# Robust Anomaly Detection in Multimodal Neuroimaging

## Doctoral project

Neuroimaging offers an unmatched description of the brain's structure and physiology, which explains its crucial role in the understanding, diagnosis, and treatment of neurological disorders. To provide a complete picture of biological processes and their alterations, it is necessary to combine multiple brain imaging modalities, including multiple magnetic resonance imaging (MRI) sequences and positron emission tomography (PET). Using such multimodal data is a difficult task for clinicians because of the large amount of information available, and the difficulty to assess deviations from normal variability. While tremendous progress has been made in the analysis of brain imaging data in the past decade, adequate frameworks for integrating multiple modalities are still lacking. There is thus a critical need to develop new analysis tools that can quantitatively process multimodal data and build computer-aided systems to support clinical decisions.

The aim of this project is to develop innovative computational imaging tools to model abnormalities from multimodal brain imaging data. To this end, topographical maps of abnormalities will be generated from multimodal neuroimaging data acquired during MRI and PET examinations. The hypothesis is that these abnormality maps will enable the extraction of the abnormal signal from the images, thus helping diagnosis by providing a clear representation of the pathology.

Unsupervised anomaly detection consists of generating a subject-specific model of healthy appearance for the targeted imaging modality, and comparing the subject's real image to the model. This results in the generation of a subject-specific map of anomalies. Different strategies exist to generate pseudo-healthy models, using either traditional image processing techniques (e.g., a registration and fusion algorithm [1]) or deep generative models [2]. However, most work focus on the detection of well-delineated lesions such as tumours [2], and none has been applied to the detection of anomalies in a wide range of imaging modalities.

In previous work, we proposed a registration and fusion algorithm [1] to generate subject-specific abnormality maps from FDG and Florbetapir PET data, and showed that this innovative approach was able to identify different stages of Alzheimer's disease and distinguish various dementia subtypes [1]. With the aim to detect subtler anomalies, and in a more computationally efficient manner, we are developing an approach relying on variational autoencoders (VAEs) [3]. During the training phase, only images of healthy subjects are used so that the network can learn the distribution of healthy images. During the application phase, the image of a patient is fed to the VAE, which only knows how to reconstruct healthy images. As a result, the reconstructed image would be a pseudo-healthy representation of the input image. Comparing the input image and its pseudo-healthy reconstruction highlights the areas of the brain presenting anomalies. This approach resulted in promising results [3] but work is still needed to improve the quality of the pseudo-healthy images, strengthen the validation of the method and extend the application to other modalities than FDG PET.

The proposed doctoral project has four main objectives:

- **Improve the quality of pseudo-healthy images** Even though they have been successfully used to detect tumours or stroke lesions, a well known limitation of VAEs is that they lead to blurry reconstructions [2], which would prevent detecting subtle lesions as found for example in dementia or epilepsy. The first objective is to improve the quality of pseudo-healthy images, for instance using different distributions to approximate the posterior [4], adding a discriminator [2] or combining the VAE with a diffusion model [5]. The use of conditional generative adversarial networks (cGANs) could also be explored [6]. As for the approach using VAEs, only healthy subjects would be used during the training phase. The cGAN would learn to generate healthy images (e.g. FDG PET images) for a specific anatomy obtained from a structural imaging modality (e.g. T1-weighted MRI). During the application phase, the structural image of a patient would be given as input. As the generator would only know how to reconstruct healthy images, the generated image would be a pseudo-healthy representation, specific to the patient's anatomy.

- **Generate robust abnormality maps by modelling uncertainty** The current deep learning based anomaly detection approaches [7] do not model the uncertainty of the reconstruction, which is crucial for an application to the clinic [8]. Uncertainty measures can provide information as to how confident the model was on reconstructing pseudo-heathy images. Voxel-wise uncertainty maps would be useful to detect potential defects in a specific area of the image while subject-level uncertainty, for example obtained by aggregating voxel-wise uncertainties, would provide a global measure of success. The general idea for this second objective would be to generate several pseudo-healthy reconstructions for a given input to obtain a variance estimate. This could be done by training a single model and repeatedly ignoring part of the neurons in the application phase, or by training several models and reconstructing a pseudo-healthy image for each of these models in the application phase. The voxel-wise uncertainty maps could be presented to clinicians along with the abnormality maps or they could be used to modulate the abnormality maps (i.e. the abnormality maps could be computed by subtracting the real patient image by the pseudo-healthy reconstruction and dividing by the uncertainty map, which would mimic a Z-score).

