Scientific report

LABEX

BRAIN

HIGHLIGHTS OF THE PERIOD 2011-2014:

- 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

- Increased **collaborative projects** (60 collaborative projects submitted to LabEx calls)

- **Tripling the number of papers published in journals of Impact Factor>10** between 2010 and 2014

- Attraction of a large amount of co-funds (**Total 42 M€; 13,5M€ from ANR and 8,6M€ from Regional Council, 5,6M€ from European Commission).**

- Regular interactions with **venture capital**, one project coached

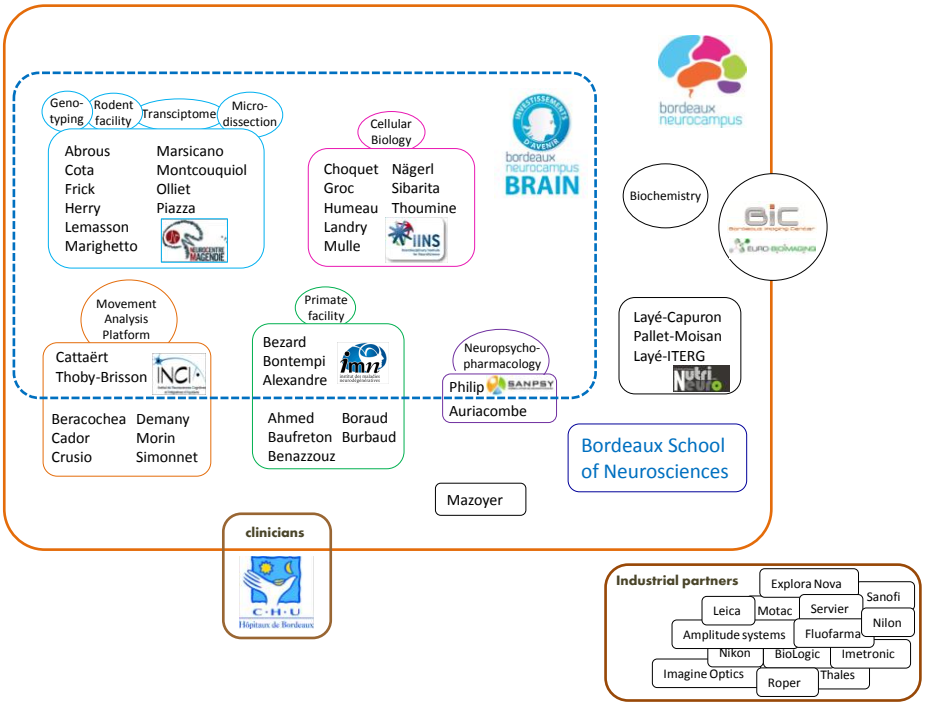
- **Selection of the Bordeaux Imaging Center within the European Infrastructure EuroBioImaging**

1. PROGRESS OF THE PROJECT

1.1 GOVERNANCE (INITIATION, ORGANIZATION AND PROJECT GOVERNANCE, MANAGEMENT AND MONITORING SYSTEMS, WAY OF INVOLVEMENT OF CONCERNED RESEARCH UNITS' DIRECTORS)

ORGANISATION OF THE NEUROSCIENCE COMMUNITY IN BORDEAUX:

Neuroscience research in Bordeaux is organized in 5 main independent research centres and institutes and a few smaller teams encompassing a total of 600 scientists. Scientists have access to 10 core facilities and the Bordeaux School of Neuroscience. All these institutes, teams and facilities are federated in Bordeaux Neurocampus.



The BRAIN LabEx project gathers 24 teams of excellent international level that collaborate to address a selected number of the major transversal challenges in modern neuroscience. Selection of the teams participating to the core of BRAIN has been performed following the ranking by the AERES evaluation international committee in 2010. The perimeter will be discussed following the 2015 AERES report.

LABEX BRAIN GOVERNANCE AND INVOLVEMENT OF CONCERNED RESEARCH UNITS' DIRECTORS

The setting-up of committees ensures the smooth implementation of the LabEx BRAIN program.

The University of Bordeaux is the sole coordinator of the "Investments for the future" projects, named PIAs (Excellence Initiative, LabEx, Cohort, EquipEx).

The board of trustees: comes under the aegis of the Investissements d'avenir steering committee of the University of Bordeaux, which is responsible for supervising all the Investissements d'avenir projects selected in Bordeaux and for approving BRAIN strategy for growth.

The steering committee: is composed of representatives of the five partners according to the laboratory's size. Daniel Choquet is the Director. The members and director are nominated for a 4-year period. The committee meets on a quarterly basis to vote the budget, to implement the general guidelines, to vote the launching of call for proposals, and to select projects.

The board of directors: is composed of three adjunct directors in charge of technology transfer, training and clinical relations and the Neurocampus project coordinator, may be appointed by the director and meet to prepare steering committee.

Among the 5 Units laboratories directors of the LabEx, 4 are part of the steering committee and members of the board of directors.

The External Scientific Advisory Board (ESAB): The members are all highly qualified international academics (currently Arthur Konnerth; Yadin Dudai; Carmen Sandi; Rob Malenka; Claudio Bassetti; Serge Przedborski). The committee advices on the overall policy and plays an advisory role regarding entry and exit of teams from BRAIN. Recommendations of the ESAB are transmitted to the steering committee. They meet every 2 years. The first meeting took place in May 2014. (http://brain.labex.u-bordeaux.fr/Actualites/BRAIN-Scientific-Advisory-Board-meeting,i1940.html http://brain.labex.u-bordeaux.fr/Actualites/Scientific-Advisory-Board-Meeting,i1887.html)

General procedure of the call for proposals and Monitoring systems

The LabEx BRAIN launches calls for proposals for the scientific projects (transversal, transfer and clinical projects) the PhD extension grant, the 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 news letter.

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, pluridisciplinarity and innovation.**

Monitoring systems: We analyze every other year the impact of the selected project on **additional grant obtained, publications published and in progress**. For core facility, we evaluate the **degree of opening 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 and the user list. We also ask for a report on the symposium activity, reporting the number of participant and speakers, from Bordeaux, vs French vs international laboratories.

1.2 Research

Transversal projects

The LabEx BRAIN calls provide a powerful framework to **encourage interdisciplinary collaborations and to strengthen the Bordeaux Neurocampus scientific community**. The scientific impact of the calls is described on section 2A.

Evolutions of the call for proposals procedure: Our efforts have first been organized and concentrated **around 5 major transversal projects** (scientific axis description in section 2A). In 2011, each research axis was attributed a lump sum of 95 K€; launched under the responsibility of the axis coordinators (2 coordinators per axis belonging to different laboratories) its own call for proposal and selection. The projects lasted one year. 9 projects were supported for a total of 475k€.

In 2012, **we modified the procedure according to the community suggestions**. We therefore decided to 1) follow a **general procedure** of an open call, with a common evaluation procedure of the projects, 2) open an additional "**blue sky axis**", expending the eligible topics to all neuroscience research area, and 3) open the eligibility to researchers belonging to **Bordeaux Neurocampus teams**

outside core LabEx. Projects could last up to 24 month. 26 projects were submitted and we could select for funding 14 projects, for a total amount of 700k€.

We established a **report on the scientific impact of the LabEx**. Following the SAB recommendations, we launched a 3rd call for proposal in 2014 where the **initial scientific axes disappeared** to become priority topics and where Bordeaux Neurocampus teams outside LabEx could be PI. The global amount of the call was significantly increased. We received 34 proposals, and we could select for funding 11 projects, represented a total of 1.2M€.

In 2015, according to the SAB suggestions and LabEx objectives, the steering committee decided to focus on **applied and clinical research** and 2 specific calls for proposals were launched.

