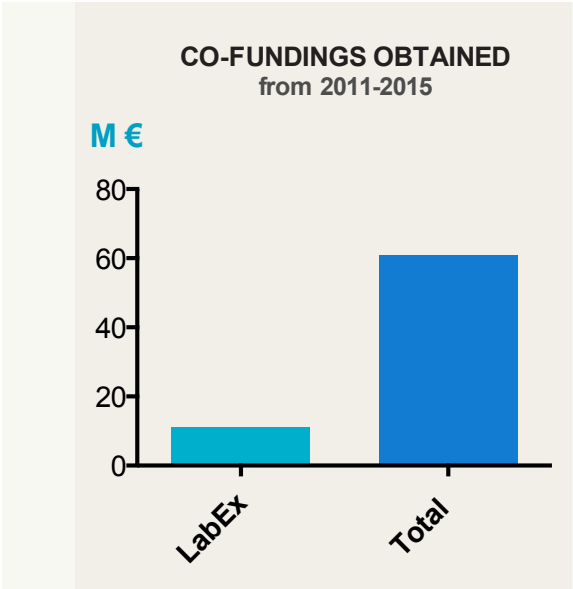
→ Co-funds:

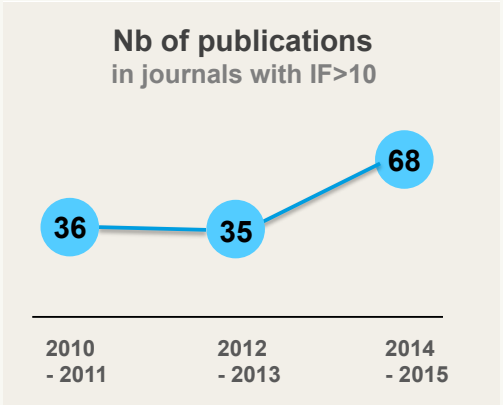
The total of resources obtained from 2011 to 2015 by the LabEx teams is **61M€**, with 17,5M€from ANR and 8,9M€ from Regional Council, 7,2M€ from European Commission. If we focus on the resources directly linked to the LabEx projects, the projects selected within the calls for proposals (general basic research, clinical and transfer calls) were so far able to obtain **10M€ of co-funds** (from diverse national or international agencies, including 8 ANR grants and 6 FRM grants).
At the European level, from 2011, 6 ERC grants were obtained (3 in 2011, 1 in 2014 and 2 in 2015). The selection of the CoE project (Center of Excellence) BIND for neurodegenerative disease at the national level permits to be part of the European Network of Centres of Excellence in Neurodegeneration (COEN).

→ The Neurocampus project:

The Regional Council supports our research community within the Neurocampus project (65 M€): it consists in the construction of a new building of 12 000 m² of new lab space to rationalize animal facilities and the imaging center. 12M€ are dedicated to high-end equipment of core facilities and laboratories, and 8M€ are devoted to attract new international teams. The main criterion for the selection of these new team leaders is the excellence, and we will try to fill gaps in the several thematic including, in particular but not exclusively: in vivo imaging, development, model organisms, clinical research, physical chemistry, biosensors

We have strong interactions with the 2 EquipEx in neuroscience: Optopath, a rodent platform entirely dedicated to innovation in experimental psychopathology, and Phenovirt, a multiface immersed environment to conduct clinical research. OptoPath and PHENOVIRT develop partnerships with industrials (Imetronic, Servier IRIS, Thales, Oktal, Continental Automotiv…)



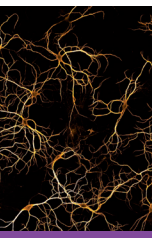


→ Strategy

→ **Pursue successful programmes:** the non-thematic call for projects, clinical and applied research calls, pursue the Ph.D. extension grants, support to facilities and symposium.

→ **Attract new teams:** the Neurocampus project is ongoing, with the new building under construction. The first international call for junior group leader was a real success (171 international candidates). The main criterion is excellence, and we will try to fill gaps in the several thematic including, in particular but not exclusively: in vivo imaging, development, model organisms, clinical research, physical chemistry, biosensors. The selection is running and a second international call will be launched next year.

→ **Reinforce innovative and transversal projects**, by stimulating inter-LabEx programmes (e.g. ExtraBrain) and developing new facilities (Protein production, Stem cells, Optopath/phenovirt)



→ **Increase European visibility and training,** with the creation of the Bordeaux School of Neuroscience and the European certification of the BIC. Indeed, the participation to the EuroBioImaging network is a unique opportunity to attract international users at the BIC and create new international collaborations. Moreover, it potentiates the visibility of the Bordeaux School of Neuroscience that has a special partnership with the BIC.

→ We wish to increase our presence at career fairs. Moreover, we need to reinforce links with patient associations and we have to identify representative icons. A large work of lobbying has to be done to increase governing bodies' awareness about neuroscience.

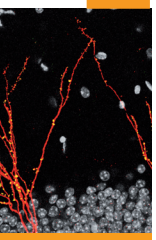
→ **Attract new funding:** we need to develop a strategy for a better communication and fundraising. Therefore, we plan to reinforce access to European funding, stimulate IP protection, and structure interactions with venture capital and creation of start-ups.

In order to prepare the next steps of the LabEx , we have identified our strengths in terms of large research projects:

→ **Centre of Excellence BIND** («Bordeaux Initiative for Neurodegenerative Disorders») and FHU TALISMENT («Diagnosis, Prevention and Treatment of Neurological , Psychiatric , Metabolic Disorders and Sleep»)
→ **Imaging with BIPSA** network («Biophotonics and Health in Aquitaine»)
→ **International training** with the Bordeaux School of Neuroscience
→ The question arises to apply for an IHU in Neurosciences

RESEARCH

- Scientific Projects
- New Team
- Core-Facilities



Morpho-functional plasticity of the tripartite synapse

Principal Investigator:	Partners:
Giovanni Marsicano (NCM)	Valentin Nägerl (IINS), Stéphane Oliet (NMC)

LabEx support : 58 K€

→ Objectives of the project:

Aim 1: Characterize morphological organization of tripartite synapse using STED
Aim 2: Investigate activity-dependent structural plasticity of tripartite synapse.
Aim 3: Study role of astrocytic coverage
Aim 4: Study role of endocannabinoid signaling
Aim 5: Study impact of CB1 signaling on behavior

→ Main results:

We imaged hyperfine astrocytic processes in proximity of dendritic spines using STED in living brain slices
We described structural changes in astrocytic coverage of dendritic spines after LTP
We identified a form of LTP in vitro that depends on astroglial CB1 receptors
We found that this is likely mediated by control of co-agonist occupancy of NMDA receptors
We found that astroglial CB1 receptors are necessary for object recognition memory.

→ Working plan to continue:

*Grant concluded. Next steps odf the collaboration will include studying the following items:
→ The link between astrocytic morphological dynamics and CB1 receptors,
→ The intracellular pathway involved in the astrocytic anatomical plasticity
→ The coupling between D-serine release and CB1Rs.
→ Developping tools (microscopy, labelling, virus...) to enable the investigation of the tripartite synapse
This will imply future applications for common grants (e.g. ANR)

→ Additional grant obtained:

Funding agency: ANR
Name of the project: SUPERtri
Total amount: 536 720 Euro
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

→ Publications in preparation or submitted:

→ LTP withdraws perisynaptic astroglia boosting glutamate escape by Christian Henneberger*, Aude Panatier*, Nikolay I. Medvedev*, Stefanie Anders, Daniel Minge, Igor Kraev, Lucie Bard, Stephane H.R. Oliet, Michael G. Stewart**, Valentin Nagerl**, Dmitri A. Rusakov**. In preparation
→ Astroglial CB1 receptors control memory via D-serine. Laurie M. Robin*, Jose F. Oliveira da Cruz*, Valentin C. Langlais*, Mathilde Metna-Laurent, Arnau Busquets-Garcia, Luigi Bellocchio, Edgar Soria-Gomez, Thomas Papouin, Barbara Bosier, Filippo Drago, Ann Van Eeckhaut, Ilse Smolders, Francois Georges, Aude Panatier, Stephane H.R. Oliet¨ and Giovanni Marsicano**. Submitted.

** equal first authorship ; ** equal senior authorship*

Impact of planar polarity on shaping neurons and synapses

Principal Investigator: Mireille Montcouquiol (NCM)	Partners: Olivier Thoumine (IINS)

LabEx support : 36 K€

→ Objectives of the project:

To understand the interplay between Planar Cell Polarity signaling and cytoskeleton dynamics during neuronal growth cone motility. For this, we combine live super-resolution imaging and genetic tools.

→ Main results:

- We found a decrease in the speed of retrograde actin flow in mouse hippocampal neurons of PCP mutants.
- We found a decrease in directed trajectories in mouse hippocampal neurons of PCP mutants.

→ Working plan to continue:

We plan to develop FRAP analysis and coverslips with specific adhesion pattern to evaluate the role of PCP proteins on adhesion molecules clustering in trans or cis.

→ Publications in preparation:

Dos Santos Carvalho S, Landmann C, Piguel N, Garcia M, Medina C, Peyroutou R, Henderson D, Sans N,Thoumine O, Montcouquiol M; Vangl2 impacts on adhesion and outgrowth of neuronal growth cone through regulation of N-Cadherin clustering

→ Communications:

- Piguel N, Landmann C, Garcia M, Al Abed S , Chazeau A, Giannonne G, Sans N, Thoumine O, Montcouquiol M. 4th Biosensor Meeting, Annual Meeting of the Biosensor Group of the GDR, Bordeaux, France 22-23 May 2014
- Dos Santos Carvalho, Decroo M, Landmann C, Piguel N, Thoumine O, Sans N, Montcouquiol M; Magendie Symposium, Bordeaux, November 2015
- Dos Santos Carvalho, Landmann C, Piguel N, Garcia M, Sans N, Thoumine O, Montcouquiol M; Ecole Doctorale, Bordeaux, April 2016
- Dos Santos Carvalho, Landmann C, Piguel N, Garcia M, Sans N, Thoumine O, Montcouquiol M; 10th FENS, Copenhagen, July 2016

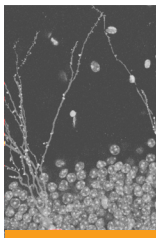
Role of neuronal and astroglial CB1 receptors in morpho-functional plasticity of the tripartite synapse

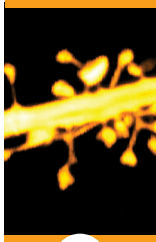
Principal Investigator: Giovanni Marsicano (NCM)	Partners: Valentin Nagerl (IINS)

LabEx support : 63,3 K€

→ Objectives of the project:

Aim 1: Morphological organization of tripartite synapse with or without cannabinoid treatments?
Aim 2: Activity-dependent structural plasticity: Do synaptic activity and endocannabinoid signaling modulate the morphological interaction of the three synaptic elements?
Aim 3: Role of astrocytic coverage: Does CB1-control of astrocytic morphology influence synaptic function and plasticity?
Aim 4: Behavioral analysis





Main results:

- We optimized the STED microscope to perform nanoscale imaging in acute brain slices
- We carried out STED time lapse imaging together with pharmacological experiments (using agonists and antagonists of CB1 signaling) in acute brain slices to screen for morphological effects in tripartite synapse structures
- We found that the object recognition memory impairment of the GFAP-CB1R-KO mice (described in the previous LabEx grant) depends on alterations in NMDARs activity
- We showed the necessity of the NMDARs activity of the hippocampus in object recognition memory and enhanced its activity to rescue the phenotype of the GFAP-CB1R-KO mice
- We identified a form of NMDAR-dependent LTP in vivo that depends on astroglial CB1 receptors
- We found that the Endocannabinoid system on astrocytes may likely control this form of LTP through the availability of D-serine, a NMDAR co agonist.

Working plan to continue:

We will address whether the impact of astroglial CB1 receptors on synaptic plasticity and memory consolidation is linked to endocannabinoid-dependent control of astroglial morphological plasticity. A similar approach will be adopted for neuronal CB1 receptors.

Additional grant obtained:

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

Published publications:

- Bethge, Avignone, Marsicano ** Nägerl, Biophysical Journal (2013)
- Soria-Gómez E*, Bellocchio L*, Reguero L, Lepousez G, Martin C, Bendahmane M, Ruehle S, Remmers F, Desprez T, Matias I, Wiesner T, Cannic A, Nissant A, Wadleigh A, Pape HC, Chiarlone AP, Quarta C, Verrier D, Vincent P, Massa F, Lutz B, Guzmán M, Gurden H, Ferreira G, Lledo PM, Grandes P*, Marsicano G* (2014) Nature Neuroscience 17(3):407-15
- Publications in revision: Astroglial CB1 receptors control memory via D-serine

In preparation:

LTP withdraws perisynaptic astroglia boosting glutamate escape by Christian Henneberger*, Aude Panatier*, Nikolay I. Medvedev*, Stefanie Anders, Daniel Minge, Igor Kraev, Lucie Bard, Stephane H.R. Oliet, Michael G. Stewart**, Valentin Nagerl**, Dmitri A. Rusakov**.

Communications:

Poster presentation at Neurophotonics meeting 2013. Poster presentations at International School on Astrocytes (2013) and oral presentations at GRC Conferences on Cannabinoids (2013), on GPCR Physiology (2013) and on Neuron-Astrocyte Interactions (2013)

Membrane dynamics of astrocytic glutamate transporter and its functional impact on synaptic functions

Principal Investigator: Laurent Groc (IINS)	Partners: Stéphane Oliet (NCM)

LabEx support : 63,3 K€

Objectives of the project:

We aim at testing the possibility that GLT-1 dynamics at the surface of astrocytes shape the glutamatergic synaptic transmission and control glutamate receptor location. Cutting edge single nanoparticle tracking and electrophysiological approaches will be used to measure, in vitro and in vivo, the impact of a pharmacologically-altered GLT-1 surface dynamics on synaptic transmission, plasticity, and receptor locations in hippocampal glutamate synapses.

Main results:

We demonstrated that GLT-1 are highly dynamics at the surface of astrocytes (Murphy Royal et al, Soc Neurosci Abstract 2012). Such a mobility is activity-dependent since it is sensitive to changes in neuronal and/or transporter activity as revealed by the use of selective pharmacological compounds. Remarkably, GLT-1 is highly retained in the vicinity of spontaneously-active glutamate synapses, suggesting that astrocyte can dynamically control the location of GLT-1 and ensure efficient glutamate buffering in synaptic areas. Finally, cross-linking the transporters to experimentally induce its immobilization affects the kinetics of excitatory postsynaptic currents. These data thus indicate that GLT-1 mobility is an important contributor to glutamatergic transmission.

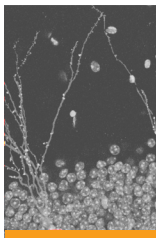
Publication:

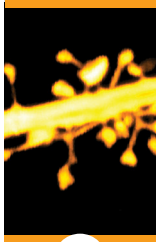
Murphy-Royal C, Dupuis JP, Varela JA, Panatier A, Pinson B, Baufreton J, Groc L*, Oliet SH*. Surface diffusion of astrocytic glutamate transporters shapes synaptic transmission. Nature Neurosci. 2015 Feb;18(2):219-26.

**Equal contribution, co-corresponding*

Communications:

- Society for Neuroscience, New Orleans 2012
- FENS Forum satellite workshop, Barcelona 2012
- Symposium of the Mediterranean Institite for Applied Science, Marseille 2013
- 3rd International Astrocyte School, Bertinoro 2013
- COST meeting, Palermo 2013
- 4th annual conference of CIPKeBiP,Ljubljana 2013
- UAB minisymposium, Birmimgham USA, 2013
- EuroGlia, Berlin, 2013
- Societe des Neurosciences, Lyon 2013
- Gordon Conference on Glial Biology, Ventura CA 2013





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

Principal Investigator: Nathalie Sans (NCM)	Partners: Grégory Giannone (IINS)

LabEx support : 63,3 K€

Objectives of the project:

Our goal is to decipher the spatiotemporal mechanisms controlled by the planar cell polarity (PCP) signaling in spine during specification and morpho-fonctional plasticity. We want to decrypt and monitor at the nanoscale level the organization and dynamics of PCP main players, Vangl2, along with its main interactors, Scribble1 and Prickle2 and to study the interplay between these PCP proteins, actin regulators and adhesion complexes in normal and pathological conditions.

Main results:

This project will provide novel conceptual insights into the nanoscale segregation of PCP proteins in spines and how individual PCP proteins control the actin cytoskeleton to build functional synapses. This project offers a multilevel and interdisciplinary approach to understand the consequences of mutations of PCP signaling at the nanoscale, cellular and physiological levels, on the establishment, maturation and function of the basic functional unit of neuronal integration in the complex circuit of the hippocampus: the dendritic spine.

Working plan to continue:

We will use well-established and new molecular, cellular and genetic tools to study PCP signaling (Sans lab) combined with single-molecule-based localization microscopy (SMLM) to study actin regulators and adhesion in spine (Giannone lab; Rossier et al., Nat Cell Biol 2012, Chazeau et al, EMBO J. 2014).

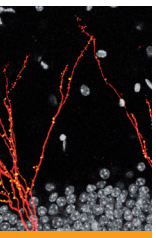
Additional grant obtained:

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

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

Principal Investigator: Jean-Baptiste Sibarita (IINS)	Partners: Jean-Philippe Domenger, CPU

LabEx support : 120 K€



Objectives of the project:

This project aims at developing a set of integrated instrumental and analytical methods for quantifying membrane receptors dynamics at the single-molecule level, in a High Content Screening (HCS) fashion. We are developing a novel HCS-SMLM imaging platform for automatic multi-well plate observation and advanced data mining to monitor active protein organization and dynamics under various conditions. This integrated platform will allow automatically quantifying and verifying whether the behavior of proteins of interest, in terms of organization and dynamics, has been altered by a particular drug.

Main results:

We have optimized our microscopy platform and acquisition pipeline to provide a fully integrated SMLM with HCS capabilities. It allows acquiring and analyzing a larger number of living cells and conditions in a very efficient workflow. A dedicated Graphical User Interface has been developed in order to handle the management of a multi-well plate and the stream acquisition, processing and data mining of targeted cells with the HCS standards.

Working plan to continue:

We now wish to validate and exploit this unique HCS-SMLM platform in collaboration with the neuroscientific community (D. Choquet, G. Giannone, O. Thoumine), both on well calibrated biological conditions and on relevant biological questions to measure the modulation of receptor dynamics in a large number of conditions. The acquisition platform pipeline still needs to be improved and automated non-supervised data mining methods are still under development, in collaboration with the bioinformatics group of M. Nikolski.

Additional grant obtained:

IdEx, program InterLabEx: 150K€
LabEx CPU: 45K€

Publications in preparation:

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

Programming support for hybrid systems applications

Principal Investigator: Daniel Cattaert (INCIA) | Partners: Gwendal Lemasson (NCM)

LabEx support : 116 K€

Objectives of the project:

The project's long-term objective is to establish a centralized facility in the Bordeaux site that will be principally engaged in the updating, customization and development of hybrid interfacing soft- and hard-ware. In a first step towards this objective, the project's aim is to set up computing/programming support for one of the principal hybrid neurobiological technologies –the dynamic clamp - used in the three partner laboratories.

Main results:

We have acquired dynamic clamp hardware (Cambridge Electornic Designs – CED) that was in common accordance with our research goals, and we have installed it in the three teams laboratories. This technology has been successfully employed on in vitro neuronal preparations to selectively replicate or suppress membrane and synaptic plasticity induced by appetitive operant learning (see bellow, article published in Current Biology).

Working plan to continue:

Our hybrid system is currently under development thanks to the recruitment of a computing software engineer paid by the present Labex grant. A library of ion channel mechanisms is being implemented. Extension of the system to include the calcium dynamics underlying KCa membrane channel operation is under study. Additional implementations (such as interfacing with NEURON simulation environment) are also planed.

Publications:

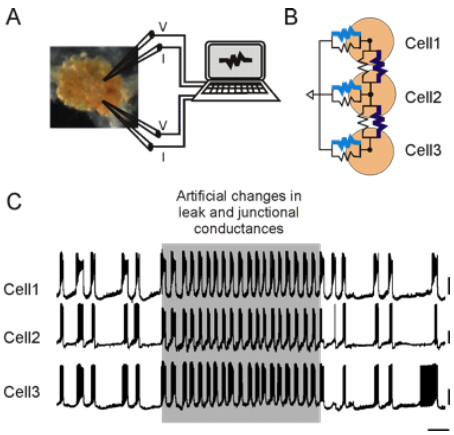
→ Sieling F, Bédécarrats A, Simmers J, Prince AA, Nargeot R (2014). Differential roles of nonsynaptic and synaptic plasticity in operant reward learning-induced compulsive behavior. Curr. Biol. 24(9) :941-950.

Book chapter:

→ Nargeot R, Bédécarrats A (2016). Electrical synapses and learning-induced plasticity in motor rhythmogenesis. In "Network functions and plasticity: perspectives from studying neuronal electrical coupling in microcircuits". Ed. J. Jing. (in press).

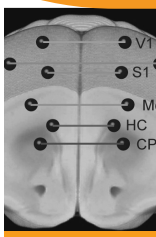
Communications:

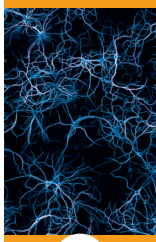
Nargeot, R. (2013) Minisymposium, Annual Meeting of the Society for Neuroscience (San Diego).



Modulation of electrical coupling between neurons is responsible for the change of activity in Aplysia feeding network.

A: Experimental procedure to control electrical coupling between neurons and their leak conductance by dynamic clamp. The voltage (V) of the two neurons is used to control current injection in their soma (i). B: Control of electrical coupling (black) and leak conductance (blue) achieved in three neurons (cell1, 2, 3) by the dynamic clamp procedure. C: The change in electrical coupling and leak conductance replicates the network activity observed during compulsive behavior.





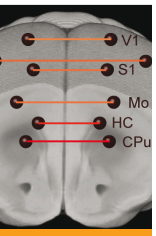
Unraveling the anatomical wiring diagram to understand the physiology and pathophysiology of the hippocampus and neocortex

Principal Investigator: Christophe Mulle (IINS)	Partners: Andreas Frick (NCM)

LabEx support : 163 K€

→ Objectives of the project:

An understanding of how the brain processes information requires knowledge of the architecture of its underlying neuronal circuits. The aim of this collaborative project is to investigate the architecture, and ultimately also the physiological function of hippocampal and neocortical circuits. To do this, we are using a sophisticated tool-box comprising novel recombinant rabies virus-based tracing approaches and whole-brain imaging techniques.



→ Main results:

- → Development of a novel anterograde RABV-based tracer. We described and characterised a novel pseudotyped form of RABV ΔG, capable of infecting the cell bodies of neurons and imparting intense labelling of all morphological features of these neurons along the entire length of their projections (see publication below).
- → Development of improved methodology for targeting mono-trans-synaptic tracing to a hippocampal CA3 starter cell population and mono-transynaptic tracing approaches to correlate the morphological input map with the receptive field properties of pyramidal neurons of layer 2/3 of the somatosensory cortex.

→ Working plan to continue:

With these tools developed to visualize the connectivity in the hippocampus and neocortex, combining RABV- base tracing, brain clearing (CUBIC method) and light sheet microscopy (ultramicroscopy in 3D). we will 1) examine the link between structure and function of neuronal circuits in the hippocampus and the neocortex and 2) study remodelling of neural circuits following learning or in physiopathological conditions (Fragile X, Alzheimer's disease).

→ Additional grant obtained:

Funding agency: FRM
→ Total amount: 2 years for the recruitment of an Engineer for the production of viral tools
Date and duration of the grant: 2014-2016
→ Equipe FRM (Christophe Mulle) – recruitment of an Engineer to continue the work.

→ Published publications:

Haberl, M.G.,Viana da Silva, S., Guest, J.M., Ginger, M., Ghanem, A., Mulle, C., Oberlaender, M., Conzelmann, K-.K. and Frick, A. An anterograde rabies virus for high-resolution large-scale reconstruction of 3D neuron morphology. Brain Struct Funct 220, 1369–1379 (2015).

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

Principal Investigator: Nora Abrous (NCM)	Partners: Christophe Mulle (IINS)

LabEx support : 100 K€

→ Objectives of the project:

The objective of this project is to scrutinize the influence of spatial learning in the water maze on the morphology and function of afferences (Task 1) and efferences (Task 2) of adult-born dentate granule neurones (Adu-DGNs) or DGNs born during development (Dev-DGNs). To identify and quantify the

inputs impinging onto Adu-DGNs or Dev-DGNs in basal condition and in response to spatial learning Abrous's lab used a novel monosynaptic rabies virus-mediated retrograde tracing system. To analyse the influence of spatial learning on synaptic properties, Dr Ashley Kees in Mulle's lab is performing whole cell patch clamp recordings in Adu-DGNs and Dev-DGNs labeled by the Abrous lab.

→ Main results:

Task 1. Using monosynaptic rabies virus-mediated retrograde tracing system, we have shown that Adu-DGNs received more inputs from granule neurons and from the pyramidal cells of the Ammon's corn when animals were submitted to spatial training. For the electrophysiological study, the main difficulty was to work on "old" hippocampal sections as this material is prone to deterioration for single cell physiology following cutting. Dr Kees have manipulated several parameters (temperatures of the cutting and resting chambers, compositions of the external and internal solutions of the slice preparation) and recording procedures to improve the quality of recordings. Currently, Dr Kees is recording miniature and spontaneous postsynaptic currents from Adu-DGNs in different experimental conditions.
Task 2.We have discovered that spatial learning influences the mossy fibers of Adu-DGNs. In particular a significant enlargement of the LMT size in the CA3 hippocampal layer was observed.

→ Working plan to continue:

For the anatomical studies our plan is to now study the influence of spatial learning on the afferents and efferents of Dev-DGNs. Concerning the electrophysiological study, Dr Kees will continue to compare relevant electrophysiological parameters in Dev-DGNs and Adu-DGNs.

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

Principal Investigator: François Georges (IMN)	Partners: Cyril Herry (NCM)

LabEx support : 120 K€

→ Objectives of the project:

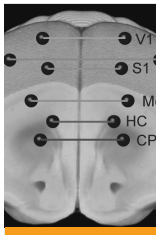
The ability to minimize contact with aversive experience is a hallmark of adaptive behavior and recent studies have demonstrated a key role of dopamine neurons in this process. Interestingly, associative learning correlate with dopamine release in the bed nucleus of the stria terminalis (BNST), a brain region that integrates cued and contextual information's and regulates emotional behavior. The main objective of the DOPABED project is to determine how DA€BNST neurons contribute to aversive associative learning.

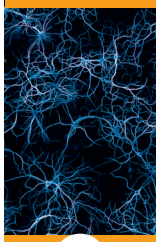
→ Main results:

To characterize the origin of the dopaminergic innervations of the BNST we combined tract-tracing approaches and juxtacellular labeling of individual neurons recorded in vivo. Surprisingly, our anatomical and electrophysiological results show that the origin of the dopaminergic innervation of the oval nucleus of the BNST was not the ventral tegmental area, but an understudied sub-population of dopaminergic neurons localized in the dorsal raphe regions.

→ Working plan to continue:

Optogenetics enables verification of physiology-based classification of neurons recorded in vivo. We will therefore paired extracellular recordings with optical tagging of dopamine neurons. This approach is necessary to characterize online the phenotype of the neurons recorded in vivo. The team of Dr. Cyril Herry is currently testing their function in a behavioral paradigm of fear conditioning using an adeno-associated virus expressing channelrhodopsin-2 targeted to dorsal raphe region of a DAT-cre mice.





Publications in preparation:

Role of dorsal raphe dopamine neurons in the acquisition and expression of conditioned fear. Fois G. ; Valerio S., Guillaumin, A., Ducrot, C., Doudnikoff, E., Girard, D., Bezard, E., Caillé, S., Herry, C., Georges F.in preparation

Communications:

The multiple dopaminergic inputs to the bed nucleus of the stria terminalis. Guillaumin, A., Ducrot, C., Doudnikoff, E., Girard, D., Bezard, E., Caillé, S., Georges F. Dopamine 2016 meeting: Poster presentation.

Neuronal circuits of contextual fear

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

LabEx support : 120 K€

Objectives of the project:

The NEUROCONTEXT project aims at precisely identifying the neuronal circuits and mechanisms involved in the acquisition, expression and extinction of contextual fear memories. The expected results will aim to:

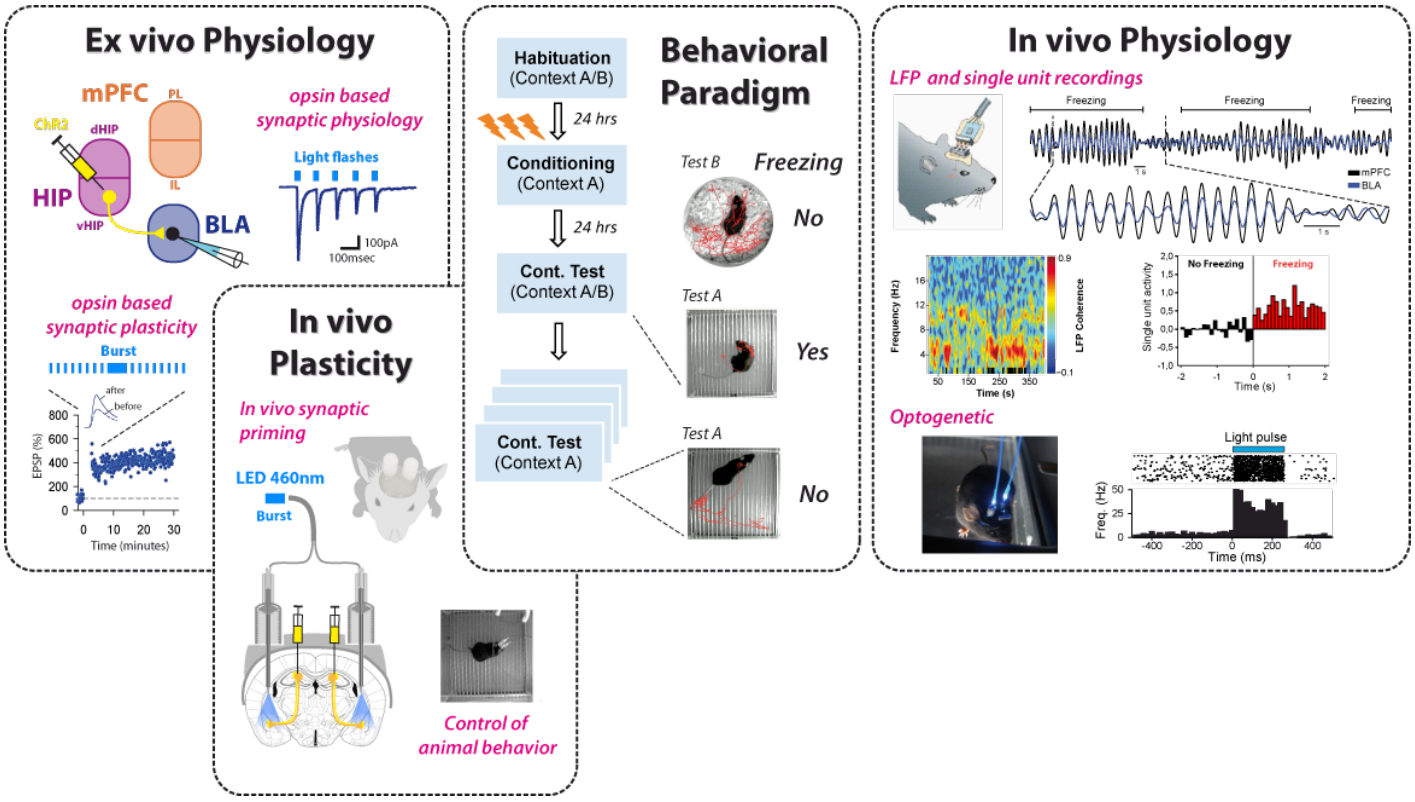
- Define the specific changes in activity that occur in mPFC, BLA and HIP neuronal circuits during the acquisition, expression and inhibition of contextual fear behaviour,
- Define the anatomical and functional connectivity of mPFC, BLA and HIP neuronal circuits implicated in contextual fear behaviour,
- Determine the causal role of excitatory and inhibitory elements of the mPFC, BLA and HIP during the acquisition, expression and extinction of contextual fear memories,
- Determine synaptic properties at specific neuronal pathways after formation, expression and extinction of contextual fear.

