Activity Report 2017

Project-Team ARAMIS

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

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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. Personnel

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    Fabrizio de Vico Fallani [Inria, Researcher, HDR]
    Stanley Durrleman [Inria, Researcher]
    Vincent Henry [Inria, Advanced Research Position, from Dec 2017]

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    Didier Dormont [Sorbonne University, Professor, HDR]
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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 University Pierre and Marie Curie.

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 (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

- Anne Bertrand spent a year half-time within the ARAMIS team, thanks to an Inria-APHP interface contract (i.e., "poste d'accueil"), from november 2016 to november 2017. At the end of this contract, she was appointed as an Assistant Professor of Radiology at Sorbonne University, on september 2017, allowing her to continue working 40% of her time within the ARAMIS team.
- Fabrizio De Vico Fallani was named associate editor of the journal Brain Topography
- Stanley Durrleman was nominated coordinator of the ICM Center of Neuroinformatics, and scientific manager of the ICM iCONICS core-facility on bioinformatics.
- The team has been awarded the projects SEMAPHORE, ATTACK and PredictICD under the "Big Brain Theory" program (ICM)

5.1.1. Awards

- Jeremy Guillon was awarded the best lighting presentation at the international conference on complex networks

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: Anatomy - Mesh - Automatic Learning - C++ - 3D modeling - 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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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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- Participants: Junhao Wen, Jorge Samper Gonzalez, Alexandre Routier, Tristan Moreau, Arnaud Marcoux, Pascal Lu, Thomas Jacquemont, Jeremy Guillon, Olivier Colliot, Stanley Durrleman, Michael Bacci, Simona Bottani, Ninon Burgos, Sabrina Fontanella and Pietro Gori

- 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

- URL: http://www.clinica.run

6.4. Platforms

6.4.1. *Platform Brain-computer interface*

Our team has coordinated the implementation 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 funded project, and demos are currently being run by different researchers of the Institute. Such technological advance contributed to the scientific visibility of Inria and ICM with two TV reports (M6 and France 5).

7. New Results

7.1. Fiberprint: A subject fingerprint based on sparse code pooling for white matter fiber analysis

Participants: Kuldeep Kumar [Correspondant], Christian Desrosiers, Kaleem Siddiqi, Olivier Colliot, Matthew Toews.

White matter characterization studies use the information provided by diffusion magnetic resonance imaging (dMRI) to draw cross-population inferences. However, the structure, function, and white matter geometry vary across individuals. Here, we propose a subject fingerprint, called Fiberprint, to quantify the individual uniqueness in white matter geometry using fiber trajectories. We learn a sparse coding representation for fiber trajectories by mapping them to a common space defined by a dictionary. A subject fingerprint is then generated by applying a pooling function for each bundle, thus providing a vector of bundle-wise features describing a particular subject's white matter geometry. These features encode unique properties of fiber trajectories, such as their density along prominent bundles. An analysis of data from 861 Human Connectome Project subjects reveals that a fingerprint based on approximately 3000 fiber trajectories can uniquely identify exemplars from the same individual. We also use fingerprints for twin/sibling identification, our observations consistent with the twin data studies of white matter integrity. Our results demonstrate that the proposed Fiberprint can effectively capture the variability in white matter fiber geometry across individuals, using a compact feature vector (dimension of 50), making this framework particularly attractive for handling large datasets.

More details in [21].

7.2. Individual analysis of molecular brain imaging data through automatic identification of abnormality patterns

Participants: Ninon Burgos [Correspondant], Jorge Samper-González, Anne Bertrand, Marie-Odile Habert, Sébastien Ourselin, Stanley Durrleman, M. Jorge Cardoso, Olivier Colliot.

We introduce a pipeline for the individual analysis of positron emission tomography (PET) data on large cohorts of patients. This pipeline consists for each individual of generating a subject-specific model of healthy PET appearance and comparing the individual's PET image to the model via a novel regularised Z-score. The resulting voxel-wise Z-score map can be interpreted as a subject-specific abnormality map that summarises the pathology's topographical distribution in the brain. We then propose a strategy to validate the abnormality maps on several PET tracers and automatically detect the underlying pathology by using the abnormality maps as features to feed a linear support vector machine (SVM)-based classifier. We applied the pipeline to a large dataset comprising 298 subjects selected from the ADNI2 database (103 cognitively normal, 105 late MCI and 90 Alzheimer's disease subjects). The high classification accuracy obtained when using the abnormality maps as features demonstrates that the proposed pipeline is able to extract for each individual the signal characteristic of dementia from both FDG and Florbetapir PET data.

