

RESEARCH CENTRE

**Inria Paris Center
at Sorbonne University**

IN PARTNERSHIP WITH:

CNRS, INSERM, Sorbonne Université

2022

ACTIVITY REPORT

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

DOMAIN

Digital Health, Biology and Earth

THEME

**Computational Neuroscience and
Medicine**

Inria

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Project-Team ARAMIS

Creation of the Project-Team: 2014 July 01

Keywords

Computer sciences and digital sciences

- A3.4. – Machine learning and statistics
- A3.4.1. – Supervised learning
- A3.4.2. – Unsupervised learning
- A3.4.4. – Optimization and learning
- A3.4.6. – Neural networks
- A3.4.8. – Deep learning
- A5.3. – Image processing and analysis
- A5.4. – Computer vision
- A5.9. – Signal processing
- A9. – Artificial intelligence
- A9.2. – Machine learning
- A9.3. – Signal analysis
- A9.6. – Decision support

Other research topics and application domains

- B2. – Health
- B2.2.6. – Neurodegenerative diseases
- B2.6. – Biological and medical imaging
- B2.6.1. – Brain imaging

1 Team members, visitors, external collaborators

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- Ninon Burgos [CNRS, Researcher, HDR]
- Marie-Constance Corsi [INRIA, Researcher, from Oct 2022]
- Baptiste Couvy-Duchesne [INRIA, Researcher]
- Stanley Durreleman [INRIA, Senior Researcher, HDR]
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- Helene Bessin Rousseau [INRIA]
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Visiting Scientist

- Camile Bousfiha [ICM, from Mar 2022 until Aug 2022]

2 Overall objectives

2.1 Context

ARAMIS is an Inria project-team within the Paris Brain Institute (ICM) at the Pitié-Salpêtrière hospital (AP-HP) 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 **Paris Brain 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 Sorbonne University). It hosts about 25 research teams as well as various high level technical facilities (neuroimaging, genotyping/sequencing, cell culture, cellular imaging, bioinformatics . . .), and gathers over 700 personnel. In addition, the ICM hosts one of the six IHU (*Instituts Hospitalo-Universitaires*).

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: 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.

We develop various clinical applications of our research, in particular in neurodegenerative disorders (Alzheimer's disease and other dementias, Parkinson's disease . . .), multiple sclerosis, developmental disorders, stroke and to design brain-computer interfaces for rehabilitation.

3 Research program

3.1 Neuroimaging-based biomarkers and decision support systems

Neuroimaging provides critical information on anatomical and functional alterations as well as on specific molecular and cellular processes. Our work is focused on the development of computational approaches to extract biomarkers and build computer-aided diagnosis (CAD) systems from MRI and PET data. More specifically, we developed: i) image translation models that can generate biomarkers of specific pathological processes from unspecific routine imaging data; ii) approaches for detecting local abnormalities; iii) frameworks for reproducible and reliable evaluation of CAD systems; iv) methods for training and validating from large-scale hospital data warehouses.

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 mathematical frameworks to analyze and model brain networks, or graphs, estimated from experimental data via network-science approaches. More specifically, we proposed analytical tools to infer brain networks, characterize their structure and dynamics, over multiple spatial and temporal scales.

3.3 Disease progression modeling with longitudinal data

Longitudinal data sets contain observations of multiple subjects observed at multiple time-points. They offer a unique opportunity to understand temporal processes such as ageing or disease progression. We aim here to develop a new generation of statistical methods to infer the dynamics of changes of a series of data such as biomarkers, images or clinical endpoints, together with the variability of such multivariate trajectories within a population of reference. We apply these new models across an array of neurodegenerative diseases to i) understand the heterogeneity in disease progression, in particular how genetic factors may control variations in disease progression, ii) forecast the progression of a new patient at entry of a clinical trial for stratification purposes and iii) the design of new clinical scales for use as outcomes in trials.

3.4 High-dimensional and multimodal data

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. Our aim is to better understand brain disorders by characterizing alterations and their progression, and to validate new tools to assist clinical decisions. While a large part of these clinical studies were in the field of dementia (Alzheimer's disease, fronto-temporal dementia), we have developed successful collaborations in other fields including multiple sclerosis, Parkinson's disease and related disorders, Huntington's disease or spino-cerebellar ataxia.

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 neurodegenerative 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. We design new approaches for extracting biomarkers from different types of data. Our tools have the potential to help clinicians in their diagnosis 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

- Lydia Chougar obtained a Poste d'accueil Inria/AP-HP for the second year.
- Marie-Constance Corsi was granted an Inria Faculty Position as Research Scientist (CRCN).
- Olivier Colliot is Conference Chair of the [SPIE Medical Imaging: Image Processing conference](#) for the period 2022-2025.
- Ninon Burgos successfully defended her "Habilitation à Diriger des Recherches" from Sorbonne Université.
- Ninon Burgos edited a book with David Svoboda entitled "Biomedical Image Synthesis and Simulation: Methods and Applications", belonging to the MICCAI Book Series ([ISBN 978-0-12-824349-7](#)).
- Daniel Racoceanu et al. published the first results of the automatic segmentation of neuritic plaques in whole slide images from human brain, in MICCAI 2022.
- S. Durreleman co-founded the spin-off company Qairnel with a former postdoc of the team Igor Koval.

5.1 Awards

-

6 New software and platforms

6.1 New software

6.1.1 Clinica

Name: 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 anatomical MRI, diffusion MRI, PET. 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.

Functional 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 anatomical MRI, diffusion MRI, PET. 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. Clinica also provides an integrated data management specification to store raw and processing data. Overall, Clinica helps to: i) apply advanced analysis tools to clinical research studies, ii) easily share data and results, iii) make research more reproducible.

URL: <http://www.clinica.run>

Publications: [hal-02308126](#), [hal-02562504](#), [hal-01518785](#), [hal-01578479](#), [hal-01858384](#), [hal-01907482](#), [hal-01654000](#), [hal-02566361](#), [hal-01950933](#)

Contact: Olivier Colliot

Participants: Olivier Colliot, Ninon Burgos, Stanley Durreleman, Nicolas Gensollen, Mauricio Diaz, Ghislain Vaillant, Matthieu Joulot, Ravi Hassanaly, Michael Bacci, Simona Bottani, Sabrina Fontanella, Pietro Gori, Jeremy Guillon, Thomas Jacquemont, Pascal Lu, Arnaud Marcoux, Tristan Moreau, Alexandre Routier, Omar El Rifai, Jorge Samper Gonzalez, Elina Thibeau-Sutre, Junhao Wen

Partners: Institut du Cerveau et de la Moelle épinière (ICM), CNRS, INSERM, Sorbonne Université

6.1.2 ClinicaDL

Keywords: Deep learning, Neuroimaging, Reproducibility

Scientific Description: As deep learning faces a reproducibility crisis and studies on deep learning applied to neuroimaging are contaminated by methodological flaws, there is an urgent need to provide a safe environment for deep learning users to help them avoid common pitfalls that will bias and discredit their results. Several tools have been proposed to help deep learning users design their framework for neuroimaging data sets. ClinicaDL has been developed to bring answers to three common issues encountered by deep learning users who are not always familiar with neuroimaging data: (1) the format and preprocessing of neuroimaging data sets, (2) the contamination

of the evaluation procedure by data leakage and (3) a lack of reproducibility. The combination of ClinicaDL and its companion project Clinica allows performing an end-to-end neuroimaging analysis, from the download of raw data sets to the interpretation of trained networks, including neuroimaging preprocessing, quality check, label definition, architecture search, and network training and evaluation.

Functional Description: ClinicaDL is a Python open-source software for neuroimaging data processing with deep learning. This software includes many functionalities, such as neuroimaging preprocessing, synthetic dataset generation, label definition, data split with similar demographics, architecture search, network training, performance evaluation and trained network interpretation. The three main objectives of ClinicaDL are to (1) help manipulate neuroimaging data sets, (2) prevent data leakage from biasing results and (3) reproduce deep learning experiments.

URL: <https://clinicadl.readthedocs.io>

Publications: [hal-03351976](#), [hal-02562504](#)

Contact: Ninon Burgos

Participants: Ninon Burgos, Olivier Colliot, Mauricio Diaz, Elina Thibeau-Sutre, Ravi Hassanaly, Camille Briancaeu, Alexandre Routier

Partners: Institut du Cerveau et de la Moelle épinière (ICM), CNRS, INSERM, Sorbonne Université

6.1.3 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!

Functional 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 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!

URL: <http://www.deformetrica.org/>

Contact: Stanley Durrleman

Participants: Alexandre Routier, Ana Fouquier, Barbara Gris, Benjamin Charlier, Cedric Doucet, Joan Alexis Glaunès, Marcel Prastawa, Michael Bacci, Pietro Gori, Stanley Durrleman

Partners: University of Utah, Université de Montpellier 2, Université Paris-Descartes

6.1.4 leaspy

Name: Learning spatiotemporal patterns in python

Keywords: Clinical analysis, Medical applications, Personalized medicine

Functional Description: Leaspy, standing for LEARNING Spatiotemporal Patterns in Python, has been developed to analyze longitudinal (or sequential) data that correspond to the measurements of a long-term progression. Said differently, each sequence of repeated observations derives from a portion of the global process, with a certain variability between sequence.

Contact: Stanley Durrleman

6.1.5 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.

URL: <https://github.com/brain-network/bnt>

Contact: Fabrizio de Vico Fallani

Participants: Fabrizio de Vico Fallani, Jeremy Guillon, Mario Chavez

6.1.6 OpenViBE

Keywords: Neurosciences, Interaction, Virtual reality, Health, Real time, Neurofeedback, Brain-Computer Interface, EEG, 3D interaction

Functional Description: OpenViBE is a free and open-source software platform devoted to the design, test and use of Brain-Computer Interfaces (BCI). The platform consists of a set of software modules that can be integrated easily and efficiently to design BCI applications. The key features of OpenViBE software are its modularity, its high performance, its portability, its multiple-user facilities and its connection with high-end/VR displays. The designer of the platform enables users to build complete scenarios based on existing software modules using a dedicated graphical language and a simple Graphical User Interface (GUI). This software is available on the Inria Forge under the terms of the AGPL licence, and it was officially released in June 2009. Since then, the OpenViBE software has already been downloaded more than 60000 times, and it is used by numerous laboratories, projects, or individuals worldwide. More information, downloads, tutorials, videos, documentations are available on the OpenViBE website.

Release Contributions: Added: - Metabox to perform log of signal power - Artifacts files for algorithm tests

Changed: - Refactoring of CMake build process - Update wildcards in gitignore - Update CSV File Writer/Reader - Stimulations only

Removed: - Ogre games and dependencies - Mensia distribution

Fixed: - Intermittent compiler bug

News of the Year: Python2 support dropped in favour of Python3 New feature boxes: - Riemannian geometry - Multimodal Graz visualisation - Artefact detection - Features selection - Stimulation validator

Support for Ubuntu 18.04 Support for Fedora 31

URL: <http://openvibe.inria.fr>

Contact: Anatole Lecuyer

Participants: Cedric Riou, Thierry Gaugry, Anatole Lecuyer, Fabien Lotte, Jussi Lindgren, Laurent Bougrain, Maureen Clerc Gallagher, Théodore Papadopoulo, Thomas Prampart

Partners: INSERM, GIPSA-Lab

6.1.7 brainMapR

Keywords: 3D rendering, Brain MRI, Clustering

Functional Description: brainMapR is an R package to analyse and plot brain association maps (results of brain-wide association studies). It is tailored for brain MRI vertex-wise analyses, and requires brain MRI to be processed with FreeSurfer (for cortical vertices) and/or ENIGMA-shape package (for subcortical vertices). Functions include annotation of the association maps to describe and locate associated brain regions, Manhattan plots for brain, high quality plots of cortical and subcortical meshes, and GIFs generation.

Publication: [hal-03118366](https://hal.archives-ouvertes.fr/hal-03118366)

Author: Baptiste Couvy-Duchesne

Contact: Baptiste Couvy-Duchesne

6.2 New platforms

Platform Brain-computer interface

Participants: Marie-Constance Corsi, Arthur Desbois, Fabrizio De Vico Fallani (*Correspondant*).

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 NNIH/ANR and ATTACK Big-brain theory funded projects, as well as experiments by different researchers of the Institute (ANR BETAPARK Project), and the BCINET ERC Consolidator grant are currently being run. To reinforce the impact of the platform we have extended the contract of our Inria ADT engineer, who is significantly contributing to the extension of the Inria software OpenVibe allowing for new functionalities based on our methodological development on brain connectivity and develop new software for the individual calibration (A. Desbois)

7 New results

7.1 Machine learning-based prediction of impulse control disorders in Parkinson's disease from clinical and genetic data

Participants: Johann Faouzi, Jean-Christophe Corvol, Olivier Colliot (*Correspondant*).

Impulse control disorders (ICDs) are frequent non-motor symptoms occurring during the course of Parkinson's disease (PD). The objective of this study was to estimate the predictability of the future occurrence of these disorders using longitudinal data, the first study using cross-validation and replication in an independent cohort. We used data from two longitudinal PD cohorts (training set: PPMI, Parkinson's Progression Markers Initiative; test set: DIGPD, Drug Interaction With Genes in Parkinson's Disease).

