IN PARTNERSHIP WITH:
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Activity Report 2016

Project-Team ARAMIS

Algorithms, models and methods for images and signals of the human brain

IN COLLABORATION WITH: Institut du Cerveau et de la Moelle Epinière

RESEARCH CENTER
Paris

THEME
Computational Neuroscience and Medecine

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Creation of the Team: 2012 October 01, updated into Project-Team: 2014 July 01

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1. Members

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2. Overall Objectives

2.1. Introduction

Understanding brain function and its alterations requires the integration of multiple levels of organization, operating at different spatial and temporal scales. The integration of such a large variety of data is now possible thanks to the recent emergence of large-scale multimodal datasets (e.g. Alzheimer's disease neuroimaging initiative [ADNI], gene expression atlases from the Allen Institute...). In this context, mathematical and computational approaches are becoming increasingly important because: i) they provide formalized, operational and flexible frameworks for integrating multiple processes and scales; ii) they allow automated processing and analysis of massive datasets. These approaches can then be used to find biomarkers of a disease, for genotype/phenotype correlations, or to characterize functional responses for instance.

3. Research Program

3.1. General aim

The overall aim of our project is to design new computational and mathematical approaches for studying brain structure (based on anatomical and diffusion MRI) and functional connectivity (based on EEG, MEG and intracerebral recordings). The goal is to transform raw unstructured images and signals into formalized, operational models such as geometric models of brain structures, statistical population models, and graph-theoretic models of brain connectivity. This general endeavor is addressed within the three following main objectives.

3.2. Modeling brain structure: from imaging to geometric models

Structural MRI (anatomical or diffusion-weighted) allows studying in vivo the anatomical architecture of the brain. Thanks to the constant advance of these imaging techniques, it is now possible to visualize various anatomical structures and lesions with a high spatial resolution. Computational neuroanatomy aims at building models of the structure of the human brain, based on MRI data. This general endeavor requires addressing the following methodological issues: i) the extraction of geometrical objects (anatomical structures, lesions, white matter tracks...) from anatomical and diffusion-weighted MRI; ii) the design of a coherent mathematical framework to model anatomical shapes and compare them across individuals. Within this context, we pursue the following objectives.

First, we aim to develop new methods to segment anatomical structures and lesions. We are most specifically interested in the hippocampus, a structure playing a crucial role in Alzheimer's disease, and in lesions of vascular origin (such as white matter hyperintensities and microbleeds). We pay particular attention to the robustness of the approaches with respect to normal and pathological anatomical variability and with respect to differences in acquisition protocols, for application to multicenter studies. We dedicate specific efforts to the validation on large populations of coming from patients data acquired in multiple centers.

Then, we develop approaches to estimate templates from populations and compare anatomical shapes, based on a diffeomorphic deformation framework and matching of distributions. These methods allow the estimation of a prototype configuration (called template) that is representative of a collection of anatomical data. The matching of this template to each observation gives a characterization of the anatomical variability within the population, which is used to define statistics. In particular, we aim to design approaches that can integrate multiple objects and modalities, across different spatial scales.

3.3. Modeling dynamical brain networks

Functional imaging techniques (EEG, MEG and fMRI) allow characterizing the statistical interactions between the activities of different brain areas, i.e. functional connectivity. Functional integration of spatially distributed brain regions is a well-known mechanism underlying various cognitive and perceptual tasks. Indeed, mounting evidence suggests that impairment of such mechanisms might be the first step of a chain of events triggering several neurological disorders, such as the abnormal synchronization of epileptic activities. Naturally, neuroimaging studies investigating functional connectivity in the brain have become increasingly prevalent.

Our team develops a framework for the characterization of brain connectivity patterns, based on connectivity descriptors from the theory of complex networks. The description of the connectivity structure of neural networks is able to characterize for instance, the configuration of links associated with rapid/abnormal synchronization and information transfer, wiring costs, resilience to certain types of damage, as well as the balance between local processing and global integration. Furthermore, we propose to extend this framework to study the reconfiguration of networks over time. Indeed, neurophysiological data are often gathered from longitudinal recording sessions of the same subject to study the adaptive reconfiguration of brain connectivity. Finally, connectivity networks are usually extracted from different brain imaging modalities (MEG, EEG,

fMRI or DTI) separately. Methods for combining the information carried by these different networks are still missing. We thus propose to combine connectivity patterns extracted from each modality for a more comprehensive characterization of networks.

3.4. Methodologies for large-scale datasets

Until recently, neuroimaging studies were often restricted to series of about 20-30 patients. As a result, such studies had a limited statistical power and could not adequately model the variability of populations. Thanks to wider accessibility of neuroimaging devices and important public and private funding, large-scale studies including several hundreds of patients have emerged in the past years. In the field of Alzheimer's disease (AD) for instance, one can cite the Alzheimer's Disease Neuroimaging Initiative (ADNI) including about 800 subjects (patients with AD or mild cognitive impairment (MCI) and healthy controls) or the French cohort MEMENTO including about 2000 subjects with memory complaint. These are most often multicenter studies in which patients are recruited over different centers and images acquired on different scanners. Moreover, cohort studies include a longitudinal component: for each subject, multiple images are acquired at different time points. Finally, such datasets often include multimodal data: neuroimaging, clinical data, cognitive tests and genomics data. These datasets are complex, high-dimensional and often heterogeneous, and thus require the development of new methodologies to be fully exploited.

In this context, our objectives are:

- to develop methodologies to acquire and standardize multicenter neuroimaging data;
- to develop imaging biomarkers based on machine learning and longitudinal models;
- to design multimodal analysis approaches for bridging anatomical models and genomics.

The first two aspects focus on neuroimaging and are tightly linked with the CATI project. The last one builds on our previous expertise in morphometry and machine learning, but aims at opening new research avenues combining imaging and "omics" data. This is developed in strong collaboration with the new biostatistics/bioinformatics platform of the IHU-A-ICM.

4. Application Domains

4.1. Introduction

We develop different applications of our new methodologies to brain pathologies, mainly neurodegenerative diseases, epilepsy and cerebrovascular disorders. These applications aim at:

- better understanding the pathophysiology of brain disorders;
- designing biomarkers of pathologies for diagnosis, prognosis and assessment of drug efficacy;
- developping brain computer interfaces for clinical applications;
- improving the localisation of stimulation targets in Deep Brain Stimulation protocol.

These applications are developed in close collaboration with biomedical researchers of the ICM and clinicians of the Pitié-Salpêtrière hospital.

4.2. Understanding brain disorders

The approaches that we develop allow to characterize anatomical and functional alterations, thus making it possible to study these alterations in different clinical populations. This can provide provide new insights into the mechanisms and progression of brain diseases. This typically involves the acquisition of neuroimaging data in a group of patients with a given pathology and in a group of healthy controls. Measures of anatomical and functional alterations are then extracted in each subject (for instance using segmentation of anatomical structures, shape models or graph-theoretic measures of functional connectivity). Statistical analyses are then performed to identify: i) significant differences between groups, ii) correlations between anatomical/functional alterations on the one hand, and clinical, cognitive or biological measures on the other hand, iii) progression of alterations over time.

We propose to apply our methodologies to study the pathophysiology of neurodegenerative diseases (mostly Alzheimer's disease and fronto-temporal dementia), epilepsy, cerebrovascular pathologies and neurodevelopmental disorders (Gilles de la Tourette syndrome). In neurodegenerative diseases, we aim at establishing the progression of alterations, starting from the early and even asymptomatic phases. In Gilles de la Tourette syndrome, we study the atypical anatomical patterns that may contribute to the emergence of symptoms. In epilepsy, we aim at studying the relationships between the different functional and structural components of epileptogenic networks.

4.3. Biomarkers for diagnosis, prognosis and clinical trials

Currently, the routine diagnosis of neurological disorders is mainly based on clinical examinations. This is also true for clinical trials, aiming to assess the efficacy of new treatments. However, clinical diagnoses only partially overlap with pathological processes. For instance, the sensitivity and specificity of clinical diagnosis of Alzheimer's disease (AD) based on established consensus criteria are of only about 70-80% compared to histopathological confirmation. Furthermore, the pathological processes often begin years before the clinical symptoms. Finally, clinical measures embed subjective aspects and have a limited reproducibility and are thus not ideal to track disease progression. It is thus crucial to supplement clinical examinations with biomarkers that can detect and track the progression of pathological processes in the living patient. This has potentially very important implications for the development of new treatments as it would help: i) identifying patients with a given pathology at the earliest stage of the disease, for inclusion in clinical trials; ii) providing measures to monitor the efficacy of treatments.

The derivation of biomarkers from image analysis approaches requires large-scale validation in well-characterized clinical populations. The ARAMIS team is strongly engaged in such efforts, in particular in the field of neurodegenerative disorders. To that purpose, we collaborate to several national studies (see section Partnerships) that involve multicenter and longitudinal acquisitions. Moreover, ARAMIS is strongly involved in the CATI which manages over 15 multicenter studies, including the national cohort MEMENTO (2000 patients).

4.4. Brain computer interfaces for clinical applications

A brain computer interface (BCI) is a device aiming to decode brain activity, thus creating an alternate communication channel between a person and the external environment. BCI systems can be categorized on the base of the classification of an induced or evoked brain activity. The central tenet of a BCI is the capability to distinguish different patterns of brain activity, each being associated to a particular intention or mental task. Hence adaptation, as well as learning, is a key component of a BCI because users must learn to modulate their brainwaves to generate distinct brain patterns. Usually, a BCI is considered a technology for people to substitute some lost functions. However, a BCI could also help in clinical rehabilitation to recover motor functions. Indeed, in current neuroscience-based rehabilitation it is recognized that protocols based on mental rehearsal of movements (like motor imagery practicing) are a way to access the motor system because they can induce an activation of sensorimotor networks that were affected by lesions. Hence, a BCI based on movement imagery can objectively monitor patients' progress and their compliance with the protocol, monitoring that they are actually imagining movements. It also follows that feedback from such a BCI can provide patients with an early reinforcement in the critical phase when there is not yet an overt sign of movement recovery. The BCI approaches that we develop are based on the characterization of the information contained in the functional connectivity patterns. We expect to significantly increase the performance of the BCI system with respect to the sole use of standard power spectra of the activity generated by single local brain areas. Such an improvement will concretely provide the user with a more precise control of the external environment in open-loop BCI tasks and a more coherent feedback in the closed-loop BCI schemes.

