Département d'évaluation de la recherche

Research Unit
Self-assessment document

EVALUATION CAMPAIGN 2020-2021

GROUP B

GENERAL INFORMATION

Name of the unit concerned by the current contract: **U1228**
Name of the unit concerned by the next contract (if different):
Acronym of the current contract: **Visages**
Acronym of the next contract (if different): **Empenn**
Scientific field (name two fields if interdisciplinary evaluation): **ST6**
Medical Imaging, Neuroimaging, Computer Sciences
Scientific sub-domains (in Hcéres' nomenclature) in descending order of importance: **ST6 (Sciences et technologies de l'information et de la communication), SVE1_LS7 (Epidémiologie, santé publique, recherche clinique, technologies biomédicales)**

Director for the current contract: **C. Barillot**
Director (or project leader) for the next contract: **P. Maurel**

Type of application:

Identical renewal ☒ Fusion, scission, restructuring ☐ *Ex nihilo* creation[1] ☐

Academic institutions and affiliated organisms:

List of Institutions and Organisms supervising the Research Unit **for the current and next contract**:

[1] Units created *ex nihilo* will be evaluated based on a project.

Current contract:	Next contract:
- Inserm	- Inserm
- IRISA CNRS UMR 6074	- IRISA CNRS UMR 6074
- University of Rennes 1	- University of Rennes 1
- Inria	- Inria

Interdisciplinary research evaluation:

Yes ☒	No ☐

Clinical research activities:

Yes ☐	No ☒

RESULTS

1- Presentation of the unit (team / theme)

Introduction

The unit is made of a single team affiliated jointly with Inria, Inserm and the University of Rennes I. It is also part of IRISA/UMR CNRS 6074. Until now it was part of the thematic department D5 (Digital Signals and Images, Robotics) but will join the thematic department D6 (Image Analysis and Processing) in the next contract. The unit is based in Rennes, both on the medical campus with the Neurinfo facility located in the Radiology department at the Rennes University Hospital and the science campus in Beaulieu, in the IRISA building. The team was created in 2006 under the name “VisAGeS”, with accreditation number U746 for Inserm. In 2017, after a competitive evaluation conducted by both HCERES and Inserm, the Inserm research unit was renewed under accreditation number U1228. Then, in 2019, after a review by internal experts, Inria created the Empenn team as a continuation of Visages. The Empenn research team focuses on research projects ranging from investigations in information sciences to original clinical experimentation with medical impact. Through this partnership, bringing together researchers in information sciences and medicine, our ambition is to develop unique multidisciplinary research. Our medium- and long-term objective is to introduce our basic research to clinical practice, while maintaining the excellence of our methodological research.

The team is involved in training for and through research through several masters :

- Master SIBM : Signaux Images et Biologie en Médecine (Resp : J.C. Ferré),
- Ecole Supérieure d’Ingénieurs de Rennes: option “Imagerie Numérique”, M1/M2 (Resp: P. Maurel).

Christian Barillot was the founding director of the unit since 2006 and sadly passed away in June 2020. Pierre Maurel has been the acting head since June 2019, and is the team leader as of June 2020.

Unit’s workforce and means

Workforce

In June 2020, the team is composed of 5 full time researchers, 1 associate professor, 4 medical doctors, 2 research engineers to run the Neurinfo facility, 7 PhD students, 6 post-docs and 2 engineers.

In the last contract the team has grown with the recruitment of two full time researchers, Camille Maumet (CR Inria, recruited in 2017) and Julie Coloigner (CR CNRS, recruited in 2018) as well as new post-docs. Claire Cury will join the team at the end of 2020 as CR Inria. Two medical doctors will join the team for the next contract : Gabriel Robert, already MCU-PH in Psychiatry and part of the EA 4712, and Anne Kerbrat, who will get a position as MCU-PH in the neurology department at the Rennes University Hospital.

In the past contract 12 PhD thesis were defended, 3 by MD-PhD candidates specialised in Radiology or Neurology and 9 by PhD candidates with background in applied mathematics and computer science.

Means

	2015	2016	2017	2018	2019
Recurrent allocations (INRIA, INSERM, U Rennes 1) (not including payroll)	102 122	104 020	101 990	107 608	100 000
Own resources	359 976	129 625	927 737	325 325	140 192
Total resources (not including payroll)	**462 098**	**233 645**	**1 029 727**	**432 933**	**240 192**

The team is operating the Neurinfo neuroimaging and neuroinformatics facility in partnership with the University of Rennes 1, the University Hospital of Rennes, Inria, CNRS and the Cancer Research Center (CRLCC).

Scientific policy

Our goal is to foster research in medical imaging, neuroinformatics and population cohorts. In particular, **the Empenn team targets the detection and development of imaging biomarkers for brain diseases and focuses its efforts on translating this research to clinical practice and clinical neuroscience.**

While mental, neurological and substance use disorders make up approximately 10% of all diseases (Patel et al. 2016), they are the leading cause of years lived with a disability. Brain disorders in particular account for 36% of disability-adjusted life years in high-income countries and 29% in low- and middle-income countries (Silberberg et al. 2015). Over this decade, mental, neurological and substance use disorders have therefore accounted for 7.5% of all disability-adjusted life years worldwide (Whiteford et al. 2013).

New practices in medicine bring new challenges in information sciences. This is true in particular for the study of brain disorders, where the main challenges include:

1. improving the understanding of the brain (especially the brain in action),
2. undertaking more effective monitoring of therapeutic procedures,
3. modeling groups of normal and pathological individuals from signal and image descriptors,
4. discovering new therapeutic and rehabilitation strategies for brain recovery.

The objective of Empenn is to propose new statistical and computing methods, and to measure and model brain morphological, structural and functional states in order to better diagnose, monitor, eventually predict disease evolution and treat neurological and psychiatric disorders. In particular, we propose to combine advanced instrumental devices and new computational models to provide advanced diagnosis, therapeutic and neuro-rehabilitation solutions for some of the major disorders of the developing and aging brain.

This includes imaging brain pathologies in order to better understand pathological behavior from the organ level to the cellular level, and even to the molecular level (using molecule (e.g. through PET-MR imaging, as well as modeling with specific ligands/nanocarriers), and the modelling of normal and pathological large groups of individuals (cohorts) from image descriptors. It also includes the challenge of the discovery of episodic findings (i.e. rare events in large volumes of images and data), data mining and knowledge discovery from image descriptors, the validation and certification of new drugs from imaging features, and, more generally, the integration of neuroimaging into neuroinformatics through the promotion and support of virtual organizations of biomedical actors by means of e-health technologies.

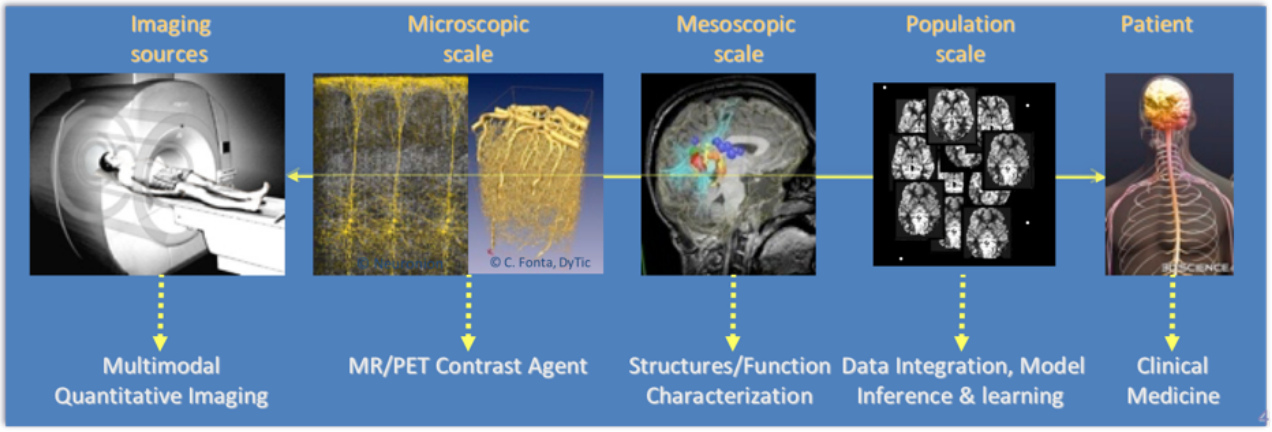

Figure 1: The major overall challenge of the team concerns the integration of data from the imaging source to the patient at different scales: from the cellular or molecular level describing the structure and function, to the functional and structural level of brain structures and regions, to the population level for the modeling of group patterns and the learning of group or individual imaging markers.

As shown in Figure 1, the research activities of the Empenn team closely link observations and models through the integration of clinical and multiscale data, and phenotypes (cellular, and later molecular, with structural or connectivity patterns in the first stage). Our ambition is to build personalized models of central nervous system organs and pathologies, and to compare these models with clinical research studies in order to establish a quantitative diagnosis, prevent the progression of diseases and provide new digital recovery strategies, while combining all these research areas with clinical validation. This approach is developed within a translational framework, where the data integration process to build the models is informed by specific clinical studies, and where the models are assessed in the context of prospective clinical trials for diagnosis and therapy planning. All of these research activities are conducted in close

collaboration with the Neurinfo platform, which benefited in 2018 from a new high-end 3T MRI system dedicated to research (3T Prisma™ system from Siemens), and through the development of multimodal hybrid imaging (from the currently available EEG-MRI and EEG-NIRS-MRI and PET-MRI in the future).

In this context, some of our major developments and newly arising issues and challenges will include:

- The generation of new descriptors to study brain structure and function (e.g. the combination of variations in brain perfusion; changes in brain structure in relation to normal, pathological, functional or structural connectivity patterns; or the modeling of brain state during cognitive stimulation using neurofeedback).
- The integration of additional spatiotemporal and hybrid imaging methods covering a larger range of observations, from the molecular level to the organ level, via the cellular level (arterial spin labeling, diffusion MRI, MR relaxometry, MR fingerprinting, MR cell labeling imaging, MR-PET molecular imaging, EEG-MRI-fNIRS functional imaging, etc.).
- The creation of computational models through the data fusion of molecular, cellular (i.e. through dedicated ligands or nanocarriers), structural and functional image descriptors from group studies of normal and/or pathological subjects.
- The evaluation of these models in relation to acute pathologies, especially for the study of degenerative, psychiatric, traumatic or developmental brain diseases (primarily multiple sclerosis, stroke, traumatic brain injury (TBI) and depression, but applicable with a potential additional impact to epilepsy, Parkinson's disease, dementia, post-traumatic brain disorder, etc.) within a translational framework.

In terms of new major methodological challenges, we will address the development of models and algorithms to reconstruct, analyze and transform the images, and to manage the mass of data to store, distribute and "semanticize" (i.e. provide a logical division of the model's components according to their meaning). As such, we expect to make methodological contributions in the fields of model inference; statistical analysis and modeling; the application of sparse representation (compressed sensing and dictionary learning) and machine learning (supervised/unsupervised classification and discrete model learning); data fusion (multimodal integration, registration, patch analysis, etc.); high-dimensional optimization; data integration; and brain-computer interfaces. As a team at the frontier between the digital sciences and clinical research in neuroscience, we do not claim to provide theoretical breakthroughs in these domains but rather to provide significant advances using these algorithms through advanced applications. In addition, we believe that by providing these significant advances, we will also contribute to exhibiting new theoretical problems that will fuel the domains of theoretical computer sciences and applied mathematics.

To summarize, we ambition with Empenn to bring significant advances in the detection and development of imaging biomarkers for diseases of the central nervous system. In particular, we are aiming at establishing a leading position in the following areas of application: imaging in multiple sclerosis and the use of neurofeedback for rehabilitation in brain pathologies such as stroke and depression. However, we are not restricted to these domains, as we believe that leadership in these disciplines will provide us with opportunities for significant advances in the other areas of our research program.

Actions taken to implement recommendations received during the previous evaluation

Previous evaluation outlined our lack of participation to European projects. The unit recently took part in the OpenAire-connect H2020 project to develop portals to share and link research artefacts (data, code, papers) in different communities. In this project Empenn acted, through CNRS, as the French coordinator to develop the link with the Neuroimaging research community. This was performed in the context of the FLI-IAM national infrastructure. Empenn is also leading the working group on multisite data integration of the European COST Action GliMR focused on developing the use of advanced MR biomarkers for progressing the development and application of advanced MR imaging for improved decision making in diagnosis, patient monitoring, and assessment of treatment response in clinical trials and clinical practice.

During the previous evaluation, the experts noted that only one member of Unit has the "habilitation à diriger des recherches" (HDR) in the Doctoral School "MathStic" (4 members have the HDR in the "Biologie&Santé" doctoral school). Olivier Commowick defended his Habilitation in June 2019. Pierre Maurel is planning to defend his Habilitation in 2021.

The existing collaborations with other IRISA team have been renewed, for example in the Hemisfer project (Panama Team and HYBRID Team) or on the topic of biomedical informatics (Dyliss team) and new

collaborations have emerged, for example on the topic of neuroimaging pipelines and machine learning (LACODAM team).

Finally, following the experts' recommendations and in addition to our constant involvement in the Master SIBM (Signaux Images et Biologie en Médecine), Pierre Maurel is now in charge of the "Imagerie Numérique" training program (two last years of engineering school ESIR, equivalent to master degree). Furthermore, Emmanuel Caruyer and Pierre Maurel are now teaching at ENS Rennes, and, in 2020, Julie Coloigner will start teaching in the master "sciences informatiques" (SIF).