We included 380 PD subjects from PPMI and 388 PD subjects from DIGPD, with at least two visits and with clinical and genetic data available, in our analyses. We trained three logistic regressions and a recurrent neural network to predict ICDs at the next visit using clinical risk factors and genetic variants previously associated with ICDs. We quantified performance using the area under the receiver operating characteristic curve (ROC AUC) and average precision. We compared these models to a trivial model predicting ICDs at the next visit with the status at the most recent visit. The recurrent neural network (PPMI: 0.85 [0.80 – 0.90], DIGPD: 0.802 [0.78 – 0.83]) was the only model to be significantly better than the trivial model (PPMI: ROC AUC = 0.75 [0.69 – 0.81]; DIGPD: 0.78 [0.75 – 0.80]) on both cohorts. We showed that ICDs in PD can be predicted with better accuracy with a recurrent neural network model than a trivial model. The improvement in terms of ROC AUC was higher on PPMI than on DIGPD data, but not clinically relevant in both cohorts. Our results indicate that machine learning methods are potentially useful for predicting ICDs, but further works are required to reach clinical relevance.

More details in [48].

7.2 Axial multi-layer perceptron architecture for automatic segmentation of choroid plexus in multiple sclerosis

Participants: Marius Schmidt-Mengin, Bruno Stankoff, Olivier Colliot (*Correspondant*).

Choroid plexuses (CP) are structures of the ventricles of the brain which produce most of the cerebrospinal fluid (CSF). Several postmortem and in vivo studies have pointed towards their role in the inflammatory process in multiple sclerosis (MS). Automatic segmentation of CP from MRI thus has high value for studying their characteristics in large cohorts of patients. To the best of our knowledge, the only freely available tool for CP segmentation is FreeSurfer but its accuracy for this specific structure is poor. In this paper, we propose to automatically segment CP from non-contrast enhanced T1-weighted MRI. To that end, we introduce a new model called "Axial-MLP" based on an assembly of Axial multi-layer perceptrons (MLPs). This is inspired by recent works which showed that the self-attention layers of Transformers can be replaced with MLPs. This approach is systematically compared with a standard 3D U-Net, nnU-Net, FreeSurfer and FastSurfer. For our experiments, we make use of a dataset of 141 subjects (44 controls and 97 patients with MS). We show that all the tested deep learning (DL) methods outperform FreeSurfer (Dice around 0.7 for DL vs 0.33 for FreeSurfer). Axial-MLP is competitive with U-Nets even though it is slightly less accurate. The conclusions of our paper are two-fold: 1) the studied deep learning methods could be useful tools to study CP in large cohorts of MS patients; 2) Axial-MLP is a potentially viable alternative to convolutional neural networks for such tasks, although it could benefit from further improvements.

More details in [90].

7.3 Disease progression score estimation from multimodal imaging and microRNA data using supervised variational autoencoders

Participants: Virgilio Kmetzsch, Emmanuelle Becker, Isabelle Le Ber, Olivier Colliot (*Correspondant*).

Frontotemporal dementia and amyotrophic lateral sclerosis are rare neurodegenerative diseases with no effective treatment. The development of biomarkers allowing an accurate assessment of disease progression is crucial for evaluating new therapies. Concretely, neuroimaging and transcriptomic (microRNA) data have been shown useful in tracking their progression. However, no single biomarker can accurately measure progression in these complex diseases. Additionally, large samples are not available for such rare disorders. It is thus essential to develop methods that can model disease progression by combining multiple biomarkers from small samples. In this paper, we propose a new framework for computing a disease progression score (DPS) from cross-sectional multimodal data. Specifically, we

introduce a supervised multimodal variational autoencoder that can infer a meaningful latent space, where latent representations are placed along a disease trajectory. A score is computed by orthogonal projections onto this path. We evaluate our framework with multiple synthetic datasets and with a real dataset containing 14 patients, 40 presymptomatic genetic mutation carriers and 37 controls from the PREV-DEMALS study. There is no ground truth for the DPS in real-world scenarios, therefore we use the area under the ROC curve (AUC) as a proxy metric. Results with the synthetic datasets support this choice, since the higher the AUC, the more accurate the predicted simulated DPS. Experiments with the real dataset demonstrate better performance in comparison with state-of-the-art approaches. The proposed framework thus leverages cross-sectional multimodal datasets with small sample sizes to objectively measure disease progression, with potential application in clinical trials.

More details in [54].

7.4 MicroRNA signatures in genetic frontotemporal dementia and amyotrophic lateral sclerosis

Participants: Virgilio Kmetzsch, Isabelle Le Ber, Olivier Colliot (*Correspondant*), Emmanuelle Becker.

MicroRNAs are promising biomarkers of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), but discrepant results between studies have so far hampered their use in clinical trials. We aim to assess all previously identified circulating microRNA signatures as potential biomarkers of genetic FTD and/or ALS, using homogeneous, independent validation cohorts of C9orf72 and GRN mutation carriers. 104 individuals carrying a C9orf72 or a GRN mutation, along with 31 controls, were recruited through the French research network on FTD/ALS. All subjects underwent blood sampling, from which circulating microRNAs were extracted. We measured differences in the expression levels of 65 microRNAs, selected from 15 published studies about FTD or ALS, between 31 controls, 17 C9orf72 presymptomatic subjects, and 29 C9orf72 patients. We also assessed differences in the expression levels of 30 microRNAs, selected from five studies about FTD, between 31 controls, 30 GRN presymptomatic subjects, and 28 GRN patients. More than half (35/65) of the selected microRNAs were differentially expressed in the C9orf72 cohort, while only a small proportion (5/30) of micro-RNAs were differentially expressed in the GRN cohort. In multivariate analyses, only individuals in the C9orf72 cohort could be adequately classified (ROC AUC up to 0.98 for controls versus presymptomatic subjects, 0.94 for controls versus patients, and 0.77 for presymptomatic subjects versus patients) with some of the signatures. Our results suggest that previously identified microRNAs using sporadic or mixed cohorts of FTD and ALS patients could potentially serve as biomarkers of C9orf72-associated disease, but not GRN-associated disease.

More details in [55].

7.5 Automatic quality control of brain T1-weighted magnetic resonance images for a clinical data warehouse

Participants: Simona Bottani, Ninon Burgos, Aurelien Maire, Didier Dormont, Olivier Colliot (*Correspondant*).

We published the first paper on AI for medical imaging based on the data warehouse of the Greater Paris hospitals (AP-HP). We developed and validated an automatic quality control system for brain MRI data. This is an important step to allow fast data curation and thus perform very-large scale studies using this data warehouse which comprises several million of participants. More details about the paper below.

Many studies on machine learning (ML) for computer-aided diagnosis have so far been mostly restricted to high-quality research data. Clinical data warehouses, gathering routine examinations from hospitals, offer great promises for training and validation of ML models in a realistic setting. However, the use of such clinical data warehouses requires quality control (QC) tools. Visual QC by experts is time-consuming and does not scale to large datasets. In this paper, we propose a convolutional neural

network (CNN) for the automatic QC of 3D T1-weighted brain MRI for a large heterogeneous clinical data warehouse. To that purpose, we used the data warehouse of the hospitals of the Greater Paris area (Assistance Publique-Hôpitaux de Paris [AP-HP]). Specifically, the objectives were: 1) to identify images which are not proper T1-weighted brain MRIs; 2) to identify acquisitions for which gadolinium was injected; 3) to rate the overall image quality. We used 5000 images for training and validation and a separate set of 500 images for testing. In order to train/validate the CNN, the data were annotated by two trained raters according to a visual QC protocol that we specifically designed for application in the setting of a data warehouse. For objectives 1 and 2, our approach achieved excellent accuracy (balanced accuracy and F1-score > 90%), similar to the human raters. For objective 3, the performance was good but substantially lower than that of human raters. Nevertheless, the automatic approach accurately identified (balanced accuracy and F1-score > 80%) low quality images, which would typically need to be excluded. Overall, our approach shall be useful for exploiting hospital data warehouses in medical image computing.

More details in [35].

7.6 Homogenization of brain MRI from a clinical data warehouse using contrast-enhanced to non-contrast-enhanced image translation with U-Net derived models

Participants: Simona Bottani, Elina Thibeau-Sutre, Aurelien Maire, Didier Dormont, Olivier Colliot, Ninon Burgos (*Correspondant*).

Clinical data warehouses provide access to massive amounts of medical images and thus offer unprecedented opportunities for research. However, they also pose important challenges, a major challenge being their heterogeneity. In particular, they contain patients with numerous different diseases. The exploration of some neurological diseases with magnetic resonance imaging (MRI) requires injecting a gadolinium-based contrast agent (for instance to detect tumors or other contrast-enhancing lesions) while other diseases do not require such injection. Image harmonization is a key factor to enable unbiased differential diagnosis in such context. Additionally, classical neuroimaging software tools that extract features used as inputs of classification algorithms are typically applied only to images without gadolinium. The objective of this work is to homogenize images from a clinical data warehouse and enable the extraction of consistent features from brain MR images, no matter the initial presence or absence of gadolinium. We propose a deep learning approach based on a 3D U-Net to translate contrast-enhanced into non-contrast-enhanced T1-weighted brain MRI. The approach was trained/validated using 230 image pairs and tested on 26 image pairs of good quality and 51 image pairs of low quality from the data warehouse of the hospitals of the Greater Paris area (Assistance Publique-Hôpitaux de Paris [AP-HP]). We tested two different 3D U-Net architectures and we chose the one reaching the best image similarity metrics for a further validation for a segmentation task. We tested two 3D U-Net architectures with the addition either of residual connections or of attention mechanisms. The U-Net with attention mechanisms reached the best image similarity metrics and was further validated on a segmentation task. We showed that features extracted from the synthetic images (gray matter, white matter and cerebrospinal fluid volumes) were closer to those obtained from the non-contrast-enhanced T1-weighted brain MRI (considered as reference) than the original, contrast-enhanced, images.

More details in [80].

7.7 Multilevel survival modeling with structured penalties for disease prediction from imaging genetics data

Participants: Pascal Lu, Olivier Colliot (*Correspondant*).

We introduced a framework for disease prediction from multimodal genetic and imaging data. We propose a multilevel survival model which allows predicting the time of occurrence of a future disease

state in patients initially exhibiting mild symptoms. This new multilevel setting allows modeling the interactions between genetic and imaging variables. This is in contrast with classical additive models which treat all modalities in the same manner and can result in undesirable elimination of specific modalities when their contributions are unbalanced. Moreover, the use of a survival model allows overcoming the limitations of previous approaches based on classification which consider a fixed time frame. Furthermore, we introduce specific penalties taking into account the structure of the different types of data, such as a group lasso penalty over the genetic modality a l2-penalty over the imaging modality. Finally, we propose a fast optimization algorithm, based on a proximal gradient method. The approach was applied to the prediction of Alzheimer's disease (AD) among patients with mild cognitive impairment (MCI) based on genetic (single nucleotide polymorphisms) and imaging (anatomical MRI measures) data from the ADNI database. The experiments demonstrate the effectiveness of the method for predicting the time of conversion to AD. It revealed how genetic variants and brain imaging alterations interact in the prediction of future disease status. The approach is generic and could potentially be useful for the prediction of other diseases.

More details in [58].

7.8 Data augmentation on neuroimaging data with variational autoencoders

Participants: Clément Chadebec, Elina Thibeau-Sutre, Ninon Burgos, Stéphanie Allassonnière (*Correspondant*).

We proposed a new method to perform data augmentation in a reliable way in the High Dimensional Low Sample Size (HDLSS) setting using a geometry-based variational autoencoder. Our approach combines a proper latent space modeling of the VAE seen as a Riemannian manifold with a new generation scheme which produces more meaningful samples especially in the context of small data sets. The proposed method is tested through a wide experimental study where its robustness to data sets, classifiers and training samples size is stressed. It is also validated on a medical imaging classification task on the challenging ADNI database where a small number of 3D brain MRIs are considered and augmented using the proposed VAE framework. In each case, the proposed method allows for a significant and reliable gain in the classification metrics. For instance, balanced accuracy jumps from 66.3% to 74.3% for a state-of-the-art CNN classifier trained with 50 MRIs of cognitively normal (CN) and 50 Alzheimer disease (AD) patients and from 77.7% to 86.3% when trained with 243 CN and 210 AD while improving greatly sensitivity and specificity metrics.

More details in [38].

7.9 ClinicaDL: an open-source deep learning software for reproducible neuroimaging processing

Participants: Elina Thibeau-Sutre, Mauricio Diaz, Ravi Hassanaly, Alexandre Routier, Didier Dormont, Olivier Colliot, Ninon Burgos (*Correspondant*).

As deep learning faces a reproducibility crisis and studies on deep learning applied to neuroimaging are contaminated by methodological flaws, there is an urgent need to provide a safe environment for deep learning users to help them avoid common pitfalls that will bias and discredit their results. Several tools have been proposed to help deep learning users design their framework for neuroimaging data sets. We present ClinicaDL, one of these software tools. ClinicaDL interacts with BIDS, a standard format in the neuroimaging field, and its derivatives, so it can be used with a large variety of data sets. Moreover, it checks the absence of data leakage when inferring the results of new data with trained networks, and saves all necessary information to guarantee the reproducibility of results. The combination of ClinicaDL and its companion project Clinica allows performing an end-to-end neuroimaging analysis, from the download of raw data sets to the interpretation of trained networks, including neuroimaging preprocessing, quality check, label definition, architecture search, and network training and evaluation. We implemented

ClinicaDL to bring answers to three common issues encountered by deep learning users who are not always familiar with neuroimaging data: (1) the format and preprocessing of neuroimaging data sets, (2) the contamination of the evaluation procedure by data leakage and (3) a lack of reproducibility. We hope that its use by researchers will allow producing more reliable and thus valuable scientific studies in our field.