4.5. Deep Brain Stimulation

Deep Brain Stimulation (DBS) is a surgical technique, which consists in sending electrical impulses, through implanted electrodes, to specific parts of the brain for the treatment of movement and affective disorders. The

technique has been initially developped for otherwise-treatment-resistant patients with essential tremors or Parkinson's disease. Its benefit in other affections, such as dystonia, obsessive-compulsive disorders, Tourette syndrome is currently investigated. The localisation of the stimulation target in specific nucleus in deep brain regions is key to the success of the surgery. This task is difficult since the target nucleus, or the precise sub-territory of a given nucleus is rarely visible in the Magnetic Resonance Image (MRI) of the patients. To address this issue, a possible technique is to personalize a high-resolution histological atlas of the brain to each patient. This personalization is achieved by registering the histological atlas, which consists of an image and meshes of deep brain structures, to the pre-operative MRI of each patient. The registration is currently done by optimally aligning image intensities in the atlas and patient's MRI using a block-matching algorithm. The linear nature of the transform makes the technique robust at the cost of a lack of precision, especially for elderly patients with expanded ventricles. We investigate the use of non-linear registration techniques to optimally align both image intensities and contours of visible structures surrounding the target. We expect to improve the localisation of the target for patients with large ventricles while keeping the method robust in all cases.

5. Highlights of the Year

5.1. Highlights of the Year

- Stanley Durrleman's ERC Starting Grant "LEASP" has started.
- H2020 project EuroPOND, under societal challenge "Personalizing Health and Care" has started.
- ANR-NIH project NETBCI, under the "Collaborative Research in Computational Neuroscience" program (CRCNS) has started.
- The team has been awarded the ANR-NIH project HIPLAY7, under the "Collaborative Research in Computational Neuroscience" program (CRCNS)
- The team has been awarded the ANR project BRANDY, under the generic call programme "Vie, Sante et Bien-etre", Project duration: 2017-2020
- ARAMIS participates to the Human Brain Project (European Flagship).
- Anne Bertrand was awarded a one year Inria-APHP interface contract (i.e., "poste d'accueil"), allowing her to work half-time in the ARAMIS project team, from november 2016 to november 2017.
- Pietro Gori and Barbara Gris successfully defended their PhD.
- S. Durrleman has been appointed associate editor of IEEE Transactions on Medical Imaging (TMI).

6. New Software and Platforms

6.1. Clinica

KEYWORDS: Multimodal neuroimaging - anatomical MRI - diffusion MRI - functional MRI - PET - EEG/MEG

FUNCTIONAL DESCRIPTION

Clinica is a software platform for multimodal brain image analysis in clinical research studies. It aims at integrating a comprehensive set of processing tools for the main neuroimaging modalities: MRI (anatomical, functional, diffusion), PET and EEG/MEG. For each modality, it allows to easily extract various types of features (regional measures, parametric maps, surfaces, curves, networks) that can be subsequently used as input of machine learning, statistical modeling, morphometry or network analysis methods. Processing pipelines are based on combinations of freely available tools developed by the community and in-house developments. It provides an integrated data management system to store raw and processing data.

- Participants: Olivier Colliot, Stanley Durrleman, Fabrizio De Vico Fallani, Michael Bacci, Alexandre Routier, Jorge Samper-Gonzalez, Junhao Wen, Jérémy Guillon, Sabrina Fontanella, Thomas Jacquemont
- Contact: Olivier Colliot

6.2. Brain Networks Toolbox

KEYWORDS: Neuroimaging - Medical imaging
FUNCTIONAL DESCRIPTION

Brain Networks Toolbox is a collection of Matlab routines developed to quantify topological metrics of complex brain networks.

- Participants: Mario Chavez and Fabrizio De Vico Fallani
- Contact: Mario Chavez
- URL: https://sites.google.com/site/fr2eborn/download

6.3. Deformetrica

KEYWORDS: 3D modeling - C++ - Automatic Learning - Mesh - Anatomy - Image analysis
SCIENTIFIC DESCRIPTION

Deformetrica is a software for the statistical analysis of 2D and 3D shape data. It essentially computes deformations of the 2D or 3D ambient space, which, in turn, warp any object embedded in this space, whether this object is a curve, a surface, a structured or unstructured set of points, or any combination of them.

Deformetrica comes with two applications:

registration, which computes the best possible deformation between two sets of objects, atlas construction, which computes an average object configuration from a collection of object sets, and the deformations from this average to each sample in the collection.

Deformetrica has very little requirements about the data it can deal with. In particular, it does not require point correspondence between objects!
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- Participants: Stanley Durrleman, Alexandre Routier, Pietro Gori, Marcel Prastawa, Ana Fouquier, Joan Alexis Glaunès, Benjamin Charlier, Cedric Doucet, Michael Bacci and Barbara Gris
- Partners: Université de Montpellier 2 - Université Paris-Descartes - University of Utah
- Contact: Stanley Durrleman
- URL: http://www.deformetrica.org/

6.4. SACHA

Segmentation Automatisée Compétitive de l'Hippocampe et de l'Amygdale
KEYWORDS: Neuroimaging - 3D - Hippocampus - Amygdala - Brain scan - Medical imaging
SCIENTIFIC DESCRIPTION

The current stable version is fully automatic and focused on cross-sectional segmentation. The software can be used both as a command-line program or through a graphical user interface (GUI). The core of the program is coded in C++. It has a dependency to the AIMS library and preprocessing steps rely on processes in Matlab from SPM. The GUI is coded in Python and is based on BrainVISA.

FUNCTIONAL DESCRIPTION

SACHA is a software for the fully automatic segmentation of the hippocampus and the amygdala from MRI 3D T1 brain scans. It has been validated in various populations including healthy controls and patients with Alzheimer's disease, epilepsy and depression. It has been successfully applied to over 3,000 subjects, both controls, from adolescents to elderly subjects, and patients with different types of pathologies.

- Participants: Marie Chupin and Ludovic Fillon
- Contact: Marie Chupin

6.5. WHASA

White matter Hyperintensity Automatic Segmentation Algorithm
KEYWORDS: Health - Neuroimaging - Biomedical imaging
SCIENTIFIC DESCRIPTION

The current stable version is fully automatic and focused on cross-sectional segmentation. The software can be used both as a Matlab command-line or through a graphical user interface (GUI). The core of the program is coded in Matlab. It has a dependency to the SPM environment. The GUI is coded in Python and is based on BrainVISA.
FUNCTIONAL DESCRIPTION

WHASA ("White matter Hyperintensity Automatic Segmentation Algorithm") is a software for the fully automatic segmentation of age-related white matter hyperintensities from MRI FLAIR and 3D T1 brain scans. It has been validated on a population showing a wide range of lesion load, and is being further evaluated on elderly subjects with few clinical abnormalisties and with different acquisition characteristics.

- Participants: Marie Chupin, Ludovic Fillon and Thomas Samaille
- Contact: Marie Chupin

6.6. QualiCATI

KEYWORDS: Health - Neuroimaging - Medical imaging
SCIENTIFIC DESCRIPTION

QualiCATI requires training for the visual parts, and is closely linked with a team of clinical research assistants. It has been used to analyse about 5000 subjects from about 15 multi centre research projects initiated before or after the CATI started. Other modules will be added in the future to embed new aspects of the MRI protocol proposed by the CATI. The Aramis team is in charge of the second and third modules and jointly in charge of the first module. The software is centered on a graphical user interface (GUI). The whole program is coded in Python within the pyPTK environment. It has dependencies to SPM and brainVISA environments as well as specific tools for DICOM management.
FUNCTIONAL DESCRIPTION

QualiCATI is a software designed for comprehensive quality control of multimodal MRI data acquisition in large multicentre clinical studies. The software is built as a platform receiving several modules, developped by several CATI engineers. The first module is dedicated to acquisition requirement checking and conversion to nifti format. The second module aims at making 3DT1 acquisition quality check more systematic, and relies both on visual inspection and quantitative indices. The third module allows a simultaneous evaluation of the clinical part of the CATI acquisition protocol. The fourth module embeds automatic indices to evaluate resting state fMRI acquisition. The fifth module is dedicated to first preprocessings and quality indices for dMRI. The sixth module is dedicated to qMRI, with visual and automated quality control together with preprocessings. The last module is dedicated to data and project management.

- Participants: Marie Chupin and Hugo Dary
- Contact: Marie Chupin

7. New Results

7.1. A Bayesian Framework for Joint Morphometry of Surface and Curve meshes in Multi-Object Complexes

Participants: Pietro Gori [Correspondant], Olivier Colliot, Linda Marrakchi-Kacem, Yulia Worbe, Alexandre Routier, Cyril Poupon, Andreas Hartmann, Nicholas Ayache, Stanley Durrleman.

We present a Bayesian framework for atlas construction of multi-object shape complexes comprised of both surface and curve meshes (Figure 1). It is general and can be applied to any parametric deformation framework and to all shape models with which it is possible to define probability density functions (PDF). Here, both curve and surface meshes are modelled as Gaussian random varifolds, using a finite-dimensional approximation space on which PDFs can be defined. Using this framework, we can automatically estimate the parameters balancing data-terms and deformation regularity, which previously required user tuning. Moreover, it is also possible to estimate a well-conditioned covariance matrix of the deformation parameters. We also extend the proposed framework to data-sets with multiple group labels. Groups share the same template and their deformation parameters are modelled with different distributions. We can statistically compare the groups'distributions since they are defined on the same space. We test our algorithm on 20 Gilles de la Tourette patients and 20 control subjects, using three sub-cortical regions and their incident white matter fiber bundles. We compare their morphological characteristics and variations using a single diffeomorphism in the ambient space. The proposed method will be integrated with the Deformetrica software package.

More details in [15].

7.2. Parsimonious Approximation of Streamline Trajectories in White Matter Fiber Bundles

Participants: Pietro Gori [Correspondant], Olivier Colliot, Linda Marrakchi-Kacem, Fabrizio de Vico Fallani, Mario Chavez, Yulia Worbe, Alexandre Routier, Cyril Poupon, Andreas Hartmann, Nicholas Ayache, Stanley Durrleman.

