Project 5:

TITLE OF THE COLLABORATIVE PROJECT

TIME-DEPENDENT EVOLUTION OF NON-MOTOR SYMPTOMS IN MODELS OF PARKINSON'S DISEASE: CHARACTERIZATION OF AND IMPACT ON THE tVTA

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1. PARTNERS INVOLVED IN THE COLLABORATION

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2. DESCRIPTION OF THE COLLABORATIVE PROJECT

Rationale. Parkinson's disease affects 4 to 6 million persons worldwide and is the second most frequent neurodegenerative disease, after Alzheimer's disease. While Parkinson's disease, characterized by the loss of dopamine neurons, is mostly known for its motor symptoms such as bradykinesia, rigidity and resting tremors, it also has deleterious non-motor consequences including weight loss, constipation, pain, anxiodepressive disorders and deficits in executive functions. Most of these non-motor symptoms even appear years before development of the motor ones. Thus, patients consulting for Parkinson's disease display around 14 symptoms as a mean at early stage of the disease, and over 20 at later stage, which stresses out the need to take this complexity and time-dependent development into consideration in preclinical research. While slowing the neurodegenerative process is a major therapeutic goal, improving yet unmanaged symptoms in already installed disease remains also critical. In this context, newly discovered brain structures can help improving our knowledge of normal brain functions and of brain disorders, and may provide new neuroanatomical targets for treatments. The tail of the ventral tegmental area, or tVTA, is a brain structure discovered in the past decade and exerting a major inhibitory control on dopamine systems. First described in rodents, the tVTA has now been observed in the primates. Recently, we demonstrated that the tVTA controls motor functions, and that its bilateral ablation improves motor performances and motor skill learning. Preliminary data suggest that inhibiting the tVTA may be beneficial on motor symptoms in models of Parkinson's disease.

Objectives. In this context, the 2 objectives of the present project are: **1)** to have a better characterization of the time-dependent development of some non-motor symptoms in 2 models of Parkinson's disease; **2)** to study the impact of a manipulation of the tVTA on these non-motor symptoms.

Content. Within this Strasbourg/Amsterdam collaborative project, we propose to characterize over time non-motor symptoms in 2 rodent models of Parkinson's disease: the partial 6-OHDA bilateral lesion of substantia nigra pars compacta (SNc) dopamine neurons, and the more recently developed AAV2-9 α-synuclein model of bilateral SNc lesion. Over the 16 weeks following induction of the models, the weekly evolution of body weight, food intake, intestinal motility, metabolism, mechanical and thermal nociceptive sensitivity, reflexes, anxiety-like behaviours and depressive-like behaviours will be characterized, thus providing the first time-chart of non-motor symptom evolution in these models of Parkinson's disease. Manipulation of the tVTA will then be done through either permanent inactivation by excitotoxic lesion or reversible inhibition through DREADD pharmacogenetic manipulation. The influence of such manipulation will be tested on the above symptoms at different time-points of the disease's evolution. Overall, these experiments will provide a first description of non-motor symptom evolution over time in relevant animal models of Parkinson's disease, as well as proof-of-concept of whether tVTA may be a relevant neuroanatomical target for these symptoms' management.

Partnership. Behavioral studies on pain-related and anxiodepressive-related symptoms (12 months) and on tVTA manipulation (12 months) will be performed in Strasbourg under the supervision of Dr. Michel Barrot. Studies on feeding behavior, metabolism and motility (9 months)

will be done in Amsterdam under the supervision of Dr. Susanne la Fleur. Final redaction will be done in Strasbourg (3 months). This project is permitted by the respective expertise of both Partners: neurobiology of dopamine systems, pain and depression for Strasbourg Partner; neurobiology of food intake and metabolism for Amsterdam Partner. This partnership will thus provide the student with a large expertise, spanning the fields of Parkinson's disease, animal models, pain, depression, feeding and metabolism.

3. DESCRIPTION OF THE EXPECTED MOBILITY TRACK

- *Oct. 1st 2016 to Sept. 30th 2017: 12 mo: Unistra: in vivo validation and characterization of the models of Parkinson's disease and time-course of the nociceptive and anxiodepressive symptoms.*
- *Oct.1st 2017 to Sept 30th 2018: 12 mo: Unistra: impact of tVTA manipulation on the time-dependent development of nociceptive and anxiodepressive symptoms.*
- *Oct. 1st 2018 to June 30th 2019: 9 mo: UvA/NIN: characterization of the time-course of the feeding and metabolism and impact of the tVTA on related symptoms.*
- *July 1st to Sep. 30th2019: 3 mo: Unistra: Redaction of the thesis manuscript.*

4. REQUIREMENTS FOR THE CANDIDATE

A **Master degree in the field of Neurosciences** is a pre-requisite for the candidate.

Previous experience of behavioral studies in rodent models would be preferred. The student should express a strong motivation to work on this project. Mastery of the English language is essential.