More details in [73].

7.10 MRI field strength predicts Alzheimer's disease: a case example of bias in the ADNI data set

Participants: Elina Thibeau-Sutre, Baptiste Couvy-Duchesne, Didier Dormont, Olivier Colliot, Ninon Burgos (*Correspondant*).

The Alzheimer's Disease Neuroimaging Initiative (ADNI) data set has been extensively used for the prediction of the progression of prodromal patients to Alzheimer's disease dementia. However, the deep learning community is not always aware of the biases that may contaminate neuroimaging data sets, which may lead to flawed results. In this case example, we demonstrated how ignoring the magnetic resonance (MR) field strength can bias performance of deep learning prediction when using MR images as input. Finally, we discussed options to overcome this problem.

More details in [91].

7.11 Pilot study of repeated blood-brain barrier disruption in patients with mild Alzheimer's disease with an implantable ultrasound device

Participants: Stéphane Epelbaum, Ninon Burgos, Alexandre Carpentier (*Correspondant*).

Temporary disruption of the blood-brain barrier (BBB) using pulsed ultrasound leads to the clearance of both amyloid and tau from the brain, increased neurogenesis, and mitigation of cognitive decline in pre-clinical models of Alzheimer's disease (AD) while also increasing BBB penetration of therapeutic antibodies. The goal of this pilot clinical trial was to investigate the safety and the efficacy of this approach in patients with mild AD using an implantable ultrasound device. An implantable, 1 MHz ultrasound device (SonoCloud-1) was extracranially implanted under local anesthesia in the skull of 10 mild AD patients to target the left supra-marginal gyrus. Over 3.5 months, seven ultrasound sessions in combination with intravenous infusion of microbubbles were performed twice per month to temporarily disrupt the BBB. 18 F-Florbetapir and 18 F-fluorodeoxyglucose positron emission tomography (PET) imaging were performed on a combined PET/MRI scanner at inclusion and at four and eight months after initiation of sonications to monitor brain metabolism and amyloid levels along with cognitive evaluations. Evolution of cognitive and neuroimaging features were compared to that of a matched sample of control participants. A total of 63 BBB opening procedures were performed in nine subjects. The procedure was well-tolerated. A non-significant decrease in amyloid accumulation at four months of -6.6% (SD=7.2%) on 18 F-Florbetapir PET imaging in the sonicated gray matter targeted by the ultrasound transducer was observed compared to baseline in six subjects that completed treatments and who had evaluable imaging scans. No differences in longitudinal change in glucose metabolism were observed compared to neighboring or contralateral regions or to the change observed in the same region in ADNI participants. No significant effect on cognition evolution was observed in comparison to the ADNI participants as expected due to the small sample size and duration of the trial. These results demonstrate the safety of ultrasound-based BBB disruption and potential of this technology to be used as a therapy for AD patients. They support further research of this technique in a larger clinical trial with a device designed to sonicate larger volumes of tissue and in combination with disease modifying drugs to further enhance the effects observed.

More details in [47].

7.12 A quantified comparison of cortical atlases on the basis of trait morphometricity

Participants: Baptiste Couvy-Duchesne (*Correspondant*).

Many different brain atlases exist that subdivide the human cortex into dozens or hundreds of regions-of-interest (ROIs). Inconsistency across studies using one or another cortical atlas may contribute to the replication crisis across the neurosciences. Here, we provide a quantitative comparison between seven popular cortical atlases (Yeo, Desikan-Killiany, Destrieux, Julich-Brain, Gordon, Glasser, Schaefer) and vertex-wise measures (thickness, surface area, and volume), to determine which parcellation retains the most information in the analysis of behavioural traits (incl. age, sex, body mass index, and cognitive ability) in the UK Biobank sample (N 40,000). We use linear mixed models to compare whole-brain morphometricity; the proportion of trait variance accounted for when using a given atlas. Commonly-used atlases resulted in a considerable loss of information compared to vertex-wise representations of cortical structure. Morphometricity increased linearly as a function of the log-number of ROIs included in an atlas, indicating atlas-based analyses miss many true associations and yield limited prediction accuracy. Likelihood ratio tests revealed that low-dimensional atlases accounted for unique trait variance rather than variance common between atlases, suggesting that previous studies likely returned atlas-specific findings. Finally, we found that the commonly-used atlases yielded brain-behaviour associations on par with those obtained with random parcellations, where specific region boundaries were randomly generated. Our findings motivate future structural neuroimaging studies to favour vertex-wise cortical representations over coarser atlases, or to consider repeating analyses across multiple atlases, should the use of low-dimensional atlases be necessary. The insights uncovered here imply that cortical atlas choices likely contribute to the lack of reproducibility in ROI-based studies.

More details in [49].

7.13 Parsimonious model for mass-univariate vertexwise analysis

Participants: Baptiste Couvy-Duchesne (*Correspondant*), Olivier Colliot.

Covariance between gray-matter measurements can reflect structural or functional brain networks though it has also been shown to be influenced by confounding factors (e.g., age, head size, and scanner), which could lead to lower mapping precision (increased size of associated clusters) and create distal false positives associations in mass-univariate vertexwise analyses. We evaluated this concern by performing state-of-the-art mass-univariate analyses (general linear model, GLM) on traits simulated from real vertex-wise gray matter data (including cortical and subcortical thickness and surface area). We contrasted the results with those from linear mixed models (LMMs), which have been shown to overcome similar issues in omics association studies. We showed that when performed on a large sample (N=8662, UK Biobank), GLMs yielded greatly inflated false positive rate (cluster false discovery rate >0.6). We showed that LMMs resulted in more parsimonious results: smaller clusters and reduced false positive rate but at a cost of increased computation. Next, we performed mass-univariate association analyses on five real UKB traits (age, sex, BMI, fluid intelligence, and smoking status) and LMM yielded fewer and more localized associations. We identified 19 significant clusters displaying small associations with age, sex, and BMI, which suggest a complex architecture of at least dozens of associated areas with those phenotypes. Conclusions: The published literature could contain a large proportion of redundant (possibly confounded) associations that are largely prevented using LMMs. The parsimony of LMMs results from controlling for the joint effect of all vertices, which prevents local and distal redundant associations from reaching significance.

More details in [43]

7.14 The role of critical immune genes in brain disorders: insights from neuroimaging immunogenetics

Participants: Baptiste Couvy-Duchesne (*Correspondant*).

Genetic variants in the human leukocyte antigen and killer cell immunoglobulin like receptor regions have been associated with many brain-related diseases, but how they shape brain structure and function remains unclear. To identify the genetic variants in HLA and KIR genes associated with human brain phenotypes, we performed a genetic association study of 30 000 European unrelated individuals using brain MRI phenotypes generated by the UK Biobank (UKB). We identified 15 HLA alleles in HLA class I and class II genes significantly associated with at least one brain MRI-based phenotypes ($P < 5 \times 10^{-8}$). These associations converged on several main haplotypes within the HLA. In particular, the human leukocyte antigen alleles within an ancestral haplotype 8.1 were associated with multiple MRI measures, including grey matter volume, cortical thickness (TH) and diffusion MRI (dMRI) metrics. These alleles have been strongly associated with schizophrenia. Additionally, associations were identified between HLA-DRB1*04, DQA1*03:01, DQB1*03:02 and isotropic volume fraction of diffusion MRI in multiple white matter tracts. This haplotype has been reported to be associated with Parkinson's disease. These findings suggest shared genetic associations between brain MRI biomarkers and brain-related diseases. Additionally, we identified 169 associations between the complement component 4 (C4) gene and imaging phenotypes. We found that C4 gene copy number was associated with cortical TH and dMRI metrics. No KIR gene copy numbers were associated with image-derived phenotypes at genome-wide threshold. To address the multiple testing burden in the phenome-wide association study, we performed a multi-trait association analysis using trait-based association test that uses extended Simes procedure and identified MRI image-specific associations. This study contributes to insight into how critical immune genes affect brain-related traits as well as the development of neurological and neuropsychiatric disorders.

More details in [34]

7.15 Functional connectivity ensemble method to enhance BCI performance (FUCONE)

Participants: Marie-Constance Corsi (*Correspondant*), Sylvain Chevallier, Fabrizio De Vico Fallani, Florian Yger.

Relying on the idea that functional connectivity provides important insights on the underlying dynamic of neuronal interactions, we propose a novel framework that combines functional connectivity estimators and covariance-based pipelines to improve the classification of mental states, such as motor imagery. A Riemannian classifier is trained for each estimator and an ensemble classifier combines the decisions in each feature space. A thorough assessment of the functional connectivity estimators is provided and the best performing pipeline among those tested, called FUCONE, is evaluated on different conditions and datasets. Using a meta-analysis to aggregate results across datasets, FUCONE performed significantly better than all state-of-the-art methods. The performance gain is mostly imputable to the improved diversity of the feature spaces, increasing the robustness of the ensemble classifier with respect to the inter- and intra-subject variability. Our results offer new insights into the need to consider functional connectivity-based methods to improve the BCI performance.

More details in [42].

7.16 Weakly supervised framework for cancer region detection of hepatocellular carcinoma in whole-slide pathologic images based on multiscale attention convolutional neural network

Participants: Songhui Diao, Yinli Tian, Wanming Hu, Jiabin Hou, Ricardo Lambo, Zhicheng Zhang, Yaoqin Xie, Xiu Nie, Fa Zhang, Daniel Racoceanu (*Correspondant*), Wenjian Qin.

Visual inspection of hepatocellular carcinoma cancer regions by experienced pathologists in whole-slide images (WSIs) is a challenging, labor-intensive, and time-consuming task because of the large scale and high resolution of WSIs. Therefore, a weakly supervised framework based on a multiscale attention convolutional neural network (MSAN-CNN) was introduced into this process. Herein, patch-based images with image-level normal/tumor annotation (rather than images with pixel-level annotation) were fed into a classification neural network. To further improve the performances of cancer region detection, multiscale attention was introduced into the classification neural network. A total of 100 cases were obtained from The Cancer Genome Atlas and divided into 70 training and 30 testing data sets that were fed into the MSAN-CNN framework. The experimental results showed that this framework significantly outperforms the single-scale detection method according to the area under the curve and accuracy, sensitivity, and specificity metrics. When compared with the diagnoses made by three pathologists, MSAN-CNN performed better than a junior- and an intermediate-level pathologist, and slightly worse than a senior pathologist. Furthermore, MSAN-CNN provided a very fast detection time compared with the pathologists. Therefore, a weakly supervised framework based on MSAN-CNN has great potential to assist pathologists in the fast and accurate detection of cancer regions of hepatocellular carcinoma on WSIs.

More details in [45].

7.17 Explainability in Artificial Intelligence; towards Responsible AI

Participants: Daniel Racoceanu (*Correspondant*), Mehdi Ounissi, Yannick Kergosien.

Essential for a good adoption, as well as for a wise and unbiased use, explicability is a real technology lock to the evolution of Artificial Intelligence (AI), in particular concerning Machine and Deep Learning. Without an effective explicability of the proposed algorithms, these techniques will remain a black box for health (and not only) professionals, researchers, engineers and technicians - who assume (and will continue to assume) the full responsibility of their actions. Increasingly, engineers and designers of AI tools will have to demonstrate their responsibility by providing algorithms that guarantee the explicability of the proposed models. This article presents the motivations of an explainable AI, the main characteristics of the conceptual landscape of explainability in AI, the major families of explainability methods - with a focus on some of the most common methods, to finally present some of the opportunities, challenges and perspectives of this exciting field of human-machine interaction. Indeed, only through a good understanding of the challenges associated with this technological revolution that we will be able to transform AI into assets for our companies as well as for our human actors, partners and customers.

More details in [143].

7.18 Computational Pathology for Brain Disorders

Participants: Gabriel Jimenez, Daniel Racoceanu (*Correspondant*).

Non-invasive brain imaging techniques allow understanding the behavior and macro changes in the brain to determine the progress of a disease. However, computational pathology provides a deeper understanding of brain disorders at cellular level, able to consolidate a diagnosis and make the bridge between the medical image and the omics analysis. In traditional histopathology, histology slides are visually inspected, under the microscope, by trained pathologists. This process is time-consuming

and labor-intensive; therefore, the emergence of Computational Pathology has triggered great hope to ease this tedious task and make it more robust. This chapter focuses on understanding the state-of-the-art machine learning techniques used to analyze whole slide images within the context of brain disorders. We present a selective set of remarkable machine learning algorithms providing discriminative approaches and quality results on brain disorders. These methodologies are applied to different tasks, such as monitoring mechanisms contributing to disease progression and patient survival rates, analyzing morphological phenotypes for classification and quantitative assessment of disease, improving clinical care, diagnosing tumor specimens, and intraoperative interpretation. Thanks to the recent progress in machine learning algorithms for high-content image processing, computational pathology marks the rise of a new generation of medical discoveries and clinical protocols, including in brain disorders.