Fiber bundles stemming from tractography algorithms contain many streamlines. They require therefore a great amount of computer memory and computational resources to be stored, visualised and processed. We propose an approximation scheme for fiber bundles which results in a parsimonious representation of weighted prototypes. Prototypes are chosen among the streamlines and they represent groups of similar streamlines. Their weight is related to the number of approximated streamlines. Both streamlines and prototypes are modelled as weighted currents. This computational model does not need point-to-point correspondences and two streamlines are considered similar if their endpoints are close to each other and if their pathways follow similar trajectories. Moreover, the space of weighted currents is a vector space with a closed-form metric. This permits easy computation of the approximation error and the selection of the prototypes is based on the minimisation of this error. We propose an iterative algorithm which approximates independently and simultaneously all the fascicles of the bundle in a fast and accurate way. We show that the resulting representation preserves the shape of the bundle and it can be used to accurately reconstruct the original structural connectivity (Figure 2). We evaluate our algorithm on bundles obtained from both deterministic and probabilistic tractography algorithms. The resulting approximations use on average only 2% of the original streamlines as prototypes. This drastically reduces the computational burden of the processes where the geometry of the streamlines is considered. We demonstrate its effectiveness using as example the registration between two fiber bundles.

More details in [14].

7.3. White matter lesions in FTLD: distinct phenotypes characterize GRN and C9ORF72 mutations

Participants: Fatima Ameur, Olivier Colliot, Didier Dormont, Alexis Brice, Isabelle Le Ber, Anne Bertrand [Correspondant].

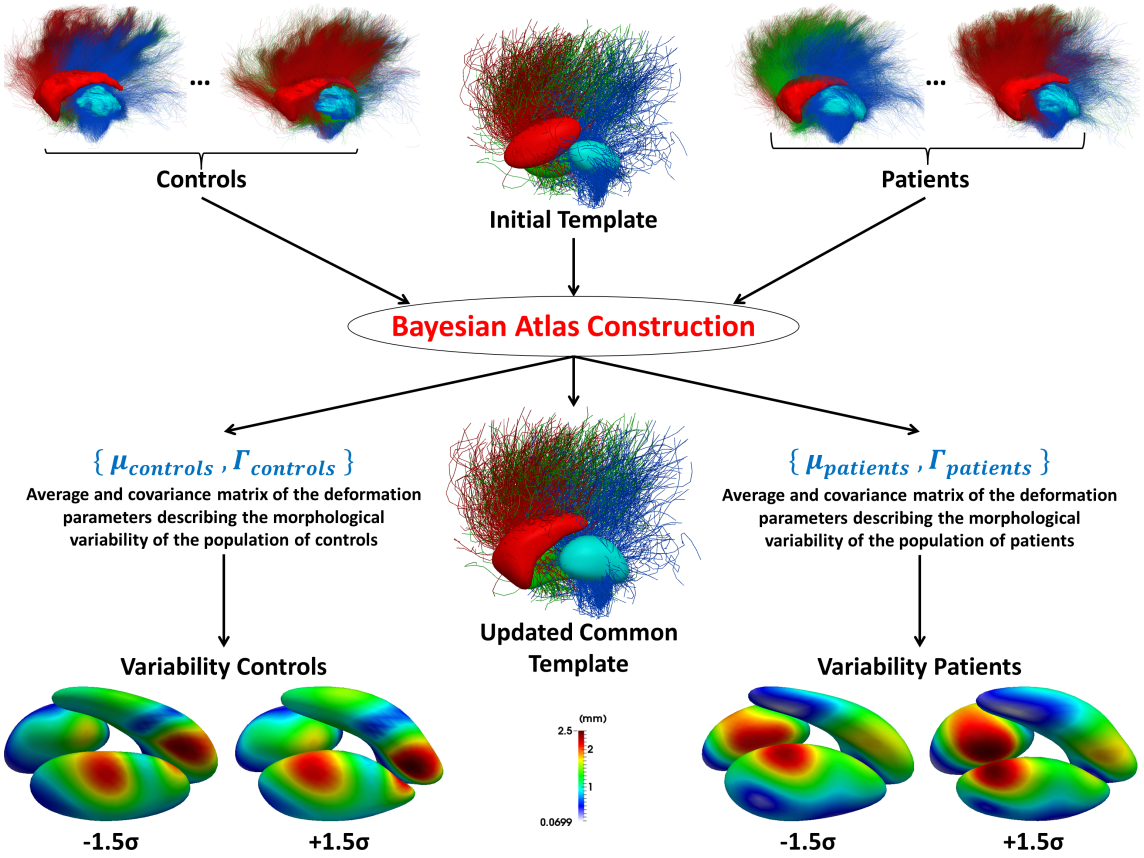

Figure 1. Bayesian framework for atlas construction of multi-object shape complexes comprised of both surface and curve meshes.

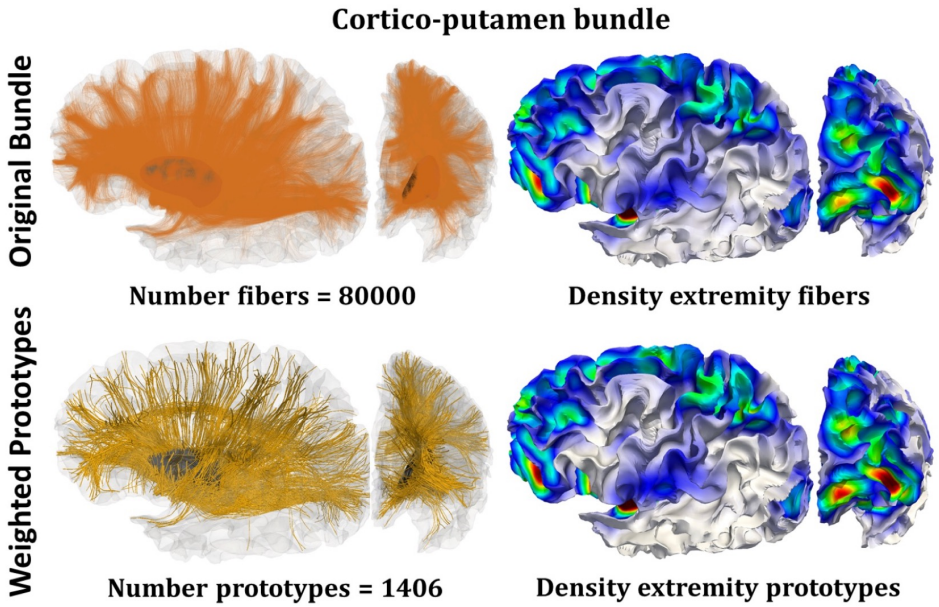

Figure 2. Weighted prototype approximations of a fiber bundle. As it is possible to notice, our approximation alters neither the global shape of the bundle nor the densities of the endpoints onto the cortical surface.

Frontotemporal lobar degeneration (FTLD) has a high frequency of genetic forms; the 2 most common are GRN (progranulin) and C9ORF72 mutations. Recently, our group reported extensive white matter (WM) lesions in 4 patients with FTLD caused by GRN mutation, in the absence of noteworthy cardiovascular risk factors in line with other studies in GRN mutation carriers. Here we compared the characteristics of frontal WM lesions in patients with behavioral variant of FTLD (bv-FTLD) caused by GRN and C9ORF72 mutations. We found that WM lesions were more frequent and more atypical on both sides in the GRN group than in the control group and the C9ORF72 group.

More details in [3].

7.4. Riemannian geometry applied to detection of respiratory states from EEG signals: the basis for a brain-ventilator interface

Participants: Xavier Navarro-Sune, Anna Hudson, Fabrizio de Vico Fallani, Jacques Martinerie, Adrien Witon, Pierre Pouget, Mathieu Raux, Thomas Similowski, Mario Chavez [Correspondant].

During mechanical ventilation, patient-ventilator disharmony is frequently observed and may result in increased breathing effort, compromising the patient's comfort and recovery. This circumstance requires clinical intervention and becomes challenging when patients are sedated or verbal communication is difficult. In this work, we propose a brain computer interface (BCI) to automatically and non-invasively detect patient-ventilator disharmony from electroencephalographic (EEG) signals: a brain-ventilator interface. Our framework exploits the cortical activation provoked by the inspiratory compensation when the subject and the ventilator are desynchronized (Figure 3). Use of a one-class approach and Riemannian geometry of EEG covariance matrices allows effective classification of respiratory states. The BVI is validated on nine healthy subjects that performed different respiratory tasks that mimic a patient-ventilator disharmony. Results evidence that classification performances, in terms of areas under ROC curves, are significantly improved using EEG signals

compared to detection based on air flow. Reduction in the number of electrodes that can achieve discrimination can often be desirable (e.g. for portable BCI systems). By using an iterative channel selection technique, the Common Highest Order Ranking (CHOrRa), we find that a reduced set of electrodes (n=6) can slightly improve for an intra-subject configuration, and it still provides fairly good performances for a general inter-subject setting. Results support the discriminant capacity of our approach to identify anomalous respiratory states, by learning from a single training set containing only normal respiratory epochs. The proposed framework opens the door to brain-ventilator interfaces for monitoring patient's breathing comfort and adapting ventilator parameters to patient respiratory needs.