2- Presentation of the unit's research ecosystem

Generic and challenging research topics in this broad domain include finding new ways to compare models and data, assist decisions and interpretation, and develop feedback from experiments. These activities are performed in close collaboration with the Neurinfo *in vivo* imaging platform, which is a critical environment for the experimental implementation of our research on challenging clinical research projects and the development of new clinical applications and collaborations (see Annex 3 for more details).

In the field of multiple sclerosis research, we have tight links with local clinical research actors (the neuroscience group of the clinical investigation unit CIC-P1414 INSERM at the University Hospital and the Biotrial CRO for instance). At the inter-regional scale, Gilles Edan, Jean Christophe Ferré and Olivier Commowick lead the MUSIC project for translating our basic research segmentation algorithms to routine clinical usage. This project results from a collaboration between pharmaceutical companies (Biogen, Novartis, Merck, Roche, Sanofi), a Clinical Research Operator (Biotrial), the IRT b-com, Inria and the University Hospital of Rennes. At the national level, we take part in the OFSEP cohort project, that has the aim of gathering MR, biological and clinical data from 70 000 multiple sclerosis patients over the majority of MS centers in France. This project started in 2010 for ten years ("Projet d'investissement d'avenir cohortes"). Moreover, Gilles Edan is the national coordinator of FCRIN4MS.

Through the Labex Cominlabs and in collaboration with the rehabilitation physicians and the psychiatrists, we led the HEMISFER project to develop an hybrid EEG-MRI neurofeedback platform. Two clinical evaluations are foreseen, one, ongoing, involving stroke patients, the other one just starting involving depressed patients. After EEG-MRI, we plan to incorporate a larger range of *in vivo* sensors such as hybrid EEG-NIRS or NIRS-MRI, later moving toward hybrid MRI-PET. This opens up a large and effective collaborative environment for the team with a view to clinical applications related to our major research topics (radiology, neurology, psychiatry, rehabilitation and nutrition) and joint projects with institutes such as Irset (Jodi Pawluski) and Inra / Numecan (David Val Laillet).

None of these research prospects would be possible without a close link between a strong clinical research environment, an advanced technological imaging platform dedicated to research and integration into a computer science institute such as IRISA/Inria Rennes. Empenn benefits from a close local collaborative environment in computational sciences at IRISA, especially on the topics of machine learning (PANAMA, LACODAM, DIVERSE, etc.), robotics (RAINBOW), human-machine interfaces (HYBRID) and in relation to omics (DYLISS, GENSCALE, GenOuest platform and Institut du Thorax UMR1087 in Nantes), with joint PhD students (HYBRID), post-docs (PANAMA, HYBRID) or engineers (DYLISS, LACODAM). We do have some collaborations with the LTSI, with the METRIQ team led by Hervé Saint-Jalmes and the MEDICIS team led by Pierre Jannin, applying and evaluating new MR pulse sequences through research projects running at the Neurinfo facility.

At the national scale, the Unit is strongly involved in France Life Imaging (FLI), a large-scale research infrastructure project to establish a coordinated and harmonized network of biomedical imaging in France. This project was selected by the call "Investissements d'Avenir - Infrastructure en Biologie et Santé". One node of this project is the node Information Analysis and Management (IAM), a transversal node built by a consortium of teams that contribute to the construction of a network for data storage and information processing. Instead of building other dedicated facilities, the IAM node use already existing data storage and information processing facilities (LaTIM Brest; CREATIS Lyon; CIC-IT Nancy; Empenn U1228 Inria Rennes; CATI CEA Saclay; ICube Strasbourg) that increase their capacities for the FLI infrastructure. Christian Barillot was the chair of the node IAM, Olivier Commowick is participating in the working group workflow and image processing and Michael Kain is the technical manager. The IAM node is now in phase 2, consisting in finding a partner company, as well as clients, in order to complete the transfer to the industrial world. Pierre Maurel and Michael Kain are overseeing, for Empenn, this phase. Camille Maumet is part of the steering committee.

Finally, at the international scale and in addition with less formal collaborations, the Unit has strong collaborations with several teams. Through the "Inria International Labs" initiative, we had a common project

(BARBANT) with the Computational Radiology Laboratory at the Boston Children's hospital (Harvard Medical School) from 2012 to 2017 and then a new one with the LTS5 (École Polytechnique Fédérale de Lausanne — EPFL) since 2019 (MMINCARAV). Through the Gundishapur Program (Partenariat Hubert Curien franco-iranien), we started in 2019 a collaboration with the Institute of medical science and technologies (Shahid Beheshti university, Iran).

3- Research products and activities for the unit

Scientific track record

3.1 Medical image computing in neuroimaging

Extraction and exploitation of complex imaging biomarkers involve an imaging workflow processing that can be quite complex. This goes from image physics and image acquisition, image processing for quality control and enhancement, image analysis for features extraction and image fusion up to the final application which intends to demonstrate the capability of the image processing workflow to issue sensitive and specific markers of a given pathology. In this context, our objectives in the recent period were directed toward several major methodological achievements:

T2 Relaxometry and myelin water fraction imaging. The Empenn team has proposed new methodologies to exploit new relaxometry sequences, able to provide direct information on tissue properties (T1, T2, T2* relaxation times) and their alteration in diseases. Such sequences have a great potential in diagnostic and evolution study of patients suffering from various neurological diseases. However, these images may be affected by various artifacts (B0 and B1 inhomogeneity, magnetization transfer, uncertainty in quantitative values estimation, etc.) and exploiting them remains a large challenge. We have contributed during the evaluation period to the development of brain imaging acquisition and processing methods, with a particular emphasis on T2 relaxometry, which is sensitive to the transverse relaxation time contrast between myelinated axons and free fluids. We developed a new multi-compartment model and an optimization technique to identify the different pools within a voxel (Chatterjee et al. 2017, 2018b), thus providing a more accurate quantification of the myelin water fraction.

Microstructure imaging using diffusion. Complementary to the microstructure information accessible with relaxometry, diffusion MRI is sensitive to the displacement of water molecules within biological tissues, which indirectly reflects the underlying microstructural organization. We proposed novel estimation schemes for diffusion multi-compartment models from diffusion MRI data (Stamm et al. 2016) and ways to use them for registration and atlas creation (Commowick et al. 2017). Novel sampling schemes based on dictionary learning and compressed sensing have been developed (Truffet, Barillot, and Caruyer 2019), paving the way to accelerated acquisitions for *in vivo* microstructure-enabled diffusion MRI; an MR pulse sequence able to play these arbitrary waveforms was developed. The research unit also contributes to an emerging field known as multi-dimensional diffusion MRI (Bates et al. 2020), which tailors the acquisition to better distinguish the effects of microscopic anisotropy.

Distortion correction of diffusion data. Further, the quality of diffusion images is impacted by inhomogeneity-induced distortions. We developed a method to correct for these effects, relying on an adapted block-matching registration between two images with reversed phase encoding directions (Hédouin et al. 2017). We have further evaluated distortion correction on spinal cord images (Snoussi et al. 2019).

Image processing on Arterial Spin Labelling images. Arterial Spin Labeling (ASL) enables measuring cerebral blood flow (CBF) in MRI without injection of a contrast agent. Perfusion measured by ASL carries relevant information for patients suffering from pathologies associated with singular perfusion patterns. However this technique suffers from drawbacks such as low signal to noise ratio and poor resolution. In this context, using similar patch-based approaches as above, a super-resolution method was developed to overcome the limitations of spatial resolution inherent to ASL (Meurée et al. 2019). This new algorithm takes advantage of a high resolution structural image to reconstruct CBF maps at a higher resolution, without increasing the acquisition time (Figure 2). This work has resulted in an industrial transfer to Siemens with the inclusion of an ASL images super-resolution module into their *MR Arterial Spin Labeling Perfusion Analysis prototype*, as a *syngo.via* Frontier application (www.siemens.com/syngo.via- frontier).

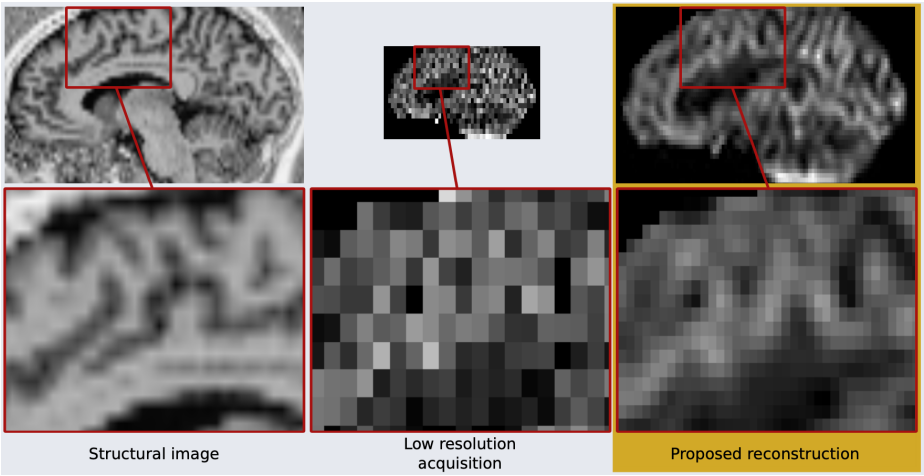

Figure 2: Super-resolution method for ASL images ASL (Meurée et al. 2019)

Second, our contributions focused on the detection of perfusion abnormalities at the subject or population level. We introduced a new locally multivariate procedure to quantitatively extract voxel-wise patterns of abnormal perfusion in individual patients. This *a contrario* approach (Maumet et al. 2016) uses a multivariate metric from the computer vision community that is suitable to detect abnormalities even in the presence of closeby hypo- and hyper-perfusions.

3.2. Applications to neuroradiology and neurological disorders

The methods presented above are applied to the diagnosis, follow-up and treatment of a range of neurological and psychiatric disorders.

Multiple sclerosis. In multiple sclerosis (MS), the longitudinal monitoring of lesions (number, location and activity) is of utmost importance for prognosis and to adapt the treatment. We have been involved throughout the evaluation period in transferring the results of our previous and current research on lesion segmentation in a software tool for the clinicians named MUSIC (see Section 2). In parallel to this transfer, we have been interested in removing contrast-agent based imaging from the MS protocol. Traditional imaging methods indeed involve gadolinium-based contrast agents, for which potential toxicity has been reported. Combining diffusion MRI and relaxometry, we have shown using machine learning the potential to predict the gadolinium-enhancement of lesions with high accuracy (85%) (Chatterjee et al. 2018a). We have also considered the use of nanoparticles to further characterize current lesion activity in the brain, showing correlation between these markers and greater tissue damage in MS patients (Kerbrat et al. 2018). A great part of our research on MS finally concerns the spinal cord (Chouteau et al. 2019; Combès, Kerbrat, et al. 2019; Combès, Monteau, et al. 2019; Eden et al. 2019; Gros et al. 2019). Imaging this region indeed brings additional information complementary to brain imaging and of great importance for the understanding of disability progression. We have notably studied the lesions spatial distribution and shown that the lesion load in the spinal cord highly correlates with motor impairment in MS (Chouteau et al. 2019; Kerbrat et al. 2020).

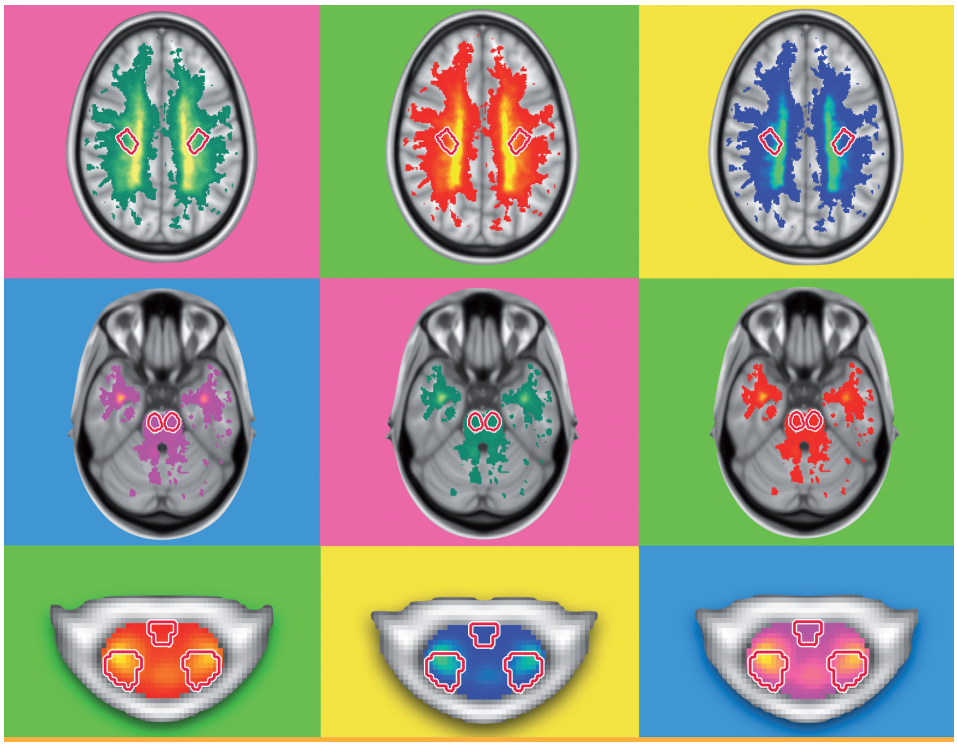

Figure 3. Brain, 2020, Cover image: Lesion frequency maps along the corticospinal tracts from the cerebral cortex to the cervical spinal cord reveal a predominant effect of intramedullary motor tract damage in explaining physical disability in patients with multiple sclerosis. From Kerbrat *et al*. Multiple sclerosis lesions in motor tracts from brain to cervical cord: spatial distribution and correlation with disability. Pp. 2089–2105.