Main results:

We are currently examining the intriguing possibility that some particular long range projecting GABA neurons may be specially involved in controlling fear behavior. To achieve that, we combine the use of optogenetic tools in vivo and ex vivo in particular Cre-line mice.

Working plan to continue:

Electrophysiology in acute slices, in vivo optogenetic manipulations.



Modulation of synaptic calcium signaling by mitochondrial type 1 cannabinoid receptor

Principal Investigator: Sandrine Pouvreau (IINS)	Partners: Federico Massa (NCM)

LabEx support : 120 K€

Objectives of the project:

The overall goal of the project is to dissect the contribution of mitochondrial type 1 cannabinoid receptors (mtCB1) in cannabinoid modulation of presynaptic calcium signaling and synaptic transmission. Our working hypothesis is that mtCB1 signaling affects mitochondrial calcium handling.

Main results:

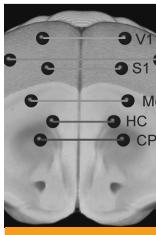
A full time postdoctoral researcher was hired in October 2015. The team is currently implementing the experimental conditions to study, in situ, the modulation of mitochondrial physiology by mtCB1. Imaging techniques coupled with synthetic and genetically encoded probes are being tested in cultured neurons isolated from CB1 KO animals, and transfected with CB1 or its mutated form excluded from mitochondria.

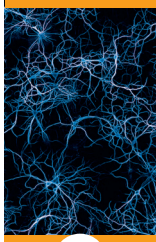
Working plan to continue:

We are currently studying the mechanisms linking mtCB1 signaling to alteration of mitochondrial physiology using cultured neurons. The relevance of such mechanisms at the synapse level will then be investigated in cultured hippocampal slices, an experimental models that retains the overall organization of the hippocampal circuit. This model is suitable for classical electrophysiology experiments, while allowing live-imaging of subcellular compartments.

Additional grant obtained:

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 K€
Date of obtention and duration of the grant: 1 march 2016
Duration: 3 years





2012:
LabEx support: 100 K€

Identifying the contribution of distinct neuronal circuits in the encoding of affective memories after drug withdrawal

Principal Investigator: Martine Cador (INCIA)	Partners: Catherine Le Moine (INCIA)

→ Objectives of the project:

Understand how affective memories associated with appetitive or aversive drug effects are encoded and retrieved within limbic structures. For this we performed multi-site single-unit and local field potential (LFP) recordings in the PFC (prefrontal cortex), BLA (basolateral amygdala), and NAC in behaving animals following opiate administration and withdrawal. The objective is to evaluate the dynamics of PFC-NAC-BLA synchronization in the coding and retrieval of opiate withdrawal memories.

→ Main results:

In the NAC we found that NAC neurons differentially encodes aversion and safety through specific gamma oscillations in opiate dependence: aversive context/high γ oscillations (80Hz) and safe context/low γ oscillations (60Hz). Moreover the G60/G80 balance strongly correlated with the strength of the conditioning. This suggest that G60/G80 interplay – established through the conditioning process- serves as a robust and versatile mechanism for a fine coding of the environment emotional weight (Dejean et al., submitted).

→ Working plan to continue:

We follow up on the study of single neuron activity in the BLA and PFC in relation to γ oscillations and emotional learning. More particularly NAC and BLA LFP show a concurrent increase in the amplitude and the synchronization of γ band oscillations at the time of memory retrieval. We are currently analyzing how coherent and synchronized activity within the PFC-NAC-BLA network dynamically encode opiate withdrawal memories (Sitko et al; 2015 poster presentations; Sitko et al., in prep).

→ Additional grant obtained:

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 K€ 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 K€; Date and duration of the grant: Jan 2015 for 3 years

→ Publications

Dejean C*, Sitko* M, Girardeau P, Bennabi A, Caillé S, Cador M, Boraud T, Le Moine C. (2016) Nucleus accumbens gamma oscillations encode memories of emotional states associated with opiate withdrawal (submitted)

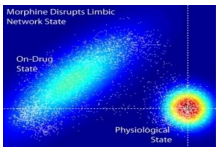
→ Communications:

- → Le Moine C, Girardeau P, Boraud T, Dejean C (2012). 8th FENS Forum of Neuroscience. Barcelone, Spain.
- → Dejean C, Boraud T, Le Moine C (2013). 11ième Colloque de la Société des Neurosciences. Lyon, France.

- Sitko M, Dejean C, Girardeau P, Caillé S, Cador M, Boraud T, et al. (2014). Colloque annuel du GDR « Systèmes multi-électrodes et traitement du signal appliqués à l'étude des réseaux neuronaux ». Gif-Sur-Yvette, France.
- Sitko M, Dejean C, Girardeau P, Caillé S, Cador M, Boraud T, et al. (2015); 12e Colloque de la Société des Neurosciences. Montpellier, France.
- Sitko M, Dejean C, Girardeau P, Caillé S, Cador M, Boraud T, et al. (2015). MMPL Symposium. Montpellier, France.
- Dejean C, Sitko M, Girardeau P, Bennabi A, Caillé S, Cador M, et al. (2016). GDR NeuroMem. Lacanau, France.

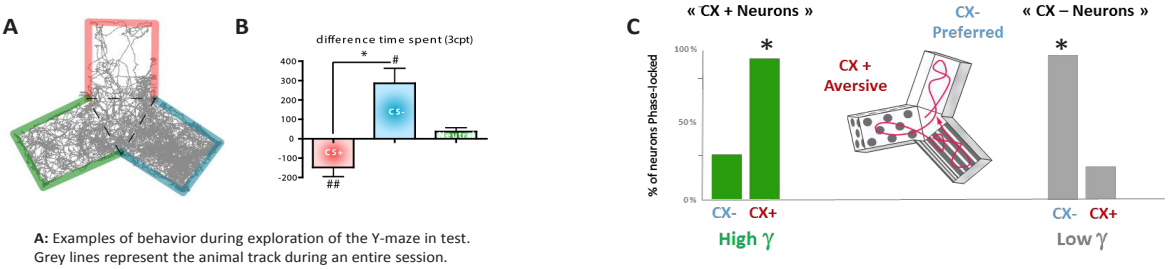
AIM 2: IDENTIFYING THE CONTRIBUTION OF DISTINCT NEURONAL CIRCUITS IN THE ENCODING OF AFFECTIVE MEMORIES AFTER DRUG WITHDRAWAL *(M. CADOR – P2)*

Initial work: Dejean C. et al. (2013) Neurobiology of Disease, 59,220-229. Opiate dependence induces network state shifts in the limbic system.



Main result: Nucleus accumbens gamma oscillations encode memories of emotional states associated with opiate withdrawal (submitted)

Cyril Dejean[1,2,*], Mathieu Sitko[1,2,*], Paul Girardeau[1,2], Amine Bennabi[3,4], Stéphanie Caillé[1,2], Martine Cador[1,2], Thomas Boraud[5,6], Catherine Le Moine[1,2]



A: Examples of behavior during exploration of the Y-maze in test. Grey lines represent the animal track during an entire session.
B: Aversion and place preference scores after conditioning. When compared to pre-test, animals in test spent significantly less time in CS+ (Naloxone, red) compartment and more time in CS- (Saline, blue) compartment. No change was observed in neutral compartment (green). The percentage of time spent in compartment also significantly differed between CS+ and CS-A

C: Compartment and γ specific modulation of context neurons phase locking in test condition. **CS+** neurons are preferentially modulated by **High γ (G80, Green)** and this entrainment specifically takes place when the animal is in the **CS+** compartment (left green bars). **CS-** neurons are preferentially modulated by **Low γ (G60, Grey)** and most particularly in the **CS-** compartment (righ gray bars). N neurons displayed entrainment for both G60 and G80.

In the Nucleus Accumbens, aversive and preferred environments are encoded by distinct groups of neurons and underpinned by specific oscillatory dynamics. Moreover G60/G80 ratio strongly correlated with the strength of the conditioning.

These data suggest that G60/G80 balance may serve as a robust and versatile mechanism for a fine coding of the environment emotional weight during conditioning.

PSYCHOBEHAVIORAL CHARACTERIZATION OF ADDICTION A NEW METHOD OF CHARACTERIZATION OF PLEASURE FOR FOOD IN OBESITY. RELATIONSHIPS WITH THE ENDOCANNABINOID SYSTEM (PLOBEC STUDY)

Principal Investigator: Daniela Cota (NCM)	Partners: Pierre Philip (SanPsy)

Objectives of the project:

Obesity is characterized by an impaired motivational processing of food. Here, we propose a recently developed and tested experimental computer-generated tool based on two separate instrumental tasks respectively exploring size (task A) and time (task B) discrimination capacities of food pictures (Aouizerate B et al., BMC Psychol 2014) for a quantitative, objective and implicit measurement of motivational responses to food-related stimuli in obese patients under either fasting or satiety (PLOBEC study).

Main results:

The preliminary results have shown that the modifications of the size perception of food images between fasting and satiety are less marked in obese patients than in normal-weight subjects. This contrasts with the more marked changes in the size perception of control images (geometric pictures) observed under fasting in obese patients as compared to normal-weight volunteers. Although the modifications in the perception of the length of presentation of food images between fasting and satiety conditions were similar among obese and normal-weight subjects, it seems that there are more prominent changes in the perception of the length of presentation of control images caused by fasting in obese patients as compared to normal-weight volunteers.

Working plan to continue:

Our findings suggest that the perception of food images appears to be less sensitive to the effects of hunger in obese patients, thereby leading to consider that our newly developed tool could be particularly appropriate for better identifying motivational malfunctions for food in obesity. The ongoing research project will then be extended to the study of the loss of motivation toward food classically associated with major depression (MOODDIS study).

Additional grant obtained:

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: 45K€
Date and duration of the grant: August 2013 – Duration: 2 consecutive years (renewed for one additional year)

Publications:

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.

Communications:

- Gouzien C., Cherifi B., Tabarin A., Philip P., Piazza P.V., Cota., D and Aouizerate B. Annual Meeting of the Graduate School of life sciences (University of Bordeaux). April 2015, Arcachon, France.
- Gouzien C., Cherifi B., Tabarin A., Philip P., Piazza P.V., Cota., D and Aouizerate B. Annual Meeting of the Neurocentre Magendie. November 2015, Bordeaux, France.

Characterization of molecular pathways in vulnerability to drug addiction

Principal Investigator: Jean-Michel Revest NCM)

Objectives of the project:

The serotonin2C receptor (5-HT2CR) is known to control dopamine (DA) neuron function by modulating DA neuronal firing and DA exocytosis at terminals. Recent studies assessing the influence of 5-HT2CRs on cocaine-induced neurochemical and behavioral responses have shown that 5-HT2CRs can also modulate mesoaccumbens DA pathway activity at post-synaptic level, by controlling DA transmission in the nucleus accumbens (NAc), independently of DA release itself. A similar mechanism has been proposed to occur at the level of the nigrostriatal DA system. Our goal is to characterize at a post-synaptic level the serotonin2C receptor downstream molecular pathways

Main results:

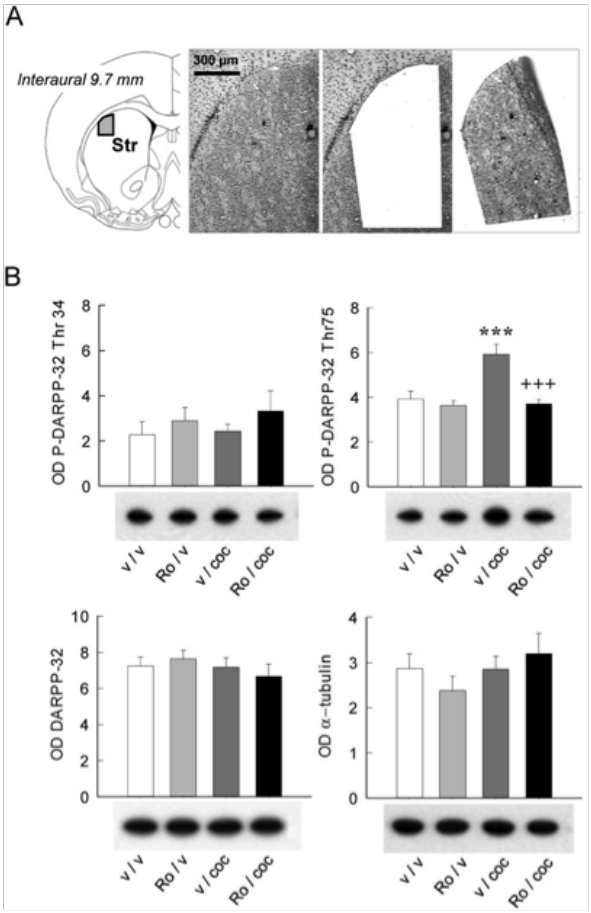
Here, using in vivo microdialysis in freely moving rats and molecular approaches, we assessed this hypothesis by studying the influence of the 5-HT2CR agonist Ro 60-0175 on cocaine-induced responses in the striatum. The intraperitoneal (i.p.) administration of 1 mg/kg Ro 60-0175 had no effect on the increase in striatal DA outflow induced by cocaine (15 mg/kg, i.p.). Conversely, Ro 60-0175 inhibited cocaine-induced Fos immunoreactivity and phosphorylation of the DA and c-AMP regulated phosphoprotein of Mr 32 kDa (DARPP-32) at threonine 75 residue in the striatum. Finally, the suppressant effect of Ro 60-0175 on cocaine-induced DARPP-32 phosphorylation was reversed by the selective 5-HT2CR antagonist SB 242084 (0.5 mg/kg, i.p.). In keeping with the key role of DARPP-32 in DA neurotransmission, our results demonstrate that 5-HT2CRs are capable of modulating nigrostriatal DA pathway activity at post-synaptic level, by specifically controlling DA signaling in the striatum.

Working plan to continue:

Now we would like to decipher the role of the prefrontal Cortex, in particular if this brain structure also participates to the mechanisms underlying the Ro 60-0175 suppressant effect on cocaine behavioral responses.

Published publications:

Devroye C, Cathala A, Maitre M, Piazza PV, Abrous DN, Revest JM, Spampinato U. Serotonin2C receptor stimulation inhibits cocaine-induced Fos expression and DARPP-32 phosphorylation in the rat striatum independently of dopamine outflow. Neuropharmacology. 2015 Feb;89:375-81.



EFFECT OF RO 60-0175 ON COCAINE-INDUCED STIMULATION OF DARPP-32 SIGNALING PATHWAY IN THE STRIATUM (STR). *Ro 60-0175 (Ro, 1 mg/kg) was intraperitoneally (i.p.) injected 15 min prior to cocaine (coc, 15 kg/kg, i.p.). Rats were sacrificed 30 min after the last injection.* ***A:*** *Schematic diagram, taken from the Paxinos and Watson atlas (1986), showing representative pictures of the Laser Microdissection and Pressure Catapulting (LMPC) treatment of the striatum before, after LMPC, and captured zone.* ***B:*** *Western blot analysis and densitometric quantification of striatal expressions of phospho(P)-DARPP-32Thr34, P-DARPP-32Thr75, DARPP-32, and a-tubulin proteins. Histograms represent the mean ± SEM optical density (OD) (n = 6-7 animals/group). DARPP-32 and a-tubulin values did not differ across the different experimental groups (ANOVA, DARPP-32: F(3,22) = 0.61, NS; a-tubulin: F(3,22) = 0.98, NS). ***p < 0.001, versus the vehicle/vehicle (v/v) group; +++p < 0.001, versus the v/coc group (Fisher's PLSD test).* ***From C. Devroye et al. Neuropharmacology 89 (2015) 375e381.***

2013:
LabEx support: 90 K€

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

Principal Investigator: Serge Ahmed (IMN)

→ Objectives of the project:

Previous research from our lab showed that when faced with a choice between two competing actions, taking cocaine or engaging in an alternative nondrug activity (i.e., drinking sweet water), ~90% rats prefer the nondrug activity, even after prolonged drug use. Only few rats prefer the drug. Our objective was to identify the behavioral and neuronal mechanisms of individual drug preferences, with an initial focus on the majority of nondrug preferring rats.

→ Main results:

Surprisingly, using large-scale brain Fos mapping, we found that among option-responsive cortical and subcortical brain subregions (~50), virtually all responded largely more to cocaine than to the preferred nondrug option. Only few brain regions responded more to the latter, notably the ventral pallidum. At the behavioral level, we found that the drug state at the time of choice profoundly influences choice outcome by shifting preference to cocaine.

→ Working plan to continue:

We plan to extend this work in at least 2 directions. First, we will compare and contrast the pattern of brain activity observed in nondrug-preferring rats to that observed in the minority of drug-preferring rats. This work will help to define brain regions and circuits involved in cocaine addiction for future interventional studies. Second, we will study the mechanisms of the influence of the drug state at the time of choice on preference expression.

→ Additional grant obtained:

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

→ Published publications:

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.

→ Publications in preparation:

→ Girardeau P, Navailles S, Durand A, Vouillac-Mendoza C, Guillem K ** Ahmed SH (2016) Discovery of an unsuspected cause for persistent vulnerability to relapse despite complete extinction of cocaine craving. Under review at Nature Communications.
→ Navailles S, Vandaele Y, Durand A, Guillem K ** Ahmed SH (2016) Large-scale Fos mapping of preference for sweet reward over cocaine in rats. In preparation.

→ Communications:

→ Navailles S, Girardeau P, Durand A, Ahmed SH. 9th FENS Forum of Neuroscience. Milan, Italy, July 5-9, 2014.
→ Girardeau P, Navailles S, Durand A, Guillem K, Ahmed SH. 45th annual meeting of the SFN. Chicago, USA, October 17-21, 2015.

Measures of motivational and hedonic states in rats

Principal Investigator: Martine Cador (INCIA)

Objectives of the project:

The project was aimed at setting the taste reactivity test (Berridge, 2000) in order to be able to get an objective evaluation of the hedonic perception of an animal. The final aim is to be able to compare the hedonic perception in rodents which have overconsummed sugar during their adolescence.

Main results:

We have used the taste reactivity test and the licking test in animals which have overconsumed sucrose during their adolescence and we have found a decreased hedonic perception of sweetness as revealed by diminished hedonic facial expression in rats which have overconsumed the sucrose during their adolescence in comparison to controls. This decreased hedonic perception is accompanied by a decrease d reactivity of nucleus accumbens neurons in terms of cfos activation.

Working plan to continue:

A next step will be to implement physiological recordings which will quantify markers of the emotional reactivity of the animal (Heart rate, temperature..). The software DSI Dataquest ™ ART for signal acquisition has been coupled with the analysis of the behavioral events (Imetronic, Pessac) and we are now validating this novel interface.

Additional grant obtained:

Funding agency: Fonds Francais Alimentation Santé
Name of the project: Un modèle neurocomportemental du plaisir alimentaire : l'exposition à des aliments sucrés à l'adolescence et ses conséquences
Amount: 130 K€
Date and duration of the grant November 2012-november 2015
Additional grant obtained in 2014
(idem as above)

Publications

- Baldo B.A., Pratt WE, Matthew J W, Hanlon EC, Bakshi VP, Cador M, Principles of motivation revealed by the diverse functions of neuropharmacological and neuroanatomical substrates underlying feeding behavior. Neurosciences Biobehavioral Reviews 2013 Nov;37(9 Pt A):1985-98.
- 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

Communications:

- Cador M, Journées Francophones de Nutrition, Lyon, 12-14, 2012
- Cador M, 6th symposium Nutrition-Neuroscience, Bordeaux, le 18 Mars 2013
- Cador M, Naneix F, Darlot F, Pape JR, Coutureau E. Annual meeting of the Society for Neuroscience, Washington (D.C.), USA, November 15-19, 2014
- Naneix F, 8th meeting of Nutrition and Neuroscience, Bordeaux, March 17, 2015
- Naneix F, Darlot F; Pape JR; Coutureau E; Cador M, EBPS-EBBS EBPS Biennal Meeting Joint EBPS-EBBS Meeting. September, 12-15 2015, Verona, Italy
- Naneix F, Herrouin C, Cathala A, Spampinato U, Coutureau E, Cador M, Dopamine 2016, Vienne, Austria, July 2016

Alteration in learning strategies associated with drug addiction

Principal Investigator:	Partners:
Véronique Deroche-Gamonet (NCM)	Vincent David (INCIA)

Objectives of the project:

Drug addicts show alterations in memory processes and learning strategies. Whether these cognitive alterations are symptoms of prolonged drug use or are specific of addiction is unknown. The addiction model implemented by VDG and the expertise of VD in drug-induced influence on learning processes, are keys to answer this issue. VD evidenced that morphine compromises spatial-guided and promotes cue-guided learning. The two partners will evaluate whether this drug-induced effect on learning is also observed for cocaine and differently affects addicted and non-addicted-like rats.

Main results:

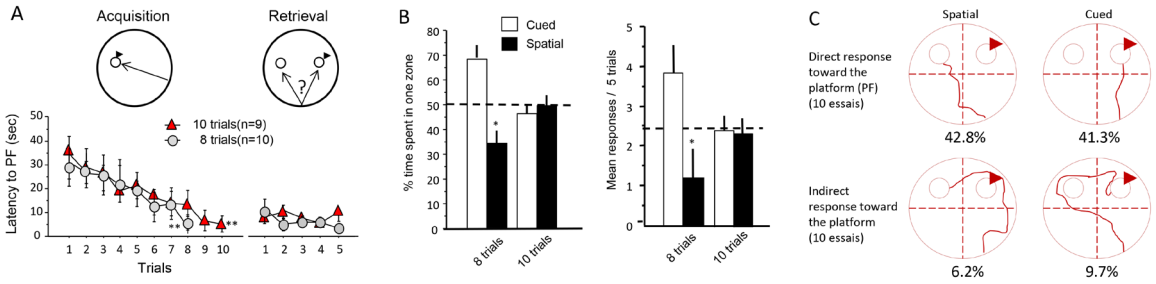
Through a series of pilot experiments, we have adapted the mouse water-maze competition protocol to rats. We are now able to measure various parameters assessing the respective use of spatial vs cued learning strategy. Importantly, we have established settings which allow a well-balanced and flexible use of these two forms of learning in naive, non drug-exposed animals (see preliminary results).

Working plan to continue:

The next step will be to compare, using this well-balanced protocol, the type of learning strategies used in naive animals prior to any drug exposure with rats with various level of cocaine exposure and rats that have reached criteria for cocaine dependence.

Additional grant obtained:

The Labex grant is used to get preliminary results in order to apply to national or European grants.



Preliminary data assessing spatial and cued learning strategies using a water-maze competition task in rats, prior to cocaine exposure. This version of the water-maze task, which was previously developed in the mouse, was adapted to Sprague-Dawley rats in order to allow a balanced expression of both cued and spatial learning strategies.

A) Escape latency during acquisition and retrieval phases. Protocols with either 8 or 10 consecutive trials allow for high performance in both acquisition and retention (repeated measure or trial ANOVA: $p<0.01$). (B) Expression of spatial and cued strategies during the retention phase. The 10-trial protocol lead to a balanced expression of these two strategies, whereas the 8-trial protocol promoted cued learning (X^2 $p<0.05$). (C) Distribution of trajectories in the 10-trial protocol, which confirm the well-balanced repartition of different types of navigation strategies.

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

Principal Investigator:	Partners:
Véronique Deroche-Gamonet (NCM)	Cyril Herry (NCM)

Objectives of the project:

Distinct, but interconnected, circuits appear at the core of pathological incentive processes and difficulties to control cocaine taking. Our goal is to characterize the function, connectivity and plasticity of dedicated nucleus accumbens (NAc), medial prefrontal cortex (mPFC) and basolateral amygdala (BLA) circuits involved in transition to cocaine addiction. For this, CH will record the same neurons from early to late cocaine use in rats resistant and vulnerable to cocaine addiction-like behavior issued from the addiction model implemented by VDG.

Main results:

We have performed simultaneous single unit and local field potential recordings in NAc, mPFC and BLA in rats behaviorally characterized as addicted or non-addicted-like after 3 months of cocaine self-administration. Our results indicated reduced functional connectivity between these neuronal structures in addicted compared to non-addicted-like rats, as assessed by long-range neuronal correlations and LFP coherence analysis. Over the last year, these preliminary results supporting that cocaine addiction is associated with functional alterations of specific neuronal circuits, have been extended by additional analyses. In particular, we evaluated the phase locking of prefrontal and accumbens neurons to theta oscillations, which revealed a significant increase in the number of neurons phase-locked to theta oscillations in non-addicted animals. Moreover, this was associated with an increased cofiring activity between pairs of neurons recorded in the mPFC, NAc and BLA in non-addicted animals compared to addicted rats.

Working plan to continue:

Our ongoing experiments aim at manipulating theta oscillations to evaluate whether this manipulation induces a behavioral switch between the addicted and non-addicted phenotype.

Additional grant obtained:

Funding agency: Eranet Neuron grant / ANR
Name of the project: COCADDICT
Total amount: 720 K€
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 K€
Date and duration of the grant: Starting June 2014 (18 months)

Published publications:

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.

Publications in preparation:

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

Communications orales:

- Deroche-Gamonet V. Conférence invitée au Barcelona Biomedical Research Park (PRBB), Barcelona, april 26 (2015).
- Deroche-Gamonet V. Conférence invitée, Journées de la SFA, Paris, march 18-20 (2015).

- Deroche-Gamonet V. Master Brain ** Cognitive Sciences Amsterdam, Study trip in Bordeaux, Conférence invitée, Bordeaux, octobre 24 (2014).
- Deroche-Gamonet V. Conférence invitée, 12th International Summer School, Catane, Italie, 28 juin – 4 juillet (2014).
- Deroche-Gamonet V. EWCBR, Brides-les-Bains, mars 15-22 (2014).
- Deroche-Gamonet V. Scientific Advisory Board visit, BRAIN Labex, Bordeaux, mai 19 (2014).
- Deroche-Gamonet V. 15th biennal meeting, EBPS, La Rochelle, septembre 6-9 (2013).
- Deroche-Gamonet V. Conférence invitée, Forum annuel GDR Psychiatrie 3557, La Rochelle, 6 septembre(2013).
- Deroche-Gamonet V. 11th Dutch Endo-Neuro-Psycho Meeting, Lunteren, Pays-Bas, mai 29-31(2013).

Communications affichées:

- Deroche-Gamonet V. et al., FENS, Copenhagen, Danemark, 2016.
- Simonnet A. et al. Eranet Neuron mid-term meeting, Helsinki, Finland, 2015.
- Garcia Rivas V. et al. Eranet Neuron mid-term meeting, Helsinki, Finland, 2015.
- Simonnet A. et al., FENS, Milan, Italy, 2014.
- Simonnet A. et al., French Neuroscience Society meeting, Lyon, France, 2013.

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

Principal Investigator: Aude Panatier (NCM)	Partners: Pier Vicenzo Piazza (NCM) ; François Georges (IINS)

LabEx support : 120 K€

Objectives of the project:

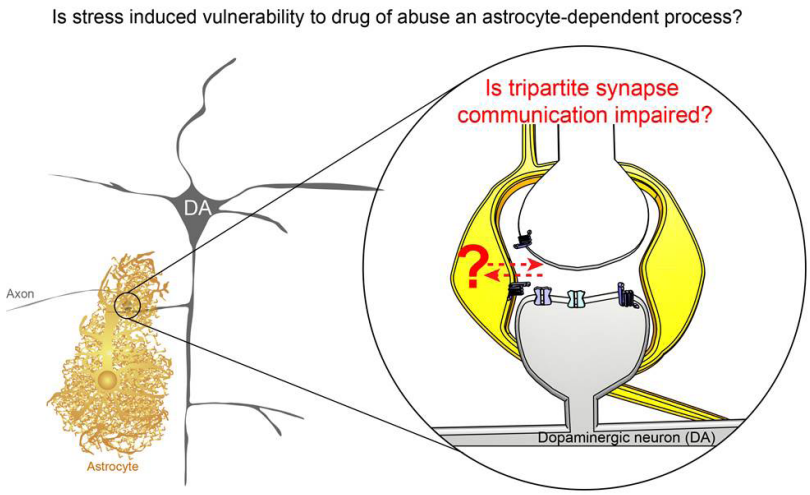
Stress is a physiological process required to adapt to environmental challenges. However, in chronic condition, it may lead to behavioral pathologies like addiction. Stress-induced vulnerability to drugs of abuse involves the activation of glucocorticoid receptors (GRs) and glutamatergic NMDA receptors (NMDARs). As astrocytes are neurons partners expressing GRs and controlling the activation of NMDARs we would like to assess whether stress induced vulnerability to drug of abuse is an astrocyte-dependent process.

Main results:

This project has started in November 2015. For now, the model of chronic stress is established in the different teams. Therefore, in vivo electrophysiological recordings as well as behavioral experiments have started. We are now trying to identify the impact of astrocyte inhibition on the activity of dopaminergic neurons as well as on the locomotion.

Working plan to continue:

Once, we will confirm in vivo the implication of astrocytes, we plan to identify at the cellular level how astrocytes are implicated in stress-induced sensitization to cocaine.



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

Principal Investigator: Bruno Bontempi (IMN)	Partners: Nora Abrous (NCM)

LabEx support : 70 K€

Objectives of the project:

By using innovative memory paradigms coupled to region-specific inactivation and imaging of newly-born hippocampal neurons in adult and aged rats, the core objective of this project is to decrypt the nature and dynamics as well as the neuronal constraints within the hippocampal-cortical interface responsible for the formation and stabilization of enduring declarative memories, and to determine how these parameters can be altered during normal aging.