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 the Bordeaux Neurocampus teams, with a reduced price. The concerned facilities are animal facilities (rodent and primate facilities, genotyping), molecular and cellular facilities (biochemistry, transcriptome, microdissection), imaging facility (the Bordeaux Imaging Center), and clinical facilities (movement analysis platform and neuropsychopharmacology).

1.3 TRAINING

PHD EXTENSION GRANTS

The LabEx BRAIN offers to students from Bordeaux a fellowship to complete their Ph.D thesis, immediately after a 3 year Ph.D, covering up a period to finish projects before leaving for a post-doc. In 2012, we selected 5 proposals out of 14 received; in 2013 and 2014, we selected 8 proposals each year out of 24 and 15 proposals received respectively. **We plan to follow on this call for proposal for the further years as this tool has been ranked by all team leaders as extremely useful and very popular.**

TRAINING PROGRAMS

We are involved **in international masters** (ISIS: Euro-Mediterranean master's degree in neurosciences and biotechnologies, Neurasmus and bio-imaging), coordinators of the PhD international programs, the Marie Curie Initial Training Network SyMBaD, the summer schools EScube and NutriBrain.

BORDEAUX SCHOOL OF NEUROSCIENCE-BSN

Unique in Europe, the vocation of the BSN is to offer the international/European Community a **platform of high technological level,** giving the opportunity **to organize training for research in neuroscience based on experimental practice.**

The BSN has been selected by FENS/IBRO to be the major partner site of the Cajal Advanced Neuroscience Training Program. This means that BSN will provide infrastructure and logistic support for the organization of 4-6 FENS courses (2-4 weeks/course) per year. The first two sessions will start 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 guarantee from IdEX Bordeaux (100k€ for the first year) and will be sought from the Regional Government.

1.4 Result exploitation

Venture capital connections

An important advance in result exploitation is that in 2013, **we got closer to venture capital** and started a series of meeting to present our team's skills and ongoing transfer projects. The venture team selected in 2014 one project and **has been coaching this project since one year**. We meet the venture capital on a regularly basis and present applied research projects and increase opportunities to make use of research results.

Call for proposal on applied projects

During the first 3 years of activities, the LabEx BRAIN has been supporting basic research within the scientific open call for proposal. In 2015, **we launched a new program for transfer and applied research** that will fund applied biological and biomedical research projects with a strong potential economic impact. The selected projects will regard discovery, development or optimization of innovative therapeutic or diagnostic products; as well as valorization of research tools dedicated to the discovery of new therapeutic or diagnostics. The projects selection will occur in May 2015.

1.5 Visibility, outreach, sharing and promoting actions of the LabEx (specify the targets and the corresponding dedicated funding)

To increase Bordeaux Neuroscience visibility at the international scientific level, the LabEx BRAIN has supported a total of **20 international symposiums** organized in Bordeaux and launched in 2014 the **International Bordeaux Neurocampus BRAIN Conferences** (see details in section 3.4). The total of the LabEx funding dedicated to scientific symposium from 2001 to 2014 is 133k€.

Bordeaux Neurocampus and the LabEx BRAIN were represented at the FENS 2014 in Milan as exhibitor in a booth.

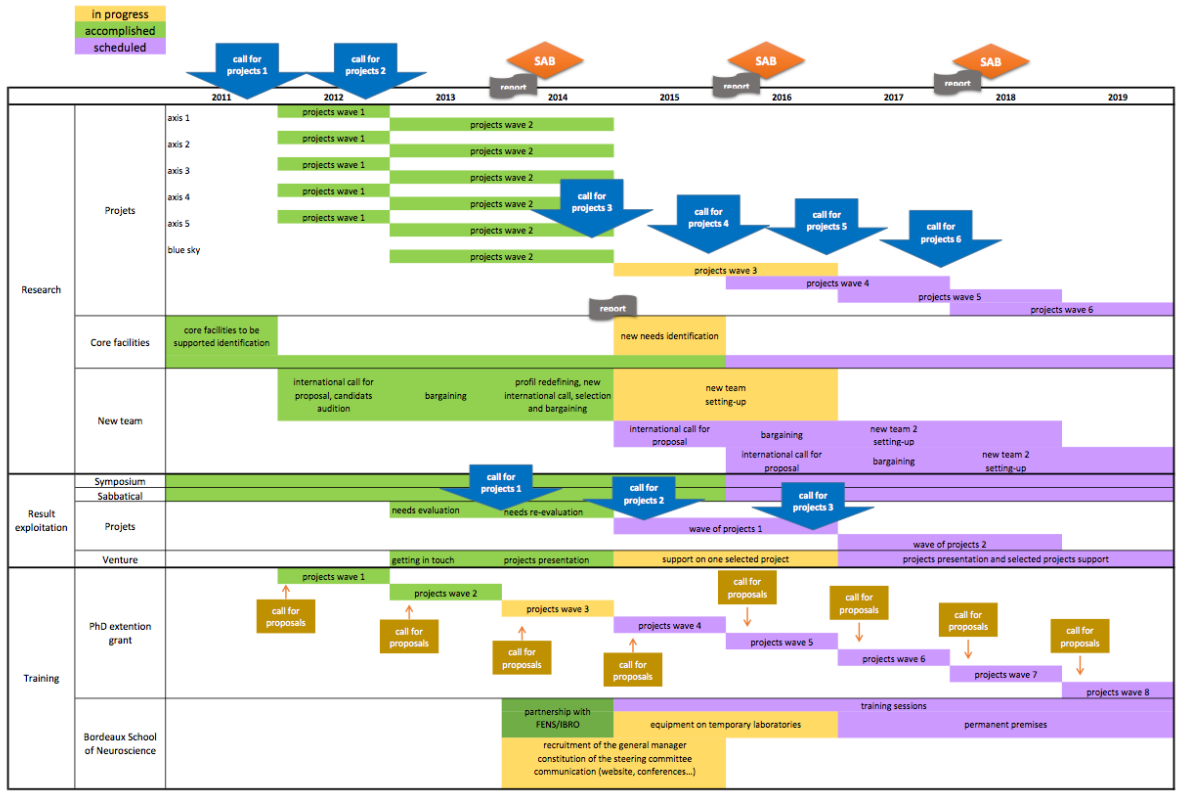
We are also involved in **popularization**; the different actions are described in section 3.4

Together with Fondation Bordeaux Université, we are working on a **fundraising strategy**.

2/ Label and associated funding impact

2.1 SCIENTIFIC ACHIEVEMENT DESCRIPTION

GLOBAL VIEW OF ACCOMPLISHED AND SCHEDULED ACTIONS:



SWOT ANALYSIS

Strengths:

-*Integration:* Among the LabEx impacts, we note the **increase in Inter-institutes collaborations** revealed by the publications (10 intra-LabEx collaborations in 2012; 25 in 2013, and 26 in 2014), the **new collaborations between basic and clinical teams** and speeding up **the structuring** of neuroscience teams in Bordeaux, initiated in 1993, by adding significant funding.

-*Attractiveness:* we were partner of **20 international symposia in Bordeaux** and we launched a new series of high visibility conferences together with Bordeaux Neurocampus (see section3.4). We are an **international research community**, hosting PhD students, post-docs and researchers from over 20 different nationalities. We are **involved in international training programs** (see below) and **the Bordeaux School of Neuroscience** is a unique hands-on training center in Europe, with a partnership with IBRO and FENS.

-*Excellence*: we facilitated the acquisition **high-end of equipment and specialized engineers services in the core facilities** in fields from molecular and cellular biology to clinical research through animal facility and imaging. The quality of the service offer has international recognition as **the Bordeaux Imaging Center (BIC) has been labeled by EuroBioImaging** as a European Imaging Facility. The "PhD extension grant" impacts on the **quality of the published paper**s as many papers from PhD students who received the LabEx supports are published in high impact factor journals (a total of **27 papers** from the 21 supported candidates, included 1 Nature, 1 cell, 2 Nature Neuroscience, 2 Neuron, 2 EMBO J, 3 PNAS, 1 J Clin Invest, 1 Cell Biol...)

