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Université Pierre et Marie Curie (Paris 6)

Activity Report 2014

Project-Team ARAMIS

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

RESEARCH CENTER
Paris - Rocquencourt

THEME
Computational Neuroscience and Medecine

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Project-Team ARAMIS

Keywords: Neuroimaging, Image Processing, Signal Processing, Networks, Medical Images, Statistical Learning

ARAMIS is a joint project-team between Inria, CNRS, Inserm and University Pierre and Marie Curie within the Brain and Spinal cord Institute (ICM). It is located in the Pitié-Salpêtrière Hospital in Paris.

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

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2. Overall Objectives

2.1. Introduction

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

3. Research Program

3.1. General aim

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

3.2. Modeling brain structure: from imaging to geometric models

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

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

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

3.3. Modeling dynamical brain networks

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

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

3.4. Methodologies for large-scale datasets

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

In this context, our objectives are:

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

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

4. Application Domains

4.1. Introduction

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

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

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

4.2. Understanding brain disorders

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

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

4.3. Biomarkers for diagnosis, prognosis and clinical trials

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

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

4.4. Brain computer interfaces for clinical applications

A brain computer interface (BCI) is a device aiming to decode brain activity, thus creating an alternate communication channel between a person and the external environment. BCI systems can be categorized on the base of the classification of an induced or evoked brain activity. The central tenet of a BCI is the capability

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

4.5. Deep Brain Stimulation

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

5. New Software and Platforms

5.1. SACHA

Participants: Marie Chupin [Correspondant], Ludovic Fillon.

SACHA ("Segmentation Automatisée Compétitive de l'Hippocampe et de l'Amygdale") is a software for the fully automatic segmentation of the hippocampus and the amygdala from MRI 3D T1 brain scans. It has been validated in various populations including healthy controls and patients with Alzheimer's disease, epilepsy and depression. It has been successfully applied to over 3,000 subjects, both controls, from adolescents to elderly subjects, and patients with different types of pathologies. The current stable version is fully automatic and focused on cross-sectional segmentation. The software can be used both as a command-line program or through a graphical user interface (GUI). The core of the program is coded in C++. It has a dependency to the AIMS library (http://www.brainvisa.info) and preprocessing steps rely on processes in Matlab from SPM (http://www.fil.ion.ucl.ac.uk/spm/). The GUI is coded in Python and is based on BrainVISA (http://www.brainvisa.info). The software has been registered at the APP (French agency for software protection).

5.2. WHASA

Participants: Marie Chupin [Correspondant], Ludovic Fillon, Thomas Samaille.

WHASA ("White matter Hyperintensity Automatic Segmentation Algorithm") is a software for the fully automatic segmentation of age-related white matter hyperintensities from MRI FLAIR and 3D T1 brain scans. It has been validated on a population showing a wide range of lesion load, and is being further evaluated on elderly subjects with few clinical abnormalisties and with different acquisition characteristics. The current stable version is fully automatic and focused on cross-sectional segmentation. The software can be used both as a Matlab command-line or through a graphical user interface (GUI). The core of the program is coded in Matlab. It has a dependency to the SPM environment (http://www.fil.ion.ucl.ac.uk/spm/). The GUI is coded in Python and is based on BrainVISA (http://www.brainvisa.info). The software has been registered at the APP (French agency for software protection).

5.3. Deformetrica

Participants: Stanley Durrleman [Correspondant], Alexandre Routier, Pietro Gori, Marcel Prastawa, Ana Fouquier, Joan Glaunès, Benjamin Charlier, Cedric Doucet.

Deformetrica is a software which estimates diffeomorphic deformations between sets of geometric objects in 2D and 3D. Those deformations are estimated either for the registration of two of such objects sets or for the construction of an atlas from several of such sets (a template model set and deformations mapping the template model to each set). Geometric objects could be grey-level images, surface meshes, polygonal lines or unstructured point sets. The method relies on the metric on currents for the comparison of point sets and the sum of squared differences for the comparison of images.

The software is written in C++ and relies on the ITK and VTK libraries. Core functions are coded with CUDA for their parallelization on GPU. It is a command-line software.

The version 2.1 of the software has been released on December 19, 2014. It is freely accessible to the scientific community at www.deformetrica.org.

5.4. qualiCATI

Participants: Marie Chupin [Correspondant], Hugo Dary, Urielle Thoprakarn, Amadou Tall, David Gay, Nicolas Vibet, Aude Costard, Cyril Poupon, Vincent Perlbarg, Mélanie Pélégrini-Issac, Alexandre Vignaud.

qualiCATI is a software designed for comprehensive quality control of multimodal MRI data acquisition in large multicentre clinical studies. The software is built as a platform receiving several modules, developped by several CATI engineers. The first module is dedicated to acquisition requirement checking and conversion to nifti format. The second module aims at making 3DT1 acquisition quality check more systematic, and relies both on visual inspection and quantitative indices. The third module allows a simultaneous evaluation of the clinical part of the CATI acquisition protocol. The fourth module embeds automatic indices to evaluate resting state fMRI acquisition. The fifth module is dedicated to first preprocessings and quality indices for dMRI. The sixth module is dedicated to qMRI, with visual and automated quality control together with preprocessings. The last module is dedicated to data and project management. QualiCATI requires training for the visual parts, and is closely linked with a team of clinical research assistants. It has been used to analyse about 5000 subjects from about 15 multi centre research projects initiated before or after the CATI started. Other modules will be added in the future to embed new aspects of the MRI protocol proposed by the CATI. The Aramis team is in charge of the second and third modules and jointly in charge of the first module. The software is centered on a graphical user interface (GUI). The whole program is coded in Python within the pyPTK environment developped by Cyril Poupon (Neurospin). It has dependencies to SPM (http://www.fil.ion.ucl.ac.uk/spm/) and brainVISA environments as well as specific tools for DICOM management.

5.5. Brain Networks Toolbox

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

Brain Networks Toolbox is a collection of Matlab routines developed to quantify topological metrics of complex brain networks. These routines are associated with published publications with application to real data and freely distributed via the FreeBorn (French Brain Networks) consortium https://sites.google.com/site/fr2eborn/download

6. New Results

6.1. Highlights of the Year

ARAMIS has contributed to the special issue on "Complex network theory and the brain" in the prestigious journal of Philosopical Transactions of the Royal Society, Series B. This work was featured by the ICM (http://icm-institute.org/en/news/complex-network-theory-and-the-brain?lang=en) and Inria (http://www.inria.fr/en/centre/paris-rocquencourt/news/complex-network-theory-and-the-brain).

6.2. Detection of volume loss in hippocampal layers in Alzheimer's disease using 7 T MRI

Participants: Claire Boutet, Marie Chupin, Stéphane Lehéricy, Linda Marrakchi-Kacem, Stéphane Epelbaum, Cyril Poupon, Christopher Wiggins, Alexandre Vignaud, Dominique Hasboun, Bénédicte Desfontaines, Olivier Hanon, Bruno Dubois, Marie Sarazin, Lucie Hertz-Pannier, Olivier Colliot [Correspondant].

