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**CNRS**

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**Sorbonne Université (UPMC)**

Activity Report 2018

# 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 Medicine**

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# Project-Team ARAMIS

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

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**Other Research Topics and Application Domains:**

B2. - Health
B2.2.6. - Neurodegenerative diseases
B2.6.1. - Brain imaging

# 1. Team, Visitors, External Collaborators

**Research Scientists**

Olivier Colliot [CNRS, Team leader, Senior Researcher, HDR]
Ninon Burgos [CNRS, Researcher, from Oct 2018]
Fabrizio de Vico Fallani [Inria, Researcher, HDR]
Stanley Durrleman [Inria, Senior Researcher, HDR]

**Faculty Members**

Anne Bertrand [Sorbonne University, Associate Professor, deceased, March 2nd 2018]
Benjamin Charlier [Univ de Montpellier, Associate Professor, secondment at Inria]
Stephane Epelbaum [Assistance publique/Hôpitaux de Paris, Chair, Hospital Neurologist]
Didier Dormont [Sorbonne University, Professor]

**Post-Doctoral Fellows**

Ninon Burgos [Inria, until Sep 2018]
Alexis Guyot [Institut du Cerveau et de la Moelle Epinière]
Takoua Kaaouana [Institut du Cerveau et de la Moelle Epinière, until Mar 2018]
Vincent Henry [Inria, until Nov 2018]
Marie-Constance Corsi [Inria]

**PhD Students**

Manon Ansart [INSERM]
Giulia Bassignana [INSERM]
Simona Bottani [Inria, from Oct 2018]
Alexandre Bône [Univ Pierre et Marie Curie]
Tiziana Cattai [Inria]

Raphaël Couronné [Inria]
Johann Faouzi [Institut du Cerveau et de la Moelle Epinière]
Fanny Grosselin [MyBrainTechnologies]
Jeremy Guillon [Sorbonne University, until Sep 2018]
Igor Koval [INSERM]
Thomas Lartigue [Inria]
Maxime Louis [Sorbonne University]
Pascal Lu [Sorbonne University]
Federica Cacciamani [ICM, from Dec 2018]
Catalina Obando Forero [Inria, until Oct 2018]
Alexandre Routier [Sorbonne University, until Nov 2018]
Jorge Samper Gonzalez [Inria]
Elina Thibeau Sutre [Sorbonne University, from Oct 2018]
Wen Wei [Inria]
Junhao Wen [Sorbonne University]

**Technical staff**

Simona Bottani [Institut du Cerveau et de la Moelle Epinière, until Sep 2018]
Mauricio Diaz Melo [Inria, from Apr 2018]
Clementine Fourrier [Institut du Cerveau et de la Moelle Epinière, until Mar 2018]
Juliana Gonzalez Astudillo [INSERM, from Oct 2018]
Arnaud Marcoux [Inria]
Benoit Martin [Inria, from May 2018]
Alexandre Routier [Inria, from Nov 2018]
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**Interns**

Paul Bertin [Inria, from Apr 2018 until Aug 2018]
Juliana Gonzalez Astudillo [Inria, from Apr 2018 until Sep 2018]
Elina Thibeau Sutre [Inria, from Feb 2018 until Jul 2018]

**Administrative Assistants**

Helene Milome [Inria]
Emmanuelle Mauduit [Institut du Cerveau et de la Moelle Epinière]

# 2. Overall Objectives

## 2.1. Context

**ARAMIS is an Inria project-team within the Brain and Spinal cord Institute (ICM - http://www.icm-institute.org) at the Pitié-Salpêtrière hospital in Paris**. ARAMIS was created as a team of the Inria Paris Center in 2012 and became a project-team in 2014. ARAMIS has a joint affiliation to Inria, CNRS, Inserm and Sorbonne University.

The **Pitié-Salpêtrière hospital** is the largest adult hospital in Europe. It is a leading center for neurological diseases: in terms of size (around 20,000 neurological patients each year), level of clinical expertise and quality of the technical facilities. Created in 2010, the **Brain and Spinal cord Institute (ICM)** gathers all research activities in neuroscience and neurology of the Pitié-Salpêtrière hospital. The ICM is both a private foundation and a public research unit (affiliated to CNRS, Inserm and University Pierre and Marie Curie). It hosts 25 research teams as well as various high level technical facilities (neuroimaging, genotyping/sequencing, cell culture, cellular imaging, bioinformatics ...), and gathers over 600 personnel. In addition, the ICM hosts one of the six IHU (*Instituts Hospitalo-Universitaires*), which are 10-year research programs funded for 55M euros each.

ARAMIS is thus located both within a leading neuroscience institute and within a large hospital. This unique position has several advantages: direct contact with neuroscientists and clinicians allows us to foresee the emergence of new problems and opportunities for new methodological developments, provides access to unique datasets, and eases the transfer of our results to clinical research and clinical practice.

## 2.2. General aim

The ARAMIS team is devoted to the design of **computational, mathematical and statistical approaches for the analysis of multimodal patient data**, with an emphasis on neuroimaging data. The core methodological domains of our team are: statistical and machine learning, statistical modeling of complex geometric data, connectivity and network analysis. These new approaches are applied to clinical research in neurological diseases in collaboration with other teams of the ICM, clinical departments of the Pitié-Salpêtrière hospital and external partners. **The team has a pluridisciplinary composition**, bringing together researchers in mathematics, computer science and engineering (N. Burgos, O. Colliot, F. De Vico Fallani, S. Durrleman) and clinicians (A. Bertrand, D. Dormont, S. Epelbaum). This general endeavor is addressed within the five following main objectives.

# 3. Research Program

## 3.1. From geometrical data to multimodal imaging

Brain diseases are associated to alterations of brain structure that can be studied in vivo using anatomical and diffusion MRI. The anatomy of a given subject can be represented by sets of anatomical surfaces (cortical and subcortical surfaces) and curves (white matter tracks) that can be extracted from anatomical and diffusion MRI respectively. We aim to develop approaches that can characterize the variability of brain anatomy within populations of subjects. To that purpose, we propose methods to estimate population atlases that provide an average model of a population of subjects together with a statistical model of their variability. Finally, we aim to introduce representations that can integrate geometrical information (anatomical surfaces, white matter tracts) together with functional (PET, ASL, EEG/MEG) and microstructural information.

## 3.2. Models of 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 tasks, and is disrupted in brain disorders. Our team develops a framework for the characterization of brain connectivity patterns, based on connectivity descriptors from the theory of complex networks. More specifically, we propose analytical tools to infer brain networks, chacterize their structure and integrate multiple networks (for instance from multiple frequency bands or multiple modalities). The genericity of this approach allows us to apply it to various types of data including functional and structural neuroimaging, as well as genomic data.

## 3.3. Spatiotemporal modeling from longitudinal data

Longitudinal data sets are collected to capture variable temporal phenomena, which may be due to ageing or disease progression for instance. They consist in the observation of several individuals, each of them being observed at multiple points in time. The statistical exploitation of such data sets is notably difficult since data of each individual follow a different trajectory of changes and at its own pace. This difficulty is further increased if observations take the form of structured data like images or measurements distributed at the nodes of a mesh, and if the measurements themselves are normalized data or positive definite matrices for which usual linear operations are not defined. We aim to develop a theoretical and algorithmic framework for learning typical trajectories from longitudinal data sets. This framework is built on tools from Riemannian geometry to describe trajectories of changes for any kind of data and their variability within a group both in terms of the direction of the trajectories and pace.

## 3.4. Decision support systems

We then aim to develop tools to assist clinical decisions such as diagnosis, prognosis or inclusion in therapeutic trials. To that purpose, we leverage the tools developed by the team, such as multimodal representations, network indices and spatio-temporal models which are combined with advanced classification and regression approaches. We also dedicate strong efforts to rigorous, transparent and reproducible validation of the decision support systems on large clinical datasets.

## 3.5. Clinical research studies

Finally, we aim to apply advanced computational and statistical tools to clinical research studies. These studies are often performed in collaboration with other researchers of the ICM, clinicians of the Pitié -Salpêtrière hospital or external partners. Notably, our team is very often involved ”ex-ante” in clinical research studies. As co-investigators of such studies, we contribute to the definition of objectives, study design and definition of protocols. This is instrumental to perform clinically relevant methodological development and to maximize their medical impact. A large part of these clinical studies were in the field of dementia (Alzheimer's disease, fronto-temporal dementia). Recently, we expanded our scope to other neurodegenerative diseases (Parkinson's disease, multiple sclerosis).

# 4. Application Domains

## 4.1. Introduction

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

- better understanding the pathophysiology of brain disorders;
- designing systems to support clinical decisions such as diagnosis, prognosis and design of clinical trials;
- developing brain computer interfaces for clinical applications.

## 4.2. Understanding brain disorders

Computational and statistical approaches have the potential to help understand the pathophysiology of brain disorders. We first aim to contribute to better understand the relationships between pathological processes, anatomical and functional alterations, and symptoms. Moreover, within a single disease, there is an important variability between patients. The models that we develop have the potential to identify more homogeneous disease subtypes, that would constitute more adequate targets for new treatments. Finally, we aim to establish the chronology of the different types of alterations. We focus these activities on neurodegeneratives diseases: dementia (Alzheimer's disease, fronto-temporal dementia), Parkinson's disease, multiple sclerosis.

## 4.3. Supporting clinical decisions

We aim to design computational tools to support clinical decisions, including diagnosis, prognosis and the design of clinical trials. The differential diagnosis of neurodegenerative diseases can be difficult. Our tools have the potential to help clinicians by providing automated classification that can integrate multiple types of data (clinical/cognitive tests, imaging, biomarkers). Predicting the evolution of disease in individual patients is even more difficult. We aim to develop approaches that can predict which alterations and symptoms will occur and when. Finally, new approaches are needed to select participants in clinical trials. Indeed, it is widely recognized that, to have a chance to be successful, treatments should be administered at a very early stage.

## 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 basis 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.

# 5. Highlights of the Year

## 5.1. Highlights of the Year

- The team has been awarded a "Fondation pour la Recherche sur la maladie d'Alzheimer" research grant.

### *5.1.1. Awards*

- Ninon Burgos received the Galileo Galilei Award 2017, best publication in the European Journal of Medical Physics - Physica Medica in 2017, for the paper 'Evaluation of a multi-atlas CT synthesis approach for MRI-only radiotherapy treatment planning'.
- S. Durrleman successfully defended his "habilitation à diriger des Recherches" from Sorbonne University
- F. De Vico Fallani received the Young Investigator award from Complex Systems Society (CSS)
- Stéphane Epelbaum was awarded the Joel Ménard prize from the "Fondation Alzheimer".

# 6. New Software and Platforms

## 6.1. Brain Networks Toolbox

KEYWORDS: Neuroimaging - Medical imaging
FUNCTIONAL DESCRIPTION: Brain Networks Toolbox is an open-source package of documented routines implementing new graph algorithms for brain network analysis. It mainly contains Matlab code of new methods developed by the team and associated to publications (e.g., brain network thresholding, extraction of the information redundancy, node accessibility, etc). It requires, as input, adjacency matrices representing brain connectivity networks. Thus, it is independent on the specific approach used to construct brain networks and it can be used to extract network properties from any neuroimaging modality in healthy and diseased subjects.

- Participants: Fabrizio De Vico Fallani, Jeremy Guillon and Mario Chavez
- Contact: Fabrizio De Vico Fallani
- URL: https://github.com/brain-network/bnt

## 6.2. 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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- Registration, which computes the optimal 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!