Weaknesses:

-lack of coherence in the visibility: of the neuroscience community caused by the multiple governance authorities in Bordeaux Neurocampus and a lack of a global communication strategy resulting in a multiple communication actions.

- No international PhD program

Opportunities:

- ***Increase capacity:*** the Neurocampus project: 75 M€ (delivery in 2016) to build 12 000 m² of new lab space to rationalize animal facilities and the imaging center and attract new international teams.

- ***Investment funds:*** IdEx program to reinforce inter-labEx collaborations, attractiveness program, CPER (regional support to infrastructure)

Threats:

- Decrease in local (IdEx and CRA) and national support

- Unbalanced focus on applied research from governing bodies (national and local)

Strategy:

- According to SAB advices, pursue successful programs and steer **towards more call for projects**, increasing the non-thematic call for projects, pursue the phD extension grants, support to facilities and symposium

- **Attracting new teams**: we dedicate a package to attract 6-8 new and/or emerging team composed by 1,8 M€ from LabEx BRAIN. The Neurocampus project involvement has to be secured. The main criterion is excellence, and we will try to fill gaps in the several thematic including, in particular but not exlusively: in vivo imaging, development, model organisms, clinical research, physical chemistry, biosensors

-**Increase European visibility and training, with the creation of the Bordeaux School of Neuroscience and the European labeled of 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 improve governing bodies' awareness on neuroscience.

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

DEVIATION FROM THE INITIAL WORK PLAN

Overall there has been little deviation from the initial work plan. However, we report that:

- More spending has been allocated to the core-facilities than initially planned to allow acquisition of equipment and ramping up of the facilities

- We only recently (in 2015) performed a call for proposal regarding translational projects.

- We have been able to create only one new team, less than initially planned. This is mainly a consequence of the shortage of space and delay in the construction of the new building.

Synapse level

The Bordeaux teams made key progress in unraveling the structure function properties of receptors involved in synaptic transmission. Focusing on the glutamatergic synapse, **Veran et al (Neuron. 2012)** showed that zinc binding stabilizes the labile GluK3 dimer interface, slows desensitization, and potentiates currents, providing a mechanism for KAR potentiation at glutamatergic synapses. **Papouin et al (Cell. 2012)** reported that synaptic and extrasynaptic NMDARs are gated by different endogenous coagonists, d-serine and glycine, respectively. Furthermore, glycine and d-serine inhibit NMDAR surface trafficking in a subunit-dependent manner, which is likely to influence NMDARs subcellular location. Taking advantage of this coagonist segregation, they demonstrated that long-term potentiation and NMDA-induced neurotoxicity rely on synaptic NMDARs only. Conversely, long-term depression requires both synaptic and extrasynaptic receptors. **Sainlos et al (Nat Chem Biol. 2011)** investigated the interactions of the AMPA receptor (AMPAR) auxiliary subunit Stargazin with PDZ domain-containing scaffold proteins, by developing biomimetic competing ligands. Their results provide evidence for a model in which the TARP-containing AMPARs are stabilized at the synapse by engaging in multivalent interactions. How AMPAR diffusion within the synapse regulates synaptic transmission on the millisecond scale remains mysterious. **Constals et al (Neuron. 2015)** demonstrated that transition from the activated to the desensitized state leads to partial loss in AMPAR-stargazin interaction that increases AMPAR mobility and allows faster recovery from desensitization-mediated synaptic depression, without affecting the overall nano-organization of AMPAR in synapses. **Pougnet et al (Neuron 2014)** demonstrated that postsynaptic P2XRs, ATP-gated cation channels widely expressed in the brain where they mediate action of extracellular ATP released by neurons or glia, play a critical role in regulating the surface expression of AMPARs and thereby regulate the synaptic strength. **Hafner et al (Neuron. 2015)** used a combination of high resolution imaging and biochemical approaches to dissect the inner mechanisms that underlie activity dependent AMPA receptor stabilization. **Letellier et al (Nat Neurosci. 2014)** investigated whether microRNAs could regulate AMPA receptor expression during activity blockade and reported that miR-92a regulates expression of synaptic GluA1-containing AMPA receptors during homeostatic scaling. **Bénard et al (Nat Neurosci. 2012)** revealed a new mechanism of action of G protein-coupled receptor signaling in the brain: they showed that the type-1 cannabinoid receptor (CB(1)) is present at the membranes of mouse neuronal mitochondria (mtCB(1)), where it directly controls cellular respiration and energy production.

Building on the strength of Bordeaux in high resolution imaging, several groups made key progress in understanding of synaptic morphofunctional properties. Because mossy fiber synapses display LTP selective for NMDARs, **Rebola et al (Nat Neurosci. 2011)** examined whether this would affect the plasticity rules at mossy fiber-CA3 synapses in mouse hippocampal slices. They founded that LTP of NMDARs serves as a metaplastic switch making mossy fiber synapses competent for generating NMDAR-dependent LTP of AMPA EPSCs. **Carta et al (Neuron. 2014)** showed that direct modulation of presynaptic Kv channels by activity-dependent release of lipids serves as a physiological mechanism for tuning synaptic transmission. The quantitative contribution of spine morphology to synapse compartmentalization and its dynamic regulation are still poorly understood. **Tønnesen et al (Nat Neurosci. 2014)** used time-lapse super-resolution stimulated emission depletion (STED) imaging in combination with fluorescence recovery after photobleaching (FRAP) measurements, two-photon glutamate uncaging, electrophysiology and simulations to investigate the dynamic link between nanoscale anatomy and compartmentalization. They established a close link between compartmentalization and spine morphology, and demonstrated that spine necks are plastic structures. Using single protein tracking and super-resolution imaging, **Chazeau et al (EMBO J. 2014)** revealed the nanoscale organization and dynamics of branched F-actin regulators in spines. Their results suggested that the specific localization of branched F-actin regulators in spines might be reorganized during spine morphological remodeling often associated with synaptic plasticity. The

group of N. Sans and M. Montcouquiol works on the planar cell polarity, the precise migration of the primary cilium at the apical surface of the cells, also referred to as translational polarity. They observed **(Ezan et al, Nat Cell Biol. 2013)** that primary cilium migration depends on G-protein signalling control of subapical cytoskeleton.

A fundamental question is our understanding of synapse function in disease. Indeed, the plasticity of excitatory synapses is an essential brain process involved in cognitive functions, and dysfunctions of such adaptations have been linked to psychiatric disorders. **Zhang et al (Mol Psychiatry. 2013)** provided the first evidence that a therapeutically used drug, here the cognitive enhancer and antidepressant tianeptine, targets the surface diffusion of AMPAR through a CaMKII-stargazin-PSD-95 pathway, to promote long-term synaptic plasticity. At the synapse, Shank3/ProSAP2 is a scaffolding protein that connects glutamate receptors to the actin cytoskeleton. Although genetic studies have repeatedly confirmed the association of SHANK3 mutations with susceptibility to psychiatric disorders, very little is known about the neuronal consequences of these mutations. **Durand et al (Mol Psychiatry. 2012)** reported the functional effects of two de novo mutations (STOP and Q321R) and two inherited variations (R12C and R300C) identified in patients with autism spectrum disorder, providing new insights into the synaptic alterations caused by SHANK3 mutations in humans and provide a robust cellular readout for the development of knowledge-based therapies. **Zhang et al (Nat Neurosci. 2014)** provided strong evidence pointing to the utility of BKCa channel openers for the treatment of the sensory hypersensitivity aspects of Fragile X Syndrome and autism spectrum disorders. **Fossat P et al (Science. 2014)** demonstrated that crayfish exhibit a form of anxiety similar to that described in vertebrates, suggesting the conservation of several underlying mechanisms during evolution. Analyses of this ancestral behavior in a simple model reveal a new route to understanding anxiety and may alter our conceptions of the emotional status of invertebrates.