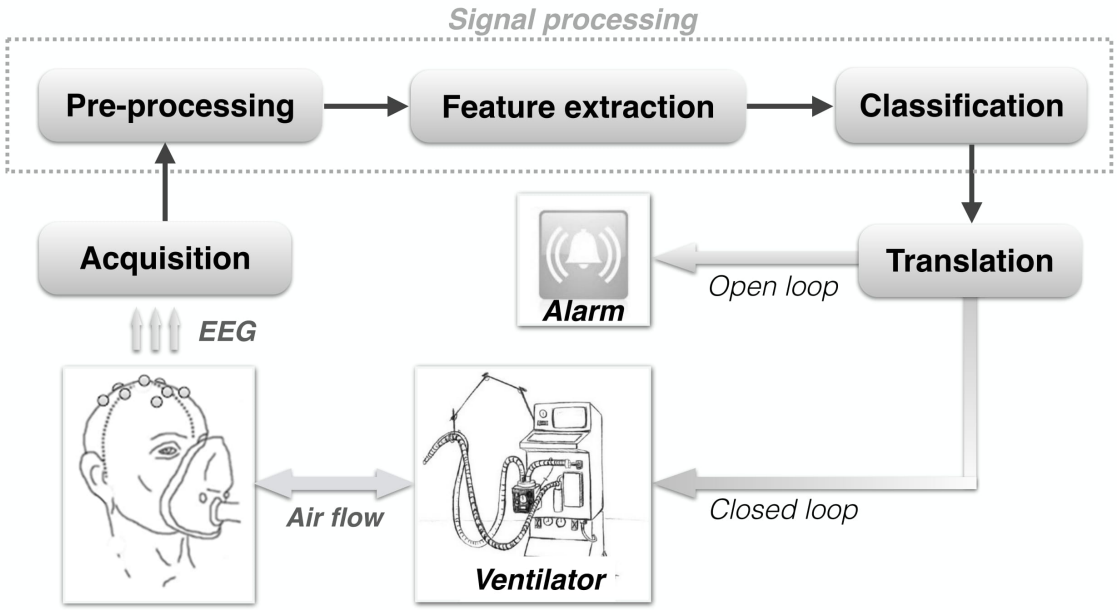

Figure 3. Scheme of a brain-ventilator interface.

More details in [25].

7.5. Interhemispheric Connectivity Characterizes Cortical Reorganization in Motor-Related Networks After Cerebellar Lesions

Participants: Fabrizio de Vico Fallani, Silvia Clausi, Maria Leggio, Mario Chavez, Miguel Valencia, Anton Giulio Maglione, Fabio Babiloni, Febo Cincotti, Donatella Mattia, Marco Molinari [Correspondant].

Although cerebellar-cortical interactions have been studied extensively in animal models and humans using modern neuroimaging techniques, the effects of cerebellar stroke and focal lesions on cerebral cortical processing remain unknown. In the present study, we analyzed the large-scale functional connectivity at the cortical level by combining high-density electroencephalography (EEG) and source imaging techniques to evaluate and quantify the compensatory reorganization of brain networks after cerebellar damage. The experimental protocol comprised a repetitive finger extension task by 10 patients with unilateral focal cerebellar lesions and 10 matched healthy controls. A graph theoretical approach was used to investigate the functional reorganization of cortical networks. Our patients, compared with controls, exhibited significant differences at global and local topological level of their brain networks. An abnormal rise in small-world

network efficiency was observed in the gamma band (30-40 Hz) during execution of the task, paralleled by increased long-range connectivity between cortical hemispheres (Figure 4). Our findings show that a pervasive reorganization of the brain network is associated with cerebellar focal damage and support the idea that the cerebellum boosts or refines cortical functions. Clinically, these results suggest that cortical changes after cerebellar damage are achieved through an increase in the interactions between remote cortical areas and that rehabilitation should aim to reshape functional activation patterns. Future studies should determine whether these hypotheses are limited to motor tasks or if they also apply to cerebro-cerebellar dysfunction in general.

More details in [11].

7.6. A topological criterion for filtering information in complex brain networks

Participants: Fabrizio de Vico Fallani [Correspondant], Vito Latora, Mario Chavez.

In many biological systems, the network of interactions between the elements can only be inferred from experimental measurements. In neuroscience, non-invasive imaging tools are extensively used to derive either structural or functional brain networks in-vivo. As a result of the inference process, we obtain a matrix of values corresponding to an unrealistic fully connected and weighted network. To turn this into a useful sparse network, thresholding is typically adopted to cancel a percentage of the weakest connections. The structural properties of the resulting network depend on how much of the inferred connectivity is eventually retained. However, how to fix this threshold is still an open issue. We introduce a criterion, the efficiency cost optimization (ECO), to select a threshold based on the optimization of the trade-off between the efficiency of a network and its wiring cost. We prove analytically and we confirm through numerical simulations that the connection density maximizing this trade-off emphasizes the intrinsic properties of a given network, while preserving its sparsity. Moreover, this density threshold can be determined a-priori, since the number of connections to filter only depends on the network size according to a power-law. We validate this result on several brain networks, from micro- to macro-scales, obtained with different imaging modalities. Finally, we test the potential of ECO in discriminating brain states with respect to alternative filtering methods. ECO advances our ability to analyze and compare biological networks, inferred from experimental data, in a fast and principled way.

More details in [12].

7.7. Robust imaging of hippocampal inner structure at 7T: in vivo acquisition protocol and methodological choices

Participants: Linda Marrakchi-Kacem [Correspondant], Alexandre Vignaud, Julien Sein, Johanne Germain, Thomas Henry, Cyril Poupon, Lucie Hertz-Pannier, Stephane Lehericy, Olivier Colliot, Pierre-François Van de Moortele, Marie Chupin.

Motion is a crucial issue for ultra-high resolution imaging, such as can be achieved with 7T MRI. An acquisition protocol was designed for imaging hippocampal inner structure at 7T. It relies on a compromise between anatomical details visibility and robustness to motion. In order to reduce acquisition time and motion artifacts, the full slab covering the hippocampus was split into separate slabs with lower acquisition time. A robust registration approach was implemented to combine the acquired slabs within a final 3D-consistent high-resolution slab covering the whole hippocampus. Evaluation was performed on 50 subjects overall, made of three groups of subjects acquired using three acquisition settings; it focused on three issues: visibility of hippocampal inner structure, robustness to motion artifacts and registration procedure performance. Overall, T2-weighted acquisitions with interleaved slabs proved robust. Multi-slab registration yielded high quality datasets in 96% of the subjects, thus compatible with further analyses of hippocampal inner structure. Multi-slab acquisition and registration setting is efficient for reducing acquisition time and consequently motion artifacts for ultra-high resolution imaging of the inner structure of the hippocampus.

More details in [22].

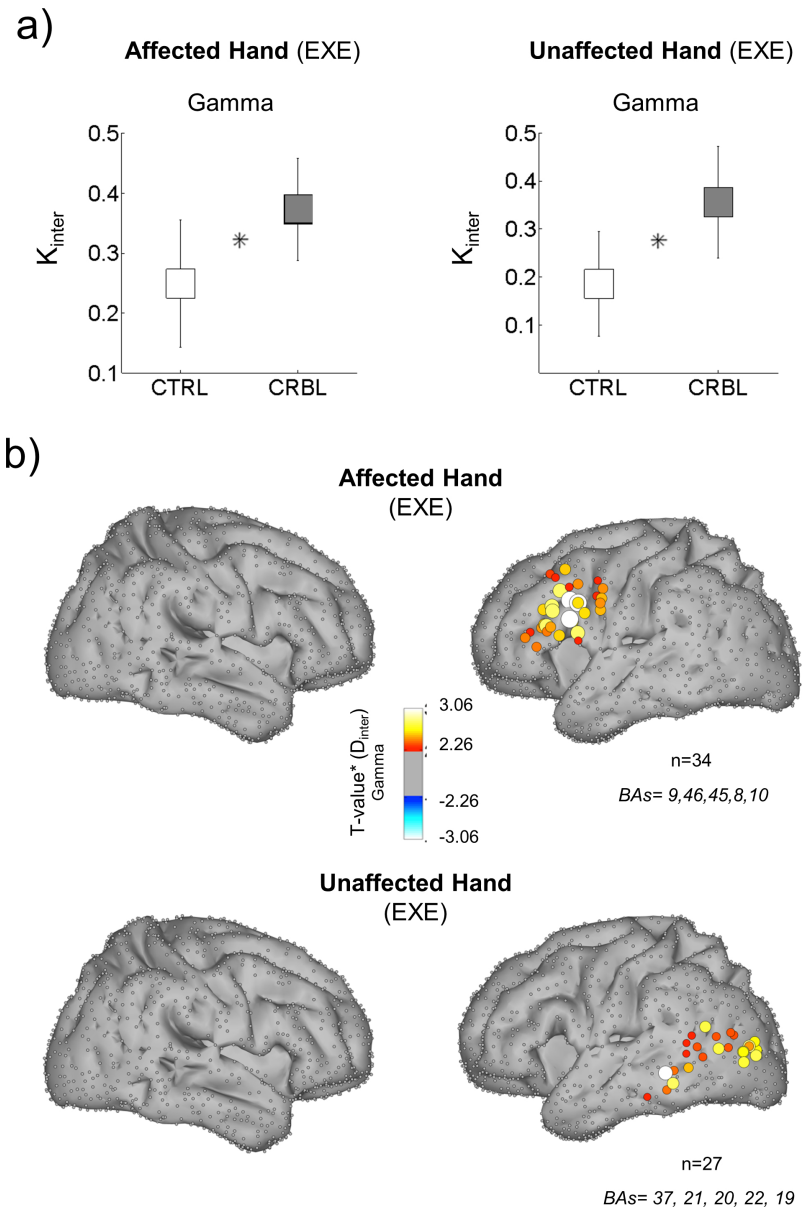

Figure 4. Gamma-band inter-hemispheric density (Kinter) and statistical contrasts of node degrees for brain networks during movement execution Panel a) Averaged Kinter values in the Gamma band for the CTRL and CRBL groups for the affected and unaffected hand conditions in the EXE phase. Panel b) T-value maps of the between-groups contrasts for the node-degree values over lateral views of the MNI cortical model in the Tailarach space in the affected (upper part) and unaffected (bottom part) hand conditions in the EXE phase.

7.8. Improved cerebral microbleeds detection using their magnetic signature on T2*-phase-contrast: a comparison study in a clinical setting

Participants: Takoua Kaaouana [Correspondant], Anne Bertrand, Fatma Ouamer, Bruno Law-Ye, Nadya Pyatigorskaya, Ali Bouyahia, Nathalie Thiery, Carole Dufouil, Christine Delmaire, Didier Dormont, Ludovic de Rochefort, Marie Chupin.

