AAP Contrats doctoraux en Intelligence artificielle

Cofinancé par l'ANR

Contribution of **Ma**chine **L**earning by deep neural networks of molecular neuroimaging data for the **Di**fferential **Di**agnosis of **P**sychiatric **Pa**thologies. **CoMaLDiPA**

1. DESCRIPTION OF THE PHD THESIS PROJECT

1.1 OBJECTIVES OF THE PROJECT BASED ON THE CURRENT STATE OF THE ART

Diagnosis of neurological diseases has greatly benefited in recent years from the contribution of biomarkers of brain imaging whereas psychiatric diagnosis is still based today on the isolated use of clinical criteria (DSM-V). This classification, although regularly revised, appears to be unsuitable for predicting the individual prognosis of patients and for defining effective specific treatments.

A paraclinical assessment including brain molecular imaging (perfusion, metabolism, dopaminergic neurotransmission) is however carried out as soon as a doubt remains on the existence of a neurological disease, in particular in patients with an initially atypical or resistant psychiatric treatment, or if neurostimulation treatment is considered (Kapucu et al., 2009). These examinations could make it possible to better clarify the diagnosis of psychiatric pathologies by identifying different profiles between these diseases (Richieri et al. 2015).

However, the interpretation of these exams remains visual and subjective today, highly impacted by doctor's experience. Anomalies, evident on average in a group of patients, or in the event of advanced disease, may be individually more difficult to assert, especially at the earliest stages of the pathological disease, when current therapies (and in development) would be the most effective. These anomalies can then be confused with those of other diseases requiring different treatments, or even with physiological variants of healthy subjects.

Individual and quantified approaches thus appear today necessary for the medical management of these pathologies (Durstewitz D et al., 2019; Walter et al., 2019). Tools developed in research in recent years are based on voxels-based processing on the whole brain, by measuring after spatial normalization and smoothing, the signal obtained in each of the image units taken individually and acquired at balance in one time. These approaches, whose performance is based on their automatic nature and the absence of a priori hypothesis, find their limits in:

• the lack of sensitivity due to the statistical thresholds used to correct the effects of multiple comparison (1 test for each of the voxels in the image, with several hundred thousand voxels per acquired image);
• the mono-parametric nature of the measured information, corresponding to the value of the signal accumulated at the voxel level over the overall time of images acquisition, without taking into account the interaction of the voxels with each other over time (no dynamic processing of information), and space (no geometric processing of information in terms of texture, including gradients, asymmetry, etc., even though these parameters are integrated into the criteria for visual interpretation of these images by doctors), and in a multimodal approach (combining the different molecular information).

The aim of this project is to understand multimodal brain molecular data from PET images, in a multidimensional based approach using deep convolutional neural networks and taking into account local tensorial methods (voxel level), global (geometric) approaches, and temporal analysis. This dynamic approach could make it possible to extract relevant parameters such cerebral functional connectivity and hence developing a computer-aided diagnosis system for psychiatric diseases.

- Deep neural networks in psychiatry. Durstewitz D, Koppe G, Meyer-Lindenberg A. Mol Psychiatry. 2019.
- Determinants of brain SPECT perfusion and connectivity in treatment-resistant depression. Richieri R, Boyer L, Faget-Agius C, Farisse J, Mundler O, Lançon C, Guedj E. Psychiatry Res. 2015 Feb 28;231(2):134-40.
- American Psychiatric Association, DSM-5 : diagnostic and statistical manual of mental disorders, 5e édition, Washington D.C. American Psychiatric Association
- EANM procedure guideline for brain perfusion SPECT using 99mTc-labelled radiopharmaceuticals, version 2. Kapucu OL, Nobili F, Varrone A, Booij J, Vander Borght T, Någren K, Darcourt J, Tatsch K, Van Laere KJ. Eur J Nucl Med Mol Imaging. 2009 Dec;36(12):2093-102.
- Translational machine learning for psychiatric neuroimaging. Walter M, Alizadeh S, Jamalabadi H, Lueken U, Dannlowski U, Walter H, Olbrich S, Colic L, Kambeitz J, Koutsouleris N, Hahn T, Dwyer DB. Prog Neuropsychopharmacol Biol Psychiatry. 2019 Apr 20;91:113-121.

1.2 METHODOLOGY

Our project is at the same time in a computer science and engineering research area and deals with life science topic also. It will strengthen existing collaboration between computer science researcher at Fresnel Institute and doctors in CERIMED and La Timone Marseille Hospital.

