Postdoctoral position - 2024

Microstructural analysis in late-life depression using diffusion MRI multi-compartments models and tractometry

Supervisors: Julie Coloigner (julie.coloigner@irisa.fr)
Gabriel Robert (g.robert@ch-guillaumeregnier.fr)

Scientific environment: Empenn U1228, IRISA, Campus de Beaulieu, Rennes - https://team.inria.fr/empenn/

Duration: 12 months

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Keywords: diffusion MRI, microstructure, tractography, connectivity, depression, apathy.

Context:

Late-life **depression** (LLD) affects 7% of the population aged over 60 years and the number of cases of LLD is likely to increase given the demographic outlook. This is of concern given that LLD is an independent risk factor for mortality, a modifiable risk factor for dementia, and significantly associated with antidepressant resistance and suicide. However, the pathophysiology of LLD is plural and involves inflammatory, degenerative and vascular processes, thereby increasing clinical heterogeneity and the need for a better understanding of its mechanisms. Among LLD heterogeneity, **apathy** is common, increases LLD burden and is a well-established additional risk factor for cognitive decline among mild cognitive impairment and the general population but the underlying mechanisms for this additional risk of cognitive decline remain unknown [1].

Regarding apathy, its measurement has to be objective, robust and reproducible. Psychometric evaluations of apathy do not reach these criteria, being limited by patients' introspection abilities or by the definition of apathy chosen by the authors. A more objective approach is to operationalize apathy as a reduction in goal-oriented behaviors, which renders accessible a range of technologies for a valid measure of apathy. **Actigraphy** is an easy to employ, non-invasive device which records one's minute-to-minute daily motor activity. Actigraphy studies have provided insightful results of ecological activity in depression as in apathy in elderly population [2].

Recently, systemic inflammation was associated with apathy across deep white matter lesions in the elderly, suggesting that apathy would be the behavioral output of central inflammation. In vivo **diffusion magnetic resonance imaging** (dMRI) is sensitive to central inflammation and, combined with appropriate models, may provide proxy biomarkers of inflammatory processes in the brain. The dMRI sequence is a non-invasive imaging method that allows the visualization of the brain. In particular, it can detect abnormalities in brain structure associated with pathology, potentially before the onset of symptoms. A recent development in MRI has been quantitative MRI, a set of techniques for characterizing quantitative parameters of the brain's interne structure: its microstructure.

In addition to providing information about the structural geometry of the brain, dMRI can also provide microstructural metrics of brain tissues using tissue-specific biophysical models, such as fractional anisotropy. The well-known diffusion tensor imaging (DTI) model is one of the simplest ways to represent anisotropic diffusion, it is also the most widely used in clinical applications and has

contributed to a better understanding of the clinical heterogeneity of major depression. However, the simplicity of DTI has its limitations. In crossed fibers, fiber dispersion, or areas with different tissues such as extra-axonal or free water, DTI cannot correctly represent the underlying microstructure. These limitations have led to the development of more complex microstructural diffusion models such as Multi-Compartment Models (MCMs), Neurite Orientation Dispersion and Density Imaging (NODDI) or Composite Hindered and Restricted Model of Diffusion (CHARMED) and its extension AxCaliber, which estimate specific properties directly from dMRI images [3]. These approaches are used to disentangle the complex signal by considering multiple isotropic and anisotropic compartments, each compartment representing a specific diffusion in cerebrospinal fluid, glial cells or axon bundles. The various three-compartment biophysical models differ in the representation used to describe the tissue-specific signal and the assumptions made about the model parameters. Promising studies have shown that MCMs appear to provide microstructural metrics with greater specificity and sensitivity to tissue properties than those obtained with conventional DTI. Indeed, subtle changes in tissue microstructure have been found in patients suffering from psychiatric disorders using an MCM [4].