- Participants: Alexandre Routier, Ana Fouquier, Barbara Gris, Benjamin Charlier, Cédric Doucet, Joan Alexis Glaunès, Marcel Prastawa, Michael Bacci, Pietro Gori and Stanley Durrleman
- Partners: University of Utah - Université de Montpellier 2 - Université Paris-Descartes
- Contact: Stanley Durrleman
- URL: http://www.deformetrica.org/

## 6.3. Clinica

KEYWORDS: Neuroimaging - Brain MRI - MRI - Clinical analysis - Image analysis - Machine learning
SCIENTIFIC DESCRIPTION: Clinica is a software platform for multimodal brain image analysis in clinical research studies. It makes it easy to apply advanced analysis tools to large scale clinical studies. For that purpose, it integrates a comprehensive set of processing tools for the main neuroimaging modalities: currently MRI (anatomical, functional, diffusion) and PET, in the future, EEG/MEG. For each modality, Clinica allows to easily extract various types of features (regional measures, parametric maps, surfaces, curves, networks). Such features are then 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. It provides an integrated data management specification to store raw and processing data. Clinica is written in Python. It uses the Nipype system for pipelining. It combines widely-used software for neuroimaging data analysis (SPM, Freesurfer, FSL, MRtrix...), morphometry (Deformetrica), machine learning (Scikit-learn) and the BIDS standard for data organization.

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NEWS OF THE YEAR: - Three clinical studies made with Clinica Clinica : Bertrand et al, JAMA Neurology, 2018 , Jacquemont et al, Neurobiol Aging, 2017, Wen et al, JNNP, 2018 - Clinica presented at OHBM 2018 conference - Clinica was the support for the tutorial "Pattern Recognition for Neuroimaging" at OHBM 2018

- Participants: Jeremy Guillon, Thomas Jacquemont, Pascal Lu, Arnaud Marcoux, Tristan Moreau, Alexandre Routier, Jorge Samper Gonzalez, Junhao Wen, Olivier Colliot, Stanley Durrleman, Michael Bacci, Simona Bottani, Ninon Burgos, Sabrina Fontanella, Pietro Gori, Mauricio Diaz Melo and Elina Thibeau-Sutre
- Partners: Institut du Cerveau et de la Moelle épinière (ICM) - CNRS - INSERM - UPMC
- Contact: Olivier Colliot
- Publications: Amyloidosis and neurodegeneration result in distinct structural connectivity patterns in mild cognitive impairment - Yet Another ADNI Machine Learning Paper? Paving The Way Towards Fully-reproducible Research on Classification of Alzheimer's Disease - Reproducible evaluation of classification methods in Alzheimer's disease: Framework and application to MRI and PET data - Neurite density is reduced in the presymptomatic phase of C9orf72 disease - Early cognitive, structural and microstructural changes in c9orf72 presymptomatic carriers before 40 years of age
- URL: http://www.clinica.run

## 6.4. Platforms

### *6.4.1. Platform Brain-computer interface*

Our team coordinates the developments of the Brain-Computer Interface (BCI) platform at the Centre EEG/MEG of the neuroimaging core facility of the ICM. Several projects, including our NETBCI NSF/NIH/ANR and ATTACK Big-brain theory funded projects, as well as experiments by different researchers of the Institute, are currently being run. To reinforce the impact of the platform we have recently recruited an engineer (J. Gonzalez-Astudillo) for the software and technical development.

# 7. New Results

## 7.1. Reproducible evaluation of classification methods in Alzheimer's disease: Framework and application to MRI and PET data

**Participants:** Jorge Samper-González, Ninon Burgos, Simona Bottani, Sabrina Fontanella, Pascal Lu, Arnaud Marcoux, Alexandre Routier, Jérémy Guillon, Michael Bacci, Junhao Wen, Anne Bertrand, Hugo Bertin, Marie-Odile Habert, Stanley Durrleman, Theodoros Evgeniou, Olivier Colliot [Correspondant].

A large number of papers have introduced novel machine learning and feature extraction methods for automatic classification of Alzheimer's disease (AD). However, while the vast majority of these works use the public dataset ADNI for evaluation, they are difficult to reproduce because different key components of the validation are often not readily available. These components include selected participants and input data, image preprocessing and cross-validation procedures. The performance of the different approaches is also difficult to compare objectively. In particular, it is often difficult to assess which part of the method (e.g. preprocessing, feature extraction or classification algorithms) provides a real improvement, if any. We proposed a framework for reproducible and objective classification experiments in AD using three publicly available datasets (ADNI, AIBL and OASIS). The framework comprises: i) automatic conversion of the three datasets into a standard format (BIDS); ii) a modular set of preprocessing pipelines, feature extraction and classification methods, together with an evaluation framework, that provide a baseline for benchmarking the different components. We demonstrated the use of the framework for a large-scale evaluation on 1960 participants using T1 MRI and FDG PET data. In this evaluation, we assessed the influence of different modalities, preprocessing, feature types (regional or voxel-based features), classifiers, training set sizes and datasets. Performances were in line with the state-of-the-art. FDG PET outperformed T1 MRI for all classification tasks. No difference in performance was found for the use of different atlases, image smoothing, partial volume correction of FDG PET images, or feature type. Linear SVM and L2-logistic regression resulted in similar performance and both outperformed random forests. The classification performance increased along with the number of subjects used for training. Classifiers trained on ADNI generalized well to AIBL and OASIS. All the code of the framework and the experiments is publicly available: general-purpose tools have been integrated into the Clinica software (http://www.clinica.run/) and the paper-specific code is available at: https://gitlab.icm-institute.org/aramislab/AD-ML.

More details in [30].

## 7.2. An automated pipeline for the analysis of PET data on the cortical surface

**Participants:** Arnaud Marcoux, Ninon Burgos, Anne Bertrand, Marc Teichmann, Alexandre Routier, Junhao Wen, Jorge Samper-González, Simona Bottani, Stanley Durrleman, Marie-Odile Habert, Olivier Colliot [Correspondant].

We developed a fully automatic pipeline for the analysis of PET data on the cortical surface. Our pipeline combines tools from FreeSurfer and PETPVC, and consists of i) co-registration of PET and T1-w MRI (T1) images, ii) intensity normalization, iii) partial volume correction, iv) robust projection of the PET signal onto the subject's cortical surface, v) spatial normalization to a template, and vi) atlas statistics. We evaluated the performance of the proposed workflow by performing group comparisons and showed that the approach was able to identify the areas of hypometabolism characteristic of different dementia syndromes: Alzheimer's disease (AD) and both the semantic and logopenic variants of primary progressive aphasia. We also showed that these results were comparable to those obtained with a standard volume-based approach. We then performed individual classifications and showed that vertices can be used as features to differentiate cognitively normal and AD subjects. This pipeline is integrated into Clinica, an open-source software platform for neuroscience studies available at http://www.clinica.run/.

More details in [24].

## 7.3. Comparative study of algorithms for synthetic CT generation from MRI: Consequences for MRI-guided radiation planning in the pelvic region

**Participants:** Hossein Arabi, Jason A. Dowling, Ninon Burgos [Correspondant], Xiao Han, Peter B. Greer, Nikolaos Koutsouvelis, Habib Zaidi.

Magnetic resonance imaging (MRI)-guided radiation therapy (RT) treatment planning is limited by the fact that the electron density distribution required for dose calculation is not readily provided by MR imaging. We compare a selection of novel synthetic CT generation algorithms recently reported in the literature, including segmentation-based, atlas-based and machine learning techniques, using the same cohort of patients and quantitative evaluation metrics. Six MRI-guided synthetic CT generation algorithms were evaluated: one segmentation technique into a single tissue class (water-only), four atlas-based techniques, namely, median value of atlas images (ALMedian), atlas-based local weighted voting (ALWV), bone enhanced atlas-based local weighted voting (ALWV-Bone), iterative atlas-based local weighted voting (ALWV-Iter), and a machine learning technique using deep convolution neural network (DCNN). Organ auto-contouring from MR images was evaluated for bladder, rectum, bones, and body boundary. Overall, DCNN exhibited higher segmentation accuracy resulting in Dice indices while ALMedian showed the lowest accuracy. DCNN reached the best performance in terms of accurate derivation of synthetic CT values within each organ, followed by the advanced atlas-based methods. ALMedian led to the highest error. Considering the dosimetric evaluation results, ALWV-Iter, ALWV, DCNN and ALWV-Bone led to similar mean dose estimation within each organ at risk and target volume with less than 1% dose discrepancy. However, the two-dimensional gamma analysis demonstrated higher pass rates for ALWV-Bone, DCNN, ALMedian and ALWV-Iter at 1%/1 mm criterion. Overall, machine learning and advanced atlas-based methods exhibited promising performance by achieving reliable organ segmentation and synthetic CT generation. DCNN appears to have slightly better performance by achieving accurate automated organ segmentation and relatively small dosimetric errors (followed closely by advanced atlas-based methods, which in some cases achieved similar performance). However, the DCNN approach showed higher vulnerability to anatomical variation, where a greater number of outliers was observed with this method. Considering the dosimetric results obtained from the evaluated methods, the challenge of electron density estimation from MR images can be resolved with a clinically tolerable error.

More details in [4].

## 7.4. Double diffeomorphism: combining morphometry and structural connectivity analysis

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

The brain is composed of several neural circuits which may be seen as anatomical complexes composed of grey matter structures interconnected by white matter tracts. Grey and white matter components may be modelled as 3D surfaces and curves respectively. Neurodevelopmental disorders involve morphological and organizational alterations which can not be jointly captured by usual shape analysis techniques based on single diffeomorphisms. We propose a new deformation scheme, called double diffeomorphism, which is a combination of two diffeomorphisms. The first one captures changes in structural connectivity, whereas the second one recovers the global morphological variations of both grey and white matter structures. This deformation model is integrated into a Bayesian framework for atlas construction. We evaluate it on a dataset of 3D structures representing the neural circuits of patients with Gilles de la Tourette syndrome (GTS). We show that this approach makes it possible to localise, quantify and easily visualise the pathological anomalies altering the morphology and organization of the neural circuits. Furthermore, results also indicate that the proposed deformation model better discriminates between controls and GTS patients than a single diffeomorphism.

More details in [15].

## 7.5. Learning distributions of shape trajectories from longitudinal datasets: a hierarchical model on a manifold of diffeomorphisms

**Participants:** Alexandre Bône, Olivier Colliot, Stanley Durrleman [Correspondant].

We propose a method to learn a distribution of shape tra-jectories from longitudinal data, i.e. the collection of individual objects repeatedly observed at multiple time-points. The method allows to compute an average spatiotemporal trajectory of shape changes at the group level, and the individual variations of this trajectory both in terms of geometry and time dynamics. First, we formulate a non-linear mixed-effects statistical model as the combination of a generic statistical model for manifold-valued longitudinal data, a deformation model defining shape trajectories via the action of a finite-dimensional set of diffeomorphisms with a man-ifold structure, and an efficient numerical scheme to compute parallel transport on this manifold. Second, we introduce a MCMC-SAEM algorithm with a specific approach to shape sampling, an adaptive scheme for proposal variances , and a log-likelihood tempering strategy to estimate our model. Third, we validate our algorithm on 2D simulated data, and then estimate a scenario of alteration of the shape of the hippocampus 3D brain structure during the course of Alzheimer's disease. The method shows for instance that hippocampal atrophy progresses more quickly in female subjects, and occurs earlier in APOE4 mutation carriers. We finally illustrate the potential of our method for classifying pathological trajectories versus normal ageing.

More details in [38].

## 7.6. Spatiotemporal Propagation of the Cortical Atrophy: Population and Individual Patterns

**Participants:** Igor Koval, Jean-Baptiste Schiratti, Alexandre Routier, Michael Bacci, Olivier Colliot, Stéphanie Allassonnière, Stanley Durrleman.

Repeated failures in clinical trials for Alzheimer's disease (AD) have raised a strong interest for the prodromal phase of the disease. A better understanding of the brain alterations during this early phase is crucial to diagnose patients sooner, to estimate an accurate disease stage, and to give a reliable prognosis. According to recent evidence, structural alterations in the brain are likely to be sensitive markers of the disease progression. Neuronal loss translates in specific spatiotemporal patterns of cortical atrophy, starting in the enthorinal cortex and spreading over other cortical regions according to specific propagation pathways. We developed a digital model of the cortical atrophy in the left hemisphere from prodromal to diseased phases, which is built on the temporal alignment and combination of several short-term observation data to reconstruct the long-term history of the disease. The model not only provides a description of the spatiotemporal patterns of cortical atrophy at the group level but also shows the variability of these patterns at the individual level in terms of difference in propagation pathways, speed of propagation, and age at propagation onset. Longitudinal MRI datasets of patients with mild cognitive impairments who converted to AD are used to reconstruct the cortical atrophy propagation across all disease stages. Each observation is considered as a signal spatially distributed on a network, such as the cortical mesh, each cortex location being associated to a node. We consider how the temporal profile of the signal varies across the network nodes. We introduce a statistical mixed-effect model to describe the evolution of the cortex alterations. To ensure a spatiotemporal smooth propagation of the alterations, we introduce a constrain on the propagation signal in the model such that neighboring nodes have similar profiles of the signal changes. Our generative model enables the reconstruction of personalized patterns of the neurodegenerative spread, providing a way to estimate disease progression stages and predict the age at which the disease will be diagnosed. The model shows that, for instance, APOE carriers have a significantly higher pace of cortical atrophy but not earlier atrophy onset.