In the context of the MUSIC project, we aimed to provide the clinicians with a graphical interface showing new lesions for MS patients, a crucial marker of disease evolution. This kind of project is a structuring one for our research as well, driving efforts to new collaborations and to research so that automatic segmentation algorithms work in a real life scenario. Christian Barillot and Olivier Commowick have worked during the evaluation period towards the transfer of research segmentation algorithms towards this platform. Jean-Christophe Ferré obtained a PHRC funding to evaluate the usefulness of the tool for clinicians. At the OFSEP level, Gilles Edan, Jean-Christophe Ferré and Elise Bannier have participated in the definition and standardisation of MR common scanning protocols. Christian Barillot, Olivier Commowick and Michael Kain have contributed to the archiving system of the MR cohort (using Shanoir).

Psychiatric disorders. Since 2017, we aimed to help to understand the pathophysiology of mood depressive disorders and to stratify precise phenotypes of depression with targeted therapeutic strategies. Reduction in maps of diffusion MRI indices in the brain were shown, confirming a frontal-limbic circuit abnormality. Our phenotypic approach has identified some specific patterns related to anxiety, anhedonia and psychomotor retardation – three core symptoms of depression (Cologner et al. 2019). Another part of our research concerns the resistance to treatments. Only 50% of patients respond, indeed, to their first treatment and remission rate with standard antidepressant treatments is only 30-40%. In a cross-sectional volumetric study with a 6 month clinical follow-up, we performed baseline brain grey matter volume analysis between 2 groups of patients suffering from depression based on illness improvement. Our study has pointed out the role of thalamus in prognosis of poor outcome at 6 months in patients with depression. These findings highlight the involvement of emotion regulation in the outcome of this disease. On this topic, we are currently working on a multimodal project in collaboration with Inserm U1000, to identify early microstructural and functional biomarkers of amygdala and its network.

Joint EEG-fMRI neurofeedback. Over the last 5 years, we developed a whole range of activities around hybrid EEG-MR imaging and neurofeedback for brain rehabilitation (Figure 4). We proposed to combine advanced instrumental devices (hybrid EEG and MRI platforms), with new man-machine interface paradigms and new computational models (source separation, sparse representations and machine learning) to provide novel therapeutic and neuro-rehabilitation paradigms in some major neurological and psychiatric disorders of the developmental and the aging brain. We developed a unique experimental and methodological framework for neurofeedback using joint electroencephalography (EEG) and functional MRI

(fMRI) (Fleury et al. 2019, 2020; Lioi, Cury, et al. 2020; Mano et al. 2017; Perronnet et al. 2017). Research is currently underway to apply this technique to patients suffering from stroke and depression (Butet et al. 2020; Lioi, Butet, et al. 2020). One of our additional scientific achievements on this topic has been to learn an fMRI-informed model which will be used to improve neurofeedback performed with EEG solely (Cury et al. 2020).

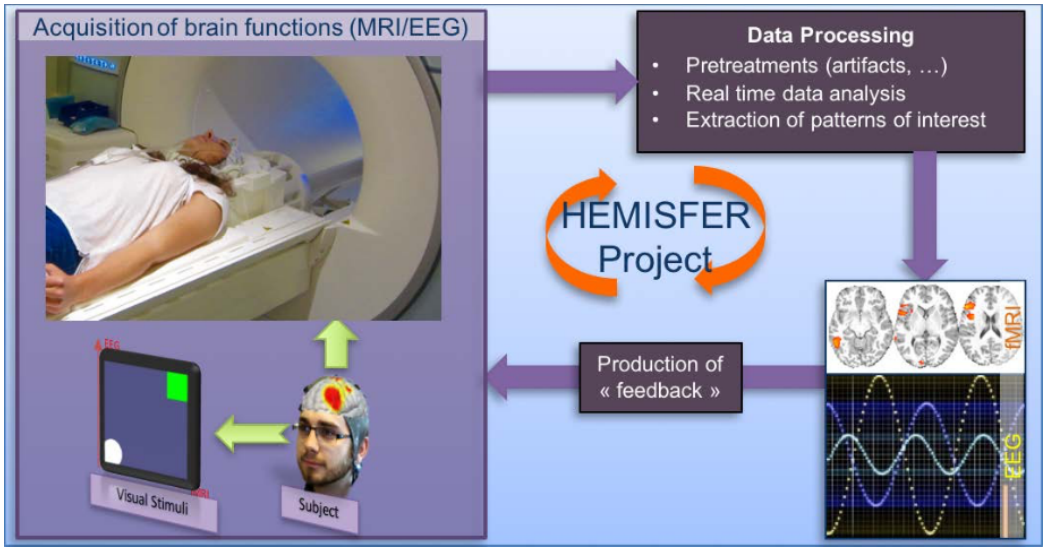

Figure 4. Joint EEG-fMRI neurofeedback

Developing brain. A last topic of interest is the study of the developing brain. We have proposed a new method (Legouhy et al. 2019) to create a diffeomorphic longitudinal atlas with the goal of studying the normal and pathological brain growth (Figure 5). This method, together with more methodological developments was applied to a cohort of nearly 200 subjects aged from 0 to 18 years old, and has proven useful in highlighting global and local evolutions both anatomically and for perfusion data (Legouhy et al. 2020; Proisy et al. 2019).

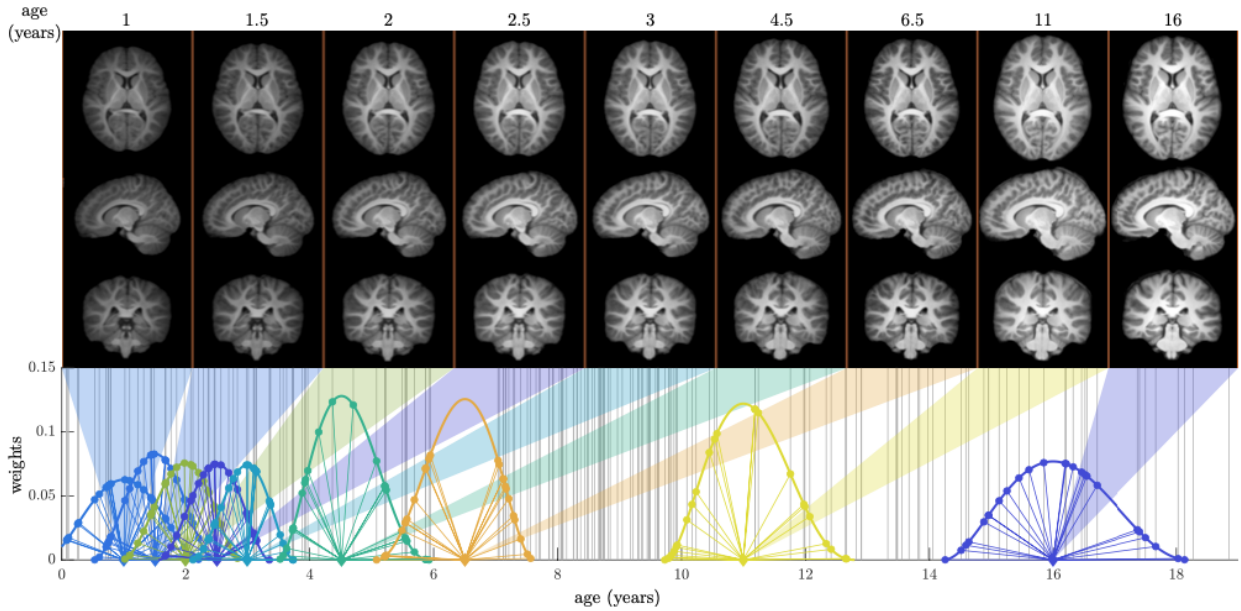

Figure 5 : longitudinal pediatric atlas obtained from 0-18 years old (Legouhy et al. 2019)

3.3 Management of Information in neuroimaging

With the objective to address issues raised by the rapid increase of both the volume and the heterogeneity of data in neuroscience and neuroimaging, Empenn contributes to the definition of international standards, to the development of software platforms for data management and processing and to original research to enable data reuse.

Standards for brain imaging. Empenn is a contributor of two international standards for brain imaging: the Brain Imaging Data Structure (BIDS) (Gorgolewski et al. 2016) and the NeuroImaging Data Model (NIDM) (Keator et al. 2013). In collaboration with a community of international researchers including Dr Ghosh from the MIT (USA), Dr Poline from McGill University (Canada) and Dr Hanke from Research Center Jülich and University of Düsseldorf (Germany) we have proposed a simplified representation to bridge the gap between those two neuroimaging standards (Maumet et al. 2019). We are also part of a regional collaboration with Institut du Thorax (Nantes) and the Dyliss team at IRISA, to tackle data modelling in biomedical research (including neuroinformatics, bioinformatics, bioimaging) (Cornet et al. 2020).

Data management and processing platforms. The development of Shanoir was consolidated to provide an open source neuroinformatics environment designed to structure, manage, archive, visualize, and share neuroimaging data for collaborative neuroimaging research projects. Besides hosting and sharing data in neuroscience, the need to share algorithms and processing pipelines also emerges in an effort towards a more open and reproducible research. With this objective, the first challenge on multiple sclerosis lesion segmentation using a data management and processing infrastructure was organized in conjunction with MICCAI 2016 (Commowick et al. 2018). This challenge aimed at evaluating state-of-the-art lesion detection and segmentation methods from the participants on a database following a standard protocol. The Shanoir solution was chosen by the OFSEP board to gather imaging data all over France. A Shanoir instance has been in use at Neurinfo since 2009, gathering 4TB of data from 60 centers, 170 studies and 7400 subjects and another Shanoir-FLI instance is in preparation.

Analytic variability. A new research axis was developed focusing on the impact of analytic pipelines on neuroimaging results. In (Bowring, Maumet, and Nichols 2019) we looked at the three main fMRI software (SPM, FSL and AFNI) and studied how using the same pipeline but a different software impacts fMRI results. We also teamed up with 200 researchers as part of an international study that looked at analytic variability in fMRI on the same dataset which led to a publication in Nature (Botvinik-Nezer et al. 2020).

Summary of scientific output

	2015	2016	2017	2018	2019	mid-2020	Total period
PhD & HdR Thesis	1	1	2	3	4	2	13
Journal	29	32	24	27	27	16	135
Conference Proceedings	16	7	11	28	32	2	96
Book & Book Chapter		2			1	1	4

Major journals in the field and, for each, number of papers co-authored by members of the project-team that have been accepted during the evaluation period:

1. Neuroimage: 8
2. Medical Image Analysis: 4
3. J. Magnetic Resonance Imaging /Magn. Reson. Med.: 4
4. IEEE-TMI: 1
5. Human Brain Mapping: 1
6. Brain: 2
7. PloS ONE : 4
8. Nature Communications: 1
9. Frontiers: 10
10. Nature: 1

Major conferences in the field and, for each, number of papers co-authored by members of the project-team that have been accepted during the evaluation period.

1. Miccai (Medical Image Computing): 9
2. IEEE-ISBI (Intl. Symposium of BioImaging): 11
3. SPIE-MI (SPIE Medical Imaging): 1
4. ISMRM (International Society of Magnetic Resonance in Medicine): 18
5. OHBM (Organization for Human Brain Mapping) : 18

Key events

The period was very rich for the Empenn unit with key events spanning from the development of original scientific research, the acquisition of state-of-the art equipment, the development of new collaborations and the organization of international events.

In October 2016, the unit organized an **international scientific challenge for automatic segmentation of brain lesions in multiple sclerosis (MS)**. This event was part of the international conference MICCAI 2016, in Athens, Greece. The challenge was performed with the OFSEP cohort and operated using the FLI-IAM computing infrastructure. Thirteen teams submitted an algorithm to take part in the competition. The results were estimated in comparison with a high-quality database of 53 MS cases coming from four centers using a harmonized acquisition protocol. Each case was annotated manually by seven experts. Results of the challenge highlighted that automatic algorithms, including recent machine learning methods were still trailing human expertise on both detection and delineation criteria.

In December 2017, an international symposium **MS - 25 years later** was organized in Rennes by Gilles Edan as President of the French Neurologic Society with the international leaders in the field of MS https://www.sf-neuro.org/content/la-journ-e-du-pr-sident-2017-en-r-sum

In January 2018, we organized a joint **workshop between Empenn and the CMIC team** led by Sebastien Ourselin at University College London. The joint workshop was on the topic of multiple sclerosis and led to new collaborations between the two teams.

In February 2018, we organized the program of the **ARSEP MRI Workshop dedicated to Spinal Cord MRI in Paris** with international leaders in the field and have been involved in the organization committee of this yearly workshop since.

In February 2018, **the Neurinfo platform launched its new MR system**. The 3T Verio MRI scanner installed in 2009 was replaced with a 3T high performance Prisma scanner (Siemens) running VE11C with higher B0 homogeneity, 80mT/m gradients and new sequences allowing shorter echo times, shorter acquisition times or increased spatial resolution for identical acquisition times.

