Meeting Report: NeuroFrance 2023 Sabine Adeline FANTA YADANG Thesis Report 24-26 May 2023, Lyon, France

It was a great pleasure to attend the NeuroFrance 2023 International meeting held on 24th to 26th May 2023 in person at the Lyon convention centre in France after 2021's virtual event. Lyon welcomed Neuroscientists from across all spectra of brain sciences to present a real-live full conference with a varied scientific programme including, plenary lectures, symposia, special sessions, posters presentations and exhibitions. As an In-Person conference, this gave the opportunity to presenters to share their cutting-edge achievements and novel concepts in the field of neuroscience making this a truly meaningful and memorable meeting. Also, attendees enjoyed the pleasure of face-to-face interactions and networking in a safe and relaxed environment discussing on their research, discovering new ideas and showcase their science.

First day in the Lyon Convention Centre hall

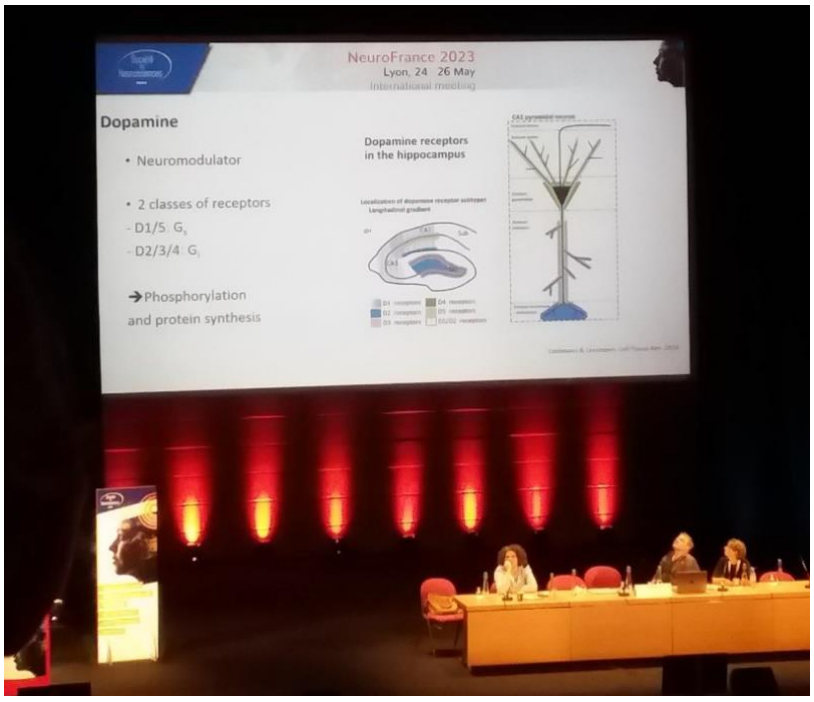
During these 3 days meeting, I had the chance to listening to some wonderful presentations with remarkable discoveries. But, there were too many interesting lectures and it was difficult to cover them all.

I attended the symposium which presents the potential role of synuclein members in Parkinson's disease and related disorders with **Prof Véronique Sgambato** and **Analia Bortolozzi** as chairs of the session. The symposium started first with the talk of **Dr Andrea Mancini** from Department of Medicine, University of Perugia, Italy on the **Clinical overview on Parkinson's disease (PD) and other synucleinopathies and relevant biomarkers**. During his talk, he presents the main histopathological features of PD represented by the progressive loss of dopaminergic neurons in the midbrain substantia nigra pars compacta and the accumulation of intraneuronal insoluble protein aggregates named Lewy bodies. He also talks on biomarkers that are required to detect the disease in the early stages. Various biomarkers providing early diagnosis of the disease include clinical, imaging, pathological, physiological, biochemical, and genetic parameters. Moreover, biomarkers alone or in combination are used to diagnose and monitor the evolution of PD.