More details in [27].

7.3. Multilevel Modeling with Structured Penalties for Classification from Imaging Genetics data

Participants: Pascal Lu [Correspondant], Olivier Colliot.

In this paper, we propose a framework for automatic classification of patients from multimodal genetic and brain imaging data by optimally combining them. Additive models with unadapted penalties (such as the classical group lasso penalty or L_1-multiple kernel learning) treat all modalities in the same manner and can result in undesirable elimination of specific modalities when their contributions are unbalanced. To overcome this limitation, we introduce a multilevel model that combines imaging and genetics and that considers joint effects between these two modalities for diagnosis prediction. Furthermore, we propose a framework allowing to combine several penalties taking into account the structure of the different types of data, such as a group lasso penalty over the genetic modality and a L_2-penalty on imaging modalities. Finally, we propose a fast optimization algorithm, based on a proximal gradient method. The model has been evaluated on genetic (single nucleotide polymorphisms-SNP) and imaging (anatomical MRI measures) data from the ADNI database, and compared to additive models. It exhibits good performances in AD diagnosis; and at the same time, reveals relationships between genes, brain regions and the disease status.

More details in [33].

7.4. Towards Fully-reproducible Research on Classification of Alzheimer's Disease

Participants: Jorge Samper-González [Correspondant], Ninon Burgos, Sabrina Fontanella, Hugo Bertin, Marie-Odile Habert, Stanley Durrleman, Theodoros Evgeniou, Olivier Colliot.

In recent years, the number of papers on Alzheimer's disease classification has increased dramatically, generating interesting methodological ideas on the use machine learning and feature extraction methods. However, practical impact is much more limited and, eventually, one could not tell which of these approaches are the most efficient. While over 90% of these works make use of ADNI an objective comparison between approaches is impossible due to variations in the subjects included, image pre-processing, performance metrics and cross-validation procedures. In this paper, we propose a framework for reproducible classification experiments using multimodal MRI and PET data from ADNI. The core components are: 1) code to automatically convert the full ADNI database into BIDS format; 2) a modular architecture based on Nipype in order to easily plug-in different classification and feature extraction tools; 3) feature extraction pipelines for MRI and PET data; 4) baseline classification approaches for unimodal and multimodal features. This provides a flexible framework for benchmarking different feature extraction and classification tools in a reproducible manner. Data management tools for obtaining the lists of subjects in AD, MCI converter, MCI non-converters, CN classes are also provided. We demonstrate its use on all (1519) baseline T1 MR images and all (1102) baseline FDG PET images from ADNI 1, GO and 2 with SPM-based feature extraction pipelines and three different classification techniques (linear SVM, anatomically regularized SVM and multiple kernel learning SVM). The highest accuracies achieved were: 91% for AD vs CN, 83% for MCIc vs CN, 75% for MCIc vs MCInc, 94% for AD-ABeta+ vs CN-ABeta- and 72% for MCIc-ABeta+ vs MCInc-ABeta+. The code is publicly available at https://gitlab.icm-institute.org/aramislab/AD-ML.

More details in [34].

7.5. Early Cognitive, Structural, and Microstructural Changes in Presymptomatic C9orf72 Carriers Younger Than 40 Years

Participants: Anne Bertrand [Correspondant], Junhao Wen, Sabrina Fontanella, Alexandre Routier, Stanley Durrleman, Olivier Colliot.