Main results:

Additional experiments with our validated village maze were added to replicate and confirm our original findings showing that the cortex can store and retrieve flexibly richly detailed familiar spatial information independently of the hippocampus but fails when information are insufficiently familiar. Identification of specific cortical sites involved in either memory storage of familiar information or their flexible expression (dissociation of function) is still ongoing, one focus being the parietal cortex. These key findings were crucial in strengthening an ANR grant proposal which we obtained in 2015 (project MemoryTrack).

Working plan to continue:

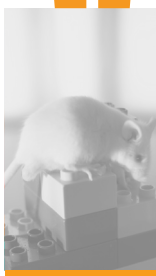
We now seek to 1) inhibit optogenetically the activity of hippocampal and cortical regions in rats previously reared in the village and therefore familiar with their spatial environment. High temporal resolutions of these inhibitions will enable to determine, in the same animal, the existence of a dissociation within the roles played by cortical regions in retrieval of remote memories (information storage versus flexible use in trials wherein an obstacle is added to the preferred route); 2) examine the functional implication of newly born hippocampal neurons in the flexible expression of consolidated memories.

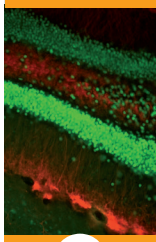
Additional grant obtained:

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 K€ (2 partner teams)
Date of obtention and duration of the grant: April 1, 2015, 60 months.

Publications in preparation:

Unraveling a new property of the cortex: the flexible expression of consolidated memories.





Early diagnosis and pleotherapy of Alzheimer Disease

Principal Investigator: Jean-Marc Orgogozo (CHU)	Partners: Pierre Philip, Jean-François Dartigues (SANPSY)

LabEx support : 45 K€

→ Objectives of the project

Contribute to a research on plasmatic proteomic biomarkers in AD, run by Pharnext, a private biotech company in Issy les Moulineaux, together with BSI, a private company, then by Pharnext alone after the withdrawal of BSI. Unlike the reasonably well validated ABeta and Tau markers in the CSF, the plasma biomarkers approach is not invasive, much less costly and is actively looked after.

→ Main results:

In total, 88 potential markers were identified, statistically differentiating controls from AD patients. Of those. Work is in progress to combine them in optimal signatures of AD versus true normals (who did not develop AD during the 5-10 years after plasma sampling) and other neurological diseases. Of those 8 are more discriminating individually and work is in progress to determine which combination could be the most discriminative as an AD "signature".
Further, 2 phase 1 clinical trials were conducted, measuring the level of these biomarkers before and after treatments based on the same rationale in order to explore the validity of these biomarkers to parralel a treatment effect, which could be of great interest for future molecules and combinations screening.

→ Working plan to continue:

This phase of the research is terminated on our side, except for complementary statistical analyses which are being done free of charge. The best combination of plasma biomarker signature for AD will be tested in subjects from the PAQUID cohort who became demented AFTER the plasma sampling. This additional phase is being financed by Pharnext (100 K€).

→ Additional grant obtained:

Funding agency: Oséo, for 120 K€ (total budget of Oséo for DIPPAL: 10,4 M€)
Name of the project: DIPPAL
Total amount: 285 K€, including the 50% co-financing of the University to Oséo
Date and duration of the grant 7 July 2011 – end of 2013

→ Publications in preparation:

patent applications

→ Communications:

only to the research team: Pharnext, University of Bordeaux ** Inserm 897 and CHU of Montpellier, because of the constraints of intellectual and industrial property of Pharnext.

Translational study of the cerebral substrates involved in pathological fear recovery

Principal Investigator: Cyril Herry (NCM)	Partners: Mélissa Bonnet (UMS CNRS 3428)

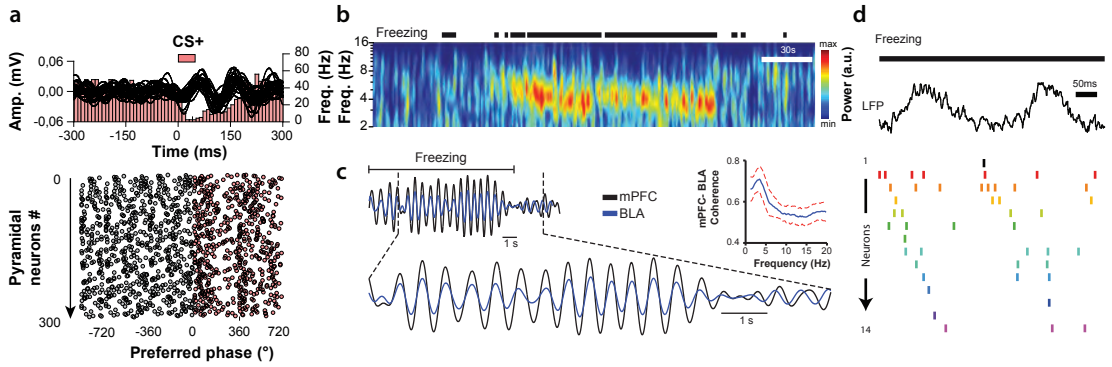
LabEx support : 70 K€

→ Objectives of the project:

The objective of this translational research project was to identify the changes in functional connectivity occurring between neuronal structures involved in emotional processing during relapse of fear behavior in animals and humans. This project combines fMRI and electroencephalography in humans as well as single unit extracellular recordings in mice.

Main results :

During the time course of this project, we have successfully developed an equivalent of the animal model of auditory fear conditioning in healthy humans and validated the protocol in a cohort of 24 volunteers submitted to fMRI imaging. In particular we identified two population of individual showing either a recovery of conditioned fear responses following extinction learning (vulnerable group) or low fear responses (resilient). Importantly, fMRI analyses revealed that activation of the Brodmann Area 10 (an equivalent of rodent prefrontal cortex) during extinction learning was predictive of low fear recovery. Functional connectivity analyses are still in process. In rodents, we identified a slow oscillation in the 2-6 Hz range in the prefrontal cortex and amygdala which coincide with fear behavior. Moreover, this 2-6 Hz oscillation synchronize the activity of prefrontal and amygdala neurons during fear behavior (Figure 1).



***Brain oscillations organize firing activities and synchronization. a**, Top, Tone-evoked (CS+) peri-stimulus time histogram (PSTH, red) for a representative mPFC PV interneuron showing a strong inhibition of activity during CS+. Overlaid CS+-evoked resetting of local theta oscillations (8-12 Hz) during PV-inhibition. Bottom, Synchronization of mPFC pyramidal cells to the peak of the theta oscillations during PV inhibition (adapted from Courtin et al., 2014, Nature). **b**, Representative spectrogram of mPFC oscillatory activity during freezing. Notre the strong power of oscillations in the 2-6 Hz band during freezing. **c**, Left: Representative example of synchronized mPFC and BLA local field potentials (LFP) recordings during freezing behavior. Right: Quantification of neuronal coherence between mPFC and BLA LFPs during freezing (n = 13 mice) (adapted from karalis et al., 2016, Nature Neuroscience). **d**, Representative example of an LFP recorded in the mPFC displaying prominent 2-6 Hz oscillations and simultaneous sequential activation of 14 mPFC neurons recorded in the same animal during freezing.*

Published publications:

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

Publications in preparation:

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

Communications:

Dejean C. et al., FENS, Milan, July 2014.

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: Bruno Bontempi (IMN)

LabEx support : 113,4 K€

→ Objectives of the project:

We seek to provide novel insights into the brain organization of recent and remote memories at the system-level by using innovative behavioral tools combining with cellular, molecular, and physiological methods. We aim to answer which are the neurons in neocortex that store the specific memories, what are the cellular plasticity mechanisms underlying this process, and to decrypt the neuronal allocation mechanisms underlying the formation and stabilization of declarative memories typically affected in Alzheimer's disease (AD).

→ Main results:

We are working on developing improved new protocols for spatial and associative memory task in mice such as one-day learning in 8-arm radial maze and social transmission of food preference. Using these protocols, we induced permanent tagging of neurons (with mCherry) in our mice during a specific time window regulated by doxycycline. Obtained data suggest that during the learning of a spatial memory task, the hippocampus recruits a significant higher number of neurons in mice that are learning than in non-learner controls.

→ Working plan to continue:

We will examine changes in intrinsic properties in tagged neurons by using whole-cell patch-clamp recordings combined with ion channel pharmacology to glean information on the ion channels involved in this plasticity. We will employ a model of AD (injection of Amyloid €oligomers) to pinpoint the deleterious effects on specific memory processes, to examine the levels of activated CREB in mice following behavioral paradigms, and determine whether increasing CREB function is sufficient to rescue the deficits observed in A€injected mice.

→ Additional grant obtained:

Funding agency: ANR
Name of the project: Neuronal allocation mechanisms of recent and remote memories in the normal and pathological brain
Total amount: 497 K€
Date of obtention and duration of the grant: 01/10/2015 for 48 months

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

Principal Investigator: Muriel Koehl (NCM)	Partners: François Georges (IMN)

LabEx support : 100 K€

→ Objectives of the project

Testing the hypothesis that sequential addition of cells across the development of the dentate gyrus (DG) is accompanied by specific changes in hippocampal network activity and by the occurrence of specific behavioral skills. We planned to first characterize the ontogenetic timeline of DG-dependent memory and of its morpho-functional properties across the different waves of neurogenesis, and second to causally relate cell populations with specific electrophysiological properties and memory skills using a transgenic approach.

Main results

We have shown in C57Bl/6J mice that 1) associative object in place recognition memory appears at 6 weeks of age, one week after simple object or place recognition memory; 2) both object in place and object in place in context memory involve activation of the DG; 3) DG cells of the same age, but arising from different developmental periods, sustain different functions; 4) 7 weeks-old DG cells are capable of LTP in response to entorhinal stimulation.

Working plan to continue

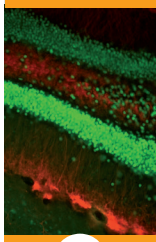
We plan to complete the time course of memory development and further analyze the specific contributions of the different populations of DG granule cells to the development of associative memory skills and that of hippocampal plasticity using functional imaging and transgenic approaches. These experiments are currently running.

Publications 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.

Communications:

Koehl M*, David J, Ladevèze E and Abrous DN. Respective involvement of juvenile and adult-born dentate cells in episodic-like memory in mice. Abcam Meeting : Adult Neurogenesis : Evolution, Regulation, and Function, Dresden, Germany, May 5-8, 2015.



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

Principal Investigator: Thomas Tourdias (NCM)	Partners: Bassem Hiba (TRAIL)

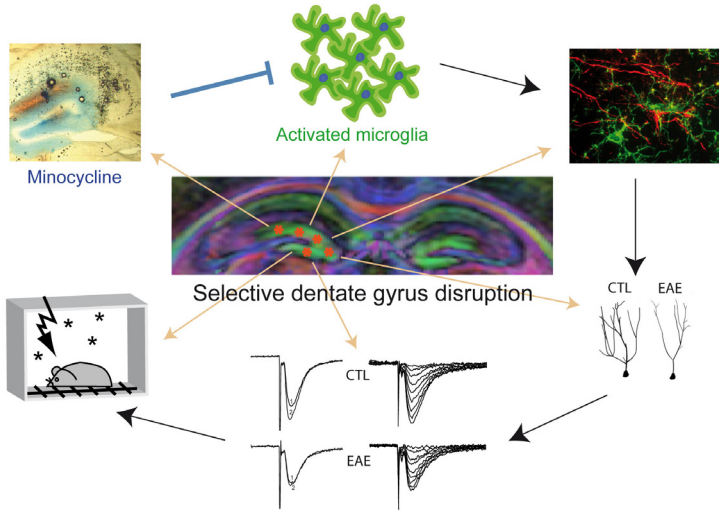
LabEx support : 119,2 K€

Objectives of the project:

This project is aimed at deciphering the pathological substrate of memory impairment associated with multiple sclerosis (MS). To do so, we developed a translational approach by phenotyping the cellular and electrical alterations associated with memory deficit in the animal model of MS (task 1). To translate these findings in vivo, we looked for magnetic resonance imaging (MRI) markers that could capture some of these features non-invasively (task 2). The same MRI markers are now being tested in patients with MS for their association with memory performances and their ability to predict future cognitive alterations (task 3).

Main results:

In the animal model of MS, we have demonstrated that early memory impairment is due to a selective disruption of the dentate gyrus caused by microglial activation (task 1). We have been able to identify MRI markers that can monitor in vivo and non-invasively such early dentate gyrus vulnerability by measuring modifications of microscopic displacement of water molecules (task 2). We have prospectively included 69 MS patients and 76 control subjects and we are currently showing that hippocampal alterations can be depicted in patients with the MR method used in animals and strongly correlate with episodic memory performances (task 3).



Summary figure:
Memory is frequently impaired from the early stage of multiple sclerosis but the biological substrate is poorly understood. In a mouse model, we show that the dentate gyrus is selectively vulnerable to microglial activation which leads to dentate gyrus selective neurodegeneration, decreased synaptic plasticity and ultimately memory deficit.

→ Working plan to continue:

We plan to continue investigating the cellular and molecular bases triggering hippocampal alteration and ultimately memory deficit in early MS. Especially, we plan to explore molecules involved in the cross-talk between neurons and microglia, which might also involve astrocytes, and which could trigger early dendritic and synaptic alterations. We have initiated new partnership with a team of immunology (UMR CNRS 5164, Nathalie Schmitt, ATIP Avenir and Junior Chair Idex) to investigate the role of the adjacent meningeal inflammation. New MRI methods (NODDI) are being developed to further improve sensitivity and specificity. A new PhD student will be hired in September 2016.

→ Additional grant obtained:

Bassem Hiba, our partner, obtained additional funding from Idex University of Bordeaux (call for proposal of November 2014) for the project entitled HL-MRI ("hippocampal layers magnetic resonance imaging"). This additional funding (146 K€) allows to conduct methodological MRI development in image acquisition and post-processing in humans in order to obtain super high resolution layer-by-layer analysis of the hippocampus that could be used to explore our MS patients.
Our neurologist partners from Bordeaux University Hospital recently obtained additional funding from pharmaceutical company (Teva; 50 K€) that will be used to continue the recruitment and the follow-up of MS patients explored with MRI and an extensive cognitive battery.
We recently responded to the annual call for research proposals of ARSEP foundation (Fondation pour l'aide à la recherche sur le sclérose en plaques) to hire a post-doctoral fellow working on the next steps of the project. Response is expected this summer.

→ Published publications:

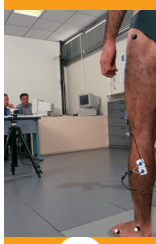
Crombé A, Alberti N, Hiba B, Dousset V, Tourdias T. "Cervical spinal cord DTI is improved by reduced-FOV with specific balance between numbers of diffusion gradient directions and numbers of averages". Accepted after revisions. American Journal of Neuroradiology 2016

→ Publications in preparation:

- Planche V, Ruet A, Coupé P, Lamargue-Hamel D, Deloire, M, Pereira B, Manjon JV, Munsch F, Moscufo N, Meier DS, Guttmann CRG, Dousset V, Brochet B, Tourdias T. "Hippocampal microstructural damage and memory impairment in clinically isolated syndrome suggestive of multiple sclerosis: a diffusion tensor MRI study". Submitted
- Planche V, Panatier A, Hiba B, Ducourneau EG, Raffard G, Cassagno N, Brochet, B, Dousset V, Desmedt A, Oliet SH, Tourdias T. "Microglial activation causes selective dentate gyrus disruption and memory impairment in experimental multiple sclerosis".
- Crombé A, Planche A, Raffard G, Cassagno N, Panatier A, Dousset V, Hiba B, Tourdias T. "Application of neurite orientation dispersion and density imaging (NODDI) to hippocampal phenotyping in a mouse model of multiple sclerosis".

Communications:

- Journées de Neurologies en Langue Française (JNLF), Nantes. Awarded as the best poster presentation by the French Society of multiple sclerosis. (2016)
- Days of Novelties in Clinical Research (JNRC), Paris, France. (2016)
- Neurology Residents Annual Meeting (JNIN), Paris, France. Awarded as the best oral presentation. (2015)
- European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), Barcelona, Spain. (2015)
- European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), Barcelona, Spain. (2015)
- 2nd International Bordeaux Neurocampus - Brain Conferences (GliSyn), Bordeaux, France. (2015)
- International Society of Magnetic Resonance in medicine (ISMRM), Toronto, Canada. Laureate of the clinical stipend program. (2015)
- Journée de l'école doctorale (EDSVS), Arcachon, France. Awarded as the best poster presentation. (2015)
- Annual meeting of the French Society of Neuroradiology (SFNR), Paris, France. (2015)



Thematic

Transversal pathophysiology and innovative therapeutics for sleep and attention disorders

Establishment of a biological resources collection

Principal Investigator: Erwan Bezard (IMN)	Partners: Wassilios Meissner (IMN)

LabEx support : 50 K€

Objectives of the project:

Setup of a repository for body fluids (cerebrospinal fluid, plasma/serum, urine) of patients with neurodegenerative disorders.

Main results:

Establishment of a repository including standard operating procedures (sample type and circuitry, preanalytics, quality control and storage) by the bioexpert. Beyond funding parts of the salary of the bioexpert, the LabEx has provided support for the necessary acquisition of a centrifuge for preanalytics and software for recording and handling of the samples. Altogether, the LabEx support has allowed creating the infrastructure necessary for the successful conduction of the BIOAMS and BIOPARK cohort studies (see below) and additional studies to come.

Working plan to continue:

The collection of samples of the BIOAMS and BIOPARK cohorts as well as the SYMPATH treatment trial is ongoing. The first scientific results based on the analysis of samples of the repository are expected for 2016/2017 (international collaboration to compare plasma exosomal alpha-synuclein levels between patients with MSA and PD as well as controls).

Additional grant obtained:

Funding agency: PHRC (French Health Ministry), PSP-France
Name of the project: BIOAMS, BIOPARK and SYMPATH
Total amount: 550 K€
Date and duration of the grant: BIOAMS (2012-2015), BIOPARK 2013-2016), SYMPATH (2014-2018)

Published publications:

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

Communications:

- 5th International Congress on MSA, Salerno, Italy, 23/04/2016.
- Joint Meeting EFAS-ISAN, Giessen, Germany, 31/07/2013.
- 4th International Congress on MSA, Toulouse, France, 20/03/2012.

Sleep, cognition and Alzheimer

Principal Investigator: Pierre Philip (SANPSY)	Partners: Stéphane Oliet (NCM)

LabEx support : 45 K€

Objectives of the project:

The increasing prevalence of neurological- and sleep-disorders associated to the aging of the population is a major issue of public health. Recent studies suggest that sleep disorders precede over the years the onset of clinical signs of Alzheimer's disease (AD).
The aim of this one-year follow-up study is to identify polysomnographic and neuropsychological risk factors that occur early in mild cognitive impairment with aging.

Main results:

29 patients with isolated memory complaints or mild cognitive impairment were recruited from the MEMENTO cohort in the CMRR of Bordeaux and compared to 29 healthy controls free of cognitive complaints and matched on age, gender and level of education.
The logistic regressions adjusted on age, gender, level of education, pathologies and medication use, shows that (1) poor sleep consolidation (i.e., the interruption of sleep by repeated awakenings) from polysomnographic data (OR 1.020, $p<.05$) is associated with higher risk of occurrence of isolated complaints of memory or mild cognitive impairment with aging, and that (2) a lower delta power (OR 1.004, $p<.05$), lower theta power (OR 1.052, $p<.05$) and lower sigma power (OR 1.411, $p<.05$) during non-REM sleep periods predicted isolated memory complaints or mild cognitive impairment in aging.

Working plan to continue:

This study confirms that the interruption of sleep by repeated awakenings, reduction of slow-wave, theta and sigma activity during NREM sleep are associated with higher risk of occurrence of isolated complaints of memory or mild cognitive impairment with aging.
A transfer process of MEMENTO data on memory performance is underway.

Additional grant obtained:

Funding agency: ANR
Name of the project: SCOAL
Total amount: 225 K€
Date and duration of the grant: October 2011, 4 years

Study of miRNA expression pattern as diagnostic and prognostic biomarker in amyotrophic lateral sclerosis

Principal Investigator: Alexandre Favereaux (IINS)	Partners: Gwendal Le Masson (NCM) ; Anne-Cécile Wielanek-Bachelet (Centre référence SLA)

LabEx support : 88 K€

Objectives of the project:

Amyotrophic Lateral Sclerosis (ALS) is a very severe neurodegenerative disease leading to muscle wasting, palsy and death due to respiratory failure within 3 to 5 years. The only effective drug (Riluzole) increases the life expectancy for about three months. We propose an innovative strategy to identify specific ALS biomarkers from a promising class of RNA molecules: miRNAs. Our principal goal is to demonstrate that a specific pattern of miRNA expression in patient's cerebrospinal fluid, blood or muscle can be correlated with the definite diagnosis of ALS. A second goal will correlate the miRNA pattern to the severity and/or progression rate of the disease.

Main results:

The clinical study protocol has been approved by the Centre Hospitalier Universitaire de Bordeaux and the Ethic committee. Therefore, the clinical study was launched on September 2013 and a dedicated CRA has been recently hired six months ago to speed-up patient inclusion. However, we performed a preliminary study which shows a specific dis-regulation of a subset of miRNAs in patients suffering from ALS. Indeed, 8 miRNAs are significantly up regulated and 3 are significantly down regulated in ALS patients when compared to control patients (Figure 1). These results strongly suggest that some miRNAs could be diagnostic biomarkers for ALS, confirming that the principal goal of our clinical study is realistic.

Working plan to continue:

Patients' inclusion should be completed within the next six months. A first batch of samples will be analyzed when half of the patients will be recruited. Final data analysis will define a specific pattern of miRNA expression that correlates to ALS diagnostic, thus enabling earlier diagnosis and medication. We should also be able to identify specific miRNA as prognostic markers of the ALS disease. This should improve patient management strategies.

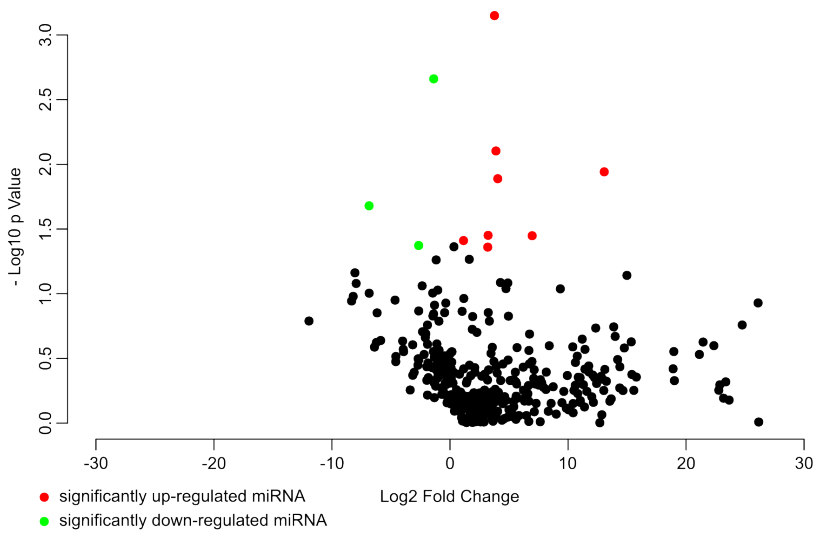
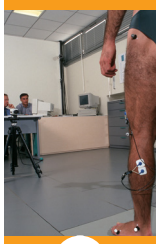


Figure 1: miRNA expression in CSF from ALS patients compared to control patients



Does the orexin system contribute to individual differences in sleep deprivation-induced changes in neurobehavioral function?

Principal Investigator: Pierre Philip (SANPSY)	Partners: Sophie Layé (NutriNeuro)

LabEx support : 45 K€

→ Objectives of the project:

Our main objective was to test whether the orexin system could contribute to individual differences in sleep loss induced impairment of neurobehavioral performance.

→ Main results:

Animal study: After sleep deprivation (SD), we found that the reaction time was increased for some mouse (sensitive to SD) but not others (resistant to SD). After at least 3 days of normal sleep, the two subgroups of animals (sensitive or resistant to SD) received an oral dose of the orexin receptor antagonist (Almorexant) right after the SD period. We found that animals sensitive to SD had a reaction time similar to resistant animals when exposed to Almorexant.

Human study: 6 narcoleptics with cataplexy (low level of orexin) and 6 healthy subjects (high level of orexin) have been sleep deprived during one night. Subjective sleepiness during SD is higher in narcoleptics but constant during all SD. In healthy subjects, Subjective sleepiness is lower at the beginning of SD and higher (same level than narcoleptics) at the end of SD.

Our data thus indicate that orexin may be a key player in sensitivity to sleep loss

→ 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 population (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

→ 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. Congres de la Société physiologie stasbourg 2014.

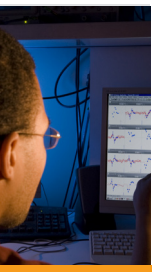
Exploring the brain extracellular space dynamics in physiology and pathology

Principal Investigator: Laurent Groc (IINS)	Partners: Erwan Bezard (IMN), Laurent Cognet (LAPHIA), Mireille Blanchard-Desce (LAPHIA)

LabEx support : 100 K€

→ Objectives of the project:

The groundbreaking objective of this project is to decrypt the intimate interplay between ECS and spatio-temporal dynamics of prion-like transmission and neurotransmitter receptor in shaping and regulating neuronal network (dys)function. A fluctuation in one compartment is sensed and transmitted to the other, and thus converted as a signaling message? To this end, we will i) image and characterize



the dynamic ECS remodeling during brain activity in physiological (development) and pathological (Parkinson's disease) conditions, and ii) manipulate pharmacologically the ECS organization to determine the impact on neurotransmitter receptor (glutamate NMDA receptor) trafficking.

Main results:

Single wall carbon nanotubes (SWCNT) have now been successfully imaged in the hippocampus and striatum of acute brain slices from both rats and mice. To note, single wall carbon nanotube are unique 1D nano-objects displaying strong and stable near-infrared luminescence, thus making them ideal for biological imaging in thick tissues. We are thus probing the ECS dynamics in these structures at an unprecedented level and revealed so far a high heterogeneity in both space and viscosity of the ECS. This breakthrough is currently submitted for publication in a very high impact journal.

Working plan to continue:

Next, we will image ECS dynamics in the developing hippocampus and in a topologically defined space (eg. Synpapses, astrocytes…) to unveil the emerging role of the ECS in the development of neuronal network. In addition, we will imgae the ECS in the striatum of primary and organotypic cultures, in "parkinsonian" mouse (and later monkey) models of Parkinson's disease based upon the prion-like hypothesis of Parkinson's disease (Luk et al., Science, 2012). Unique models based upon native PD patient Lewy bodies (LBs)-derived €synuclein were successfully developed in Bezard's lab (Recasens et al., Ann. Neurol., 2014). Spreading of misfolded synuclein in a prion-like manner involves a cell-to-cell transfer thereby placing the ECS in a key position for enabling or slowing such propagation.

Additional grant obtained:

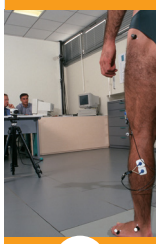
ANR OH-Risk 2015
Funding agency: Agence National Recherche
Name of the project: NanoSpace
Total amount: 600 keuros
Date of obtention and duration of the grant: 2015-2020 (Go-No-Go in 2017)

Publications in preparation:

Single carbon nanotube tracking reveals live brain extracellular space nanoscale organization
Authors: Antoine G. Godin#, Juan A. Varela#, Zhenghong Gao#, Noémie Danné, Brahim Lounis, Laurent Groc* and Laurent Cognet*.

#Co-first authors

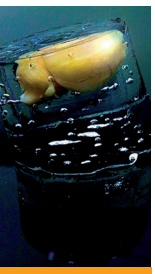
**Equal contribution, co-corresponding*



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: Pascal Fossat (INCIA), Bruno Quesson (CNRS UMS 3428,TRAIL); Klaus Petry (INSERM U1049); Erik Dumont (Image Guided Therapy)

LabEx support : 86,6 K€



→ Objectives of the project:

- → Objective 1: Adapting the existing HIFU technology to our specific aim: a lumbar bulge targeted deletion of the Cav1.2 gene in mice
- → Objective 2: Creation and characterization of the Cav1.2 heat-inducible knock-out mouse
- → Objective 3: Analyzing the effect of the lumbar bulge targeted deletion of the Cav1.2 gene in neuropathic pain model mice

→ Main results:

We have tailored a programmable bench-top HIFU system, named 3BOP (IGT, Bordeaux). This system allows a non-invasive, tightly controlled and precisely regionalized hyperthermia in the anesthetized live mouse. The use of the 3BOP was extended to two projects dealing with thermo-sensitive nanoparticles for the therapeutical delivery of bioactive peptides or miRNA (see Additional grant obtained).
We have generated the Cav1.2 heat-inducible knock-out mice (hsp-Cre/Cav1.2flox/flox) and a reporter mouse strain (hsp-Cre/R26-YFP) to establish the ultrasonic parameters necessary to obtain a non-invasive, non-painful gene deletion in the lumbar bulge of the spinal cord while preserving the tissues integrity. As expected, this newly created strain showed some rare spontaneous, sporadic gene deletion presumably due to hsp promoter activation by environmental stress factors. Preliminary results were nonetheless very encouraging. Unfortunately, environmental stress becoming uncontrollable due to building work and crowded animal houses, we decided to put on hold this project for ethical concerns until we could have access to a more suitable environment in the new Neurocampus building.

→ Working plan to continue:

While looking for a more appropriate work environment to pursue our innovative non-invasive targeted transgenesis approach, we decided to test a somewhat more invasive, less innovative method to create the Cav1.2DH-/DH- mice which carry a lumbar bulge targeted deletion of the Cav1.2 gene. Indeed, we are currently performing localized intrathecal/intraspinal injection of AAV expressing a tagged Cre recombinase.
This new animal model will then be thoroughly characterized at the molecular, biochemical and electrophysiological level.
Subsequently, the animals will be subjected to sciatic nerve lesion, a neuropathic pain model, in order to decipher the role of the L-type calcium channel Cav1.2 gene in the mechanisms of central pain sensitization.

→ Additional grant obtained:

Funding agency: Institut National Du Cancer (INCA)
Name of the project: MicroRNAs: an innovative target for cancer patients suffering from severe pain.
Total amount: 301,6 K€
Date of obtention and duration of the grant 2: 10 Août 2015: 3 ans

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)	Partners: Valentin Nägerl (IINS)

LabEx support : 20 K€

Objectives of the project:

Using a multidisciplinary approach combining STED microscopy, calcium imaging and computer simulations, this project aims at: 1) understanding the basic rules that govern information distribution in axonal arbors of CA3 pyramidal neurons; 2) analyzing the functional significance of axon morphology and structural changes induced by LTP/LTD.