In the field of chronic pain, characterized by long-term sensitization of spinal cord neurons that relay nociceptive information to the brain, **Favereaux et al (EMBO J. 2011)** identified a single microRNA, miR-103, as a novel possible therapeutic target in neuropathic chronic pain.

Some groups developed high-end methods to selectively address specific synapses. Indeed, studying the roles of different proteins and the mechanisms involved in synaptogenesis is hindered by the complexity and heterogeneity of synapse types, and by the spatial and temporal unpredictability of spontaneous synapse formation. **Czöndör et al (Nat Commun. 2013)** demonstrated a robust and high-content method to induce selectively presynaptic or postsynaptic structures at controlled locations that opens the way to both fundamental and therapeutic studies of various synaptic systems. **Biesemann et al (EMBO J. 2014)** established a novel Fluorescence Activated Synaptosome Sorting (FASS) method that enables high-resolution biochemical analyses of specific synapse subpopulations in health and disease.

Plasticity and memory storage

A peculiar strength of Bordeaux is plasticity and memory storage. **Combining behavioral, molecular and optogenetic approaches, major progress has been obtained towards understanding of brain wiring. Lesburguères et al (Science. 2011)** presented evidence that neurons in the rat cortex must undergo a "tagging process" upon encoding to ensure the progressive hippocampal-driven rewiring of cortical networks that support remote memory storage, a crucial neurobiological process for remote memory formation whose functional properties fit the requirements imposed by the extended time scale of systems-level memory consolidation. Posttraumatic stress disorder (PTSD) is characterized by a hypermnesia of the trauma and by a memory impairment that decreases the ability to restrict fear to the appropriate context. **Kaouane et al (Science. 2012)** reported that infusion of glucocorticoids in the hippocampus after fear conditioning induces PTSD-like memory impairments and an altered pattern of neural activation in the hippocampal-amygdalar circuit. Mice become unable to identify the context as the correct predictor of the threat and show fear responses

to a discrete cue not predicting the threat in normal conditions. These data demonstrate PTSD-like memory impairments in rodents and identify a potential pathophysiological mechanism of this condition. Although neuronal synchrony has been demonstrated to be crucial for sensory, motor and cognitive processing, it has not been investigated at the level of defined circuits involved in the control of emotional behaviour. **Courtin et al (Nature. 2014)** used single-unit recordings and optogenetic manipulations in behaving mice to show that fear expression is causally related to the phasic inhibition of prefrontal parvalbumin interneurons (PVINs). Inhibition of PVIN activity disinhibits prefrontal projection neurons and synchronizes their firing by resetting local theta oscillations, leading to fear expression. The results identify two complementary neuronal mechanisms mediated by PVINs that precisely coordinate and enhance the neuronal activity of prefrontal projection neurons to drive fear expression. The findings of **Revest et al (Mol Psychiatry. 2014)** complete our knowledge of the molecular cascade through which GC enhance contextual fear memory and highlight the role of tPA-BDNF-TrkB-Erk1/2(MAPK) signaling pathways as one of the core effectors of stress-related effects of GC.

Food intake

Our understanding of the regulation of appetite has improved considerably over the last few decades. **Recent works from Bordeaux teams have unraveled some of the complex pathways regulating energy homeostasis**. **Soria-Gómez et al (Nat Neurosci. 2014)** data indicate that cortical feedback projections to the main olfactory bulb crucially regulate food intake via CB1 receptor signaling, linking the feeling of hunger to stronger odor processing. Thus, CB1 receptor-dependent control of cortical feedback projections in olfactory circuits couples internal states to perception and behavior. The corollaries of the obesity epidemic that plagues developed societies are malnutrition and resulting biochemical imbalances. **Lafourcade et al (Nat Neurosci. 2011)** found that lifelong nutritional omega-3 deficiency specifically ablates long-term synaptic depression mediated by endocannabinoids in the prelimbic prefrontal cortex and accumbens and that the dietary-induced reduction of CB(1)R functions in mood-controlling structures was associated with impaired emotional behavior.

Parkinson disease

Bordeaux Neurocampus teams are working hard to discover the mechanism of action of Parkinson disease on order to develop new treatments to help patients living with Parkinson's, a chronic, progressive neurological disease. Among the main advances regarding Parkinson's research made by our groups we can cite the observations of **Tass et al (Ann Neurol. 2012)** that encourage further development of coordinated reset neuromodulation, a hallmark feature of Parkinson's disease pathophysiology, for treating motor symptoms in Parkinson disease patients. Indeed, they showed that coordinated reset neuromodulation of the subthalamic nucleus has both acute and sustained long-lasting aftereffects on motor function in parkinsonian nonhuman primates. **Porraset al (J Clin Invest. 2012)** demonstrated in rat and macaque models that disrupting the interaction between D1R and PSD-95 in the striatum reduces L-DOPA-induced dyskinesia development and severity. Single quantum dot imaging revealed that this benefit was achieved primarily by destabilizing D1R localization, via increased lateral diffusion followed by increased internalization and diminished surface expression. These findings indicate that altering D1R trafficking via synapse-associated scaffolding proteins may be useful in the treatment of dyskinesia in Parkinson's patients.

Dopamine dysregulation syndrome shares some core behavioral features with psychostimulant addiction, suggesting that dopamine replacement therapy can acquire psychostimulantlike properties in some patients with Parkinson disease (PD). **Engeln et al (Ann Neurol. 2013)** reported strong experimental evidence supporting this hypothesis in an α-synuclein rat model of PD. Although levodopa had no effect in controls, it acquired 2 prominent psychostimulantlike properties in Parkinsonian rats: (1) it produced intense reward on its own and in parallel (2) decreased interest in

other nondrug reward. These 2 effects may combine to explain the addictive use of levodopa after loss of midbrain dopamine neurons in some PD patients.

Addiction

A group of Bordeaux Neurocampus has made a major discovery which opens up promising therapeutic approaches for the treatment of addiction to cannabis. Effective treatments for cannabis use disorders are critically needed. Pregnenolone is considered the inactive precursor of all steroid hormones, and its potential functional effects have been largely uninvestigated. **Vallée et al (Science. 2014)** observed that the administration of the main active principle of Cannabis sativa (marijuana), Δ(9)-tetrahydrocannabinol (THC), substantially increases the synthesis of pregnenolone in the brain via activation of the type-1 cannabinoid (CB1) receptor. Pregnenolone then, acting as a signaling-specific inhibitor of the CB1 receptor, reduces several effects of THC. This negative feedback mediated by pregnenolone reveals a previously unknown paracrine/autocrine loop protecting the brain from CB1 receptor overactivation that could open an unforeseen approach for the treatment of cannabis intoxication and addiction. Defining the drug-induced neuroadaptations specifically associated with the behavioral manifestation of addiction is a daunting task. **Kasanetz et al (Mol Psychiatry. 2013)** were able to describe the specific synaptic impairments in the pPFC associated with addiction and supported the idea that alterations of synaptic plasticity are core markers of drug dependence.

NEW NATIONAL AND INTERNATIONAL SCIENTIFIC PARTNERSHIPS RELATED TO THE DEVELOPMENT OF THE LABEX

Research:

International:

The LabEx teams have international recognition and collaborate with many international groups. The number of international collaborations has doubled between 2011 and 2014, measurable effect on co-signatory groups on Bordeaux-Neurocampus publications.

IdEx Bordeaux developed several collaborations with international universities. As part of the IdEx Bordeaux, we also developed collaborations in the context of the visit of **Kyoto University** delegation in Bordeaux. The Japanese colleagues visited the Bordeaux Imaging Center.

We have strong relationships with **Quebec**. (i.e with **Laval University** through the Neurophotonics Meeting and through the Nutrineuro laboratory; we are in discussion with **McGill** directors to facilitate the collaborations, most probably with the offer of grants for student/post-doc exchanges). We also were involved in the IdEx/**Euskampus** scientific meeting organizing a symposium.