Presymptomatic carriers of chromosome 9 open reading frame 72 (C9orf72) mutation, the most frequent genetic cause of frontotemporal lobar degeneration and amyotrophic lateral sclerosis, represent the optimal target population for the development of disease-modifying drugs. Preclinical biomarkers are needed to monitor the effect of therapeutic interventions in this population. The aim of our study was to assess the occurrence of cognitive, structural, and microstructural changes in presymptomatic C9orf72 carriers. The PREV-DEMALS study is a prospective, multicenter, observational study of first-degree relatives of individuals carrying the C9orf72 mutation. Eighty-four participants entered the study between October 2015 and April 2017; 80 (95%) were included in cross-sectional analyses of baseline data. All participants underwent neuropsychological testing and magnetic resonance imaging; 63 (79%) underwent diffusion tensor magnetic resonance imaging. Gray matter volumes and diffusion tensor imaging metrics were calculated within regions of interest. Anatomical and microstructural differences between individuals who carried the C9orf72 mutation (C9+) and those who did not carry the C9orf72 mutation (C9-) were assessed using linear mixed-effects models. Data were analyzed from October 2015 to April 2017.Of the 80 included participants, there were 41 C9+ individuals (24 [59%] female; mean [SD] age, 39.8 [11.1] years) and 39 C9- individuals (24 [62%] female; mean [SD] age,45.2 [13.9] years). Compared with C9- individuals, C9+ individuals had lower mean (SD)praxis scores (163.4 [6.1] vs 165.3 [5.9]; P = .01) and intransitive gesture scores (34.9 [1.6] vs 35.7 [1.5]; P = .004), atrophy in 8 cortical regions of interest and in the right thalamus, and white matter alterations in 8 tracts. When restricting the analyses to participants younger than 40 years, compared with C9- individuals, C9+ individuals had lower praxis scores and intransitive gesture scores, atrophy in 4 cortical regions of interest and in the right thalamus, and white matter alterations in 2 tracts.Our work demontrates that cognitive, structural and microstructural alterations are detectable in young C9+ individuals. Early and subtle praxis alterations, underpinned by focal atrophy of the left supramarginal gyrus, may represent an early and nonevolving phenotype related to neurodevelopmental effects of C9orf72 mutation. White matter alterations reflect the future phenotype of frontotemporal lobar degeneration/amyotrophic lateral sclerosis, while atrophy appears more diffuse. Our results contribute to a better understanding of the preclinical phase of C9orf72

More details in [5].

7.6. Loss of brain inter-frequency hubs in Alzheimer's disease

Participants: Jeremy Guillon, Yohan Attal, Olivier Colliot, Valentina La Corte, Bruno Dubois, Denis Schwartz, Mario Chavez, Fabrizio de Vico Fallani [Correspondant].

Alzheimer's disease (AD) causes alterations of brain network structure and function. The latter consists of connectivity changes between oscillatory processes at different frequency channels. We proposed a multi-layer network approach to analyze multiple-frequency brain networks inferred from magnetoencephalographic recordings during resting-states in AD subjects and age-matched controls. Main results showed that brain networks tend to facilitate information propagation across different frequencies, as measured by the multi-participation coefficient (MPC). However, regional connectivity in AD subjects was abnormally distributed across frequency bands as compared to controls, causing significant decreases of MPC. This effect was mainly localized in association areas and in the cingulate cortex, which acted, in the healthy group, as a true inter-frequency hub. MPC values significantly correlated with memory impairment of AD subjects, as measured by the total recall score. Most predictive regions belonged to components of the default-mode network that are typically affected by atrophy, metabolism disruption and amyloid-β deposition. We evaluated the diagnostic power of the MPC and we showed that it led to increased classification accuracy (78.39%) and sensitivity (91.11%). These findings shed new light on the brain functional alterations underlying AD and provide analytical tools for identifying multi-frequency neural mechanisms of brain diseases.

More details in [17].

7.7. A statistical model for brain networks inferred from large-scale electrophysiological signals

Participants: Catalina Obando, Fabrizio de Vico Fallani [Correspondant].

