The Stankoff/Lubetzki team
(Brain repair in Multiple Sclerosis: from biology to clinical translation)
is recruiting a Master student with a possible extension to PhD position

6 month internship

Paris 13ème

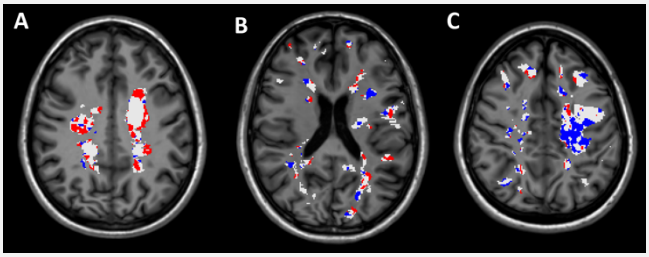
The Institut du Cerveau et de la Moelle épinière is a private foundation which objective is fundamental and clinical research of the nervous system. United in one site, 600 researchers, engineers and clinicians cover most of the disciplines in neurosciences, neurology and psychiatry with the aim to accelerate discoveries in brain functioning, and developments of treatment of diseases such as Alzheimer, Parkinson, multiple sclerosis, epilepsy, depression, etc.

Keywords: molecular imaging; positron emission tomography; magnetization transfer imaging; diffusion weighted imaging; deep learning; multiple sclerosis; myelin; remyelination; neurodegeneration

DESCRIPTION OF THE TEAM

The Stankoff/Lubetzki's team focuses on central nervous system myelination and repair using complementary approaches, from basic science to human imaging, in multiple sclerosis (MS) patients.

In the imaging field the team has recently developed a unique method to quantify demyelination and remyelination by PET imaging (Stankoff et al, 2006 ; 2011 ; Bodini et al., 2016, Ann Neurol). They uncovered inter-individual heterogeneity of repair capacity in MS patients, and for the first time showed a correlation between individual remyelination profiles and patient disability. The group also developed a set of innovative imaging methods assessing the biological substrate underlying neurodegeneration in MS now allowing to 1) visualize and quantify activated microglia in MS patients using second generation PET TSPO tracer; 2) specifically assess the neuronal component of grey matter damage by PET (Freeman L et al., 2015); 3) generate individual maps of microglial activation and neuronal loss in MS patients; 4) measure energetic dysregulation using diffusion spectroscopy (Bodini et al; 2017, Mult Scler). Combination of methods is currently used to reconstruct the pathological mechanisms involved in MS progression as they unfold in vivo. The team recently initiated a collaborative approach with Olivier Colliot (ARAMIS team) and INRIA applying deep learning methods to reproduce PET imaging using multimodal MRI.



Patterns of dynamic demyelination (red) and remyelination (blue) obtained from a combination of PET and MRI in MS patients


The Stankoff/Lubetzki team

THE PROJECT

Multiple sclerosis (MS) is the most common chronic demyelinating neurological disease and the leading cause of non-traumatic disability in young adults. The characteristic lesion of the disease is an inflammatory demyelinating lesion in the white matter. Current therapeutic approaches, which target the autoimmune inflammatory component of lesions, significantly reduce the frequency of clinical relapses, but have little effect on the slow progression of neurological disability, which is secondary to a neurodegenerative process. Insufficient remyelination of lesions has been identified as a major mechanism of neurodegeneration, justifying the development of specific imaging tools for demyelination and remyelination applicable to patients.

Conventional magnetic resonance imaging (MRI) is very sensitive for the detection and monitoring of MS lesions, but does not specifically quantify their myelin content. More advanced sequences such as diffusion or magnetization transfer have shown good sensitivity to variations in myelin content, but are not yet sufficiently specific when used alone. We have developed a more specific approach applying positron emission tomography (PET) and repurposed myelin tracers such as [11C] PiB whose myelin binding property has been demonstrated, and have been able to quantify demyelination and spontaneous remyelination in MS patients. We have observed that patients are characterized by very heterogeneous profiles of remyelination and that this remyelination potential determines neurological disability. In parallel, we have developed (in collaboration with INRIA) a deep-learning approach that uses multimodal MRI data (diffusion and magnetization transfer) to reproduce the myelin PET signal in lesions.