In Alzheimer's disease (AD), the hippocampus is an early site of tau pathology and neurodegeneration. Histological studies have shown that lesions are not uniformly distributed within the hippocampus. Moreover, alterations of different hippocampal layers may reflect distinct pathological processes. 7 T MRI dramatically improves the visualization of hippocampal subregions and layers. In this study, we aimed to assess whether 7 T MRI can detect volumetric changes in hippocampal layers in vivo in patients with AD. We studied four AD patients and seven control subjects. MR images were acquired using a whole-body 7 T scanner with an eight channel transmit-receive coil. Hippocampal subregions were manually segmented from coronal T2*-weighted gradient echo images with $0.3 \times 0.3 \times 1.2$ mm3 resolution using a protocol that distinguishes between layers richer or poorer in neuronal bodies (Figure 1). Five subregions were segmented in the region of the hippocampal body: alveus, strata radiatum, lacunosum and moleculare (SRLM) of the cornu Ammonis (CA), hilum, stratum pyramidale of CA and stratum pyramidale of the subiculum. We found strong bilateral reductions in the SRLM of the cornu Ammonis and in the stratum pyramidale of the subiculum ($p < 0.05$), with average cross-sectional area reductions ranging from -29% to -49%. These results show that it is possible to detect volume loss in distinct hippocampal layers using segmentation of 7 T MRI. 7 T MRI-based segmentation is a promising tool for AD research.

More details in [3].

6.3. White matter lesions in patients with frontotemporal lobar degeneration due to progranulin mutations

Participants: Paola Caroppo, Isabelle Le Ber, Agnès Camuzat, Fabienne Clot, Lionel Naccache, Foudil Lamari, Anne Bertrand, Serge Belliard, Olivier Colliot [Correspondant], Alexis Brice.

Mutations in the progranulin (GRN) gene are responsible for 20% of familial cases of frontotemporal dementias. All cause haploinsufficiency of progranulin, a protein involved in inflammation, tissue repair, and cancer. Carriers of the GRN mutation are characterized by a variable degree of asymmetric brain atrophy, predominantly in the frontal, temporal, and parietal lobes. We described four GRN mutation carriers with remarkable widespread white matter lesions (WML) associated with lobar atrophy shown on magnetic resonance imaging. The WML were predominantly in the frontal and parietal lobes and were mostly confluent, affecting the periventricular subcortical white matter and U-fibers. In all patients, common vascular, metabolic, inflammatory, dysimmune, and mitochondrial disorders were excluded and none had severe vascular risk

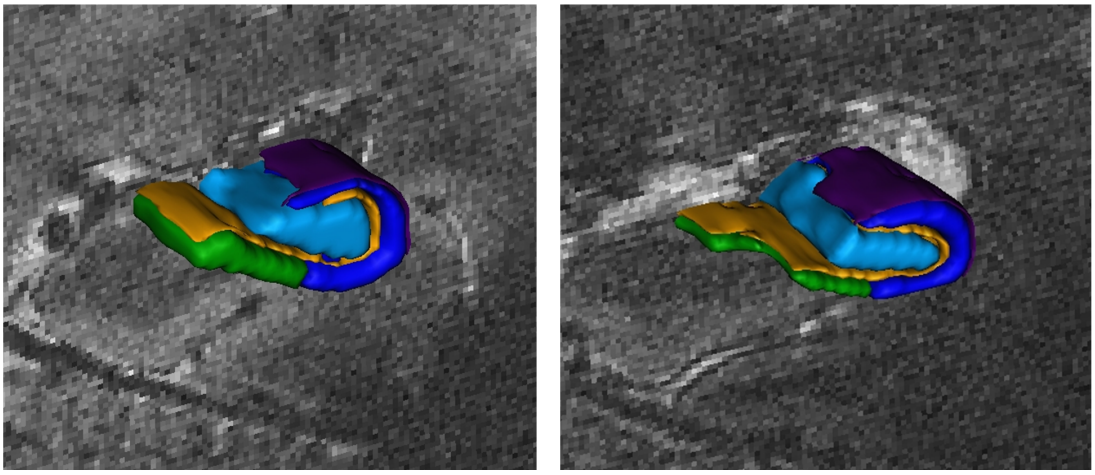

Figure 1. Segmentation of hippocampal layers using in vivo 7 Tesla MRI. were performed on the second echo image. Left panel: control subject. Right panel: patient with Alzheimer's disease. Purple, alveus; dark blue, stratum pyramidale of CA1-3; yellow, strata radiatum,lacunosum and moleculare of CA1-3, strata lacunosum and moleculare of the subiculum and stratum moleculare of gyrus dentatus; cyan, stratum pyramidale of CA4 and stratum granulosum and polymorphic layer of gyrus dentatus; green, stratum pyramidale of the subiculum.

factors. Our data suggest that white matter involvement may be linked to progranulin pathological processes in a subset of GRN mutation carriers. The plasma progranulin measurement, which is predictive of GRN mutations, and GRN sequencing should thus be included in investigations of patients with frontotemporal lobar degenerations who show unusual white matter hyperintensities and atrophy on magnetic resonance imaging.

More details in [4].

6.4. Template-based morphometry using diffeomorphic iterative centroids

Participants: Claire Cury [Correspondant], Joan Glaunès, Marie Chupin, Olivier Colliot.

A common approach for the analysis of anatomical variability relies on the estimation of a representative template of the population, followed by the study of this population based on the parameters of the deformations going from the template to the population. The Large Deformation Diffeomorphic Metric Mapping framework is widely used for shape analysis of anatomical structures, but computing a template with such framework is computationally expensive. We proposed a fast approach for template-based analysis of anatomical variability. The template is estimated using an iterative approach which quickly provides a centroid of the population. Statistical analysis is then performed using principal component analysis on the initial momenta that define the deformations between the centroid and each subject of the population. This approach was applied to the analysis of hippocampal shape on 80 patients with Alzheimer's Disease and 138 controls from the ADNI database.

More details in [22] and [36].

6.5. Structural connectivity differences in left and right temporal lobe epilepsy

Participants: Pierre Besson, Vera Dinkelacker [Correspondant], Romain Valabrègue, Lionel Thivard, Xavier Leclerc, Michel Baulac, Daniela Sammler, Olivier Colliot, Stéphane Lehéricy, Séverine Samson, Sophie Dupont.