7.19 Visual Deep Learning-Based Explanation for Neuritic Plaques Segmentation in Alzheimer's Disease Using Weakly Annotated Whole Slide Histopathological Images.

Participants: Gabriel Jimenez, Anuradha Kar, Mehdi Ounissi, Lea Ingrassia, Susana Boluda, Benoit Delatour, Lev Stimmer, Daniel Racoceanu (*Correspondant*).

Quantifying the distribution and morphology of tau protein structures in brain tissues is key to diagnosing Alzheimer's Disease (AD) and its subtypes. Recently, deep learning (DL) models such as UNet have been successfully used for automatic segmentation of histopathological whole slide images (WSI) of biological tissues. In this study, we propose a DL-based methodology for semantic segmentation of tau lesions (i.e., neuritic plaques) in WSI of postmortem patients with AD. The state of the art in semantic segmentation of neuritic plaques in human WSI is very limited. Our study proposes a baseline able to generate a significant advantage for morphological analysis of these tauopathies for further stratification of AD patients. Essential discussions concerning biomarkers (ALZ50 versus AT8 tau antibodies), the imaging modality (different slide scanner resolutions), and the challenge of weak annotations are addressed within this seminal study. The analysis of the impact of context in plaque segmentation is important to understand the role of the micro-environment for reliable tau protein segmentation. In addition, by integrating visual interpretability, we are able to explain how the network focuses on a region of interest (ROI), giving additional insights to pathologists. Finally, the release of a new expert-annotated database and the code will be helpful for the scientific community to accelerate the development of new pipelines for human WSI processing in AD.

More details in [83].

7.20 3D reconstruction of H&E whole slide images in melanoma.

Participants: Janan Arslan, Mehdi Ounissi, Haocheng Luo, Daniel Racoceanu (*Correspondant*).

Cutaneous melanoma is an invasive cancer with a worldwide annual death toll of 57,000 (Arnold et al., JAMA Dermatol 2022). In metastatic state, surgical interventions are not curative and must be coupled with chemotherapy. However, even with targeted therapies, late-stage prognosis can remain poor. The complexity of melanoma stems from its tumor microenvironment; these cancer cells continually adapt to modified metabolic changes, ensuring survival and proliferation under stressful conditions. Our primary assumption is that chemotherapeutic resistance stems from a series of non-genetic transitions and changed metabolic states. Using Whole Slide Images (WSI) of melanoma tumors from Patient Derived Xenograft (PDX) mouse models, we build 3D vascular models to predict the metabolic states within the tumor. PDX samples underwent serial sectioning over 2mm depth and were stained with Hematoxylin and Eosin (H&E). Our 3D reconstruction pipeline involves three primary steps, including 2D vessel segmentation using Deep Learning, intensity and affine-based image registration, and 3D reconstruction

using interpolation and 3D rendering (allowing a better interaction with biologists, pathologists, and clinicians). The originality of our computer-assisted pipeline is its capability to (a) deal with sparse data (i.e., not all tissue sections were readily available), and (b) adapt to a multitude of WSI-related challenges (e.g., epistemic uncertainty, extended processing times due to WSI scale, etc.). We posit both our 3D reconstruction pipeline, quantitative results of the major stages of the process and a detailed illustration of the challenges faced, presenting resolutions to improve the pipeline's efficiency.

More details in [79].

7.21 A meta-graph approach for analyzing whole slide histopathological images of human brain tissue with Alzheimer disease biomarkers

Participants: Gabriel Jimenez, Pablo Mas, Anuradha Kar, Lea Ingrassia, Susana Boluda, Benoit Delatour, Lev Stimmer, Daniel Racoceanu (*Correspondant*).

Recently, high performance deep learning models have allowed automatic and precise analysis of high-content medical images. In digital histopathology, a typical challenge lies in analyzing whole slide images (WSI) due to their large dimensions which most often requires splitting them into small patches for feeding deep learning models. This leads to loss in global tissue level information and is particularly limiting to classification or clustering of patients based on tissue characteristics. In this study, a meta-graph approach is developed for a semantic spatial analysis of histopathological Whole Slide Images (WSI) of human brain tissue containing tau protein aggregates, one of the hallmark lesions of Alzheimer disease (AD) in brain gray matter. We propose a pipeline that extracts morphological features of tau aggregates like neuritic plaques or neurofibrillary tangles using a pre-trained U-Net model and uses these to build a graph based on Delaunay triangulation at the WSI level, in order to extract topological features from them. This pipeline is generating morphological and topological tabular data from WSI for classification and clustering patients. Further, combining locally extracted morphological features - at the neuritic plaques or neurofibrillary tangle level - with the Delaunay graph constructed at the WSI level, allows constructing a meta-graph that can be efficiently fed to graph neural network models, instead of the voluminous WSI. This pipeline is developed and tested on a dataset of 60 WSIs from various cohorts of patients having classic and rapidly advancing AD. The purpose of this pipeline is to identify novel insights into AD evolution, as well as provide a generic framework for creating knowledge rich graphs for WSI characterization and analysis.

More details in [84].

7.22 The impact of aging on human brain network target controllability

Participants: Giulia Bassignana, Olivier Colliot, Fabrizio De Vico Fallani (*Correspondant*).

Understanding how few distributed areas can steer large-scale brain activity is a fundamental question that has practical implications, which range from inducing specific patterns of behavior to counteracting disease. Recent endeavors based on network controllability provided fresh insights into the potential ability of single regions to influence whole brain dynamics through the underlying structural connectome. However, controlling the entire brain activity is often unfeasible and might not always be necessary. The question whether single areas can control specific target subsystems remains crucial, albeit still poorly explored. Furthermore, the structure of the brain network exhibits progressive changes across the lifespan, but little is known about the possible consequences in the controllability properties. To address these questions, we adopted a novel target controllability approach that quantifies the centrality of brain nodes in controlling specific target anatomo-functional systems. We then studied such target control centrality in human connectomes obtained from healthy individuals aged from 5 to 85. Main results showed that the sensorimotor system has a high influencing capacity, but it is difficult for other areas to influence it. Furthermore, we reported that target control centrality varies with age and that temporal-parietal regions,

whose cortical thinning is crucial in dementia-related diseases, exhibit lower values in older people. By simulating targeted attacks, such as those occurring in focal stroke, we showed that the ipsilesional hemisphere is the most affected one regardless of the damaged area. Notably, such degradation in target control centrality was more evident in younger people, thus supporting early-vulnerability hypotheses after stroke.

More details in [33].

7.23 Multiscale modeling of brain network organization

Participants: Charley Presigny, Fabrizio De Vico Fallani (*Correspondant*).

A complete understanding of the brain requires an integrated description of the numerous scales of neural organization. It means studying the interplay of genes, synapses, and even whole brain regions which ultimately leads to different types of behavior, from perception to action, while asleep or awake. Yet, multiscale brain modeling is challenging, in part because of the difficulty to access simultaneously to information from multiple spatiotemporal scales. While some insights have been gained on the role of specific microcircuits (e.g., thalamocortical), a comprehensive characterization of how changes occurring at one scale can have an impact on other ones, remains poorly understood. Recent efforts to address this gap include the development of new analytical tools mostly adapted from network science and dynamical systems theory. These theoretical contributions provide a powerful framework to analyze and model interconnected complex systems exhibiting interactions within and between different scales, or layers. Here, we present recent advances for the characterization of the multiscale brain organization in terms of structure-function, oscillation frequencies and temporal evolution. Efforts are reviewed on the multilayer network properties underlying higher-order organization of neuronal assemblies, as well as on the identification of multimodal network-based biomarkers of brain pathologies, such as Alzheimer's disease. We conclude this Colloquium with a perspective discussion on how recent results from multilayer network theory, involving generative modeling, controllability and machine learning, could be adopted to address new questions in modern neuroscience.

More details in [67].

7.24 Temporal exponential random graph models of longitudinal brain networks after stroke

Participants: Catalina Obando, Fabrizio De Vico Fallani (*Correspondant*).

Plasticity after stroke is a complex phenomenon. Functional reorganization occurs not only in the perilesional tissue but throughout the brain. However, the local connection mechanisms generating such global network changes remain largely unknown. To address this question, time must be considered as a formal variable of the problem rather than a simple repeated observation. Here, we hypothesized that the presence of temporal connection motifs, such as the formation of temporal triangles (T) and edges (E) over time, would explain large-scale brain reorganization after stroke. To test our hypothesis, we adopted a statistical framework based on temporal exponential random graph models (tERGMs), where the aforementioned temporal motifs were implemented as parameters and adapted to capture global network changes after stroke. We first validated the performance on synthetic time-varying networks as compared to standard static approaches. Then, using real functional brain networks, we showed that estimates of tERGM parameters were sufficient to reproduce brain network changes from 2 weeks to 1 year after stroke. These temporal connection signatures, reflecting within-hemisphere segregation (T) and between hemisphere integration (E), were associated with patients' future behaviour. In particular, interhemispheric temporal edges significantly correlated with the chronic language and visual outcome in subcortical and cortical stroke, respectively. Our results indicate the importance of time-

varying connection properties when modelling dynamic complex systems and provide fresh insights into modelling of brain network mechanisms after stroke.

More details in [65].

7.25 Safety and efficacy of riluzole in spinocerebellar ataxia type 2 in France (ATRIL): a multicentre, randomised, double-blind, placebo-controlled trial

Participants: Giulia Coarelli, Sophie Tezenas du Montcel (*Correspondant*), Alexandra Durr.

Riluzole has been reported to be beneficial in patients with cerebellar ataxia; however, effectiveness in individual subtypes of disease is unclear due to heterogeneity in participants' causes and stages of disease. Our aim was to test riluzole in a single genetic disease, spinocerebellar ataxia type 2. We did a randomised, double-blind, placebo-controlled, multicentre trial (the ATRIL study) at eight national reference centres for rare diseases in France that were part of the Neurogene National Reference Centre for Rare Diseases. Participants were patients with spinocerebellar ataxia type 2 with an age at disease onset of up to 50 years and a scale for the assessment and rating of ataxia (SARA) score of at least 5 and up to 26. Patients were randomly assigned centrally (1:1) to receive either riluzole 50 mg orally or placebo twice per day for 12 months. Two visits, at baseline and at 12 months, included clinical measures and 3T brain MRI. The primary endpoint was the proportion of patients whose SARA score improved by at least 1 point. Analyses were done in the intention-to-treat population (all participants who were randomly assigned) and were done with only the observed data (complete case analysis). This trial is registered at ClinicalTrials.gov (NCT03347344) and has been completed. Between Jan 18, 2018, and June 14, 2019, we enrolled 45 patients. 22 patients were randomly assigned to receive riluzole and 23 to receive placebo. Median age was 42 years (IQR 36–57) in the riluzole group and 49 years (40–56) in the placebo group and 23 (51%) participants were women. All participants presented with moderate stage disease, characterised by a median SARA score of 13.5 (IQR 9.5–16.5). The primary endpoint, SARA score improvement of at least 1 point after 12 months, was observed in seven patients (32%) in the treated group versus nine patients (39%) in the placebo group, with a mean difference of –10.3% (95% CI –37.4% to 19.2%; $p=0.75$). SARA score showed a median increase (ie, worsening) of 0.5 points (IQR –1.5 to 1.5) in the riluzole group versus 0.3 points (–1.0 to 2.5) in the placebo group ($p=0.70$). No serious adverse event was reported in the riluzole-treated group whereas four patients in placebo group had a serious adverse event (hepatic enzyme increase, fracture of external malleolus, rectorrhagia, and depression). The number of patients with adverse events was similar in both groups (riluzole 16 [73%] patients vs placebo 19 [83%] patients; $p=0.49$). We were able to recruit 45 patients moderately affected by spinocerebellar ataxia type 2 for this trial. Riluzole did not improve clinical or radiological outcomes in these patients. However, our findings provide data on progression of spinocerebellar ataxia type 2 that might prove to be valuable for the design of other clinical trials.

More details in [41].

7.26 Trajectory pattern of cognitive decline in CADASIL

Participants: Sandrine Brice, Sophie Tezenas du Montcel (*Correspondant*), Hugues Chabriat.

The course and pattern of cognitive decline in ischemic cerebral small vessel disease remain poorly characterized. We analyzed the trajectory pattern of cognitive decline from age 25 to 75 years in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). We applied latent process mixed models to data obtained from patients with CADASIL who were repeatedly scored during their follow-up using 16 selected clinical scales or cognitive tests. The modeled evolutions of these scores obtained from 1,243 observations in 265 patients recruited at the French National Referral Centre (50.1 years on average and 45.3% men) showed wide and heterogeneous variations in amplitude

along the age-related progression of the disease. Although the Backward Digit Span remained essentially stable, a linear deterioration of scores obtained using the Symbol Digit Numbers or Number of Errors of Trail Making Test B was detected from 25 to 75 years. By contrast, the largest score changes were observed at midlife using the Digit Cancellation Task. All other tests related to executive functions, memory performances, or global cognitive efficiency showed a rate of change accelerating especially at the advanced stage of the disease. Male gender and the presence of gait disorders or of some disability at baseline were found to predict earlier or large changes of 4 scores (Index of Sensitivity to Cueing, Delayed Total Recall, Initiation/Perseveration, and Barthel Index) in a subgroup of individuals distinct from the rest of the sample. Cognitive alterations develop heterogeneously during the progression of CADASIL and vary largely according to the stage of the disease. These results suggest that not only the target population and study duration but also the stage of disease progression should be considered in preparing future clinical trials aimed at reducing cognitive decline in any such condition.