More details in [19].

## 7.7. A Fanning Scheme for the Parallel Transport Along Geodesics on Riemannian Manifolds

**Participants:** Maxime Louis, Benjamin Charlier, Paul Jusselin, Susovan Pal, Stanley Durrleman.

Parallel transport on Riemannian manifolds allows one to connect tangent spaces at different points in an isometric way and is therefore of importance in many contexts, such as for statistics on manifolds. The existing methods to compute parallel transport require either the computation of Riemannian logarithms, such as the Schild's ladder, or the Christoffel symbols. The Logarithm is rarely given in closed form, and therefore costly to compute whereas the number of Christoffel symbols explodes with the dimension of the manifold, making both these methods intractable. From an identity between parallel transport and Jacobi fields, we propose a numerical scheme to approximate the parallel transport along a geodesic. We find and prove an optimal convergence rate for the scheme, which is equivalent to Schild's ladder's. We investigate potential variations of the scheme and give experimental results on the Euclidean two-sphere and on the manifold of symmetric positive-definite matrices.

More details in [23].

## 7.8. Reduction of recruitment costs in preclinical AD trials. Validation of automatic pre-screening algorithm for brain amyloidosis.

**Participants:** Manon Ansart, Stéphane Epelbaum, Geoffroy Gagliardi, Olivier Colliot, Didier Dormont, Bruno Dubois, Harald Hampel, Stanley Durrleman [Correspondant].

We propose a method for recruiting asymptomatic Amyloid positive individuals in clinical trials, using a two-step process. We first select during a pre-screening phase a subset of individuals which are more likely to be amyloid positive based on the automatic analysis of data acquired during routine clinical practice, before doing a confirmatory PET-scan to these selected individuals only. This method leads to an increased number of recruitments and to a reduced number of PET-scans, resulting in a decrease in overall recruitment costs. We validate our method on 3 different cohorts, and consider 5 different classification algorithms for the pre-screening phase. We show that the best results are obtained using solely cognitive, genetic and socio-demographic features, as the slight increased performance when using MRI or longitudinal data is balanced by the cost increase they induce. We show that the proposed method generalizes well when tested on an independent cohort, and that the characteristics of the selected set of individuals are identical to the characteristics of a population selected in a standard way. The proposed approach shows how Machine Learning can be used effectively in practice to optimize recruitment costs in clinical trials.

More details in [3].

## 7.9. Multiplex core-periphery organization of the human connectome

**Participants:** Federico Battiston, Jeremy Guillon, Mario Chavez, Vito Latora, Fabrizio de Vico Fallani [Correspondant].

What is the core of the human brain is a fundamental question that has been mainly addressed by studying the anatomical connections between differently specialized areas, thus neglecting the possible contributions from their functional interactions. While many methods are available to identify the core of a network when connections between nodes are all of the same type, a principled approach to define the core when multiple types of connectivity are allowed is still lacking. Here, we introduce a general framework to define and extract the core–periphery structure of multi-layer networks by explicitly taking into account the connectivity patterns at each layer. We first validate our algorithm on synthetic networks of different size and density, and with tunable overlap between the cores at different layers. We then use our method to merge information from structural and functional brain networks, obtaining in this way an integrated description of the core of the human connectome. Results confirm the role of the main known cortical and subcortical hubs, but also suggest the presence of new areas in the sensori-motor cortex that are crucial for intrinsic brain functioning. Taken together these findings provide fresh evidence on a fundamental question in modern neuroscience and offer new opportunities to explore the mesoscale properties of multimodal brain networks.

More details in [6].

## 7.10. Integrating EEG and MEG signals to improve motor imagery classification in brain-computer interfaces

**Participants:** Marie-Constance Corsi, Mario Chavez, Denis Schwartz, Laurent Hugueville, Ankit Khambhati, Danielle Bassett, Fabrizio de Vico Fallani [Correspondant].

We adopted a fusion approach that combines features from simultaneously recorded electroencephalogram (EEG) and magnetoencephalogram (MEG) signals to improve classification performances in motor imagery-based brain–computer interfaces (BCIs). We applied our approach to a group of 15 healthy subjects and found a significant classification performance enhancement as compared to standard single-modality approaches in the alpha and beta bands. Taken together, our findings demonstrate the advantage of considering multimodal approaches as complementary tools for improving the impact of noninvasive BCIs.

More details in [10].

## 7.11. Role of inter-hemispheric connections in functional brain networks

**Participants:** Johann Martinez [Correspondant], Javier Buldu, David Papo, Fabrizio de Vico Fallani, Mario Chavez.

Today the human brain can be modeled as a graph where nodes represent different regions and links stand for statistical interactions between their activities as recorded by different neuroimaging techniques. Empirical studies have lead to the hypothesis that brain functions rely on the coordination of a scattered mosaic of functionally specialized brain regions (modules or sub-networks), forming a web-like structure of coordinated assemblies (a network of networks). The study of brain dynamics would therefore benefit from an inspection of how functional sub-networks interact between them. In this paper, we model the brain as an interconnected system composed of two specific sub-networks, the left (L) and right (R) hemispheres, which compete with each other for centrality, a topological measure of importance in a networked system. Specifically, we considered functional brain networks derived from high-density electroencephalographic (EEG) recordings and investigated how node centrality is shaped by interhemispheric connections. Our results show that the distribution of centrality strongly depends on the number of functional connections between hemispheres and the way these connections are distributed. Additionally, we investigated the consequences of node failure on hemispherical centrality, and showed how the abundance of inter-hemispheric links favors the functional balance of centrality distribution between the hemispheres.

More details in [25].

## 7.12. Statistical shape analysis of large datasets based on diffeomorphic iterative centroids

**Participants:** Claire Cury, Joan Glaunès, Olivier Colliot.

We proposed an approach for template-based shape analysis of large datasets, using diffeomorphic centroids as atlas shapes. Diffeomorphic centroid methods fit in the Large Deformation Diffeomorphic Metric Mapping (LDDMM) framework and use kernel metrics on currents to quantify surface dissimilarities. The statistical analysis is based on a Kernel Principal Component Analysis (Kernel PCA) performed on the set of initial momentum vectors which parametrize the deformations. We tested the approach on different datasets of hippocampal shapes extracted from brain magnetic resonance imaging (MRI), compared three different centroid methods and a variational template estimation. The largest dataset is composed of 1,000 surfaces, and we are able to analyse this dataset in 26 h using a diffeomorphic centroid. Our experiments demonstrate that computing diffeomorphic centroids in place of standard variational templates leads to similar shape analysis results and saves around 70% of computation time. Furthermore, the approach is able to adequately capture the variability of hippocampal shapes with a reasonable number of dimensions, and to predict anatomical features of the hippocampus, only present in 17% of the population, in healthy subjects.

More details in [12].

## 7.13. Multi-modal brain fingerprinting: a manifold approximation based framework

**Participants:** Kuldeep Kumar, Olivier Colliot, Christian Desrosiers.

We proposed an efficient framework, based on manifold approximation, for generating brain fingerprints from multi-modal data. The proposed framework represents images as bags of local features, which are used to build a subject proximity graph. Compact fingerprints are obtained by projecting this graph in a low-dimensional manifold, using spectral embedding. Experiments using the T1/T2-weighted MRI, diffusion MRI, and resting state fMRI data of 945 Human Connectome Project subjects demonstrate the benefit of combining multiple modalities, with multi-modal fingerprints more discriminative than those generated from individual modalities. Results also highlight the link between fingerprint similarity and genetic proximity, monozygotic twins having more similar fingerprints than dizygotic or non-twin siblings. This link is also reflected in the differences of feature correspondences between twin/sibling pairs, occurring in major brain structures and across hemispheres. The robustness of the proposed framework to factors like image alignment and scan resolution, as well as the reproducibility of results on retest scans, suggest the potential of multi-modal brain fingerprinting for characterizing individuals in a large cohort analysis. In addition, taking inspiration from the computer vision community, the proposed rank retrieval evaluation based on the task of twin/sibling identification and using Mean Average Precision (MAP) can be used for a standardized comparison of future brain fingerprints.

More details in [20].

## 7.14. Structural, Microstructural, and Metabolic Alterations in Primary Progressive Aphasia Variants

**Participants:** Alexandre Routier [Correspondant], Marie-Odile Habert, Olivier Colliot, Marc Teichmann.

Neuroimaging studies have described the brain alterations in primary progressive aphasia (PPA) variants (semantic, logopenic, nonfluent/agrammatic). However, few studies combined T1, FDG-PET, and diffusion MRI techniques to study atrophy, hypometabolism, and tract alterations across the three PPA main variants. We therefore explored a large early-stage cohort of semantic, logopenic and nonfluent/agrammatic variants (N = 86) and of 23 matched healthy controls with anatomical MRI (cortical thickness), FDG PET (metabolism) and diffusion MRI (white matter tracts analyses), aiming at identifying cortical and sub-cortical brain alterations, and confronting these alterations across imaging modalities and aphasia variants. In the semantic variant, there was cortical thinning and hypometabolism in anterior temporal cortices, with left-hemisphere predominance, extending toward posterior temporal regions, and affecting tracts projecting to the anterior temporal lobes (inferior longitudinal fasciculus, uncinate fasciculus) and tracts projecting to or running nearby posterior temporal cortices: (superior longitudinal fasciculus, inferior frontal-occipital fasciculus). In the logopenic variant metabolic alterations were more extensive than atrophy affecting mainly the left temporal-parietal junction and extending toward more anterior temporal cortices. Metabolic and tract data were coherent given the alterations of the left superior and inferior longitudinal fasciculus and the left inferior frontal-occipital fasciculus. In the nonfluent/agrammatic variant cortical thinning and hypometabolism were located in the left frontal cortex but Broca's area was only affected on metabolic measures. Metabolic and tract alterations were coherent as reflected by damage to the left uncinate fasciculus connecting with Broca's area. Our findings provide a full-blown statistically robust picture of brain alterations in early-stage variants of primary progressive aphasia which has implications for diagnosis, classification and future therapeutic strategies. They demonstrate that in logopenic and semantic variants patterns of brain damage display a non-negligible overlap in temporal regions whereas they are substantially distinct in the nonfluent/agrammatic variant (frontal regions). These results also indicate that frontal networks (combinatorial syntax/phonology) and temporal networks (lexical/semantic representations) constitute distinct anatomo-functional entities with differential vulnerability to degenerative processes in aphasia variants. Finally, the identification of the specific damage patterns could open an avenue for trans-cranial stimulation approaches by indicating the appropriate target-entry into the damaged language system.

More details in [29].

## 7.15. Neurite density is reduced in the presymptomatic phase of C9orf72 disease

**Participants:** Junhao Wen, Hui Zhang, Daniel Alexander, Stanley Durrleman, Olivier Colliot, Isabelle Le Ber, Anne Bertrand [Correspondant].