Main results:

The induction of LTP increases CA3 axon diameters and the velocity of action potential (AP) propagation. Our findings indicate 1) that CA3 axons become wider upon LTP induction, 2) that AP conduction velocity is increased upon LTP induction. Realistic simulations using the NEURON software, had predicted that such diameter changes would result in velocity increase in CA3 axonal branches. This prediction was confirmed by measuring antidromic spike propagation during the above experiments.

Working plan to continue:

In a next step, similar experiments and simulations will be used to explore the effects of LTD-induced changes in diameters. This question is crucial because decreasing axon diameters could result in propagation failure. This possibility will be analyzed both experimentally and using simulations to assess the risk of failure and analyze the involved mechanisms.

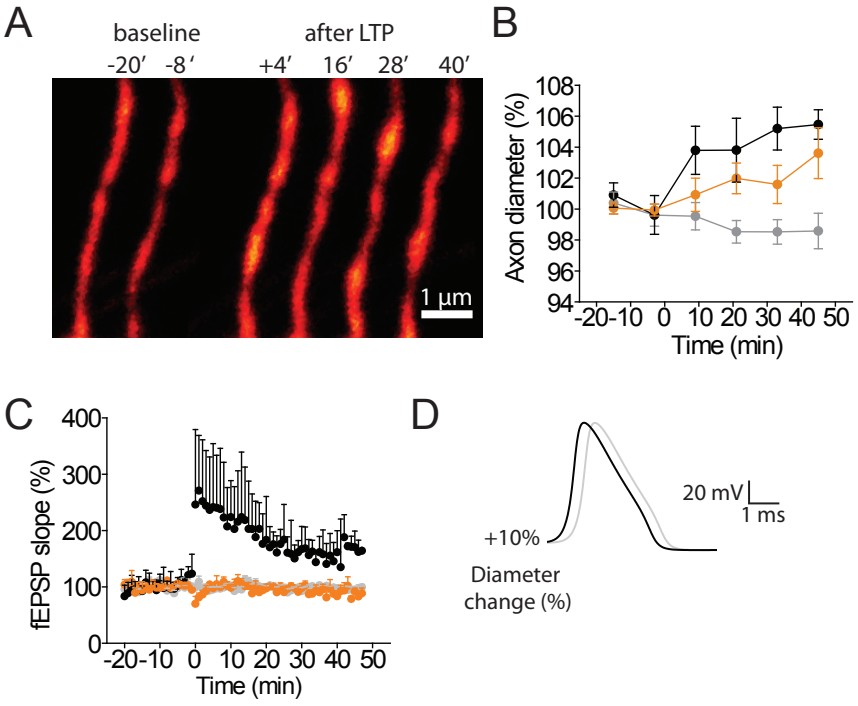
Publications in preparation :

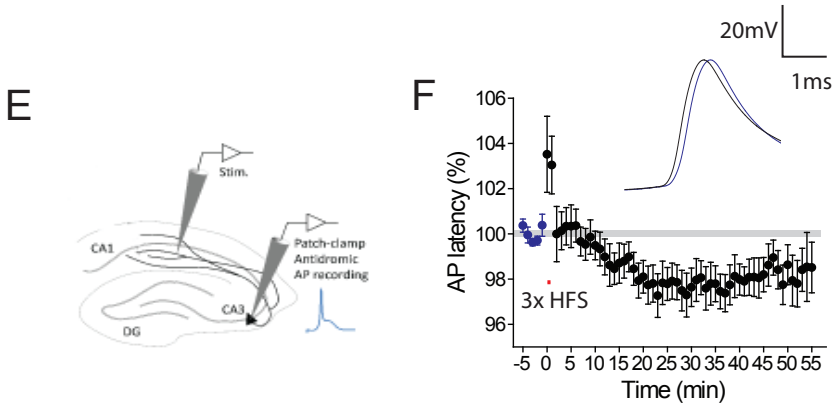
Ronan Chéreau, G. Ezequiel Saraceno, Julie Angibaud, Daniel Cattaert, U. Valentin Nägerl. Nanoscale axon plasticity tunes action potential conduction velocity.

Communications:

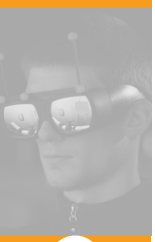
Chereau R, Cattaert D, Nagerl Vu (2013) Annual Meeting of the Society For Neuroscience, San Diego, USA, Novembre 2013.

Chereau R, Cattaert D, Nagerl Vu (2013) Frontiers in Neurophotonics Meeting, Bordeaux, Octobre 2013





Induction of LTP increases axon diameters and the velocity of AP propagation
A-B, Axons increase in diameters after LTP protocole. **C**, LTP induction. **D**, Simultions predict an increase of AP conduction velocity. **E-F**, This prediction was confirmed during intracellular recordings from CA3 cell body while stimulating axon branches. E: Protocole; F: Time course of the AP velocity change after LTP.



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

Principal Investigator: Daniel Cota (NCM)	Partners: Nora Abrous (NCM); Sophie Layé (NutriNeuro)

LabEx support : 49 K€

→ Objectives of the project :

In this project, we propose to investigate whether the relative balance between neurogenesis and neuroinflammation is critical for the CNS regulation of energy balance and if the alteration of the cell-proliferative response resulting from the adaptation to a hypercaloric diet is sufficient to cause rapid changes in food intake and body weight.

→ Main results :

Cell proliferation and neuroinflammation in the adult hypothalamus may both contribute to the pathogenesis of obesity. Our study shows that cell proliferation can be specifically induced in the hypothalamus in a diet-dependent manner. Increased proliferation results, in turn, in increased microglia cells. Such microglia expansion is associated with development of obesity and both central and peripheral inflammation. Conversely, inhibition of cell proliferation, while only partially preventing body weight gain, abrogates both hypothalamic and peripheral inflammatory responses.
These findings suggest that development of obesity depends on the rapid proliferation of pro-inflammatory microglia in the hypothalamus and that blocking microglia expansion effectively prevents inflammation and metabolic dysregulation due to caloric overload.

→ Publications in preparation:

André A, Guzman-Quevedo A, Rey C, Rémus-Borel J, Ladeveze E, Leste-Lasserre T, Nadjar A, Abrous DN, Layé S, Cota D. Diet-dependent microglia expansion in the adult hypothalamus determines the onset of obesity. Submitted.

→ Communications:

André C, Ladevèze E, Rémus-Borel J, Layé S, Abrous DN ** Cota D. Society for the Study of Ingestive Behavior (SSIB) international conference, July 29-Aug 2, 2014

Thermosensitive nanoparticules as a carrier of bioactive peptide against pain sensitization

Principal Investigator: Marc Landry (IINS)	Partners: Valérie Heroguez (UMR CNRS 5629); Klaus Petry (INSERM U1049)

LabEx support : 146,6 K€

Objectives of the project:

Our general objective is to perform a proof-of-concept study that validates a non-invasive approach to target the 14-3-. The expected outcome is to prevent GABAB dedimerization and to alleviate pain. Our project will therefore test the therapeutical potential of combining Polynorbornene (PNb)-nanoparticles (NPs) and Highly Focused Ultra Sounds (HIFU) stimulation in an animal model of neuropathic pain. The specific objectives aim (1) to assess the efficiency of -PNb thermo-sensitive NPs to encapsulate, and subsequently deliver CPP-conjugated anti-14-3-3ζpeptides, (2) to improve the penetration of NPs through the brain blood barrier (BBB), (3) to trigger focal drug delivery in vivo upon HIFU-mediated elevation of temperature, (4) to assess the antalgic potential of this protocol in animal models of pain.

Main results:

We evaluated and compared two systems of polymeric NPs to entrap a model peptide labeled with a fluorochrome (FITC): a system including linear PNb chains and a system including a cross-linked PNb network (5 w% of a reticulating agent added for the NPs synthesis). The conditions of peptide loading and release have been investigated at storage temperature (5°C), room temperature (25°C), and upon elevated temperature (45°C) for this two types of NPs (Fig. 1). Using Rhodamine B fluorochome attached to Nb-chain extremity, we demonstrated NPs time-dependent penetration through the Blood Brain Barrier with a maximum at 24h after injection in the blood stream. Finally, we have defined the initial conditions for HIFU shots to increase body tissue temperature.

Working plan to continue:

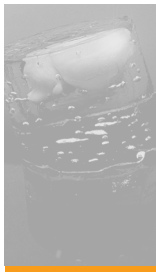
We will further improve the NPs accumulation in the spinal cord. Here again, we will take advantage of the HIFU properties that can temporarily and reversibly increase BBB permeability without long-term tissue damage when used in combination with preformed gas microbubbles, a phenomenon known as acoustic cavitation. We will then establish the sonication protocol to achieve a high yield of release for shorter time of exposure at elevated temperatures, around 43°C. The inflammation parameters are being assessed when BBB is disrupted by our collaborator (Klaus Petry). He is using inflammation markers on histological sections obtained after HIFU shots to evaluate possible detrimental consequences of acoustic cavitation. It is a risk that the packaging of anti-14-3-3ζ peptide and their temperature-driven release turn to be difficult to control. In this case, we will load he particle with RNA instead of peptides. This strategy is the subject of another grant that we obtained in 2015 from the French National Cancer Institute.

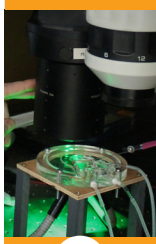
Additional grant obtained:

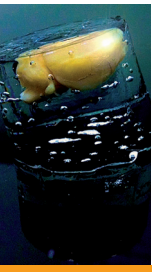
Funding agency: InCA
Name of the project : Les microARNs: une cible thérapeutique innovante pour les patients cancéreux souffrant de douleurs sévères
Total amount: 301,6 K€
Date and duration of the grant: 10/08/2015, 36 mois

Communications:

FENS 2014, Milan; SFN 2015, Montpellier







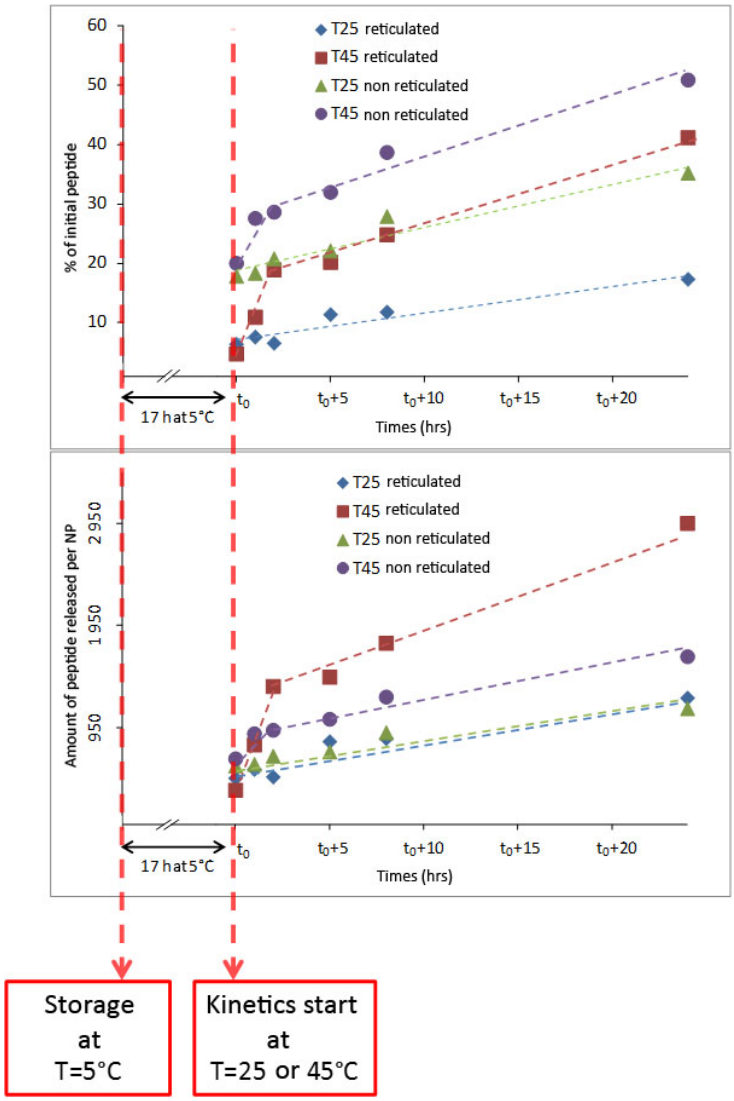


Figure 1. Conditions of peptide release from NPs at different temperatures

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

Principal Investigator: Matthieu Sainlos (IINS)	Partners: Cameron Mackereth (IECB)

LabEx support : 94 K€

→ Objectives of the project:

We aim at undertaking structural NMR-based studies to understand the precise mode of binding of the tandem PDZ domains of PSD-95-like proteins and biomimetic divalent ligands that we have recently developed. Indeed, these divalent ligands derived from the C-termini of Stargazin, an AMPAR auxiliary subunit, and GluN2A show a remarkable efficiency to acutely disrupt the synaptic anchoring of both types of endogenous receptors in a sequence-specific manner. Our goal is therefore to fully characterize the mode of binding of these synthetic biomimetic ligands and ultimately provide a molecular model for the PDZ domain-mediated interactions involved in the anchoring of Stargazin-containing AMPARs and GluN2A-containing NMDARs.

Main results:

Structural determination of PSD-95 tandem PDZ domains. The first step has consisted in the extensive characterization of the PSD-95 tandem PDZ domains (domains 1 and 2) in order to later be able to analyze the various complexes. We took advantage of the fact that the tandem is composed of two stable domains to employ a bottom-up approach in assigning first the backbone nuclei of the isolated domains in order to simplify assignment of the tandem.
Analysis of the complex with biomimetic divalent ligands. We have focused on two of our most efficient and best characterized divalent ligands, which are derived from Stargazin and GluN2A subunit respectively. We have studied the complexes formed by each monovalent ligands with both the isolated domains and the tandem and identified the specific residues involved in their binding.
Interactomics. In parallel, we have determined the dissociation constants between the various ligands and the PDZ domains and precisely identified by proteomics the cellular targets of the ligands.

Working plan to continue:

We are investigating by NMR the multivalent complexes and comparing these ensembles of dataset to determine the mode of interaction of each peptide constructs. The results of our analysis will be verified by production of relevant mutants and binding affinity measurements in order to strengthen and validate our model. Besides the definition of a precise molecular model, the studies will enable us to design ligands with improved efficiency.

Additional grant obtained:

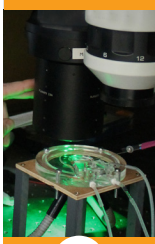
Funding agency: ANR 2013
Name of the project: CheMoPPI
Total amount: 434 747 €
Date and duration of the grant: 01/10/2013-30/09/2016 (36 months)

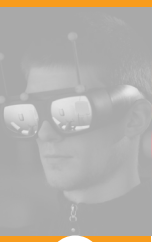
Publications in preparation:

When the results of the multivalent complexes are obtained, we anticipate one publication on the structural model/interactomics and one on the design of an improved generation of ligands.

Communications:

Poster in the 2nd Meeting of the RSEQ Chemical Biology Group in Bilbao (February 2014)





Transfer/applied research

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

Principal Investigator: Pier-Vincenzo Piazza (NCM)

LabEx support : 300 K€

→ Objectives of the project:

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 acts as signaling specific inhibitors of the CB1 receptors. AEF0117 is being developed as a therapy of cannabis use disorders (CUD) for which there are no available pharmacological therapeutic tools.

→ Main results:

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.

→ Working plan to continue :

The final step of this project it is the submission of an Investigative New Drug (IND) application to the FDA. The IND will be submitted in June and phase I clinical trials should start in October.

→ Additional grant obtained:

This project obtained in 2016 a NIDA grant (pending IND approval), that has been obtained in collaboration with Prof. Margaret Haney (Columbia University, US). This is a two years grant of 3.3M$ in direct costs that will cover the costs of the phase I trials
The data obtained in the grant will be included in a publication that will be submitted in 2017.

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

Principal Investigator: Vincent Studer (IINS)

LabEx support : 300 K€ Go/no go step

→ 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 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 sofware able to analyze multicolor single molecule fluorescence, colocalization and photobleaching steps (quantification).

→ Working plan to continue :

→ In the following year we will benchmark our plateform on various protein complexes.
→ Increase the throughput of the system (software and liquid handling).
→ Develop an industrial demonstrator of the liquid handling robot with Alveole.
→ Develop an integrated single molecule analysis software in collaboration with Alveole and Nikon.

Clinical 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)

LabEx support : 100 K€

→ Objectives of the project:

The SOMNET project is developed with the aim of improving the differential diagnosis of insomnia. We investigate the role of physiological hyperarousal, on structural and functional brain connectivity in both insomnia patients and volunteers without insomnia, and relate these measures to sleep variables. These data can lead to the definition of new insomnia phenotypes and to new customized and effective insomnia treatment, focused not only on improving sleep but also on changing dysfunctional hyperarousal levels that currently put insomniacs at risk of numerous severe health problems.

→ Main results:

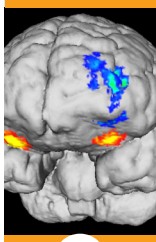
We have recruited a postdoctoral researcher to work on the project, and a neuroimaging expert to focus on the MRI setup and data analysis of the project (1 April 2016). We tested the MRI protocol, including structural and functional sequences, analyzed their sensitivity and customized their acquisition parameters. So far we pre-recruited 25 insomniacs and 30 controls willing to participate in the project that can be planned in for screening upon CPP approval. Questionnaires on emotion processing, hyperarousal and sleep symptoms have been acquired and we consulted sleep experts to design an optimal screening procedure for both patients and healthy volunteers. The project has received hospital support and is currently awaiting CPP approval.

→ Working plan to continue :

Awaiting CPP approval for the project, we are pre-recruiting participants and finalizing pilot studies for the different aspects of the project.

→ Additional grant obtained:

We have applied for an additional grant with SFRMS (French sleep research society) for postdoctoral researcher Yannick Daviaux to continue on this project for 1 year. We are currently applying for different national and international grants to continue our research line and team based on SOMNET results. An Idex Visiting Scholar grant obtained by Dr. Altena for the currently ongoing work visit of prof. Charles Morin will lead to further collaborations based on the results of this study.



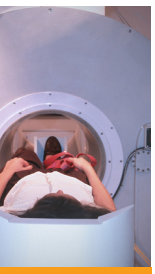
Use of an innovative and easy-to-use tool based on the perception of visual food stimuli for assessing hedonic and motivational states in major depression. Relationships with peripheral endocannabinoids

Principal Investigator: Bruno Aouizerate (NCM)	Partners: P.Philip (SANPSY)

LabEx support : 50 K€

→ Objectives of the project:

Major depression is classically characterized by a loss of pleasure and motivation or even disgust leading to disrupted behaviors directed toward primary reinforcers such as food. The main objective of our study will be to objectively and quantitatively assess motivational impairments in depressed patients using a new computer-generated and easy-to-use experimental tool exploring either size or time discrimination of food-related stimuli.

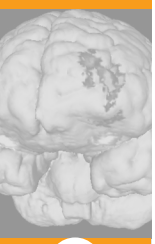


→ Work plan :

36 depressed patients along with 36 normal healthy subjects will be recruited from November 2016 over the 24 subsequent months after approval of the Committee for the protection of persons concerned (CPP). They will be asked to view on a computer screen and to compare two stimuli, an appetitive one (food picture in the original color) and its devalued counterpart (same image in grayscale), at each trial, assessing either the size or the duration of presentation of the pictures during two experimental sessions in fasting and satiety, respectively.

→ Expected results:

Depressed patients will be expected to exhibit blunted modifications in the perception of size or presentation time of the viewed food images between fasting and satiety conditions or even perceptual changes in the opposite direction, as compared to those found in normal healthy subjects.



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)	Partners: Cyril Herry (NCM), M. Bonnet (IBIO/NCM)

LabEx support : 50 K€

Neurocognitive impact of adolescent obesity

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

LabEx support : 64 K€

→ Objectives of the project:

The present project aims at providing a clinical characterization of cognitive and emotional impact of obesity in adolescents focusing on hippocampal and amygdala-dependent functions. This will be achieved by performing standardized and sophisticated tests of hippocampal and amygdala-dependent functions in obese adolescent subjects and by evaluating brain functioning and connectivity between hippocampus and amygdala using functional magnetic resonance imagery (fMRI).

→ Main results:

We are currently preparing the study protocol to submit to Ethic Committees and Administrative Instances for approval. We plan to recruit a post-doc in October 2016 (for 12 months) who will be dedicated to behavioural data and fMRI images analyses. The first fMRI sessions should start in November

2016 and we expect to recruit from the University Hospital (CHU) of Bordeaux the 30 participants in 6-8 months (15 obese adolescents, aged 12-15, and 15 non-obese teenagers of the same age).

→ Working plan to continue:

In parallel to the LabEx application, we applied to an ANR international call with Mexico that we obtained in October 2015 (see below). This will allow us to consistently increase the number of participants included in the fMRI study and to extend the post-doc position for an additional year.
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

LabEx support : 40 K€

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

LabEx support : 50 K€

→ Objectives of the project:

- → to identify abnormal FOG brain activity patterns during active walking in the OFF medication state,
- → to assess the effect of walking tasks that are known to worsen or improve FOG on abnormal brain activity patterns in the OFF medication state, and to assess the effect of levodopa on abnormal brain activity patterns. The ultimate goal is the establishment of an objective and non-invasive test-bed for assessing interventions targeting FOG in PD patients.

→ Main results:

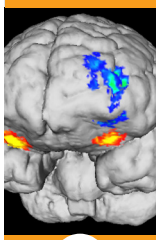
The clinical study has not started yet because of the delayed delivery and implementation of the NIRS system. The technical set-up is ongoing and should be completed within the next few weeks.

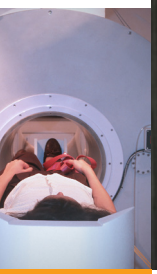
→ Working plan to continue

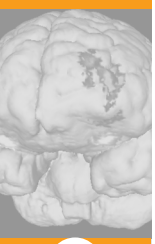
Study duration will be two years. The first six months will be necessary for drafting a detailed protocol and obtaining approval from regulatory authorities. Patients will be recruited between months 7 and 22. Their participation requires a two-day visit (day 1: MRI and clinical evaluation, followed by admission to the movement disorders unit at Pellegrin Hospital because of the necessary overnight withdrawal of dopaminergic treatments; day 2: simultaneous VICON and NIRS recordings in OFF and ON medication states). The last two months will be devoted to data analysis and drafting of the manuscript.

→ Additional grant obtained:

Funding agency: FRC
Name of the project: Cognition and motor behaviour networks assessed with near infrared spectroscopy
Total amount: 200 K€ for acquisition of the NIRS system necessary for conducting the study
Date and duration of the grant: 2015







Team installation Dr. Ellemarije Altena

Since November 2014, Dr. Ellemarije Altena has been installed as a Young Team Leader by a Labex Brain grant at the SANPSY Unit (USR CNRS 3413), Université de Bordeaux. Within this unit, directed by Prof. Pierre Philip, she has developed a new research line investigating insomnia and its relation to cognition and emotions applying innovative techniques such as functional neuroimaging (fMRI) and virtual reality.

She developed a unique protocol inducing real-life stressful events in a driving simulator with her team at the SANPSY unit. To our knowledge, this is the most complete and realistic driving simulation protocol focused on stress induction yet developed. Combining this protocol and EEG recordings, Dr. Altena and a newly recruited post-doctoral researcher, Dr. Yannick Daviaux, currently run an experiment to investigate how pre-existing sleep problems affect stressful reactions in real life, and how this induced stress affects, in turn, night-time sleep.

Dr. Altena further acquired financing for a Labex Brain Clinical Research project, SOMNET, which was ranked as first in an international grant competition. This project has been set up as a collaboration with investigators Dr. Marc Joliot and Dr. Ernesto Sanz-Arigita of the functional neuroimaging lab (GIN, Bordeaux). The project aims to describe the role of physiological hyperarousal in insomnia through a brain model of the emotion regulation system based on functional and structural connectivity of the emotion processing brain network. This project constitutes a first step into the development of insomnia phenotypes improving personalized treatment for this limiting disorder. Hospital support has been received for this project which is currently awaiting CPP approval and expected to start in June 2016.

Dr. Altena had had three papers accespted for publication so far in 2016 and four more in preparation. With colleagues of the GIN, SANPSY unit and Université Paris Descartes, dr. Altena recently published in Behavioral Neuroscience on the bi-directional relation between sleep and emotional reactivity. She and Dr Daviaux will be presenting their first findings at invited presentations at the international Federation of European Physiological Societies (FEPS) conference in June, the European Sleep Research Society (ESRS) conference in September and the French Sleep Society conference (SFRMS) in November of 2016. Dr. Altena was further recently elected as board member of the International Society for Behavioral Neuroscience.

Since her installation Ellemarije Altena has applied for several research grants to consolidate her position and team beyond her Labex Brain starting grant (ending in November 2016) as well as to start national and international collaborations. One of these allowed insomnia expert prof. Charles Morin of Laval University (Quebec, Canada) to visit the SANPSY unit on a 2 month work visit. This visit is leading to a new international collaboration which so far has resulted in two publications under preparation. Further grant applications may hopefully lead to consolidation of her research line in the SANPSY unit.

Core Facility Personnel

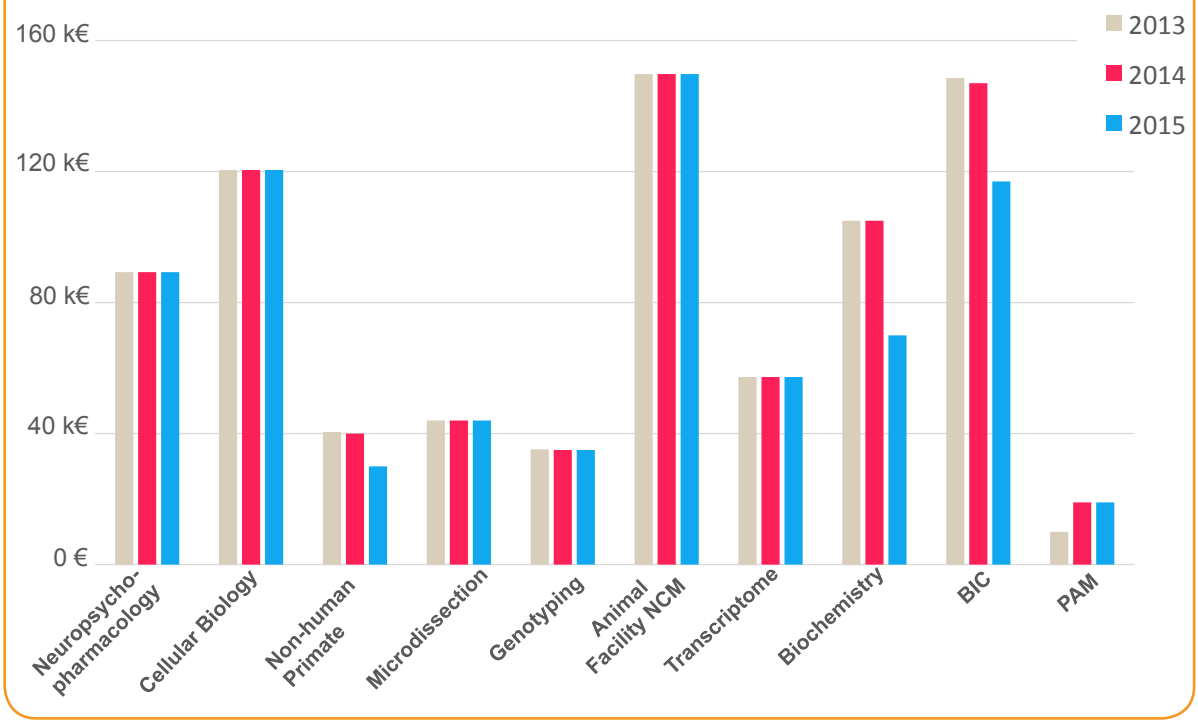
79 CORE FACILITY STAFF

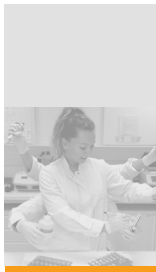
43 permanent

36 non- permanent

19 persons are financially supported by the LabEx (entirely or partially)

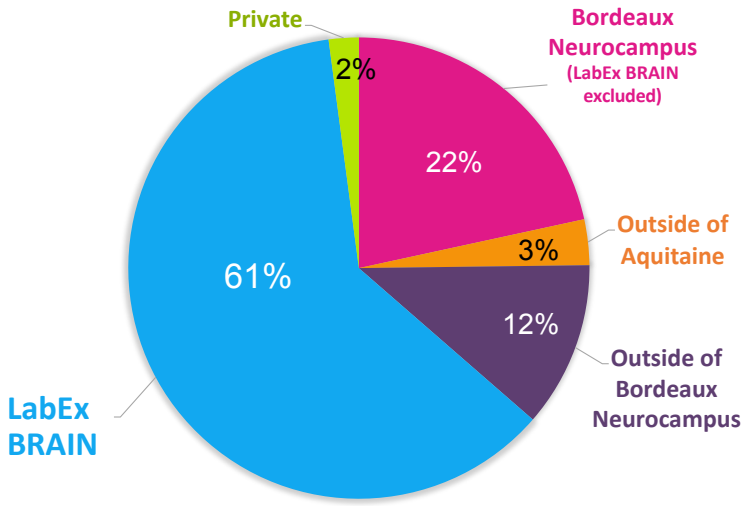
Distribution of the LabEx funds for supporting the facilities



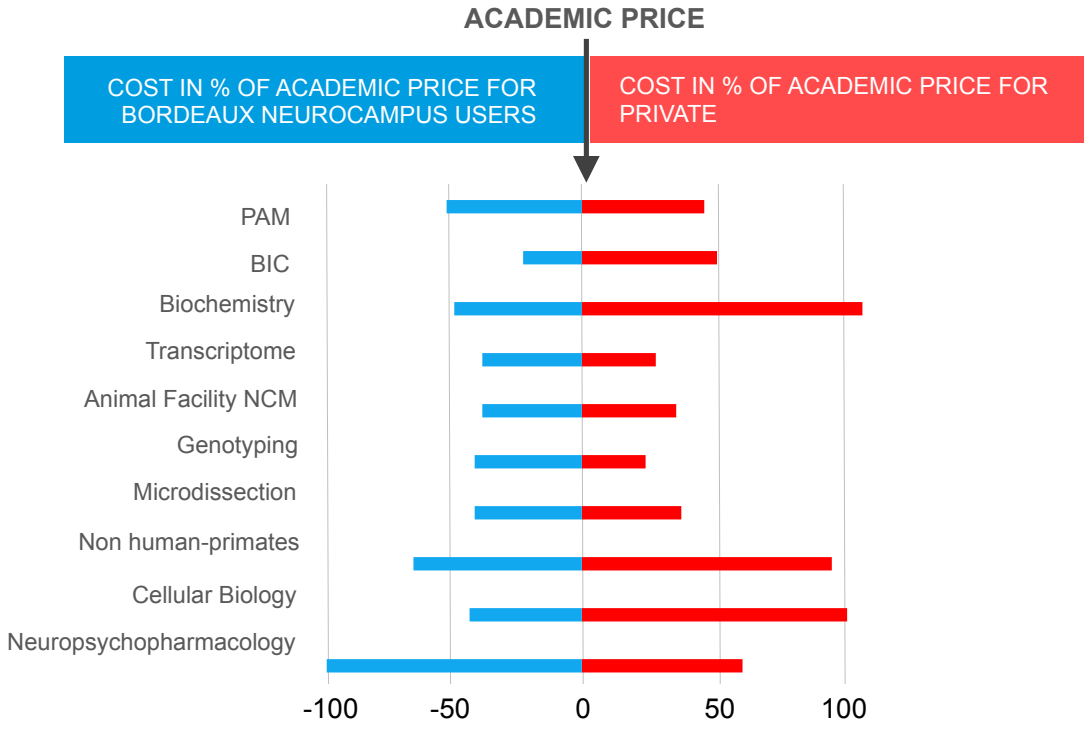


Core Facilities

Facility users



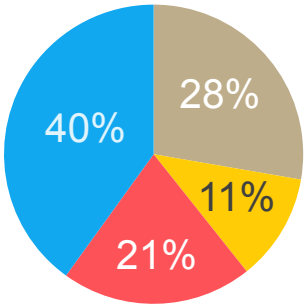
Facility cost reduction for all Bordeaux Neurocampus users



→ **50% off** for all Bordeaux Neurocampus members supported by LabEx BRAIN

Budget

Incomes



Neuropsychopharmacology

Microdissection

Transcriptome

Animal Facility NCM

Genotyping

Biochemistry

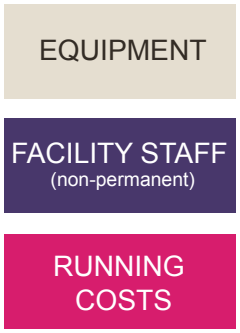
PAM

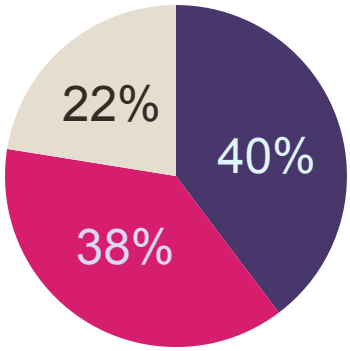
Non-human primates

Cellular Biology

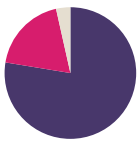
BIC

Outcomes





Neuropsychopharmacology



Microdissection

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Genotyping

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Non-human primates

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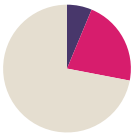
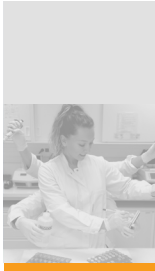




TRAINING

PhD Extension Grants

Bordeaux School of Neuroscience

2012

Role of NMDA receptor surface trafficking during synaptic maturation and plasticity

Student name : Laurent Ladepeche (IINS)	Supervisor : Laurent Groc

→ Objectives of the project:

During my PhD I unraveled an unexpected regulation of NMDA receptor surface dynamics by ambient neuromodulators and coagonists, which plays a major role in the plastic range of synapses. We then wanted to investigate the differential mechanisms underlying these processes during maturation (ex. coagonist and subunit dependence), their potential implication in pathophysiological conditions (ex. neurotoxicity) and test them in more integrated models.