In December 2018 **we scanned the first stroke patient on our fMRI-EEG neurofeedback protocol**, following 4 years of research on EEG-MRI Neurofeedback on healthy controls. In June 2019, based on this experience, we were selected to organize the symposium "*Multimodal Neurofeedback: The next generation of Neurofeedback for advanced brain self-regulation*" at OHBM 2019, the major international conference on brain mapping.

In June 2019, we launched the Multimodal Microstructure-Informed Connectivity: Acquisition, Reconstruction, Analysis and Validation (MMINCARAV) **bilateral exchange program with LTS5 lab, École Polytechnique Fédérale de Lausanne** — EPFL, funded by the Inria associate team program. The main objective of this new partnership is to develop novel methods for the quantification of microstructure properties in brain tissues using diffusion MRI and relaxometry, in relation with the macrostructure organization of the brain connectome.

In October 2019, a**n MRI and EEG compatible NIRS system** with 8 sources and 8 detectors was acquired, the first of its kind in Europe for the NIRX company. This evolution of our experimental platform will allow new advances in quantitative imaging as well as the development of new paradigms of human-machine interfaces, paving the way for novel therapeutic strategies in neurological and psychiatric disorders.

Over the period, we developed our internal scientific activities towards more openness and **took a leading role internationally in open science**. We hosted two "Brainhack" hackathons (2018 & 2019) – those hackathon targeted for the neuroscience community – as part of the international initiative Brainhack Global in which a myriads of such events happen simultaneously worldwide. In June 2020, with the OHBM Open Science SIG, we also were **running the international OHBM Hackathon and the Open Science Room**, two spaces next to the OHBM conference for collaborative projects and open discussions.

Our unit also has **a long standing history of leading and taking part in science outreach** for the general public, clinicians or the industry. For the period, those included: the National Science weeks (Village des Sciences 2017 & 2018), the Brain awareness weeks (2017-2020), Visits of the Neurinfo MR facility for

secondary schools (2018 & 2019), my thesis in 180 seconds (2017 & 2019) and even the "Music and Science festival" 2019 in collaboration with the Inria PANAMA team. We also demonstrated our MedInria platform during the celebration of the 50 years of Inria in November 2017 and presented our work at the "AI in health" days for the 80 years of CNRS. Every year we also meet clinicians and showcase our research at the French radiology days.

During the evaluation period, we have worked towards having long term development secured for some key software platforms. We have done so through the construction of a consortium for the Shanoir platform for archiving MR data for research. The consortium for Shanoir was created in 2018.

4- Organisation and life of the unit (team / theme if relevant)

Steering, life, organisation in the unit

As of this new contract, the director of the Empenn unit will be Pierre Maurel, associate professor at Université de Rennes 1. The Empenn unit is of limited size with a single team. The unit does not hold a formal « Conseil de Laboratoire » but relies on regular staff meetings as described below. When necessary, a formal general assembly is called (usually during the bi-monthly scientific seminar). Internally, **the director leads the unit and works closely with other permanent staff**. To steer the unit, the director strives for building consensus among permanent staff for any important decisions, those are discussed during the "permanent staff meetings". As the director he retains the final decision and responsibility on the steering of the unit.

Permanent staff meetings: a monthly two-hours meeting takes place with all researchers, medical doctors and engineers with permanent position. All aspects concerning the daily life of the team are addressed, from new grant proposals to the need of equipment, recruitment of new masters or proposal of new PhD or Postdoctoral positions. This is where decisions are discussed. Once a year, the official report prepared for the "Comité de Coordination" is also shared with permanent staff.

Out-of-town seminar: Once a year, the whole team takes a two-day seminar away from Rennes in a leisure residential area in Brittany. It is of tradition that the program of this seminar is built by a 2nd year PhD student in collaboration with one permanent staff. The program is rather flexible, but in general, there is a balance between social activities and general-purpose presentations (introduction to computer programming good practices, medical presentations, short introduction of new PhD topics or new equipment…). Regularly, this seminar is also performed jointly with the people from our international Inria team (with S. Warfield's lab, at Harvard Medical School, Boston or more recently with J-Ph. Thiran's lab at EPFL, Lausanne)).

Other responsibilities are shared across permanent staff as follows:

- **Internal scientific seminars and invited talks** (led by Olivier Commowick): A scientific seminar takes place every two weeks in the team, with a program scheduled ahead of time for the academic year. It provides team members with the opportunity to present recent work, review a scientific paper, demonstrate a platform and/or tool or report from conferences. In addition, invited talks are regularly organized with national and international collaborators (in the past period: US, Canada, Switzerland, Germany, Iran).
- **Preprints** (led by Julie Coloigner): As part of the commitment of our unit to participate in open science, we have a designated role to help researchers submit their first preprint on our institutional archive (HAL).
- **Communication & social media working group** (led by Camille Maumet): The goal of this working group is to disseminate information about Empenn on multiple communication channels (including the Empenn website, Twitter) sharing news about: recent publications, talks, events we attended and organized, etc.
- **IT representative** (Emmanuel Caruyer): Liaise with Inria/IRISA IT department including: requesting computers for newcomers, material renewal, etc.
- **BioGenouest Representative** (Isabelle Corouge): Liaise with BioGenouest, the regional network of technological platforms.
- **Biblio Inserm Representative** (Jean-Christophe Ferré): Liaise with Inserm bibliographic database and forward login information to all lab members.

In terms of logistics, the team is organized with an **administrative assistant** (Armelle Mozziconacci) (60% FTE) in charge of the management of the Inria/CNRS/Inserm administration at IRISA/Inria. There is currently no administrative assistant for the University, whether for the Medical Faculty nor for Neurinfo duties.

As part of **IRISA (UMR CNRS 6074)** and its D5 department Signal, Images and Robotics); the Empenn team participates to the instances of IRISA and abide by its general organization ("conseil de laboratoire", internal chart of rules, general seminars, Sigima seminars…).

Since the creation of the Visages Team in 2006 (then followed by Empenn in 2019) by **Inserm and Inria**, a convention has been signed between the presidents of Inria and Inserm (CNRS and University mandated Inria to represent them under the IRISA UMR agreement) in order to specify the rights and commitments of the different institutional partners, the director and the different members of the Unit/project. Through this agreement, Inserm mandated Inria to manage all of their recurrent funding support. Based on this convention, the director of the team has to present every year a complete financial and scientific report to a "*coordination committee*" where University of Rennes I, CNRS-INS2I and directors of UMR IRISA are permanently invited.

Equipment and technological platforms

The University of Rennes I, Inria, CNRS, the University Hospital of Rennes and the Cancer Institute of Rennes are partners for the creation of the in-vivo imaging platform called Neurinfo. Neurinfo is labelled by the GIS IBISA national coordination since 2015 and is now part of the Western France node of France Life Imaging (the national infrastructure of life imaging). The role of Empenn is to operate Neurinfo, provide scientific and institutional support, apply for major grant applications involving imaging at Neurinfo and report to the institutions yearly. The director of Neurinfo is a member of Empenn. The two research engineers working at Neurinfo are also members of Empenn. Once a month the steering committee - consisting of the director, the technical manager, medical doctors (Pr. Edan, Pr Gauvrit) and representatives of the different partners - meet to discuss new projects applying for MR scanner time (from pharmaceutical clinical studies to academic research studies), human resources and organisational issues. The board (comité de concertation) with representatives of each institution meets once a year. Further details on the Neurinfo platform is provided in Annex 3.

Parity; scientific integrity; health and safety; sustainable development and environmental impacts; intellectual property and business intelligence.

Our team has traditionally been balanced in terms of gender. We currently have 17 men and 11 women. As part of both our institutional partnerships, we benefit from the actions of their committees on **men-women equality** including: mentoring of early career scientists, grants for childcare when attending conferences (Inria staff only), onsite lactation room (IRISA Rennes), policies on the selection of speakers for conferences funded by Inria. We follow good practices for recruiting of staff including the use of gender inclusive writing in our job proposals.

Our team is committed to the respect of **scientific integrity**. In the past couple of years, we have started to work towards more transparency on our research practices. In particular we communicate about our research through multiple channels: e.g. we use preprints to share our latest results ahead of time, we share our experience attending conferences on our blog, we use our twitter account to share our latest news. Moreover, the unit benefits from the University of Rennes 1 policy in this domain and from awareness-raising activities for staff (e.g. the yearly "Training in Research Ethics and Scientific Integrity" for PhD students).

All members of the Empenn unit benefit from the Inria / IRISA **CHSCT** (both locally and nationally) and can reach out to the 5 local representatives identified on the Inria intranet for any queries related to health and safety.

IRISA is involved in actions supporting **sustainable development**, from infrastructure design to energy supply and the impact of digital technologies, We benefit from the actions of the ecoinfo GDS, actions at IRISA, and the initiative recently started by the IRMAR. In our participation to run scientific events, we also commit to share online as much as we can including slides and posters from our participation to conferences, we also live tweet conference contents when attending. As organizers of the 2020 OHBM hackathon and Open Science Room we live broadcasted part of the event for the first time.

In terms of intellectual property and transfer to clinicians or companies, it is first worth noting that our research produces two main kinds of outputs: development or adaptation of MR sequences, and image management as well as image processing softwares to be used by the community or by clinicians. Our strategy for new MR sequences developments is to bear on a Master Research agreement we have with Siemens, granting us access to the software environment for sequence development and to the specific source code of MR pulse sequences we want to work on, after applying for this source code with a detailed project. As such, a diffusion sequence able to play arbitrary gradient waveforms was developed in the context of the FastMicroDiff project led by Emmanuel Caruyer. A research licence allows us to run the developed sequences on our MR scanner. In addition, such developments may also be transferred as sequence binaries to other Siemens sites under a Master Research Agreement via a C2P agreement. This MRA was renewed for the new Prisma scanner with help of the SATT. As for software property and transfer,

our choice is twofold. We first mainly contribute to open source libraries and resources (open data). We believe that this will bring more visibility to our unit as well as new collaborations. Examples of these developments include medInria (visualization and image processing platform), the Anima library (including softwares from research of the team), autoMRI (ASL and fMRI processing). All of these softwares are developed under open-source licenses. In addition to this open-source developments, when a software is of crucial importance to a company or to us, we resort to filing patents (e.g for hybrid EEG-fMRI neurofeedback) or signing specific contracts (e.g. : Integration of a super-resolution ASL module, through a SIEMENS-CIFRE PhD, into the Siemens Healthineers postprocessing syngo.via Frontier prototype: MR ASL Perfusion Analysis). As mentioned earlier, we are also involved in the FLI-IAM project, whose objectives are to integrate some of our database tools and processing pipelines from the community in a software platform. Finally, we also favor the integration of our software into clinically driven applications thanks to our integration into the clinical teams (e.g. the MUSIC project with Rennes hospital). All these aspects of intellectual property and transfer are facilitated by the interactions with the legal departments of our institutions.

FIVE-YEAR PROJECT AND STRATEGY

1. Past Evaluation resume and SWOT analysis

Since 2015, the Empenn team has been evaluated and awarded in parallel by national and international evaluation panels: by HCERES for Inserm in 2016, and at the same time by the scientific evaluation committees of Inserm (Evaluation Committee in Health Technologies and Scientific Council of Inserm), and again by Inria in 2018, always at the highest ranks or labelled as “internationally excellent”. Though stringent, we feel that these processes of evaluation were very profitable to us for preparing the continuous evolution of our research project and to set up the best scientific strategy. This helped us to provide a SWOT analysis of the team that helps to build its prospect.

Strengths	Weaknesses
• Close integration in both the scientific and the medical campuses • Deep interdisciplinarity of the team members at each level (from staff to PhD and masters) • Projet multidisciplinarity: most projects address both methodological and clinical research challenges • Experimental platform in clinical environment (Neurinfo) • High level of international collaborations • Complementarity between the different national partners (INSERM, Inria, CNRS) and Close relations with the stakeholders (Hospital, Industry) • Research team well focused on Imaging biomarkers and Clinical Neurosciences • Complementarities between the clinical applications addressed • Attractiveness to PhD candidates at the national and international level • Technological transfer (patents, software)	• Lack of professorship position without clinical duties • Lack of basic funding to support emergence of new internal research topics • Lack of administrative support at the Neurinfo platform as an impediment that significantly prejudices the scientific fulfillment of our research engineers • No Inserm permanent staff (several applications for researcher positions: no admissibility interviews although recruited at CNRS and Inria the same year, no support staff positions either)

Opportunities	Threats
• Participation to several “investissement d’avenir” projects (1 LabEx, 1 IRT, 1 Infrastructure, 1 Cohort) • Potentiality of the Neurinfo Platform to develop new cutting-edge projects • Cutting edge imaging systems arrived in the recent period at Neurinfo (MR-compatible EEG & NIRS, MRI) • Potentiality to build European clusters through the H2020 OpenAire-Connect project and FLI-IAM • High support of the local institutions (Regional councils, Hospital, University) • Leading position on new cutting edge large scale clinical research projects (Multiple Sclerosis, Psychiatry Cohorts, ... • Collaboration framework with Siemens through the Neurinfo platform • Involvement in the SIBM Master program to attract students, whether medical residents or engineers • Pull up of talented young investigators at the national and international levels	• Multidisciplinarity: can lead to difficulties to credit individual contributions • Heterogeneity of the academic culture (i.e. medical vs scientific campuses) for organization of research, authorship. . . • High dependency of the basic research to project funding • High demand for processing of data acquired in clinical research studies but little funding : it is difficult to recruit, train and keep engineers to support our clinical studies with short-term discontinued contracts. This demand translates into a risk for the research staff to invest too much time in data processing rather than in original methodological research. Both need to be maintained. • Tendency of the evaluation system to support individualism of researchers • Pressure for rapid and fragmented publications rather than qualitative ones

2. Structure, workforce and scientific orientations

For the next contract, while our core objective regarding the detection and development of imaging biomarkers for brain diseases and the translation of this research to clinical practice and clinical neuroscience remains, new scientific thematics will be emphasized to fulfill new scientific objectives through increased workforce and innovative technological set up.
In particular, our interest for population imaging will be sustained by an emerging research area in the team around the modeling of analytic variability of image processing pipelines, for which Camille Maumet, recruited in 2017, will be the key researcher. Furthermore, the medical image computing "learning" axis will be reinforced by the recruitment of Julie Coloigner with the objective to develop multimodal approaches combining multiple MRI sequences (e.g., DWI, BOLD and ASL) as well as multimodal sensors (MRI, EEG, NIRS) to provide for instance better estimates of the brain connectome. On the applicative side, Gabriel Robert, who should join the team for the next contract, will bring new insights in the field of behavioral disorders in order to better understand pathophysiological processes thanks to image computing methods. Last, the "neurofeedback" strategy for brain rehabilitation and recovery will be pursued with an arising translation to clinical research for instance in stroke and depression. These new developments will be led in close collaboration with the Neurinfo facility, whose technological evolution offers outstanding opportunities in this field.