Also in the same way, **Marie-Laure Arotcarena** from the Institute of Neurodegenerative diseases, University of Bordeaux presented on 'the role of Alpha-Synuclein as a key player in animal models of Parkinson's disease'. The team developed an experimental model of PD particularly in non-human primate in which a pathophysiological amount of α-syn purified from PD patients' brains was injected. They injected in baboon monkeys PD patient-derived Lewy Body fractions containing large and insoluble α-syn aggregates and PD patient-derived noLB fractions, containing small aggregates and mainly soluble α-syn. They observed a nigrostriatal neurodegeneration and dopaminergic neurodegeneration associated with α-syn pathology localized in many brain regions. Taking advantage of a machine learning approach, they obtained unique pathological signatures of induced pathology between LB and noLB groups, leading to the same dopaminergic lesion level. In the same large cohort of NHPs, they compare the pathological consequences of either intrastriatal or enteric injection of asynuclein containing Lewy body extracts from patients with PD. The results showed that patient-derived a-synuclein aggregates are able to induce nigrostriatal lesions and enteric nervous system pathology after either enteric or striatal injection in a NHP model. This finding suggests that the progression of a-synuclein pathology might be either caudo-rostral or rostro-caudal, varying between patients and disease subtypes. In parallel with mechanistic studies, they aimed to develop therapeutical strategies to counteract α-syn accumulation, propagation, and aggregation. The team aims to develop autophagy-based approaches to reestablish physiological levels of α-synuclein in different models of synucleinopathy. To this aim, they have developed different strategies (genetic or chemical) which showed promising results in increasing α-synuclein degradation in various rodent models of PD. Now, they are exploring such therapeutic strategies in NHP models to provide more robust preclinical outcomes.

One other talk was from **Pola Tuduri**, who is a PhD student at the "Institut de Génomique Fonctionnelle", CNRS, Inserm, University of Montpellier, France. The team focused their investigation on the **Contribution of Dopamine Receptor 2 (D2R)**

expressing-Gabaergic cells on hippocampal synaptic plasticity. She started her talk with a few description of hippocampus as a brain region involved in a wide range of functions including motivation, learning and memory which are modulated by dopamine. Dopamine receptor 2 plays an important role in the regulation of hippocampal neuronal excitability and contributes to the regulation of synaptic plasticity, the encoding of hippocampusdependent memories and the regulation of affective state. During her talk, she states that, in their study, they identified a cluster of D2 receptor-expressing somatostatin (Sst) cells in the dorsal prosubiculum (PSd), a region neighboring the CA1 area whose role remains relatively unknown. The PSd is suggested to be the integrating center of the hippocampus and the output pathway for information from the CA1 area. Through behavioural studies, they demonstrated that D2 receptor located in Sst cells plays a key role in detecting environmental changes coupling an association between a sound and a shock separated in time by an interval. Finally, they showed that D2 receptor in Sst cells is necessary for the plasticity phenomena underlying this paradigm by coupling the behaviour and ex-vivo electrophysiological recordings. The findings of the team will be essential to understand the mechanisms by which D2R alteration, specifically in Sst neurons, is involved in deficits associated with memory impairments.



Ms Pola TUDURI's talk

There was another exciting symposium title '**Single domain antibodies as novel therapeutic agents for brain diseases**', presenting various finding covering this topic.

Dr. Kirill Martemyanov from the University of Florida, Department of Neuroscience, United States started the first talk with the title '**Targeting brain orphan receptors with nanobodies for therapeutic benefits**'. Dr. Martemyanov state that, orphan

receptors offer substantial promise as new targets for the development of innovative interventions for brain disorders. Thus, understanding their biology, signaling mechanisms and development of compounds that target orphan receptors is a highly relevant goal. His study focus on GPR158, an abundant brain receptor implicated in depression. Especially on the understanding of the structural organization of this receptor using CryoEM. Also, they elucidates the endogenous ligand for GPR158 deorphanizing this receptor. Followed the understanding organization and function of GPR158, the team have developed specific nanobodies targeting extracellular portion of the receptor and demonstrated their ability to alter GPR158 signaling and resultant anti-depressant effects in mice. The results of this study raise the possibility to guide the development of nanobody based therapeutics for depression.