→ Main results:

Using high resolution dynamic imaging techniques (e.g. single particle tracking, FRAP) and high specificity molecular tools (e.g. antibodies, competing peptides), we thus discovered that:

→ GluN2B-NMDAR are dynamically redistributed away from glutamate synapses through increased lateral diffusion during LTP in immature neurons.

→ NMDAR coagonist switch from glycine to D-serine at maturing synapses drives the replacement of GluN2B- by GluN2A-NMDARs by selectively impacting the surface diffusion of NMDAR (collaboration Dr. Oliet).

→ Direct interaction with tissue plasminogen activator (tPA, acts as a neurotoxic factor in strokes) modulates extrasynaptic NMDAR dynamic (collaboration Dr. Vivien).

→ Blocking NMDAR mobility prevented in vivo LTP in CA1 and memory of temporal association between discrete stimuli (collaboration Dr. Marighetto).

→ Working plan to continue:

Some experiments are still ongoing in the lab concerning the publications in preparation and to keep further the investigation on the detailed mechanism that is responsible for the selectivity of the effect of the coagonists as well as the modulation by the dopaminergic receptors. I recently joined a group in Barcelona to characterize the influence of the dynamic of NMDAR in psychotic disorders looking at the distribution of receptors at the nanoscale using super-resolution techniques.

→ Published publications:

→ 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.

Publications 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, in preparation.
- 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, in preparation.
- 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, in preparation.

Communications:

- 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 NMDA receptors dynamic modulation of glutamate synapse plasticity. Barcelona, Spain, November 2013. Invited seminar
- Ladepeche L.#, Dupuis J.P.#, Seth H., Bard L., Varela J., Mikasova L., Bouchet D., Rogemond V., Honnorat J., Hanse E. and Groc L. Plasticity of maturing glutamate synapses requires NMDA receptors lateral mobility. Frontiers in Neurophotonics, Bordeaux, October 2013. Selected talk
- Ladepeche L., Dupuis J.P., Papouin T., Mikasova L., Bouchet D., Bard L., Rogemond V., Imperiali B., Honnorat J., Sainlos M., Oliet S. and Groc L. Surface dynamics of glutamate receptors: lateral shaping of synaptic plasticity. Tsukuba, Japan, April 2013. Invited seminar
- Ladepeche L.#, Dupuis J.P.#, Seth H., Bard L., Varela J., Mikasova L., Bouchet D., Rogemond V., Honnorat J., Hanse E. and Groc L. Plasticity of maturing glutamate synapses requires NMDA receptors lateral mobility. #Equal contribution 4th European Synapse Meeting, Bordeaux, August 2013. Poster
- Ladepeche L., Dupuis J.P., Bouchet D., Dounikoff E., Yang L., Campagne Y., Grea H., Bezard E., Hosy E. and Groc L. Single molecule crosstalk between surface NMDA and dopamine D1 receptors tunes plasticity at excitatory synapses. 4th European Synapse Meeting, Bordeaux, August 2013. Poster

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

Student name : Anael Chazeau (IINS)	Supervisor : Grégory Giannone

Objectives of the project:

The objective of my Ph.D. project was to unravel how actin-binding proteins and N-cadherin adhesion regulate the organization and dynamics of F-actin network in dendritic spines.

Main results:

In a first study, by performing quantitative live imaging experiments and computer simulations, we demonstrated that engagement of a mechanical connection between trans-synaptic N-cadherin adhesions and the actin/myosin network stabilizes dendritic spines.
In a second study, using single protein tracking and super-resolution imaging we revealed the dynamic nano-organizations of branched F-actin regulators within spines. Branched F-actin nucleations occur at the PSD vicinity, while elongations occur at membrane protrusion tips.

Working plan to continue:

The first study will be submitted beginning of June, while the second one will be resubmitted in March. To widen our first study, we plan to focus on the intracellular signaling pathways leading to spine head expansion during the transition from a filopodium to a spine. To go beyond our second study, we want to understand how the nanoscale organization and dynamics of branched F-actin networks in dendritic spines are reorganized during synaptic plasticity protocols. To do so we are developing a new microscope to be able to perform super-resolution microscopy on organotypic slices. Finally we are

also developing a new simulation program to reach a detailed understanding of actin, actin regulators and adhesion protein dynamics within a variety of subcellular structures.

Publications:

- Chazeau A. and Giannone G. Organization and dynamics of the actin cytoskeleton during dendritic spine morphological remodeling. Cellular and Molecular Life Sciences. in press
- 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.
- Chazeau A., Garcia M., Czöndör K., Perrais D., Tessier B., Giannone G., Thoumine O. A mechanical coupling between trans-synaptic N-cadherin adhesions and the actin flow stabilizes dendritic spines. Mol Biol Cell, 26, 859-73.

Communications:

Poster presentations: «Evidence for a mechanical coupling between N-cadherin adhesions and F-actin in stabilizing dendritic spines». Journée de l'école doctorale Arcachon (Mars 2010, 2011, 2012); EMBO Workshop Heraklion (Mai 2011); FENS Barcelone (Juillet 2012); 10th Göttingen Meeting (Mars 2013).
Oral presentation: «Nanoscale organization and dynamics of branched actin network regulators within dendritic spines» Frontiers in Neurophotonics Bordeaux (Octobre 2013).

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

Student name : Pierre Cardinal (NCM)	Supervisor : Daniela Cota

Objectives of the project:

The endocannabinoid system impacts energy balance regulation at both central and peripheral level. The hypothalamus is one of the main regions involved in the control of food intake and body weight. Different hypothalamic nuclei exert specific functions in this context. The main objective of this project was to determine the role of the cannabinoid type 1 (CB1) receptor in the regulation of energy balance when its expression is deleted in specific hypothalamic nuclei.

Main results:

Our studies on the role of the CB1 receptor in the ventromedial hypothalamus (VMN) demonstrate that this receptor regulates the organism's metabolic flexibility to environmental dietary changes by orchestrating peripheral use of energy substrates and behavioral and metabolic responses to the adipocyte-derived hormone leptin.
Differently, the studies carried out in mice specifically lacking CB1 receptors in the paraventricular nucleus (PVN) have shown that deletion of CB1 protects from diet-induced obesity by inducing increased sympathetic nervous activity (SNS), with consequent heightened energy expenditure.

Published publications:

- 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

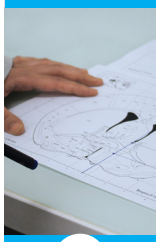
→ Bosier B, Bellocchio L, Metna-Laurent M, Soria-Gomez E, Matias I, Cannich A, Maitre M, Verrier D, Leste-Lasserre T, Cardinal P, Mendizabal-Zubiaga J, Canduela MJ, Reguero L, Chaouloff F, Hermans E, Grandes P, Cota D, Marsicano G. Critical role of astroglial CB1 cannabinoid receptors in the regulation 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.

→ Publications in preparation:

Mancini G, Ruiz de Azua I, Srivastava RK, Aparisi Rey A, Cardinal P, Tedesco L, Zingaretti CM, Sassmann A, Quarta C, Schwitter C, Conrad A, Wettschureck N, Vemuri K, Makriyannis A, Bindila L, Monory K, Cinti S, Nisoli E, Marsicano G, Offermanns S, Pagotto U, Cota D, Lutz B. Adipocyte cannabinoid CB1 receptor is a key regulator of energy homeostasis. In revision.

→ 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

Student name : Thomas Larrieu (NutriNeuro)	Supervisor : Sophie Layé

→ Objectives of the project:

The nutritional omega-3 content of the diet can influence brain functions and protect from the development of mood disorders. However, the mechanisms underlying the protective effects of dietary omega-3 on brain activity and mood disorders remain largely unknown. In the present project we unravel molecular and cellular mechanisms linking nutritional omega-3, stress and depressive-like behavior in mice.

→ Main results:

In this work, our findings can be summarized in two major observations:
→ Dietary omega-3 deficiency induces a chronic stress state reflected by hypothalamic-pituitary-adrenal (HPA) axis hyperactivity. This leads to neuronal atrophy in the dorso- and ventro-medial prefrontal cortex (mPFC) and mood-related behaviours alteration, similarly to chronic social defeat stress (Larrieu et al., 2014, 2016).
→ Dietary omega-3 supplementation protects from depressive-like behavior developed after a chronic social defeat stress by preventing HPA axis hyperactivity and neuronal atrophy in mPFC (Larrieu et al., 2014, 2016).

→ Additional grant obtained:

Société Française de Nutrition (SFN) prize

Publications:

- Larrieu T., Hilal M., De Smedt-Peyrusse V., Sans N. and Layé S., Nutritional omega-3 deficiency alters glucocorticoid receptor-signalling pathway and neuronal morphology in regionally-distinct brain structures associated with emotional deficits, Neural Plasticity, vol. 2016, Article ID 8574830, 9 pages, 2016. doi:10.1155/2016/8574830.
- Larrieu T., Hilal M., de Smedt-Peyrusse V., Sans N., Capuron L., Layé. S. Hypothalamo-pituitary-adrenal axis mediates n-3 polyunsaturated fatty acids deficient-diet induced depressive- and anxiety-like symptoms along with neuronal atrophy, Translational Psychiatry, 2014, 4:e437 (IF 4.360)-This paper has been highlighted in Nature Neuroscience Reviews by Katherine Whalley, Mood Food, Nature Reviews Neuroscience 15, 698 (2014)

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

Student name : Audrey Bonnan (NCM)	Supervisor : Andreas Frick

Objectives of the project:

The aim was to use the LabEx support to complete the two projects I've been working on during my PhD:

- my PhD project focused on the dysfunction of dendritic excitability in somatosensory neurons of Fmr1(-/y) mice;
- a project in collaboration with Prof. R. Kramer to control dendritic excitability with light in a variety of different cell types using a small molecule photoswitch (QAQ).

Main results:

For the first project, we were unfortunately unable to perform the calcium imaging experiments of populations of pyramidal neuron dendrites in response to sensory stimulation in vivo which were originally planned in collaboration with Dr. M. Larkum, due to issues with the animal transfer agreement. However, we performed in vivo electrophysiological recordings from single layer 5 pyramidal neurons in anesthetized mice in our own laboratory and found changes in the same dendritic/cellular parameters as in our in vitro recordings from these neurons. We also used western blots experiments to probe the mechanisms of h-channel dysfunction in the dendrites of Fmr1(-/y) mice. We found a reduction in the expression level of HCN1 but not HCN2 in the somatosensory barrel cortex, which was consistent with our electrophysiological and calcium imaging data (cf. figure). This project was completed and the results were published in Nature Neuroscience in November 2014.

For the second project, we performed new experiments showing that the use of QAQ can be used to photocontrol plasticity. We focused on depolarization-induced suppression of inhibition (DSI), a form of short-term plasticity that requires calcium-dependent release of endocannabinoids from the post-synaptic neuron. By introducing QAQ in CA1 pyramidal neurons through the recording pipette, we found that we could reversibly manipulate DSI with light. This project is still ongoing and the paper reporting our findings is in preparation.

Publications:

- 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.

** = equal contribution*

Communications:

«Channelopathies in neocortical dendrites in Fragile X Syndrome», Max Planck Florida Institute (July 12th, 2013)

2013

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

Student name : Philipp Bethge (IINS)	Supervisor : Valentin Nägerl

Objectives of the project:

- Optimize the homebuilt two-photon excitation STED microscope
- Use the microscope to study the role of the endocannabinoid system on morpho-functional plasticity using pharmacological tools
- Apply the microscope to in vivo STED imaging of spines in the murine cortex
- Advance collaborative projects
- Train new team members to use the microscope
- Write and defend the PhD Thesis and find a post-doctoral position

Main results:

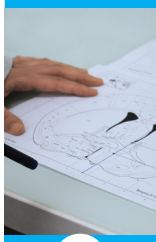
- The custom two-photon excitation STED microscope has been updated with critical optical components (new scan- and tube lens combination) to reduce chromatic aberrations and thus improve optical performance over larger fields-of-view. Extensive troubleshooting has reduced mechanical vibrations and image artifacts due to electrical interference (ground-loops) affecting the beam scanner.
- Preliminary experiments suggest that bath application of a cannabinoid receptor 1 (CB1) agonist leads to acute changes in spine morphology of CA1 pyramidal neurons.
- In vivo imaging of dendritic spines in the barrel cortex has been established.
- More data for a collaborative project on the morphology of dendrites in the dentate gyrus has been collected and a new project has started with the group of Christophe Mulle, IINS Bordeaux, investigating Alzheimer related morphological alterations in CA3 of the hippocampus.
- Two new PhD students were trained to operate the microscope.
- I successfully defended my PhD thesis on March 27th, 2014.
- I started my postdoc in the lab of Fritjof Helmchen at the University of Zürich (Fall 2014).

Published results:

- Springer Book: Nanoscale Imaging of Synapses: New Concepts and Opportunities. U. Valentin Nägerl and Antoine Triller (Eds.) Chapter 11: Two-photon STED microscopy for imaging synapses and glia in acute brain slices. Philipp Bethge and U. Valentin Nägerl (Authors)
- Bethge P, Chéreau R, Avignone E, Marsicano G, Nägerl UV. Two-photon excitation STED microscopy in two colors in acute brain slices. Biophys J. 2013 Feb 19;104(4):778-85.
- Silvia Viana da Silva, Matthias Georg Haberl, Pei Zhang, Philipp Bethge, Cristina Lemos, Nélio Gonçalves, Adam Gorlewicz, Meryl Malezieux, Francisco Q. Gonçalves, Noëlle Grosjean, Christophe Blanchet, Andreas Frick, U. Valentin Nägerl, Rodrigo A. Cunha, Christophe Mulle. Early synaptic deficits in Alzheimer's disease involve neuronal adenosine A2A receptors (under review at Nature Communications)

Communications:

Poster presentation at the 'Frontiers in Neurophotonics 2013' Bordeaux, France



Analysis of synaptic plasticity in CA3 pyramidal cells in vivo

Student name : Stefano Zucca (IINS)	Supervisor : Christophe Mulle

Objectives of the project:

My project aims at deciphering how granule cells control the activity of CA3 pyramidal cells in the intact hippocampal network. For this I combined electrophysiological recordings in vivo (extracellular and whole-cell patch clamp) and optogenetics.

Main results:

In my project I explored new optogenetic tools to control the activity of granule cells with pulses of light. Optogenetic stimulation, which relies on the activation of the light-gated ion channel channelrhodopsin-2 (ChR2) by blue light reliably induced action potentials over a wide range of frequencies of stimulation. Optical stimulation can be used to trigger short term plasticity at mossy fiber-CA3 synapses in vitro. In the second part I refined optogenetic stimulation methodology in vivo for non-invasive characterization of synaptic functioning of the mf-CA3 synapses. With the support of the Labex, I managed to extend the study, which was then continued by Marilena Griguoli and Meryl Malezieux when I left for a post-doc. The summary of the results obtained overall is the following. I have used an optogenetic approach to selectively target and control the activity of DG granule cells (GCs) while performing whole cell and juxtacellular recordings of CA3 neurons in vivo. In contrast with previous measurements in vitro, mf-CA3 pyramidal cells (PCs) exhibited relatively moderate short-term plasticity. Light stimulation of GCs at frequencies between 0.05 and 40 Hz faithfully induced spike transfer at DG-CA3 interneurons. This resulted in a robust and long-lasting feedforward inhibition of spike transfer at mf-CA3 PC synapses which was counterbalanced by short-term plasticity of excitatory postsynaptic potentials with increasing frequency of presynaptic activity. The long-lasting inhibition of spiking activity required the activation of GABAB receptors in CA3 PCs. Altogether these properties define the temporal rules for efficient information transfer at DG-CA3 synaptic connections in the intact circuit.

Article submitted

Synaptic mechanisms controlling the efficacy of spike transfer at hippocampal mossy fibers in vivo. Stefano Zucca#, Marilena Griguoli#, Meryl Malézieux, Mario Carta and Christophe Mulle

Article in preparation

Griguoli M, Zucca S, Mulle C. Cholinergic modulation of neuronal oscillation and hippocampal CA3 circuits using in vivo recordings and optogenetics.

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

Student name : Chloé Boitard (NutriNeuro)	Supervisor : Guillaume Ferreira

Objectives of the project:

During my PhD work, I evidenced the vulnerability of the juvenile period (compared to adulthood) to the detrimental effects of high-fat diets on endocrinology, neurophysiology and memory. We now need to achieve the peer-review process on our submitted articles and to publish our recent work, obtained at the end of my PhD, on the mechanisms explaining how the diet can impact on brain functioning as well as on the reversibility of the detrimental effects induced by high-fat diet (HFD) when animals are shifted back to standard diet.

Main results:

We evidenced that juvenile high-fat diet exposure leads to impaired hippocampal function together with enhanced amygdala function, a bidirectional pattern that can be induced by glucocorticoids action (PhD work). Interestingly, glucocorticoid release is modified in obese, and we demonstrated that

juvenile high-fat diet exposure protracts the normal corticosterone release after stress. Moreover, we were able to demonstrate this protracted corticosterone release was responsible for amygdala-dependent memory enhancement since blockade of glucocorticoid action directly in the basolateral nucleus of the amygdala was sufficient to restore normal memory in juvenile high-fat fed rats.
In another study, we also demonstrated that shifting adult rats back to control diet after exposure to high-fat during the juvenile period was sufficient to restore all the detrimental effects (i.e. on memory, neurophysiology and endocrinology) induced by the high-fat diet.

Working plan to continue

It should now be assessed how the detrimental effects we described after juvenile high-fat diet exposure interact with each other. If we demonstrate that modified glucocorticoid release is responsible for amygdala enhancement, we did not assess its role on hippocampal impairment. Moreover, juvenile high-fat diet exposure appears to rapidly decrease hippocampal neurogenesis, which can be responsible for protracted glucocorticoid release. Thus the temporal pattern of emergence of the detrimental effects of juvenile high fat diet exposure and the causality between those effects remains to be assessed (see Fig. 1).

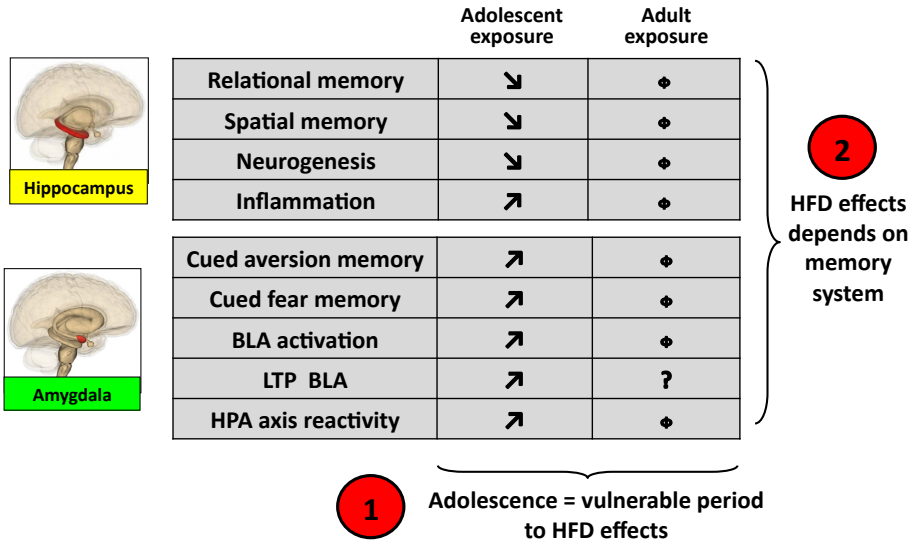


Figure: Temporal scheme showing the different effects of HFD we revealed after juvenile exposure. Our hypothesis concerning the causality of these effects is represented by the black arrows.

Published publications:

Boitard C, Etchamendy 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(11):2095-100.

Publications in preparation:

- Boitard C, Cavaroc A, Sauvant J, Aubert A, Castanon N, Layé S & Ferreira G. Impairment of hippocampal-dependent memory induced by juvenile high-fat diet intake is associated with enhanced hippocampal inflammation in rats. Special Issue «Diet, Inflammation and the Brain» in Brain, Behaviour and Immunity, Submitted.
- Boitard C, Maroun M, Tantot F, Cavaroc A, Sauvant J, Coutureau E, Marchand A, Capuron L, Castanon N, Darnaudéry M, Layé S, Vouimba RM & Ferreira G. Juvenile obesity enhances emotional memory and amygdala plasticity through glucocorticoids. In progress
- Boitard C, Cavaroc A, Sauvant J, Layé S & Ferreira G. Endocrinology, neurophysiology and memory disruptions induced by juvenile high-fat diet exposure are restored following a shift back to control diet exposure at adulthood. In progress

Communications:

My PhD work was already presented through 16 posters and 2 invited lectures during my PhD internship. Additional work supported by the LabEx BRAIN was presented during the 3rd "Doc/post-doc day" of NutriNeuro's lab (28/01/2014, Bordeaux), "Endocrinology, neurophysiology and memory disruptions induced by juvenile high-fat diet exposure are restored following control diet exposure". This work may also be presented to the 7th Nutrition & Neurosciences Symposium (14/03/2014).

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

Student name : Julien Courtin (NCM)	Supervisor : Cyril Herry

Objectives of the project:

The main objective of the research project was to evaluate if the neuronal changes occurring in specific population of cortical inhibitory interneurons was causally related to expression of conditioned fear behavior in mice. To this purpose we used a combination of extracellular recordings, optogenetic manipulations and behavioral approaches.

Main results:

Thanks to the Labex Brain support we have been able to demonstrate using optogenetics that neuronal inhibition of a subpopulation of prefrontal inhibitory interneurons –expression the calcium binding protein parvalbumin (PV) was causally related to fear expression in behaving mice. Inhibition of prefrontal PV interneurons disinhibits projection neurons to drive fear expression. Moreover, we observed that inhibition of these interneurons during fear behavior is also associated with the genesis of cortical oscillations in the theta range that allow the synchronization of principal neuron activity during fear expression. These results identify two complementary mechanisms mediated by PV interneurons that precisely coordinate and enhance the neuronal activity of prefrontal projection neurons to drive fear expression (Figure 1).

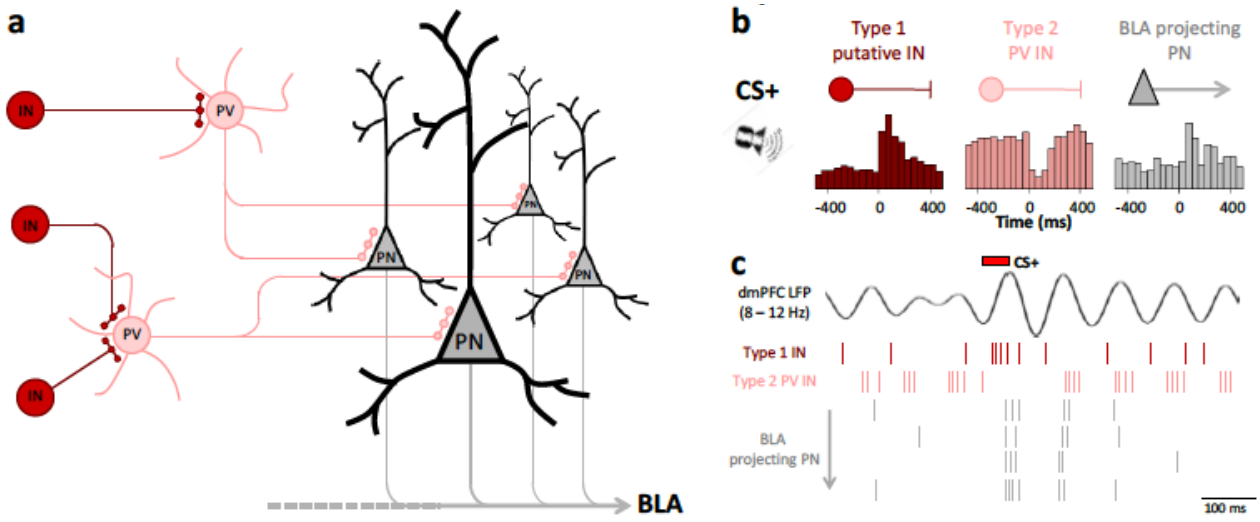


Figure 1: ***Prefrontal Parvalbumin-expressing interneurons control fear behavior. a****. Schema of the identified connectivity between two types of interneurons (IN) (red = unidentified interneurons and pink = parvalbumin-expressing interneurons (PV)) in the medial prefrontal cortex and excitatory projection neurons (PN).* ***b****. During presentation of a conditioned auditory stimulus (the CS), type 1 INs displayed an increase in CS-evoked activity, which was associated with the inhibition of type 2 PV INs and the disinhibition of prefrontal PNs.* ***c****. CS presentations was associated with a resetting of ongoing prefrontal theta oscillations and the synchronization of prefrontal PNs projecting to the amygdala.*

Moreover, we recently identified within the prefrontal cortex and the basolateral amygdala a specific neuronal oscillation (2-6 Hz) occurring specifically during freezing behavior. These data identify for the first time a physiological signature of fear memory in prefrontal-amygdala networks.

Published publications:

- 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

Communications:

Courtin, J., Wurtz, H., and Herry, C., Prefrontal interneurons in fear behavior, FENS meeting, Milan, July 2014

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

Student name : Mikael Garcia (IINS)	Supervisor : Olivier Thoumine

Objectives of the project:

The objectives of my project were to characterize the role of the mechanical coupling between the actin motile machinery and N-cadherin adhesions in two important brain developmental processes, namely axonal outgrowth and synaptic morphological plasticity. To reach these objectives, I performed high resolution live imaging experiments in hippocampal neurons expressing fluorescently-tagged adhesion and cytoskeletal proteins.

Main results:

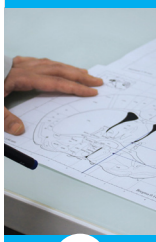
Thanks to the Labex BRAIN funding, I was able to perform Fluorescence Recovery After Photobleaching (FRAP) experiments to measure actin-GFP turnover in dendritic filopodia and spines. The actin recovery is faster in immature dendritic filopodia than in spines, indicating a more dynamic actin network. We expressed either wild type N-cadherin to strengthen N-cadherin adhesions, or a non-adhesive N-cadherin mutant acting as a competitor for catenin scaffolding molecules. Fluorescence recovery was faster in dendritic spines expressing the N-cadherin mutant, consistent with the concept that actin is stabilized through a linkage with N-cadherin adhesions. We have also built computer simulations describing the motion of single actin molecules in model dendritic structures, and are adjusting kinetic parameters to fit the model to experimental data.
In parallel, we developed computer simulations describing the motion of single actin and N-cadherin molecules in adhesive and non adhesive area within growth cones, based on diffusion and kinetic parameters obtained from our previous spt-PALM experiments using mEOS2-tagged molecules. These simulations were compared to FRAP experiments to be performed on GFP-tagged N-cadherin, ∝-catenin, and actin, accumulated at N-cadherin coated micropatterns. Interestingly, enrichments and slowing events calculated from these simulations are comparable with the ones observed experimentally.