In this study, we aimed to assess the added value of neurite orientation dispersion and density imaging (NODDI) compared to conventional DTI and anatomical MRI to detect changes in presymptomatic carriers of chromosome 9 open reading frame 72 (C9orf72) mutation. The PREV-DEMALS study is a prospective, multicenter, observational study of first-degree relatives of individuals carrying the C9orf72 mutation. Sixty-seven participants (38 presymptomatic C9orf72 mutation carriers [C9+], 29 non carriers [C9-]) were included in the present cross-sectional study. Each participant underwent one single-shell, multi-shell diffusion MRI and 3DT1 MRI. Volumetric measures, DTI and NODDI metrics were calculated within regions of interest. Differences in white matter integrity, gray matter volume and free water fraction between C9+ and C9- individuals were assessed using linear mixed-effects models. Compared with C9-, C9+ demonstrated white matter abnormalities in 10 tracts with neurite density index, and only 5 tracts with DTI metrics. Effect size was significantly higher for the neurite density index than for DTI metrics in two tracts. No tract had a significantly higher effect size for DTI than for NODDI. For gray matter cortical analysis, free water fraction was increased in 13 regions in C9+, whereas 11 regions displayed volumetric atrophy. In conclusion, NODDI provides higher sensitivity and greater tissue-specificity compared to conventional DTI for identifying white matter abnormalities in the presymptomatic C9orf72 carriers. Our results encourage the use of neurite density as biomarker of the preclinical phase.

More details in [34].

## 7.16. Learning myelin content in multiple sclerosis from multimodal MRI through adversarial training

**Participants:** Wen Wei, Emilie Poirion, Benedetta Bodini, Stanley Durrleman, Nicholas Ayache, Bruno Stankoff, Olivier Colliot [Correspondant].

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS). A reliable measure of the tissue myelin content is therefore essential to understand the physiopathology of MS, track progression and assess treatment efficacy. Positron emission tomography (PET) with [ 11 C]PIB has been proposed as a promising biomarker for measuring myelin content changes in-vivo in MS. However, PET imaging is expensive and invasive due to the injection of a radioactive tracer. On the contrary, magnetic resonance imaging (MRI) is a non-invasive, widely available technique, but existing MRI sequences do not provide, to date, a reliable, specific, or direct marker of either demyelination or remyelination. In this work, we therefore propose Sketcher-Refiner Generative Adversarial Networks (GANs) with specifically designed adversarial loss functions to predict the PET-derived myelin content map from a combination of MRI modalities. The prediction problem is solved by a sketch-refinement process in which the sketcher generates the preliminary anatomical and physiological information and the refiner refines and generates images reflecting the tissue myelin content in the human brain. We evaluated the ability of our method to predict myelin content at both global and voxel-wise levels. The evaluation results show that the demyelination in lesion regions and myelin content in normal-appearing white matter (NAWM) can be well predicted by our method. The method has the potential to become a useful tool for clinical management of patients with MS.

More details in [40].

## 7.17. COGEVIS: A New Scale to Evaluate Cognition in Patients with Visual Deficiency

**Participants:** Claire Meyniel, Dalila Samri, Farah Stefano, Joel Crevoisier, Florence Bonté, Raffaela Migliaccio, Laure Delaby, Anne Bertrand, Marie-Odile Habert, Bruno Dubois, Baram Bodaghi, Stéphane Epelbaum [Correspondant].

We evaluated the cognitive status of visually impaired patients referred to low vision rehabilitation (LVR) based on a standard cognitive battery and a new evaluation tool, named the COGEVIS, which can be used to assess patients with severe visual deficits. We studied patients aged 60 and above, referred to the LVR Hospital in Paris. Neurological and cognitive evaluations were performed in an expert memory center. Thirty-eight individuals, 17 women and 21 men with a mean age of 70.3(SD=1.3 years) and a mean visual acuity of 0.12(SD=0.02), were recruited over a one-year period. Sixty-three percent of participants had normal cognitive status. Cognitive impairment was diagnosed in 37.5% of participants. The COGEVIS score cutoff point to screen for cognitive impairment was 24 (maximum score of 30) with a sensitivity of 66.7% and a specificity of 95%. Evaluation following 4 months of visual rehabilitation showed an improvement of Instrumental Activities of Daily Living (p = 0.004), National Eye Institute Visual Functioning Questionnaire (p = 0.035), and Montgomery-Åsberg Depression Rating Scale (p = 0.037). This study introduces a new short test to screen for cognitive impairment in visually impaired patients.

More details in [27].

## 7.18. Neural correlates of episodic memory in the Memento cohort

**Participants:** Stéphane Epelbaum [Correspondant], Vincent Bouteloup, Jean François Mangin, Valentina La Corte, Raffaela Migliaccio, Hugo Bertin, Marie Odile Habert, Clara Fischer, Chabha Azouani, Ludovic Fillon, Marie Chupin, Bruno Vellas, Florence Pasquier, Frederic Blanc, Audrey Gabelle, Mathieu Ceccaldi, Pierre Krolak-Salmon, Jacques Hugon, Olivier Hanon, Olivier Rouaud, Renaud David, Genevieve Chene, Bruno Dubois, Carole Dufouil.

The free and cued selective reminding test is used to identify memory deficits in mild cognitive impairment and demented patients. It allows assessing three processes: encoding, storage, and recollection of verbal episodic memory. We investigated the neural correlates of these three memory processes in a large cohort study. The Memento cohort enrolled 2323 outpatients presenting either with subjective cognitive decline or mild cognitive impairment who underwent cognitive, structural MRI and, for a subset, fluorodeoxyglucose-positron emission tomography evaluations. Encoding was associated with a network including parietal and temporal cortices; storage was mainly associated with entorhinal and parahippocampal regions, bilaterally; retrieval was associated with a widespread network encompassing frontal regions. The neural correlates of episodic memory processes can be assessed in large and standardized cohorts of patients at risk for Alzheimer's disease. Their relation to pathophysiological markers of Alzheimer's disease remains to be studied.

## 7.19. Cognitive and neuroimaging features and brain amyloidosis in individuals at risk of Alzheimer's disease

**Participants:** Bruno Dubois [Correspondant], Stéphane Epelbaum, Francis Nyasse, Hovagim Bakardjian, Geoffroy Gagliardi, Olga Uspenskaya, Marion Houot, Simone Lista, Federica Cacciamani, Marie Claude Potier, Anne Bertrand, Foudil Lamari, Habib Benali, Jean François Mangin, Olivier Colliot, Remy Genthon, Marie-Odile Habert, Harald Hampel.

Improved understanding is needed of risk factors and markers of disease progression in preclinical Alzheimer's disease. We assessed associations between brain amyloidosis and various cognitive and neuroimaging parameters with progression of cognitive decline in individuals with preclinical Alzheimer's disease. The INSIGHT-preAD is an ongoing single-centre observational study at the Salpêtrière Hospital, Paris, France. Eligible participants were age 70-85 years with subjective memory complaints but unimpaired cognition and memory (Mini-Mental State Examination [MMSE] score $\geq$ 27, Clinical Dementia Rating score 0, and Free and Cued Selective Reminding Test [FCSRT] total recall score $\geq$ 41). We stratified participants by brain amyloid deposition on 18F-florbetapir PET (positive or negative) at baseline. All patients underwent baseline assessments of demographic, cognitive, and psychobehavioural, characteristics, APOE $\epsilon 4$ allele carrier status, brain structure and function on MRI, brain glucose-metabolism on 18F-fluorodeoxyglucose (18F-FDG) PET, and event-related potentials on electroencephalograms (EEGs). Actigraphy and CSF investigations were optional. Participants were followed up with clinical, cognitive, and psychobehavioural assessments every 6 months,

neuropsychological assessments, EEG, and actigraphy every 12 months, and MRI, and 18F-FDG and 18F-florbetapir PET every 24 months. We assessed associations of amyloid deposition status with test outcomes at baseline and 24 months, and with clinical status at 30 months. Progression to prodromal Alzheimer's disease was defined as an amnestic syndrome of the hippocampal type. From May 25, 2013, to Jan 20, 2015, we enrolled 318 participants with a mean age of 76·0 years (SD 3·5). The mean baseline MMSE score was 28·67 (SD 0·96), and the mean level of education was high (score >6 [SD 2] on a scale of 1-8, where 1=infant school and 8=higher education). 88 (28showed amyloid deposition and the remainder did not. The amyloid subgroups did not differ for any psychobehavioural, cognitive, actigraphy, and structural and functional neuroimaging results after adjustment for age, sex, and level of education More participants positive for amyloid deposition had the APOE $\epsilon 4$ allele (33 [38%] vs 29 [13%], p<0·0001). Amyloid concentration in CSF significantly correlated with mean 18F-florbetapir uptake at baseline (r=-0·62, p<0·0001) and the ratio of amyloid to amyloid (r=-0·61, p<0·0001), and identified amyloid deposition status with high accuracy (mean area under the curve values 0·89, 95% CI 0·80-0·98 and 0·84, 0·72-0·96, respectively). No difference was seen in MMSE (28·3 [SD 2·0] vs 28·9 [1·2], p=0·16) and Clinical Dementia Rating scores (0·06 [0·2] vs 0·05 [0·3]; p=0·79) at 30 months (n=274) between participants positive or negative for amyloid. Four participants (all positive for amyloid deposition at baseline) progressed to prodromal Alzheimer's disease. They were older than other participants positive for amyloid deposition at baseline (mean 80·2 years [SD 4·1] vs 76·8 years [SD 3·4]) and had greater 18F-florbetapir uptake at baseline (mean standard uptake value ratio 1·46 [SD 0·16] vs 1·02 [SD 0·20]), and more were carriers of the APOE $\epsilon 4$ allele (three [75%] of four vs 33 [39%] of 83). They also had mild executive dysfunction at baseline (mean FCSRT free recall score 21·25 [SD 2·75] vs 29·08 [5·44] and Frontal Assessment Battery total score 13·25 [1·50] vs 16·05 [1·68]). Brain amyloidosis alone did not predict progression to prodromal Alzheimer's disease within 30 months. Longer follow-up is needed to establish whether this finding remains consistent.

More details in [13].

# 8. Bilateral Contracts and Grants with Industry

## 8.1. Bilateral Grants with Industry

### *8.1.1. Carthera*

**Participants:** Stéphane Epelbaum [Correspondant], Alexandre Carpentier, Anne Bertrand, Marie Odile Habert.

Project title: Open label phase 1/2 study evaluating the safety and usefulness of transient opening of the blood-brain barrier using low intensity pulsed ultrasounds generated by the implantable device SONOCLOUD in patients with mild Alzheimer's disease

Started in 2016

Amount: 400 K€

Coordinator: Stéphane Epelbaum

Other partners: UPMC, AP-HP

Abstract: This project aims at opening the blood brain barrier (BBB) in 10 mild Alzheimer's disease patients in order to improve the clearance of beta-amyloid and tau deposits in their brain as suggested in mice models of the disease. This first in man study will evaluate the safety and efficacy of an implanted device, SONOCLOUD, to open the BBB 7 times in each participant. Efficacy will be evaluated on the ability of the method to decrease the amyloid load evidenced by AV45 Positron Emission Tomography (PET), increase the brain metabolism analyzed by Fluorodeoxyglucose PET and improve cognition. If successful, this study will pave the way for future trials in which drugs can be used in addition to BBB opening to maximize their effect.

# 9. Partnerships and Cooperations

## 9.1. National Initiatives

### *9.1.1. ANR*

*9.1.1.1. ANR-NIH-NSF NETBCI*

**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, UPenn, USA

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-NIH-NSF HIPLAY7*

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

Project acronym: HIPLAY7

Project title: Hippocampal layers: advanced computational anatomy using very high resolution MRI at 7 Tesla in humans

Duration: Jan 2017 - Jan 2020

Amount: 770k€

Coordinator: Olivier Colliot and Pierre-François Van de Moortele

Other partners: University of Minnesota, Neurospin

Abstract: The overall goal of this proposal is to develop a coherent mathematical framework for computational anatomy of the internal structures of the hippocampus based on cutting edge MRI acquisition techniques at 7 Tesla. These mathematical and computational approaches are expected to significantly advance the field of computational anatomy of the human brain, breaking down the millimeter barrier of conventional brain morphometry and providing a coherent analysis framework for anatomical data at ultra-high spatial resolution.

*9.1.1.3. 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.

*9.1.1.4. 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, 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 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. Inria Project Labs*

*9.1.2.1. IPL Neuromarkers*

**Participants:** Stanley Durrleman [Correspondant], Olivier Colliot [Correspondant], Fabrizio de Vico Fallani, Anne Bertrand, Stéphane Epelbaum.