Our knowledge on temporal lobe epilepsy (TLE) with hippocampal sclerosis has evolved towards the view that this syndrome affects widespread brain networks. Diffusion weighted imaging studies have shown alterations of large white matter tracts, most notably in left temporal lobe epilepsy, but the degree of altered connections between cortical and subcortical structures remains to be clarified. We performed a whole brain connectome analysis in 39 patients with refractory temporal lobe epilepsy and unilateral hippocampal sclerosis (20 right and 19 left) and 28 healthy subjects. We performed whole-brain probabilistic fiber tracking using MRtrix and segmented 164 cortical and subcortical structures with Freesurfer. Individual structural connectivity graphs based on these 164 nodes were computed by mapping the mean fractional anisotropy (FA) onto each tract. Connectomes were then compared using two complementary methods: permutation tests for pair-wise connections and Network Based Statistics to probe for differences in large network components. Comparison of pair-wise connections revealed a marked reduction of connectivity between left TLE patients and controls, which was strongly lateralized to the ipsilateral temporal lobe. Specifically, infero-lateral cortex and temporal pole were strongly affected, and so was the perisylvian cortex. In contrast, for right TLE, focal connectivity loss was much less pronounced and restricted to bilateral limbic structures and right temporal cortex. Analysis of large network components revealed furthermore that both left and right hippocampal sclerosis affected diffuse global and interhemispheric connectivity. Thus, left temporal lobe epilepsy was associated with a much more pronounced pattern of reduced FA, that included major landmarks of perisylvian language circuitry. These distinct patterns of connectivity associated with unilateral hippocampal sclerosis show how a focal pathology influences global network architecture, and how left or right-sided lesions may have differential and specific impacts on cerebral connectivity.

More details in [2].

6.6. Morphometry of anatomical shape complexes with dense deformations and sparse parameters

Participants: Stanley Durrleman [Correspondant], Marcel Prastawa, Nicolas Charon, Julie Korenberg, Sarang Joshi, Guido Gerig, Alain Trouvé.

We propose a generic method for the statistical analysis of collections of anatomical shape complexes, namely sets of surfaces that were previously segmented and labeled in a group of subjects. The method estimates an anatomical model, the template complex, that is representative of the population under study. Its shape reflects anatomical invariants within the dataset. In addition, the method automatically places control points near the most variable parts of the template complex. Vectors attached to these points are parameters of deformations of the ambient 3D space. These deformations warp the template to each subject's complex in a way that preserves the organization of the anatomical structures. Multivariate statistical analysis is applied to these deformation parameters to test for group differences. Results of the statistical analysis are then expressed in terms of deformation patterns of the template complex, and can be visualized and interpreted. The user needs only to specify the topology of the template complex and the number of control points. The method then automatically estimates the shape of the template complex, the optimal position of control points and deformation parameters. The proposed approach is completely generic with respect to any type of application and well adapted to efficient use in clinical studies, in that it does not require point correspondence across surfaces and is robust to mesh imperfections such as holes, spikes, inconsistent orientation or irregular meshing.

The approach is illustrated with a neuroimaging study of Down syndrome (DS). Results demonstrate that the complex of deep brain structures shows a statistically significant shape difference between control and DS subjects. The deformation-based modeling is able to classify subjects with very high specificity and sensitivity, thus showing important generalization capability even given a low sample size. We show that results remain significant even if the number of control points, and hence the dimension of variables in the statistical model, are drastically reduced. The analysis may even suggest that parsimonious models have an increased statistical performance.

The method has been implemented in the software Deformetrica, which is publicly available at www.deformetrica.org

More details in [14].

6.7. Iconic-Geometric Nonlinear Registration of a Basal Ganglia Atlas for Deep Brain Stimulation Planning

Participants: Ana Fouquier, Stanley Durrleman, Jérôme Yelnik, Sara Fernandez-Vidal, Eric Bardinet.

We evaluated a nonlinear registration method for warping a 3D histological atlas of the basal ganglia into patient data for deep brain stimulation (DBS) planning. The power of the method is the possibility to combine iconic registration with geometric constraints under a unified diffeomorphic framework. This combination aims to ensure robust and accurate atlas-to-patient warping and anatomy-preserving deformations of stimulation target nuclei. A comparison of the method with a state-of-the-art diffeomorphic registration algorithm reveals how each approach deforms low-contrasted image regions where DBS target nuclei often lie. The technique is applied to T1-weighted magnetic resonance images from a cohort of Parkinsonian subjects, including subjects with standard-size and large ventricles. Results illustrate the effects of iconic or geometric registration alone, as well as how both constraints can be integrated in order to contribute for registration precision enhancement. See Fig. 2.

More details in [25].

6.8. Evaluation of morphometric descriptors of deep brain structures for the automatic classification of patients with Alzheimer's disease, mild cognitive impairment and elderly controls

Participants: Alexandre Routier [correspondant], Pietro Gori, Ana Fouquier, Sophie Lecomte, Olivier Colliot, Stanley Durrleman.

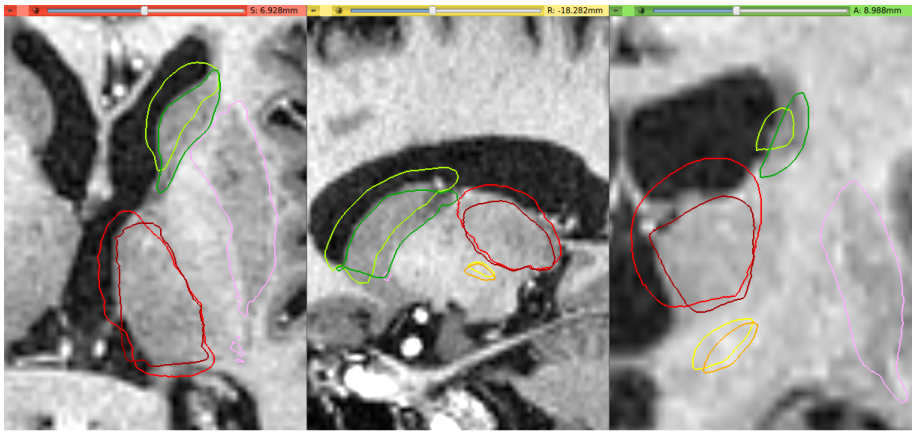

Figure 2. Superimposition of deformed meshes of the histological atlas with a patient pre-operative MRI. Meshes in bright colors result from a block-matching algorithm based on image intensity. Meshes in dark colors result from our iconic-geometric approach with non-linear deformation. We observe a better alignment of the structures, as well as a realistic deformation of the sub-thalamic nucleus (in yellow/orange), which is not visible in the image and therefore has not been taken into account for estimating the optimal deformation. This nucleus is the stimulation target for patients with Parkinson's disease.

We participated in the Computer-Aided Diagnosis of Dementia based on structural MRI data (http://caddementia.grand-challenge.org/). Our approach was to select shapes of 12 brain structures: the caudate nucleus, putamen, pallidum, thalamus, hippocampus and amygdala of each hemisphere. The structure segmentation was based on a FreeSurfer segmentation and the marching-cubes algorithm was used to get 3D triangular meshes. Using our software Deformetrica, anatomical models (mean shape and typical variations) of these brain structures were built for patients with Alzheimer's disease (AD), Mild Cognitive Impairments (MCI) and cognitively normal controls (CN) based on the data of 509 ADNI subjects. The models for AD, MCI and CN were registered to the test subjects by maximizing the likelihood of the test image to be derived from each model. The final classification was made by thresholding this criterion taking into account the covariance of the deformation parameters. The thresholds were either optimized on the ADNI data or on the provided training data. The method was fully automatic and the computation time was 4 days for training the anatomical models plus 11 hours per subject for registration and classification. For the 30 training subjects, the algorithm had accuracies of 73% (if optimized on training data) and 50% (if optimized on ADNI data). On the test set of 354 images, our method yields an accuracy of 49.2% (43.5 - 54.2), true positive fraction of 94.6% (89.8 - 97.7) for CN, 11.5% (6.2 - 17.7) for MCI and 36.9% (27.4 - 46.5) for AD.