Network science has been extensively developed to characterize the structural properties of complex systems, including brain networks inferred from neuroimaging data. As a result of the inference process, networks estimated from experimentally obtained biological data represent one instance of a larger number of realizations with similar intrinsic topology. A modelling approach is therefore needed to support statistical inference on the bottom-up local connectivity mechanisms influencing the formation of the estimated brain networks. Here, we adopted a statistical model based on exponential random graph models (ERGMs) to reproduce brain networks, or connectomes, estimated by spectral coherence between high-density electroencephalographic (EEG) signals. ERGMs are made up by different local graph metrics, whereas the parameters weight the respective contribution in explaining the observed network. We validated this approach in a dataset of N ¼ 108 healthy subjects during eyes-open (EO) and eyes closed (EC) resting-state conditions. Results showed that the tendency to form triangles and stars, reflecting clustering and node centrality, better explained the global properties of the EEG connectomes than other combinations of graph metrics. In particular, the synthetic networks generated by this model configuration replicated the characteristic differences found in real brain networks, with EO eliciting significantly higher segregation in the alpha frequency band (8–13 Hz) than EC. Furthermore, the fitted ERGM parameter values provided complementary information showing that clustering connections are significantly more represented from EC to EO in the alpha range, but also in the beta band (14–29 Hz), which is known to play a crucial role in cortical processing of visual input and externally oriented attention. Taken together, these findings support the current view of the functional segregation and integration of the brain in terms of modules and hubs, and provide a statistical approach to extract new information on the (re)organizational mechanisms in healthy and diseased brains. More details in [23].

7.8. A Topological Criterion for Filtering Information in Complex Brain Networks

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

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

More details in [11].

7.9. Preclinical Alzheimer's disease: a systematic review of the cohorts underlying the concept

Participants: Stéphane Epelbaum [Correspondant], Remy Genthon, Enrica Cavedo, Marie Odile Habert, Foudil Lamari, Geoffroy Gagliardi, Simone Lista, Marc Teichmann, Hovagim Bakardjian, Harald Hampel, Bruno Dubois.

Preclinical Alzheimer's disease (AD) is a relatively recent concept describing an entity characterized by the presence of a pathophysiological biomarker signature characteristic for AD in the absence of specific clinical symptoms. There is rising interest in the scientific community to define such an early target population mainly due to failures of all recent clinical trials despite evidence of biological effects on brain amyloidosis for some compounds. A conceptual framework has recently been proposed for this preclinical phase of AD. However, few data exist on this silent stage of AD. We performed a systematic review in order to investigate how the concept is defined across studies. The review highlights the substantial heterogeneity concerning the three main determinants of preclinical AD: "normal cognition", "cognitive decline" and "AD pathophysiological signature". We emphasize the need for a harmonized nomenclature of the preclinical AD concept and standardized population-based and case-control studies using unified operationalized criteria.

More details in [12].

7.10. Free and Cued Selective Reminding Test - accuracy for the differential diagnosis of Alzheimer's and neurodegenerative diseases: A large-scale biomarker-characterized monocenter cohort study (ClinAD)

Participants: Marc Teichmann [Correspondant], Stéphane Epelbaum, Dalila Samri, Marcel Levy Nogueira, Agnes Michon, Harald Hampel, Foudil Lamari, Bruno Dubois.

The International Working Group recommended the Free and Cued Selective Reminding Test (FCSRT) as a sensitive detector of the amnesic syndrome of the hippocampal type in typical Alzheimer's disease (AD). But does it differentiate AD from other neurodegenerative diseases? We assessed the FCSRT and cerebrospinal fluid (CSF) AD biomarkers in 992 cases. Experts, blinded to biomarker data, attributed in 650 cases a diagnosis of typical AD, frontotemporal dementia, posterior cortical atrophy, Lewy body disease, progressive supranuclear palsy, corticobasal syndrome, primary progressive aphasias, "subjective cognitive decline," or depression. The FCSRT distinguished typical AD from all other conditions with a sensitivity of 100% and a specificity of 75%. Non-AD neurodegenerative diseases with positive AD CSF biomarkers ("atypical AD") did not have lower FCSRT scores than those with negative biomarkers. The FCSRT is a reliable tool for diagnosing

typical AD among various neurodegenerative diseases. At an individual level, however, its specificity is not absolute. Our findings also widen the spectrum of atypical AD to multiple neurodegenerative conditions.

More details in [13].

7.11. Parallel transport in shape analysis : a scalable numerical scheme

Participants: Maxime Louis, Alexandre Bône, Benjamin Charlier, Stanley Durrleman.

