NENS Exchange Grant 2020 – Final Report

Grantee: Pablo Machuca-Márquez, PhD Candidate.

Host lab: Behavioral Genetics Laboratory (Dr. Carmen Sandi Lab); Brain-Mind Institute, École Polytechnique Fédérale de Lausanne (BMI-EPFL; Lausanne, Switzerland).

Home lab: Mitochondrial Neuropathology Laboratory (Dr. Albert Quintana Lab); Institut de Neurociències, Autonomous University of Barcelona (INc-UAB; Barcelona, Spain).

Project title of the training stay: Deciphering the mitochondrial mesolimbic contribution in the severity and susceptibility of motion sickness.

Background

Motion sickness (MS) is a physiological alteration occurring in individuals undergoing passive movement. In the brainstem, vestibular nuclei (VN) are classically associated to MS. Provocative motion activates VN neurons, recapitulating MS-related autonomic and aversive behavioral signs. However, the cell-type specific contribution of VN neurons mediating MS regulation and their MS-relevant downstream projections remain unknown. In the context of my PhD project, we have untangled novel cell-type specific neural substrates and a circuit crucially controlling select MS responses.

Additionally, our results suggest a key role of motivation in influencing MS. Nucleus accumbens (NAc) is a mesolimbic dopaminergic brain region considered central in controlling motivation-, reward- and aversion-related behaviors. Furthermore, it is extensively known that susceptibility to MS largely varies across individuals. Noteworthy, growing evidences indicate that mitochondrial activity decisively mediates NAc function, since rats with NAc possessing higher mitochondrial function correlates with higher social ranks and lower anxiety levels. However, the specific role of the NAc itself and its mitochondrial influence in regulating MS severity and susceptibility remain largely unknown.

Training at the EPFL

Dr. Carmen Sandi Laboratory is a world-class Swiss team, leader in unravelling the mitochondrial role of the mesolimbic system in motivation- and anxiety-related behaviors. Therefore, my internship at the Behavioral Genetics Laboratory in Lausanne (Switzerland) constitutes a unique opportunity for the exchange of research and education across the European Neuroscience Community, running a dedicated training plan focused in acquiring the relevant knowledge and techniques to assess the mesolimbic and mitochondrial influences in MS neurobiological regulation. In this sense:

- I attended our weekly lab meetings, BMI-EPFL seminars and relevant Swiss conferences, since Swiss Neuroscience is particularly strong in the Stress field, which helped me to learn about the mesolimbic circuitry and its involvement in behavior.

- I developed computer-based analyses of Electron Microscopy stack images, which contributed to the characterization of a novel association between anxiety and distinct mitochondrial and dendritic morphologies in NAc neurons of rats, leading to the acquisition of expertise for the future characterization of the mitochondrial NAc involvement in MS regulation.
- I learnt specific motivation-related behavioral tests (tube test, elevated plus maze and social interaction), relevant for the characterization of the mesolimbic contribution in MS behavioral responses, once combined with my *in vivo* model of MS at the home institution.
- I acquired notions in state-of-the-art techniques for mitochondrial function assessments (Oroboros tests), necessary to unravel their potential contribution in MS modulation.
- I acquired notions in fiber photometry and miniscopes by attending other lab members' experiments, real-time *in vivo* technologies that may allow the characterization of the NAc activity during MS.

Implementation at home institution

After this unique internship, I am fully prepared to enable this European collaboration once I am back at my home institution, INc-UAB in Barcelona (Spain). I plan to combine these techniques, previously not available in my home lab, with my *in vivo* mouse model of MS, including neural interrogation techniques such as optogenetics and chemogenetics which I already mastered. Additionally, I plan to transfer my new know-how to other lab members.

Career development

The NENS Exchange Grant allowed me to enjoy a highly-productive experience in Switzerland, learning new techniques and further enriching my PhD project. The EPFL is part of the vibrant Swiss Neuroscientific environment, which facilitates scientific exchange and has truly improved my career prospects. Here, I have met extraordinary colleagues always willing to kindly collaborate with invaluable scientific and career development insights. This international environment has also boosted my network and my communication skills, as being recognized by obtaining a Best Poster Prize at the NCCR-SYNAPSY – 3rd Conference on the Neurobiology of Mental Health (Campus Biotech, Geneva).

Acknowledgements

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