Local :

In 2014, the LabEx Brain call for proposals, in accordance with the IdEx strategy, encouraged inter-labEx collaborations. Supported by IdEx Bordeaux and the LabEx BRAIN, the project **ExtraBrain** involves a consortium of teams from BRAIN and the **cluster Laphia**. The project is based on a set of innovative multidisciplinary approaches, from optical nano-imaging reporters to state-of-the-art rodent and primate Parkinson's disease models. The project tests the original hypothesis that the extracellular space dynamics plays a pivotal role in receptor physiological signaling and in a cell-to-cell prion transfer model of Parkinson's disease.

The project **SuperClass** aims at reinforcing a newly started collaboration with a bioinformatic research group from **the cluster CPU** to develop new acquisition, quantification and classification methods for HCS super-resolution microscopy. Through this collaborative work, we expect to provide an integrated solution for multi-well plates observation to monitor active protein organization and dynamics under several tens conditions accompanied by rigorous classification methods.

The objective of the translational research project **Transfear** conducted with researchers from the **LabEx TRAIL** is 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.

Training:

The Bordeaux School of Neuroscience has a **partnership with FENS and IBRO** within the Cajal Advanced Neuroscience Training Program.

We are involved in international trainings, with the **coordination of the Marie Curie Initial Training Network SyMBaD** ("Synapses: from Molecules to higher Brain function and Diseases"), ENI-Net network, ENC network (European Neuroscience Campus), Erasmus Mundus networks at Master and Doctoral levels, the Summer Schools ESCube and NUTRIBRAIN.

DESCRIBE THE CALLS FOR PROJECTS: OBJECTIVES, METHODS AND DESCRIPTION OF FUNDED PROJECTS.

Five scientific projects, resulting from a combination of bottom-up and top down approaches were first identified and described in the BRAIN program. They all transversally involve teams from different partner research centres and all reflect our motto: "From molecules to behaviour for understanding brain function and its pathologies".

The LabEx BRAIN supported transversal scientific projects for 2,7M€ through 3 call for proposals (500k€ in 2011-2012, 1M€ in 2012-2013; 1,2M€ in 2014-2015). **The projects selected during the first 2 calls for proposals were so far able to get 4,7M€ of co-funds** (from 7 ANR grants, 2 FRM grants, 1 Eranet, 2 grants from the french foundation eating health, 1 OSEO grant, 1 PHRC grant, 1 PEPS-IdEx-CNRS). **The research teams published 17 publications from these projects and 14 papers are in preparation**.

Among the main results, we can cite the following:

In the axis Patho-Dyn-Syn, the teams of Laurent Groc (IINS) and Stéphane Oliet (NCM) recently published their results in Nature Neuroscience from the LabEx project “Membrane dynamics of astrocytic glutamate transporter and its functional impact on synaptic functions”. The control of the glutamate time course is mainly ensured by astrocytic transporters. **Murphy-Royal et al (Nature Neuroscience 2015) provided the first evidence for a physiological role of GLT-1 surface diffusion in shaping synaptic transmission.**

The LabEx brain project “Role of neuronal and astroglial CB1 receptors in morpho-functional plasticity of the tripartite synapse”, had his first results published in 2013 **(Bethge et al (Biophys J. 2013)**). Indeed, the teams of Giovanni Marsicano (NCM) and Valentin Nägerl (IINS) were able to imaging the morphology of dendritic spines and microglial cells well below the surface of acute brain slices using a nanoscopy approach. Indeed, they developed a new microscope based on two-photon excitation and pulsed stimulated emission depletion microscopy, which provides unprecedented spatial resolution and excellent experimental access in acute brain slices using a long-working distance objective. **The new microscope improves on the spatial resolution of a regular two-photon microscope by a factor of four to six, and it is compatible with time-lapse and simultaneous two-color superresolution imaging in living cells**.

In the axis Ipsynet, **Andreas Frick (NCM) and Christophe Mulle (IINS) developed a tool providing new possibilities for the investigation of the anatomy and physiology of neural circuits** for their project “Unraveling the anatomical wiring diagram to understand the physiology and pathophysiology of the hippocampus and neocortex”. They used (**Haberl et al (Brain Struct Funct. 2014)**) a vector that permits the unambiguous long-range and fine-scale tracing of the entire axonal

arbor of individual neurons throughout the brain. Notably, this level of labeling can be achieved following infection with a single viral particle. The vector is effective over a range of ages (>14 months) aiding the studies of neurodegenerative disorders or aging, and infects numerous cell types in all brain regions tested.

Within the axis MAD, the project "Psychobehavioral characterization of addiction", lead by **Daniela Cota (NCM), Pierre Philip (SanPsy) provided a quantitative and objective measurement of motivational states in humans.** Using a novel experimental computer-based and easy-to-use tool, **Aouizerate et al (BMC Psychol. 2015)** observed that hunger specifically affects the perception of visual food stimuli. Véronique Deroche Gamonet and Cyril Herry studied loss of control over drug taking in their project "Specifying the brain circuits involved in pathological incentive responses and the loss of control over drug taking during the development of addiction". **Martín-García et al (Neuropsychopharmacology. 2014)** observed that high-frequency intake promotes a prelimbic-dependent control of cocaine seeking, with the prelimbic exerting a facilitatory or inhibitory effect, depending on operant contingencies. Thus, individual differences in cocaine-induced prelimbic activation might be a source of vulnerability for poorly controlled cocaine-induced seeking and/or cocaine intake.

Projects supported in the Itera-AMC and Itera-MSA axes are based on clinical studies. The teams had to get the ethical committee agreements and to be approved by the CHU of Bordeaux before to start the patient's inclusion. The project "Early diagnosis and pleotherapy of Alzheimer Disease", lead by JM. Orgogozo, P Philip and J-F Dartigues run by Pharnext, a private biotech company, is conducting clinical trials **measuring the levels of plasma biomarkers signature for AD, a non invasive approach for an early diagnostic of Alzheimer disease**. Patent applications are underway. The project "Study of miRNA expression pattern as diagnostic and prognostic biomarker in amyotrophic lateral sclerosis" lead by Alexandre Favereaux (IINS), Gwendal Le Masson (NCM) ; Anne-Cécile Wielanek-Bachelet (Centre référence SLA) started patient's inclusion. **Final data analysis will define a specific pattern of miRNA expression that correlates to ALS diagnostic, thus enabling earlier diagnostic and medication.**

List of LabEx BRAIN

Patho-Dyn-Syn - The Dynamic Organization of Synapses; a new frontier to understanding the molecular basis of brain function and neurological disorders

- Morpho-functional plasticity of the tripartite synapse, *Giovanni Marsicano (NMC), Valentin Nägerl (IINS), Stéphane Oliet (NMC)*

- Impact of planar polarity on shaping neurons and synapses, *Mireille Montcouquiol (NMC), Olivier Thoumine (IINS)*

- Membrane dynamics of astrocytic glutamate transporter and its functional impact on synaptic functions, *Laurent Groc (IINS); Stéphane Oliet (NCM)*

- Role of planar polarity proteins in the cytoskeleton dynamics of dendritic spines, *Mireille Montcouquiol (NCM); Grégory Giannone (IINS)*

- Role of neuronal and astroglial CB1 receptors in morpho-functional plasticity of the tripartite synapse, *Giovanni MARSICANO (NCM); Valentin NAGERL (IINS)*

- New methods of aquisition ad classification for high content screening of membrane receptor organization and dynamics using super-resolution microscopy, *Jean-Baptiste Sibarita, IINS, Jean-Philippe Domenger, CPU*

Ipsynet - Integrative Physiology of Synapses and Networks

- Unraveling the anatomical wiring diagram to understand the physiology and pathophysiology of the hippocampus and neocortex, *Christophe Mulle (IINS), Andreas Frick (NCM)*