Our participation to this challenge was the opportunity to test our software Deformetrica for classification tasks. It ran on more than 800 images, thus showing its ability to deal with large data sets.

More details in [27].

6.9. A Prototype Representation to Approximate White Matter Bundles with Weighted Currents

Participants: Pietro Gori [correspondant], Olivier Colliot, Linda Marrakchi-Kacem, Fabrizio de Vico Fallani, Mario Chavez, Sophie Lecomte, Cyril Poupon, Andreas Hartmann, Nicholas Ayache, Stanley Durrleman.

Quantitative and qualitative analysis of white matter fibers resulting from tractography algorithms is made difficult by their huge number. To this end, we propose an approximation scheme which gives as result a more concise but at the same time exhaustive representation of a fiber bundle. It is based on a novel computational model for fibers, called weighted currents, characterized by a metric that considers both the pathway and the anatomical locations of the endpoints of the fibers. Similarity has therefore a twofold connotation: geometrical and related to the connectivity. The core idea is to use this metric for approximating a fiber bundle with a set of weighted prototypes, chosen among the fibers, which represent ensembles of similar fibers. The weights are related to the number of fibers represented by the prototypes. The algorithm is divided into two steps. First, the main modes of the fiber bundle are detected using a modularity based clustering algorithm. Second, a prototype fiber selection process is carried on in each cluster separately. This permits to explain the main patterns of the fiber bundle in a fast and accurate way. See Fig. 3

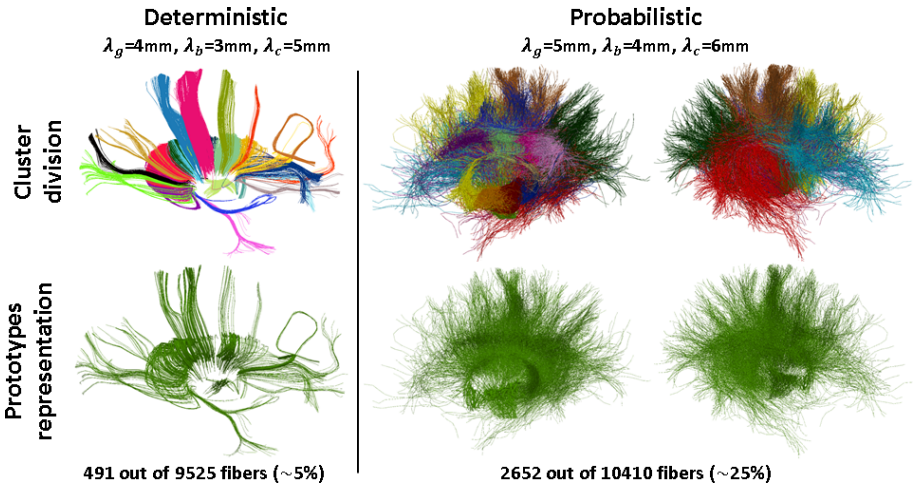

Figure 3. Illustration of our method to cluster fibers and approximate clusters based on a weighted currents metric, which measures differences in the locations of fibers extremities and the geometry of their pathway. 2 examples are shown using fibers from a deterministic tractography (left) and probabilistic tractography (right). Clustering (top row) and approximation of fibers within each cluster (bottom row) are shown.

More details in [24].

6.10. Non-parametric resampling of random walks for spectral network clustering

Participants: Fabrizio de Vico Fallani [correspondant], Vincenzo Nicosia, Vito Latora, Mario Chavez.

Parametric resampling schemes have been recently introduced in complex network analysis with the aim of assessing the statistical significance of graph clustering and the robustness of community partitions. We proposed a method to replicate structural features of complex networks based on the non-parametric resampling of the transition matrix associated with an unbiased random walk on the graph. We tested this bootstrapping technique on synthetic and real-world modular networks and we showed that the ensemble of replicates obtained through resampling can be used to improve the performance of standard spectral algorithms for community detection.

More details in [10].

6.11. Graph analysis of functional brain networks: practical issues in translational neurosciences

Participants: Fabrizio de Vico Fallani [correspondant], Sophie Achard, Jonas Richiardi, Mario Chavez.

The brain can be regarded as a network: a connected system where nodes, or units, represent different specialized regions and links, or connections, represent communication pathways. From a functional perspective, communication is coded by temporal dependence between the activities of different brain areas. In the last decade, the abstract representation of the brain as a graph has allowed to visualize functional brain networks and describe their non-trivial topological properties in a compact and objective way. Nowadays, the use of graph analysis in translational neuroscience has become essential to quantify brain dysfunctions in terms of aberrant reconfiguration of functional brain networks. Despite its evident impact, graph analysis of functional brain networks is not a simple toolbox that can be blindly applied to brain signals. On the one hand, it requires the know-how of all the methodological steps of the pipeline that manipulate the input brain signals and extract the functional network properties. On the other hand, knowledge of the neural phenomenon under study is required to perform physiologically relevant analysis. The aim of our work is to provide practical indications to make sense of brain network analysis and contrast counterproductive attitudes.