Project acronym: Neuromarkers

Project title: Design of imaging biomarkers of neurodegenerative diseases for clinical trials and study of their genetic associations

Duration: 2017-2021

Coordinators: Stanley Durrleman and Olivier Colliot

Other partners: Inria GENSCALE, Inria BONSAI, Inria DYLISS, Inria XPOP, ICM, IHU/ICM iConics

Abstract: The Inria Project Lab Neuromarkers aims to develop new statistical and computational approaches to integrate multimodal imaging and omics data and to demonstrate their potential to identify early alterations and predict progression of neurodegenerative diseases. To tackle this challenge, the project brings together multidisciplinary expertise from Inria and ICM (Brain and Spine Institute) in the fields of statistical learning, brain imaging, bioinformatics, knowledge modeling, genomics and neurodegenerative diseases.

### *9.1.3. IHU*

*9.1.3.1. General program*

**Participants:** Olivier Colliot, Stanley Durrleman, Didier Dormont, Ninon Burgos, Stéphane Epelbaum, 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.

*9.1.3.2. ICM-Internal Research projects*

**Participants:** Anne Bertrand [Correspondant], Takoua Kaaouana, Benoit Delatour, Alexandra Petiet, Olivier Colliot, Arnaud Marcoux.

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

Started 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.

*9.1.3.3. ICM-Internal Research projects*

**Participants:** Mario Chavez, 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

Started 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.

*9.1.3.4. ICM BBT Program - project PredictICD*

**Participants:** Olivier Colliot [Correspondant], Jean-Christophe Corvol [Correspondant], Johann Faouzi.

Project title: Predict impulse control disorders in Parkinson’s disease (PREDICT-ICD)

Started in 2018

Coordinators: Olivier Colliot and Jean-Christophe Corvol (ICM)

In Parkinson’s disease (PD), the therapeutic strategy is based on the dopamine replacement therapy. Although available since the 1960s’, it is only relatively recently that behavioral disorders associated with these drugs have been described. Gathered under the term of “behavioral addiction”, they include impulse control disorders (ICDs), dopamine dysregulation syndrome (DDS), and punding. Interestingly, whereas addiction to L-dopa itself occurs quasi exclusively with L-dopa, ICDs appear electively under dopamine agonist (DA) therapy. The objectives of this project are: i) to elucidate the genetic basis of DA induced ICDs in PD patients from several international cohorts; ii) to develop and validate a machine learning model to predict the occurrence of ICDs from the combination of clinical and genetic data.

*9.1.3.5. ICM BBT Program - project DYNAMO*

**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

Started in 2016

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.

*9.1.3.6. ICM BBT Program - project SEMAPHORE*

**Participants:** Stanley Durrleman [Correspondant], Stéphane Lehéricy [Correspondant], Jean-Christophe Corvol, Marie Vidailhet, Raphael Couronné, Safia Said.

Project title: Personalized progression model of Parkinson's disease

Started in 2018

Coordinator: Stanley Durrleman and Stéphane Lehéricy

Other partners: Neurology and Neuro-radiology departments, Pitié-Salpêtrière Hospital, AP-HP

The aim of this project is to build a personalizable model of Parkinson's disease (PD) progression integrating the complex dynamical interplay between phenotypic, imaging, genetic and metabolic alterations. We will identify and validate markers for monitoring of progression of brain damage in early and prodromal PD and identify conversion markers in subjects at risk of PD (idiopathic rapid eye movement sleep behavior disorders iRBD, PD- related mutation carriers). We will describe the appearance, characterize clinical phenotypes of PD, and identify modifier genes of disease phenotype. To this aim, we will relie on a novel statistical learning method using Bayesian non-linear mixed-effects model allowing to combine and realign short term sequence data to estimate

a long-term scenario of disease progression. This method is able to estimate individual stages of disease progression and to analyze automatically non-linear spatiotemporal patterns of data change. It estimates both a group-average scenario of PD progression as well as the inter-individual variability of this model in terms of age at onset, pace of disease progression and variability in the spatiotemporal trajectory of data changes. We will analyse the effect of genetic variants in the modulation of these non-linear progression patterns, and assess the statistical power of the individual parameters encoding for these patterns. The method will be applied to two sets of longitudinal data from the local prospective NUCLEIPARK (60 PD patients, 20 patients with iRBD, 60 controls) and ICEBERG studies (200 early idiopathic PD, 50 iRBD, 30 GBA and LRRK2 PD-related mutation carriers, 50 controls). Examinations included clinical, biological, and neurophysiological data, and multimodal 3T MRI, DATScan, and skin and salivary gland biopsies. The models of PD progression for each category of subjects will be released to the community, as well as the software for reproducibility purposes.

*9.1.3.7. ICM BBT Program - project ATTACK*

**Participants:** Fabrizio de Vico Fallani [Correspondant], Charlotte Rosso [Correspondant], Marie-Constance Corsi, Laurent Hugueville.

Project title: ATTACK Brain Network Models Of Motor Recovery After Stroke

Started in 2018

Coordinator: Fabrizio De Vico Fallani, Charlotte Rosso

Other partners: Neurology and Stroke departments, Pitié-Salpêtrière Hospital, AP-HP

Like in other connected systems, studying the structure of the interactions between different brain regions has profound implications in the comprehension of emergent complex phenomena as, for example, the capability of the human brain to functionally reorganize after cerebrovascular "attacks" or stroke. This dynamic skill, which is known in neuroscience as neural plasticity, is not only interesting from a network science perspective, but it also plays a crucial role in determining the motor/cognitive recovery of patients who survive a stroke. As a critical innovation, this project proposes to develop a systematic and rigorous approach based on neuroimaging techniques, signal processing, and network science for the modeling and analysis of temporally dynamic neural processes that characterize motor recovery after stroke. To achieve these goals, this project is organized around the following objectives: i) acquiring a comprehensive longitudinal dataset of brain and behavioral/clinical data after stroke, ii) developing new analytic tools to characterize and generate temporally dynamic brain networks, iii) building network-based models of motor recovery after stroke, accounting for individual patients. These objectives involve an intensive gathering of heterogeneous mass data, their processing, the subsequent outcome interpretation and statistical simulation, as well as the development of longitudinal models and network-based diagnostics of the patient's motor recovery progress. Results will be first characterized from pure network-theoretic and neuroscience perspectives, so as to highlight fundamental research challenges, and then validated to clarify the importance and the applicability to the clinical scenario. Our results will unveil multiscale properties of dynamic brain networks and identify predictive neuromarkers for motor recovery after stroke. This project has a two-fold impact on the society. On the one hand, it will provide new methods and robust tools to properly characterize and model temporally dynamic networks in neuroscience. On the other hand, it will provide longitudinal models of motor recovery in stroke patients that can potentially unveil the neural substrate that underpins rehabilitation, improve prognosis, and eventually lower cost of hospitalization time. From a broader perspective this interdisciplinary project proposes a transformative approach to analyze large-scale neural systems.

### *9.1.4. National Networks*

- GdR Statistics and Medicine - http://gdr-stat-sante.math.cnrs.fr/spip/
- GdR (MaDICS) Masses de Données, Informations et Connaissances en Sciences Big Data - Data ScienceStatistics and Medicine - http://www.madics.fr/reseaux/

- F. De Vico Fallani participated to the GdR (HANDICAP) in the framework of the future strategy of Inria
- F. De Vico Fallani was founding member of the CORTICO national network for brain-computer interfaces

### *9.1.5. Other National Programs*

*9.1.5.1. Programme Hospitalier de Recherche Clinique (PHRC)*

**Participants:** Olivier Colliot, Stanley Durrleman, Didier Dormont.

- 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: 2016-

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).
- F. De Vico Fallani has a collaboration with the University of Rome, Italy (Prof. Stefania Colonnese).
- O. Colliot has an enduring collaboration with the Center for Magnetic Resonance Research, University of Minnesota, USA (P-F Van de Moortele, T. Henry).
- S. Durrleman and O. Colliot have a collaboration with the Center for Medical Image Computing (CMIC) at University College London (UCL), London, UK (D. Alexander, H. Zhang).

## 9.4. International Research Visitors

### *9.4.1. Visits of International Scientists*

- Dr. Sarah-Christine Villeneuve spent a year from the 4th of December 2017 to the 30th of November 2018 as a clinical research fellow in Pitié Salpêtrière Hospital under the supervision of Stéphane Epelbaum (Sabbatical program).

# 10. Dissemination

## 10.1. Promoting Scientific Activities

### *10.1.1. Scientific Events Organisation*

*10.1.1.1. General Chair, Scientific Chair*

- S. Durrleman served as Program Chair for the eight International Workshop on Biomedical Image Registration (WBIR'18, Leiden, The Netherlands)
- F. De Vico Fallani served as Program Chair for the Network Neuroscience Satellite (NETSCI'18, Paris, France)
- F. De Vico Fallani served as Program Chair for the Brainhack Networks workshop (ICM, Paris, France)

*10.1.1.2. Member of the Organizing Committees*

N. Burgos co-organized the international workshop on Simulation and Synthesis in Medical Imaging (SASHIMI) 2018, a satellite workshop of MICCAI 2018.

S. Epelbaum was session co-chair at the Alzheimer Association International Conference in Chicago 14-18th July 2018

### *10.1.2. Scientific Events Selection*

*10.1.2.1. Member of the Conference Program Committees*

- O. Colliot served as Program Committee member for the international conference SPIE Medical Imaging (Houston, USA, 2018) and for the international workshop PatchMI (Granada, Spain, 2018).
- F. De Vico Fallani served as Program Committee member for the following international conferences: NETSCI (Paris, 2018), Complex Networks (Cambridge, UK, 2018), ComplNet (Zaragoza, Spain, 2018)

*10.1.2.2. Reviewer*

- N. Burgos acted as a reviewer for the international workshops on Deep Learning in Medical Image Analysis (DLMIA) and on Simulation and Synthesis in Medical Imaging (SASHIMI).
- O. Colliot acted as a reviewer for the international conferences SPIE Medical Imaging, Annual meeting of the Organization for Human Brain Mapping (OHBM) and the international workshop PatchMI.

### *10.1.3. Journal*

*10.1.3.1. Member of the Editorial Boards*

- S. Durrleman is associate editor of the journals: IEEE Transactions on Medical Imaging, and Neurons, Behavior, Data analysis, and Theory (NBDT)
- F. De Vico Fallani is associate editor of the journal PLoS One
- O. Colliot is a member of the Editorial Board of the journal Medical Image Analysis (Elsevier).
- S. Epelbaum is member of the editorial board for the "Médecine, Cognition et Vieillissement" Scientific Journal.

*10.1.3.2. Reviewer - Reviewing Activities*

- N. Burgos acted as a reviewer for IEEE Transactions on Medical Imaging; NeuroImage; Medical Image Analysis; Journal of Nuclear Medicine; IEEE Transactions on Radiation and Plasma Medical Sciences; IEEE Journal of Biomedical and Health Informatics; EJNMMI Physics; International Journal of Radiation Oncology, Biology, Physics; Sensors.
- Olivier Colliot acted as a reviewer for Medical Image Analysis, NeuroImage, NeuroImage: Clinical, IEEE Transactions on Medical Imaging.
- F. De Vico Fallani acted as a reviewer for IEEE TNRSE, Neuroimage, PLoS Comp Biol, PLoS One, Cereb Cortex.
- S. Epelbaum acted as a reviewer for Alzheimer's & Dementia, the Journal of Alzheimer's disease, Brain and BMJ Neurology.

### *10.1.4. Invited Talks*

N. Burgos gave an invited lecture at the workshop on Machine Learning in Radiology in Lausanne, Switzerland, November 2018.

N. Burgos gave an invited presentation at the course "Pattern Recognition for Neuroimaging" at the Annual Meeting of the Organization for Human Brain Mapping, Singapore, June 2018.

O. Colliot gave an invited presentation at the Singapore-France Artificial Intelligence Workshop, Singapore, June 2018.

O. Colliot gave an invited presentation at the Netherlands-France "Erasmus-Descartes" Artificial Intelligence Workshop, Paris, France, November 2018.