In vivo detection of cerebral microbleeds (CMBs) from T2* gradient recalled echo (GRE) magnitude image suffers from low specificity, modest inter-rater reproducibility and is biased by its sensitivity to acquisition parameters. New methods were proposed for improving this identification, but they mostly rely on 3D acquisitions, not always feasible in clinical practice. A fast 2D phase processing technique for computing internal field maps (IFM) has been shown to make it possible to characterize CMBs through their magnetic signature in routine clinical setting, based on 2D multi-slice acquisitions. However, its clinical interest for CMBs identification with respect to more common images remained to be assessed. To do so, systematic experiments were undertaken to compare the ratings obtained by trained observers with several image types, T2* magnitude, Susceptibility Weighted Imaging reconstructions (SWI) and IFM built from the same T2*-weighted acquisition. 15 participants from the MEMENTO multi-center cohort were selected: six subjects with numerous CMBs (20+/-6 CMBs), five subjects with a few CMBs (2 +/-1 CMBs) and four subjects without CMB. 2D multi-slice T2* GRE sequences were acquired on Philips and Siemens 3T systems. After pilot experiments, T2* magnitude, Susceptibility Weighted Imaging (SWI) minimum intensity projection (mIP) on three slices and IFM were considered for the rating experiments. A graphical user interface (GUI) was designed in order to consistently display images in random order. Six raters of various background and expertise independently selected “definite” or “possible” CMBs. Rating results were compared with respect to a specific consensus reference, on both lesion and subject type points Results: IFM yielded increased sensitivity and decreased false positives rate (FPR) for CMBs identification compared to T2* magnitude and SWI-mIP images. Inter-rater variability was decreased with IFM when identifying subjects with numerous lesions, with only a limited increase in rating time. IFM thus appears as an interesting candidate to improve CMBs identification in clinical setting.

More details in [19].

8. Bilateral Contracts and Grants with Industry

8.1. Bilateral Contracts with Industry

8.1.1. Air-Liquide Medical Systems

Participants: Mario Chavez [Correspondant], Xavier Navarro.

Project title: Real-time characterisation of respiratory states from EEG

Funded in 2014

Amount: 370 K€

Coordinator: Thomas Similowski

Other partners: UPMC, Inserm UMR 1158

Abstract: The project aims at developing a real-time brain computer interface (BCI) for the monitoring of respiratory states from scalp EEG data of healthy volunteers and patients, recorded at the laboratory, hospital ward, operating room or intensive care units..

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. ANR

9.1.1.1. ANR-NIH CRCNS

Participants: Fabrizio de Vico Fallani [Correspondant], Mario Chavez, Denis Schwartz.

Project acronym: NETBCI

Project title: Modeling and predicting brain-computer interface learning from dynamic networks

Duration: Avr 2016 - Avr 2020

Amount: 322k€

Coordinator: Fabrizio De Vico Fallani

Other partners: Complex system group, Université Penn, Etats-units

Abstract: This project will bring together expertise in computational and experimental neuroscience, signal processing and network science, statistics, modeling and simulation, to establish innovative methods to model and analyze temporally dynamic brain networks, and to apply these tools to develop predictive models of brain-computer interface (BCI) skill acquisition that can be used to improve performance. Leveraging experimental data and interdisciplinary theoretical techniques, this project will characterize brain networks at multiple temporal and spatial scales, and will develop models to predict the ability to control the BCI as well as methods to engineer BCI frameworks for adapting to neural plasticity. This project will enable a comprehensive understanding of the neural mechanisms of BCI learning, and will foster the design of viable BCI frameworks that improve usability and performance.

9.1.1.2. ANR PREV-DEMALS

Participants: Olivier Colliot [Correspondant], Marie Chupin, Stanley Durrleman, Anne Bertrand.

Project acronym: PREV-DEMALS

Project title: Predict to prevent frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS)

Duration: Avr 2015 - Avr 2019

Amount: 487k€

Coordinator: Isabelle Le Ber

Other partners: ICM, AP-HP, CHR de Lille, CHU Limoges, CHU Rouen, Laboratory of Biomedical Imaging

Abstract: The project focuses on C9ORF72, the most frequent genetic form of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). Since 2006, major discoveries have helped elucidate the pathological bases and linked FTLD and ALS: 1) TDP-43 aggregates in neurons and 2) C9ORF72 mutations in both disorders. Two major pathological subtypes are now defined in FTLD, FTLD-TDP and FTLD-TAU. C9ORF72 mutations (associated to FTLD-TDP) are the most frequent genetic causes of FTLD (15%), FTLD-ALS (65%) and ALS (40%). No curative treatment actually exists, but therapeutics emerged against tau aggregation. The objectives of the project are to develop appropriate cognitive, brain imaging markers and peripheral biomarkers of the early phase of FTLD, to follow disease progression and to guide future targeted therapeutic trials. To address this questions, we will conduct a multimodal study (cognition, brain structural MRI, brain metabolism - FDG-PET) in C9ORF72 families. The cohort will be followed at 3-time points (M0, M18, M36). Longitudinal analyses will aim at characterizing the trajectory of decline across time. Brain structural changes will be evaluated by 1) morphometric analysis to assess global brain atrophy, cortical thickness and study of the cortical sulci; 2) functional connectivity analysis of resting-state MR data; 3) structural connectivity analysis of diffusion-weighted MRI. Brain metabolism will be evaluated with FDG-PET. We will use the most recent RNA sequencing technology to detect gene expression and RNA splicing alterations in lymphocytes of patients and presymptomatic carriers. The discovery of new markers involved in FTLD will have practical consequences for early and accurate diagnosis of FLD and ALS disease.

9.1.1.3. ANR IVMRS

Participants: Anne Bertrand [Correspondant], Alexandra Petiet, Mathieu Santin, Francesca Branzoli, Benoit Delatour, Marc Sanson.

Project acronym: IVMRS

Project title: Implantable miniaturized probe for In-vivo Magnetic Resonance Spectroscopy: Application to Murine models of Alzheimer's disease and Gliomas.

Duration: Oct 2016 - Oct 2020

Amount: 633k€

Coordinator: Luc Hebrard

Other partners: ICube - Unistra, Strasbourg; ISA Laboratory, Lyon; NYU School of Medicine, NY, USA.

Abstract: During the development of new therapeutics against brain diseases, the pre-clinical phase, i.e. the validation of treatment delivery, safety and efficacy in animal models of the disease, represents a crucial step. Magnetic Resonance Imaging (MRI) is a method of particular interest at this stage, as it provides non-invasive surrogate endpoints that can help selecting appropriate candidates during the process of drug development. Single Voxel Magnetic Resonance Spectroscopy (SVS) provides non-invasive, in-vivo quantitative measurements of brain metabolites, which reflects functional changes at the cellular and subcellular levels, and can be repeated longitudinally. As high-field MRI has become the benchmark in preclinical research on animal models, it appears possible to investigate the cerebral metabolomics changes in animals, and to use it as a surrogate marker in preclinical therapeutic trials. However, the number of relevant metabolites is much higher than the low number of measurable metabolites with conventional in-vivo high-field SVS. Moreover, considering also the subtle changes of these metabolites at the early stage of the disease, the use of conventional high-field SVS in preclinical studies remains strongly limited. The high volume of the Voxel-of-Interest (VOI), ranging from 10 to 30mm3, which is required to have a usable signal in conventional SVS, and the inherent variability of longitudinal SVS measurement due to the variable position of the VOI in the successive experiments, remain the two major issues when looking during time for small changes in metabolic concentrations and metabolites ratios in a specific small region of the animal brain. The IvMRS project aims at filling this gap by developing the first chronic implantable MRS micro-probe (μ- probe), minimally invasive, exhibiting very high signal sensitivity, and sharp spectral peaks, from sub-millimetric VOI. Such a probe will allow detecting a much higher number of metabolites than conventional in-vivo SVS. The μ-probe will work at frequencies ranging from 300MHz to 500MHz in ultra-high field Magnetic Resonance Imaging scanners, 7T and 11.7T. It will embed a specific micro-coil antenna, a low-noise signal conditioning circuit designed in CMOS microelectronics technology, as well as an accurate on-chip positioning sensor. It will be dedicated to the study of changes in brain metabolite markers of two major diseases, Alzheimer's disease and cerebral gliomas, and to the assessment of effective therapeutic strategies.

9.1.2. IHU

9.1.2.1. General program

Participants: Olivier Colliot, Mario Chavez, Stanley Durrleman, Marie Chupin, Didier Dormont, Dominique Hasboun, Damien Galanaud, Fabrizio de Vico Fallani.

Project acronym: IHU-A-ICM

Project title: Institute of Translational Neuroscience

Founded in 2011

General Director: Bertrand Fontaine

The IHU-A-ICM program was selected, in 2011, in a highly competitive national call for projects. A 10-year, 55M€ program, has been implemented by a recently created foundation for scientific cooperation. Based on the clinical and scientific strenghts of the ICM and the hospital Department of Nervous System Diseases, it mainly supports neuroscience research, but is also invested in improving care and teaching. ARAMIS is strongly involved in the IHU-A-ICM project, in particular in WP6 (neuroimaging and electrophysiology), WP7 (biostatistics), WP2 (Alzheimer) and WP5 (epilepsy). We have started collaborations with the new bioinformatics/biostatistics platform (IHU WP7, head: Ivan Moszer), in particular through a joint project on the integration of imaging and genomics data.

9.1.2.2. ICM-Internal Research projects

Participants: Anne Bertrand [Correspondant], Takoua Kaaouana, Benoit Delatour, Alexandra Petiet.

Project title: The Histo-MRI project: targeting MR signature of tauopathy from micro- to macroscopy

Founded in 2014

Coordinator: Anne Bertrand

Identifying morphological MR signatures of brain diseases usually follows a top-down process, which starts by describing a pattern of MR signal changes in patients, hypothesizes an underlying pathological mechanism, and confirms this mechanism by correlating the observed MR signal changes with histological lesions on post-mortem examination. This top-down process, relevant for large, centimetric brain lesions, becomes inappropriate when targeting the MR signal intensity changes associated with microscopic lesions. Our project aims at developing an MR biomarker of NFT using a new bottom-up approach. We will start by identifying the MR signal changes associated with the presence of NFT at the level of the histological slice, and utilize these findings to develop a method of NFT quantification on clinical, millimetric 3D MR images. To achieve this goal, we will develop and implement a 11.7T histological coil dedicated to the scanning of histological slices, which allows both ultra-high resolution MR imaging (up to 33 microns in-plane) and perfect co-registration with histological staining, performed subsequently on the same slice. This method has the potential to provide a novel biomarker of tauopathy that could not have been identified using the usual top-down approach. It also envisions the possibility to describe and understand new MRI contrasts in other neurodegenerative diseases associated with microscopic deposition of various proteins.