***Mouloud Adel** will bring signal, image processing and machine learning expertise while **Eric Guedj** will bring medical and clinical aspects in the project.*

We propose in the framework of this thesis work associating brain imaging and approach to AI by deep neural networks:

- *to study the diagnosis value of molecular brain imaging on the clinical classification of psychiatric illnesses as currently defined (machine learning using a multidimensional approach),*
- *to define a new syndromic classification based on imaging data and clinical data (clustering), by checking the existence or not of similar results with current international classification research projets.*

To this end, to carry out this project, we propose to organize it around four workpackages:

***Handling Image database and state of the art on data analysis in psychiatric diseases**: A cohort of 580 patients with psychiatric pathology confirmed during follow-up, with initial clinical data and cerebral molecular imaging, has been constituted and authorized for scientific exploitation by the APHM (CIL-201750). In this task, we will define the psychiatric diseases on which the study will be done, summarize the state of the art on the topic as well include more data to the study either by acquiring image from new subject but also by numerical data augmentation.*

***Using segmentation by unsupervised clustering methods**: Using an atlas for PET/SPECT images segmentation of anatomical interest volumes as first approach has shown its limitations. It seems important to develop more*

individualized models based on unsupervised segmentation as clustering methods to customize extraction of anatomical features. It will then be possible to "redraw" the map of the brain not on anatomical volumes, but on functional volumes of PET/SPECT images from the uptake of different tracers.

***Extraction of other features on the brain volumes of interest images**: It is important to bring another information than the one provided by the statistical attributes from the brain volumes of interest. These new features may be used by other types of parameters that physicians may have to use qualitatively. Thus the asymmetry of volumes (left vs right hemisphere), texture and tracers uptake gradients are important features that it seems important to consider.*

***Using multidimensional representation of data and classification**: The classification of brain PET/SPECT images through a model of representation at the individual level but also at the level of subjects of the same class groups. We plan to combine clinical data with feature extraction from image data through a tensor representation. This step will enable us to assess our ability to differentiate between individuals when inputting features extracted from these representations into a classifier. To this end, a neural network architecture will be designed to find an optimal and low dimensional representation of the data. A framework on autoencoder representation will be studied and developed in this task. The second step in this task will be devoted to the development of a classifier based on neural network. In this context, we will have to define an architecture (input , hidden, output layers) of a supervised classifier but also rank the features extracted from previous using the concept of Heat maps in order to ensure an optimal set of relevant features.*

1.3 WORK PLAN

(Including a chronogram of the activities or Gantt chart)

The research project is scheduled for three years including 4 tasks. A Gantt chart of the different tasks is shown below.

Task 1 : ***Handling Image database and state of the art on data analysis in psychiatric diseases***

Task 2 : ***Segmentation by unsupervised clustering methods***

Task 3 : ***Feature extraction on the brain volumes of interest images***

Task 4 **: *Multidimensional representation of data and classification***

months	*T0*	*+6*	*+12*	*+24*	*+36*
Task 1					
Task 2					
Task 3					
Task 4					

1.4 SUPERVISOR AND RESEARCH GROUP DESCRIPTION

The research program, one aspect of which is described in the thesis, is part of a global project within the Fresnel Institute for the implementation of artificial intelligence techniques for the interpretation of biomedical data. It is about developing digital tools to aid medical diagnosis

2. RECENT PUBLICATIONS

Book Chapter

M. Adel, I. Garali, X. Pan, C. Fossati, T. Gaidon, J. Wojak, S. Bourennane, **E. Guedj**

"Alzheimer's Disease Computer-Aided Diagnosis on Positon Emitting Tomography Brain Images Using Image Processing Techniques" in "**Computer Methods and Programs in Biomedical Signal and Image Processing**" INTECH OPEN ACCESS PUBLISHER, ISBN 978-953-51-6311-4, 2019

International journals

- *I. Garali, **M. Adel**, S. Bourennane, M. Ceccaldi, **E. Guedj**, "Brain Region of Interest Selection for 18FDG Positrons Emission Tomography Computer-aided Image Classification", **Innovation and Research in Biomedical Engineering Journal (IRBM)** 37, 23-30 , 2016.*

- *I. Garali, **M. Adel**, S. Bourennane, **E. Guedj**, "Brain Region Ranking for 18FDG-PET Computer-Aided Diagnosis of Alzheimer's Disease", **Biomedical Signal Processing and Control Journal** 27, 15-23, 2016.*

- *I. Garali, **M. Adel**, S. Bourennane, **E. Guedj**, " Histogram-based features selection and volume of interest ranking for brain PET image classification", **IEEE Journal of Translational Engineering in Health and Medecine**, Vol (6) DOI : 10.1109/JTEHM.2018.2796600, 2018.*

- *X. Pan, **M. Adel**, C. Fossati, T. Gaidon and **E. Guedj**, " Multi-level Feature Representation of FDG-PET Brain Images for Diagnosing Alzheimer's Disease", **IEEE Journal of Biomedical and Health Informatics,** 23 (4), 1499-1506**,** DOI **:** 10.1109/JBHI.2018.2857217, 2019*

