MASTER 2 Fundamental and Clinical Neurosciences

Internship proposal 2023-2024

(internship from January to June 2024)

Host laboratory:

Stem Cell and Brain Research Institute INSERM 1208
18 Avenue du Doyen Lépine 69500 Bron France
http://www.sbri.fr

Host team:

Chronobiology and Affective disorders
http://www.sbri.fr/team/chronobiology-and-affective-disorders

Internship:

Nasser Haddjeri, PhD
DR2 INSERM, Nasser.haddjeri@inserm.fr

Project title:

Role of the Axonal initial Segment in the Antidepressant Response of Psychedelics

Project summary:

With a lifetime prevalence rate of 20% in the general population, major depression (MD) is the most common psychiatric disorder. Actual pharmacotherapies remain insufficient due to a delayed onset of antidepressant action, a lack of full therapeutic effects and refractory forms of MD occurring in one third of the patients. These issues emphasize the urgency to intensify the research to develop more efficacious treatments.

Disruptions of serotonin (5-HT) signaling is a common feature of many psychiatric diseases, most notoriously affective disorders including MD. Therefore, the major goal of commonly antidepressant pharmacotherapy is to restore efficient 5-HT signaling.

Recently unveiled as a 5-HT-sensitive key element in synaptic homeostasis, the axon initial segment (AIS) is a unique structure, where action potentials (AP) are initiated. Hence, our recent data highlight the importance of AIS plasticity by revealing a link between 5-HT-

mediated AIS shifts and mood phenotype. We propose to gain insight into this novel finding of 5-HT-dependent AIS neuromodulation that will likely uncover critical roles for AIS plasticity in regulating mood. The candidate will approach this theme by using mainly in vivo electrophysiological and behavioural techniques in mice. Ultimately, our proof of concept study, supporting that AIS neuromodulation acts as “key player” in the antidepressant response of psychedelics, will bring forward original alternative hypothesis for innovative therapeutic strategies.

3-5 recent publications:

Etievant A, Oosterhof C, Betry C, Abrial E, Novo-Perez E, Rovera R, Scarna H, Devader C, Mazella J, Wegener G, Sánchez C, O Dkhissi-Benyahya, C Gronfier, Coizet V, Beaulieu JM, Blier P, Lucas G and Haddjeri N (2015): Astroglial control of the antidepressant effects of prefrontal cortex deep brain stimulation. *EBioMedicine*. 2(8): 898-908.

Delcourte S, Abrial E, Etiévant A, Rovera R, Arnt J, Didriksen M, Haddjeri N (2017): Asenapine modulates mood-related behaviors and 5-HT1A/7 receptors-mediated neurotransmission. *CNS Neuroscience & Therapeutics*. 23(6):518-525.

Kanzari A, Bourcier-Lucas C, Freyssin A, Abrous N, Haddjeri N and Lucas G (2018): Inducing a long-term potentiation in the dentate gyrus is sufficient to produce rapid antidepressant-like effects. *Molecular Psychiatry*. 23(3):587-596.

Manfredi-Lozano M, Leysen V, Adamo M, Paiva I, Rovera R, Pignat JM, Timzoura FE, Candlish M, Eddarkaoui S, Malone SA, Silva MSB, Trova S, Imbernon M, Decoster L, Cotellessa L, Tena-Sempere M, Claret M, Paoloni-Giacobino A, Plassard D, Paccou E, Vionnet N, Acierno J, Maceski AM, Lutti A, Pfrieger F, Rasika S, Santoni F, Boehm U, Ciofi P, Buée L, Haddjeri N, Boutillier AL, Kuhle J, Messina A, Draganski B, Giacobini P, Pitteloud N, Prevot V. (2022). GnRH replacement rescues cognition in Down syndrome. *Science*. 377(6610): eabq4515.