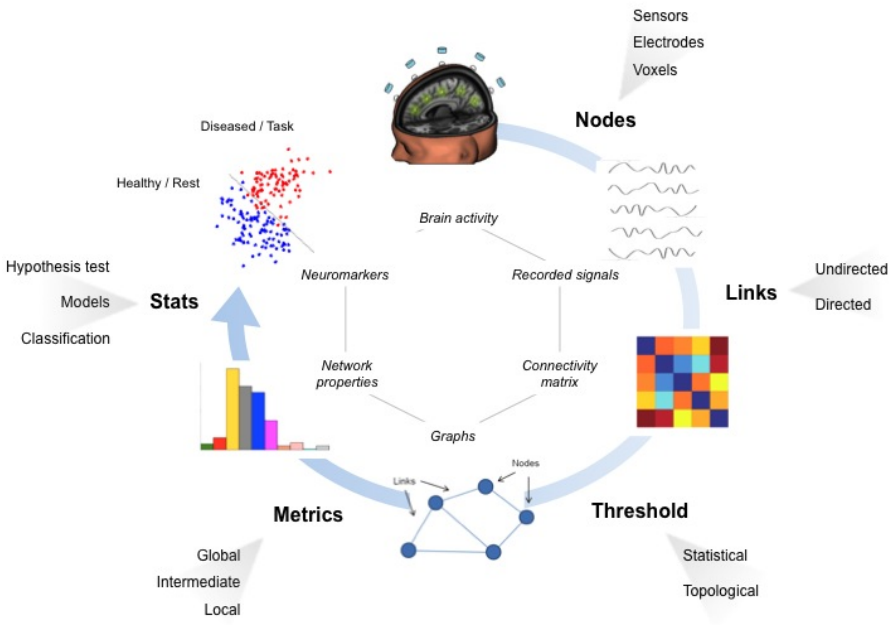

Figure 4. Processing pipeline for functional brain connectivity modeling and analysis. Nodes correspond to specific brain sites according to the used neuroimaging technique. Links are estimated by measuring the functional connectivity (FC) between the activity of brain nodes; this information is contained in a connectivity matrix. By means of filtering procedures, based on thresholds, only the most important links constitute the brain graph. The topology of the brain graph is quantified by different graph metrics (or indices) that can be represented as numbers (e.g. the colored bars). These graph indices can be input to statistical analysis to look for significant differences between populations/conditions (e.g. red points correspond to brain graph indices of diseased patients or tasks, blue points stand for healthy subjects or resting states).

More details in [11].

6.12. Hierarchy of neural organisation in the zebra fish spinal cord: causality analysis of in-vivo calcium imaging data

Participants: Fabrizio de Vico Fallani [correspondant], Martina Corazzol, Jnena Sternberg, Kevin Fidelin, Claire Wyart, Mario Chavez.

The recent development of genetically encoded calcium indicators enables monitoring in vivo the activity of neuronal populations. Most analysis of these calcium transients relies on linear regression analysis based on the sensory stimulus applied or the behavior observed. To estimate the basic properties of the functional neural circuitry, we propose a network-based approach based on calcium imaging recorded at single cell resolution. Differently from previous analysis based on cross-correlation, we used Granger causality estimates to infer activity propagation between the activities of different neurons. The resulting functional networks were then modeled as directed graphs and characterized in terms of connectivity and node centralities. We applied our approach to calcium transients recorded at low frequency (4 Hz) in ventral neurons of the zebrafish spinal cord at the embryonic stage when spontaneous coiling of the tail occurs. Our analysis on population calcium imaging data revealed a strong ipsilateral connectivity and a characteristic hierarchical organization of the network hubs that supported established propagation of activity from rostral to caudal spinal cord. Our method could be used for detecting functional defects in neuronal circuitry during development and pathological conditions.

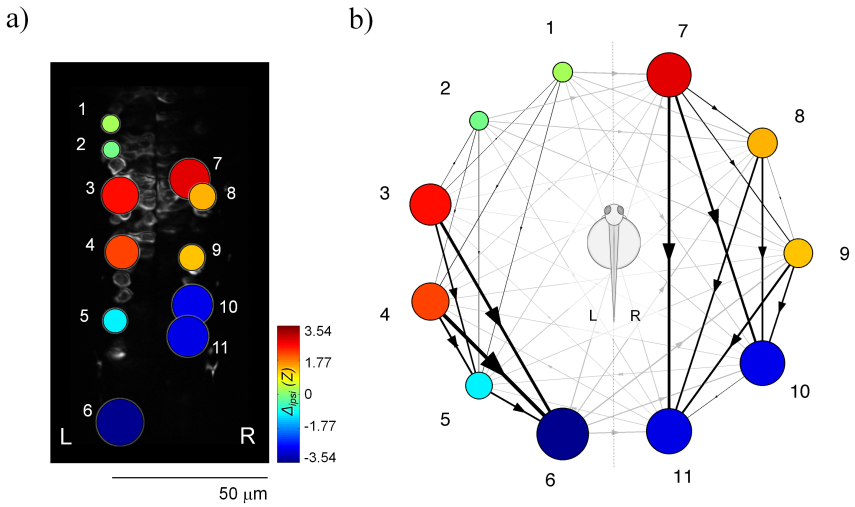

Figure 5. Rostro-caudal distribution of the nodal delta centrality in the representative zebrafish embryo. Panel a) The normalized ipsi value is represented for each node (motoneuron) as a colored circle superimposed on the field of view. The larger the circle, the more central is the node in terms of its tendency to act as a transmitter (red color, positive value) or receiver (blue color, negative value) hub of information flow. Panel b) The same normalized ipsi centrality values are here represented within the neuronal GC network. Statistically significant GC influences are illustrated as directed arrows. The thicker the arrow the stronger the GC value is. Inter-hemicord directed links are illustrated in gray color for the sake of simplicity.

More details in [9].

6.13. 2D harmonic filtering of MR phase images in multicenter clinical setting: towards a magnetic signature of cerebral microbleeds

Participants: Takoua Kaaouana [correspondant], Ludovic de Rochefort, Thomas Samaille, Nathalie Thiery, Carole Dufouil, Christine Delmaire, Didier Dormont, Marie Chupin.

Cerebral microbleeds (CMBs) have emerged as a new imaging marker of small vessel disease. Composed of hemosiderin, CMBs are paramagnetic and can be detected with MRI sequences sensitive to magnetic susceptibility (typically, gradient recalled echo T2* weighted images). Nevertheless, their identification remains challenging on T2* magnitude images because of confounding structures and lesions. In this context, T2* phase image may play a key role in better characterizing CMBs because of its direct relationship with local magnetic field variations due to magnetic susceptibility difference. To address this issue, susceptibility-based imaging techniques were proposed, such as Susceptibility Weighted Imaging (SWI) and Quantitative Susceptibility Mapping (QSM). But these techniques have not yet been validated for 2D clinical data in multicenter settings. Here, we introduce 2DHF, a fast 2D phase processing technique embedding both unwrapping and harmonic filtering designed for data acquired in 2D, even with slice-to-slice inconsistencies. This method results in internal field maps which reveal local field details due to magnetic inhomogeneity within the region of interest only. This technique is based on the physical properties of the induced magnetic field and should yield consistent results. A synthetic phantom was created for numerical simulations. It simulates paramagnetic and diamagnetic lesions within a "brain-like' tissue, within a background. The method was evaluated on both this synthetic phantom and multicenter 2D datasets acquired in a standardized clinical setting, and compared with two state-of-the-art methods. It proved to yield consistent results on synthetic images and to be applicable and robust on patient data. As a proof-of-concept, we finally illustrate that it is possible to find a magnetic signature of CMBs and CMCs on internal field maps generated with 2DHF on 2D clinical datasets that gives consistent results with CT-scans in a subsample of 10 subjects acquired with both modalities. See Fig. 6

More details in [16].

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

7.1.1. Air-Liquide Medical Systems

Participants: Mario Chavez [Correspondant], Xavier Navarro.