Publications:

- 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, Czondor* 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

Mikael Garcia has found an engineer job in the company Poietis (Mérignac).
https://www.youtube.com/watch?v=DI5VJDr9eHY



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

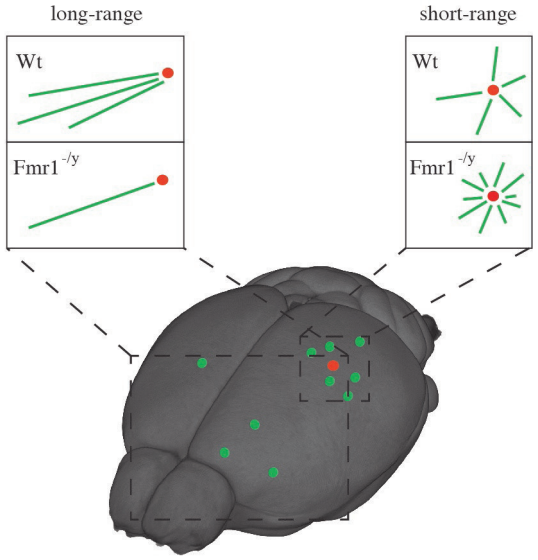
Student name : Matthias Haberl (NCM)	Supervisor : Andreas Frick

Objectives of the project:

Fragile X syndrome is the most common inherited cause of mental retardation and autism in humans and leads to deficits of learning and memory and a high prevalence of autistic behavior, seizures, hypersensitivity to sensory stimuli and alterations in the processing of sensory information. Here we were investigating the structural and functional alterations that occur in the neocortical wiring of the Fmr1-/y mouse model.

Main results:

We found connectivity changes in the Fmr1-/y mice on large-scale and fine-scale. In particular, we found deficits on the structural level and a functional decoupling of several cortical areas using diffusion-tensor-imaging (DTI) and functional magnet-resonance-imaging (fMRI) measurements. The fine-scale structural deficits are composed of an alteration in the short- and long-range connectivity. To study the deficits on a cellular level we also developed a novel anterograde (i.e. infecting cells at the cell body) tracer using a modified rabies virus (SADΔG(chimera glycoprotein)). This tracer permits sparse labeling of neurons and the visualization of all morphological details such as dendritic spines or axonal boutons (Haberl et al., 2014). We used a combination of retrograde (Wickersham et al., 2007 Nat Meth) and the novel anterograde (Haberl et al., 2014) rabies virus tracing to map the cellular components of the structural wiring deficits in the primary visual cortex (V1) of Fmr1-/y mice. We found an increased short-range connectivity and decreased long-range connectivity, supporting the evidence for the functional uncoupling of distant brain areas that we found in the Fmr1-/y mice. Alterations in the anatomical wiring provide a potential mechanism for the devastating effects on sensory processing in Fragile X Syndrome.



Reorganization of structural and functional connectivity in the Fmr1 (-/y) mouse model of autism.
The representative model highlights the phenotype of short-range hyperconnectivity and long-range hypoconnectivity in the Fmr1-/y mice (Haberl et al., 2015)

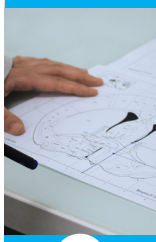
Funding:

This project was supported by the European Commission FP7 Erasmus Mundus Doctoral Fellowship (M.G.H.) as well as funding from INSERM, Conseil de la Region, d'Aquitaine, LABEX BRAIN ANR-10-LABX-43, and the Euro-BioImaging initiative. The MR instrument was acquired with the (partial) support of Nederlandse Organisatie voor Wetenschappelijk Onderzoek (investment grant no. 91106021).
Reorganization of structural and functional connectivity in the Fmr1 (-/y) mouse model of autism. The representative model highlights the phenotype of short-range hyperconnectivity and long-range hypoconnectivity in the Fmr1-/y mice (Haberl et al., 2015).

Publications:

- 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 20 Nov 2015: Vol. 1, no. 10, e1500775
- Haberl, M.G.*, 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 largescale reconstruction of 3D neuron morphology. *equal contributions. Brain Structure and Function 220 (3), 1369-1379.
- Ginger, M.*, Haberl, M.*, Conzelmann, K.K., Schwarz, M.K., Frick, A. (2013) Revealing the secrets of neuronal circuits with recombinant rabies virus technology. Front Neural Circuits. 2013;7:2. *equal contributions.
- Ginger M.*, Bony G.*, Haberl M.G. and Frick A. (2015) Use of Rhabdoviruses to Study Neural Circuitry. *equal contributions (Book Chapter) Biology and Pathogenesis of Rhabdo- and Filoviruses (World Scientific Publisher)
- Haberl, M.G., Ginger, M. and Frick, A. Dual anterograde and retrograde viral tracing of reciprocal connectivity. Invited contribution to „Synapse Development" in Methods in Molecular Biology. In Press
- Viana da Silva, S. , Haberl M.G., Zhang, P., Bethge, P., Lemos, C., Gonçalves, N., Gorlewicz, A., Malezieux, M., Gonçalves, F., Grosjean, N., Blanchet, C., Frick, A., Nägerl, U.V., Cunha, R.A., Mulle, C. (Under revision) Early synaptic deficits in the APP/PS1 mouse model of Alzheimer's disease involve neuronal adenosine A2A receptors

**Equal contributions*



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

Student name : Anne-Sophie Hafner (IINS)	Supervisor : Daniel Choquet

Objectives of the project:

The difference between TARPγ-2 (stg) and γ-8 might come from differences in their primary structures. Although they share 59% identity and 74% homology, γ-8 possesses unique insertions that make its intracellular C-terminus domain 76 amino-acids longer than γ-2. The objective of the project is to determine the impact of TARP C-terminus domain length on the properties of AMPAR complexes.

Main results :

Artificially increasing γ-2 (stg) cytoplasmic C-tail length increases AMPAR mediated synaptic transmission. Our data have identified the precise mechanism through which phosphorylation of a stretch of serine in the intracellular domain of stargazin regulates its interaction with PSD95. Our data demonstrates that phosphorylation of Stargazin intracellular serine domain triggers its repulsion from the plasma membrane and increases the ability of the C-terminus to bind to PSD95. Using a variety of approaches including electrophysiology, fret measurements, super resolution imaging, we have been able to directly measure in live cells the regulation of interaction between Stargazin and PSD95

Publications:

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.

Communications:

Poster "Extension of the stargazin (€2) cytoplasmic tail controls synaptic transmission" at the Biophysical Society Annual Meeting 2014 in San Francisco

Neuromodulation by ATP P2X receptors of excitatory synapses

Student name : Johan-Till Pougnet (IMN)	Supervisor : Eric Boue-Grabot

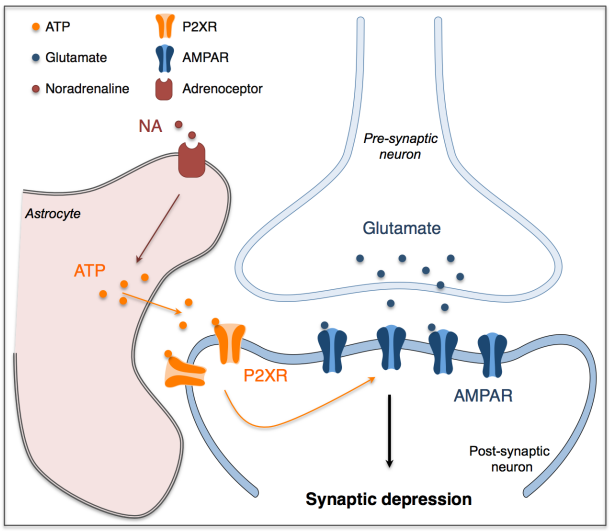
Objectives of the project:

Ionotropic AMPA receptors (AMPAR) activated by glutamate are the main actors of the fast excitatory synaptic transmission in the brain. They also play a crucial role in synaptic plasticity that are widely recognized to be the basis cognitive functions. The objective of this study is to demonstrate that P2X receptors modulate AMPAR trafficking and consequently post-synaptic efficacy in hippocampus.

Main results:

ATP-gated P2X receptors are widely expressed in the brain and we showed that postsynaptic P2X receptors may be activated by ATP released from astrocytes and function to modulate AMPA receptor and membrane trafficking that is critical for synaptic plasticity. Activation of postsynaptic P2X2 by astrocytic release of ATP causes an enduring decrease of the postsynaptic AMPAR current in hippocampal neurons and a depression of field potentials recorded in CA1 region from brain slices. The Ca2+ entry through the opening of P2X2 triggers internalization of AMPARs leading to reduced surface AMPARs in dendrites and at synapses. In addition, NMDA- and ATP-dependent depression were additive in CA1 neurons indicating that P2X- and NMDAR-dependent internalization of AMPAR used distinct signaling pathways (Pougnet et al., 2014).

We next described the transduction mechanism for the P2X2-mediated internalization of AMPAR and ATP-driven synaptic depression in the hippocampus. This work showed that GluA1 phosphorylation at two CamKII sites S567 and S831 located in the first intracellular loop and in the C-terminal tail of GluA1, respectively is critical for P2X2-mediated internalization and inhibition of AMPAR and that dephosphorylation of GluA1 S567 is a mechanism for ATP-driven synaptic depression (Pougnet et al, submitted).



Postsynaptic P2X receptors activated by glial ATP regulate AMPAR surface trafficking and synaptic strength in the hippocampus, providing a new regulatory mechanism of synaptic plasticity that may underlie learning and memory (Pougnet et al. 2014).V

Published publications:

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. (IF= 15.98)

Submitted Publications:

Pougnet J-T, Compans B, Martinez A, Choquet D, Hosy E, and Boué-Grabot E. P2X-mediated AMPA receptor internalization and synaptic depression is controlled by two CamKII phosphorylation sites on GluA1 in hippocampal neurons. (submitted)

Communications :

Boué-Grabot, E. P2X receptors and glial ATP regulate AMPAR trafficking and synaptic plasticity, International Purine meeting, Bonn, Germany, July 2014

Boué-Grabot, E. Neuromodulation by ATP and post-synaptic P2X receptors : diversity of the mechanisms. Centre de Psychiatrie et Neurosciences, Université Paris Descartes, Paris, Nov. 2013

2014

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

Student name : Elisabetta Aloisi (NCM) | Supervisor : Andreas Frick

Objectives of the project

Metabotropic glutamate receptor subtype 5 (mGluR5) is crucially implicated in the pathophysiology of Fragile X Syndrome (FXS), however, its dysfunction at the sub-cellular level, and related synaptic and cognitive phenotypes are unexplored. We investigated the consequences of the previously reported mGluR5/Long Homer scaffold disruption for mGluR5 cell-surface mobility, synaptic N-methyl-D-aspartate receptor (NMDAR) function, and behavioral phenotypes in Fmr1 knockout (KO) mice.

Main results

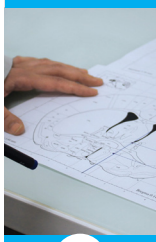
We used a combination of high-resolution single molecule tracking, electrophysiological and knockdown approaches in hippocampal neurons from wild type (WT) and Fmr1 KO mice, together with behavioral analysis. We found that the lateral mobility of mGluR5 was increased specifically at the synaptic sites in Fmr1 KO hippocampal neurons and correlated with an increased synaptic confinement and co-clustering of mGluR5 and NMDAR, likely resulting from the mGluR5/Long Homer disruption. This led us to investigate changes in synaptic NMDAR currents and their long-term depression following mGluR5 activation. These synaptic phenomena were recapitulated in WT neurons by a peptide-based approach that disrupted the mGluR5/Long Homer scaffold. Importantly, we found that restoring this mGluR5/Long Homer interaction by reducing the expression of Homer1a (a dominant negative regulator of mGluR5 signaling that disrupts the binding between mGluR5 and Long Homer) in the hippocampus rescued abnormal NMDAR function and plasticity as well as cognitive deficits in Fmr1 KO mice.

Working plan to continue

We propose that therapeutic approaches aimed at restoring the normal mGluR5/Long Homer and mGluR5/NMDAR interactions might provide a promising alternative for the treatment of FXS. It is hoped that these findings will contribute to the development of alternative, targeted therapies for this disorder and its co-morbidities, and provide mechanistic links to other genetic causes of autism.

Published publications

- Di Marco B., Bonaccorso C.M., Aloisi E., D'Antoni S., Catania M.V. Neuro-inflammatory mechanisms in developmental disorders associated with Intellectual Disability and Autism Spectrum Disorder: a neuro-immune perspective. CNS Neurol Disord Drug Targets. 2016;15(4):448-63 Book Chapter:
- D'Antoni S., Spatuzza M., Bonaccorso C.M., Aloisi E., Musumeci S., Catania M.V. Fragile X Syndrome: From Pathophysiology to New Therapeutic Perspectives. Latest Findings in Intellectual and Developmental Disabilities Research, Prof. Uner Tan (Ed.), ISBN: 978-953-307-865-6, InTech, DOI: 10.5772/31387. Published: February 15, 2012 under CC BY 3.0 license



Publications in preparation:

- 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

Communications:

Oral Communications:

- 27th ECNP Congress, 18-21 October 2014, Berlin – Germany. "Altered surface dynamics of mGlu5 receptor in a mouse model of Fragile X Syndrome"
- 12th Synapse Day Meeting. 28 March 2014 – Bordeaux, France. "Altered surface dynamics of mGlu5 receptor in a mouse model of Fragile X Syndrome"
- ECNP Workshop for Junior Scientists in Europe. 6-9 March 2014 – Nice, France. "Altered surface dynamics of mGlu5 receptor in a mouse model of Fragile X Syndrome"
- 36th Meeting of the Italian Society of Pharmacology. 23-26 October 2013 - Turin, Italy. "Pharmacological investigation into the mechanisms underlying altered mGlu5 receptor dynamics in a mouse model of Fragile X Syndrome"

Poster Communications:

- 8th International Meeting on Metabotropic Glutamate Receptors, 28 September - 3 October 2014, Taormina - Italy
- 9th FENS forum of Neuroscience, 5-9 July 2014 - Milan, Italy
- ECNP Workshop for Junior Scientists in Europe. 6-9 March 2014 - Nice, France
- Society for Neuroscience. 9-13 November 2013 - San Diego (CA), USA
- 4th European Synapse Meeting. 28-30 August 2013 - Bordeaux, France
- 1st European ENCODS Conference. 18-19 April 2013 - Bordeaux, France
- Conférences Jacques-Monod. Mechanisms of intellectual disability: from genes to treatment. 3-7 October 2012 - Roscoff, France

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

Student name : Alexis Bédécarrats (INCIA)	Supervisor : Romuald Nargeot

Objectives of the project:

The project aimed to analyze ionic mechanisms of pacemaker properties in an identified neuron (B63) that activity is associated to an internal motivation state for feeding behavior in Aplysia. Using electrophysiology, pharmacology and functional imaging, we investigated contribution of different intracellular calcium fluxes and their interaction in genesis of the spontaneous and irregular activity in B63 that drive the buccal motor patterns.

Main results

We found that the pacemaker and bursting properties of neurons B63 resulted from interaction between two distinct calcium fluxes: one of them was provided by rhythmic release of calcium from intracellular stores. A second flux of calcium was permitted by voltage-activated cationic membrane conductances that underlie plateau potential. Pharmacological tools and calcium imaging indicated that these fluxes interact in two ways: (1) the regular oscillation of calcium release from internal stores

induces regular membrane depolarization activation of the cationic membrane channels; (2) transmembrane calcium influx during plateau potential activates calcium release from the internal stores. A computational model indicated that these calcium dynamics replicate spontaneity and variability of the neuronal drive in the buccal network that is correlated with motivation state for feeding behavior.

Working plan to continue:

Motivational states in Aplysia are modified by appetitive learning and modulatory transmitters such as dopamine and serotonin. Future researches, including use of the recently developed functional magnetic resonance imaging at single cell resolution in Aplysia, will determine whether and how learning and bioanimes modify Ca2+ dynamics and pacemaker properties in identified neurons, such as B63, in the decision-making network for feeding behavior.

Publications 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.
Book chapter in preparation:
Nargeot R, Bédécarrats A. Associative learning in invertebrates. Eds JH Byrne, Oxford University Press. New York.

Communications:

- 10th Forum of Neuroscience of the Federation of European Neurosciences Societies (Copenhagen, Denmark) (2016) Nargeot R, Bédécarrats A, Castro J, Lade Q, Cattaert D, Simmers J. Poster: Intracellular calcium dynamics underlying neuronal pacemaker properties for food-seeking behavior in Aplysia.
- Annual Meeting of the Society For Neurosciences (Chicago ,USA) (2015) Bédécarrats A, Castro J, Lade Q, Cattaert D, Simmers J, Nargeot R. Poster: Role of intracellular calcium dynamics in the spontaneous drive for feeding behavior in Aplysia.
- Neurocampus/BRAIN symposium (Bordeaux, France) (2015) Bédécarrats A, Castro J, Lade Q, Cattaert D, Simmers J, Nargeot R. Poster: Role of calcium dynamics in the drive for feeding behavior in Aplysia.

The role of mitochondrial cannabinoid receptor type 1 in the brain

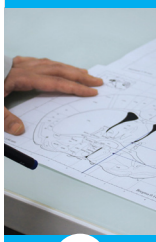
Student name : Tifany Desprez (NCM)	Supervisor : Giovanni Marsicano

Objectives of the project:

The cannabinoid receptor type 1 (CB1R) modulates diverse physiological processes. Recently, our laboratory showed the functional presence of CB1R in brain mitochondrial membranes (mtCB1R). The project aims at determining the impact of mtCB1R signaling on behavioral functions, in particular memory process and motor control. The study of the role(s) of mtCB1R implies the design and the validation of suitable tools to discriminate the role(s) of mtCB1R from the other pools of CB1R.

Main results:

Our results showed that mtCB1R are required for cannabinoid-induced memory impairment and catalepsy, which are the major side effects of cannabis consumption. We found that intra-mitochondrial soluble-adenylyl cyclase (sAC) activity mediates the effects of mtCB1R signaling on brain cellular respiration. Inhibition of sAC in the substantia nigra pars reticulata mediates the cannabinoid-induced catalepsy. Additionally, intra-hippocampal inhibition of sAC blocked cannabinoid-induced amnesia. We generated a mutant CB1 protein (DN22-CB1) lacking mitochondrial localization but it is functionally present at the plasma membrane. Cannabinoid-induced memory impairment was rescued by viral hippocampal re-expression of wild-type CB1 in CB1-KO mice, but not of DN22-CB1. The data directly link mitochondrial activity to memory and motor control.



Working plan to continue:

- Development of a conditional cell type-specific DN22-CB1 knock-in mutant mouse, which will express the mutant protein at the place of wild-type CB1.
- Understanding the mechanisms of mitochondrial targeting of CB1R.
- Testing the cellular "post-mitochondrial" mechanisms of action of mtCB1R modulating brain functions.

Publications:

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.

Publications in preparation:

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

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

Communications:

Poster presentation

44 annual meeting of the society for neuroscience (2014).

Cannabinoid-induced acute Memory impairments depend on mitochondrial CB1 receptors.

Tifany Desprez, Etienne Hebert-Chatelain, Edgar Soria-Gomez, Luigi Bellocchio, Anna Delamarre, Federico Massa, Pedro Grandes, Giovanni Bénard, Giovanni Marsicano.

Lecturer

7th european workshop on cannabinoid research & iacm 8th conference on cannabinoids in medicine (2015).

Mitochondrial CB1 receptors are required for amnesic effects of cannabinoids.

Tifany Desprez, Etienne Hebert-Chatelain, Román Serrat, Edgar Soria-Gomez, Luigi Bellocchio, Anna Delamarre, Federico Massa, Pedro Grandes, Giovanni Bénard, Giovanni Marsicano

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

Student name : Sabine Fièvre (IINS)	Supervisor : Christophe Mulle

Objectives of the project

In CA3 pyramidal cells, a subtype of ionotropic glutamate receptor: kainate receptors, are present at mossy fiber synapses and absent from other glutamatergic inputs. The mechanisms for the subcellular segregation is not known. We have investigated the molecular determinants responsible for the subcellular segregation of KARs at mf-CA3 synapses.

Main results

Using functional mapping of glutamate receptors by focal glutamate uncaging we show that KARs display a strictly confined expression on thorny excrescences, the postsynaptic elements of mf-CA3 synapses. We have identified a sequence in the GluK2a C-terminal domain necessary for restricted expression of KARs which is responsible for GluK2a interaction with N-Cadherin. Targeted deletion of N-Cadherin in CA3 PCs induce a destabilization of KARs at the mf-CA3 synapses. Our findings suggest that multiple mechanisms combine to control the compartimentalization of KARs at mf-CA3 synapses, including a limited number of slots for KARs, and the recruitment/stabilization of KARs by N- Cadherins.

Working plan to continue

We would like to better characterize the NCadh flox KO and the subcellular localization on N-Cadherins in CA3 pyramidal cells.

Published publications

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

Publications in preparation

Fièvre S*, Carta M*, Chamma I, Labrousse V, Thoumine O, Mulle C: Molecular determinants for the strictly compartimentalized expression of kainate receptors in CA3 pyramidal cells. (* equal first authors)

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

Student name : Senka Hadzibegovic (IMN)	Supervisor : Bruno Bontempi

Objectives of the project

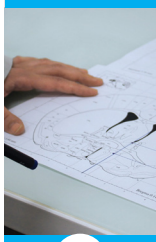
Amyloid ß peptides (Aß) bind preferentially to the postsynaptic density of neuronal excitatory synapses where the scaffolding proteins organize the subunit composition of NMDARs and their subcellular location (synaptic versus extrasynaptic). Our objectives have been to identify the potential deleterious effects of Aß oligomers (Aßo) on the NMDARs organization at the synapse and to possibly prevent these effects using innovative tools in transgenic and other inducible mouse models of Alzheimer's disease (AD).

Main results:

The 8-month PhD extensions grant (November 2014 to June 2015) gave me the opportunity to defend successfully my PhD thesis in the best condition on September 10, 2015 and to finalize my first publication. Because an array of deleterious mechanisms is triggered in transgenic mouse models of AD, additional experiments were required to demonstrate the functional relevance and properties of such mechanisms in a more controlled manner by using C57BL/6 mice injected intracerebrally with soluble Aßos. We have developed an innovative behavioral procedure tailored to maximizing spatial cognitive demand coupled to in vivo recordings of hippocampal sharp wave-ripples (SWRs) in freely moving animals and pinpointed the crucial roles of SWRs in driving the formation of spatial memory (Nicole/Hadzibegovic et al., 2016). Based on this model, I am currently examining synaptic accumulation of Aßos as an early marker of cognitive deficits associated with AD (Moustié et al., in preparation). In parallel, we have been developing a specific protocol to evaluate the impact of displacing subunit specific-NMDARs in or out of synapses by using specific NMDAR modulators and determining the outcome on memory performance in adult C57BL/6 mice.

Working plan to continue:

We will study the capability of antibodies and drugs to block the synaptic accumulation of Aß peptides and to further prevent the Aß effect on synaptic disorganization of NMDARs. The impact of these manipulations on cognitive performance will be examined using our innovative spatial discrimination paradigm in the Y-Maze, for which we have already demonstrated the high throughput potential for detecting subtle changes in memory functions.



Published publications:

- 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).

Publications in preparation:

- S. Hadzibegovic, B. Bontempi, O. Nicole. NMDAR subcellular location and memory functions are altered in the APPswe/PS1dE9 mouse model of Alzheimer's disease.
- O. Moustié, S. Hadzibegovic, F. El gaamouch, B. Bontempi, T. Freret, E. Maubert, K.Brodji, A. Buisson, O. Nicole. Accumulation of amyloid €oligormers in the post-synaptic compartment as an early marker of cognitive deficits in transgenic mouse model of Alzheimer's disease.

Communications:

- April 2015: European Neuroscience Campus (ENC) Network annual meeting, Coimbra, Portugal
  Oral presentation: Expression and subcellular location of GluN2B in APP/PS1 mice: Impact on cognitive performance.
- April 2015: 2nd European Neuroscience Conference by Doctoral Students, Sesimbra, Portugal
  Poster title: Mislocalization of NMDA receptors in Alzheimer's disease. S. Hadzibegovic, Y. Cho, N. Macrez, B. Bontempi, O. Nicole.
- April 2015: 15th "Journée Scientifique de l'Ecole Doctorale", Arcachon, France
  Poster title: Absence of learning-induced increase in hippocampal ripple rate is associated with memory consolidation deficits in a mouse model of Alzheimer's disease. O. Nicole*, S. Hadzibegovic*, J. Gajda, B. Bontempi, T. Bem, P. Meyrand.

Visualisation and Perturbation of the spatio-temporal dynamics of endocytosis

Student name : Morgane Rosendale (IINS)	Supervisor : David Perrais

Objectives of the project:

During my PhD, I developed tools to visualise and perturb endocytosis in various cellular contexts. The characterisation of a red pH-sensitive protein had been submitted to the Journal of Cell Biology. The first objective of the LabEx extension was to perform the revisions for this paper. The second was to visualise the endocytosis of AMPA receptors under plasticity inducing conditions in neurons. The third was to decipher the molecular mechanism of dynamin with great temporal resolution.

Main results:

First, the characterisation of pHuji as the best red-shifted pH sensor for dual colour imaging was published in the Journal of Cell Biology in November 2014. Furthermore, we published a collaborative work with the Pasteur Institute (Paris) using pHuji to decipher the functional recruitment of a Rab-based molecular switch in Current Biology in January 2016. Second, we attained our goal of mapping the endocytic activity of neuronal dendrites for various receptors under several stimulation conditions. Among others, we monitored the kinetics of internalisation of AMPA receptors with a 2 s temporal resolution during chemically induced long term depression (LTD). Third, we performed biophysical assays that confirm our hypothesis that dynamin binds the SH3-domain of amphiphysin via multimeric interactions. Finally, we were able to inhibit dynamin acutely using a photoactivatable inhibitor in fibroblasts, thus getting unprecedented insight on its kinetics of action.

Working plan to continue:

I am focusing my attention on writing manuscripts: one describing our findings on the spatial and temporal regulation of endocytosis in neuronal dendrites, the other on the functional recruitment of dynamin by multimeric interactions at endocytic sites. I plan to submit them in spring 2016. The team has also recruited a new PhD student to continue working on the development and characterisation of photoactivatable inhibitors of dynamin to acutely inhibit endocytosis in neurons during LTD.

Published publications:

- Yi Shen[1], Morgane Rosendale1, Robert E. Campbell and David Perrais, pHuji, a pH-sensitive red fluorescent protein for imaging of exo- and endocytosis J. Cell Biol., 10 Nov 2014, 207(3):419-32 ; doi: 10.1083/jcb.201404107
  [1]Shared 1st authorship
- Cauvin C, Rosendale M, Gupta-Rossi N, Rocancourt M, Larraufie P, Salomon R, Perrais D, Echard A. Curr Biol., 2016 Jan 11; 26(1):120-8. doi: 10.1016/j.cub.2015.11.040. Epub 2015 Dec 24. Rab35 GTPase Triggers Switch-like Recruitment of the Lowe Syndrome Lipid Phosphatase OCRL on Newborn Endosomes.

Publications in preparation:

- Morgane Rosendale, Damien Jullié, Daniel Choquet and David Perrais, Spatio-temporal dynamics of dendritic endocytosis during synaptic plasticity
- Morgane Rosendale[1], Thi Nhu Ngoc Van[1], Dolors Grillo-Bosh, Isabel Gauthereau, Daniel Choquet, Matthieu Sainlos[2] and David Perrais[2]; Dynamin requires multimeric interactions with SH3 domain containing proteins for efficient endocytosis
  [1] Shared 1st authorship
  [2] Shared corresponding authorship
- Morgane Rosendale, Léa Claverie, David Perrais, Control of cytoplasmic composition reveals GTP hydrolysis by dynamin is a limiting factor for membrane scission in living cells

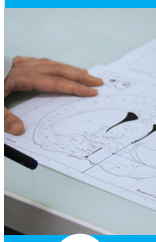
Communications:

Poster Communications

- Visualising the dynamics of endocytic zones in neuronal dendrites, 18th edition of the «Exocytosis-Endocytosis club» congress, Evian, France, May 2015
- Visualising the dynamics of endocytic zones in neuronal dendrites, EMBO international conference 'The Multidisciplinary Era of endocytic mechanics and functions', Mandelieu-la-Napoule, France, September 2015

Oral Communications

- Visualisation and perturbation of the spatio-temporal dynamics of endocytosis. Visit at the RIKEN Brain Science Institute. Invited by Dr. Y. Hayashi, Laboratory for Learning and Memory. Wakoshi, Saitama, Japan, July 2015
- Visualisation and perturbation of the spatio-temporal dynamics of endocytosis. Visit at the University of Tokyo, Graduate School of Medicine. Invited by Dr. H. Bito, Department of Neurochemistry. Tokyo, Japan, July 2015



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

Student name : Christelle Glangetas (IMN)	Supervisor : François Georges

Objectives of the project:

The aim of this study was to functionally and anatomically dissect the neuronal pathway between the ventral subiculum (vSUB) and the dopamine (DA) neurons of the ventral tegmental area (VTA) using in vivo electrophysiology in anesthetized rats and tracing.

Main results:

We show that high-frequency stimulation of the vSUB (HFSvSUB) enhances ventral tegmental area (VTA) dopamine neurons activity in vivo and triggers long-lasting modifications of synaptic transmission measured ex vivo. This potentiation is mediated by NMDA-dependent plastic changes occurring in the bed nucleus of the stria terminalis (BNST). In addition, we report that the modification of the BNST-VTA neural circuits induced by HFSvSUB potentiates locomotor activity induced by a sub-threshold dose of cocaine. Our findings unravel a neuronal circuit encoding behavioral effects of cocaine in rats and highlight the importance of adaptive modifications in the BNST, a structure that influences motivated behavior as well as maladaptive behaviors associated with addiction.

Working plan to continue:

Based on these results, we would like to specifically address the functional relevance of that vSUB-BNST pathway in normal condition and after stress exposure using chemo- and optogenetic approaches.

Published publications

Ventral subiculum engages BNST to increase dopamine neuron activity and gate drug-driven locomotor activity

Christelle Glangetas*, Giulia Fois*, Marion Jalabert, Salvatore Lecca, Kristina Valentinova, Frank J Meye, Marco Diana, Philippe Faure, Manuel Mameli, Stéphanie Caille and François Georges. Cell Report , 2015

Publications in preparation:

Christelle Glangetas ,Léma Massi , Giulia Fois , Marion Jalabert ,Delphine Girard ,Marco Diana , Keisuke Yonehara ,Botond Roska ,Chun Xu ,Andreas Luthi ,Stephanie Caillé and Francois Georges In vivo single-cell homeostatic plasticity in the Bed Nucleus of the Stria terminalis triggers long-term anxiolysis

Communications:

SFN 2014, Washington, United States: Poster "In vivo homeostatic plasticity at the single-cell level in the BNST triggers persistent anxiolytic effect"

Compressive Fluorescence Microscopy for Biological Imaging and Super Resolution Microscopy

Student name :
Makhlad Chahid (IINS)

Supervisor : Vincent Studer (IINS) & Maxime Dahan (Physico-Chimie, Curie)

Objectives of the project

We propose to use Compressive Sampling theory as a new architecture to capture compressed data as the signal is being acquired, not after fact. This modality is particularly interesting for reducing measurements, releasing bandwidth, allowing multicolor imaging and also for super resolution imaging, as a serious alternative to current PALM/STORM techniques. Tests have been performed on simple samples, fluorescent beads.