9.1.2.3. ICM-Internal Research projects

Participants: Mario Chavez [Correspondant], Fabrizio de Vico Fallani [Correspondant].

Project title: Non-invasive manipulation of brain synchrony to enhance brain function and rehabilitate faulty cognition in humans: A proof of concept

Founded in 2014

Coordinator: Antoni Valero Cabre (ICM-team “Dynamiques Cérébrales, Plasticité et Rééducation”)

Other partners: Service des Urgences Cérébro-Vasculaires de l’Hôpital Pitié-Salpêtrière, Paris.

The long-term goal of this project is to develop the use of non-invasive manipulation of abnormal cerebral oscillations underlying cognitive activity to restore brain function in neurological patients. Cognitive functions emerge from large distributed networks organized in space and time. The short-term goal of this application is to study the causal role played by oscillatory activity in visual awareness and test whether their manipulation by non-invasive brain stimulation has the potential to restore its function in stroke patients.

9.1.2.4. ICM Big Brain Theory Program

Participants: Stanley Durrleman [Correspondant], Harald Hampel [Correspondant], Sabrina Fontanella, Simone Lista, Olivier Colliot, Stephanie Allassonniere, Jean-Baptiste Schiratti, Bruno Dubois, Hovagim Bakardjian, Remi Genthon, Enrica Cavedo, Katrine Rojkowa.

Project title: Dynamic models of disease progression across Alzheimer's disease stages informed by multimodal neuroimaging and biological data

Founded in 2016-2017

Coordinator: Stanley Durrleman and Harald Hampel

Other partners: Institut de la Mémoire et de la maladie d'Alzheimer

The estimation of data-driven models of disease progression for neurodegenerative diseases, including Alzheimer's disease (AD), is crucial to confirm, refine and extend the current hypothetical models. The estimation of such quantitative models from longitudinal data sets is notably difficult because of the lack of principled methodological frameworks for the analysis of spatiotemporal data.

The project builds on an innovative mathematical, statistical, and computational framework to automatically align the dynamics and the direction of individual trajectories of the evolving pathology, and then to infer a normative scenario of disease progression across different disease stages. The estimated scenario will combine spatiotemporal maps of lesion propagation, such as maps of amyloid deposition or cortical atrophy, and global measurements such as levels of CSF biomarkers. It will be possible to estimate not only a normative scenario but also the inter-individual variability in the values, dynamics and direction of both topographical and pathophysiological biomarkers changes during the course of the disease.

The application of this technology to publicly available and in-house longitudinal data sets of individuals from the asymptomatic at risk to the prodromal and dementia stages will yield new insights into the pathophysiology of AD from the preclinical to the AD dementia stages. This quantitative data-driven approach will be exploited to assess and refine the current qualitative hypothetical models of AD progression. Notably, it will complement these models with typical pathways of lesion propagation in the brain during disease progression. It will also highlight the effect of the known risk factors of AD such as apolipoprotein E genotype on the disease progression profile.

The project will open up the concrete possibility to derive a computer-aided diagnosis, staging, and prognosis tool for a better recruitment of patients in clinical studies and to assist clinicians in the diagnosis and the monitoring of both disease progression and treatment efficacy.

9.1.2.5. IFR49-Internal Research projects

Participants: Mario Chavez [Correspondant], Fabrizio de Vico Fallani [Correspondant].

Project title: Exploring the impact and time frequency signature of rhythmic patterns of Transcranial Magnetic Stimulation (TMS) on network activity by Magneto-Encephalography (MEG)

Founded in 2014

Coordinator: Antoni Valero Cabre (ICM-team "Dynamiques Cérébrales, Plasticité et Rééducation")

Other partners: TMS, EEG and MEG technical platforms of the ICM at the Hopital Pitié-Salptrière; and Service des Urgences Cérébro-Vasculaires de l'Hôpital Pitié-Salpêtrière, Paris.

The long-term goal of this project is to better understand the ability of non invasive neurostimulation to induce lasting local and distributed reorganization effects in the human brain to better plan and document therapies for patients. The short-term goal of this application is to develop a new mapping procedure to be able to capture and characterize in terms of oscillatory activity the lasting impact of repetitive Transcranial Magnetic Stimulation (TMS) on specific brain regions and associated networks.

9.1.3. CATI (Alzheimer Plan)

Participants: Olivier Colliot [Correspondant], Marie Chupin [Correspondant], Stanley Durrleman, Didier Dormont, Chabha Azouani, Ali Bouyahia, Johanne Germain, Kelly Martineau, Sonia Djobeir, Hugo Dary, Ludovic Fillon, Takoua Kaaouana, Alexandre Routier, Mathieu Dubois.

Project acronym: CATI

Project title: Centre d'Acquisition et de Traitement des Images

Funded in 2011

Amount: 9M€

Coordinator: Jean-François Mangin

Other partners: Neurospin, CENIR, Inserm U678, IM2A

Abstract: The CATI project (funded by the National Alzheimer Plan for 9M€, 2.1M€ for ARAMIS) aims at creating a national platform for multicenter neuroimaging studies. CATI aims to be a national resource for the scientific, medical and industrial research community and will provide a wide range of services: access to a national acquisition network, standardization of acquisitions, image quality control, image analysis, databasing/archiving, meta-analyses. Through CATI, our team coordinates a large network composed of over 30 image acquisition centers. CATI already supports over 15 multicenter projects including the national cohort MEMENTO (2300 subjects). CATI is integrated with France Life Imaging (PI: F. Lethimonnier) and the Neugrid for you (N4U, PI: G. Frisoni) network.

9.1.4. National Networks

- GdR Statistics and Medicine - http://gdr.statsante.fr/Accueil.html
- GdR (MaDICS) Masses de Données, Informations et Connaissances en Sciences Big Data - Data ScienceStatistics and Medicine - http://www.madics.fr/reseaux/

9.1.5. Other National Programs

9.1.5.1. Programme Hospitalier de Recherche Clinique (PHRC)

Participants: Olivier Colliot, Marie Chupin, Stanley Durrleman, Didier Dormont, Damien Galanaud.

- PHRC PredictPGRN, co-funding by Alzheimer Plan, *Caractérisation multimodale prospective de la démence frontotemporale dûe à des mutations du gène PGRN à un stade symptomatique et présymptomatique*. (Coordinator : A. Brice)
- PHRC ImaBio3, co-funding by Roche (pharmaceutical industry), *Rôle des réactions cellulaires sanguines, inflammatoires et immunitaires anti-amyloïde centrales et périphériques dans la maladie d'Alzheimer débutante*. (Coordinator : M. Sarazin)
- PHRC CAPP, *Caractérisation linguistique, anatomique/métabolique et biologique des différentes formes d'aphasie primaire progressive : vers le rationnel pour des essais pharmacologiques et des rééducations du langage ciblées*. (Coordinator: M. Teichmann)

9.1.5.2. Institut Universitaire d'Ingénierie pour la Santé (IUIS)

Participants: Mario Chavez, Xavier Navarro.

Project acronym: DYSPEV

Project title: Dépistage de la dyspnée par potentiels évoqués visuels

Funded in 2014

Amount: 38K€

Coordinator: Thomas Similowski

Other partners: UPMC, Inserm UMR 1158

Abstract: Steady state visual evoked potentials (SSVEP) have been widely utilized in brain computer interfacing (BCI) in last years. In this project, we explore the possibilities of SSVEP to manage the communication between patients suffering from respiratory disorders and health care providers. By imposing different breathing constraints, we use a SSVEP-based brain computer interface to help those subjects to communicate their breathing sensations (breathing well/breathing bad).

9.2. European Initiatives

9.2.1. FP7 & H2020 Projects

9.2.1.1. H2020 - Project EuroPOND

Participants: Olivier Colliot, Stanley Durrleman, Manon Ansart, Igor Koval, Alexandre Bône.

Project acronym: EuroPOND
Project title: Data-driven models for Progression Of Neurological Disease
Duration: Jan 2016 - Dec 2019
Amount: 6M€
Coordinator: Daniel Alexander
Other partners: University College London (UK), EMC Rotterdam (The Netherlands), VUMC (The Netherlands), Fate Bene Fratelli (Italy), Carol Besta Institute (Italy), Université de Genève (Switzerland), Icometrix (Belgium)
Abstract: EuroPOND will develop a data-driven statistical and computational modeling framework for neurological disease progression. This will enable major advances in differential and personalized diagnosis, prognosis, monitoring, and treatment and care decisions, positioning Europe as world leaders in one of the biggest societal challenges of 21st century healthcare. The inherent complexity of neurological disease, the overlap of symptoms and pathologies, and the high comorbidity rate suggests a systems medicine approach, which matches the specific challenge of this call. We take a uniquely holistic approach that, in the spirit of systems medicine, integrates a variety of clinical and biomedical research data including risk factors, biomarkers, and interactions. Our consortium has a multidisciplinary balance of essential expertise in mathematical/statistical/computational modelling; clinical, biomedical and epidemiological expertise; and access to a diverse range of datasets for sporadic and well-phenotyped disease types.The project will devise and implement, as open-source software tools, advanced statistical and computational techniques for reconstructing long-term temporal evolution of disease markers from cross-sectional or short-term longitudinal data. We will apply the techniques to generate new and uniquely detailed pictures of a range of important diseases. This will support the development of new evidence-based treatments in Europe through deeper disease understanding, better patient stratification for clinical trials, and improved accuracy of diagnosis and prognosis. For example, Alzheimer's disease alone costs European citizens around €200B every year in care and loss of productivity. No disease modifying treatments are yet available. Clinical trials repeatedly fail because disease heterogeneity prevents bulk response. Our models enable fine stratification into phenotypes enabling more focussed analysis to identify subgroups that respond to putative treatments.

9.2.1.2. FET Flagship - Human Brain Project

Participants: Olivier Colliot, Stanley Durrleman.