The analysis of manifold-valued data requires efficient tools from Riemannian geometry to cope with the computational complexity at stake. This complexity arises from the always-increasing dimension of the data, and the absence of closed-form expressions to basic operations such as the Riemannian logarithm. In this work, we adapted a generic numerical scheme recently introduced for computing parallel transport along geodesics in a Riemannian manifold to finite-dimensional manifolds of diffeomorphisms. We provided a qualitative and quantitative analysis of its behavior on high-dimensional manifolds, and investigated an application with the prediction of brain structures progression.

More details in [32].

7.12. Statistical learning of spatiotemporal patterns from longitudinal manifold-valued networks

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

We introduced a mixed-effects model to learn spatiotemporal patterns on a network by considering longitudinal measures distributed on a fixed graph. The data come from repeated observations of subjects at different time points which take the form of measurement maps distributed on a graph such as an image or a mesh. The model learns a typical group-average trajectory characterizing the propagation of measurement changes across the graph nodes. The subject-specific trajectories are defined via spatial and temporal transformations of the group-average scenario, thus estimating the variability of spatiotemporal patterns within the group. To estimate population and individual model parameters, we adapted a stochastic version of the Expectation-Maximization algorithm, the MCMC-SAEM. The model was used to describe the propagation of cortical atrophy during the course of Alzheimer's Disease. Model parameters show the variability of this average pattern of atrophy in terms of trajectories across brain regions, age at disease onset and pace of propagation. We showed that the personalization of this model yields accurate prediction of maps of cortical thickness in patients.

More details in [29]

7.13. Prediction of the progression of subcortical brain structures in Alzheimer's disease from baseline

Participants: Alexandre Bône, Maxime Louis, Alexandre Routier, Jorge Samper, Michael Bacci, Benjamin Charlier, Olivier Colliot, Stanley Durrleman.

We proposed a method to predict the subject-specific longitudinal progression of brain structures extracted from baseline MRI, and evaluated its performance on Alzheimer's disease data. The disease progression is modeled as a trajectory on a group of diffeomorphisms in the context of large deformation diffeomorphic metric mapping (LDDMM). We first exhibited the limited predictive abilities of geodesic regression extrapolation on this group. Building on the recent concept of parallel curves in shape manifolds, we then introduced a second predictive protocol which personalizes previously learned trajectories to new subjects, and investigate the relative performances of two parallel shifting paradigms. This design only requires the baseline imaging data. Finally, coefficients encoding the disease dynamics are obtained from longitudinal cognitive measurements for each subject, and exploited to refine our methodology which was demonstrated to successfully predict the follow-up visits.

More details in [28]

7.14. Prediction of amyloidosis from neuropsychological and MRI data for cost effective inclusion of pre-symptomatic subjects in clinical trials

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

We proposed a method for selecting pre-symptomatic subjects likely to have amyloid plaques in the brain, based on the automatic analysis of neuropsychological and MRI data and using a cross-validated binary classifier. By avoiding systematic PET scan for selecting subjects, it reduces the cost of forming cohorts of subjects with amyloid plaques for clinical trials, by scanning fewer subjects but increasing the number of recruitments. We validated our method on three cohorts of subjects at different disease stages, and compared the performance of six classifiers, showing that the random forest yields good results more consistently, and that the method generalizes well when tested on an unseen data set.

More details in [25]

7.15. Geodesic shape regression with multiple geometries and sparse parameters

Participants: James Fishbaugh, Stanley Durrleman, Marcel Prastawa, Guido Gerig.

Many problems in medicine are inherently dynamic processes which include the aspect of change over time, such as childhood development, aging, and disease progression. From medical images, numerous geometric structures can be extracted with various representations, such as landmarks, point clouds, curves, and surfaces. Different sources of geometry may characterize different aspects of the anatomy, such as fiber tracts from DTI and subcortical shapes from structural MRI, and therefore require a modeling scheme which can include various shape representations in any combination. In this paper, we present a geodesic regression model in the large deformation (LDDMM) framework applicable to multi-object complexes in a variety of shape representations. Our model decouples the deformation parameters from the specific shape representations, allowing the complexity of the model to reflect the nature of the shape changes, rather than the sampling of the data. As a consequence, the sparse representation of diffeomorphic flow allows for the straightforward embedding of a variety of geometry in different combinations, which all contribute towards the estimation of a single deformation of the ambient space. Additionally, the sparse representation along with the geodesic constraint results in a compact statistical model of shape change by a small number of parameters defined by the user. Experimental validation on multi-object complexes demonstrate robust model estimation across a variety of parameter settings. We further demonstrate the utility of our method to support the analysis of derived shape features, such as volume, and explore shape model extrapolation. Our method is freely available in the software package deformetrica which can be downloaded at www.deformetrica.org.