As part of this master's work (with the possibility of pursuing a doctorate), the following objectives will be developed from the PET and MRI imaging data available within our pilot cohort of MS patients:

- To evaluate the Impact of lesions demyelination and remyelination on the microstructural damage of connected white matter tracts. The assessment of the dynamic remyelination of each white matter lesion over time will be extracted from the [^{11}C]PiB PET data where each lesion voxel has been classified during a prospective follow up as "stable normally myelinated voxel", "dynamic demyelinating voxel", "dynamic remyelinating voxel" and "stable demyelinated voxel". The analysis of the microstructural consequences on white matter tracts will be carried out using diffusion acquisition and tractographic reconstruction of the main white matter tracts connected to the lesions. An analysis based on the distance from the lesion will be performed. Similarly, the impact on the thickness of the cortical region connected to the tracts will be analyzed.

- To evaluate remyelination using multimodal MRI acquisitions. An algorithm recently generated using deep-learning and an "adversarial training" approach has made it possible to reproduce the quantification of demyelination obtained by PET using multimodal diffusion and magnetization transfer MRI acquisitions. This algorithm will be applied to a longitudinal dataset to reproduce the PET quantification of remyelination using MRI data. In parallel, the multimodal MRI data available for this cohort of patients will be combined to extract an "MRI signature" of remyelinated areas. These remyelinated areas will be defined by voxels classified as remyelinated on PET analysis.
  This work will justify the learning and application of various image processing techniques: conventional MRI sequence processing (registration, segmentation, volumetry); quantitative

diffusion imaging and magnetization transfer; tractography; deep learning. Analysis pipelines will have to be set up, in particular by combining the Freesurfer and Tracula software, as a first step. Tract-based analysis will be developed through the generation of distance maps from lesions along tracts.

ORGANISATION OF THE INTERNSHIP

The trainee will be integrated into the "Brain repair in Multiple Sclerosis: from basic science to clinical translation" team co-directed by Bruno STANKOFF and Catherine LUBETZKI at the Institut du Cerveau et de la Moelle épinière (ICM) in the Pitié-Salpêtrière Hospital (Paris 13e). He will be supervised by a research engineer and an associate professor both expert in data processing. The work will be carried out in close collaboration with the ARAMIS team (www.aramislab.fr) co-directed by Olivier COLLIOT and Stanley DURRLEMAN

SKILLS TO DEVELOP AND/OR LEARN DURING THE INTERNSHIP

- Experience with the Linux environment and the necessary terminal
- Strong programming skills, ideally in Python
- Knowledge of image processing
- Machine learning skills would be appreciated but are not essential

RELATED PUBLICATIONS

Wen Wei, Emilie Poirion, Benedetta Bodini, Stanley Durrleman, Nicholas Ayache, Bruno Stankoff, and Olivier Colliot. Learning Myelin Content in Multiple Sclerosis from Multimodal MRI Through Adversarial Training. Springer Nature Switzerland AG 2018 ; A. F. Frangi et al. (Eds.): MICCAI 2018, LNCS 11072, pp. 1–9, 2018. https://doi.org/10.1007/978-3-030-00931-1_59

Stankoff B, Poirion E, Tonietto M, Bodini B. Exploring the heterogeneity of MS lesions using positron emission tomography: a reappraisal of their contribution to disability. Brain Pathology, 2018, in press.

Bodini B, Veronese M, Garcia-Lorenzo D, Battaglini M, Poirion E, Chardain, A, Freeman L, Louapre C, Tchikviladze, Papeix C, Dolle F, Zalc B, Lubetzki c, Bottlaender M, Turkeimer F, Stankoff B. Dynamic imaging of individual remyelination profiles in multiple sclerosis. Ann Neurol, 2016. Feb 18. doi: 10.1002/ana.2462

Stankoff B, Freeman L, Aigrot MS, Chardain A, Dolle F, Williams A, Galanaud D, Armand L, Lehericy S, Lubetzki C, et al.: Imaging central nervous system myelin by positron emission tomography in multiple sclerosis using [methyl-(1)(1)C]-2-(4'-methylaminophenyl)- 6-hydroxybenzothiazole. Ann Neurol 2011,69:673-680.

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