More details in [36].

7.27 Temporal dynamics of the Scale for the Assessment and Rating of Ataxia in Spinocerebellar ataxias

Participants: Paul Moulaire, Pierre-Emmanuel Poulet, Sophie Tezenas du Montcel (*Correspondant*).

The Scale for the Assessment and Rating of Ataxia (SARA) is the reference clinical scale to assess the severity of cerebellar ataxia. In the context of upcoming therapeutic trials, a reliable clinical outcome is needed to assess the efficiency of treatments. The aim is to precisely assess and compare temporal dynamics of SARA and a new f-SARA. We analyzed data from four cohorts (EUROSCA, RISCA, CRC-SCA, and SPATAX) comprising 1210 participants and 4092 visits. The linearity of the progression and the variability were assessed using an ordinal Bayesian mixed-effect model (Leaspy). We performed sample size calculations for therapeutic trials with different scenarios to improve the responsiveness of the scale. Seven of the eight different items had a nonlinear progression. The speed of progression was different between most of the items, with an average time for a one-point increase from 3.5 years [3.4; 3.6] (median, 95% credible interval) for the fastest item to 11.4 [10.9; 12.0] years. The total SARA score had a linear progression with an average time for a one-point increase of 0.95 [0.92; 0.98] years. After removing the four last items and rescaling all items from 0 to 4, variability increased and progression was slower and thus would require a larger sample size in a future therapeutic trial. Despite a heterogeneous temporal dynamics at the item level, the global progression of SARA was linear. Changing the initial scale deteriorates the responsiveness. This new information about the temporal dynamics of the scale should help design the outcome of future clinical trials.

More details in [62].

7.28 Forecasting individual progression trajectories in Huntington disease enables more powered clinical trials

Participants: Igor Koval, Thomas Dighiero-Brecht, Sophie Tezenas du Montcel, Alexandra Durr, Stanley Durrleman (*Correspondant*).

Variability in neurodegenerative disease progression poses great challenges for the evaluation of potential treatments. Identifying the persons who will experience significant progression in the short term is key for the implementation of trials with smaller sample sizes. We apply here disease course mapping to forecast biomarker progression for individual carriers of the pathological CAG repeat expansions responsible for Huntington disease. We used data from two longitudinal studies (TRACK-HD and TRACK-ON) to synchronize temporal progression of 15 clinical and imaging biomarkers from 290 participants with Huntington disease. We used then the resulting HD COURSE MAP to forecast clinical endpoints from the baseline data of 11,510 participants from ENROLL-HD, an external validation cohort. We used

such forecasts to select participants at risk for progression and compute the power of trials for such an enriched population. HD COURSE MAP forecasts biomarkers 5 years after the baseline measures with a maximum mean absolute error of 10 points for the total motor score and 2.15 for the total functional capacity. This allowed reducing sample sizes in trial up to 50% including participants with a higher risk for progression ensuring a more homogeneous group of participants.

More details in [56].

7.29 Progression models for imaging data with Longitudinal Variational Auto Encoders

Participants: Benoît Sauty, Stanley Durrleman (*Correspondant*).

Disease progression models are crucial to understanding degenerative diseases. Mixed-effects models have been consistently used to model clinical assessments or biomarkers extracted from medical images, allowing missing data imputation and prediction at any timepoint. However, such progression models have seldom been used for entire medical images. In this work, a Variational Auto Encoder is coupled with a temporal linear mixed-effect model to learn a latent representation of the data such that individual trajectories follow straight lines over time and are characterised by a few interpretable parameters. A Monte Carlo estimator is devised to iteratively optimize the networks and the statistical model. We apply this method on a synthetic data set to illustrate the disentanglement between time dependant changes and inter-subjects variability, as well as the predictive capabilities of the method. We then apply it to 3D MRI and FDG-PET data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) to recover well documented patterns of structural and metabolic alterations of the brain.

More details in [88].

7.30 Riemannian metric learning for progression modeling of longitudinal datasets

Participants: Benoît Sauty, Stanley Durrleman (*Correspondant*).

Explicit descriptions of the progression of biomarkers across time usually involve priors on the shapes of the trajectories. To circumvent this limitation, we propose a geometric framework to learn a manifold representation of longitudinal data. Namely, we introduce a family of Riemannian metrics that span a set of curves defined as parallel variations around a main geodesic, and apply that framework to disease progression modeling with a mixed-effects model, where the main geodesic represents the average progression of biomarkers and parallel curves describe the individual trajectories. Learning the metric from the data allows to fit the model to longitudinal datasets and provides few interpretable parameters that characterize both the group-average trajectory and individual progression profiles. Our method outperforms the 56 methods benchmarked in the TADPOLE challenge for cognitive scores prediction.

More details in [89].

7.31 Identifying health conditions associated with Alzheimer’s disease up to 15 years before diagnosis: an agnostic study of French and British health records

Participants: Thomas Nedelec, Baptiste Couvy-Duschesne, Timothy Daly, Manon Ansart, Stéphane Epelbaum, Carole Dufouil, Stanley Durrleman (*Correspondant*).

The identification of modifiable risk factors for Alzheimer’s disease is paramount for early prevention and the targeting of new interventions. We aimed to assess the associations between health conditions diagnosed in primary care and the risk of incident Alzheimer’s disease over time, up to 15 years before

a first Alzheimer's disease diagnosis. In this agnostic study of French and British health records, data from 20 214 patients with Alzheimer's disease in the UK and 19 458 patients with Alzheimer's disease in France were extracted from The Health Improvement Network database. We considered data recorded from Jan 1, 1996, to March 31, 2020 in the UK and from Jan 4, 1998, to Feb 20, 2019, in France. For each Alzheimer's disease case, a control was randomly assigned after matching for sex and age at last visit. We agnostically tested the associations between 123 different diagnoses of the International Classification of Diseases, 10th revision, extracted from health records, and Alzheimer's disease, by running a conditional logistic regression to account for matching of cases and controls. We focused on three time periods before diagnosis of Alzheimer's disease, to separate risk factors from early symptoms and comorbidities. Unadjusted odds ratios (ORs) and 95% CIs for the association between Alzheimer's disease and various health conditions were estimated, and p values were corrected for multiple comparisons. Depression was the first comorbid condition associated with Alzheimer's disease, appearing at least 9 years before the first clinical diagnosis, followed by anxiety, constipation, and abnormal weight loss. Interpretation These results from two independent primary care databases provide new evidence on the temporality of risk factors and early signs of Alzheimer's disease that are observable at the general practitioner level. These results could guide the implementation of new primary and secondary prevention policies.

More details in [64].

7.32 Deterministic Approximate EM Algorithm; Application to the Riemann Approximation EM and the Tempered EM

Participants: Thomas Lartigue, Stéphanie Allasonnière (*Correspondant*), Stanley Durrleman.

The Expectation Maximisation (EM) algorithm is widely used to optimise non-convex likelihood functions with latent variables. Many authors modified its simple design to fit more specific situations. For instance, the Expectation (E) step has been replaced by Monte Carlo (MC), Markov Chain Monte Carlo or tempered approximations, etc. Most of the well-studied approximations belong to the stochastic class. By comparison, the literature is lacking when it comes to deterministic approximations. In this paper, we introduce a theoretical framework, with state-of-the-art convergence guarantees, for any deterministic approximation of the E step. We analyse theoretically and empirically several approximations that fit into this framework. First, for intractable E-steps, we introduce a deterministic version of MC-EM using Riemann sums. A straightforward method, not requiring any hyper-parameter fine-tuning, useful when the low dimensionality does not warrant a MC-EM. Then, we consider the tempered approximation, borrowed from the Simulated Annealing literature and used to escape local extrema. We prove that the tempered EM verifies the convergence guarantees for a wider range of temperature profiles than previously considered. We showcase empirically how new non-trivial profiles can more successfully escape adversarial initialisations. Finally, we combine the Riemann and tempered approximations into a method that accomplishes both their purposes.

More details in [57].

7.33 Asymptotic Analysis of a Matrix Latent Decomposition Model

Participants: Clément Mantoux, Stéphanie Allasonnière (*Correspondant*), Stanley Durrleman.

Matrix data sets arise in network analysis for medical applications, where each network belongs to a subject and represents a measurable phenotype. These large dimensional data are often modeled using lower-dimensional latent variables, which explain most of the observed variability and can be used for predictive purposes. In this paper, we provide asymptotic convergence guarantees for the estimation of a hierarchical statistical model for matrix data sets. It captures the variability of matrices by modeling a truncation of their eigendecomposition. We show that this model is identifiable, and that consistent

Maximum A Posteriori (MAP) estimation can be performed to estimate the distribution of eigenvalues and eigenvectors. The MAP estimator is shown to be asymptotically normal for a restricted version of the model.

More details in [59].

8 Bilateral contracts and grants with industry

8.1 Bilateral grants with industry

8.1.1 Sanofi

Participants: Stanley Durrleman (*Correspondant*).

- This project aims at modeling Parkinson disease progression for patients with mutations in the GBA genes, selecting potential good responders in clinical trials based on their progression profile, and evaluating new measures of drug efficacy.
- Coordinator: Stanley Durrleman
- Started in 2020

8.1.2 Biogen

Participants: Stanley Durrleman (*Correspondant*).

- This project aims at analysing clinical trial data in neurodegenerative diseases.
- Coordinator: Stanley Durrleman
- Started in 2022

9 Partnerships and cooperations

9.1 International research visitors

9.1.1 Visits of international scientists

Other international visits to the team

Name of the researcher Bruno Jedynak

Status Professor

Institution of origin: Portland State University

Country: USA

Dates: May-July 2022

Context of the visit: collaboration on disease progression modeling

Mobility program/type of mobility: research stay

9.2 European initiatives

9.2.1 H2020 projects

BCINET [BCINET project on cordis.europa.eu](https://cordis.europa.eu/project/BCINET)

Title: Non-invasive decoding of brain communication patterns to ease motor restoration after stroke

Duration: From October 1, 2020 to September 30, 2026

Partners:

- INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET AUTOMATIQUE (INRIA), France
- INSTITUT DU CERVEAU ET DE LA MOELLE EPINIÈRE (ICM), France

Inria contact: Fabrizio De Vico Fallani

Coordinator:

Summary: Human-computer interfaces are increasingly explored to facilitate interaction with the external world. Brain-computer interfaces (BCIs), bypassing the skeletomuscular system, are particularly promising for assisting paralyzed people in control and communication, but also for boosting neuromotor rehabilitation.

Despite their potential, the societal impact of BCIs is dramatically limited by the poor usability in real-life applications. While many solutions have been proposed - from the identification of the best classification algorithm to the type of sensory feedback - the accuracy is still highly variable across subjects and BCIs cannot be used by everyone. Critically, these approaches have implicitly assumed that the user's intent could be decoded by examining the activity of single brain areas. Today, we know that this is not true as the brain functioning essentially depends on a complex network of interactions between differently specialized areas.

The grand challenge of this project is to develop a novel generation of BCIs that integrate the user's brain network information for enhancing accuracy and usability. Based on this approach, we will experiment innovative BCI prototypes to restore the lost motor functions in patients suffering from stroke.

This project relies on a unifying framework that analyses and models brain networks by means of analytical tools derived from graph theory and complex systems science. By recruiting diverse neuroimaging and experimental methods, within a modern computational framework, we aim to i) identify new control features for enhancing BCI accuracy, ii) study the brain dynamics of human learning for improving adaptive BCI architectures, and iii) optimize brain stimulation techniques for boosting BCI skill acquisition.

This project can significantly improve BCI usability as well as determining how brain lesions compromise brain functioning and which solutions are most effective to unlock motor restoration after stroke.