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

Founded in 2014

Amount: 370 K€

Coordinator: Thomas Similowski

Other partners: UPMC, Inserm UMR 1158

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

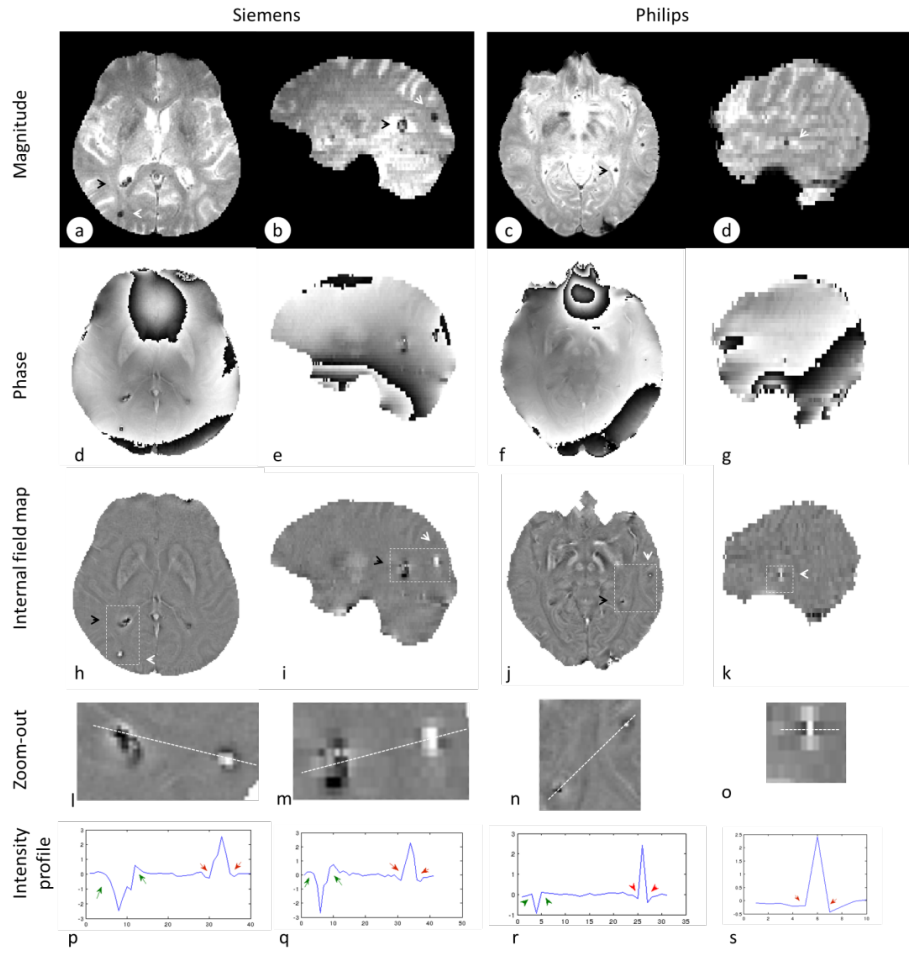

Figure 6. Siemens (left) and Philips (right) axial and sagittal views. Magnitude image (first row), native phase image (second row) and internal field map (third row). Fourth row shows a zoomed out region corresponding to the white rectangle showing CMB with a dipolar pattern (white arrow) and a physiologic calcification of the choroid plexus (black arrow). Note that panel l was rotated. A 1D intensity profile calculated through CMBs and calcification in the zoomed region is displayed in the last row. Note the intensity sign inversion for both side of CMBs (red arrow head), and the calcification (green arrow head). Double headed arrows on panels (l-o) indicate the location of the lines used to generate the intensity profiles.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR

8.1.1.1. ANR HM-TC

Participants: Olivier Colliot [Correspondant], Marie Chupin, Didier Dormont, Denis Schwartz, Dominique Hasboun, Linda Marrakchi-Kacem, Claire Cury.

Project acronym: HM-TC

Project title: Model of the hippocampo-cortical connectivity in "temporal consciousness" in normal and pathological memory derived from multimodal anatomical and functional brain imaging (aMRI, DT-MRI, MEG, fMRI)

Duration: Nov 2009- Nov 2014

Amount: 2M€

Coordinator: Olivier Colliot (ARAMIS) and Gianfranco Dalla Barba

Other partners: CENIR, ENS Cachan, Neurospin, Grenoble Institut des Neurosciences

Abstract: The aim of this project is to evaluate the role of the medial temporal lobe and its connections with various cortical regions in temporal consciousness related tasks and to derive a neuro-computational model of memory processing from multimodal imaging data. Temporal consciousness is defined as the ability to specify one's own time-location with respect to past, present and future, and is thus a more general framework than episodic memory. Based on an original cognitive model and relying on memory dysfunctions called confabulations, different groups of participants (controls, patients with Alzheimer's disease, patients with several memory disorders) will be evaluated through cognitive tests, MEG, anatomical, functional and diffusion-tensor MRI. New signal and image processing methods will be developed for all these modalities, in order to describe in a more robust and precise way both the anatomy and the function of the medial temporal lobe. First, using in vivo ultra high field MRI acquisitions (7 Tesla), we will build a precise anatomical atlas of the hippocampus and its inner structure. This model will allow designing efficient MEG source reconstruction in these regions, and new methods to analyse anatomical and functional connectivity. Using the most recent mathematical achievements in the theory of diffeomorphic deformations, we will propose new registration and morphometry methods in order to analyze very precisely the structural alterations of the medial temporal lobe. These new methods will be applied to the neuroimaging data acquired for the project in order to analyse extensively the relationships between memory disorders and structural and functional brain alterations revealed by neuroimaging.

8.1.1.2. ANR PREV-DEMALS

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

Project acronym: PREV-DEMALS

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

Duration: Avr 2015 - Avr 2019

Amount: 487k€

Coordinator: Isabelle Le Ber

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

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

8.1.2. IHU

8.1.2.1. General program

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

Project acronym: IHU-A-ICM

Project title: Institute of Translational Neuroscience

Founded in 2011

General Director: Bertrand Fontaine

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

8.1.2.2. Internal Research projects

Participants: Mario Chavez, Fabrizio de Vico Fallani.

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

Founded in 2014

Coordinator: Antoni Valero Cabre

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

8.1.3. CATI (Alzheimer Plan)

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

Project acronym: CATI

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

Founded in 2011

Amount: 9M€

Coordinator: Jean-François Mangin

Other partners: Neurospin, CENIR, Inserm U678, IM2A

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

8.1.4. National Networks

- GdR Statistics and Medicine - http://gdr.statsante.fr/Accueil.html

8.1.5. Other National Programs

8.1.5.1. Programme Hospitalier de Recherche Clinique (PHRC)

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

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

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

Participants: Mario Chavez, Xavier Navarro.

Project acronym: DYSPEV

Project title: Dépistage de la dyspnée par potentiels évoqués visuels

Founded in 2014

Amount: 38K€

Coordinator: Thomas Similowski

Other partners: UPMC, Inserm UMR 1158

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

8.2. European Initiatives

8.2.1. FP7 & H2020 Projects

Participants: Stefan Thurner, Vito Latora, Albert Diaz-Guilera, Maxi San Miguel, Cecilia Mascolo, Mirco Murolesi, Mario Chavez [Correspondant].