As a result of these scientific orientations and as illustrated in Figure 6, our research project is organized around three major technological and basic science topics (*Population Imaging, Detection and Learning,* and *Quantitative Imaging*) and three major translational axes (*Behavior, Neuro-inflammation* and *Recovery*) that are generic enough to address a large range of central nervous system diseases.

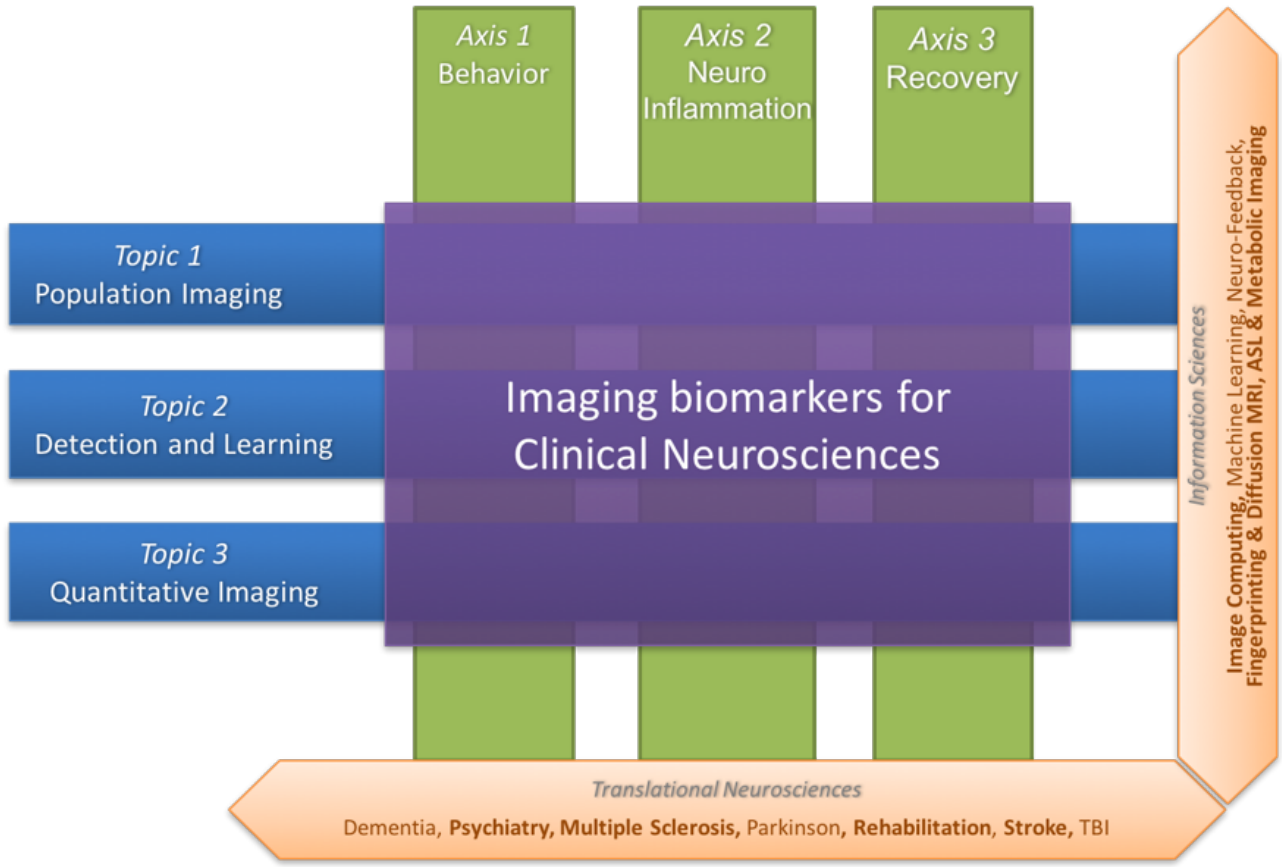

Figure 6: Scientific organization of the research team through three basic research topics in information sciences (Population Imaging, Detection and Learning and Quantitative Imaging) and three translational axes on CNS diseases (Behavior, Neuro-inflammation and Recovery). These projects will intersect around the new core scientific objective of the "Imaging Biomarkers for Clinical Neurosciences" team.

2.1. Basic research

2.1.1. Population imaging

Key investigators: O. Commowick, G. Edan, A. Kerbrat, J-C. Ferré, C. Maumet

A major ambition of many neuroimaging researchers and clinicians is to derive brain models of targeted populations. Building such models requires large-scale experiments.

However, developing and using multi-site, large-scale resources poses specific challenges regarding the management of the huge quantity of data produced and their diversity. Empenn will focus on two challenges in particular:

1. Providing computational environments for the computation and use of imaging biomarkers for the targeted brain diseases, a solution to be used by radiologists and neurologists/psychiatrists for the clinical follow-up of a large patient population.
2. Modeling the analytic variability of image processing pipelines to better understand and predict the behavior of imaging biomarker detection solutions, and improve reproducibility and productivity in clinical neuroimaging research.

Sharing scientific resources (data storage and processing) is a top priority for research funding agencies in order to improve the efficacy and the reproducibility of research. Sharing data and image processing services for translational research is required for: (1) the integration of large data sets for population-wide studies and the construction of imaging cohorts; (2) the validation of image processing tools on reference datasets for the validation and quality control of image processing procedures; (3) the reuse of image processing pipelines on different datasets and from peers in order to share processing tools and improve research productivity and reproducibility; and (4) the validation of research results based on the proofed control statistical analysis of images for the validation and quality control of experimental research.

The joint analysis of data from diverse sources also makes it necessary to consider new levels of heterogeneity. Differences in imaging instruments, protocols, acquisition sites and also processing pipelines induce unwanted variabilities in the data. In the coming years, we will investigate how this analytical

variability impacts large-scale analyses and propose new methods to better understand and predict the behavior of image processing solutions, and improve reproducibility and productivity in clinical neuroimaging.

In this context, based on our successful involvement in large-scale population imaging projects, we expect in the next period to extend our research and development efforts in order to provide the medical imaging community with dedicated IT solutions able to integrate cloud services. Through the French national infrastructure project “France Life Imaging” (FLI), from which we are leading the “digital node”, and with the support of the French bioinformatics infrastructure project (in particular, FBI is supporting the INEX-MED project), we plan to build and extend infrastructure for storing, managing and disseminating in vivo imaging data and processing solutions in the field of human neurosciences, and interoperating with omics IT solutions. We propose building versatile software platforms and disseminating them in the community:

- We are developing an archiving and management infrastructure for in vivo images, as well as providing solutions to process and manage the acquired data through dedicated software and hardware solutions.
- We believe that a single system will not be able to meet all the needs of the neuroimaging community. Instead, we propose building versatile image analysis and data management solutions for in vivo neuroimaging that will allow interoperability between production sites and distributed users, while allowing interoperability with other third-party solutions that may emerge within the community. This will provide heterogeneous and distributed storage solutions implementing raw and metadata indexing (e.g. through the use of semantic models or ontologies).
- We will build a versatile computing environment that allows interoperation between medical imaging and omics infrastructure.

This type of population imaging IT infrastructure will open up new opportunities for modeling groups and sub-groups of populations and comparing these groups to individual patients, both at a single time point and through longitudinal series. Such comparisons are currently based on image similarity or transformation residuals to minimize inter-subject variability. So far, these approaches have not fully succeeded, partly due to the limits of the embedded information from images.

In the next period, we will study other criteria derived from prior knowledge of the disease that may be seen in the images to help characterize different developments in a population of patients. The evaluation of all these criteria will be crucial to either help build sub-atlases describing the disease, or characterize a specific patient with respect to a known database of images.

In the next period, we will also develop new methods for the construction of longitudinal population-specific atlases for patient populations. We will develop data fusion strategies that are robust to the presence of pathological morphologies (i.e. lesions). In this topic, we will primarily address applications relating to neonates (especially premature babies), vascular or perfusion-related pathologies, and multiple sclerosis, in which the evolution of lesions is crucial to grade the pathology and evaluate the treatment. This part of the work was initially supported by the ANR project MAIA (PI: F. Rousseau, LATIM, Brest). This research will progress through multidisciplinary research topics such as non-linear image registration robust to the presence of pathologies, and we will therefore investigate how to reject the outlier deformations generated by these lesions when registering either anatomical images or diffusion images. Since we will be studying many modalities at the same time, we will also investigate registration combining multiple and multidimensional channels (e.g. DTI, T1, T2 qMRI, etc.) to consider the information contributed by each imaging sequence and combine them for optimal fusion strategies.

These methodological developments will be used, for example, to compare MS patients and controls to evaluate how the disease may damage normal-appearing white matter, or to determine different patterns in a population (e.g. different patterns of evolution in MS or patients suffering from dementia syndromes) and measure the outcome according to this pattern. This framework will also be used for classifying new patients into one group or another, and thereby used to model the natural history of the pathology or predict its development in an individual.

Expected results

- On the technological side, we expect to set up and extend large-scale virtual computational infrastructure such as FLI-IAM at a national scale, for clinical research, and MUSIC at a regional scale, to set up a digital healthcare solution for all MS patients in western France. In the longer term, we expect to extend the virtual computational infrastructure at an international scale, with connection to open science infrastructure (e.g. OpenAire) for distributed data management and image processing solutions. We also expect to develop an interoperability solution to link the

imaging infrastructure to the omics infrastructure in order to give a more comprehensive view of a pathology.

- On the basic science side, we expect to develop new atlas-based population models built from normal and pathological populations, and robust to the presence of pathologies, and apply these new methods to a specific population (those treated for MS and depression in particular). Over the longer term, we expect to develop new statistical population models robust to the analytical variability arising from the large discrepancy embedded in imaging cohorts and population data. We will focus our work on analytic variability on developing both: brain imaging standards to model provenance and statistical models to compensate analytic variability and enable combining open datasets.

On the topic of population imaging, we intend to play a significant role and make major contributions in two key domains:

1- Providing computational environments for the development and integration of data processing algorithms (e.g. machine learning algorithms) that will be used to provide imaging biomarkers for multiple sclerosis, a solution to be used by radiologists and neurologists for the clinical follow-up of patient populations on a large scale. *Olivier Commowick and Gilles Edan will be the key researchers on this topic.*

2- Modeling the analytic variability of image processing pipelines to better allow combination of open datasets, and ultimately improve reproducibility in clinical neuroimaging research. *Camille Maumet will be the key researcher on this topic.*

2.1.2. Detection and learning

Key investigators: O. Commowick, P. Maurel

Detection and learning from large sets of data: Due to the growth in the size of medical image databases in the last few decades, dedicated data management systems and image processing pipelines providing dimensionality reduction methods have become necessary to handle them. Nowadays, statistical analysis is a central tool for the study of brain anatomy and function based on medical imaging. The issue at stake is the extraction of statistically significant information from large public image databases. For example, in the case of MRI brain images, physicians have to manage large image databases containing several imaging sequences (T1, T2, FLAIR, dMRI, etc.) for each patient, and potentially several time points in addition to quantitative sequences (relaxometry, magnetization transfer ratio (MTR), etc.). A more recent objective brought to the community is the coupling of data analysis and processing methods capable of combining imaging and genetic information (Hibar et al. 2015). From this impressively large amount of data, we can expect to derive smarter approaches to integrate this information than the standard brute force meta-analysis of image signatures using a genome-wide association study (GWAS). Imaging databases often show high levels of redundancy across the same patient, and therefore the same brain structures, being repeated through different modalities and different time points. As a result, the current challenges are to be able to provide clinically relevant metadata extracted from images, using classification and machine learning approaches, or from high-level data that will become available through the rapid extension of computational pan-genomics linked to imaging studies.