Recent advances in diffusion models and tractography methods have led to the development of a new framework, called tractometry, for better assessment of WM microstructure. Specific fiber bundles can be reconstructed via tractography from diffusion models, and then the dMRI-derived measures are projected along the white matter tracts. Analysis of these bundle profiles can provide a more specific and localized investigation than looking at a region of interest or tract-averaged measures. Briefly, along-fiber approaches generate a bundle profile for each fiber, map the DTI metrics onto a centroid line, and then perform statistical analysis of the DTI metrics at multiple points along the centroid line to identify specific locations where the DTI metrics are different. This can be used to study normal brain development and to characterize areas of the brain in different brain conditions. As described previously, MCMs provide sensitive and specific metrics for certain microstructural properties. Recently, some studies have proposed to analyze each of the multiple tissue microstructural measures derived from these models independently using univariate analysis.

To advance in the understanding of apathy physiopathology in LLD, we conducted a study which evaluated the relationship between patterns of motor activity measured by actigraphy, and brain modifications of white matter microstructure. This study found two patterns of motor activity associated with apathy: a reduced diurnal mean activity, and an early chronotype pattern. These patterns of motor activity were associated with modified intra-network resting-state functional connectivity in key regions associated with the default-mode, the cingulo-opercular and the frontoparietal network. However, our preliminary work on microstructure metrics estimated from diffusion weighted imaging did not find significant associations between microstructural metrics of white matter and patterns of motor activity after adjustment for multiple. To detect more subtle links such as those between patterns of motor activity and microstructure, our approach needs to be improved [3].

Aims of this position:

This project will focus on two major subjects:

- Developing a more accurate estimation and projection of microstructure metrics along the fiber as well as a new statistical method taking into account the shape complexity of the fibers.
- Extracting more accurate markers of patterns of motor activity measured by actigraphy such as in [5]

The developed approach will be tested on a cohort of patients suffering from **late-life depression**, with the aim of better estimating the microstructure and thus better understanding the neuronal modifications caused by this disease and apathy.

Location: The recruited person will work at Inria/IRISA, UMR CNRS 6074, among the Empenn U1228 team. The work will be in close link with Dr Gabriel Robert and Dr Jean-Charles Roy, psychiatrists from **Centre Hospitalier Guillaume Regnier (CHGR).**

Requirements: We look for candidates strongly motivated by challenging research topics in Neuroimaging and clinical projects. The applicant should present a good background in neuroimaging analysis and signal processing. Good knowledge of computer science aspects is also mandatory, especially in Python.

How to apply?
Please send us the following information and documents:
- Updated CV
- A list of publications
- A motivation letter
- A recommendation letter, or the contact of a supervisor who could recommend your application.

References :

[1] Yuen, G. S. et al. Apathy in late-life depression: common, persistent, and disabling. The Am. J. Geriatr. Psychiatry 23,488–494 (2015).

[2] Jean-Charles Roy, Renaud Hédouin, Thomas Desmidt, Sébastien Dam, Iris Miréa-Grivel, Weyl Louise, Elise Bannier, Laurent Barantin, Dominique Drapier, Jean-Marie Batail, Renaud David, Julie Coloigner, Gabriel H. Robert, Quantifying Apathy in Late-Life Depression: Unraveling Neurobehavioral Links through Daily Activity Patterns and Brain Connectivity Analysis Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 2024, pp.1-30.

[3] Panagiotaki, E. et al. Compartment models of the diffusion mr signal in brain white matter: a taxonomy and comparison, Neuroimage 59, 2241–2254 (2012).364

[4] Renaud Hédouin, Jean-Charles Roy, Thomas Desmidt, Gabriel Robert, Julie Coloigner, Microstructural brain assessment in late-life depression and apathy using diffusion MRI multi-compartments models and tractometry Scientific Reports, In press

[5] Abbas, M., Roy, J. C., Robert, G., & Jeannès, R. L. B. (2022, August). Utility of actimetry to detect apathy in old-age depression: A pilot study. In 2022 30th European Signal Processing Conference (EUSIPCO) (pp. 1203-1207). IEEE.