- **Extend the detection of anomalies to multimodal neuroimaging data** The third objective of this doctoral project is to extend the methods for now only applied to PET images (both FDG and amyloid PET) to other imaging modalities, mainly anatomical MR images processed to extract tissue probability maps and parametric maps obtained from diffusion MRI (e.g. fractional anisotropy or mean diffusivity maps).

- **Validate the approach with the support of clinicians** In the proposed project, the approaches will be applied to neuroimaging data for the computer-aided diagnosis of dementia, such as Alzheimer's disease and frontotemporal dementia, and epilepsy. Abnormality maps will be generated for multiple imaging modalities and applied on large data sets obtained from public studies (e.g. ADNI[1], NIFD[2]). For all the imaging modalities considered, abnormality maps will be generated for normal controls to verify that the method does not create false positives. Abnormality maps will then be generated for patients with known diseases and used as features to feed classification algorithms to perform tasks such as 'healthy versus disease' or 'disease A versus disease B'. This will ensure that the abnormality maps are able to differentiate different conditions. Finally, the classification results obtained using the abnormality maps as features will be compared to the classification results obtained using features directly obtained from the images, e.g. grey matter maps for structural MRI or standardised uptake value ratio for PET. This will confirm the ability of the method to detect pathologies in the images.

  Once the ability of the abnormality map to detect pathologies will be validated, their ability to assist diagnosis will be assessed using independent multimodal data sets managed at the Paris Brain Institute on pre-clinical Alzheimer's disease, genetic frontotemporal dementia and epilepsy. This will be done by retrospectively comparing visual interpretations made from the original images and from the original images together with the abnormality maps. In a first phase, clinicians (e.g., resident radiologists recruited with the help of the clinicians from the Paris Brain Institute) will be asked to provide diagnosis and diagnostic confidence based on the original images. In a second phase, the abnormality maps will be made available along with the original images and clinicians will be asked again to provide diagnosis and diagnostic confidence. The diagnoses obtained during the two phases will be compared to consensus diagnoses, and differences in diagnostic confidence will be analysed.

## A vibrant scientific, technological, clinical and ethical environment

The candidate selected will work within the ARAMIS lab (www.aramislab.fr) at the Paris Brain Institute (https://institutducerveau-icm.org). The institute, affiliated to Sorbonne Université, CNRS, Inserm and AP-HP, is ideally located at the heart of the Pitié-Salpêtrière hospital, downtown Paris. The ARAMIS lab, which is also part of Inria, is devoted to the design of computational, mathematical and statistical approaches for the analysis of multimodal patient data in brain disorders, with an emphasis on imaging data. With about 40 people, the lab has a multidisciplinary composition, bringing together researchers in machine learning and statistics and medical doctors (neurologists, neuroradiologists). The thesis will be directed by Ninon Burgos, CNRS researcher and junior fellow of PRAIRIE, the Paris Artificial Intelligence Research Institute. She completed her PhD in 2016 at University College London and obtained her HDR in 2022. In 2019, she received the ERCIM Cor Baayen Young Researcher Award, awarded each year to a promising young researcher in computer science or applied mathematics. Her research focuses on the processing and analysis of medical images, on the use of images to guide diagnosis, and on the application of these methods to the clinic.

## Your profile

- Master or engineering degree with a specialisation in machine learning
- Strong interest for medical applications
- Good programming skills in Python
- Knowledge in digital image processing and medical imaging
- Good writing skills
- Good relational and communication skills

## References


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[1] Alzheimer's Disease Neuroimaging Initiative: https://adni.loni.usc.edu/

[2] Neuroimaging in Frontotemporal Dementia: https://ida.loni.usc.edu/home/projectPage.jsp?project=NIFD