- Programming support for hybrid systems applications, *John Simmers (INCIA), Gwendal Lemasson (NCM), Daniel Cattaert (INCIA)*

- Functional characterization of a dopaminergic projection to the bed nucleus of the stria terminalis during aversive learning, *François Georges, IINS, Cyril Herry, NCM*

- Comparison of the plastic properties of adult-born and developmentally-born granule dentate neurons, *Nora Abrous, NCM, Christophe Mulle, IINS*

- Neuronal circuits of contextual fear, *Yann Humeau, IINS, Cyril Herry, NCM*

- Modulation of synaptic calcium signaling by mitochondrial type 1 cannabinoid receptor, *Sandrine Pouvreau, IINS, Federico Massa, NCM*

MAD - Molecular Basis of Transition to Addiction

- Psychobehavioral characterization of addiction, *Daniela Cota (NCM), Pierre Philip (SanPsy)*

- Measures of motivational and hedonic states in rats, team, *Martine Cador (INCIA)*

- Alteration in learning strategies associated with drug addiction, *Véronique Deroche Gamonet (NCM), Vincent David (INCIA)*

- Specifying the brain circuits involved in pathological incentive responses and the loss of control over drug taking during the development of addiction, *Véronique Deroche Gamonet (NCM), Cyril Herry (NCM)*

- Identifying the contribution of distinct neuronal circuits in the encoding of affective memories after drug withdrawal, *Martine Cador (INCIA)*

- Probing the role of dedicated valuation neuronal circuits in the development of pathological decision making in addicted individuals, *Serge Ahmed (IMN)*

- Characterization of molecular pathways in vulnerability to drug addiction, *Jean-Michel Revest (NCM)*

- Is stress-induced vulnerability to drug of abuse an astrocyte-dependent process?, *Aude Panatier, NCM ; Pier Vicenzo Piazza, NCM ; François Georges, IINS*

ITHERA-AMC - Transversal Pathophysiology and Innovative Therapeutics of Aging, Memory and Cognition disorders in the context of ageing

- Early diagnosis and pleotherapy of Alzheimer Disease, *JM. Orgogozo, P Philip, J-F Dartigues*

- Functional contribution of newly born neurons to the formation of remote memories during normal aging, *Nora Abrous (NCM), Bruno Bontempi (IMN)*

- Translational study of the cerebral substrates involved in pathological fear recovery, *Cyril Herry (NCM); Mélissa Bonnet (UMS CNRS 3428)*

- Neuron-type specific cellular mechanisms underlying the organization of recent and remote memories in the normal and diseased brain*, Andreas Frick, NCM, Bruno Bontempi, IMN*

- Pathophysiology and imaging biomarker of memory impairment in early multiple sclerosis – from animal model to patients, *Thomas Tourdias, NCM, Bassem Hiba, TRAIL*

- Contribution of the dentate gyrus to the ontogeny of learning and memory skills, *Muriel Koehl, NCM, François Georges, IINS*

ITHERA-MSA - Transversal Pathophysiology and Innovative Therapeutics of Motor, Sleep and Attention disorders

- Sleep, cognition and Alzheimer, *Pierre Philip (SanPsy)*

- Establishment of a biological resources collection, *Erwan Bezard (IMN), Wassilios Meissner (IMN)*

- Does the orexin system contribute to individual differences in sleep deprivation-induced changes in neurobehavioral function? *Pierre Philip (Sanpsy) ; Sophie Layé (NutriNeuro)*

- Study of miRNA expression pattern as diagnostic and prognostic biomarker in amyotrophic lateral sclerosis, *Alexandre Favereaux (IINS), Gwendal Le Masson (NCM) ; Anne-Cécile Wielanek-Bachelet (Centre référence SLA)*

- Exploring the brain extracellular space dynamics in physiology and pathology, *Laurent Groc, IINS, Erwan Bezard, IMN, Laurent Cognet, LAPHIA, Mireille Blanchard-Desce, LAPHIA*

Blue sky program

- 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, *Christel Baudet (IINS), Pascal Fossat (INCIA), Bruno Quesson (CNRS UMS 3428,TRAIL); Klaus Petry (INSERM U1049); Erik Dumont (Image Guided Therapy)*

- Relative contribution of the hypothalamic proliferative and neuroinflammatory responses to the obese phenotype, *Daniela Cota (NCM); Nora Abrous (NCM); Sophie Layé (INRA)*

- The impact of structural changes in axons on information transfer in CA3 neurons: a combined computational and nanoscale imaging study, *Daniel Cattaert (INCIA); Valentin Nagerl (IINS)*

- Thermosensitive nanoparticules as a carrier of bioactive peptide against pain sensitization, *Marc Landry (IINS); Valérie Heroguez (UMR CNRS 5629); Klaus Petry (INSERM U1049)*

- Determining the mode of binding of PSD-95 tandem PDZ domains, *Matthieu Sainlos (IINS); Cameron Mackereth (IECB)*

- Nanoparticles as a carrier of bioactive peptide against pain sensitization, *Marc Landry, IINS, Valérie Heroguez, AMADEUS*

2.2 HUMAN RESOURCES

The **Human Resources policy of the LabEx BRAIN has been implemented in several configurations**, **adapted to each instrument**

For the ***PhD student recruitment***, the LabEx organizes on an annual basis a specific call for proposal (described in section 1.3) to support students after 3 years of PhD for a duration up to one year, selected on scientific excellence, according to the procedure described above.

Regarding the recruitment for the ***research projects and the core facility personnel***, the LabEx BRAIN has no policy as such, but gives the flexibility to adapt to specific laboratory or core-facility policies. The platform managers and project leaders are in charge of recruitment according to their specific needs. LabEx directly provided funds for recruitment in laboratories or platforms.

Concerning the ***creation of the new team,*** the selection of the team leader has been organized collectively with Bordeaux Neurocampus and the University for the tenure track. An accompanying policy was set up for the creation of the new team within the SanPsy Unit in 2014, mainly for the information campaign, the evaluation and the selection of the candidate and the final decision for the recruitment. A selection committee was gathered composed by the directors of the LabEx, SanPsy Unit, Bordeaux Neurocampus and the Vice-President of the University in charge of research.

The total of permanent recruitment from 2011 in LabEx teams is 55, including 27 new positions and 28 mobilities (new permanent positions for 7 Researchers, 5 Assistant Professor, 5 research engineers, 10 technicians). Among these, one researcher has been attracted by an IdEx post-doc position prior to obtain a permanent position at CNRS, as well as one technician supported by the LabEx. In a general context of decrease in the number of permanent position available at the national level, we can observe the positive effect of the LabEx on the number of recruitment. Indeed, the number of recruitments in the laboratories of the LabEx has remained at a high level (around 10 new positions per year) since 2011.