VirtualBrainCloud [VirtualBrainCloud project on cordis.europa.eu](https://cordis.europa.eu/project/VirtualBrainCloud)

Title: Personalized Recommendations for Neurodegenerative Disease

Duration: From December 1, 2018 to May 31, 2023

Partners:

- INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET AUTOMATIQUE (INRIA), France
- HELSINGIN YLIOPISTO, Finland
- INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE, France

- FORSCHUNGSZENTRUM JULICH GMBH (FZJ), Germany
- UNIVERSITAT WIEN (UNIVIE), Austria
- FRAUNHOFER GESELLSCHAFT ZUR FORDERUNG DER ANGEWANDTEN FORSCHUNG EV (FHG), Germany
- TP21 GMBH (TP21), Germany
- FUNDACIO INSTITUT DE BIOENGINYERIA DE CATALUNYA (IBEC-CERCA), Spain
- INSTITUT DU CERVEAU ET DE LA MOELLE EPINIÈRE (ICM), France
- EODYNE SYSTEMS SL (EODYNE SYSTEMS), Spain
- UNIVERSIDAD COMPLUTENSE DE MADRID (UCM), Spain
- CHARITE - UNIVERSITAETSMEDIZIN BERLIN, Germany
- THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD (UOXF), United Kingdom
- UNIVERSITE D'AIX MARSEILLE (AMU), France
- UNIVERSITA DEGLI STUDI DI GENOVA (UNIGE), Italy
- CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE CNRS (CNRS), France
- CODEMART SRL (CODEMART), Romania
- CODEBOX GMBH (CODEBOX), Germany
- ALZHEIMER EUROPE (AE), Luxembourg

Inria contact: Bertrand Thirion

Coordinator:

Summary: The annual worldwide cost of Alzheimer's dementia was 777.81 billion Euro in 2015. This number will rise to 7.41 trillion Euro in 2050. Early diagnosis would save up to \$7.9 trillion in medical and care costs by 2050 in the US alone. However, the emergent pathology is highly variable across people, need highly variable across people, necessitating individualized diagnostics and interventions. The VirtualBrainCloud addresses this by bridging the gap between computational neuroscience and subcellular systems biology, integrating both research streams into a unifying computational model that supports personalized diagnostics and treatments in NDD. The VirtualBrainCloud not only integrates existing software tools, it also merges the efforts of two big EU initiatives, namely The Virtual Brain large scale simulation platform of the EU Flagship Human Brain Project and IMI-EPAD initiative (European prevention of Alzheimer's dementia consortium). VirtualBrainCloud will develop and validate a decision support system that provides access to high quality multi-disciplinary data for clinical practice. The result will be a cloud-based brain simulation platform to support personalized diagnostics and treatments in NDD. The EU PRACE (Partnership for Advanced Computing in Europe) initiative, will provide the required computing infrastructure. The VirtualBrainCloud will develop robust solutions for legal and ethical matters by interacting with EU projects such as European Open Science Cloud (EOSC), 'cloud4health', Alzheimer's Europe patient organizations and ELIXIR, an organization that manages and safeguards EU research data. Our software developers have already produced highly successful brain simulation and clinical decision support tools. The resulting software will be a cloud based computational modeling system that is tailored to the individual, and bridges multiple scales to identify key mechanisms that predict NDD progression and serves as Precision Decision Support System.

9.3 National initiatives

Health Data Hub

Participants: Stanley Durrleman.

- Project acronym: Precise-PD-HDH
- Project title: Modélisation et prédiction de la progression de la maladie de Parkinson
- Duration: 1 year (pilot project)
- Coordinator: Jean-Christophe Corvol
- Other partners: Inserm, réseau NS-PARK, ICM

AVIESAN - ITMO Cancer

Participants: Ovidiu Radulescu, Daniel Racoceanu, Laurent Le Cam, Janan Arslan.

- Project acronym: MALMO
- Project title: Mathematical Approaches to Modelling Metabolic Plasticity and Heterogeneity in Melanoma
- Duration: 3 years (2021-2023)
- Coordinator: Ovidiu Radulescu
- Other partners: University of Montpellier (LPHI - UMR CNRS 5235, LIRMM - UMR CNRS 5506) and the Institut de Recherche en Cancérologie de Montpellier (IRCM – Inserm U1194), Paris Brain Institute (CNRS UMR 7225 – Inserm U 1127).
- Abstract: Cutaneous melanoma is a highly invasive tumor and despite recent therapeutic advances, most patients with advanced melanoma have a poor clinical outcome. At the molecular level, the most frequent mutations in melanoma affect the BRAF oncogene, a protein kinase of the MAPK pathway. Therapies targeting BRAF/MEK are effective for only 50% of the patients and almost systematically generate resistance. Some non-genetic mechanisms of drug resistance are associated with the strong heterogeneity and the plasticity and melanoma cells that still remain poorly understood. In the proposed project, we will address the importance of metabolic plasticity in melanoma cells in the context of drug resistance. In order to understand the mechanistic origin of the resistance to targeted therapies, we will build a predictive multiscale mathematical model. This model describes intracellular dynamics of the metabolic pathways and the dynamics of the melanoma cell sub- populations in interaction with their micro-environment. The model has spatial extension and takes into account cellular heterogeneity. Model initial conditions and parameters describing the microenvironment are learned from image analysis of tumour sections using deep learning as segmentation approach. In order to validate the model, we use a multiplexed imaging technique applied to the detection of metabolic markers in samples prepared from murine xenografted tumours submitted to treatment. Using the mathematical model and the in situ imaging data, we expect to prove the role of the metabolic reprogramming in generating melanoma heterogeneity and its contribution to resistance to targeted therapies. Our predictive mathematical model will also allow us to investigate in silico the relationship between micro-environment, metabolic/cellular plasticity and drug resistance, as well as the potential of combining several therapies simultaneously or with optimized scheduling.

9.3.1 ANR

ANR-PRC BETPARK

Participants: Fabrizio De Vico Fallani (*Correspondant*).

- Project acronym: BETPARK

- Project title: Neurofeedback for Parkinson's disease
- Duration: Apr 2021 - Mar 2025
- Amount: 712k€
- Coordinator: Nathalie George
- Other partners: CNRS CCLE; ICM
- Abstract: Parkinson's disease (PD) is a complex neurodegenerative disease caused by death of midbrain dopaminergic neurons. This calls for better understanding the pathophysiology of PD in order to pave the way to new non-pharmacological and non-invasive treatment options for PD. We propose to use neurofeedback (NF) to test whether PD patients can learn to self-regulate their brain activity to reduce pathological neural activity and thereby motor symptoms. We will leverage NF to target regulation of pathological beta band (8-35 Hz) oscillations, and we will characterize training-induced changes in cortical network activity and their relationship with symptom severity. Our goal is to provide direct evidence of the functional role of beta rhythms in the pathophysiology of PD while assessing NF as a new non-pharmacological and non-invasive tool for ameliorating PD motor symptoms.

ANR-PRC BRANDY

Participants: Fabrizio De Vico Fallani (*Correspondant*).

- Project acronym: BRANDY
- Project title: Brain attention network's dynamics
- Duration: Apr 2019 - Mar 2023
- Amount: 650k€
- Coordinator: Paolo Bartolomeo
- Other partners: ICM
- Abstract: Attention allows us to explore the environment and to effectively respond to external events. Attention sets priorities on the basis of our goals and of the salience of external stimuli. Human visual attention relies on distinct dorsal and ventral fronto-parietal networks, but little is known about their dynamics, because hitherto our knowledge mostly depends on fMRI, which has limited temporal resolution. BRANDY aims at building an anatomo-functional model of human visual attention. Specifically, BRANDY has three main objectives: Work Package (WP) 1 will determine the precise dynamics of normal visual attention on a fine-scale; WP2 will provide important evidence on neurotypical and impaired attention in neglect patients using a network-perspective. WP3 will build comprehensive anatomical and functional models of neurotypical and pathological human visual attention.

ANR-NIH-NSF CANDT

Participants: Fabrizio De Vico Fallani (*Correspondant*).

- Project acronym: CANDT
- Project title: Advancing neuroscientific discovery and training by lowering the barrier of entry to network neuroscience via open science

- Duration: Oct 2019 - Sep 2023
- Amount: 137k€
- Coordinator: Fabrizio De Vico Fallani
- Other partners: Indiana Univ., US; UPenn, US
- Abstract: This project will use open science methods and cloud-computing, effectively lowering the barrier of entry to network neuroscience and increase the widespread availability of well-maintained and reproducible network neuroscience tools. We will use the platform brainlife.io as a digital marketplace for network neuroscience analysis methods; network neuroscience tools and software will be packaged into self-contained, standardized, reproducible Apps, shared with and modified by a burgeoning community of users, and seamlessly integrated into existing brainlife.io processing and analysis pipelines. This approach will engage both experts in network science, scientists from other domains, and users of the proposed methods. In addition, it will ensure correct implementation, a high level of reproducibility, and maximal reusability of network neuroscience methods. As a requirement, Apps will also be accompanied by links to primary sources, in-depth tutorials, and documentation, and worked-through examples, highlighting their correct usage and offering solutions for mitigating possible pitfalls. This proposed research lowers the barrier of entry to network neuroscience, standardizes the software sharing process, and provides a cloud-based repository of expertly-maintained network neuroscientific tools and software that is made available to the broader neuroscientific community.

JPND project E-DADS

Participants: Stanley Durrleman (*Correspondant*), Nemo Fournier.

- Project acronym: E-DADS
- Project title: Early Detection of Alzheimer's Disease Subtypes
- Duration: 2019 - 2023
- Amount: 170k€
- Coordinator: Daniel Alexander (UCL)
- Other partners: University College London, Stichting VU University Medical Center, IRCCS Fatebenefratelli Brescia, Commonwealth Scientific and Industrial Research Organisation
- Abstract: Alzheimer's disease (AD) is a global health and economic burden with currently about 47 million affected individuals worldwide. No provably disease-modifying treatments exist. Delaying disease onset in dementia patients by five years can reduce care costs by 36% about €88B per year across the EU. A key confound preventing successful outcomes in most treatment trials to date has been AD's high variation in onset, mechanism, and clinical expression. E-DADS aims to untangle this heterogeneity by defining data-driven subtypes of the clinical manifestation of AD based on brain imaging, cognitive markers, and fluid biomarkers that are robustly identifiable from predictive risk factors (genetics, co-morbidities, physiological and lifestyle factors) years before disease onset. To achieve this we develop a novel multi-view learning strategies that relates end-stage disease manifestations observable in clinical cohorts to features of early-stage or at-risk individuals in preclinical cohorts and the general pre-affected population from population or aging studies. This approach is only possible now due to the availability of large population data, richly phenotyped AD cohorts and advances in machine learning. E-DADS uniquely assembles the necessary data and expertise. The ability to identify AD subtypes and predict them years before onset will significantly advance AD research and clinical management via precision medicine. First, it identifies distinct homogeneous groups, shedding new light on that nature and variability of disease mechanisms

ultimately pinpointing effective drug targets. Second, it enables enrichment of future clinical trials for specific groups of patients likely to benefit from a particular intervention. Third, it highlights potential lifestyle interventions that may affect or delay disease onset at very early stages. E-DADS delivers the underpinning technology to achieve this through machine learning and big-data analytics together with a prototype software tool enabling future translation and uptake.

JPND project Lemerend

Participants: Stanley Durrleman (*Correspondant*), Octave Guinebretière, Thomas Nedelec.

- Project acronym: Lemerend
- Project title: Leveraging medical records to identify patients at risk of neurodegenerative disease
- Duration: 2022 - 2025
- Amount: 260k€
- Coordinator: Stanley Durrleman
- Other partners: Aix-Marseille université, Karolinska Institute, University of Queensland
- Abstract: Neurodegenerative diseases represent one of the main public health issues in our western societies and one of the greatest challenges in drug development. Prevention policies have become essential to address these issues: primary prevention to prevent disease onset by acting on actionable risk factors, or secondary prevention to slow disease progression with very early therapeutic interventions, ideally at pre-symptomatic stages. Key to the implementation of such prevention measures is the identification of at-risk patients, at the point of care, and preferably long before disease onset. Our project, LeMeReND, proposes to use electronic health records (EHR) to identify biomedical risk factors through studying previous diagnoses (pre-clinical comorbidities), drug prescription, clinical care usage, and biological test results. This analysis will use longitudinal data in EHR registries including millions of patients who have been followed for at least 10 years before diagnosis in 4 different healthcare systems: Australia, France, the UK and Sweden and across 4 therapeutic areas: Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies and motor neuron diseases. We will identify the biomedical risk factors that are common to these diseases and the ones differentiating them. We will stratify patients based on the progression profile of their exposure to the set of risk factors, in order to design tailored primary prevention measures. We will also design a screening tool which will give each patient a propensity score to develop one of these neurodegenerative diseases. Such a tool could be deployed at the point of care to prioritise at-risk individuals for further inclusion in secondary prevention trials. We will evaluate the economic and social benefits of this new generation of precision prevention measures. We will study the public acceptability of a secondary-prevention effort, among the French population, and the feasibility of its implementation in primary care practices in France, Australia, and Sweden. Eventually, we will progress our understanding of the genetic and imaging markers of the disorders by studying the identified prodromal biomedical factors, using the UK BioBank and GWAS summary statistics. This will progress our understanding of the pathological processes which result in an increased risk to develop a specific neurodegenerative disease. LeMeReND gathers a multidisciplinary research group with a leading expertise in epidemiology, statistics and machine learning, in particular for the analysis of longitudinal EHR data. Partners have demonstrated a strong track record on neurodegenerative diseases (Sweden, France, Australia), analyses of large-scale data including neuroimaging (France), genetics (Australia), longitudinal modelling (Sweden, France), and machine learning (Australia, France). An expert team in health economics and health policy complements the consortium. LeMeReND will therefore provide invaluable insights to inform health policies and highlight possible new therapeutic targets. It will provide unique screening tools to facilitate the large-scale recruitment of patients in secondary prevention trials.

9.3.2 IHU

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
- Since 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 strengths 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.

ICM BBT Program - project ImagingDealInMS

Participants: Olivier Colliot (*Correspondant*), Bruno Stankoff (*Correspondant*), Arya Yazdan-Panah.