Main Results

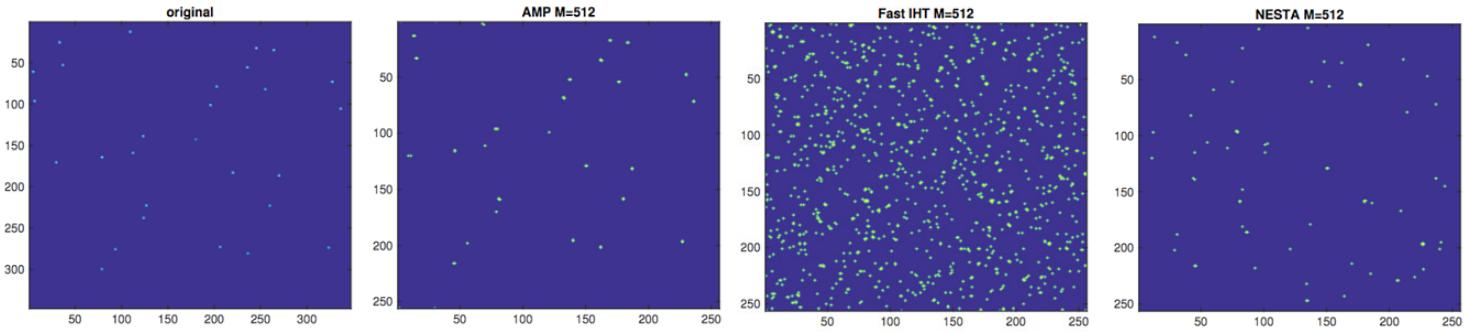
Using a new class of algorithm, named Approximate Message Passing (AMP), we have been able to study its behavior for reconstruction of approximately sparse signals. The images, in this case, are highly sparse in the direct pixel space. The AMP overcomes the l1 optimization solvers in terms of reconstruction quality, speed and minimum under-sampling ratio to get good results
The last figure shows a clear advantage for AMP: its reconstruction and location of the beads is perfect (up to these systematic data-dependent errors) until M = 512 whereas comparably good results (yet not perfect, whereas the AMP results are) are obtained with NESTA only for M ≥ 4096 or with Fast-IHT at M ≥ 8192. So the gain with AMP is substantial, and the location is way more accurate. Furthermore, the speed of convergence of AMP is always 2 to 10 times faster than the convex optimization solvers used here. For M < 512 approximatively, the AMP performances start to worsen continuously, and actual beads disappear while new «fake» ones start to appear as seen on the last figure.

Working plan to continue

A natural continuation is to try the algorithm on real biological samples, where fluorescent labels (single molecules or QDs) are used to selectively study cell structures. Another natural idea would be to try spatial coupling combined with Hadamard patterns. But as the noise is high (typically a relative intensity of O(10−2/10−3) with respect to the beads intensity in the present experiments). Finally, we would like to try the same algorithm for single molecule localization microscopy to refine previous works.

Publications in preparation

A publication is in preparation in collaboration with Jean Barbier (EPFL): Approximate Message Passing for compressive fluorescence microscopy.



Comparison of the reconstruction results of the 3 algorithms used here: AMP, NESTA and Fast Iterative Hard Thresholding with the original picture. The number of measurements is here M= 512.

Thalamocortical control of goal-directed behaviors in Rats

Student name : Fabien Alcaraz (INCIA)	Supervisor : Etienne Coutureau & Mathieu Wolff

Objectives of the project:

This 6 months project aims to understand the functional contribution of thalamocortical interactions in adaptive decision-making. To do so, we have adopted a strategy enabling to assess specifically the behavioural outcome of the reversible chemogenetic inactivation of either the thalamocortical or corticothalamic pathways that connect the prelimbic cortex (PL) and the mediodorsal thalamus (MD) to each other in an instrumental learning paradigm.

Main results:

To date, our results suggest that inhibition of the MD-PL or the PL-MD pathways lead to dissociable deficits. While the former pathway appears to be necessary when updating the causal link between an action and its consequence is required, the later appears to critically support the representation of goal value. In their current state, these data suggest that MD-PL and PL-MD pathways route dissociable aspects of adaptive decision-making, illuminating the functional importance of the direction of information flows within neural circuits.

Working plan to continue:

Our preliminary results suggest a stronger involvement of the thalamocortical and corticothalamic pathways when updating of already acquired information is necessary. We are currently running dedicated groups of rats to examine this issue further, by inhibiting cortical and thalamic neurons only during specific phases of the instrumental training. In addition in vivo electrophysiological controls for MD-PL and PL-MD inhibition are expected to be finalized by end of May 2016.

Publications in preparation:

Thalamocortical circuits of goal-directed behaviors – Submission planned end of June 2016.

Communications:

- March 2016: "Thalamoprefrontal networks of goal-directed behaviors", Synapse symposium, Bordeaux, France (Invited presentation).
- January 2016: "Thalamocortical networks of decision-making", NutriNeuro seminar, NutriNeuro laboratory, Bordeaux, France (Invited presentation).

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

Student name : Benjamin Bessieres (IMN)	Supervisor : Olivier Nicole

Objectives of the project

The experiments performed during my PhD identify, in adult rats, the existence of a learning-induced surface redistribution of cortical GluN2B-NMDARs, which drives the progressive stabilization of remote memories within cortical networks and their subsequent forgetting over time. However, to provide indisputable evidence that an increase in the synaptic GluN2A/GluN2B ratio acts as a crucial cortical switch underlying the speed of memory stabilization within cortical networks, we adopted an innovative strategy which relies on the use of competing biomimetic peptides (specifically displacing surface GluN2B-NMDARs) in order to increase artificially the synaptic GluN2A/GluN2B ratio and to examine the outcome on the formation of remote memories.

Main results

My extension grant has started on February 15th 2016. As initially planned, it enabled me to finalize my PhD thesis in the best conditions and to successfully defend it on March 31th, 2016. Since the beginning of April, I have concentrated my efforts on performing stereotaxic surgery on rats that will be injected intracerebrally with the biomimetic compounds aimed at modifying the synaptic GluN2A/GluN2B ratio in the orbitofrontal cortex. Rats will be tested for remote memory using the social transmission of food preference task. Experiments are ongoing.

Working plan to continue

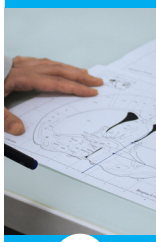
The consequence of the manipulation of the synaptic GluN2A/GluN2B ratio on the kinetics of hippocampal-cortical interactions (faster hippocampal disengagement and earlier cortical recruitment reflecting accelerated stabilization of the memory trace) will be revealed by examining memory performances after pharmacological inactivation (using CNQX) of the hippocampus or the orbitofrontal cortex before memory retrieval.
Also, based on the pertinent suggestions made by the Labex committee, we have added a series of parallel electrophysiological experiments aimed at examining the synaptic properties of cortical neurons obtained from brain slices of rats tested for recent and remote memory (collaboration with the group of Laurent Groc at IINS).
Experiments including surgery, behavior, electrophysiology and biochemistry will require 6 months, from now to September 2016. Two additional months will be dedicated to performing data analysis and finalizing the manuscript that will be submitted at the end of the year.

Publications in preparation

- 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.

Communications

Thesis defense (March 31th, 2016) : Implication fonctionnelle des récepteurs NMDA corticaux au cours des processus de consolidation systémique et d'oubli de la mémoire associative chez le rat.
http://www.bordeaux-neurocampus.fr/fr/formation-doctorale/theses-2016/benjamin-bessi



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

Student name : Marine Chazalon (IMN)	Supervisor : Jérome Baufreton

Objectives of the project:

The external globus pallidus (GPe) is a key GABAergic nucleus in the basal ganglia (BG), a neuronal network involved in motor control. During my Ph. D, I discovered a deficit in GABA uptake by GPe astrocytes due to a down-expression of GAT-3 transporters leading to aberrant 'tonic inhibition' (TI) in parkinsonian rodents. TI can participate to GPe neurons hypoactivity which is one of the electrophysiological signatures of Parkinson's disease (PD). The specific objectives of the project are: 1) to record astrocytes to directly demonstrate the reduction of uptake (by measuring ionic currents generated by GAT-3 uptake), 2) to investigate morphological modifications of the tripartite synapse in GPe using STED microscopy.

Main results:

We have identified astrocytes of GPe based on their intrinsic electrophysiological properties in whole-cell patch-clamp recordings. The majority of astrocytes in the GPe displayed large voltage independent currents, low membrane resistance and a rest membrane potential near to -80 mV.
Then we measured and compared the current generated by GABA uptake across GAT-3 (electrogenic transport of Na+) in GPe astrocytes between control and parkinsonian rodents. Our preliminary data suggest a decrease of GABA uptake in pallidal astrocytes recorded from parkinsonian rats compared to control rats (Figure 1).

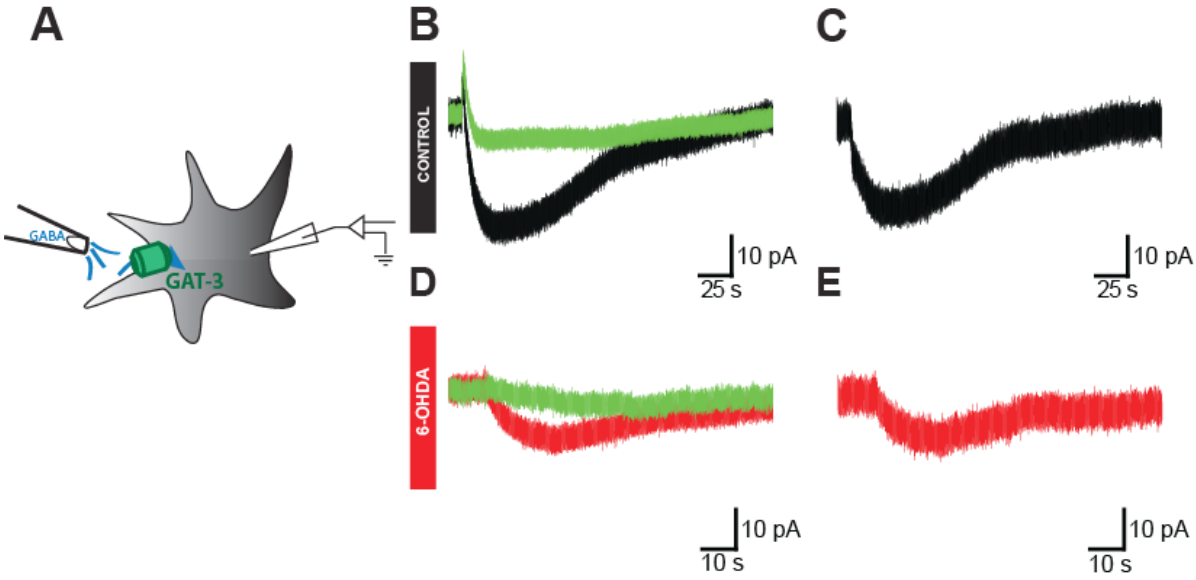


Figure 1: GAT-3-mediated currents are reduced in GPe astrocytes of PD rodents. (A) Schematic representation of the experiment. (B) Representative traces of current produced by puff of GABA (10Mm; 150ms, 20 PSI) in absence (black trace) and in presence (green trace) of SNAP-5114 (xxµM; a selective blocker of GAT-3) in pallidal astrocytes recorded from a control animal. (C) Representative trace of the SNAP-5114 sensitive current in a control animal. (D-E) Same as in B and C but obtain in a parkinsonian animal.

Working plan to continue:

First, we will continue to record GAT-3 currents in astrocyte to confirm the reduction we have observed. Then if we have enough time, we will investigate morphological modifications of the tripartite synapse in GPe using STED microscopy as astrogliosis has been demonstrated in the GPe.

Publications in preparation

- Du Z, Chazalon M, Bestaven E, Cazalets JR, Baufreton J, Cho Y, Garret M. Alteration in GABAergic transmission in basal ganglia in asymptomatic and symptomatic R6/1 mouse model of Huntington's disease. In revision in Neuroscience.
- Chazalon M, Miguelez C, Martinez A, Morin S, Cristóvão-Ferreira S, Vaz S, Sebastiao A, Bioulac B, Boué-Grabot E & Baufreton J. GAT-3 down expression is responsible for tonic inhibition in external globus pallidus in experimental Parkinsonism. In preparation.

Communications:

Posters:

- M. Chazalon, C. Miguelez, A. Martinez , S. Morin, S. Cristóvão-Ferreira, S. Vaz , A. Sebastiao , B. Bioulac, E. Boué-Grabot & J. Baufreton. GAT-3 down expression is responsible for tonic inhibition in external globus pallidus in experimental Parkinsonism. 12th meeting of "société des neurosciences", Montpellier, France - May 2015.
- M. Chazalon, C. Miguelez, S. Morin, S. Cristóvão-Ferreira, S. Vaz , A. Sebastiao , B. Bioulac & J. Baufreton, GAT-3 dysfunction promotes GABAergic tonic inhibition in external Globus Pallidus in experimental Parkinsonism 44th Society for Neuroscience meeting, Washington DC, USA - Nov.

15-19, 2014.

- M. Chazalon, C. Miguelez, S. Morin, S. Cristóvão-Ferreira, S. Vaz , A. Sebastiao , B. Bioulac & J. Baufreton, Glial regulation of pallidal GABAergic tonic inhibition in experimental Parkinsonism. 9th FENS forum of Neuroscience, Milan, Italy - July 5-9, 2014.
- Miguelez C, Morin S, Chazalon M, Ugedo L, Baufreton J. Aberrant GABAergic tonic inhibition is present in the GP of parkinsonian rodents. Dopamine Congress, Alghero, Italy - May 24-28, 2013.
- Miguelez C, Morin S, Chazalon M, Ugedo L, Bioulac B & Baufreton J. Development of aberrant GABAergic tonic inhibition in the GP of parkinsonian rodents. 11th International Basal Ganglia Society Meeting, Eilat, Israel - March 3-7, 2013.

Oral presentations:

- M. Chazalon; Alterations of GABAergic transmission in external Globus pallidus in parkinson and huntington rodent models; "Basal ganglia symposium", Bordeaux - France - September 2015
- M. Chazalon; Alteration of GABAergic transmission in the external globus pallidus of parkinsonian rodent models. Invited speaker, Zurich-Switzerland - July 2015.
- M. Chazalon; GAT-3 down expression is responsible for tonic inhibition in external globus pallidus in experimental Parkinsonism. '13ème Journée de la synapse' ; Bordeaux - France - March 2015.

Non-canonical action of psychotomimetic molecules on NMDA receptor trafficking

Student name : Julie Jezequel (IINS)	Supervisor : Laurent Groc & Pr. Constantine-Paton

Objectives of the project:

The ambitious objective of my PhD project is to address the following non-canonical question: Could an alteration of NMDA receptor (NMDAR) surface diffusion contribute to the emergence of psychotic disorders? Using a multidisciplinary approach, my thesis aims at understanding how NMDAR signaling is altered in this pathological context, and whether an Ariadne's thread emerges between several models of psychosis.

Main results:

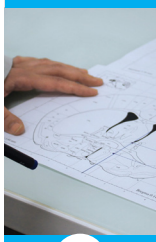
To tackle this question, I compared the impact of 2 families of psychotomimetic molecules (i.e. able to induce a psychotic state), and observed whether they lead to common NMDAR-mediated dysfunctions. The first part of my project focuses on the molecular impact of NMDAR autoantibodies (NMDAR-Ab) isolated from the serum of few schizophrenic patients and very few healthy subjects. Using a combination of single-molecule tracking, super-resolution imaging and classical histology methods, we showed that NMDAR-Ab purified from schizophrenic patients, but not from healthy subjects, strongly alter the surface dynamics and nanoscale organization of NMDAR in hippocampal glutamatergic synapses. Moreover, the EphrinB2 receptor, a key anchoring partner of synaptic NMDAR, is also impacted by NMDAR-Ab from schizophrenic patients, which most likely contributes to NMDAR dysregulation.

Working plan to continue:

The second part of my project aims at exploring the impact of NMDAR antagonists with psychotomimetic properties on NMDAR. Preliminary results indicate that ketamine and MK-801 disturb NMDAR surface dynamics and distribution. The LabEx grant will allow me to deeper explore the molecular mechanisms leading to such alterations, and in particular to investigate the effects of NMDAR antagonists on NMDAR synaptic retention.

Publications in preparation:

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)



Communications:

Posters

- J.Jezequel, E.Johansson, H.Gréa, V.Rogemond, B.Kellermeyer, N.Hamadani, E.Le Guen, C.Rabu, E.Mathias, J.Varela, D.Bouchet, R.H.Yolken, R.Tamouza, J.Dalmau, J.Honnorat, M.Leboyer, and L. Groc. Specific alteration of NMDA receptor synaptic organization and trafficking in autoimmune psychosis. GliSyn Meeting, Pessac, France, October 2015
- J.Jezequel, E.Johansson, H.Gréa, V.Rogemond, N.Hamadani, E.Le Guen, C.Rabu, E.Mathias, D.Bouchet, R.H. Yolken, R.Tamouza, J.Honnorat, M.Leboyer, and L.Groc. Alteration of NMDA receptor surface dynamics in the presence of autoantibodies from encephalitic and psychotic patients.
  - The Lancet Neurology Autoimmune Disorders Conference, Barcelona, Spain, March 2015
  - Society For Neuroscience Meeting, Washington, USA, November 2014
- J.Jezequel, D.Bouchet, V.Rogemond, J.Honnorat, M.Leboyer and L.Groc. NMDAR surface trafficking in psychotic models: new place to regulate an old actor.
  - Ecole d'été FENS-SFN «Neurodevelopmental Psychiatric Disorders», Bertinoro, Italy, June 2014
  - Journée de l'Ecole Doctorale des Sciences de la Vie et de la Santé, Bordeaux, France, April 2014
- J.JEZEQUEL, L.Mikasova, D.Bouchet, V.Rogemond, J.Honnorat and L.Groc. Altered surface interplay between NMDA and dopamine receptors in a neuropsychiatric disorder.
  - Société Française des Neurosciences, Lyon, France, May 2013
  - European Synapse Meeting, Bordeaux, France, August 2013

Oral presentations

Specific alteration of NMDA receptor synaptic organization and trafficking in autoimmune psychosis. 5th Biennial Schizophrenia International Research Society Conference, Florence, Italy, April 2016

Molecular impact of anti-NMDAR IgGs from schizophrenic patients.

- IECB 8th Young Scientist Symposium, Pessac, France, May 2015
- Journée de l'Ecole Doctorale des Sciences de la Vie et de la Santé, Bordeaux, France, April 2015

Identification of exocytosis proteins involved in postsynaptic trafficking

Student name : Julia Krapivkina (IINS)	Supervisor : David Perrais

Objectives of the project:

In my PhD project I tested the involvement of Vamp4 and Vamp2 in postsynaptic exocytosis by using imaging methods and knock-down experiments together with acute exocytosis blocking. The first objective of the Labex thesis extension is to perform the mEPSCs recordings in VAMP4 knock-down neurons with a view to characterize the role of VAMP4 in synaptic physiology. The second objective is to assess the involvement of VAMP4 in the long term plasticity in electrophysiological experiments.

Main results (10 lines max)

4 months out of 12 into the Labex thesis extension we have the following results:

- We finished the characterization of Vamp4 involvement in basal synaptic transmission by recording miniature EPSCs in Vamp4 knock-down cultured neurons.
- We set up an experimental protocol where we will perform the LTP induction in CA1 pyramidal neurons of the organotypic slices electroporated with Vamp4 shRNA through the single cell electroporation technic.

Publications in preparation:

Vamp4 involvement in recycling endosomes trafficking.

Julia Krapivkina, Damien Jullié, Jennifer Petersen, Natacha Retailleau, David Perrais.

Communication:

FENS forum 2016, Copenhgagen, Denmark. The identity of vSNAREs involved in recycling endosome exocytosis in neuronal dendrites.

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

Student name : Charlotte Rimbault (IINS)	Supervisor : Matthieu Sainlos

Objectives of the project:

Developing new approaches to address current technical hurdles to investigate endogenous Protein-protein interactions (PPI) in their cellular context. We are interested in the PDZ domain-mediated interactions (PDMI) involved in the trafficking of glutamate receptors and particularly AMPARs, which mediates most fast excitatory synaptic transmission in the CNS. For practical reasons, PPI are commonly investigated by means of destabilization; here we want to exploit the expertise of the lab on acute perturbation of PDMI to achieve the opposite, ie stabilization.

Main results:

- Validation of our methodology by isolating FN3-derived clones targeting the tandem PDZ domains of PSD-95, which show high specificity and no competition behavior or interference with normal protein function, confirmed by their fully defined epitopes. They constitute excellent tools to image endogenous PSD-95 and synapses in live neurons.
- Isolation of a promising affinity clamps for GluN2A binding motifs, constituting an inhibitor of the GluN2A-PSD-95 interaction and a starting point for the evolution of a stabilizer.
- Isolation of one stabilizer for the Stargazin-PSD-95 interaction; an important interaction contributing to AMPAR synaptic retention.

Publications in preparation:

Directed Evolution of highly specific FN3 monobody binders of PSD-95 tandem PDZ domains.
Rimbault C, Breillat C, Gauthereau I, Genuer C, Poujol C, Thibaut C, Compans B, Toulme E, Wong Jun Tai F, Choquet D, Mackereth C, Sainlos M.

Synaptic vesicle mobility and turnover at VGLUT1 excitatory axons in mice

Student name : Xiaomin Zhang (IINS)	Supervisor : Etienne Herzog

Objectives of the project:

In neurons, synaptic vesicles (SVs) cluster at presynaptic terminals for exocytosis and release of neurotransmitter. Recent, dynamic microscopy on living samples helped identify a pool of SVs named super-pool. Super pool SVs traffic along the axon and are shared among several en passant synapses contacted by the same axon. My goal is to bring more knowledge regarding SV super pool function in neurons and in neurotransmission.

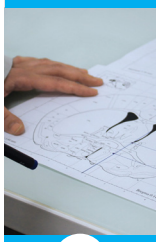
Main results:

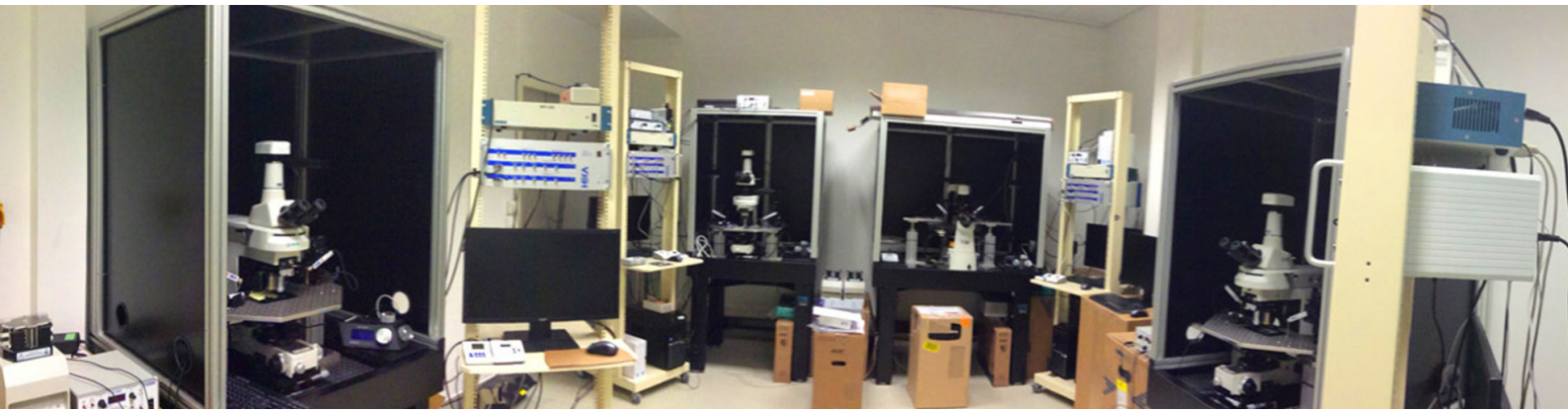
At excitatory neurons, synaptic vesicles (SVs) accumulate and release glutamate, an amino acid that serve as the main excitatory transmitter. Vesicular GLUtamate Transproter 1 (VGLUT1) uploads glutamate into SV and is a specific maker of glutamatergic synapses and SVs.

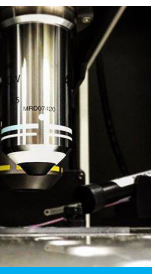
1) I first studied SVs super-pool by tagging VGLUT1 with fluorescent tag (Venus and mEOS2)
2) I then characterized a new mechanism by which VGLUT1 influences SV super pool homeostasis.

Publications in preparation:

A 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







Bordeaux School of Neuroscience

BORDEAUX SCHOOL OF NEUROSCIENCE

Unique in Europe, the BSN ambitions 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 is in fact a modern neuroscience research laboratory fully dedicated to hands-on training activities.

The BSN was selected by FENS/IBRO to be the major partner site of the Cajal Advanced Neuroscience Training Program. This means that BSN provides infrastructure and logistic support for the organization of 4 FENS courses (2-4 weeks/course) per year. The first two sessions started in 2015, and four will be organized in 2016.

The LabEx BRAIN has allowed to secure up to 1.7M€ for the equipment and initial running costs of the Bordeaux School of Neuroscience. Additional support is guaranteed from IdEX Bordeaux (100k€ for the first year) as well as from the Regional Government (147k€).

During the first year of its existence, the BSN staff (Antonella Caminiti, General Manager and Marc Chevalier, technical manager) and its Director Christophe Mulle have started to install the BSN laboratory, by purchasing the necessary equipment in order to organize the first two Cajal training courses on Bioinformatics for Neuroscience (BIN, september 2015) and on Advanced Synapse Biology (ASB, october 2015).

The **BIN Cajal course** was a two-week school, organized at the Functional Genomic Centre of Neurocampus. The training room was equipped with 13 computers configured to perform the bioinformatics analyses planned in the course. 11 students coming from 10 countries and 23 instructors attended the school. Each day methodological seminars were followed by practical activities. There was a diversity of topics which included cutting-edge methodologies to perform different types of analysis: data analysis with R, galaxy, biological databases, differential gene expression with RNAseq, splicing, fusion, SNP INDEL with RNASeq, proteomics, epigenetics with the ChIPseq case study, genomes sequence (SNP calling, CNV) and structure (chromosome abnormalities), genotyping with examples of associated studies (taste genetics, hepatitis C infection, obesity), metabolomics, logic models, DisGenet and network processing for psychiatric diseases, parameter estimation in dynamic/kinetic models using COPASI, electrophysiological models of neurons. Moreover a part of the course was focused on the notion of networks and pathways: how to represent and analyse them, their structure, what we can do with them, chemical kinetics, network inference. The 10 days course was split into two blocks with one day off, when a boat tour of the Arcachon Bay was organized and followed by a dinner. This course was highly appreciated and definitely allowed the students to have a global view of the bio-informatics applied to the neuroscience.

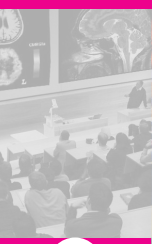
The **ASB Cajal course** was a three-week school with lectures from keynote speakers organized in the morning and hand-on experiments in the afternoon. 20 students from 13 countries from all over the world (US, New Zealand, and many European countries were represented) and 18 instructors attended the school. The course was split into two blocks of 10 days and the students worked on a single project by pair during each block. The 10th day of each block was dedicated to the presentation of the project that the students carried out. Nine instructors were involved in the first block and 9 other instructors in the second block, each of them assisting the 2 students working on the same project. The experiments were carried out at the BSN lab, completely equipped with electrophysiology set-ups and equipment for molecular and cellular biology. The lectures were given by renowned scientists, which highly stimulated the interest of all the participants in a very interactive atmosphere. The presentations were not only open to the students, but also to the scientific community of Bordeaux Neurocampus. Through the hands-on experiments, this advanced course trained the students to innovative techniques, which are expected to be central in synapse biology research in the coming decade. Techniques included in vitro and in vivo gene transfer (including viral vector technology and single cell electroporation), cellular imaging of proteins by super-resolution microscopy (STED and PALM/STORM), photo-manipulation in living tissue and optophysiology, synaptogenesis studies in living neurons, cellular trafficking, single-particle tracking methodologies, patch clamp electrophysiology, live imaging of protein interactions (FRET, FLIM) at synapses and electron microscopy. Rodent and human model systems were central but successful invertebrate models such as Drosophila and C. elegans were also available for hands-on work by the students. The program also included evening activities like the skype sessions with the chief editors of leading journals (EMBO J., Neuron) or with clinicians and decision makers in pharmaceutical industry (Roche, Astra Zeneca).

Several social events were organized during each block and a boat tour of the Arcachon Bay, followed by a dinner took place at the rest day between the 2 ten-days blocks. At the end of the course a farewell dinner was also organised in the Garonne river, which was attended by all the students and the instructors of the second block. The course was extremely intensive, but completely met the expectations of all the participants, as revealed by the survey. The overall outcome of the ATSB course was highly satisfactory.