More details in [14]

7.16. A sub-Riemannian modular framework for diffeomorphism based analysis of shape ensembles

Participants: Barara Gris, Stanley Durrleman, Alain Trouvé.

Deformations, and diffeormophisms in particular, have played a tremendous role in the field of statistical shape analysis, as a proxy to measure and interpret differences between similar objects but with different shapes. Diffeomorphisms usually result from the integration of a flow of regular velocity fields, whose parameters have not enabled so far a full control of the local behaviour of the deformation. In this work, we propose a new mathematical and computational framework, in which diffeomorphisms are built on the combination of local deformation modules with few degrees of freedom. Deformation modules contribute to a global velocity field, and interact with it during integration so that the local modules are transported by the global diffeomorphic deformation under construction. Such modular diffeomorphisms are used to deform shapes and to provide the shape space with a sub-Riemannian metric. We then derive a method to estimate a Fréchet mean from a

series of observations, and to decompose the variations in shape observed in the training samples into a set of elementary deformation modules encoding distinctive and interpretable aspects of the shape variability. We show how this approach brings new solutions to long lasting problems in the fields of computer vision and medical image analysis. For instance, the easy implementation of priors in the type of deformations offers a direct control to favor one solution over another in situations where multiple solutions may fit the observations equally well. It allows also the joint optimisation of a linear and a non-linear deformation between shapes, the linear transform simply being a particular type of modules. The proposed approach generalizes previous methods for constructing diffeomorphisms and opens up new perspectives in the field of statistical shape analysis.

More details in [16]

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

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

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

More details in [15]

7.18. A Bayesian mixed-effects model to learn trajectories of changes from repeated manifold-valued observations

Participants: Jean-Baptiste Schiratti, Stéphanie Allassonnière, Olivier Colliot, Stanley Durrleman.

We propose a generic Bayesian mixed-effects model to estimate the temporal progression of a biological phenomenon from observations obtained at multiple time points for a group of individuals. The progression is modeled by continuous trajectories in the space of measurements. Individual trajectories of progression result from spatiotemporal transformations of an average trajectory. These transformations allow to quantify the changes in direction and pace at which the trajectories are followed. The framework of Rieman-nian geometry allows the model to be used with any kind of measurements with smooth constraints. A stochastic version of the Expectation-Maximization algorithm is used to produce produce maximum a posteriori estimates of the parameters. We evaluate our method using series of neuropsychological test scores from patients with mild cognitive impairments later diagnosed with Alzheimer's disease, and simulated evolutions of symmetric positive definite matrices. The data-driven model of the impairment of cognitive functions shows the variability in the ordering and timing of the decline of these functions in the population. We show also that the estimated spatiotemporal transformations effectively put into correspondence significant events in the progression of individuals.

More details in [40]

8. Bilateral Contracts and Grants with Industry

8.1. Bilateral Contracts with Industry

8.1.1. *Air-Liquide Medical Systems*
Participants: Mario Chavez [Correspondant], Xavier Navarro.

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

Funded in 2014

Amount: 370 K€

Coordinator: Thomas Similowski

Other partners: UPMC, Inserm UMR 1158

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

8.2. Bilateral Grants with Industry

8.2.1. *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

Funded 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 (μ- probe), minimally invasive, exhibiting very high signal sensitivity, and sharp spectral peaks, from sub-millimetric VOI. Such a probe will allow detecting a much higher number of metabolites than conventional in-vivo SVS. The μ-probe will work at frequencies ranging from 300MHz to 500MHz in ultra-high field Magnetic Resonance Imaging scanners, 7T and 11.7T. It will embed a specific micro-coil antenna, a low-noise signal conditioning circuit designed in CMOS microelectronics technology, as well as an accurate on-chip positioning sensor. It will be dedicated to the study of changes in brain metabolite markers of two major diseases, Alzheimer's disease and cerebral gliomas, and to the assessment of effective therapeutic strategies.