2.3 FINANCIAL RESOURCES, LEVERAGE EFFECT

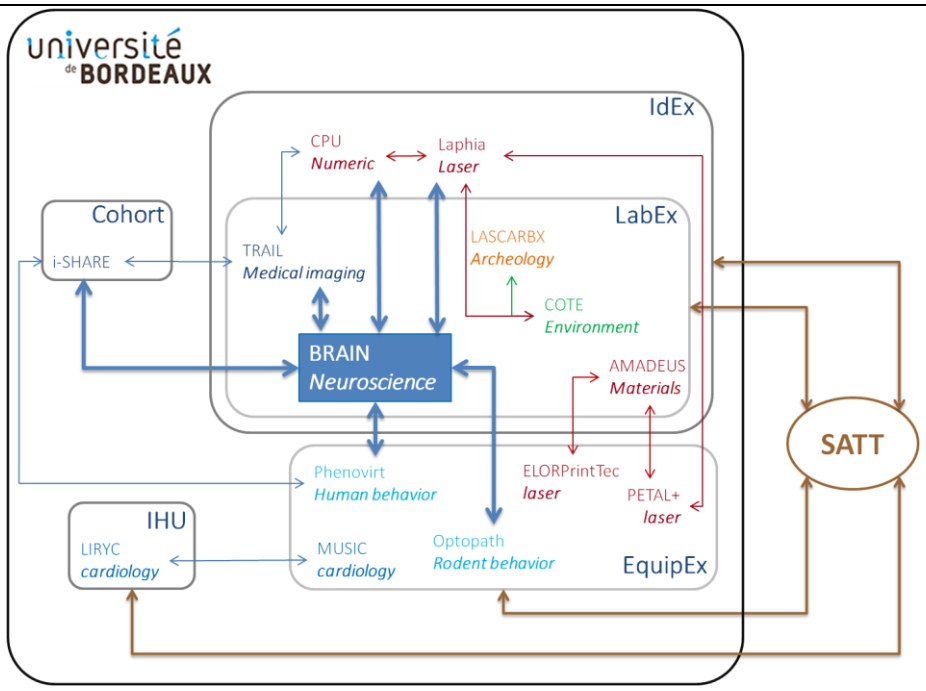
The laboratories have their own strategy; the impact of the LabEx BRAIN in terms of general strategy to attract new funds was to bring a comprehensive strategy at the Bordeaux Neurocampus level. Therefore, we observe that the laboratories redefined their strategy by taking into account the overall strategy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

The total of resources obtained from 2011 to 2014 by the LabEx teams is 41,8M€, with 13,5M€ from ANR and 8,6M€ from Regional Council, 5,6M€ from European Commission. If we focus on the resources directly linked to the LabEx projects, the projects selected during the first 2 calls for proposals were so far able to obtain **4,7M€ of co-funds** (from 7 ANR grants, 2 FRM grants, 1 Eranet, 2 grants from the French foundation eating health, 1 OSEO grant, 1 PHRC grant, 1 PEPS-IdEx-CNRS).

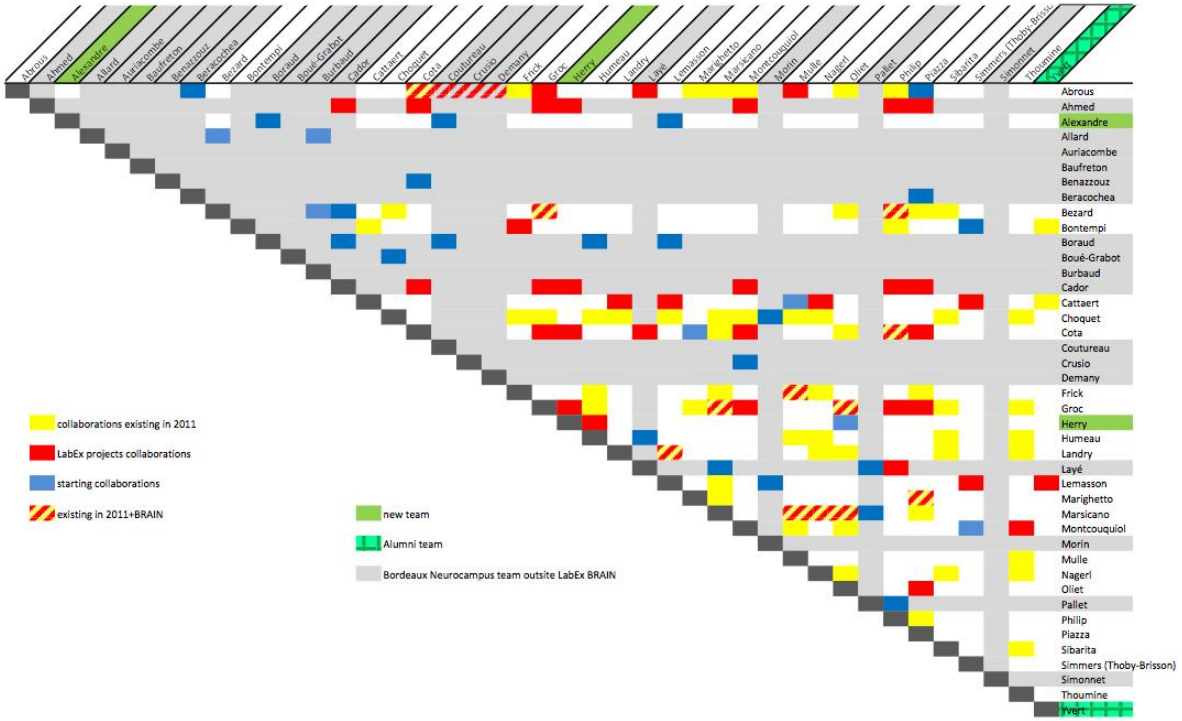
2.4 LABEX IMPACT ON ITS ECOSYTEM POLICY

The University of Bordeaux is the sole coordinator of the “Investments for the future” projects, named PIAs (Excellence Initiative, LabEx, Cohort, EquipEx). This ensures that there is consistency and synergy between the areas of excellence represented in these projects. In terms of implementing these projects, this consistency is provided by the Excellence Initiative (IdEx) Management Committee, which has oversight of the PIAs. The governance of the LabEx is integrated in the governance of IdEx project (LabEx board of trustees come under the aegis of IdEx Management Committee). LabEx directors hold regular meetings (which are also attended by those managing PIAs at the University of Bordeaux) and there are also monthly meetings of LabEx and IdEx project managers. LabEx directors are also invited to present their projects to the IdEx Management and Strategic Committees and a scientific in charge of the relation between LabEx and IdEx projects

The LabEx BRAIN is one of the 5 LabEx of the IdEx Bordeaux. 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. To ensure a smooth communication between the LabEx and these EquipEx, the directors of these EquipEx are members of the Steering Committee of the LabEx BRAIN. We have interactions with the other LabEx in health, the LabEx TRAIL, dedicated to Medical Imaging, with an important component in neuroscience and the cohort i-share. Some collaborations exist between BRAIN and 2 clusters created at the local level by the IdEx Bordeaux: Laphia (in laser) and CPU (in numerical technology).



The LabEx BRAIN had a strong impact in reinforcing the Bordeaux Neurocampus collaborations, mainly because the projects submitted to our call for proposals had to be collaborative. In the figure below, we reported the collaborations that existed before 2011 (in yellow), and add the new collaborations induced by the LabEx dynamic:



The policy of the Labex to strongly support the core facilities has had a major impact on the site policy. This is particularly visible for the animal facilities and for the *in vivo* experiment facility which were strongly re-inforced, for the biochemistry facility which underwent a major upgrade and for the

biological imaging facility that reached European recognition. Regarding the latter, it was at the origin of the creation of a regional network of activity in BioImaging (BIPSA: http://www.routedeslasers.com/fr/actualites/2012/07/bipsa-%E2%80%93-bio-imagerie-photonique-et-sante-en-aquitaine-171.html) that postulates in 2015 for recognition as a transversal action of Bordeaux University.

3/ SOCIO-ECONOMIC IMPACT

3.1 PARTNERHIPS WITH SOCIAL AND ECONOMIC ACTORS (INDUSTRIAL ACTORS, COMPETITIVENESS CLUSTERS, FUNDATIONS...) AND ESTABLISHED AGREEMENTS; START-UP CREATION; HOSTING OF INDUSTRIAL ACTORS IN THE LABEX FOR INSTANCE...

We have partnerships with industrials **through the EquipEx projects OptoPath and PHENOVIRT**.

OptoPath development involves a tight collaboration with 3 industrial partners: **Imetronic**, the first French manufacturer of scientific instruments for behavioral research in Neuroscience. The extreme flexibility and adaptive capability of this company able to produce on demand unique and very high quality equipment. Through a close partnership, Imetronic and the Faculty partners have designed and developed products adapted to Optopath's scientific challenges. **Fluofarma** actively contributes to the project by providing a "customer oriented" project management for the development of Optopath's new services. **Servier IRIS**, in close collaboration with faculty working on aging-related memory deficits using a reverse translational strategy, is involved in testing memory test tools in humans.

