2019 Call for projects

Hypothalamic alterations as a cause of weight loss and clinical progression in ALS

Acronym: HypothALS

Principal Investigator: Luc DUPUIS

Grant: 250 000€

Duration: three years

Summary of the research project

ALS is associated with a dramatic weight loss, that is a recognized prognostic factor and nutritional correction of weight loss was able to extend lifespan of mice with ALS, and delayed motor neuron degeneration. Weight loss is associated with profound rearrangements of whole body energy homeostasis and increased energy expenditure. Most importantly, a recent clinical trial provided proof of concept that hypercaloric diet could extend lifespan of gastrostomized ALS patients. Determining the causes of weight loss could thus provide us with therapeutic targets not only to treat weight loss and ameliorate quality of life of these severely ill patients, but also to improve their survival.

Very recently, we have shown that the hypothalamus, a key brain region controlling food intake and energy expenditure, was atrophied in ALS patients, as well as in presymptomatic gene carriers. Importantly, this atrophy was correlated with body mass index. Moreover, we observed functional abnormalities in the hypothalamic response to orexigenic peripheral cues in both ALS patients and mouse models. Last, our unpublished results demonstrate that ALS-related pathology is mostly confined to lateral hypothalamic area (LHA) in both mouse models and patients, and that a specific neuronal population of the LHA could be responsible of weight loss.

Our objective in this project is to understand the role of the LHA and its major neuronal populations in weight loss and disease progression of ALS. In particular, we will :

(i) identify the LHA neuronal types affected in ALS progression

(ii) characterize the LHA connectome in relation with disease progression

(iii) determine the functional role of LHA neuronal types in ALS-related weight loss

(iv) determine the functional role of LHA neuronal types in ALS-related motor dysfunction

Hypothalamic alterations as a cause of weight loss and clinical progression in ALS

To this aim, we will use a translational approach combining original animal models, with state of the art neuroscience techniques such as viral tracing and chemogenetics. Our results will be validated in tissues of patients affected with ALS. This project will allow to understand the mechanisms of weight loss in ALS, in order to conceive rationally-designed pharmacological strategies to treat weight loss and prolong lifespan of ALS patients.

The study will be conducted by **Luc Dupuis**, Inserm/Université de Strasbourg, Strasbourg, France and **Francesco Roselli**, Dept. of Neurology, Ulm University School of Medicine.

Luc Dupuis

Francesco Roselli