S. Durrleman gave an keynote presentation at the MICCAI workshop ShapeMI (Shape in medical imaging), Granada, Septembre 2018, and an invited presentation at the Symposium on Multivariate analyses, Modelling and Machine Learning in Neuroimaging Research, University Paul Sabatier of Toulouse.

S. Epelbaum and S. Durrleman gave a plenary lecture at College de France for the colloquium “Imagerie médicale et apprentissage automatique : vers une intelligence artificielle ?”

F. De Vico Fallani gave invited lectures at CuttingEEG International conference (ICM, Paris, 2018)

F. De Vico Fallani gave a plenary lectures at Neurospin CEA Institute (Saclay, France)

### *10.1.5. Scientific Expertise*

- Olivier Colliot is a member of the "Commission des emplois scientifiques" of the Inria Paris Center, in charge of evaluating applications for PhD fellowships, postdoc fellowships and secondments.
- Olivier Colliot acts as an expert for GENCI (the national facility for high-performance computing).

### *10.1.6. Research Administration*

- S. Durrleman serves as the coordinator of the ICM Center for Neuroinformatics, and the scientific director of the iCONICS core facility on data management and analytics.

## 10.2. Teaching - Supervision - Juries

### *10.2.1. Teaching*

Master: Olivier Colliot coordinates the course "Méthodes d’imagerie médicale" of the Master 2 in Computer Science of Sorbonne University.

Master: Olivier Colliot, Master in Computer Science, 4.5 hours (eqTD), Sorbonne University

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: Didier Dormont, 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

S. Durrleman, Geometrical approaches in Statistical Learning, 21 hours, Master 2 "Mathématiques, Vision, Apprentissage", ENS Paris Saclay, France.

Master: Stéphane Epelbaum, Master in Neuroscience, 4 hours (eqTD), Université Pierre et Marie Curie

Medical school: Stéphane Epelbaum gives lectures in Neurology on the topic of degenerative diseases for medical students of the UPMC (10 hours/year) and is regional supervisor of the national Inter University Diploma on Alzheimer’s disease and Related disorders for Paris since 2015.

### *10.2.2. Supervision*

PhD in progress : Giulia Bassignana, “Identification of driver nodes in biological networks”, Inserm, started in 2017, advisors: Fabrizio De Vico Fallani, Olivier Colliot, Violetta Zujovic

PhD in progress : Tiziana Cattai, “Leveraging brain connectivity networks to detect mental states in brain-computer interfaces”, Inria, started in 2017, advisor: Fabrizio De Vico Fallani

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”, 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, Anne Bertrand 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: 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: Raphael Couronné, “Spatiotemporal analysis of the progression of the Parkinson’s Disease informed by multimodal longitudinal data”, advisor: S. Durrleman

PhD in progress: Thomas Lartigue, “Mixture Models in Gaussian Graphical Models”, advisors: S. Allassonnière and S. Durrleman

PhD in progress: Vianney Debavelaere, “Analysis of distribution of spatiotemporal trajectories in heterogeneous populations”, advisors: S. Allassonnière and S. Durrleman

PhD in progress: Lou Albessard, “analyse de la covariation du crâne et de l’endocrâne dans le genre *Homo*”, advisors: D. Grimaud-Hervé and S. Durrleman

PhD in progress: Johann Faouzi, “Machine learning approaches to predict impulse control disorders in Parkinson’s disease”, advisors: O. Colliot and J.-C. Corvol

PhD in progress: Simona Bottani, “Machine learning for differential diagnosis of neurodegenerative diseases from multimodal data”, advisors: O. Colliot and N. Burgos

PhD in progress: Elina Thibeau–Sutre, “Unsupervised learning from neuroimaging data to identify disease subtypes in Alzheimer’s disease and related disorders”, advisors: D. Dormont and N. Burgos

PhD in progress: Federica Cacciamani, “Awareness for cognitive decline in the earliest stages of Alzheimer’s disease”, advisor: S. Epelbaum

### *10.2.3. Juries*

- Olivier Colliot participated, as referee, to the PhD committee of Matthieu Van Houtte (University of Lille).
- Olivier Colliot participated, as examiner, to the HDR committee of Stanley Durrleman (Sorbonne University).
- Olivier Colliot participated to the progress report PhD committee of Ekaterina Kalinicheva (ISEP).
- S. Durrleman participated, as examiner, to the PhD committee of W. Huizinga at Erasmus University Rotterdam, The Netherlands.
- S. Durrleman participated, as co-supervisor, to the PhD committee of L. Albessard at Museum National d'Histoire Naturelle, Paris, France.
- Stéphane Epelbaum participated, as examiner, to the PhD committee of Benoît Souchet (CEA).
- Stéphane Epelbaum participated, as examiner, to the PhD committee of Adrien Julian (University of Poitiers).

## 10.3. Popularization

### *10.3.1. Articles and contents*

- S. Durrleman's interviews were published in the magazines Le Point, Sciences et Avenir, Usine Nouvelle, Le Temps, revue Pharma, and were broadcasted on the radio France Culture. He published also an article in the special issue on artificial intelligence of the newspaper Libération.
- S. Durrleman did popularization presentations at Rotary Club Chamonix, Cercle des amis de l'ICM, and Salon de l'argus de l'assurance.
- F. De Vico Fallani did a popularization presentation at La Française - Investing group, Paris
- Olivier Colliot gave an interview for the TV channel France 5, for the program "Magazine de la Santé.
- Stéphane Epelbaum participated to multiple events dedicated to general audience outreach including: articles in journals (L'Express, Cerveau & Psycho, Sciences Avenir), Radio shows and podcasts (France inter: Grand Bien vous fasse, Figaro Live) and TV shows (Pourquoi docteur, Questions aux experts).
- The team contributed to the book "Le Grand Atlas du Cerveau" (Glénat).

### *10.3.2. Interventions*

- O. Colliot gave a presentation to members of the German Bundestag, Paris, France, December 2018.
- Stéphane Epelbaum participated to a charity event at the Foire internationale d'Art Contemporain (FIAC) 2018 on the 20th of November 2018.

### *10.3.3. Internal action*

- O. Colliot gave a presentation for the charity event ("Evènement solidaire" of Inria, September 2018.

# 11. Bibliography

## Publications of the year

### Doctoral Dissertations and Habilitation Theses

[1] J. GUILLON. *Multilayer approach to brain connectivity in Alzheimer's disease*, Pierre and Marie Curie University, November 2018, https://tel.archives-ouvertes.fr/tel-01985286

[2] A. M. ROUTIER. *Multimodal brain imaging for the study of progressive primary aphasia*, Sorbonne Université , UPMC, December 2018, https://tel.archives-ouvertes.fr/tel-01992799

## Articles in International Peer-Reviewed Journals

[3] M. ANSART, S. EPELBAUM, G. GAGLIARDI, O. COLLIOT, D. DORMONT, B. DUBOIS, H. HAMPEL, S. DURRLEMAN. *Reduction of recruitment costs in preclinical AD trials. Validation of automatic pre-screening algorithm for brain amyloidosis*, in "Statistical Methods in Medical Research", January 2019, 096228021882303 p. [*DOI :* 10.1177/0962280218823036], https://hal.archives-ouvertes.fr/hal-01964942

[4] H. ARABI, J. DOWLING, N. BURGOS, X. HAN, P. GREER, N. KOUTSOUVELIS, H. ZAIDI. *Comparative study of algorithms for synthetic CT generation from MRI: Consequences for MRI-guided radiation planning in the pelvic region*, in "Medical Physics", September 2018 [*DOI :* 10.1002/MP.13187], https://hal.inria.fr/hal-01890646

[5] N. BADAT, C. CHOLET, G. HERVÉ, N. PYATIGORSKAYA, S. TRUNET, D. DORMONT, B. LAW-YE. *Malignant transformation of epidermoid cyst with diffuse leptomeningeal carcinomatosis on skull base and trigeminal perineural spread*, in "Journal de Neuroradiologie / Journal of Neuroradiology", September 2018, vol. 45, n$^{o}$ 5, pp. 337-340 [*DOI :* 10.1016/J.NEURAD.2018.07.002], https://hal.inria.fr/hal-01966083

[6] F. BATTISTON, J. GUILLON, M. CHAVEZ, V. LATORA, F. DE VICO FALLANI. *Multiplex core–periphery organization of the human connectome*, in "Journal of the Royal Society Interface", September 2018, vol. 15, n$^{o}$ 146 [*DOI :* 10.1098/RSIF.2018.0514], https://hal.archives-ouvertes.fr/hal-01874871

[7] A. BEAUDET, J. DUMONCEL, F. DE BEER, S. DURRLEMAN, E. GILISSEN, A. OETTLÉ, G. SUBSOL, J. F. THACKERAY, J. BRAGA. *The endocranial shape of Australopithecus africanus : surface analysis of the endocasts of Sts 5 and Sts 60*, in "Journal of Anatomy", February 2018, vol. 232, n$^{o}$ 2, pp. 296-303 [*DOI :* 10.1111/JOA.12745], https://hal-lirmm.ccsd.cnrs.fr/lirmm-01636811

[8] A. BERTRAND, J. WEN, D. RINALDI, M. HOUOT, S. SAYAH, A. CAMUZAT, C. FOURNIER, S. FONTANELLA, A. ROUTIER, P. COURATIER, F. PASQUIER, M.-O. HABERT, D. HANNEQUIN, O. MARTINAUD, P. CAROPPO, R. LEVY, B. DUBOIS, A. BRICE, S. DURRLEMAN, O. COLLIOT, I. LE BER, P. STUDY. *Early cognitive, structural and microstructural changes in c9orf72 presymptomatic carriers before 40 years of age*, in "JAMA neurology", February 2018, vol. 75, n$^{o}$ 2, pp. 236-245 [*DOI :* 10.1001/JAMANEUROL.2017.4266], https://hal.inria.fr/hal-01654000

[9] S. COLONNESE, M. BIAGI, T. CATTAI, R. CUSANI, F. DE VICO FALLANI, G. SCARANO. *Green Compressive Sampling Reconstruction in IoT Networks*, in "Sensors", August 2018, vol. 18, n$^{o}$ 8, 2735 p. [*DOI :* 10.3390/S18082735], https://hal.inria.fr/hal-01965543

[10] M.-C. CORSI, M. CHAVEZ, D. SCHWARTZ, L. HUGUEVILLE, A. KHAMBHATI, D. S. BASSETT, F. DE VICO FALLANI. *Integrating EEG and MEG Signals to Improve Motor Imagery Classification in Brain–Computer Interface*, in "International Journal of Neural Systems", April 2018, https://arxiv.org/abs/1711.07258v2 [*DOI :* 10.1142/S0129065718500144], https://hal.archives-ouvertes.fr/hal-01893132

[11] C. CURY, S. DURRLEMAN, D. CASH, M. LORENZI, J. M. NICHOLAS, M. BOCCHETTA, J. C. VAN SWIETEN, B. BORRONI, D. GALIMBERTI, M. MASELLIS, M. C. TARTAGLIA, J. ROWE, C. GRAFF, F. TAGLIAVINI, G. B. FRISONI, R. LAFORCE, E. FINGER, A. DE MENDONÇA, S. SORBI, S. OURSELIN, J. ROHRER, M. MODAT, C. ANDERSSON, S. ARCHETTI, A. ARIGHI, L. BENUSSI, S. BLACK, M.