9.1.2. 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

Amount: 633k€

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

Project acronym: IHU-A-ICM

Project title: Institute of Translational Neuroscience

Founded in 2011

General Director: Bertrand Fontaine

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

9.1.3.2. ICM-Internal Research projects

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

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

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 [Correspondant], Fabrizio de Vico Fallani [Correspondant].

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

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 Big Brain Theory Program

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

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

Founded in 2016-2017

Coordinator: Stanley Durrleman and Harald Hampel

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

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

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

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

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

9.1.3.5. IFR49-Internal Research projects
Participants: Mario Chavez [Correspondant], Fabrizio de Vico Fallani [Correspondant].

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

Founded in 2014

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

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

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

9.1.4. 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/

9.1.5. Other National Programs

9.1.5.1. Programme Hospitalier de Recherche Clinique (PHRC)
Participants: Olivier Colliot, Marie Chupin, Stanley Durrleman, Didier Dormont, Damien Galanaud.

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

9.1.5.2. Institut Universitaire d'Ingénierie pour la Santé (IUIS)
Participants: Mario Chavez, Xavier Navarro.

> Project acronym: DYSPEV
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> Project title: Dépistage de la dyspnée par potentiels évoqués visuels
>
> Funded in 2014
>
> Amount: 38K€
>
> Coordinator: Thomas Similowski
>
> Other partners: UPMC, Inserm UMR 1158
>
> Abstract: Steady state visual evoked potentials (SSVEP) have been widely utilized in brain computer interfacing (BCI) in last years. In this project, we explore the possibilities of SSVEP to manage the communication between patients suffering from respiratory disorders and health care providers. By imposing different breathing constraints, we use a SSVEP-based brain computer interface to help those subjects to communicate their breathing sensations (breathing well/breathing bad).

9.2. European Initiatives

9.2.1. FP7 & H2020 Projects

9.2.1.1. H2020 - Project EuroPOND
Participants: Olivier Colliot, Stanley Durrleman, Manon Ansart, Igor Koval, Alexandre Bône.

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

9.2.1.2. FET Flagship - Human Brain Project
Participants: Olivier Colliot, Stanley Durrleman.

Project acronym: HBP

Project title: Human Brain Project

Sub-project: SP8 - Medical Informatics Platform

Duration (for this phase): 2016-2018

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

9.2.1.3. ERC - LEASP
Participants: Stanley Durrleman, Raphael Couronné.

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. Inria International Partners

9.3.1.1. Informal International Partners

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

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

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

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

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

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

S. Durrleman has a collaboration with the department of Computer Science at New York University (NYU) (G. Gerig and J. Fishbaugh)

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

9.4. International Research Visitors

9.4.1. Visits of International Scientists

- Professor Tom Fletcher from the University of Utah visited ARAMIS from January 23 to January 27.

9.4.1.1. Internships

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

9.4.2. Visits to International Teams

9.4.2.1. Research Stays Abroad

Junhao Wen, PhD candidate, did a 3-month internship in the team of Hui Zhang, UCL, to develop pipelines of analysis for advanced diffusion MRI acquisitions (Neurite Orientation Dispersion and Density Imaging). This internship was funded by the ICM Carnot Program.

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific Events Organisation

10.1.1.1. General Chair, Scientific Chair

- S. Durrleman was co-chair of the 6th international workshop on the Mathematical Foundations of Computational Anatomy (MFCA) in Quebec City on September 14.