- Project title: Translating the biological mechanisms underlying neurodegeneration into multimodal imaging signatures using deep learning in Multiple Sclerosis (ImagingDealInMS)
- Started in 2021
- Coordinators: Olivier Colliot and Bruno Stankoff (ICM)
- Following the impressive advancements in the treatment of the relapsing phase of multiple sclerosis (MS), the major challenge remaining ahead is the development of treatments effective for preventing or delaying the irreversible accumulation of disability in this disease. A deep understanding of the mechanisms underlying neuro-axonal degeneration, which is the substrate of clinical progression, together with the development of reliable biomarkers, are pre-conditions for the advent and the evaluation of breakthrough therapies. The Stankoff group has pioneered an innovative imaging approach combining positron emission tomography and MRI, and succeeded in generating individual maps of key biological processes such as endogenous remyelination, neuroinflammation, or early damage preceding lesion formation. We further showed that these mechanisms were influencing disability worsening over the disease course, and recently obtained preliminary results suggesting that a multimodal combination of advanced MRI sequences may have the potential to identify these mechanisms and reproduce the PET results. In this project we propose a totally novel imaging approach that will capture remyelination of lesions, ongoing inflammation invisible on T1 and T2 MRI sequences (subacute/chronic active lesions) and to predict short-term future disease activity (identify prelesional areas), from a single multimodal MRI acquisition in patients with MS. Using PET results as a reference, multimodal signatures of these processes will be identified, and a deep learning approach integrating the whole MRI information in the training procedure will be applied to generate masks for each of them. The accuracy of the discovered algorithms will be validated on independent datasets acquired on a PET-MR system,

and their long-term clinical relevance will be tested in a clinical study evaluating patients around 10 years following their enrolment in pilot PET studies. As a result, novel tools assessing key biological processes driving neurodegeneration and disability worsening in MS will become largely available for the medical community, allowing an improved patients' stratification and prognostication, and opening the perspective of tailored care. These tools could also be used as novel endpoints in clinical trials, and may serve to capture similar processes in other neurological diseases.

ICM BBT3 Program - project StratifiAD

Participants: Daniel Racoceanu (*Correspondant*), Benoit Delatour (*Correspondant*), Stanley Durrleman, Lev Stimmer, Anuradha Kar, Gabriel Jimenez.

- Project title: STRATIFIAD - Refining Alzheimer Disease Patients' stratification using effective, traceable and explicable artificial intelligence approaches in computational histopathology.
- Duration: 2 years (2021-2023)
- Coordinators: Daniel Racoceanu and Benoit Delatour (ICM)
- Other partners: Histology Core platform (HYSTOMICS) and the Data Analysis Core platform (DAC), IHU/ICM
- Alzheimer's Disease (AD), the most frequent neurodegenerative disease, is defined by the misfolding and accumulation of A β peptides and of tau proteins in the brain. Sporadic AD is most commonly present in later life as an amnesic syndrome. However, the clinical presentation of the patients is heterogeneous and different subtypes of the disease have been described, including a rapidly progressive subtype of AD (rAD). Until now, neuropathological assessment of rAD cases was not able to identify specific neuropathological traits for this clinico-pathological entity, despite its unusual fast progression and clinical presentation leading to frequent misdiagnosis as Creutzfeldt-Jakob disease. Our hypothesis is that rAD brains, as well as other atypical variants of AD, display subtle histological changes that would be uncovered by high-throughput automated microscopic analysis. The topography and morphology of the tau and A β aggregates, the two main brain lesions characterizing the disease are heterogeneous. A β accumulation takes the form of focal deposits or diffuse plaques; tau lesions form the so-called neurofibrillary tangles but also present different morphologies in dendrites or axons. We propose to study the topography and morphology of these aggregates to better understand the morphological substratum of AD heterogeneity. To address this question at a large scale, one needs to develop software systems for the automatic segmentation, annotation and quantitation of brain lesions in histo-pathological whole slide images (WSI). Therefore, the goal of the STRATIFIAD project is twofold:
 1. to develop fully automated, traceable and explainable artificial intelligence (AI) approaches for the histological location and characterization of the tau and A β aggregates in whole slide brain images, and to deploy it for routine use on the Histomics core facility of the Paris Brain Institute,
 2. to use the previous analytics tool to study to which extent the topography and morphology of the different peptide aggregates present in the brain can be associated with the diversity of symptoms observed in various AD variants.

We propose to design, test and implement a modern supervised (initial stratification) and semi-supervised (advance refined stratification) deep reinforcement learning pipeline, combining methods able to generate high performances (quality and speed), high traceability / explicability and facilitate its usability in biomedical research and discovery. Our pathologists have started to acquire and to extensively annotate a unique set of histological images of postmortem brains from the rare form of rPAD and from other identified AD variants. Preliminary results of the consortium suggests that morphological features analysis is eligible for the first level of stratification. We believe that combining these features with topology and semantic-driven image exploration approaches (see

MICO TecSan project's references) would be able to guide our research toward a refined stratification. Therefore, causal knowledge-based elements, together with semantic-driven WSI exploration will be likely to create a reusable pipeline, able to structure our experience plan, as to justify the numeric results. The tools within this project will contribute to open-source initiatives, and would be therefore available to the scientific community for replicable massive data analysis. STRATIFIAD will therefore contribute to advance the knowledge in AD and push forward the technological development in this area.

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 rely 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.

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.

9.3.3 3IA Institutes - PRAIRIE

Participants: Ninon Burgos, Olivier Colliot, Stanley Durrleman.

- Project acronym: PRAIRIE
- Project title: Paris Artificial Intelligence Research Institute
- Since 2019
- Director: Isabelle Ryl
- Website: [PRAIRIE](#)
- PRAIRIE is one of the four selected French Institutes of AI. It was selected within a call for creation of interdisciplinary AI research institutes (or "3IAs" for "Instituts Interdisciplinaires d'Intelligence Artificielle"), as part of the national French initiative on Artificial Intelligence (AI). PRAIRIE aspires to become within five years a world leader in AI research and higher education, with an undeniable impact on economy and technology at the French, European and global levels. ARAMIS team members N. Burgos, O. Colliot and S. Durrleman hold a chair at PRAIRIE.

9.3.4 National Networks

- [GdR Statistics and Medicine](#)
- [GdR \(MaDICS\) Masses de Données, Informations et Connaissances en Sciences Big Data - Data Science, Statistics and Medicine](#)

- 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
- M.-C. Corsi serves as Secretary General of the CORTICO national network for brain-computer interfaces
- [GdR ISIS \(Signal and Image Processing\)](#)

9.3.5 Other National Programs

Fondation Vaincre Alzheimer

Participants: Olivier Colliot, Vincent Henry, Martin Hoffman-Apitius

France Parkinson

Participants: Jean-Christophe Corvol, Olivier Colliot, Stanley Durrleman

- Project title: PRECISE-PD - From pathophysiology to precision medicine for Parkinson's disease
- 2019-2024
- Amount: 3M€
- Coordinator: Jean-Christophe Corvol
- Other partners: Inserm CIC-1436, Inserm CIC-P1421, Inserm U1171, Université de Bordeaux (IMN), University of Glasgow, University of Calgary,
- Abstract: Parkinson's disease (PD) is a complex neurodegenerative disease characterized by the progression of motor and non-motor symptoms resulting from the spreading of the disease into dopaminergic and non-dopaminergic areas. Clinical trials have failed to demonstrate efficacy to slow PD progression because the relationships between progression profiles and their underlying molecular mechanisms remain to be identified. The objective of PRECISE-PD is to propose a mechanismsbased progression model of PD by combining genetic and longitudinal clinical data from a large cohort of patients. We will implement a biobank to the NS-PARK/FCRIN cohort collecting motor and non-motor symptoms from >22,000 PD patients followed in the 24 expert centers in France. Genomic data will be generated by using a microarray platform developed for neurodegenerative diseases studies, and brain imaging will be obtained from a subgroup of patients. Computational and machine learning approaches will be developed to address the challenges of analyzing the high dimensionality and the mixture of data necessary to move beyond empirical stratification of patients. Replication will be performed in independent cohorts, and biological validation will combine biomarkers and preclinical research. PRECISE-PD is an unprecedented opportunity to open the path to the new era of precision and personalized medicine for PD.

10 Dissemination

10.1 Promoting scientific activities

10.1.1 Scientific events: organisation

General chair, scientific chair

- O. Colliot is Conference Chair of the **SPIE Medical Imaging: Image Processing conference** for the period 2022-2025.

Member of the organizing committees

- O. Colliot (with other researchers from 3IA Institutes), organization of the First French Congress on Artificial Intelligence for Biomedical Imaging, Paris, France, 2023
- O. Colliot, ICM/Inria/SCAI joint workshop “Computational and mathematical approaches for neuroscience”, 2022
- S. Durrleman and N. Burgos co-organized the AI4Health 2022 winter school with the Health Data Hub, held virtually.
- B. Couvy-Duchesne was part of the 2022 organising faculty for the International Statistical Genetics Workshop, held virtually.
- D. Racoceanu was a member of the organising committee of MICCAI 2022, the 25th International Conference on Medical Image Computing and Computer Assisted Intervention, Singapore.

10.1.2 Scientific events: selection

Member of the conference program committees

- O. Colliot, Program Committee member SPIE Medical Imaging: Image Processing conference 2022
- O. Colliot, Meta-Reviewer, IEEE International Symposium on Biomedical ISBI 2023
- N. Burgos, Technical Committee member, Medical Imaging with Deep Learning (MIDL), 2022

Reviewer

- O. Colliot acted as a reviewer for the international conferences IEEE International Symposium on Biomedical Imaging (IEEE ISBI) and IEEE/CVF Computer Vision and Pattern Recognition (IEEE/CVF CVPR).
- N. Burgos acted as a reviewer for the International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI), the international workshop on Simulation and Synthesis in Medical Imaging (SASHIMI), and the IEEE International Symposium on Biomedical Imaging (IEEE ISBI).
- B. Couvy-Duchesne acted as a reviewer for Frontiers in genetics, Frontiers in Psychiatry, Nature Neuroscience, the IEEE International Symposium on Biomedical Imaging, as well as the MESSIDOR call (Methodology of Innovative Clinical Trials) funded by Inserm.
- D. Racoceanu acted as a reviewer for ECDP 2022 - European Congress on Digital Pathology, and for IABM 2023 - Colloque Français d’Intelligence Artificielle en Imagerie Biomédicale.
- F. De Vico Fallani acted as a reviewer for NetSCI, Complenet, Complex networks, CCS.

10.1.3 Journal

Member of the editorial boards

- O. Colliot is an Associate Editor and a member of the Editorial Board of the journal Medical Image Analysis (Elsevier).
- O. Colliot is an Associate Editor of the journal Frontiers in Brain Imaging Methods.
- B. Couvy-Duchesne is an Associate Editor of the journal Frontiers Genetics (section Behavioral and Psychiatric Genetics).

- F. De Vico Fallani is an Associate Editor of the journal PLoS One.
- F. De Vico Fallani is an Associate Editor of the journal Brain Topography.
- S. Durrleman is an associate editor of the Journal of Imaging

Reviewer - reviewing activities

- O. Colliot acted as a reviewer for the IEEE Journal of Biomedical and Health Informations, for the SPIE Journal of Medical Imaging and for Neuroradiology.
- N. Burgos acted as a reviewer for Medical Image Analysis, IEEE Transactions on Medical Imaging, Computer Methods and Programs in Biomedicine, Artificial Intelligence In Medicine, the SPIE Journal of Medical Imaging, PLOS ONE, Communications Biology, and the International Journal of Radiation Oncology • Biology • Physics.
- M.-C. Corsi acted as a reviewer for eNeuro, NeuroImage: Clinical, Brain Topography, Brain Connectivity, Journal of Neural Engineering, Frontiers in Human Neuroscience, Scientific Reports, PLOS ONE, Sensors, Int. Journal of Neural Systems, Brain-Computer Interfaces, and IOP Biomed. Phys.
- D. Racoceanu acted as a reviewer for the Medical Image Analysis (MEDIA) and Nature Scientific Reports.
- F. De Vico Fallani acted as a reviewer for Brain, Nature Communications, and NeuroImage.
- S. Tezenas du Montcel acted as a reviewer for Annals of Clinical and Translational Neurology, IEEE Journal of Biomedical and Health Informatics, Plos One, Brain, BMC Medical Genetics, Journal of Neurology, Journal of Neurology, Neurosurgery and Psychiatry, Movement Disorders, Journal of Huntington's Disease, Therapeutic advances in Rare Disease.

10.1.4 Invited talks

- N. Burgos gave an invited talk during the Journée Scientifique PLBS - ImAgerie & IA (Lille, France).
- N. Burgos gave an invited talk during the AI4Health Winter School (virtual).
- N. Burgos gave an invited seminar at the BME Paris Seminars "Open Your Mind" (Paris, France).
- N. Burgos gave an invited seminar at the Master Mathématiques pour les Sciences du Vivant (virtual).
- S. Durrleman gave an invited lecture at the seminar: AI in experimental biology and bio-medicine.
- S. Durrleman gave an invited lecture at the translational neuroscience day by NeurATRIS.
- F. De Vico Fallani gave an invited lecture at the Lake Como Summer school on complex networks.
- F. De Vico Fallani gave an invited lecture at the Mediteranean school on complex networks.
- F. De Vico Fallani gave an invited talk at the AI and neuroscience workshop at the KTH Stockolm.
- F. De Vico Fallani gave an invited lecture at the FRCCS French Regional Conference on Complex Systems.
- S. Tezenas du Montcel gave an invited lecture at 2nd Ataxia Global Initiative conference.
- S. Tezenas du Montcel gave an invited lecture at the AGI's Tools & Methods studio series.