Project acronym: LASAGNE

Project title: multi-LAyer SpAtiotemporal Generalized NEtworks

Founded in 2012

Amount: 1.6M€

Coordinator: Stefan Thurner

Other partners: Medical University of Vienna, Queen Mary University of London, Universitat de Barcelona, Universitat de les Illes Balears,University of Cambridge, University of Birmingham.

Abstract: The aim of the LASAGNE project is to provide a novel and coherent theoretical framework for analyzing and modelling dynamic and multi-layer networks in terms of multi-graphs embedded in space and time. To do this, we will treat time, space and the nature of interactions not as additional dimensions of the problem, but as natural, inherent components of the very same generalized network description. The theory will be validated on real-world applications involving large and heterogeneous data sets of brain networks, on- and off-line social systems, healthcare systems, and transportation flows in cities. The LASAGNE project will provide new quantitative opportunities in different fields, ranging from the prediction of pathologies to the diffusion of ideas and trends in societies, and for the management of socio-technological systems.

8.3. International Initiatives

8.3.1. Inria International Partners

8.3.1.1. Non-contractual International Partners

S. Durrleman has an enduring collaboration with the Scientific Computing and Imaging (SCI) Institute at the University of Utah (USA). He is consultant for NIH Grant "4D shape analysis for modeling spatiotemporal change trajectories in Huntington's Disease "predict-HD". He is part of the PhD committees of J. Fishbaugh and A. Sharma supervised by professor Guido Gerig.

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

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

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

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

8.4. International Research Visitors

8.4.1. Visits to International Teams

8.4.1.1. Research stays abroad

M. Chavez spent 45 days as visiting researcher in the Physics Department of the Universitat de Barcelona, Spain (February, 2014)

9. Dissemination

9.1. Promoting Scientific Activities

O. Colliot acts as an expert for the World Health Organization (WHO) panel for setting research priorities in the field of dementia.

O. Colliot acts as an expert for the Canada Foundation for Innovation (CFI), Fonds National de la Recherche Scientifique (Belgium), Alzheimer Nederland, and the FCS Sciences et Technologies pour l'Aéronautique et l'Espace.

F. De Vico Fallani gave invited talk at the Workshop "Controversies in EEG source analysis" - Key Lab of Neuroinformation of the Ministry of Education, Chengdu, China (August 2014).

F. De Vico Fallani gave invited talk "6th Congress of Society Research Cerebellum", IRCCS Fondazione Santa Lucia, Rome, Italy (April 2014).

F. De Vico Fallani acts as an expert for the Research Foundation - Flanders, Belgium.

S. Durrleman acted as an expert for INdAM Fellowships in Mathematics cofounded with Marie Curie Actions and for ANEP (Spanish National Agency for Scientific Evaluation (ANEP)) CONEX Program

S. Durrleman gave an invited presentation at the workshop "comprendre et analyser les phénomènes temporels" of the conference RFIA (Reconnaissance des Formes et Intelligence Artificielle) Rouen, (July 2014)

S. Durrleman gave an invited presentation at the workshop "Statistical challenges in Neurosciences" at Warwick University, UK (September 2014)

S. Durrleman gave an invited presentation at the workshop "Spatiotemporal Image Analysis for Longitudinal and Time-Series Image Data" of the MICCAI Conference, Boston, USA (September 2014)

M. Chavez gave an invited presentation at the "Mediterranean School of Complex Networks" Salina, Italy (June 2014)

M. Chavez gave an invited seminar at the Universitat Pompeu Fabra, Barcelona, Spain (February 2014)

M. Chavez gave an invited seminar at the Universitat Politecnica de Cataluna, Terrasa, Spain (February 2014)

9.1.1. Scientific events organisation

9.1.1.1. General chair, scientific chair

F. De Vico Fallani is publicity chair for the IEEE BIoMS Workshop, University "Roma TRE", Rome, Italy 2014

F. De Vico Fallani acted as chairman for 3rd congress of the Society for Research on the Cerebellum, IRCCS F. Santa Lucia, Rome, Italy 2014.

S. Durrleman was co-chair of the 2nd MICCAI Workshop on Deep Brain Stimulation Methodological Challenges (DBSMC), Boston, USA, 2014

S. Durrleman was co-chair of the 3rd International MICCAI Workshop on Spatiotemporal Image Analysis for Longitudinal and Time-Series Image Data (STIA), Boston, USA, 2014

9.1.2. Scientific events selection

9.1.2.1. Member of the conference program committee

D. Dormont is member of the board of the French Society for Neuroradiology.

S. Durrleman was member of the program committee of the 6th International Workshop on Biomedical Registration (WBIR), London, 2014

9.1.2.2. Reviewer

O. Colliot acted as a reviewer for the conference Medical Image Computing and Computer Aided Intervention (MICCAI) .

9.1.3. Journal

9.1.3.1. Member of the editorial board

O. Colliot was a member of the Editorial Board of the ISTE-Wiley-Hermes "Neural Engineering" book series.

9.1.3.2. Reviewer

During the past year the members of the team acted as reviewers for numerous journals:

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

F. De Vico Fallani acted as a reviewer for IEEE TBME, IEEE TNRSE, Hum Brain Mapp, Neuroimage, Plos Comp Bio, J Neurosci Meth, Brain Topolography, Clin Neurophisiology, Plos One, Scientific Reports.

S. Durrleman acted as a reviewer for Medical Image Analysis, Neuroimage, IEEE Trans. Medical Imaging (TMI), IEEE Trans. Image Processing (TIP), Image and Vision Computing, International Journal of Computer Vision (IJCV), Annals of Applied Statistics, Journal of Computational and Applied Mathematics, SIAM Journal on Imaging Sciences, Journal of Alzheimer's disease.

M. Chavez acted this year as a reviewer for IEEE TBME, PLoS Comput Biol, PLoS One, J Royal Soc Interface, Phil Trans Royal Soc B, and Neurosc Behav Rev.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

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

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

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

Master: Olivier Colliot, Master in Cognitive Science, 4.5 hours (eqTD), Ecole Normale Supérieure (Ulm)

Master: Stanley Durrleman, Master in Applied Mathematics, 2 hours (eqTD), Ecole Normale Supérieure (Cachan)

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

Master: Dominique Hasboun, Master in Biology, 4 hours, Ecole Normale Supérieure (Ulm)

Master: Dominique Hasboun, Master in Cognitive Science, 12 hours, Ecole Normale Supérieure (Ulm)

Master: Dominique Hasboun, Master in Biology, 15 hours, Université Pierre et Marie Curie

Master: Dominique Hasboun, Master in Medical Physics, 7 hours, Université Paris-Sud

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

PhD school: Fabrizio De Vico Fallani, "Data analysis and modeling in cognitive and clinical neuroscience" - 3hours - Faculty of Psychology and Educational Sciences, Ghent, Belgium.