PHENOVIRT is developed in collaboration with 4 industrial: **Thales** is involved in the project to develop innovative products and solutions to enhance the safety of aircraft and crew performance. In aviation, this work may, in some cases, allow the implementation of dual solutions (civil and military), but also have an impact in other areas (automotive, ...). **Immersion** develops virtual reality products (hardware and software) dedicated to the study of attention disorders, alertness and cognitive decline associated with aging and neurological diseases. These new products allow the rehabilitation of people with attention or cognitive impairment. **Oktal** develops driving scenarios tailored specifically to the study of older participants or cognitively impaired. **Continental Automotiv** develops driving support systems with particular emphasis on the interaction with the human system and monitoring of the pilot. Oktal and continental will work together to define and implement driving scenarios with particular emphasis on the development and validation of adaptive approaches to help the driver and driver control embedded systems....

The SANPSY Unit has integrated the **OpenLab PSA Peugeot Citroen** in 2014, developed projects labelled by **Aerospace Valley** and the TIC Santé Cluster. The Platform collaborates with the Bordeaux Clinical Research Network **Accelence** to promote clinical research and collaborates with **Physip** to develop and analyze EEG and sleep structure. The SANPSY Unit is certified as sleep laboratory by **Clinilab**.

The Neuropsychopharmacology Platform has several contracts with Pharmaceutical companies and CRO for clinical trials (**Unither, Sanofi, UCB, Inspire, Merck, RESMED, IPSEN**) that represent a total budget of 780 k€ during the period 2011-2014.

The BIC and IINS teams have developed strong partnerships with industrials in the field of BioImaging and microscopy. Patents have been licensed to Molecular device (Sibarita team). A startup has been created (Alveol, V Studer). Joint patents have been granted together with Imagine Optics (Sibarita team). Research contracts have been established with Leica Microsystems.

The BioImaging community, largely represented in the Labex BRAIN, created the network BIPSA – Bio-Imagerie Photonique et Santé en Aquitaine - that is a forum of exchange between academic and

industrial teams in the field and has labeled over 25 projects in the last 3 years. It has been hosted by the pole de compétitivité “route des laser”.

IMN has collaborations together with **Merk-serono, UCB Pharma, Modag GMBH**

3.2 Relationship with the SATT (Tech-Transfert Societies), where possible, IRT (Technological research instituts) or ITE (Technological research instituts in the field of energy) and with other transfer systems involved in higher education and research institutions

Aquitaine Science Transfert® assists LabEx BRAIN researchers in all stages of technology transfer: from the detection of potential applied results to the negotiation of licensing agreements through investment in maturing (technical, intellectual property, legal, commercial), the management and transfer of intellectual property and support to the creation of innovative start-ups.

All protection approaches are made by Aquitaine Science Transfert® (or the CNRS and INSERM laboratory based), the cost of the priority application is the responsibility of applicants (institutions) and those of the extensions is supported by Aquitaine Science Transfert®.

The projects that require maturation phase of the technical, legal and business aspects are submitted to a committee of independent experts for advice on exploitation strategy, development plan and project management. The investment capacity of Aquitaine Science Transfert® over the next three years is 10M€ over 80 projects.

The **maturation phase supported by the SATT** secures the transfer operation by finalizing technical aspects (feasibility validation, prototyping, characterization, industrialization), intellectual property rights (freedom of exploitation, industrial protection, international extensions, procedures examination), legal process (risk assessment, contractual agreements, respects the standards and regulations) and commercial strategy (market analysis and target identification, value chain and economic model, market access strategy).

The **transfer phase** is the implementation to companies that can be licensing or transfer of rights (patent, software or know-how) or start-up creation. All exploration, promotion, analysis of the value and trading are conducted by Science Transfert® Aquitaine.

The LabEx BRAIN consortium agreement was written with support of the lawyers of the SATT, **the LabEx teams filed 13 patents with SATT or INSERM Transfer, 2 projects are on maturation phase supported by the SATT**. In addition, the SANPSY Unit is supported by the Aquitaine Sciences Transfert (SATT) for its project of start-up creation.

The SATT Aquitaine Science Transfert® organizes coffee breaks with LabEx laboratories to discuss the development and transfer of technology.

3.3 Commercial relations with European public-private partnership research institute, within the Framework Programmes, etc.

Not applicable

3.4 Promotion measures for knowledge dissemination ; schedule, durability of the measures (excluding publications in scientific journals)

Since 2011, the **LabEx BRAIN has supported a total of 20 international symposiums** organized in Bordeaux (ELMI, on optic microscopy, FINS in neurophotonics, new therapeutic avenues on Parkinson disease, etc…). Among these symposia, we strongly supported the first edition of the European Neuroscience Conference by Doctoral Students, and we were glad to learn that the success of this first meeting leaded the organization of a second edition in April in Portugal.

This intense activity of dissemination has had a major impact on the international visibility of Bordeaux as an excellence center for neuroscience.

For further visibility, together with Bordeaux Neurocampus, the LabEx BRAIN launched in 2014 the **International Bordeaux Neurocampus BRAIN Conferences**, a series of neuroscience meetings, organized in Bordeaux. The purpose of the conferences is to present and discuss recent findings in a topic field in neuroscience, bringing together leading international experts and young researchers. The International Bordeaux Neurocampus BRAIN conferences are 3-day meetings that take place in autumn at Bordeaux University. About 20 presentations are given by invited speakers, and the schedule encourages lively discussion, in particular during the poster sessions. The number of participants around 150, including invited speakers. The first edition, "**MitoBrain**" for 'Mitochondrial Functions and Dysfunctions in the Central Nervous System', focused on the role of mitochondria in the cells in the Central Nervous System in normal and pathological states, was scheduled in October, 2014. The second edition, "**GliSyn**" for "Astrocytes and microglia, key partners in synaptic transmission", scheduled in October 2015, will focus on the possible partnership of astrocytes and microglia in synaptic transmission.

The LabEx BRAIN communication is in tight connection with Bordeaux Neurocampus. The number of **Bordeaux Neurocampus website visits** increased from 2008 with 143.494 visitors and 398.000 consulted pages, through 203.855 visitors and 402.230 consulted pages in 2013, to more than 234.000 visitors and more than 600.000 consulted pages in 2014. Bordeaux Neurocampus is also present on Facebook and Twitter (>200 followers).

We also are 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") on a yearly basis. We also developed communication to the patients associations, through the association "la maison du cerveau".

FREE COMMENTS

A major risk identified at the beginning of the Labex BRAIN was the split of the community and the confusion induced by the multiplicity of instruments and large scale projects (Neuroscience federation, regional Neurocampus project, Labex national initiatives,…). We can securely state that the Bordeaux Neuroscience community has overcome this risk by a clear federation of all its components through Bordeaux Neurocampus. The policies of the Labex BRAIN and the Neurocampus project, the most visible instruments, serve the whole community and are fully integrated.
At the end of this first phase of the Labex BRAIN, we can modestly feel proud of its accomplishments. Beyond the quantitative results presented above, we can arguably state that the Labex has gone beyond its initial objectives and that the activity of BRAIN has contributed massively to reinforce the feeling of the Bordeaux Neurocampus teams of "being part of a cohesive community of international significance".
The development of BRAIN has been harmoniously supported by the Bordeaux University and Idex Bordeaux. BRAIN has contributed to the general development of the policy of the Idex and vice versa, a large number of BRAIN teams and initiatives have directly benefited from the Idex support. One of the most visible impact of Idex has certainly been the incentive for inter-labex project and fostering of truly interdisciplinary research.

Securing the organization and funding of both the Idex and Labex is certainly key to the future of Bordeaux Neuroscience success. The ongoing dynamic must absolutely be preserved to warrant further success.