10.1.5 Leadership within the scientific community

- Olivier Colliot is a member of the steering committee of the European infrastructure EBRAINS.
- F. De Vico Fallani is a member of the Executive Committee of the Complex Systems Society (CSS).
- D. Racoceanu was a member (2018 to 2022) of the Board of Directors of the Medical Image Computing and Computer-Assisted Intervention Society (MICCAI).
- D. Racoceanu is a member of the Advisory Board of the European Society of Integrative Digital Pathology (ESDIP).
- S. Tezenas du Montcel is a member of the Critical Path to Therapeutics for the Ataxias (CPTA)

10.1.6 Scientific expertise

- O. Colliot acts as an expert for GENCI (the national facility for high-performance computing).
- Stanley Durrleman is member of the scientific advisory board of the Health Data Hub.
- D. Racoceanu is member of the HCERES committee for a CNRS lab evaluation.
- S. Tezenas du Montcel is a member of the scientific board of the National Bank for Rare Diseases (Banque Nationale de Données Maladies Rares, BNDMR).
- S. Tezenas du Montcel is a member of the Comité de Protection des Personnes (CPP) Ile de France 6.
- S. Tezenas du Montcel is a member of scientific board of the CERMOI study.

10.1.7 Research administration

- O. Colliot is a member of the "Bureau du Comité des Projets" of the Inria Paris Center.
- F. De Vico Fallani is a member of the "Comité d'Evaluation Scientifique" of the Inria Paris Center.

10.2 Teaching - Supervision - Juries

10.2.1 Teaching

- Master: Olivier Colliot coordinates the course "Deep Learning for Medical Imaging" of the Master 2 MVA (Mathematics, Vision, Learning) of ENS Paris-Saclay, University of Paris, Centrale-Supelec and teaches 15 hours (CM).
- Master: Olivier Colliot coordinates the course "Artificial Intelligence" of the Master 2 Bioentrepreneur of Paris-Descartes University and teaches 20 hours (CM).
- Master: Daniel Racoceanu coordinates the teaching module (UE) "Introduction to Artificial Intelligence" of the Master 1 : Control Sciences and Robotics (AR - Automatique, Robotique) and Electronics, Electrical Energy, Control Sciences (E3A - Électronique, Énergie Électrique, Automatique) at Sorbonne University, Faculty of Science and Engineering (110 students / 3 ECTS) and teaches 30 hours (CM/courses and TP/labs).
- Master: Daniel Racoceanu coordinates the teaching module (UE) "Computer Vision for Biomedical" of the Master 1 : Electronics, Electrical Energy, Control Sciences (E3A - Électronique, Énergie Électrique, Automatique) at Sorbonne University, Faculty of Science and Engineering (50 students / 3 ECTS) and teaches 32 hours (CM/courses and TP/labs).
- Master: Daniel Racoceanu coordinates the teaching module (UE) "Image Processing" of the Master 1 : Control Sciences and Robotics (AR - Automatique, Robotique) at Sorbonne University, Faculty of Science and Engineering (80 students / 3 ECTS) and teaches 36 hours (CM/courses and TP/labs) - courses in English.

- Master: Daniel Racoceanu coordinates the teaching module (UE) "3D Computer Graphics" of the Master 1 : Computer Sciences (Informatique) at Sorbonne University, Faculty of Science and Engineering (20 students / 3 ECTS) and teaches 24 hours (CM/courses and TP/labs) - courses in English (within the european programme EIT Health).
- Engineering school: Olivier Colliot, 5 hours (eqTD), Mines ParisTech
- Medical school: Didier Dormont is the Director of the University Diploma (DIU) "Diagnostic and Therapeutic Neuroradiology", Sorbonne University
- Medical school: Didier Dormont, Courses for Medical Students, Sorbonne University
- Medical school: Stéphane Epelbaum organizes the national teaching course on Alzheimer's disease and related diseases.
- 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
- Master: F De Vico Fallani gave a lecture at UE Closed-loop Neuroscience, Central Supélec)
- Master: Daniel Racoceanu gives lectures / labs (14 hours) in "Visual Perception for Robotics" - Master 2 : Control Science and Robotics (AR - Automatique, Robotique) at Sorbonne University, Faculty of Science and Engineering.
- Master: Daniel Racoceanu gives lectures / labs (14 hours) in "Machine Learning" - Master 1 : Control Science and Robotics (AR - Automatique, Robotique) at Sorbonne University, Faculty of Science and Engineering.
- Master: Daniel Racoceanu gives lectures / labs (20 hours) in "Object-Oriented Programming" - Master 1 : Control Science and Robotics (AR - Automatique, Robotique) at Sorbonne University, Faculty of Science and Engineering.
- Licence: Daniel Racoceanu gives seminars (TD) and labs (TP) in "Programming" - Licence 1 : all Licences - option Control Sciences at Sorbonne University, Faculty of Science and Engineering.
- Master : S. Durreleman gave 21 hours lecture for the Master MVA (Mathématiques, Vision et Apprentissage), ENS Paris-Saclay
- Master : S. Durreleman gave 4hrs lecture for the Master bio-entrepreneur of the University of Paris.
- F De Vico Fallani was invited to give a teaching lesson at School on Complex Networks, Lake Como School Advanced Studies, Italy.
- S. Durreleman gave a lecture at the DU Intelligence artificielle et santé of the Université de Paris.
- B. Couvy-Duchesne was invited to be a tutor at the International Statistical Genetics Workshop, organised in Boulder, Colorado (remote).
- B. Couvy-Duchesne gave a lecture in the NeuroEthics session of the IMind Master.
- N. Burgos gave lectures on deep learning for medical imaging as part of the AI4Health Winter School, DU IA appliquée en santé, DIU Neuroradiologie diagnostique et thérapeutique and the CENIR courses.
- M.-C. Corsi gave lectures on Brain-Computer Interfaces as part of the DU IA Santé, M2 Computational Neuroscience and Neuroengineering, and the CENIR courses.

- Master: S. Tezenas du Montcel coordinates the Master 1 of Public Health of Sorbonne University.
- Master: S. Tezenas du Montcel coordinates the course of Biostatistics of the Master 1 of Health of Sorbonne University and teaches 18 hours (CM).
- Master: S. Tezenas du Montcel coordinates the course of "Bases de données médico-administratives: aspects épidémiologiques" of the Master 2 of Public Health of Sorbonne University and teaches 9 hours (CM).
- Medical school: S. Tezenas du Montcel gives courses for Medical students (First year, 32 hours TD).

10.2.2 Supervision

- PhD in progress: Élise Delzant, "Methods for big-data neuroimaging analyses", started in 2022, advisors: B. Couvy-Duchesne and O. Colliot
- PhD in progress: Ravi Hassanaly, "Deep generative models for the detection of anomalies in the brain", started in 2020, advisors: O. Colliot and N. Burgos
- PhD in progress: Guanghui Fu, "Segmentation, classification and generative models for computer-aided diagnosis of neurological diseases from neuroimaging data", started in 2021, advisors: O. Colliot and D. Dormont
- PhD in progress: Sophie Loizillon, "Deep learning for assisting diagnosis of neurological diseases using a very large-scale clinical data warehouse", started in 2021, advisors: O. Colliot, N. Burgos and D. Dormont
- PhD in progress: Lisa Hemforth, "Deep learning for rating of atypical anatomical patterns on MRI data", started in 2021, advisors: O. Colliot, B. Couvy-Duchesne and C. Cury
- PhD in progress: Arya Yazdan-Panah, "Deep learning for multimodal image analysis in multiple sclerosis", started in 2021, advisors: O. Colliot and B. Stankoff
- PhD in progress: Mehdi Ounissi, "Explainable Artificial Intelligence", started in 2021, advisor: D. Racoceanu
- PhD in progress: Gabriel Alexandro Jimenez Garay, "Interpretable Deep Learning in Computational Histopathology for Alzheimer Disease Patients' Stratification Refinement", started in 2021, advisor: D. Racoceanu
- PhD in progress: Clément Mantoux, Statistical analysis of graphs, started in 2019, advisors: S. Durrleman and S. Allasonnière
- PhD in progress: Benoit Sauty, Multimodal models of neurodegenerative disease progression, started in 2020, advisor: S. Durrleman
- PhD in progress: Pierre-Emmanuel Poulet, Models of progression of multiple risks, started in 2020, advisor: S. Durrleman
- PhD in progress: Nemo Fournier, Heterogeneous Population Stratification using Longitudinal and Genetic Data, started in 2021, advisor: S. Durrleman
- PhD in progress: Juliette Ortholand, Modeling changes of dynamics with longitudinal data, started in 2021, advisor: S. Durrleman and S. Tezenas du Montcel
- PhD in progress: Octave Guinebretière, Analysis of electronic health records for assessing the risk to develop neurological diseases, advisor: S. Durrleman, Th. Nédelec
- PhD in progress: Vito Dichio, Statistical models of brain networks, started in 2020, advisor: F. De Vico Fallani

- PhD in progress: Charley Presigny, Multilayer analysis of brain networks, started in 2020, advisor: F. De Vico Fallani
- PhD in progress: Remy BenMessaoud, Controllability of brain networks, started in 2020, advisor: F. De Vico Fallani, M Chavez
- PhD in progress: Tristan Venot, Multimodal brain-computer interfaces, started in 2020, advisor: F. De Vico Fallani, L. Saint-Bauzel
- PhD in progress: Sophie Skriabine, Vascular networks, started in 2020, advisor: F. De Vico Fallani, N. Renier
- PhD in progress: Sofia Kaisaridi, Modélisation multimarqueurs de l'évolution clinique et en imagerie cérébrale de patients CADASIL et de l'influence des données manquantes, started in 2022, advisor: S. Tezenas du Montcel

10.2.3 Juries

- O. Colliot participated, as reviewer, to the PhD committee of Stenzel Cackowski (Université Grenoble-Alpes).
- O. Colliot participated, as reviewer, to the PhD committee of Benoît Dufumier (Université Paris-Saclay).
- O. Colliot participated, as examiner, to the HDR committee of Ninon Burgos (Sorbonne Université).
- O. Colliot participated, as thesis supervisor, to the PhD committee of Dario Saracino (Sorbonne Université).
- O. Colliot participated, as thesis supervisor, to the PhD committee of Simona Bottani (Sorbonne Université).
- O. Colliot participated, as thesis supervisor, to the PhD committee of Virgilio Kmetzsch (Sorbonne Université).
- N. Burgos participated, as examiner, to the PhD committee of Gauthier Dot (HESAM Université).
- N. Burgos participated, as president, to the PhD committee of Lydia Chougar (Sorbonne Université).
- D. Racoceanu participated, as president, to the PhD committee of Rudan Xiao (Université Côte d'Azur).
- D. Racoceanu participated, as reviewer, to the PhD committee of Sébastien Pilouso (Université Paris-Saclay).
- D. Racoceanu participated, as reviewer, to the PhD committee of Sarah Laroui (Université Côte d'Azur).
- F. De Vico Fallani participated, as president, to the PhD committee of Theophile Bieth (Sorbonne Université).
- F. De Vico Fallani participated, as Reviewer, to the PhD committee of Anthony Baptista (Université Aix-Marseille).

10.3 Popularization

10.3.1 Internal or external Inria responsibilities

- B. Couvy-Duchesne is a member of the ethics committee of the Paris Brain Institute (COMETH).

10.3.2 Articles and contents

- N. Burgos participated to the podcast ‘Braincast - La voix des neurones’ by the Cerveau & Psycho magazine (www.cerveauetpsycho.fr/sr/braincast).

10.3.3 Interventions

- O. Colliot gave a presentation for ICM donors hosted by the Publicis group.
- S. Durrleman participates to a round table for investors at ODDO-BHF.
- D. Racoceanu participated to a round table about Integrative Pathology and Clinical Integration of AI at the European Congress on Digital Pathology 2022, Berlin, Germany.

11 Scientific production

11.1 Major publications

- [1] M. Ansart, S. Epelbaum, G. Bassignana, A. Bône, S. Bottani, T. Cattai, R. Couronné, J. Faouzi, I. Koval, M. Louis, E. Thibeau-Sutre, J. Wen, A. Wild, N. Burgos, D. Dormont, O. Colliot and S. Durrleman. ‘Predicting the Progression of Mild Cognitive Impairment Using Machine Learning: A Systematic, Quantitative and Critical Review’. In: *Medical Image Analysis* 67 (Jan. 2021), p. 101848. DOI: [10.1016/j.media.2020.101848](https://doi.org/10.1016/j.media.2020.101848). URL: <https://hal.archives-ouvertes.fr/hal-02337815>.
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- [14] B. Couvy-duchesne, L. T. Strike, F. Zhang, Y. Holtz, Z. Zheng, K. E. Kemper, L. Yengo, O. Colliot, M. Wright, N. Wray, J. Yang and P. M. Visscher. ‘A unified framework for association and prediction from vertex-wise grey-matter structure’. In: *Human Brain Mapping* (20th July 2020). DOI: [10.1002/hbm.25109](https://doi.org/10.1002/hbm.25109). URL: <https://hal.archives-ouvertes.fr/hal-02904458>.
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11.2 Publications of the year

International journals

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