COSSEDDU, M. FALLSTRM, C. G. FERREIRA, C. FENOGLIO, N. FOX, M. FREEDMAN, G. FUMAGALLI, S. GAZZINA, R. GHIDONI, M. GRISOLI, V. JELIC, L. JISKOOT, R. KEREN, G. LOMBARDI, C. MARUTA, L. MEETER, R. VAN MINKELEN, B. NACMIAS, L. IJERSTEDT, A. PADOVANI, J. PANMAN, M. PIEVANI, C. POLITO, E. PREMI, S. PRIONI, R. RADEMAKERS, V. REDAELLI, E. ROGAEVA, G. ROSSI, M. ROSSOR, E. SCARPINI, D. TANG-WAI, H. THONBERG, P. TIRABOSCHI, A. VERDELHO, J. WARREN. *Spatiotemporal analysis for detection of pre-symptomatic shape changes in neurodegenerative diseases: Initial application to the GENFI cohort*, in "NeuroImage", March 2019, vol. 188, pp. 282-290 [*DOI :* 10.1016/J.NEUROIMAGE.2018.11.063], https://www.hal.inserm.fr/inserm-01958916

[12] C. CURY, J. GLAUNÈS, R. TORO, M. CHUPIN, G. SCHUMANN, V. FROUIN, J.-B. POLINE, O. COLLIOT. *Statistical Shape Analysis of Large Datasets Based on Diffeomorphic Iterative Centroids*, in "Frontiers in Neuroscience", November 2018, vol. 12, 803 p. [*DOI :* 10.3389/FNINS.2018.00803], https://hal.inria.fr/hal-01920263

[13] B. DUBOIS, S. EPELBAUM, F. NYASSE, H. BAKARDJIAN, G. GAGLIARDI, O. USPENSKAYA, M. HOUOT, S. LISTA, F. CACCIAMANI, M.-C. POTIER, A. BERTRAND, F. LAMARI, H. BENALI, J.-F. MANGIN, O. COLLIOT, R. GENTHON, M.-O. HABERT, H. HAMPEL. *Cognitive and neuroimaging features and brain $\beta$-amyloidosis in individuals at risk of Alzheimer's disease (INSIGHT-preAD): a longitudinal observational study*, in "Lancet Neurology", April 2018, vol. 17, n$^{O}$ 4, pp. 335 - 346, For the INSIGHT-preAD study group [*DOI :* 10.1016/S1474-4422(18)30029-2], https://hal.sorbonne-universite.fr/hal-01777834

[14] S. EPELBAUM, V. BOUTELOUP, J. F. MANGIN, V. LA CORTE, R. MIGLIACCIO, H. BERTIN, M. O. HABERT, C. FISCHER, C. AZOUANI, L. FILLON, M. CHUPIN, B. VELLAS, F. PASQUIER, J. F. DARTIGUES, F. BLANC, A. GABELLE, M. CECCALDI, P. KROLAK-SALMON, J. HUGON, O. HANON, O. ROUAUD, R. DAVID, G. CHÊNE, B. DUBOIS, C. DUFOUIL. *Neural correlates of episodic memory in the Memento cohort*, in "Alzheimer's & Dementia: Translational Research & Clinical Interventions", 2018, vol. 4, pp. 224-233, https://arxiv.org/abs/1812.08031 [*DOI :* 10.1016/J.TRCI.2018.03.010], https://hal.sorbonne-universite.fr/hal-01958834

[15] P. GORI, O. COLLIOT, L. M. KACEM, Y. WORBE, A. ROUTIER, C. POUPON, A. HARTMANN, N. AYACHE, S. DURRLEMAN. *Double diffeomorphism: combining morphometry and structural connectivity analysis*, in "IEEE Transactions on Medical Imaging", September 2018, vol. 37, n$^{O}$ 9, pp. 2033-2043 [*DOI :* 10.1109/TMI.2018.2813062], https://hal.archives-ouvertes.fr/hal-01709847

[16] E. HAINQUE, A. BLANCHER, V. MESNAGE, S. RIVAUD-PECHOUX, A. BERTRAND, S. DUPONT, V. NAVARRO, E. ROZE, I. GOURFINKEL-AN, E. APARTIS. *A clinical and neurophysiological motor signature of Unverricht–Lundborg disease*, in "Revue Neurologique", January 2018 [*DOI :* 10.1016/J.NEUROL.2017.06.005], https://hal.archives-ouvertes.fr/hal-01562621

[17] H. HAMPEL, N. TOSCHI, C. BABILONI, F. BALDACCI, K. L. BLACK, A. BOKDE, R. S. BUN, F. CACCIOLA, E. CAVEDO, P. A. CHIESA, O. COLLIOT, C.-M. COMAN, B. DUBOIS, A. DUGGENTO, S. DURRLEMAN, M.-T. FERRETTI, N. GEORGE, R. GENTHON, M.-O. HABERT, K. HERHOLZ, Y. KORONYO, M. KORONYO-HAMAOUI, F. LAMARI, T. LANGEVIN, S. LEHÉRICY, J. LORENCEAU, C. NÉRI, R. NISTICÒ, F. NYASSE, C. W. RITCHIE, S. ROSSI, E. SANTARNECCHI, O. SPORNS, S. R. VERDOONER, A. VERGALLO, N. VILLAIN, E. YOUNESI, F. GARACI, S. LISTA, A. L. BOKDE. *Revolution of Alzheimer Precision Neurology. Passageway of Systems Biology and Neurophysiology*, in "Journal of Alzheimer's Disease", June 2018, vol. 64, n$^{O}$ s1, pp. S47 - S105 [*DOI :* 10.3233/JAD-179932], https://hal.archives-ouvertes.fr/hal-01910402

[18] J. P. KIESELMANN, C. P. KAMERLING, N. BURGOS, M. J. MENTEN, C. D. FULLER, S. NILL, M. J. CARDOSO, U. OELFKE. *Geometric and dosimetric evaluations of atlas-based segmentation methods of MR images in the head and neck region*, in "Physics in Medicine and Biology", 2018, vol. 63, n° 14, 00000 [*DOI :* 10.1088/1361-6560/AACB65], https://hal.inria.fr/hal-01827187

[19] I. KOVAL, J.-B. SCHIRATTI, A. M. ROUTIER, M. BACCI, O. COLLIOT, S. ALLASSONNIÈRE, S. DURRLEMAN. *Spatiotemporal Propagation of the Cortical Atrophy: Population and Individual Patterns*, in "Frontiers in Neurology", May 2018, vol. 9, 235 p. [*DOI :* 10.3389/FNEUR.2018.00235], https://hal.inria.fr/hal-01910400

[20] K. KUMAR, L. CHAUVIN, M. TOEWS, O. COLLIOT, C. DESROSIERS. *Multi-modal brain fingerprinting: a manifold approximation based framework*, in "NeuroImage", December 2018, vol. 183, pp. 212 - 226 [*DOI :* 10.1016/J.NEUROIMAGE.2018.08.006], https://hal.inria.fr/hal-01910367

[21] B. LAW-YE, P. DODET, B. HERMANN, S. TRUNET, D. DORMONT, N. PYATIGORSKAYA, D. LECLERCQ. *Progressive white-matter demyelination in delayed CO poisoning encephalopathy*, in "Journal de Neuroradiologie / Journal of Neuroradiology", February 2018, vol. 45, n° 1, pp. 59-62 [*DOI :* 10.1016/J.NEURAD.2017.09.008], https://hal.inria.fr/hal-01966086

[22] B. LAW-YE, D. DORMONT, C. CHOLET. *MR angiography of reversible cerebral vasoconstriction syndrome*, in "Diagnostic and Interventional Imaging", September 2018, vol. 99, n° 9, pp. 525-526 [*DOI :* 10.1016/J.DIII.2018.07.001], https://hal.inria.fr/hal-01966085

[23] M. LOUIS, B. CHARLIER, P. JUSSELIN, S. PAL, S. DURRLEMAN. *A Fanning Scheme for the Parallel Transport Along Geodesics on Riemannian Manifolds*, in "SIAM Journal on Numerical Analysis", 2018, https://hal.archives-ouvertes.fr/hal-01560787

[24] A. MARCOUX, N. BURGOS, A. BERTRAND, M. TEICHMANN, A. ROUTIER, J. WEN, J. SAMPER-GONZALEZ, S. BOTTANI, S. DURRLEMAN, M.-O. HABERT, O. COLLIOT. *An Automated Pipeline for the Analysis of PET Data on the Cortical Surface*, in "Frontiers in Neuroinformatics", December 2018, vol. 12 [*DOI :* 10.3389/FNINF.2018.00094], https://hal.inria.fr/hal-01950933

[25] J. MARTINEZ, J. BULDÚ, D. PAPO, F. DE VICO FALLANI, M. CHAVEZ. *Role of inter-hemispheric connections in functional brain networks*, in "Scientific Reports", December 2018, vol. 8, n° 1, 10246 p. [*DOI :* 10.1038/S41598-018-28467-X], https://hal.inria.fr/hal-01964406

[26] A. MENDES, S. TÉZENAS DU MONTCEL, M. LEVY, A. BERTRAND, M.-O. HABERT, H. BERTIN, B. DUBOIS, S. EPELBAUM. *Multimorbidity Is Associated with Preclinical Alzheimer's Disease Neuroimaging Biomarkers*, in "Dementia and Geriatric Cognitive Disorders", August 2018, vol. 45, n° 5-6, pp. 272-281 [*DOI :* 10.1159/000489007], https://hal.sorbonne-universite.fr/hal-01958870

[27] C. MEYNIEL, D. SAMRI, F. STEFANO, J. CREVOISIER, F. BONTÉ, R. MIGLIACCIO, L. DELABY, A. BERTRAND, M. O. HABERT, B. DUBOIS, B. BODAGHI, S. EPELBAUM. *COGEVIS: A New Scale to Evaluate Cognition in Patients with Visual Deficiency*, in "Behavioural Neurology", June 2018, vol. 2018, pp. 1-7, https://arxiv.org/abs/1812.07328 [*DOI :* 10.1155/2018/4295184], https://hal.sorbonne-universite.fr/hal-01958688

[28] E. PIEKARSKI, N. PYATIGORSKAYA, D. DORMONT, D. GALANAUD, A. KAS. *Increased 18F-FDG Uptake in Lhermitte-Duclos Disease With Cowden Syndrome Revealed by PET-MRI*, in "Clinical Nuclear Medicine", 2018, vol. 43, n$^{o}$ 10, 1 p. [*DOI :* 10.1097/RLU.0000000000002248], https://hal.inria.fr/hal-01966082

[29] A. ROUTIER, M.-O. HABERT, A. BERTRAND, A. KAS, M. SUNDQVIST, J. MERTZ, P.-M. DAVID, H. BERTIN, S. BELLIARD, F. PASQUIER, K. BENNYS, O. MARTINAUD, F. ETCHARRY-BOUYX, O. MOREAUD, O. GODEFROY, J. PARIENTE, M. PUEL, P. COURATIER, C. BOUTOLEAU-BRETONNIÈRE, B. LAURENT, R. MIGLIACCIO, B. DUBOIS, O. COLLIOT, M. TEICHMANN. *Structural, Microstructural, and Metabolic Alterations in Primary Progressive Aphasia Variants*, in "Frontiers in Neurology", September 2018, vol. 9 [*DOI :* 10.3389/FNEUR.2018.00766], https://hal.inria.fr/hal-01897015

[30] J. SAMPER-GONZALEZ, N. BURGOS, S. BOTTANI, S. FONTANELLA, P. LU, A. MARCOUX, A. ROUTIER, J. GUILLON, M. BACCI, J. WEN, A. BERTRAND, H. BERTIN, M.-O. HABERT, S. DURRLEMAN, T. EVGENIOU, O. COLLIOT. *Reproducible evaluation of classification methods in Alzheimer's disease: Framework and application to MRI and PET data*, in "NeuroImage", December 2018, vol. 183, pp. 504-521 [*DOI :* 10.1016/J.NEUROIMAGE.2018.08.042], https://hal.inria.fr/hal-01858384

[31] C. SANCHES, A. ROUTIER, O. COLLIOT, M. TEICHMANN. *The structure of the mental lexicon: what primary progressive aphasias reveal*, in "Neuropsychologia", January 2018, vol. 109, pp. 107-115 [*DOI :* 10.1016/J.NEUROPSYCHOLOGIA.2017.12.018], https://hal.inria.fr/hal-01672932

[32] M. SCHERTZ, M. BENZAKOUN, N. PYATIGORSKAYA, S. BELKACEM, M. SAHLI-AMOR, V. NAVARRO, C. CHOLET, D. LECLERCQ, D. DORMONT, B. LAW-YE. *Specificities of arterial spin labeling (ASL) abnormalities in acute seizure*, in "Journal de Neuroradiologie / Journal of Neuroradiology", November 2018 [*DOI :* 10.1016/J.NEURAD.2018.11.003], https://hal.inria.fr/hal-01966079