Project acronym: HBP
Project title: Human Brain Project
Sub-project: SP8 - Medical Informatics Platform
Duration (for this phase): 2016-2018
Abstract: The Human Brain Project (HBP) is a European Commission Future and Emerging Technologies Flagship. The HBP aims to put in place a cutting-edge, ICT-based scientific Research Infrastructure for brain research, cognitive neuroscience and brain-inspired computing. The Project promotes collaboration across the globe, and is committed to driving forward European industry. Our team is involved in the Subproject SP8 (Medical Informatics Platform). The Medical Informatics Platform (MIP) is an innovative data management system that gives researchers the means to access and analyse large amounts of anonymized clinical neuroscience data. Within that framework, we will develop and implement a method to construct disease progression models from longitudinal biomarkers. The method will use statistical learning techniques to infer a long-term disease progression model from multiple short term data from a series of individuals. The model will account for variability in age at disease onset, pace of disease progression and trajectories of biomarkers changes across individuals in the observed population.

9.2.1.3. ERC - LEASP

Participant: Stanley Durrleman.

Project acronym: LEASP

Project title: Learning Spatiotemporal Patterns in Longitudinal Image Data Sets of the Aging Brain

Duration: 2016-2021

Abstract: Time-series of multimodal medical images offer a unique opportunity to track anatomical and functional alterations of the brain in aging individuals. A collection of such time series for several individuals forms a longitudinal data set, each data being a rich iconic-geometric representation of the brain anatomy and function. These data are already extraordinary complex and variable across individuals. Taking the temporal component into account further adds difficulty, in that each individual follows a different trajectory of changes, and at a different pace. Furthermore, a disease is here a progressive departure from an otherwise normal scenario of aging, so that one could not think of normal and pathologic brain aging as distinct categories, as in the standard case-control paradigm.

Bio-statisticians lack a suitable methodological framework to exhibit from these data the typical trajectories and dynamics of brain alterations, and the effects of a disease on these trajectories, thus limiting the investigation of essential clinical questions. To change this situation, we propose to construct virtual dynamical models of brain aging by learning typical spatiotemporal patterns of alterations propagation from longitudinal iconic-geometric data sets.

By including concepts of the Riemannian geometry into Bayesian mixed effect models, the project will introduce general principles to average complex individual trajectories of iconic-geometric changes and align the pace at which these trajectories are followed. It will estimate a set of elementary spatiotemporal patterns, which combine to yield a personal aging scenario for each individual. Disease-specific patterns will be detected with an increasing likelihood.

This new generation of statistical and computational tools will unveil clusters of patients sharing similar lesion propagation profiles, paving the way to design more specific treatments, and care patients when treatments have the highest chance of success.

9.3. International Initiatives

9.3.1. Informal International Partners

F. De Vico Fallani has a collaboration with the University Penn, Philadelphia, US (Prof. Danielle Bassett).

S. Durrleman has an enduring collaboration with professor Guido Gerig, Tandon School of Engineering, NYU. He is consultant for NIH Grant "4D shape analysis for modeling spatiotemporal change trajectories in Huntington's Disease "predict-HD".

M. Chupin and O. Colliot have an enduring collaboration with the Center for Magnetic Resonance Research, University of Minnesota, USA (P-F Van de Moortele, T. Henry, M. Marjanska, K. Ugurbil) a leading center in 7T MRI.

S. Durrleman and O. Colliot have a collaboration with the Center for Medical Image Computing (CMIC) at University College London (UCL), London, UK (S. Ourselin, D. Alexander, M. Modat).

D. Galanaud has an enduring collaboration with the Massachusetts General Hospital, Harvard University, USA (R. Gupta).

M. Chavez has different collaborations with the Mathematics Departement of the Queen Mary University of London, UK (Prof. V. Latora); and the Physics Department of the Universitat de Barcelona, Spain (Prof. Albert Diaz-Guilera)

F. De Vico Fallani has an enduring collaboration with the University Sapienza, Rome, Italy (Profs. Fabio and Claudio Babiloni) and with the IRCCS Fondazione Santa Lucia, Rome, Italy (M. Molinari and D. Mattia).

A. Bertrand has an enduring collaboration with professor Youssef Z. Wadghiri, head of the Preclinical Imaging Core, Center for Biomedical Imaging, NYU School of Medicine, New York, NY, USA.

9.4. International Research Visitors

9.4.1. Visits of International Scientists

9.4.1.1. Internships

Kuldeep Kumar (Ecole de Technologie Supérieure, Montréal, Canada) is visiting ARAMIS from October 2016 to March 2017 under the MITACS programme.

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific Events Selection

10.1.1.1. Member of the Conference Program Committees

O. Colliot was a member of program committee of the Workshop on Patch-based Techniques in Medical Imaging (Patch-MI) held in conjunction with the MICCAI conference.

S. Durrleman was on the advisory panel of MICCAI Workshop on Spectral and Shape Analysis in Medical Imaging (SESAMI)

F. De Vico Fallani was member of the program committee of the Satellite on Brain networks, International Conference on Network Science (NetSci), Seoul, South Korea, 2016

F. De Vico Fallani was member of the program committee of5th International Workshop on Complex Networks and their Applications, Milan, Italy, 2016

10.1.1.2. Reviewer

O. Colliot acted as a reviewer for the annual meeting of the Organization for Human Brain Mapping (OHBM).

S. Durrleman acted as a reviewer for Computer Vision and Pattern Recognition (CVPR), International Conference on Computer Vision (ICCV), and Workshop on Biomedical Image Registration (WBIR).

10.1.2. Journal

10.1.2.1. Member of the Editorial Boards

O. Colliot is a member of the Editorial Board of Medical Image Analysis (Elsevier).

S. Durrleman is associate editor of IEEE Transactions on Medical Imaging (TMI)

10.1.2.2. Reviewer - Reviewing Activities

O. Colliot acted as a reviewer for NeuroImage, NeuroImage: Clinical, IEEE Trans Medical Imaging, Medical Image Analysis and Neurobiology of Aging.

S. Durrleman acted as a reviewer for NeuroImage, IEEE Trans Medical Imaging, Medical Image Analysis, Frontiers in Neuroimaging, International Journal of Computer Assisted Radiology and Surgery (IJCARS), Advances in Data Analysis and Classification, among others.

A. Bertrand acted as a reviewer for Neurobiology og Aging, Frontiers in Neuroscience, American Journal of Neuroradiology, Journal of Neuroradiology.

F. De Vico Fallani acted as a reviewer for Brain, Cerebral Cortex, IEEE TBME/TNRSE, Human Brain Mapping, Neuroimage, Plos Computational Biology, J Neurosci Meth, Sci Rep, Brain Connectivity.

10.1.3. Invited Talks

S. Durrleman gave an invited lecture at the International Colloquium "Evolution du cerveau et des capacités cognitives des Hominidés fossiles depuis Sahelanthropus tchadensis, il y a sept millions d'années jusqu'à l'Homme moderne" in Tautavel.

F. De Vico Fallani gave an invited talk at the Workshop on Complex networks, Lipari, Italy, 2016

F. De Vico Fallani gave an invited talk Meeting on Dynamics and synchronization on complex networks, Tarragona, Spain, 2016

F. De Vico Fallani gave an invited talk Workshop on Dynamic networks, Institut Systèmes Complexes, Toulouse, France, 2016

F. De Vico Fallani gave an invited talk Satellite on Brain networks, International Conference on Network Science (NetSci), Seoul, South Korea, 2016

10.1.4. Scientific Expertise

S. Durrleman has served in the "Commission de développement technologique" (CDT) of the Inria Paris center.

S. Durrleman has led a working group on neuroinformatics at the ICM (Brain and Spine Institute).

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

Master: Olivier Colliot coordinates the module "Méthodes d'imagerie médicale" of the Master 2 in Computer Science of Université Pierre et Marie Curie.

Master: Olivier Colliot, Master in Computer Science, 4.5 hours (eqTD), Université Pierre et Marie Curie

Master: Stanley Durrleman, Master in Computer Science, 9 hours (eqTD), Université Pierre et Marie Curie

Master: Marie Chupin, Master in Computer Science, 3 hours (eqTD), Université Pierre et Marie Curie

Master: Fabrizio De Vico Fallani, Master in "Méthodologies et applications en imagerie médicale", 3 hours (eqTD), Université Pierre et Marie Curie

Master: Damien Galanaud, Master in Medical Physics, 4 hours, Université Paris-Sud

Engineering school: Olivier Colliot, 3 hours (eqTD), Mines ParisTech

Medical school: Didier Dormont is the Director of the University Diploma (DIU) "Diagnostic and Therapeutic Neuroradiology", Université Pierre et Marie Curie

Medical school: Anne Bertrand gives lectures in Neuroimaging of degenerative diseases and normal aging for residents in Radiology and Neurology, for Radiology technicians, for License students in Orthophony, and in various "University Diploma" medical programs (Neurogeriatrics, Neuroradiology, Alzheimer's Disease and related disorders, Neurovascular Imaging, Emergency-Stroke, Neuroresuscitation), for a total of 50 hours a year.