In this context, one of our objectives is to apply dedicated dimensionality reduction frameworks in order to deal with large image databases. This will include the study of sparse representations, which will take into account the redundancy of the information embedded in multidimensional and longitudinal MRI images. The goal is to achieve a more suitable representation of the data for image analysis and the detection of features specific to a form or grade of pathology, or specific to a population of subjects (e.g. patients to group comparison). An initial idea will be to apply multimodal joint sparse decomposition techniques. Further developments could include multiple layers of dictionary-learning steps, which would hierarchically adapt dictionaries to a specific class of images or image patterns, or to a specific class or form of pathology. Such a framework for representing large databases has proven successful in diverse uses (denoising, inpainting, compression and classification) and would be a worthwhile tool in a very wide range of applications in the domain of neurological, neurodegenerative, psychiatric and neurodevelopmental brain diseases.

Detection and learning for multi-sensor fusion: Another issue in detecting and learning patterns from data concerns data fusion from multiple sensors. When it comes to modeling the functional organization of the human brain, multimodal sensing can provide additional information about the underlying functional processes. This is especially true when studying brain functions in which the neuronal activity is recorded

at different spatial and temporal scales (e.g. BOLD or perfusion MRI and EEG), and of particular interest when these signals are recorded during a neurofeedback protocol.

One of our objectives in this domain will be to learn a multi-sensor coupling model combining brain functional signals with neurofeedback scores. Different sparsity-enforcing penalties can be evaluated in order to exhibit which spatial brain areas are activated at a certain time for a certain activation performance. To address this issue, we primarily envision the learned model extracting only the useful signals related to brain state performance (as measured by neurofeedback scores) by combining (*a*) a common high-resolution spatiotemporal model of brain activity, characterized by sparsity in an appropriate domain; and (*b*) models of the acquisition process in each of the considered modalities. Learning a multi-sensor coupling model will therefore consist in learning both the domain in which brain activity is sparse (e.g. through dictionary learning), and adjusting a parametric model of the acquisition processes (this can be seen as a calibration process). Alternative methods based on Bayesian inference or machine learning with out-of-sampling strategies will also be considered. We expect to demonstrate the significance of the methods and the effectiveness of the algorithms through in vivo experiments (normal controls, and patients with psychiatric disorders and/or stroke). In this methodological domain, there is already close collaboration with local groups on sparse representation and machine learning (PANAMA team).

Expected results

- Provide a computational environment that combines data-driven (machine learning) and Bayesian solutions to improve the detection of abnormal patterns in images through decision or evidence theory data fusion strategies. The major initial application will be for MS. Over the longer term, we also expect to adapt these methods to address a wider range of neurological diseases (epilepsy, stroke, tumors, etc.) in neonate and adult brains.
- Develop solutions for combining brain state measurements from multimodal sensors or sequences (e.g. fMRI, ASL, EEG, NIRS, etc.) with applications in the spatiotemporal reconstruction of brain activity from MRI-EEG or the combined detection of the endogenous hemodynamic and resting state network of the brain from ASL. Over the longer term, the advent of new hybrid brain imaging sensors (e.g. PET-MRI) will require these methods to be extended to a larger spectrum of information combining structural, morphological, metabolic, electrophysiological and cellular/molecular information (e.g. through the use of specific ligands/nanocarriers).

On the topic of detection and learning, we intend to make significant contributions with major impacts in learning coupling models between functional recordings during neurofeedback procedures. These advances will provide a breakthrough in brain-computer interfaces for rehabilitation protocols. *Pierre Maurel will be the key researcher on this topic.*

2.1.3. Quantitative imaging

Key investigators: E. Bannier, E. Caruyer, J. Coloigner, O. Commowick, I. Corouge, J-C. Ferré, JY Gauvrit, P. Maurel, G. Robert

Quantitative brain function: Several techniques such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), functional MRI (fMRI) and arterial spin labeling (ASL) may be used to image brain function. However, ASL is the only contrast media-free method for measuring quantitative cerebral perfusion. This completely non-invasive MRI technique magnetically labels arterial blood water as an endogenous tracer for perfusion and can measure resting-state cerebral blood flow (CBF). ASL has great potential for use in a clinical setting (e.g. for stroke, epilepsy, Parkinson's disease, dementia, brain tumors, developmental disorders and neuropsychiatric disorders) and can also be used in healthy controls due to its non-invasive nature. The two main difficulties encountered with ASL concern its low signal-to-noise ratio (SNR) and the blood flow variability across brain regions, time and subjects; difficulties that lead to errors in the CBF estimation. Previous work (including our own) has focused on the robust estimation of CBF, correction of the partial volume effect and enhancement of the inherently low ASL resolution.

To advance further, over the medium term, we will investigate both the acquisition and modeling aspects of ASL. Acquisition investigations will be carried out within the framework of our collaboration with Siemens, which provides us with work-in-progress sequences (e.g. the 3D multi-TI sequence) that we will jointly optimize. Modeling investigations will focus not only on CBF estimation, but also on the multiparametric estimation of hemodynamics (e.g. CBF and arterial transit times). A central problem inherent in complementing the representation of brain structural maps is the retrieval of quantitative parameters able to exhibit local metabolic or functional behavior, such as the dynamic aspect of the brain. Our objective in the next period, which has not really been addressed in the literature in this context, will be to provide new

features and enhanced parametric maps of brain perfusion and mental state connectivity at rest, and to develop new analytical models of dynamic regional perfusion. These advanced perfusion-derived functional models will be matched to structural models of connectomics features in order to infer indices of dynamic brain local perfusion from normal and pathological populations. From these maps, statistical descriptors will be derived to represent significant differences between groups of individuals. In the longer term, we hope to extend these technical and methodological advances to even more challenging domains such as neonates and antenatal neurodevelopment.

Tissue compartment imaging: In addition to quantitative perfusion parameters, we will evaluate and apply novel imaging techniques to improve our ability to delineate neural circuits and characterize the tissue microstructure present in these circuits. For instance, in neuro-inflammatory diseases (e.g. MS), disease burden and progression are usually assessed by measuring the lesion load in the brain using T2w or gadolinium-enhanced T1w MRI. Unfortunately, while these measures indicate the general rate of progression to disability, they correlate poorly with individual patient symptoms, as they do not directly reflect the nature of the damage to the brain tissue. There is therefore a need for novel imaging techniques (acquisition and processing) to non-invasively characterize the alterations in the tissue compartments associated with disease progression. In addition, the spatial location of lesions with respect to these neural circuits likely plays a central role in the progression of disease burden. To address this paradox between clinical and MRI observations, we aim to:

- Develop improved diffusion imaging of tissue microstructure. Our main objective will be to develop and exploit new imaging sequences using arbitrary scattering gradient waveforms particularly well adapted for their sensitivity to brain microstructure parameters, thus allowing more accurate diffusion compartment imaging (DCI) (Drobnjak, Siow, and Alexander 2010; Topgaard 2017). These new sampling schemes are based on a close coupling between the trajectories of water molecules and the geometry of tissues (axons, neurites, glial cells, ...) that hamper their movements. The main challenge in these acquisitions is the large size of the sampling domain. We believe that these largely underexploited degrees of freedom in the acquisition, as well as an adequate representation of the diffusion signal within this more general framework, will allow the development of faster acquisition strategies using compressive sensing. In complementarity with these new sampling schemes, we will develop new techniques in the field of DCI. These models show great potential for the fine explanation of disease progression at the microstructural level. However, their estimation is complex and very sensitive to the quality of the acquisition. We will therefore study how to make the estimation more robust and efficient by introducing anatomical priors and estimation techniques based on the use of adapted dictionaries. In this field of DCI, we will also develop a series of methods ranging from model interpolation to data registration and tractography to enable the study of patients as part of clinical follow-up, in combination with other quantitative imaging modalities.
- Develop new relaxometry imaging techniques and reconstruction techniques to identify brain tissue compartments. As recently revived by the concept of fingerprinting (Ma et al. 2013), normal brain tissue consists of several tissue compartments including myelin-bound water, extra-axonal water and cerebrospinal fluid. However, conventional imaging that exhibits ranges of T1w and T2w contrasts only provides an indirect and entangled scalar value derived from all these tissues. There is thus a pressing interest in moving from voxel level to tissue compartment level, such as myelin-bound water level, to clearly evaluate their disease-related changes and provide critical new insights into disease burden. We will therefore develop imaging sequences and image processing techniques to provide quantitative tissue compartment measurements from T1 and T2 relaxometry with clinically acceptable acquisition time, improved spatial resolution and increased accuracy.
- Assess the efficiency of measures of disease burden and progression from compartment imaging in comparison to conventional imaging measures. To do this, we will develop and study new combined metrics of microstructure damage from diffusion and relaxometry sequences. These provide additional information about myelin and brain microstructure in general that could be used to better understand and model the diseases. We will then develop new anomaly-detection frameworks along the major neural fiber bundles using compartment-specific measurements along these bundles. We will evaluate the effectiveness of these new tissue compartment imaging methods by comparing conventional measures of disease severity and progression with a more precise delineation of neuronal circuits, measures of severity of brain damage in the tissue compartment, and an assessment of disease burden in the neuronal circuit.

Expected results

- Provide new solutions to better characterize brain function and microstructure damage by using ASL, on the one hand, and multicompartment imaging from diffusion and relaxometry MRI, on the other hand, and apply the developed methodologies to some specific brain pathologies (MS,

depression, neonatal disorders, mild traumatic brain injury, those affecting neonates, etc.). Over the longer term, we expect to develop new quantitative MR sequences and computational solutions incorporating multimodal metrics in order to derive imaging biomarkers based on multiparametric measures (e.g. hybrid qMRI measures, fingerprinting, PET-MRI, qBOLD, resting state ASL, etc.).

On the topic of quantitative imaging, we plan to make major contributions with significant impacts in two key domains:

1- Providing specific biomarkers of brain microstructure damage by combining quantitative MRI metrics and assessing these metrics in relation to specific pathologies, primarily multiple sclerosis and depression**.** *Emmanuel Caruyer, Olivier Commowick and Elise Bannier will be the three key researchers for this topic.*

2- Providing specific biomarkers of brain perfusion and functional connectivity from multiparametric ASL on youth and adult populations (estimating functional and resting state ASL from standard perfusion protocols), and neonates. *Pierre Maurel, Isabelle Corouge and Jean-Christophe Ferré will be the three key researchers on this topic*.

2.2. Translational research

2.2.1. Behavior

Key investigators: E. Bannier, I. Bonan, E. Caruyer, J. Coloigner, O. Commowick, I. Corouge, J-C. Ferré, J-Y Gauvrit, P. Maurel, G. Robert

Advances in the field of in vivo imaging offer new opportunities to address the management of resistant affective disorders and their consequences (suicide risk and socio-professional impact), the management of spatial cognition disorders after stroke and their consequences (postural perturbations and the loss of autonomy). Our objective, and the main challenge in this context, will be to introduce medical image computing methods to the multidisciplinary field of behavioral disorders (cognitive disorders, particularly spatial and postural control disorders or anterograde memory impairment, and mood disorders, notably resistant depression, schizophrenic disorders, pervasive developmental disorders, attention disorders, etc.) in order to gain a better understanding of the pathology and devise innovative therapeutic approaches. In vivo brain imaging using functional imaging techniques, such as arterial spin labeling, BOLD fMRI or new brain computer interfaces with hybrid MRI-EEG, MRI-NIRS, EEG-NIRS or PET-MRI, with different markers and structural imaging techniques (anatomical MRI, diffusion MRI and connectomics) may help to better characterize the pathophysiological processes. In particular in the context of resistant depression in its various forms (unipolar, bipolar or depression in the elderly), its components (lack of motivation or emotional distress), tools are needed to better highlight their early developmental factors and their prognosis (therapeutic response to innovative strategies (brain neuromodulation and neurofeedback for example) or resistance/cognitive impairment. Using PET, a lower affinity for serotonin in the prefrontal cortex or a decrease in glucose metabolism in the prefrontal and anterior cingulate gyrus has been found in suicidal depressed patients. Functional MRI studies show different responses, such as greater activation of the right orbitofrontal cortex and lesser activation of the right anterior frontal gyrus. More generally, very few neuroimaging studies on behavioral disabilities using ASL have been reported. Even less studies have tried to combine perfusion and metabolism with microstructural information from DCI or MR relaxometry. In this area, we have been involved in a first preliminary study using ASL, which demonstrates significant hyperperfusion in the bilateral subgenual anterior cingulate cortex (sACC) in chronically depressed and treatment-resistant patients. On this topic, we are currently involved in a national project funded by the “Fondation de France” for the next two years (in collaboration with Inserm U1000 at Paris Descartes University). We expect our methods to help clarify the diagnosis (unipolar/bipolar, involutional depression, the nature of initial memory impairment, the nature of postural perturbations and the loss of autonomy), make a prognosis, propose innovative therapies or validate and optimize current and new treatments.

In methodological terms, our objective in this project will consist in reconciling observations (i.e. imaging biomarkers) and treatment processes through new brain stimulation paradigms (e.g. multimodal neurofeedback), integrating functional, morphological and structural data, and performing feature selection, detection and classification in order to provide patient-to-population or between-group comparisons. In particular, we will pursue the differentiation of patients within these groups in order to highlight developments in longitudinal data or at the group level in relation to the therapeutic protocols studied and healthy controls (in this respect, we will be able to compare our patient population to the IMAGEN cohort). Specific attention will be given to cortico-subcortical loops involved in limbic functions and related cortices (anterior cingulate and orbitofrontal) and basal ganglia (particularly the subthalamic nucleus). There are great opportunities locally to gather expertise in information processing, neuropsychiatry and neuroradiology. We will investigate this domain with the Neurinfo platform, in collaboration with the Cancer Institute of Rennes (Prof.