[33] C. SCOTT, J. JIAO, A. MELBOURNE, N. BURGOS, D. CASH, E. DE VITA, P. MARKIEWICZ, A. O'CONNOR, D. THOMAS, P. S. WESTON, J. SCHOTT, B. HUTTON, S. OURSELIN. *Reduced acquisition time PET pharmacokinetic modelling using simultaneous ASL–MRI: proof of concept*, in "Journal of Cerebral Blood Flow and Metabolism", September 2018 [*DOI :* 10.1177/0271678X18797343], https://hal.inria.fr/hal-01871983

[34] J. WEN, H. ZHANG, D. C. ALEXANDER, S. DURRLEMAN, A. ROUTIER, D. RINALDI, M. HOUOT, P. COURATIER, D. HANNEQUIN, F. PASQUIER, J. ZHANG, O. COLLIOT, I. LE BER, A. BERTRAND. *Neurite density is reduced in the presymptomatic phase of C9orf72 disease*, in "Journal of Neurology, Neurosurgery and Psychiatry", 2018 [*DOI :* 10.1136/JNNP-2018-318994], https://hal.inria.fr/hal-01907482

[35] C. ZAVANONE, Y. SAMSON, C. ARBIZU, S. DUPONT, D. DORMONT, C. ROSSO. *Critical brain regions related to post-stroke aphasia severity identified by early diffusion imaging are not the same when predicting short- and long-term outcome*, in "Brain and Language", November 2018, vol. 186, pp. 1-7 [*DOI :* 10.1016/J.BANDL.2018.08.005], https://hal.inria.fr/hal-01966081

### Invited Conferences

[36] A. BÔNE, M. LOUIS, B. MARTIN, S. DURRLEMAN. *Deformetrica 4: an open-source software for statistical shape analysis*, in "ShapeMI @ MICCAI 2018 - Workshop on Shape in Medical Imaging", Granada, Spain, September 2018, https://hal.inria.fr/hal-01874752

### International Conferences with Proceedings

[37] M. ANSART, I. KOVAL, A. BERTRAND, D. DORMONT, S. DURRLEMAN. *Design of a decision support system for predicting the progression of Alzheimer's disease*, in "Alzheimer's Association International Conference", Chicago, United States, July 2018, vol. 14, n° 7, P433 p. [*DOI :* 10.1016/J.JALZ.2018.06.371], https://hal.inria.fr/hal-01988912

[38] A. BÔNE, O. COLLIOT, S. DURRLEMAN. *Learning distributions of shape trajectories from longitudinal datasets: a hierarchical model on a manifold of diffeomorphisms*, in "CVPR 2018 - Computer Vision and Pattern Recognition 2018", Salt Lake City, United States, June 2018, https://hal.archives-ouvertes.fr/hal-01744538

[39] V. J. HENRY, I. MOSZER, O. DAMERON, M.-C. POTIER, M. HOFMANN-APITIUS, O. COLLIOT. *Converting Alzheimer's disease map into a heavyweight ontology: a formal network to integrate data*, in "DILS 2018 - 13th International Conference on Data Integration in the Life Sciences", Hannover, Germany, DILS 2018 - 13th International Conference on Data Integration in the Life Sciences, November 2018, pp. 1-9, https://hal.archives-ouvertes.fr/hal-01917742

[40] W. WEI, E. POIRION, B. BODINI, S. DURRLEMAN, N. AYACHE, B. STANKOFF, O. COLLIOT. *Learning Myelin Content in Multiple Sclerosis from Multimodal MRI through Adversarial Training*, in "MICCAI 2018 – 21st International Conference On Medical Image Computing & Computer Assisted Intervention", Granada, Spain, September 2018, vol. 11072 [*DOI :* 10.1007/978-3-030-00931-1_59], https://hal.inria.fr/hal-01810822

[41] J. WEN, J. SAMPER-GONZALEZ, S. BOTTANI, A. ROUTIER, N. BURGOS, T. JACQUEMONT, S. FONTANELLA, S. DURRLEMAN, A. BERTRAND, O. COLLIOT. *Using diffusion MRI for classification and prediction of Alzheimer's Disease: a reproducible study*, in "AAIC 2018 - Alzheimer's Association International Conference", Chicago, United States, July 2018, https://hal.inria.fr/hal-01758167

### Conferences without Proceedings

[42] G. BASSIGNANA, J. FRANSSON, O. COLLIOT, V. ZUJOVIC, F. DE VICO FALLANI. *Identification of Driver Nodes in Genetic Networks Regulating Macrophage Activation*, in "Conference on Complex Systems - CSS", Thessaloniki, Greece, September 2018, https://hal.archives-ouvertes.fr/hal-01967797

[43] M.-C. CORSI, M. CHAVEZ, D. SCHWARTZ, L. HUGUEVILLE, A. KHAMBHATI, D. S. BASSETT, F. DE VICO FALLANI. *Integrating EEG and MEG information to enhance motor-imagery classification in brain-computer interface*, in "BIOMAG 2018 - 21st International Conference on Biomagnetism", Philadelphia, United States, August 2018, https://hal.archives-ouvertes.fr/hal-01966311

[44] M.-C. CORSI, M. CHAVEZ, D. SCHWARTZ, L. HUGUEVILLE, A. KHAMBHATI, D. S. BASSETT, F. DE VICO FALLANI. *M/EEG integration to enhance motor-imagery-based brain-computer interface performances*, in "Seventh International BCI Society Meeting", Asilomar, United States, May 2018, https://hal.archives-ouvertes.fr/hal-01966314

[45] V. HENRY, I. MOSZER, O. DAMERON, M.-C. POTIER, M. HOFMANN-APITIUS, O. COLLIOT. *Integrating ontological representation and reasoning into a disease map: application to Alzheimer's disease*, in "DMCM 2018 - 3rd Disease Maps Community Meeting", Paris, France, June 2018, pp. 1-2, https://hal.archives-ouvertes.fr/hal-01873474

[46] A. MARCOUX, N. BURGOS, A. BERTRAND, A. ROUTIER, J. WEN, J. SAMPER-GONZALEZ, S. BOTTANI, S. DURRLEMAN, M.-O. HABERT, O. COLLIOT. *A pipeline for the analysis of 18F-FDG PET data on*

*the cortical surface and its evaluation on ADNI*, in "Annual meeting of the Organization for Human Brain Mapping - OHBM 2018", Singapour, Singapore, June 2018, https://hal.archives-ouvertes.fr/hal-01757646

[47] A. ROUTIER, J. GUILLON, N. BURGOS, J. SAMPER-GONZALEZ, J. WEN, S. FONTANELLA, S. BOTTANI, T. JACQUEMONT, A. MARCOUX, P. GORI, P. LU, T. MOREAU, M. BACCI, S. DURRLEMAN, O. COLLIOT. *Clinica: an open source software platform for reproducible clinical neuroscience studies*, in "Annual meeting of the Organization for Human Brain Mapping - OHBM 2018", Singapore, Singapore, June 2018, https://hal.inria.fr/hal-01760658

[48] A. ROUTIER, M.-O. HABERT, A. BERTRAND, A. KAS, P.-M. DAVID, H. BERTIN, O. GODEFROY, F. ETCHARRY-BOUYX, O. MOREAUD, F. PASQUIER, P. COURATIER, K. BENNYS, C. BOUTOLEAU-BRETONNIÈRE, O. MARTINAUD, B. LAURENT, J. PARIENTE, M. PUEL, S. BELLIARD, R. MIGLIACCIO, B. DUBOIS, O. COLLIOT, M. TEICHMANN. *Structural, microstructural and metabolic alterations in Primary Progressive Aphasia variants*, in "Annual meeting of the Organization for Human Brain Mapping - OHBM 2018", Singapore, Singapore, June 2018, https://hal.inria.fr/hal-01764289

[49] J. SAMPER-GONZALEZ, S. BOTTANI, N. BURGOS, S. FONTANELLA, P. LU, A. MARCOUX, A. ROUTIER, J. GUILLON, M. BACCI, J. WEN, A. BERTRAND, H. BERTIN, M.-O. HABERT, S. DURRLEMAN, T. EVGENIOU, O. COLLIOT. *Reproducible evaluation of Alzheimer's Disease classification from MRI and PET data*, in "Annual meeting of the Organization for Human Brain Mapping - OHBM 2018", Singapour, Singapore, June 2018, https://hal.inria.fr/hal-01761666

[50] W. WEI, E. POIRION, B. BODINI, S. DURRLEMAN, O. COLLIOT, B. STANKOFF, N. AYACHE. *FLAIR MR Image Synthesis By Using 3D Fully Convolutional Networks for Multiple Sclerosis*, in "ISMRM-ESMRMB 2018 - Joint Annual Meeting", Paris, France, June 2018, pp. 1-6, https://hal.inria.fr/hal-01723070

[51] J. WEN, J. SAMPER-GONZALEZ, S. BOTTANI, A. ROUTIER, N. BURGOS, T. JACQUEMONT, S. FONTANELLA, S. DURRLEMAN, A. BERTRAND, O. COLLIOT. *Comparison of DTI Features for the Classification of Alzheimer's Disease: A Reproducible Study*, in "OHBM 2018 - Organization for Human Brain Mapping Annual Meeting", Singapour, Singapore, June 2018, https://hal.inria.fr/hal-01758206

[52] J. WEN, H. ZHANG, D. ALEXANDER, S. DURRLEMAN, A. ROUTIER, D. RINALDI, M. HOUOT, J. ZHANG, O. COLLIOT, I. LE BER, A. BERTRAND. *NODDI Highlights Promising New Markers In Presymptomatic C9orf72 Carriers*, in "OHBM 2018 - Organization for Human Brain Mapping Annual Meeting", Singapour, Singapore, June 2018, https://hal.inria.fr/hal-01758137

## Other Publications

[53] A. BÔNE, M. LOUIS, O. COLLIOT, S. DURRLEMAN. *Learning low-dimensional representations of shape data sets with diffeomorphic autoencoders*, December 2018, working paper or preprint, https://hal.inria.fr/hal-01963736

[54] C. CURY, S. DURRLEMAN, D. M. CASH, M. LORENZI, J. M. NICHOLAS, M. BOCCHETTA, J. C. VAN SWIETEN, B. BORRONI, D. GALIMBERTI, M. MASELLIS, M. C. TARTAGLIA, J. ROWE, C. GRAFF, F. TAGLIAVINI, G. B. FRISONI, R. J. LAFORCE, E. FINGER, A. DE MENDONÇA, S. SORBI, S. OURSELIN, J. D. ROHRER, M. M. MODAT. *Spatiotemporal analysis for detection of pre-symptomatic shape changes in neurodegenerative diseases: applied to GENFI study*, August 2018, working paper or preprint [*DOI :* 10.1101/385427], https://hal.inria.fr/hal-01856906

[55] C. CURY, J. A. GLAUNÈS, R. TORO, M. CHUPIN, G. SCHUMANN, V. FROUIN, J. B. POLINE, O. COLLIOT. *Statistical shape analysis of large datasets based on diffeomorphic iterative centroids*, July 2018, working paper or preprint [*DOI :* 10.1101/363861], https://hal.inria.fr/hal-01832191

[56] I. KOVAL, A. BÔNE, M. LOUIS, S. BOTTANI, A. MARCOUX, J. SAMPER-GONZALEZ, N. BURGOS, B. CHARLIER, A. BERTRAND, S. EPELBAUM, O. COLLIOT, S. ALLASSONNIÈRE, S. DURRLEMAN. *Simulating Alzheimer's disease progression with personalised digital brain models*, 2018, working paper or preprint, https://hal.inria.fr/hal-01964821

[57] M. LOUIS, B. CHARLIER, S. DURRLEMAN. *Learning Riemannian geometry for mixed-effect models using deep generative networks*, July 2018, working paper or preprint, https://hal.inria.fr/hal-01828949

[58] C. OBANDO FORERO, F. DE VICO FALLANI. *Temporal metrics for exponential random graph models of time-evolving networks*, June 2018, NetSci 2018 - International School and Conference in Complex Science, https://hal.inria.fr/hal-01967589