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

Engineering school: Olivier Colliot, 4.5 hours (eqTD), Telecom ParisTech

Engineering school: Dominique Hasboun, 3 hours, ENSEA

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

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

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

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

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

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

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

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

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

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

9.2.2. Supervision

PhD in progress : Claire Cury, Analyse statistique de la variabilité anatomique de l'hippocampe à partir de grandes populations, Université Pierre et Marie Curie, Started in 2011, advisor: Olivier Colliot

PhD in progress : Takoua Kaaouana, Détection automatique et analyse des micro-saignements cérébraux : Application à des séquences d'imagerie cliniques et à de grandes populations de sujets, Université Pierre et Marie Curie, Started in 2012, advisor: Didier Dormont, co-advisors: Marie Chupin, Ludovic de Rochefort

PhD in progress: Pietro Gori, Statistical analysis of neuronal connectivity in patients with Gilles de la Tourette syndrome based on anatomical structures extracted from both structural and diffusion images, Université Pierre et Marie Curie, Started in 2012, advisors: N. Ayache, O. Colliot and S. Durrleman

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

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

Visiting PhD student (Janvier - April 2014): Johann Heinz Martinez, Characterization of functional interactions between neural oscillations from EEG recordings, Universidad Politecnica de Madrid, Spain. Responsable: Mario Chavez

Visiting PhD student (September - November 2014): Anton Giulio Maglione, Functional brain connectivity during neuroaesthetics experimental paradigms, Universita Sapienza, Roma, Italy. Responsable: Mario Chavez

Master 2: Kevin Roussel, Morphométrie de la structure interne de l'hippocampe en IRM 7 Tesla, Université Pierre et Marie Curie, Mar-Sept 2014, advisor: Olivier Colliot

Master 2: Evgeny Zuenko, Segmentation des hypersignaux de la substance blanche chez le sujet âgé : amélioration de la méthode WHASA et évaluations sur plusieurs cohortes, Université Paris Sud, Mars-Aout 2014, advisor: Marie Chupin

Master 2: Kanza Dekkiche, Cartographie de susceptibilité magnétique (CSM): Optimisation et comparaison entre méthodes sur des données multicentriques, Université Nice Sophia Antipolis, Mar-Aout 2014, advisor: Marie Chupin

End-of-course internship: Maxime Corduant, Interface graphique interactive pour la segmentation automatisée des sous régions de l'hippocampe humain in-vivo en IRM à très hauts champs, ENSIIE, Mar-Sept 2014, advisor: Marie Chupin

End-of-course internship: Fanny Grosselin, MATLAB graphical interface for statistical analysis of physiological recordings from monitoring of human respiratory states, Université Paris Est Cre´teil Val-de-Marne, March - August 2014, advisor: Mario Chavez

End-of-course internship: Guillaume Ruffin, Utilisation de la géométrie Riemannienne pour la caractérisation de la dynamique épileptique chez l'homme, Université Paris Est Créteil Val-de-Marne, March - August 2014, advisor: Mario Chavez

End-of-course internship: Antoine Latrille, Données Syndromiques et Forçages Climatiques en Epidémiologie, ESIEE-Paris, March - August 2014, advisor: Mario Chavez

9.2.3. Juries

Olivier Colliot participated, as referee, to the PhD committee of Jonathan Young (University College London), 2014 (supervisors: Sébastien Ourselin and John Ashburner).

Olivier Colliot participated, as examiner, to the PhD committee of Pierre Besson (Université de Lille), 2014 (supervisor: Louise Tyvaert).

Olivier Colliot participated, as examiner, to the PhD committee of Hao Xu (Ecole Polytechnique), 2014 (supervisors: Stéphanie Allassonnière and Bertrand Thirion).

Fabrizio De Vico Fallani participated, as referee, to the PhD committee of Jonas Chatel-Goldman (Université de Grenoble), 2014 (supervisor: Marco Congedo, Jean-Luc Schwartz and Christian Jutten).

Fabrizio De Vico Fallani participated, as examiner, to the PhD committee of Aude Costard (Université de Grenoble), 2014 (supervisor: Olivier Michel, Patrice Arby, Sophie Achard and Pierre Borgnat).

Fabrizio De Vico Fallani participated, as referee, to the PhD committee of Guillame Lio (Université de Lyon 1), 2014 (supervisor: Philippe Boulingez).

Stanley Durrleman participated, as examiner, to the PhD defense of J. Fishbaugh (University of Utah), 2014 (supervisor: Guido Gerig).

Mario Chavez participated, as referee, to the PhD committee of Alessio Cardillo (Universidad de Zaragoza, Saragose, Spain), 2014 (supervisor: Jesus Gardenes).

Mario Chavez participated, as referee, to the PhD committee of Rafael Romero-Garcia (Universidad Pablo de Olavide, Seville, Spain), 2014 (supervisor: Jose Luis Cantero).

9.3. Popularization

The team is involved in the BrainCatalogue project (coordinator: Roberto Toro, Institut Pasteur) dedicated to the popularization of neuroanatomical knowledge. The project features MRI scans and 3D reconstructions for various vertebrates species (bear, mouse, macaque, dolphin, leopard, rhinoceros, human, squirrel ...).

The team coordinates the activity of the FreeBorn consortium which aims at promoting the interaction and visibility of the French research teams working on brain connectivity and network theory: https://sites.google.com/site/fr2eborn/

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Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] P. VARGAS. *Study of white matter damage related to motor and speech performance of stroke patients*, Université Pierre et Marie Curie - Paris VI, February 2014, https://tel.archives-ouvertes.fr/tel-00987601

Articles in International Peer-Reviewed Journals

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[3] C. BOUTET, M. CHUPIN, S. LEHÉRICY, L. MARRAKCHI-KACEM, S. EPELBAUM, C. POUPON, C. WIGGINS, A. VIGNAUD, D. HASBOUN, B. DEFONTAINES, O. HANON, B. DUBOIS, M. SARAZIN, L. HERTZ-PANNIER, O. COLLIOT. *Detection of volume loss in hippocampal layers in Alzheimer's disease using 7 T MRI: a feasibility study*, in "Neuroimage: Clinical", July 2014, vol. 5, pp. 341-8, https://hal.inria.fr/hal-01099185

[4] P. CAROPPO, I. LE BER, A. CAMUZAT, F. CLOT, L. NACCACHE, F. LAMARI, A. DE SEPTENVILLE, A. BERTRAND, S. BELLIARD, D. HANNEQUIN, O. COLLIOT, A. BRICE. *Extensive white matter involvement in patients with frontotemporal lobar degeneration: think progranulin*, in "JAMA Neurology", December 2014, pp. 1562-6, https://hal.inria.fr/hal-01098828

[5] G. CASTAGNETO-GISSEY, M. CHAVEZ, F. DE VICO FALLANI. *Dynamic Granger-causal networks of electricity spot prices: A novel approach to market integration*, in "Energy Economics", May 2014, vol. 44, pp. 422-432 [*DOI :* 10.1016/J.ENECO.2014.05.008], https://hal.inria.fr/hal-01023418

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