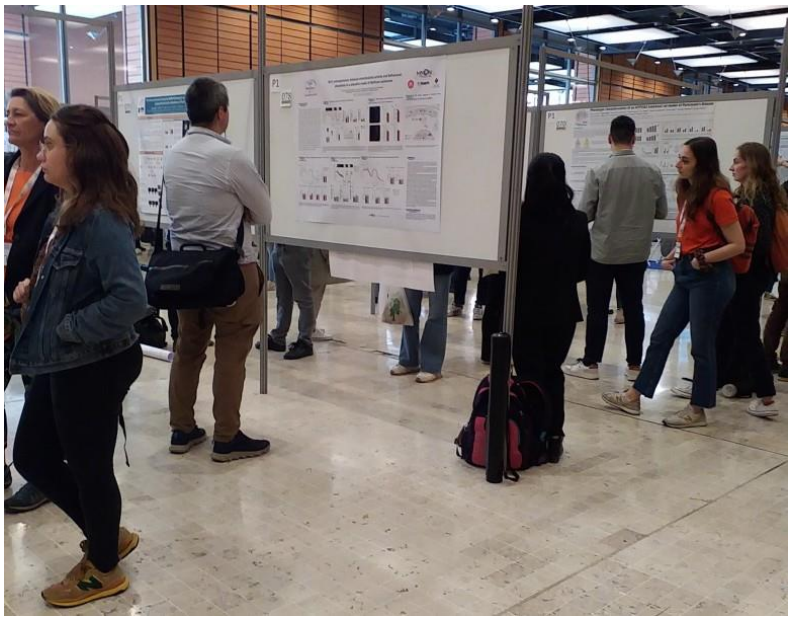
The second interesting presentation within the symposium was the talk of Dr. Julie Le Merrer from Inserm, Université de Tours, France. Dr Le Merrer talk was on the 'adenosine A2Areceptor-targeting nanobody relieves autistic-like behavior in mice'. A2AR is an interesting target for the discovery of new compounds with clinical applications. And most recently, immunotherapies have demonstrated their high potential for drug discovery. Specifically, single domain antibodies (SdAbs) have risen as innovative tools with advantages in terms of selectivity and reduced size in comparison with a whole immunoglobulin. In their study, the team used a novel in silico approach (3D structure-based method MabCross®) to find SdAbs targeting A2AR. Four novel SdAbs binding A2AR were identified and characterized in vitro, ex vivo and in vivo. Among these four SdAbs, DRA2-02 behaves as a positive allosteric modulator (PAM) of the human version of A2AR (hA2AR), but as a negative allosteric modulator (NAM) of its murine equivalent (mA2AR) in HEK cells. Using mutant receptors, they evidenced that the molecular determinants of DRA2-02 binding at A2AR were localized in the extracellular loops of the receptor, and that PAM versus NAM properties on hA2AR and mA2AR, respectively, were driven by the sequence of these extracellular loops. They finally explored the binding specificity of DRA2-02 on ex-vivo tissues and its ability to cross the BBB to modulate behavior in mice. Their study identifies the first antibody fragment with allosteric modulator properties at A2AR.

The plenary lecture of Alfred FESSARD 2023 was given by **Vincent Prévot**, Director of Research at the University of Lille, Inserm, Laboratory of Development and Plasticity of the Neuroendocrine Brain, Lille Neuroscience & Cognition, UMR-S1172. Professor Prévot gives his talk on '**the neuroendocrine key to the brain aging enigma**'.

1Vincent Prévot talks at the Alfred Fessard lecture

Professor Vincent Prévot has notably established that tanycytes, which are specific ependymocytes lining the floor of the third ventricle and which form a bridge via their extensions between the cerebrospinal fluid and the pituitary portal circulation, play a fundamental role in neuroendocrine processes. They are not only involved in the control of neurosecretion of GnRH, the hypothalamic neurohormone controlling reproduction function, but also in the transport across the blood-brain barrier of peptide hormones, such as leptin secreted by adipose tissue which informs the brain of the individual's metabolic state and controls appetite. He also showed that these tanycytes transports are altered in conditions of obesity and that this alteration is at the origin of a breakdown in communication between the brain and the rest of the organism, which can predispose the brain to pathological aging. Also he showed that hypothalamic tanycytes, whose cell bodies line the ventricular wall and send long processes to the underlying pituitary portal capillary bed, take up and transport Tau from the CSF and release it into these capillaries, whence it travels to the pituitary and eventually the systemic circulation. This was an excited work which showed the role for the fertility hormone GnRH and tanyctes.

During this meeting, poster presentations were very interesting as well as symposia and lectures with diverse topics given the chance to discuss with the poster presenters and to discover surprising results. These 3 days allows the audience to learn some new technique in the study of some pathological disorders, new behavioural studies with new apparatus and advance general knowledge on the range of topics. This also helps to make new contacts with possible collaborations.