- *X. Pan, **M. Adel**, C. Fossati, T. Gaidon, J. Wojak and **E. Guedj**, "Multiscale spatial gradient features for ^{18}FDG-PET image guided diagnosis of Alzheimer's Disease", **Computer Methods and Programs in Biomedecine,** 180, 105027, DOI : 10.1016/j.cmpb.2019.105027, 2019.*

International conferences

- *I. Garali, **M. Adel**, S. Takerkart, S. Bourenanne and **E. Guedj** "Region of interest selection using statistical parameters on brain ^{18}FDG Positron Emission Tomography images" **IEEE International Conference on Image Processing Theory, Tools and Applications ,** Paris, 27-30 Octobre 2014.*

- *I. Garali, **M. Adel**, S. Bourennane, **E. Guedj** " A novel feature selection in the case of brain pet image classification" **IEEE European Signal Processing Conference**, **EUSIPCO**, Nice, France, 31 august-4 september 2015.*

- *I. Garali, **M. Adel**, S. Bourennane, **E. Guedj** "Region-based brain selection and classification on pet images for Alzheimer disease computer aided diagnosis", **IEEE International conference on Image processing**, **ICIP**, Montreal, Canada, 27-30 september 2015.*

- *I. Garali, **M. Adel**, S. Bourennane, **E. Guedj**, "Classification of Positron Emission Tomography Brain Images using first and second derivative features", **6th European Workshop on Visual Information Processing,** Marseille, France, 25-27 october 2016.*

♦ *X. Pan, **M. Adel**, C. Fossati, T. Gaidon and **E. Guedj**, "Alzheimer Disease Diagnosis with FDG-PET Brain Images by Using Multilevel Features", **IEEE International Conference on Image Processing** October 7-10, Athens, Greece 2018.*

♦ *T. Le Phan, **M. Adel**, S. Bourennane and **E. Guedj**, " Region-Based Segmentation and Graph Representation on PET Images to Diagnose Alzheimer's Disease " **IEEE 16th International Symposium on Biomedical Imaging (ISBI),** april 8-11, Venise, Italy, 2019.*

♦ *X. Pan, **M. Adel**, C. Fossati, T. Gaidon, J. Wojak and **Eric Guedj**. First and Second Order Gradients for Alzheimer's Disease Diagnosis. **5th International Conference on Frontiers of Signal Processing (ICFSP),** september 18-20, Marseille, France, 2019.*

3. EXPECTED PROFILE OF THE CANDIDATE

The candidate should have a master's degree in signal and image processing or mathematical engineering, artificial intelligence, biomedical engineering, or a similar degree with an equivalent academic level.

He or She should have a strong mathematically-oriented background and should have obtained good grades. The candidate has to show that he or she is able to do independent research (e.g. excellent grades on a MSc thesis, etc.)

The candidate should have hands-on experience with machine learning and deep neural network toolboxes and a genuine interest in signal and image processing and machine learning

The candidate should have strong social abilities allowing an active participation to the multidisciplinary network, fruitful exchanges with other students and researchers, and an excellent integration in the team of your research group.

4. SUPERVISORS' PROFILE

- *(Insert a short professional profile of the SUPERVISOR)*

  ***Mouloud Adel** is a professor at Aix-Marseille University since September 2014. He is a member of the Multidimensional Signal Group of Institut Fresnel. His research areas concern signal and image processing applied to biomedical and industrial images. He has been involved in many international research programs. He is the author of more than 60 papers in peer-reviewed international journals and international conferences. He is member of the editorial board of Journal of Biomedical Engineering and Informatics.*
  ***Eric Guedj** is Professor of Biophysics and Nuclear Medicine at Timone Hospital since 2013 (Aix-Marseille University), and Director of DHU-Imaging. He is a Head of IMOTHEP team at Institut Fresnel. Eric Guedj has been working in molecular neuroimaging for more than 15 years, with more 200 articles in peer reviewed journals (h-index 34).*

- *(Please mention the number of theses currently being supervised, and their starting date.)*
  - *MA: 3 theses currently supervised at 50% each one (two as principal supervisor), started in November 2017, March 2018, and September 2019*
  - *EG: 1 these currently supervised at 50% (principal supervisor), started in September 2018*

VISA DU RESPONSABLE DE L'INSTITUT ET DU DIRECTEUR DE LABORATOIRE CONCERNÉS

Visa du responsable de l'institut,
NOM Prénom

Fait à Marseille, le 15 mai 2020

Signature

Visa du directeur du laboratoire,
NOM Prénom
Sophie Brasselet

Fait à Marseille, le 15 /05/2020

Signature

Sophie BRASSELET
Directrice de l'Institut Fresnel