F. Le Jeune for the PET platform), the Psychiatric Hospital of Rennes (Prof. D. Drapier and Drs. J.-M. Batail and G. Robert), and also through the National Consortium of Psychiatric Research (GDR CNRS 3557).

Expected results

- Provide new imaging markers of mental diseases, especially in the context of depression and mood disorders. The new biomarkers will be derived from the metabolic (ASL and later ASL+PET) point of view, functional (resting state and task functional MRI) as well as from the microstructural point of view (multicompartment diffusion MRI and relaxometry). Similarly, we expect to exhibit imaging biomarker regularities combining metabolic and structural information. Over the longer term, we expect these biomarkers to be the target of neurofeedback rehabilitation procedures. Also, over the longer term, we expect to supplement the MRI markers with molecular marker ones coming from new PET tracers, especially those associated with serotonin intake, at one time point or during a rehabilitation protocol under hybrid PET-EEG-MRI neurofeedback procedures.

On the topic of behavior, we expect to become a major player in the future and make important contributions with significant impacts, primarily in drug-resistant depression in young and old populations. In particular, we expect to provide new image-related metrics combining perfusion, metabolism and microstructural information regarding the brain in order to better characterize pathologies, provide prospective evolution values and potentially provide new brain stimulation targets that could be used in neurofeedback rehabilitation protocols or other types of brain stimulation procedure. *Gabriel Robert, Jean-Yves Gauvrit, Isabelle Corouge and Julie Coloigner will be the key researchers on this topic.*

2.2.2. Neuro-inflammation

Key investigators: E. Bannier, E. Caruyer, O. Commowick, G. Edan, A. Kerbrat J-C. Ferré, J-Y Gauvrit

Some of the major ongoing research issues in the neuroimaging of neuro-inflammatory diseases concern the definition of new biomarkers for tracking the development of the pathology using high-dimensional data (e.g. nD+t MRI). This includes the use of white matter-specific imaging, such as magnetization transfer MRI, relaxometry, diffusion-weighted imaging (DW-MRI) (Chatterjee et al. 2017) and cell/molecular labeling neuroimaging (e.g. from MRI or PET), and the comparison of MR and PET data using standard and experimental MR contrast agents or radiolabeled PET tracers for activated microglia. Our objective will be (1) to develop information-processing tools to tag the spatiotemporal evolutions of MS patterns at the brain parenchyma and spinal cord levels from their different signatures (inflammatory cells, persistent black holes, slowly evolving lesions, eloquent regional atrophy and microstructure signatures (Kerbrat et al. 2018)), or with PET signatures from dedicated fluorine-18-labeled second-generation TSPO ligands (e.g. [18F]-FEPPA (FEPPA) or [18F]-DPA-714); and (2) to test these new tools on new imaging cohorts. In this respect, we will, for instance, continue conducting studies on spinal cord imaging with the recently funded MS-TRACTS (PI : Raphaël Chouteau, Elise Bannier, Virginie Callot) and MS-CSI (PI : Aymeric Stamm, Anne Kerbrat) projects, in collaboration with Marseille and Nantes respectively. We will thus pursue the research project started with the multicenter EMISEP project (PI: G. Edan and A. Kerbrat), where we could demonstrate that metrics extracted from lesion and quantitative imaging in the spine are correlated to the ambulatory ability of the patient (and thereby explain the clinical scores) (Chouteau et al. 2019; Combès, Kerbrat, et al. 2019). To this end, we rely on new image acquisition protocols focused on the spinal cord and tested at dedicated centers with expertise in these techniques. Whole spinal cord imaging is challenging, as the anatomy varies greatly in the head and neck region, and the image quality may be lower going down the cord due to movement artifacts. We will therefore continue developing new approaches towards lesion segmentation and damage evaluation along the whole spine, which will contribute to the global understanding of the influence of MS on the parenchyma and spinal cord, and its effect on the clinical evolution of the patient.

These various projects heavily rely on close collaboration with actors from the research team, the clinical neuroscience team of CICP1414 (Gilles Edan, national coordinator of FCRN4MS, Anne Kerbrat, Laure Michel and the neuroradiological unit directed by Prof. J.-Y. Gauvrit, the neuro-nuclear medicine unit directed by Prof. F. Le Jeune (for the CRLCC Rennes PET platform) and the Neurinfo platform. These research developments will be crucial for the evaluation of new therapeutics and their impact on patient evolution, as we demonstrated recently with the Translate-MS-Repair (ANR) and MS-SPI (MedDay Inc.) national projects, for which we were responsible for managing and processing the temporal data using different modalities, ranging from conventional anatomical imaging to diffusion imaging, relaxometry and magnetization transfer MRI.

In order to extend this experiment to a larger MS population, based on our expertise from the OFSEP cohort (Brisset et al. 2020; Cotton et al. 2015) we also plan to improve the MS therapeutic decision process through the MUSIC project (Multiple Sclerosis Imaging Check out, a public/private project). Our goal is to develop and assess a standardized monitoring tool that provides a robust, long-term computerized MRI follow-up that will become the gold standard in clinical practice for therapeutic decisions in MS treatment. This will provide an unprecedented large-scale solution for MS patient care. The patient, the radiologist and the neurologist will have direct access to the MRI data with evidence of lesion changes during follow-up. As part of this project, Empenn will share its expertise in data management systems (Shanoir and FLI-IAM) and automatic processing tools (through the medInria and Anima software repositories) to extract quantitative indices from the images (Commowick et al. 2018). In addition, the project will involve actors/partners in one or more areas of expertise: (*i*) private and public neurologists and radiologists (the West Network for Excellence in MS); (*ii*) IRT b<>com, which will provide the innovative software and infrastructure for integrating the MS clinical/research components into a comprehensive, operational solution (in collaboration with SIB for the health data repository); (*iii*) Biotrial, which will set up and run the appropriate procedures and check the capacity of each site involved to follow the expected imaging protocols; and (*iv*) the strong support of major pharmaceutical companies (Biogen, Roche, Novartis, Sanofi, etc.), which have a direct interest in the outcomes of this project for the evaluation of their new drug treatments. We plan to extend this project through a RHU grant application involving Rennes and Nantes.

Expected results

- In the short term, thanks to our involvement in the OFSEP and MUSIC projects, we expect our data management and image processing tools to provide valuable biomarkers at the population scale (i.e. on large cohorts) for the brain parenchyma and the spine. We expect to provide objective measures of the longitudinal evolution of the disease through the detection and tracking of lesion evolution. In the longer term, we expect to provide new generations of imaging biomarkers that will combine quantitative brain and cord MRI and the complementary multi-compartment microstructural models (e.g. diffusion MRI, relaxometry). We expect these new biomarkers of MS to better align the images of the pathology to the clinical observations (and thus go beyond the "clinical radiological paradox").

On the topic of neuro-inflammation, we aim to play a leading role and make major contributions, with significant impacts primarily in multiple sclerosis. In particular, we expect to provide new evaluation metrics to assess the efficacy of new drugs on the follow-up treatment of a large population of patients. *Gilles Edan, Jean-Christophe Ferré, Olivier Commowick and Elise Bannier will be the key researchers on this topic.*

2.2.3. Recovery

Key investigators: E. Bannier, I. Bonan, I. Corouge, J-C. Ferré, J-Y. Gauvrit, P. Maurel, G. Robert

As mentioned previously, mental and neurological disorders are the leading cause of years lived with a disability. In this field, major depressive disorders are the second leading psychiatric cause of years lived with a disability. Studies of real-world effectiveness suggest that about a third of patients will recover with antidepressant medication, while another third need additional medication. The remaining third of patients are diagnosed with treatment-resistant depression, which has a very low likelihood of recovery (10–15%). Treatment-resistant depression affects approximately 2% of the European population (i.e. 10 million out of the 30 million people suffering from major depressive disorders in the European Union). Meanwhile, in the case of brain disorders, almost 1.5 million Europeans (15 million people worldwide) suffer a stroke event each year (an equivalent of two strokes per minute), making stroke the leading cause of acquired disability in adults (World Health Organization). Similarly, according to the World Health Organization, traumatic brain injury (TBI) will surpass many diseases as the major cause of death and disability in the next decade. With an estimated 10 million people affected annually by TBI, the burden of mortality and morbidity that this condition imposes on society makes TBI a pressing public health and medical concern (Roozenbeek, Maas, and Menon 2013).

Overall, Mental, Neurological and Substance use (MNS) disorders have increased by almost 40% in the past two decades (~2% per year); for most disorders, this is driven by population growth and aging. This trend is likely to continue in the coming decades, highlighting the importance of access to better care and more effective treatment options.

The science of recovery from brain disorders requires the development and application of new technologies, systems and protocols for restoring functions altered by disease. Although the field generally concerns the rehabilitation of motor function, cerebral functions in mental/neurological disorders have become

increasingly acute (Patel et al. 2016; Silberberg et al. 2015; Whelan et al. 2012; Wykes et al. 2015). Current recovery methods for brain disorders and TBI remain limited, preventing many from achieving full recuperation. We propose to address the issue of brain recovery by introducing new advances from recent breakthroughs in computational medical imaging, data processing and human-machine interfaces, and to demonstrate how these new concepts can be used, in particular for the treatment of stroke and major depressive disorders, and the prospect of recovery in TBI.

Neurofeedback to stimulate the brain

Current rehabilitation strategies for mental / neurological disorders are limited by their technology and computational solutions and leave many people by the wayside. This has for instance recently motivated research in computational medical imaging to improve brain sensing and brain stimulation through brain-computer interfaces (BCI) and neurofeedback (NF). We propose to combine advanced instrumental devices (Hybrid EEG, NIRS and MRI platforms), with new hybrid brain computer interface paradigms and new computational models to provide novel therapeutic and neuro-rehabilitation paradigms in some of the major mental and neurological disorders of the developmental and the aging brain (stroke, language disorders, Although the concept of using neurofeedback paradigms for brain therapy has already been tested in several ways (mostly through case studies), to date, neurofeedback has rarely been performed through simultaneous fMRI and EEG (this has been done by two teams in the world, including ours (Lioi, Butet, et al. 2020; Mano et al. 2017; Perronnet et al. 2017)).

Neurofeedback (NF) involves using a brain-computer interface that provides an individual with real-time biofeedback about his or her brain activity in the form of sensory feedback. It enables individuals to learn to better control their brain activity (Perronnet et al. 2016), which can be measured in real time using various non-invasive sensors as described above. Although EEG is currently the only modality used by NF clinical practitioners, it lacks specificity due to its low spatial resolution. Dynamic research into fMRI-NF has held promise for treating depression (Fovet, Jardri, and Linden 2015; Young et al. 2014), chronic pain and stroke (Berman et al. 2012; Chiew, LaConte, and Graham 2012), since it offers the prospect of real-time imagery of the activity in deep brain structures with high spatial resolution. However, the low temporal resolution and high cost of fMRI-NF has hampered the development of many applications. Though promising, current NF technologies still suffer from the antagonism between high-burden (fMRI) and low-burden (EEG) solutions. **We believe that the future belongs to hybrid responses that combine multimodal sensors and intend to demonstrate this in the Empenn project**.

A key challenge for modeling brain states is describing how a continuous stream of multimodal sensors can represent the brain in action. This becomes even more acute when the brain is interacting with its environment (e.g. through NF) in order to maximize certain cumulative activities by controlling its reward and then rapidly changing its cognitive environment. There is currently a lack of modeling for the brain undergoing training for whole brain analyses under complex experimental NF paradigms. Multimodal sensing is considered the most relevant solution for addressing this challenge, but the joint analysis of this multimodal data is performed only in asymmetric ways: fMRI-constrained EEG or EEG-constrained fMRI analysis. New models have recently been introduced to predict the signal of one modality using the other with machine learning approaches (De Martino et al. 2010; Lahat, Adali, and Jutten 2015). These methods address issues of classification or correlation, but fail to learn integrated models of evolving brain states during training. In this project, we propose learning and using brain state models during training by resolving issues in compact representation and machine learning.

While coordinated from our team, this transversal project will be also conducted through a very complementary set of competences over the different teams involved (HYBRID and PANAMA Teams from Inria/Irisa Rennes, and ATHENA team from Inria Sophia-Antipolis) on the basic science side, and the Rehabilitation Unit of the University Hospital of Rennes (Prof. I. Bonan and Drs S. Butet and S. Leplaideur) or the Psychiatric Hospital of Rennes (Prof. D. Drapier and Drs. J.-M. Batail and G. Robert) for the application side. This work will benefit from the research 3T MRI and MRI-compatible EEG and NIRS systems provided by the Neurinfo platform on which these new research protocols are set up.