Poster presentation hall

During the French Neuroscience Society General assembly, the organizers announced with great excitement that the next NeuroFrance meeting will be held in Montpellier from 14-16 May 2024. One other purpose of this award was to visit some French labs to expand my research network and to grab some collaboration. I had to visit 3 labs:

1. **The team of Professor Ivo VAZETTA** at the 'Institut des Neuroscience de la Timote (INT)' in Marseille, France.

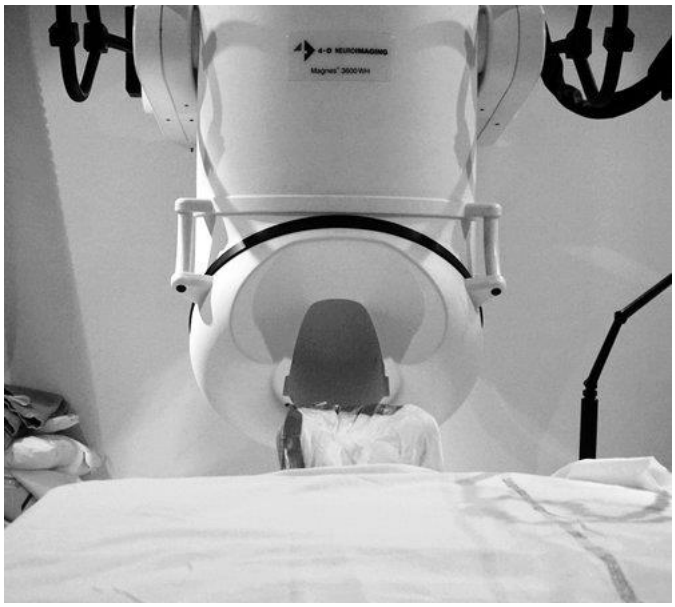
   The team of Prof Ivo work on the photonic neuroimaging using 2 photons calcium imaging. This technique is quite interesting as it helps to visualize signal/activity transmitted from a selective brain cells. During my visit, I was introduce to the team and I had the pleasure to enjoy a presentation gave by Professor from the Canadian Institute of Research on the use of marmoset as animal models.

2. **The laboratory of Professor Christian-G. Bénar** in Marseille MEG center, Institut de Neurosciences des Systèmes (INS), Marseille, France.

   Prof. Bénar is the Team leader of the Dynamical Brain Mapping in the 'Institut de Neurosciences des Systèmes'. The general objective of the Dynamap team is to develop signal processing strategies for characterizing the spatio-temporal dynamics of brain networks, for both physiological and pathological activity. The first strategy of the team is to combine the strength of different modalities such as EEG, MEG, fMRI, with particular emphasis on simultaneous recordings (EEG-MEG, EEG-fMRI) that allow recording the exact same activity under different points of view. The second strategy is to take the opportunity

of intracerebral recordings performed in patients with epilepsy for providing a 'ground truth' to which non-invasive methods can be confronted.

This visit was very interesting as I get introduce to a novel technique which is the **Magnetoencephalography (MEG)**.



Picture is from the 'Institut de Neurosciences des Systèmes', https://ins-amu.fr/platforms-clinics

MEG is the recording of the brain's magnetic activity. This activity is the counterparts of the electrical activity that originate from the brain, recorded by EEG. These techniques are the only ones that are directly related to the neural activity and have enough time resolution to track brain activity. One of the great advantages of the MEG over EEG is the very small effect of the geometry of the different media of the head, especially the skull, on the recorded signals.

3. The laboratory of Professor Suliann Ben Hamed at the 'Institut des Sciences Cognitives Marc Jeannerod', University of Lyon 1.

Prof Ben Hamed team focus on Neural Bases of Spatial Cognition and Action. Specially, on visual attention and perception, where they are interested in understanding how individual neurons, local neuronal networks and distributed cortical networks implement these two fundamental cognitive functions. Also on multisensory and social spaces, they are interested in understanding how neurons and cortical networks combine sensory information from multiple sensory organs in order to construct our internal representations of space, of self and of others.

I got introduce to the team of Prof Ben Hamed and had the opportunity to discuss with the different team members. This was a nice opportunity to get in contact with them.

Acknowledgements

I would like to thank the **French Neuroscience Society** and the **Tianqiao and Chrissy Chen Institute** for the travel award I received to participate in the NeuroFrance 2023 meeting. This was a wonderful opportunity to present my research work to the audience and to participate to some special lectures, symposium and poster presentations.