Medical school: Didier Dormont, Courses for Medical Students, Université Pierre et Marie Curie

Medical school: Dominique Hasboun, Courses for Medical Students, Université Pierre et Marie Curie

Medical school: Damien Galanaud, Courses for Medical Students, Université Pierre et Marie Curie

Medical school: Anne Bertrand, Courses for Medical Students, Université Pierre et Marie Curie

Medical school: Didier Dormont organizes and participates in the practical teaching of Neuroradiology for Medical Students in the Department of Diagnostic Neuroradiology of Pitié Salpêtrière University Hospital

Medical school: Didier Dormont organizes and participates in the practical teaching of Neuroradiology for Radiology Specializing Residents in the Department of Diagnostic Neuroradiology of Pitié Salpêtrière University Hospital

Medical school: Didier Dormont, Courses to the university diplomas (DU) : "Maladie d'Alzheimer", and "Imagerie Vasculaire non Invasive"

Medical school: Damien Galanaud, courses to the University Diploma (DIU) "Diagnostic and Therapeutic Neuroradiology", Université Pierre et Marie Curie

Paramedical studies: Dominique Hasboun, Psychomotricity, 50 hours, Université Pierre et Marie Curie

10.2.2. Supervision

PhD in progress : Catalina Obando-Forero, "Graph models of cortical plasticity in temporal brain networks", Inria, started in 2015, advisor: Fabrizio De Vico Fallani

PhD in progress : Jeremy Guillon, "Méthode d'analyse multimodale de connectivités neuronales basée sur la théorie des réseaux complexes multicouches", EDITE Université Pierre et Marie Curie, started in 2015, advisors: Fabrizio De Vico Fallani and Mario Chavez

PhD Cifre in progress : Fanny Grosselin, "Fouille des données EEG et suivi longitudinal grande échelle pour le diagnostic et la prédiction du niveau de stress chez l'homme", EDITE Université Pierre et Marie Curie, started in 2016, advisors: Fabrizio De Vico Fallani and Mario Chavez,

PhD in progress : Junhao Wen, "Cortical morphometry for discovering new biomarkers of neurodegenerative diseases", Université Pierre et Marie Curie, Started in 2015, advisors: Olivier Colliot and Stanley Durrleman

PhD in progress : Jorge Samper-Gonzalez, "Learning from heterogeneous data for prediction of Alzheimer's disease", Université Pierre et Marie Curie, Started in 2015, advisors: Olivier Colliot and Theodoros Evgeniou

PhD in progress : Alexandre Routier, "Multimodal neuroimaging for characterization of primary progressive aphasias", Université Pierre et Marie Curie, Started in 2015, advisors: Marc Teichmann, Olivier Colliot and Marie-Odile Habert

PhD in progress: Jean-Baptiste Schiratti, "Méthodes et algorithmes pour l'analyse statistique de données anatomiques longitudinales – application à la caractérisation des phases pré-symptomatiques des maladies neurodégénératives", Ecole Polytechnique, Started in 2013, advisors: S. Allassonnière and S. Durrleman

PhD in progress: Barbara Gris, "Approche modulaire des méthodes de grandes déformations pour l'appariement de formes", Ecole Normale Supérieure de Cachan, Started 2013, advisors: A. Trouvé and S. Durrleman

PhD in progress: Pascal Lu, "Machine learning from multimodal genetic and neuroimaging data for personalized medicine", Université Pierre et Marie Curie, Started 2016, advisor: O. Colliot

PhD in progress: Wen Wei, "Learning brain alterations in multiple sclerosis from multimodal neuroimaging data", Université de Nice Sophia-Antipolis, Started 2016, advisors: N. Ayache, O. Colliot and S. Durrleman

PhD in progress: Alexandre Bône, "Learning methods for the spatiotemporal analysis of longitudinal image data : application to the diagnosis, prognosis and monitoring of Alzheimer's disease", started 2016, advisors: O. Colliot and S. Durrleman

PhD in progress: Manon Ansart, "Automatic recommendation systems built on the statistical exploitation of longitudinal medical data sets", started 2016, advisors: D. Dormont and S. Durrleman

PhD in progress: Maxime Louis, "Learning spatiotemporal trajectories of iconic-geometric data sets", started 2016, advisors: S. Durrleman

PhD in progress: Igor Koval, “Construction of disease progression models from multimodal longitudinal data”, started 2016, advisors: S. Allassonnière and S. Durrleman

PhD in progress: Lou Albessard, “Etude de la co-variation morphologique entre le crâne et le cerveau dans le genre Homo”, started 2015, advisors: D. Grimaud-Hervé and S. Durrleman

Master 2: Alexandre Morin, Master in Neuroscience, Université Pierre et Marie Curie, Oct 2015-Aug 2016, advisor: Olivier Colliot

Master 2: Thomas Jacquemont, Master in Neuroscience, Université Pierre et Marie Curie, Oct 2015-Aug 2016, advisor: Olivier Colliot

Master 2: Martina Sundqvist, Master in Cognitive Science, Ecole Normale Supérieure, Oct 2015-Aug 2016, advisors: Olivier Colliot and Marc Teichmann

Master 2: Enrico Valenti, Master in Psychiatry, Université Sapienza, Rome, Italy, Sep 2016-Dec 2016, advisor: Fabrizio De Vico Fallani

Master 2: Carlos Tor Diez, Master in BioMedical Engineering, ParisTech Universite Paris Descartes, Mar-Sept 2016, advisor: Marie Chupin

Internship: Ayoub Louati, Tunisia Polytechnic School, Mar-Sept 2016, advisor: Marie Chupin

10.2.3. Juries

Fabrizio De Vico Fallani participated, as referee, to the PhD committee of Aziz Adebimpe (Université Picardie), 2016 (supervisors: Fabrice Wallois and Ardalan Aarabi).

Mario Chavez participated, as referee, to the PhD committee of Aziz Adebimpe (Université Picardie), 2016 (supervisors: Fabrice Wallois and Ardalan Aarabi).

Olivier Colliot participated, as referee, to the PhD committee of Mehdi Hadj-Hamou (Inria Sophia), 2016 (supervisors: Xavier Pennec and Nicholas Ayache).

Olivier Colliot participated, as examiner, to the PhD committee of Bishesh Kanal (Inria Sophia), 2016 (supervisors: Xavier Pennec and Nicholas Ayache).

Olivier Colliot participated, as examiner, to the PhD committee of Baptiste Morel (Telecom ParisTech), 2016 (supervisors: Isabelle Bloch and Catherine Adamsbaum).

Olivier Colliot participated, as examiner, to the PhD committee of Romain Colle (Université Paris-Sud), 2016 (supervisor: Emmanuelle Corruble).

10.3. Popularization

With the precious help of the communication department of the Inria Paris Center, ARAMIS prepared and presented games on brain data analysis, presented at the "Salon Culture et Jeux Mathématiques" and at the "Fête de la Science".

11. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] P. GORI. *Statistical models to learn the structural organisation of neural circuits from multimodal brain images - Application to Gilles de la Tourette syndrome*, UPMC - Université Paris 6 Pierre et Marie Curie, January 2016, https://hal.archives-ouvertes.fr/tel-01352477

Articles in International Peer-Reviewed Journals

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[3] F. AMEUR, O. COLLIOT, P. CAROPPO, S. STROER, D. DORMONT, A. BRICE, C. AZUAR, B. DUBOIS, I. LE BER, A. BERTRAND. *White matter lesions in FTLD: distinct phenotypes characterize GRN and C9ORF72 mutations*, in "Neurology: Genetics", 2016, vol. 2, n^{o} 1 [*DOI :* 10.1212/NXG.0000000000000047], https://hal.inria.fr/hal-01266596

[4] J.-L. BACQUET, N. WEISS, C. MEYNIEL, C. ALGRIN, S. CHOQUET, V. LEBLOND, D. GALANAUD, P. LEHOANG, B. BODAGHI, V. TOUITOU. *Neither the patient nor the physician could see anything: Atypical Bing-Neel syndrome*, in "American Journal of Hematology", 2016, vol. 91, n^{o} 8, pp. 858 - 859, https://hal.inria.fr/hal-01377870

[5] A. BEAUDET, J. DUMONCEL, F. DE BEER, B. DUPLOYER, S. DURRLEMAN, E. GILISSEN, J. HOFFMAN, C. TENAILLEAU, J. F. THACKERAY, J. BRAGA. *Morphoarchitectural variation in South African fossil cercopithecoid endocasts*, in "Journal of Human Evolution", September 2016, vol. 101, pp. 65-78 [*DOI :* 10.1016/J.JHEVOL.2016.09.003], https://hal.inria.fr/hal-01440065

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[7] E. CAVEDO, B. DUBOIS, O. COLLIOT, S. LISTA, B. CROISILE, G. L. TISSERAND, J. TOUCHON, A. BONAFE, P. J. OUSSET, O. ROUAUD, F. RICOLFI, A. VIGHETTO, F. PASQUIER, S. GALLUZZI, C. DELMAIRE, M. CECCALDI, N. GIRARD, S. LEHERICY, F. DUVEAU, M. CHUPIN, M. SARAZIN, D. DORMONT, H. HAMPEL. *Reduced Regional Cortical Thickness Rate of Change in Donepezil-Treated Subjects With Suspected Prodromal Alzheimer's Disease*, in "Journal of Clinical Psychiatry", October 2016 [*DOI :* 10.4088/JCP.15M10413], https://hal.inria.fr/hal-01388951

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[9] R. COLLE, C. CURY, M. CHUPIN, E. DEFLESSELLE, P. HARDY, N. GHAIDAA, B. FALISSARD, D. DUCREUX, O. COLLIOT, E. CORRUBLE. *Hippocampal volume predicts antidepressant efficacy in depressed patients without incomplete hippocampal inversion*, in "Neuroimage-Clinical", 2016 [*DOI :* 10.1016/J.NICL.2016.04.009], http://hal.upmc.fr/hal-01310464

[10] R. COLLE, I. DUPONG, O. COLLIOT, E. DEFLESSELLE, P. HARDY, B. FALISSARD, D. DUCREUX, M. CHUPIN, E. CORRUBLE. *Smaller hippocampal volumes predict lower antidepressant response/remission rates in depressed patients: A meta-analysis*, in "World Journal of Biological Psychiatry", July 2016, pp. 1-23, https://hal.inria.fr/hal-01372398

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[14] P. GORI, O. COLLIOT, L. MARRAKCHI-KACEM, Y. WORBE, F. DE VICO FALLANI, M. CHAVEZ, C. POUPON, A. HARTMANN, N. AYACHE, S. DURRLEMAN. *Parsimonious Approximation of Streamline Trajectories in White Matter Fiber Bundles*, in "IEEE Transactions on Medical Imaging", 2016, vol. PP, n^{o} 99 [*DOI :* 10.1109/TMI.2016.2591080], https://hal.archives-ouvertes.fr/hal-01346067

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[36] M. HABERT, M. DAVID, A. BERTRAND, G. BERA, N. YENI, M. BERTAUX, N. PYATIGORSKAYA, D. DORMONT, A. VILLANUEVA, A. KAS. *Imagerie hybride TEP/IRM dans le bilan des pathologies neurodégénératives : retour d'expérience*, in "2es Journées Francophones de Médecine Nucléaire", Grenoble, France, May 2016, vol. 40, n^{o} 3, pp. 169 - 170 [*DOI :* 10.1016/J.MEDNUC.2016.03.003], https://hal.inria.fr/hal-01427374

Other Publications

[37] B. GRIS, S. DURRLEMAN, A. TROUVÉ. *A sub-Riemannian modular framework for diffeomorphism based analysis of shape ensembles*, May 2016, working paper or preprint, https://hal.archives-ouvertes.fr/hal-01321142