DISSEMINATION

Meetings

Sabbatical Stays



12th Synapse Day - 28 Mars 2014

Scientific Organisers : Nath Sans & Maurice Garret	
Total number of participants: 90 à 110	Nb of participants from International laboratories: 2
Total nb of speakers: 10	Nb of speakers from international laboratories: 2
Other grants obtained: Bx Neurocampus	

13th Synapse Day - 27 Mars 2015

Scientific Organisers : Nath Sans & Maurice Garret	
Total number of participants: 90 à 110	Nb of participants from International laboratories: 2
Total nb of speakers: 10	Nb of speakers from international laboratories: 2
Other grants obtained: Bx Neurocampus	

Looking at the neuronal diversity in the external globus pallidus: a view from development to behavior - 17-18 Sept. 2015

Scientific Organisers : J. Baufreton / M. Mallet	
Total number of participants: 35	Nb of participants from International laboratories: 8
Total nb of speakers: 9	Nb of speakers from international laboratories: 3
Other grants obtained: FNB	

Eurogenesis meeting - 24-26 juin 2013

Scientific Organisers : Nora Abrous	
Total number of participants: 125	Nb of participants from French laboratories:21 Nb of participants from International laboratories: 104
Total nb of speakers: 36	Nb of speakers from international laboratories: 29
Other grants obtained: ANR pôle Prod'Innov, Neurocentre Magendie, Bordeaux Neuroscience, Marie Curie, Idex, MNS	

Decision making - 8 Avril 2015

Scientific Organisers : Etienne Coutureau & Serge Ahmed	
Total number of participants: 80 (morning session); 50 (afternoon session)	Nb of participants from International laboratories: 3
Total nb of speakers: 9	Nb of speakers from international laboratories: 3 (but Peter Dayan could not come due to strike)
Other grants obtained: Bordeaux Neurocampus	

Biosensor - 4th Biosensor Group Meeting (GDR 2588) - 22-23 mai 2014

Scientific Organisers : Sandrine Pouvreau & Matthieu Sainlos	
Total number of participants: 65	Nb of participants from International laboratories: 5
Total nb of speakers: 7	Nb of speakers from international laboratories: 5
Other grants obtained: GDR2588 - CRA - FBN - FBI - Industry sponsoring (9 500 €) - LabEx Brain : 3 000 € (-)	

SMLMS 2015 - Single Molecule Localization Microscopy Symposium

26-28 août 2015

Scientific Organisers : Jean-Baptiste Sibarita	
Total number of participants: 143	Nb of participants from International laboratories: 70
Total nb of speakers: 15	Nb of speakers from international laboratories: 9
Other grants obtained: SFR/FBN 4 500 € - IdEx Bx ? - LabEx Laphia 1 500 € - CRA 1 500 € - GDR2588 3 000 € + Industry sponsoring LabEx Brain : 3 000 €	

MitoBrain 2014 - Fonctions et dysfonctions mitochondriales dans le système nerveux central - 1er au 3 octobre 2014

Scientific Organisers : Erwan Bézard, Giovanni Marsicano, Sandrine Pouvreau, Giovanni Bénard, Gwendal Le Masson, Rodrigue Rossignol	
Total number of participants: 134	Nb of participants from International laboratories: 62
Total nb of speakers: 19	Nb of speakers from international laboratories: 17
Other grants obtained: LabEx Brain : 17 000 €	

GliSyn 2015 - Astrocytes et microglie : partenaires clés au cours de la transmission synaptique - 30 septembre au 2 octobre 2015

Scientific Organisers : Elena Avignone, Agnès Nadjar, Aude Panatier	
Total number of participants: 116	Nb of participants from International laboratories: 34
Total nb of speakers: 19	Nb of speakers from international laboratories: 17
Other grants obtained: SFR/FBN 17 000 € - CRA 500 € - IdEx Bx 4 500 € + Industry sponsoring LabEx Brain : 17 000 €	

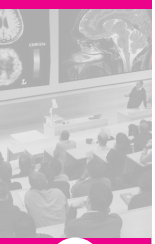
8th Imaging the Cell - 24-26 Juin 2015

Scientific Organisers : Violaine Moreau, Frédéric Saltel, Christel Poujol, Isabelle Sagot and Fabrice Cordelières	
Total number of participants: 80	Nb of participants from International laboratories: 1
Total nb of speakers: 16	Nb of speakers from international laboratories: 8
Other grants obtained: France Bio-Imaging, Idex Université Bordeaux, ITMO-BCDE, SFR Neuro-campus	

6th Annual Scientific Days on Autophagy - CFATG Conference

12 - 14th octobre 2016

Scientific Organisers : Marion Bouchecareilh, Nadine Camougrand, Benjamin Dehay, Raul Duran, Mojgan Mergny, Jean-Max Pasquet, Muriel Priault, Iban Seiliez, Harry Wodrich	
Total number of participants: 110-120	Nb of participants from International laboratories: 50
Total nb of speakers: 3	Nb of speakers from international laboratories: 3
Other grants obtained: Peprotech : 1800 € - Biotechne : 1800 € - Enzo: 1800 € - Sanofi : 1000 € - BCF : 1000 € - INRA : 1000 € - Labex Brain : 3000 € - Neurocampus : 1000 € - GSO/Cancéropole : 2000€ - Fédération de Recherche Biologie Végétale et Intégrative: 1000 € - ALPHA 1-France association : 1000 € - SIRIC/BIO : Voyage + Hébergement Kévin Ryan Idex Bordeaux: 3000 €	



Sabbatical stay

→ **Prof. Frederic Meunier** (Queensland Brain Institute)
in the team of Daniel Choquet at the Interdisciplinary Institute for Neuroscience
2 months from May 2014

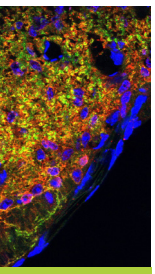
→ **Prof. Peter Kind** (University of Edinburgh)
in the team of Valentin Nägerl at the Interdisciplinary Institute for Neuroscience
4 months from June 2014

→ **Prof Henrique von Gersdorff** (Oregon Health & Science University)
Didier Dulon at the laboratory INSERM UMR1120 Genetics and Physiology of Hearing & David Perrais at the Interdisciplinary Institute for Neuroscience
1 month from June 2015

→ **Andrew Plested** (Leibniz-Institut für Molekulare Pharmakologie (FMP) & Cluster of Excellence NeuroCure, Charité Universitätsmedizin)
in the team of Daniel Choquet at the Interdisciplinary Institute for Neuroscience
4 months from October 2015

Annexes

IINS - Interdisciplinary Institute for Neuroscience



DYNAMICS OF SYNAPSE ORGANIZATION AND FUNCTION

DANIEL CHOQUET

Our team pursues a transdisciplinary approach to study the interplay between the dynamics of molecular components and synaptic function. Based on advanced imaging techniques, chemistry and bio-chemistry, cell biology and electrophysiology, we study the dynamic organization and function of AMPA receptors and its molecular partners. We obtained breakthrough data on the synapse nano-scale organization, dynamics and interaction between synaptic proteins. Our efforts are focused on the understanding of the synaptic components dynamics involved in higher cognitive functions and pathologies, such as Alzheimer's or Huntington's diseases.

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 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 at the cellular to the circuit level. Our recent results show that several intellectual disability (ID) mouse models exhibit behavioural deficits that could be attributed to discrete synaptic defects. Interestingly, at several occasions, our results show that behavioural adaptation rather than learning per se are affected by the ID gene mutation. Furthermore, in most cases, the synaptic defects that are impacting network physiology could be corrected phenotypically, without gene reintroduction, opening new interesting therapeutic avenues from ID treatments.

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 chronic pain. We investigate the role of excitation/inhibition balance and plasticity leading to chronic pain. We also focus on microRNA-based regulatory mechanisms influencing nociceptive transmission. In particular, we explore how exosomes could mediate miRNA transfer between cells, thus representing a new mode of neuronal communication. We are investigating network-based regulation of spinal neuron activity, with special emphasis on peptidergic modulation of sensory afferent fibres and descending inputs. Such mechanisms may have strong implications in our understanding of pain comorbidity with mental disorders.

SYNAPTIC CIRCUITS OF MEMORY

CHRISTOPHE MULLE

Synaptic plasticity is thought to be essential for forming memories, although how synaptic circuits actually encode novel information is poorly understood. The CA3 subregion of the hippocampus, a main focus of the group, is involved in the rapid encoding of memory, by instantaneous representation of a context. The project aims at understanding how the diverse properties of synaptic contacts in CA3 circuits are implemented and maintained. In parallel the group studies the operation and plasticity of local hippocampal synaptic circuits in the context of episodic-like memory encoding. Me-

thods are developed for interrogating the connectivity and function of local circuits in vivo in behavioural conditions. These studies address control conditions as well as models of cognitive disorders mainly Alzheimer's disease.

SYNAPTIC PLASTICITY AND SUPER-RESOLUTION MICROSCOPY

VALENTIN NÄGERL

Our research is focused on understanding the nano-anatomical rules and correlates of neural plasticity that underlie higher brain function and brain disorders. We develop and apply novel super-resolution microscopy techniques (STED microscopy) to give us a much more complete and refined view of the dynamic behaviour of synapses and their interactions with glia cells in living brain tissue and in vivo. The super-resolution imaging approach is combined with neurophysiological techniques (2-photon glutamate uncaging, patch-clamp electrophysiology, optogenetics) and biophysical modeling to unravel the complex relationship between neural structure and function at the nanoscale.

QUANTITATIVE IMAGING OF THE CELL

JEAN-BAPTISTE SIBARITA

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

CELL ADHESION MOLECULES IN SYNAPSE FORMATION

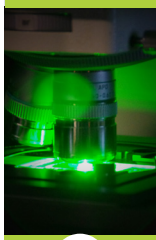
OLIVIER THOUMINE

At the synapse, neurons are glued together by cell adhesion molecules. These molecules expressed on the surface of pre- and postsynaptic neurons, maintain a physical connection between those compartments, but also serve as templates for signaling mechanisms.
Our team focuses on a specific family of trans-synaptic adhesion molecules: neurexins and neuroligins. Our studies reveal that the neurexin-neuroligin complex is a key modulator in the formation and stabilization of synapses, and works as an organizer of several synaptic proteins including scaffolding molecules and glutamate receptors. Through the development of novel imaging computational tools, we are tracking the mobility of these complexes and their partners at the synapse.

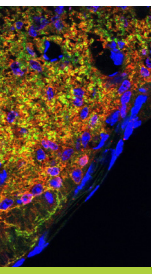
SPATIOTEMPORAL AND MECHANICAL CONTROL OF MOTILE STRUCTURES

GRÉGORY GIANNONE

Our group aims at deciphering at the molecular level the spatiotemporal and mechanical mechanisms that control the architecture and dynamics of motile structures including integrin-based adhesions, actin-based lamellipodia, neuronal growth cones and dendritic spines. The general objective is to elucidate how the dynamic landscape of interactions between integrins, actin filaments and their respective regulators control the life cycle of adhesion sites and membrane protrusions during cell and growth cone migration but also during actin-dependent synaptic structural plasticity. A main contribution of our work is the development of new strategies, for single protein tracking and super-resolution imaging, enabling to track and analyse at the nanoscale level interactions between proteins of adhesive and protrusive structures.



NMC – NeuroCentre Magendie



PHYSIOPATHOLOGY OF ADDICTION

PIER-VINCENZO PIAZZA

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, and developed a new class of pregnenolone-derived pharmacological compounds that will be soon used in clinical trials.

NEUROGENESIS AND PATHOPHYSIOLOGY

NORA ABROUS

Our laboratory studies the role(s) played by neurogenesis in hippocampal-dependent functions (memory and emotion) in healthy and pathological conditions. Using a longitudinal approach from embryonic stages to senescence, and by coupling in vivo electroporation, transgenic and viral tools, DREADDs and optogenetic technologies, we investigate the relationship between adult-born neurons, memory, emotion and hippocampal plasticity. We are also interested in the influence of early life experiences and their role both in shaping the dentate network and the appearance of vulnerabilities (memory and/or mood disorders) later in life. These studies will open new avenues in the development of strategies to prevent or cure memory /emotional disorders (depression/anxiety) occurring in some individuals in the course of aging.

NEURON-GLIA INTERACTIONS

STÉPHANE OLIET

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

PLANAR POLARITY AND PLASTICITY

MIREILLE MONTCOUQUIOL
NATHALIE SANS

The general aim of our group is to understand the pathophysiology of Planar Cell Polarity (PCP) signaling in mammals, a pathway coordinating tissue polarity in 3 dimensions, through the regulation of cytoskeleton dynamic. More specifically, we want to identify and define the molecular and cellular mechanisms of PCP, and the consequences of early and late deletion of PCP signaling. Mutations in PCP genes affect dramatically both the inner ear and the nervous system, and recently mutations affecting PCP signaling have been associated to neurodevelopmental disorders (autism syndrome disorders), sensory impairments (deafness) and neurological disorders (epilepsy or ataxia). The original combination of scientific expertise in our group (epithelia and neuronal), together with a multidisciplinary approach of PCP integrating cellular, developmental and functional approaches and a series of specific conditional mutants has allowed us to contribute to the understanding of PCP signaling participation in critical processes such as neuronal maturation, dendritic arborization, synaptogenesis, migration and the associated behavioural consequences of a disruption of these mechanisms.

ENDOCANNABINOIDS AND NEUROADAPTATION

GIOVANNI MARSCIANO

Our team aims at uncovering the functions of the endocannabinoid system in the brain as well as the cannabinoid regulation of the pathophysiology of behavior. By the coordinate use of different experimental approaches, 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 mouse behavior.

ENERGY BALANCE AND OBESITY

DANIELA COTA

Our research goal is to identify the key modulators controlling food intake and body weight. Our work is focused on the role of the endocannabinoid system (ECS), an important neuromodulatory system, and of the mammalian target of rapamycin (mTOR), an essential cellular energy sensor, in the physiopathology of obesity. We are currently studying the relationship between the cannabinoid type 1 receptor (a molecular actor of the ECS) and mTORC1-dependent signaling in the control of neuronal circuits involved in feeding behavior and energy balance. Our work also focuses on characterizing obese sub-phenotypes in humans and on defining the therapeutic potential of novel CB1 antagonists for the treatment of obesity and metabolic disorders.

CORTICAL PLASTICITY

ANDREAS FRICK

Our research topic is focused on the structure, function and dynamic regulation of cortical circuits in various conditions such as during learning, development and disease. We investigate ion channel functions in the different neuronal compartments to analyse the coding properties of cortical neurons alone or in assembly. Using genetic models, we revealed the implication of ion channel dysfunctions in sensory hypersensitivity and its association with neocortical hyperexcitability, the hallmark feature of fragile X syndrome and autism. Also, trough the exploration of the anatomical connectivity of neocortical circuits, we showed that its alterations named «connectopathy,» can cause functional defects that may explain mental retardation states

PATHOPHYSIOLOGY OF DECLARATIVE MEMORY

ALINE MARIGHETTO

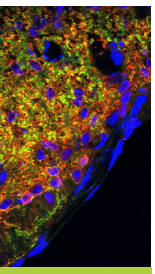
Our research activity is aimed at identifying the psychobiological bases of memory degradation occurring in aging and in post-traumatic stress disorder (PTSD). We first needed to develop satisfactory animal models of the memory form which preferentially degrades in aging and PTSD, i.e. declarative memory (DM), a typically human form of memory. As in aging DM declines, whilst in PTSD there is a paradoxical memory profile in which DM degradation is coupled with enhanced non DM, we develop two main lines of research, each based on a specific behavioural model in mice. Regarding aging, we have validated our radial-maze model of the preferential DM degradation by translating it to humans and identified specific defects in the encoding phase of DM, and critical pharmacological/hormonal and nutritional factors, like estrogens. Regarding stress, we have established the first behavioral model which assesses qualitative features distinguishing normal/adaptive and maladaptive fear memory characteristic of PTSD, and observed that an hypoactivation of the hippocampus and hyperactivation of the amygdala is associated with the development of PTSD-like memories. By continuing our integrative approach, we expect to help developing new therapeutics and prevention strategies of memory alterations in aging and PTSD.

NEURONAL CIRCUITS OF ASSOCIATIVE LEARNING

CYRIL HERRY

Our research group works towards mapping prefrontal and amygdala circuits involved in fear behaviour. Our objectives are threefold: 1- address the anatomical and physiological properties of defined excitatory/inhibitory mPFC circuits controlling fear expression, 2- selectively manipulate these circuits during behaviour, 3- understand the encoding mechanisms required for the animal to perform the learning task. To develop these projects we combine in vivo electrophysiological recordings, selective optogenetic manipulations and behavioural approaches. Our results will provide a detailed knowledge of the cellular basis of fear behaviour and have obvious potential applications for anxiety disorders.

IMN – Institut des maladies neurodégénératives



PATHOPHYSIOLOGY OF PARKINSONIAN SYNDROMES

ERWAN BÉ ZARD

Our translational research is dedicated to uncovering the pathophysiology of Parkinson's disease and works towards development of therapeutic solutions either symptomatic or disease-modifying. 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 the cerebral vascular organization associated with memory processing in healthy and pathological conditions such as Alzheimer's disease. The team has made important breakthroughs, such as the identification of early tagging of cortical networks as a prerequisite for the formation of enduring associative memory. We also unraveled some molecular mechanisms involved in the formation of remote memories, including the interaction of the CaMKII protein with NMDA receptors known to play a key role in neuronal plasticity. Currently, our research mainly focuses on: 1- understanding the functional contributions of NMDA receptors subtypes and its molecular partners, 2- deciphering the roles of vascular networks in the stabilization of remote memories during the course of systems-level memory consolidation.

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, stress…) and of dopamine-associated disorders (Parkinson's disease, addiction, anxiety…).

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 Parkisnon's Disease, dystonia and obsessive-compulsive disorder. Our approach combines theoretical and network modelling with validation of these models by experimental data. We perform up to date electrophysiological, genetic based tool (optognetic, dreds, etc...) and pharmacological studies in behaving or anaesthetized animals. We also study the involvement of the cortex-basal ganglia loop in spatial navigation to unravel the mechanism underlying routine and switching to goal directed behavior.

NEUROFUNCTIONAL IMAGING GROUP (GIN)

NATHALIE TZOURIO-MAZOYER

We are a multidisciplinary research team gathering scientists from various domains: mathematics, medical imaging, nuclear medicine, signal processing, psychiatry and cognitive neurosciences. Our research attempts at understanding the determinants of brain network that underlies cognitive functions. We investigate the cognitive, behavioural, genetic, and brain morphological/functional underpinnings of the human brain hemispheric specialization (HS). We work on neuroimaging cohorts of healthy volunteers in order: 1- to determine how the two hemispheres are differentially involved in a given task, how HS variability is associated with cognitive functioning and how gene shapes HS. To this aims, we have acquired the Brain Imaging of Lateralization by the Groupe d'Imagerie Fonctionnelle "BIL & GIN" database of 453 healthy participants; 2- to characterise the neural support of the late maturational stages of healthy brain within the frame of the I-Share cohort of students' health conducted by C Tzourio. We are currently acquiring brain anatomical and functional images in 2,000 students of Bordeaux University.

NEUROCHEMISTRY, DEEP BRAIN STIMULATION AND PARKINSON'S DISEASE

PHILIPPE DE DEURWAERDERE
ABDELHAMID BENAZZOUZ

Our team has a long-standing interest on the identification of the origins and consequences of neuronal network changes in Parkinson's disease to improve existing therapeutic strategies and develop new ones. Our main research topics are the understanding of: 1- the link between neuronal oscillatory activities in given basal ganglia structures and motor and non-motor functions, 2- the role of monoaminergic systems (dopamine, noradrenaline and serotonin) in the pathophysiology of Parkinson's disease, 3- the neurochemical changes induced by L-Dopa treatment or subthalamic nucleus deep brain stimulation, two treatments that significantly improve Parkinsonian symptoms.

MNEMOSYNE: MNEMONIC SYNERGY

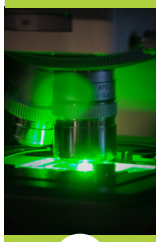
FRÉDÉRIC ALEXANDRE

Our laboratory has a particular research focus geared towards a systemic approach in computational neuroscience, building brain models from data and knowledge obtained from neuroscience and medical science and exploiting them for the study of neuronal mechanisms involved in animal and human behaviour and neurodegenerative diseases. We propose to model the brain as a system of active memories in synergy and in interaction with the internal and external world. Special emphasis is given to decision making, focusing on corresponding brain regions (i.e. basal ganglia, amygdala, prefrontal cortex, hippocampus…). These original models also permit to revisit and enrich algorithms and methodologies in machine learning and in autonomous robotics, in addition to elaborate hypotheses to be tested in neuroscience and medicine, while offering to these latter domains a new ground of experimentation similar to their daily experimental studies.

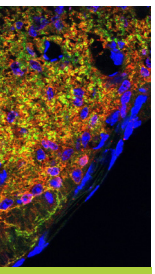
PATHOLOGICAL DECISION-MAKING IN ADDICTION

SERGE AHMED

Our research activities focus on brain mechanisms that explain how situational and individual factors influence the different stages of addiction (i.e., escalation of drug use, transition to compulsion, abstinence, and relapse) to drugs of abuse (i.e., cocaine, heroin and nicotine) and also to other substances, such as sugar and some drug medications. We first seek to recreate in an animal model (i.e., rodents) different "individual x situation" interactions, then we study how these interactions influence substance use behavior and, finally, we attempt to identify the underlying brain mechanisms. Our methodological approach involves a combination of original behavioral and neurobiological procedures and techniques (see below, "Innovative approaches").



INCIA – Institut de Neurosciences Cognitives et Intégratives d'Aquitaine



ORGANIZATION AND ADAPTABILITY OF MOTOR SYSTEMS (OASM)

MURIEL THOBY-BRISSON

The research developed in our team aims to investigate the neural bases of the generation and functional short- and long-term plasticity of motor acts controlled by central neural networks in the context of development, sensory signalling, modulatory influences and post-lesion changes. Our studies examine these processes from the cellular level up to the final integrated behavior, using different animal models (aplysia, xenopus, rodents) and with both in vitro and in vivo approaches. We combine cellular and integrative neurobiology with behavioral analysis. Our main research axis are: 1) Learning-induced plasticity in the feeding network in Aplysia, 2) Developmental adaptation of motor neuronal networks to metamorphic-induced changes in body architecture and physiology, 3) Organization and plasticity of the respiratory network in the mouse embryo. Overall our goal is to better understand the neurobiology of motor systems with a more specific focus on the central neural networks controlling organized motor activities such as breathing, locomotion and feeding behavior.

COORDINATION AND PLASTICITY OF SPINAL GENERATORS (CPGs)

SANDRINE BERTRAND

The aim of the CPGs team is to study spinal neural networks involved in motor functions such as locomotion, respiration and posture. Using an experimental dialogue between neuronal (membrane and synaptic properties), integrative (network operation) and behavioral levels, we aim to determine the mechanisms implicated in motor activity generation and adaptations in physiological and pathophysiological conditions. We are part of the few teams working on the fundamental question of motor network interactions and, to the best of our knowledge, we are the only group so far to address activity-dependent synaptic plasticity in the mammalian motor spinal cord.

DEVELOPMENT OF SPINAL MOTOR NETWORKS (DSMN)

PASCAL BRANCHEREAU

The objective of our team is to understand the mechanisms involved in embryonic development of mammal spinal motor networks in normal and pathological conditions such as amyotrophic lateral sclerosis (ALS). In particular, we focus our efforts on: 1) deciphering the role of first GABAergic interneuron in the genesis of spontaneous activity that is expressed by all immature neural networks at early developmental stages and that drives the maturation of the synaptic transmission and 2) identifying cellular and molecular mechanisms involved in the early motor deficits observed in spinal motoneurons in mouse models of ALS.

HYBRID SENSORIMOTOR PERFORMANCE (HYBRID)

AYMAR DE RUGY

Our research 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 movement. Instead of being pre-programmed in the brain, movement coordination largely depends upon multiple feedback loops that operate at various levels of the sensorimotor control system. For instance, muscle mechanics provides an instantaneous functional response to small perturbations, while spinal and cortical reflexes are able to absorb larger perturbations by coordinating muscles for the complex design of our limbs. Using a range of hybrid systems, we investigate how these lower feedback loops contribute to the production of normal, coordinated movements, and how to exploit them to improve brain machine interfaces and prosthesis controls.

ADDICTEAM

MARTINE CADOR

Our research in rodents investigates the behavioural and neurobiological processes involved in addiction to pharmacological rewards such as cocaine,nicotine and opiates as well as to natural rewards such as sugar. We contributed to a better understanding of the behavioral and biological substratesunderlying 1) the vulnerability to take drugs and 2) to the renewal of drug seeking following abstinence or extinction with specific focus on the synaptic and circuit neuroadaptations at the mesocorticolimbic network level. We are also trying to study specific populations of rodents such as the adolescent population.

DECISION & ADAPTATION (DECAD)

ÉTIENNE 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.

MEMORY INTERACTING NETWORKS UNDER DRUGS AND STRESS (MINDS)

DANIEL BERACOCHEA
VINCENT DAVID

Our research is interested in the interactions between positive or negative emotions and cognitive processes in normal conditions and pathological states (short and long-stress, aging, addiction). Our main project aims at characterizing the neuronal substrates underlying the emotion-memory interactions in normal young adult mice, focusing on epigenetic mechanisms. 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.

NEUROBIOLOGY OF BEHAVIOUR

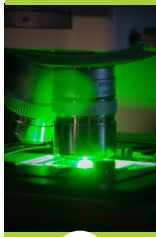
YOON H. CHO

Scientific objectives of the team are to dissect, at the molecular, cellular, synaptic, and network levels, the neural bases of cognitive functions and behaviors in normal and pathological conditions. We cover neural functional changes associated with cognitive and behavioral alterations during neurodevelopment (Fragile X syndrome, Autism spectrum disorder) and neurodegeneration (Huntington's disease, Alzheimer's disease). Special emphasis is placed on multilevel analysis of social behaviors using notably in vivo electrophysiological recordings in freely behaving mice.

SEARCHING TARGETS TO REGULATE STRESS SYSTEMS (STRESS)

ANGELO CONTARINO

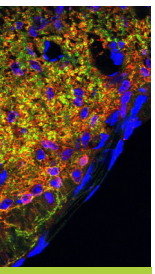
By using rodent models, we aim to understand the brain mechanisms involved in drug-induced vulnerability to stress, cognitive impairments and emotional deficits. Our studies highlighted a major role for the corticotropin-releasing factor (CRF) stress-responsive system in the expression of behavioural hallmarks of substance withdrawal. We also observed a critical, but complex, contribution of the CRF and other stress-responsive systems to vulnerability linked to administration of substances of abuse. Currently, our studies aim at better understanding the mechanisms underlying the long-lasting vulnerability linked to the administration of and to the withdrawal from substances of abuse. We also strive to identify the genes encoding neuropeptide precursors in transgenic Drosophila models. Neuropeptides are instrumental in orchestrating complex physiological and adaptive behavioural processes, ranging from drug responses to stress vulnerability/resilience. Through genetic-driven loss/gain of function, we investigate the role of a relatively large variety of neuropeptides and their function to control behaviour. We also are interested in the evolution of the neuropeptide repertoire along different animal species.



BRAIN MOLECULAR IMAGING

JÉRÔME BADAUT,
PAOLO ZANOTTI-FREGONARA

Single or repeated mild traumatic brain injury (mTBI) may be associated with transitory change of mental status, cognitive impairment and neurodegeneration. Traditional neuroimaging techniques may not detect any abnormality and the diagnosis of mTBI usually relies only on the patient's verbal report. Through a translational approach and by developing quantitative PET imaging techniques associated with MRI neuroimaging, our research focuses on the characterization of the pathophysiological changes following mTBI. In particular, we aim to quantify neuroinflammation and to identify new targets to reduce the neurovascular alterations and edema following injury.



NEUROIMAGING AND HUMAN COGNITION

IGOR SIBON
JOEL SWENDSEN

Our research explores the anatomical integrity and functional connectivity of brain regions and networks underlying cognitive processes associated with brain-based disorders, in particular for neurovascular conditions, cognitive decline and dementia, and psychiatric syndromes. The novel methodological contribution of our research is found in the combination of multimodal imaging techniques with mobile technologies (smartphones, actigraphy and connected devices). This combination allows us to examine how brain markers are associated with changes in daily life functioning and symptom expression in real-time, as well as to identify more subtle (or early) markers of dysfunction through neuroimaging. In addition to providing descriptions of the pathophysiology of these conditions, a significant portion of our investigations is applied to improving treatment and prevention strategies.

AUDITORY PERCEPTION TEAM (APT)

LAURENT DEMANY

Our team conducts experimental and clinical research on human auditory perception and memory using mainly the methods of psychophysics. The scope of research covers normal hearing and the perceptual consequences of cochlear damage. Our most recent studies have been concerned with the phenomenon of harmonic fusion, auditory divided attention, and the perceptual salience of sounds as a function of their temporal profile.

NutriNeuro

NUTRITION AND PSYCHONEUROIMMUNOLOGY: EXPERIMENTAL AND CLINICAL APPROACHES

LUCILE CAPURON
SOPHIE LAYÉ

The aim of our research is to elucidate the role of nutrition in neuropsychiatric disorders. We develop translational approaches from animal models to humans and vice et versa to study 1) the relationshipbetween lipid nutrition and neuroimmune interactions in depression, 2) the neurobiological mechanisms involved in the neuropsychiatric comorbidities of obesity 3) the molecular and cellular mechanisms of n-3 polyunsaturated fatty in neuroinflammation and mesolimbic system 4) the development of specific nutritional approaches to prevent neuropsychiatric disorders in animal models and humans.

NUTRITION, MEMORY AND GLUCOCORTICOIDS

MARIE-PIERRE MOISAN
GUILLAUME FERREIRA

It is now well established that the evolution of memory across life depends on our lifestyle and that nutrition determines strongly brain health. The main goal of our team, in a perspective of healthy brain aging, is to better understand i) how unbalanced diets alter memory processes and ii) how nutritional supplementation can correct or prevent such memory decline. Two populations vulnerable to memory decline are targeted: obese children/teenagers and aged people. At the mechanistic level, the impact of nutritional status on glucocorticoids regulation is specifically studied since glucocorticoids play a critical role in memory processes as well as in metabolic response to nutrition. These scientific questions are examined through animal studies by behavioral, molecular and cellular approaches but also through clinical studies (Nutrimemo, Neurophenol, Corticodiab, Obeteen).

SANPSY

SLEEP, ATTENTION, NEUROPSYCHIATRY

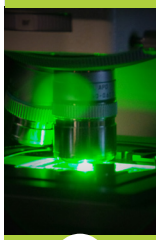
PIERRE PHILIP

SANPSY is dedicated not only to phenotype humans but also to better understand the main determinants of neuropsychiatric diseases. Our research explores the human characteristics accounting for the vulnerability or resistance to sleepiness, attention deficit and pathological cognitive decline. For this aim we combine electrophysiology, chronobiology, cognitive psychology and original technologies (simulation and virtual reality). Identify new innovative biomarkers for individual vulnerabilities to these disorders and the development of personalized treatments or countermeasures both in patients with neurological or psychiatric disorders and healthy subjects are also major scientific challenges for our unit. We also develop and validate embodied conversational agents for the diagnosis and the treatment of neurological and psychiatric diseases.

ADDICTION AND PSYCHIATRY

MARC AURIACOMBE

Our research is focused on commonalities of appetitive behaviors in humans. Appetitive behavior is the phenomenology of addiction. The focus of our research is on determinants of relapse in appetitive behaviors whether related to substances (tobacco, alcohol, cannabis, heroin, cocaine and other drugs) or such other appetitive behaviors as gambling, internet use, food intake, etc. The objective is to better characterize the phenomenology of addictive behavior and its determinants. A multidisciplinary approach is used, drawing on the research models of clinical neurobiology, epidemiology, psychology and sociology and is implemented with innovative techniques such as advanced mobile technologies that allow us to record data in the natural environment of live humans. The main research tool is an open prospective cohort of over 3500 patients: the Addiction Aquitaine Cohort (ADDICTAQUI). We have created a Human model of relapse based on individual cues and craving. Our research has paramount implications for science-based diagnosis, treatment and prevention of addiction.



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→ **Pictograms :** The noun project

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