10.1.1.2. Member of the Organizing Committees

Fabrizio De Vico Fallani is member of the scientific board for the ICM conferences

10.1.2. Scientific Events Selection

10.1.2.1. Member of the Conference Program Committees

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

O. Colliot was a member of the program committee of SPIE Medical Imaging conference.

F. De Vico Fallani was member of the program committee of the Satellite on Brain networks, International Conference on Network Science (NetSci), Indianapolis, US, 2017

F. De Vico Fallani was member of the program committee of 5th International Workshop on Complex Networks and their Applications, Lyon, France, 2017

S. Epelbaum was a member of the French medical board on the management of Early phase Alzheimer's Disease, Issy les moulineaux, France, 2017

10.1.2.2. Reviewer

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

10.1.3. Journal

10.1.3.1. Member of the Editorial Boards

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

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

10.1.3.2. Reviewer - Reviewing Activities

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

S. Epelbaum acted as a reviewer for Alzheimer's & Dementia and the Journal of Alzheimer's disease.

A. Bertrand acted as a reviewer for European Radiology, Journal of Magnetic Resonance Imaging, Journal of Neuroradiology.

F. De Vico Fallani acted as a reviewer for Cerebral Cortex, Brain Topography, IEEE TBME/TNRSE, Neuroimage, Sci Rep, Brain Connectivity, PLOS ONE

10.1.4. Invited Talks

A. Bertrand gave an invited lecture at the French-Quebecois Colloquium of the National Academy of Medicine "Towards news preventive and therapeutic strategies for neurodegenerative diseases: the role of imaging" in Québec City, Québec, september 2017.

F. De Vico Fallani gave an invited lecture at the international workshop on complex networks in Lipari, Italy, september 2017.

F. De Vico Fallani gave an invited lecture at the Neuroscience School of Advanced Studies in Siena, Italy, April 2017.

O. Colliot gave an invited lecture at the ICM/Supelec Workshop 2017.

S. Durrleman gave an invited lecture at the BIOVISION congress in Lyon.

S. Durrleman gave an invited lecture at the conference "Topological and Geometrical Science of Information" at Centre International de Rencontre Mathématiques, Luminy

S. Durrleman gave an invited lecture for the "diplôme inter-universitaire: diagnostic et prise en charge de la Maladie d'Alzheimer et apparentée", Lille

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

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

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

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

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

Master: S. Durrleman, Master 2 "Mathematics, Vision and Learning", 31,5 jours (eqTD), ENS Paris-Saclay

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

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

Medical school: 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 neurode-generative 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 ex-ploitation 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 longi-tudinal 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

10.2.3. Juries

Olivier Colliot participated, as referee, to the PhD committee of Elaheh Moradi (TU Finland) (supervisor: J. Tohka).

Olivier Colliot participated, as examiner, to the HdR committee of Roberto Toro (Institut Pasteur).

Anne Bertrand participated, as examiner, to the PhD committee of Clémence Dudeffant (Université Paris Sud), 2017 (supervisor: Marc Dhenain).

S. Durrleman participated, as examiner, to the PhD committees of Jean Dumoncel (Université Paul Sabatier, Toulouse) and Pierre Roussillon (Université Paris Descartes).

10.3. Popularization

With the precious help of the communication department of the ICM, ARAMIS prepared and presented games on brain data analysis at the "Fête de la Science" 2017.

Fabrizio De Vico Fallani was invited speaker at the Neuroplanete conference held in Nice 2017. In that occasion, a live BCI experiment has been presented to the public. This event has been reported by France 3.

Fabrizio De Vico Fallani was invited speaker at the Palais Decouverte in Paris for the theme "Vers le meilleur des mondes" 2017.

Olivier Colliot was invited speaker at the Palais Decouverte in Paris for the theme "Vers le meilleur des mondes" 2017.

Stanley Durrleman and Stéphane Epelbaum were invited speakers at the "Open Brain Bar: Artificial intelligence and Alzheimer's disease" event orginized by the ICM in Paris 2017.

Olivier Colliot was invited speaker for the "Olympiades académiques de mathématiques", Paris, 2017.

S. Durrleman gave a presentation for the 50th anniversary of Inria featuring 50 ERC laureates

S. Durrleman gave two interviews for the magazine Sciences et Avenir (1 video interview, one article)

S. Durrleman and S. Epelbaum took part in the program "Priorité Santé" of the radio Radio France International

S. Durrleman gave a video interview for FrenchWeb.fr

S. Durrleman gave an talk at the event S3 Odéon (www.s3odeon.fr)

ARAMIS was featured in a video of the Agence France Presse (AFP)

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