Expected results

- In the next 5 years, the major breakthrough will come from the coupling associating functional and metabolic information from magnetic resonance imaging (fMRI) with electroencephalography (EEG) to “optimize” the neurofeedback protocol. This will be based on our recent developments in the integration and the synchronization of a 64-channel MR-compatible EEG solution from Brain Products and 3T MRI. Based on preliminary studies on normal controls, we are able to provide a technical validation of the system. For the first time, we have introduced hybrid EEG-fMRI-NF visual metaphors that integrate both EEG and fMRI signals simultaneously in a single virtual reality (VR)-based feedback system. These experiments demonstrated the significant added value of the hybrid

procedure in terms of the fMRI signal percent change in the brain with respect to EEG- or fMRI-NF only (Mano et al. 2017, n.d.; Perronnet et al. 2017). In the coming years, we will show how these methods apply to recovery from stroke and major depressive disorders. Over the longer term, we expect to provide extended results on combining the NF clinical protocols with the learning of computational models of the brain state during training. We will investigate how the NF protocol can make use of hybrid EEG-fMRI brain state models in order to train the brain when one sensor (e.g. MRI) is missing.

On the topic of recovery, we intend to become a major player in the future and make significant contributions with large impacts, primarily in providing the community with novel neurofeedback solutions enabling recovery from specific pathologies such as stroke and drug-resistant depression. We expect to provide the community with an integrated software solution for the dissemination of our technology. We also intend to provide new metaphors and neurofeedback methods (not only visual, but also haptic or auditory), and lastly to design new clinical rehabilitation that will be evaluated on large patient populations. *Isabelle Bonan, Gabriel Robert, Pierre Maurel and Jean-Yves Gauvrit will be the key researchers on this topic.*

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ANNEXES

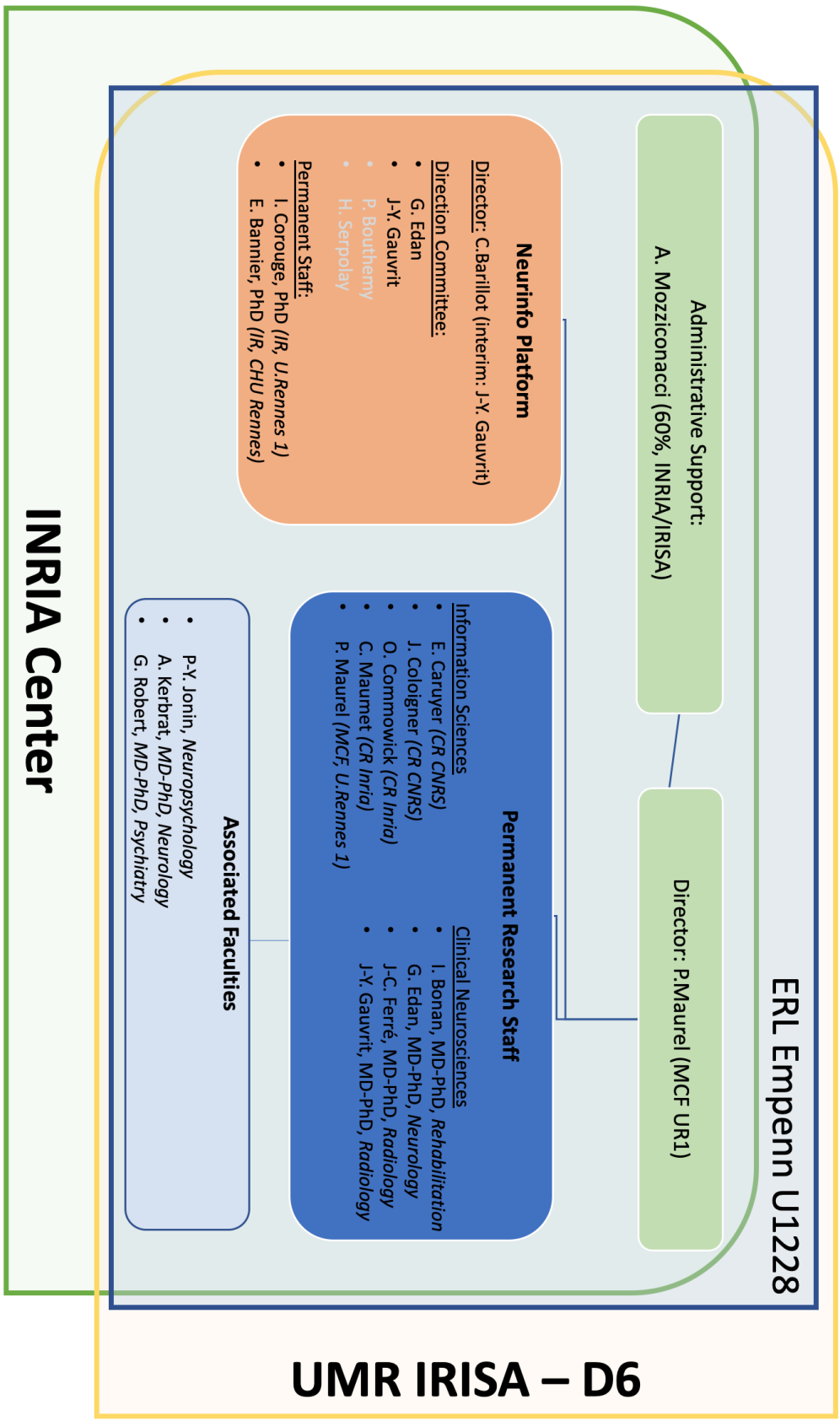
Annex 1: Letter of commitment

Rennes, 25th August 2020

I, the undersigned, Pierre Maurel, Director of the research unit U1228 Empenn, certify, by the present letter, the exactitude of all data presented in this self-evaluation file, containing the self-evaluation document, and two Excel files named « Current contract data » and « Next contract date ».

Signature

Annex 2: Operational organisation chart



Annex 3: Equipment, platforms

Experimental platform: Neurinfo

The Empenn U1228 unit is the founding and managing actor of the Neurinfo experimental research platform. The University of Rennes 1, Inria, CNRS for the academic side and the University Hospital of Rennes and the Cancer Institute of Rennes for the clinical side, are partners of this imaging and neuroinformatics platform. Neurinfo is integrated into Biogenouest, the life science and environment core facility network in Western France, and has been labelled by the GIS IBISA since 2015. The IBISA label is a national label for technological platforms awarded by the GIS IBISA.
The activity domain of the Neurinfo platform is a continuum between methodological and technological research built around specific clinical research projects. The ambition is to do innovation in information science and technology and medical technology transfer for translational research. In the medical field, the translational research domain mainly concerns medical imaging and more specifically clinical neurosciences. Among them are multiple sclerosis, epilepsy, neurodegenerative, neurodevelopmental and psychiatric diseases, surgical procedures of brain lesions and neuro-rehabilitation. Beyond its primary interest in central nervous system (CNS) applications, the platform is open to other organs (e.g., heart, liver) and pathologies (e.g., fibrosis, hemochromatosis). The Neurinfo platform is also open to a large community of users, both clinicians and scientists, from academy or industry, at the local, regional, national and international level.

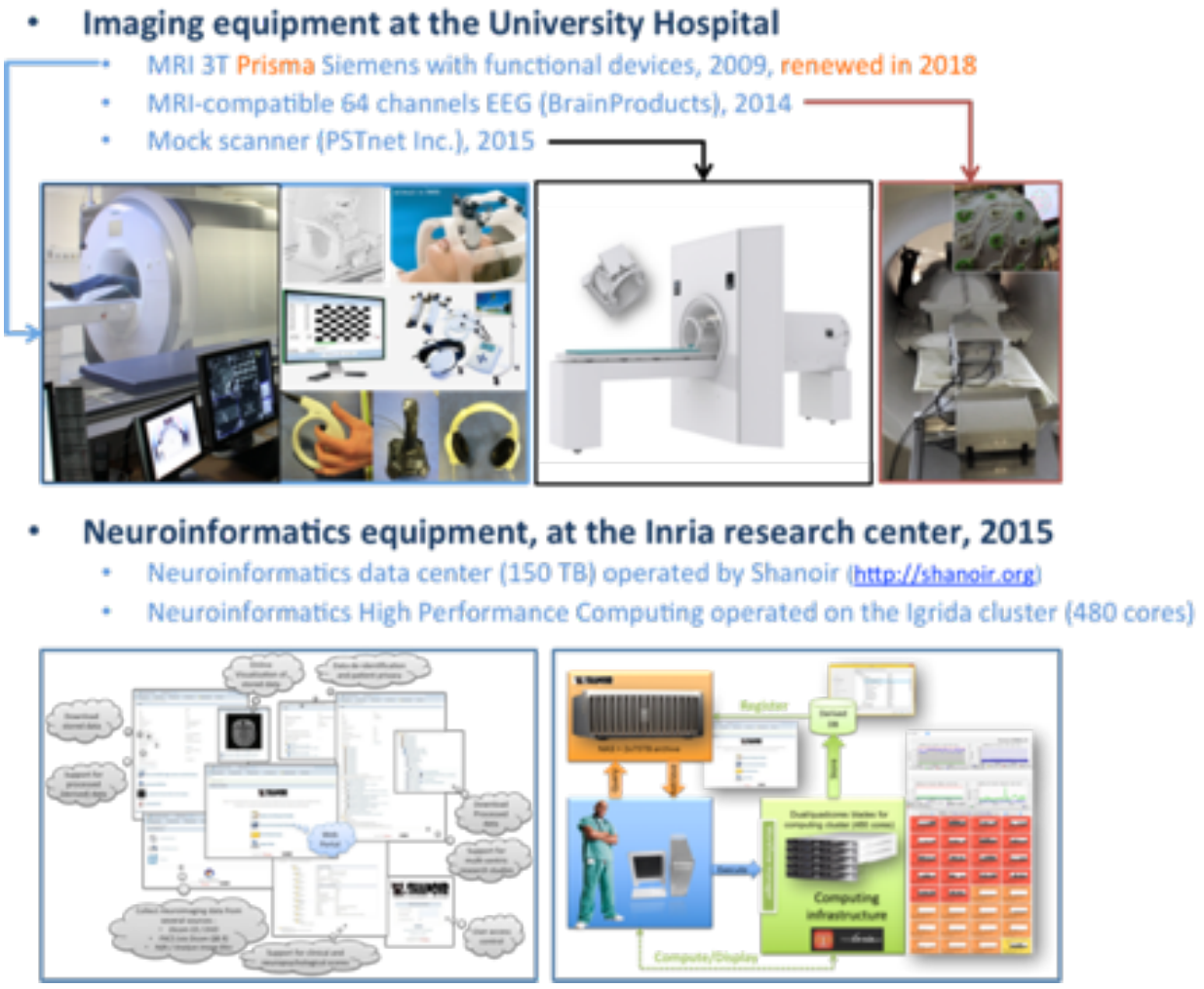


Figure 7: Summary of the Neurinfo imaging resources

Neurinfo ambitions to support the emergence of research projects based on their level of innovation, their multidisciplinary (especially between information and medical sciences) and their ability to foster collaborations between different actors (public and private research entities, different medical specialties, different scientific profiles).

As illustrated in Figure 7, a research 3T MRI system (Siemens Verio™) was acquired in mid-2009 and replaced by a high performance 3T system in 2018 (Siemens Prisma™) in order to develop the clinical research in the domain of morphological, functional and structural in vivo imaging. Neurinfo is also equipped with a mock scanner for the experimental setup of advanced imaging protocols and for the preparation of subjects to these protocols, which allows to improve the MRI data quality.
In 2014, Neurinfo started to develop its "hybrid imaging" activity within the HEMISFER project funded by the CominLabs Labex, with a focus on the simultaneous recording under MRI of EEG and MRI signals (thanks to a new MRI compatible 64-channels EEG equipment). These capabilities have been extended in late 2019 with the acquisition of a functional near-infrared spectroscopy (fNIRS or NIRS) system which is compatible with both EEG and MRI. This new MRI and EEG compatible fNIRS system is the first of its kind in Brittany, and even a unique set of equipments in Europe.
On the neuro-informatics side, Neurinfo has acquired a High-Performance Computing environment made of one large computing cluster and a data center that is shared and operated by the IRISA / Inria-Rennes center. The computation cluster (480 cores) and the data center (2x75 TB) are dedicated to host and process imaging data produced by the Neurinfo platform, but also by other research partners that share their protocols on the Neurinfo neuroinformatics system (currently around 70 sites). The data center operates the home-made software platform Shanoir. To this end, Neurinfo offers different processing services using either home-made tools (MedInria, AutoMRI, …), or publicly available software (e.g., SPM, FSL, Freesurfer, …) that can be executed on the Neurinfo dedicated cluster. In this context, Neurinfo is integrated in the French national infrastructure "France Life Imaging" (The "Grand Ouest" node).
Through this environment, Neurinfo is committed to use the research platform for developing new regional, national and international collaborations around fundamental and applied clinical research projects dealing and sharing *in vivo* medical imaging. The technical staff supports the investigators in all the phases of their project (75 running projects in 2019), from the protocol elaboration to the publication of their results and including experimental set-up, data processing and data management.
In the continuation of the 2007-2013 State-Region plan contract, an evolution of the existing Neurinfo platform is requested : **Neurinfo-NF** : New frontier of *multimodal hybrid imaging* and *computer imaging platform* for translational research around of neuroimaging, oncology but also open to other application fields such as cardiology and abdominal pathologies. This new Frontier of the Neurinfo platform aims to broaden the field of skills and investigations in terms of research and applications of **hybrid multimodal in vivo imaging** and **imaging-informatic** on the Rennes site. Equipment concerns the acquisition of a PET-MRI hybrid imaging platform. This equipment project is in line with the road map of the national in-vivo imaging infrastructure France Life Imaging, which has already included this equipment project in its recommendations for the post-2020.

Annex 4: Products and research activities

See attached file