**PhD PROPOSAL FOR THE**

**PASTEUR - PARIS UNIVERSITY INTERNATIONAL DOCTORAL PROGRAM**

Time for applicants to contact host laboratories: September 13 – November 2, 2017

Deadline for full application: November 13, 2017

Interviews: January 30, February 2, 2018

Start of the Ph.D.: October 1, 2018

**Title of the PhD project:** Deciphering the functional role of adult-born neuron integration and its effect on established networks

**Keywords:** Adult neurogenesis, sensory systems, olfactory bulb, structural plasticity, computational modeling

**Department:** Neuroscience

**Name of the lab:** Perception and Memory

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***Doctoral school affiliation and University*:** Université Paris 6, ED3C

Presentation of the laboratory and its research topics:

The laboratory of Perception and Memory strives to discover causal mechanisms of brain circuit structure and function with memory, learning and behavior. A major field of interest is adult neurogenesis, the persistent proliferation and integration of newborn neurons the adult brain. Adult neurogenesis presents as an extreme form of structural plasticity where newborn neurons have the capacity to establish almost unhindered, novel connectivity which may allow for expanded ability to adapt to novel sensory environments. Our laboratory has shown that these adult-born cells in the primary olfaction processing brain region, the olfactory bulb, have differential characteristics when compared to the pre-existing population including: A lower threshold for long-term synaptic potentiation1, enhance learning when the neurons are stimulated2, they have unique inhibitory synapses3 and during their integration they have a period of heightened structural plasticity and may drive synaptic turnover in their connected partners4. These studies in our lab opened the door to numerous questions including: What is the functional role and potential advantages of circuits with adult-born neurons? What is their effect on the output of the network?

Description of the project:

It was long thought that the adult brain was established in development without any addition of new neurons in adulthood. This principle was overturned in the late 1900s with the discovery of adult neurogenesis where new neurons were found to integrate into the host circuit in brain regions associated with short-term memory (hippocampus) and for processing olfactory information (olfactory bulb)5. Since the rest of the brain was essential devoid of any form of new neuron integration, a fundamental question in the field is why do these brain regions need new neurons?

Our laboratory has developed tools for probing adult-born neurons and their integrated circuits, the circuits connected to the olfactory bulb, tools for monitoring neuronal activity and behavioral assays to track learning and memory in mice. With the data from these experiments we aim to establish a new computational model to integrate neuronal activity changes associated with learning to predict the behavior of the animal in a learning task.

**Aim #1: Determine how adult-born neurons and top-down connectivity modify the olfactory bulb network output.**

To determine the role of adult-born neurons in behavior, it is essential to first map their functional connectivity and how this connectivity evolves during a learning task. In our laboratory, we developed techniques in awake behaving animals allowing monitoring of defined, individual neuron activity while an animal performs a monitored behavioral task. Since the network is intact, this aim will decipher connectivity of adult-born cells, as they mature and incorporate, as compared to the pre-existing neurons of the same type. This neuron type, granule cell neurons, is relatively unique in the brain since it does not have an axon and instead makes reciprocal connections in its dendritic spines with the principal output neurons of the olfactory bulb. Granule cells cause inhibition on connected principal neurons as a method to de-correlate odors for enhancing odor discrimination6. Additionally, these cells receive a high amount of top-down input from the olfactory cortex and various modulatory regions, implying tight control of the circuit as a possible means to encode prediction or reward7. By labeling adult-born or pre-existing granule cell neurons with activating and silencing methods controlled with light pulses (optogenetics) or pharmacology (DREADD), the change in network output will be monitored. In addition, the individual top-down inputs to the olfactory bulb will have the same activity manipulation, and the output of the network will be monitored with their stimulation and inhibition during a learning task. The impact of various components of the circuit will be weighed to help establish an accurate computational model.

**Aim #2: Develop a computational model of the olfactory bulb circuit for predicting behavior in a reward-associated discrimination task.**

Using the data from aim #1, a computation model will be developed. The first goal is to implement an already established model, in collaboration with Hermann Riecke at Northwestern University, to determine the effects of the maturation state of an adult-born neuron and how it can control the output of the network. This will help to determine if there is a critical period in adult-born neurons that causes enhancement of their effect on the network. Next, the model will be modified to incorporate a reward-based odor discrimination task to explore the role of converging inputs onto the granule cell neurons and what neuronal weights are required to drive the circuit to discriminate between reward and no-reward associated odors. Ultimately the behavior-associated data from aim #1 will be the input for the model and simulations will be run to predict the behavior of the animal based on the network output.

References:

1. Nissant, A., Bardy, C., Katagiri, H., Murray, K. & Lledo, P.-M. Adult neurogenesis promotes synaptic plasticity in the olfactory bulb. *Nature Neuroscience* **12,** 728–730 (2009).

2. Alonso, M. *et al.* Activation of adult-born neurons facilitates learning and memory. *Nature Neuroscience* **15,** 897–904 (2012).

3. Valley, M. T., Henderson, L. G., Inverso, S. A. & Lledo, P.-M. Adult neurogenesis produces neurons with unique GABAergic synapses in the olfactory bulb. *J. Neurosci.* **33,** 14660–14665 (2013).

4. Sailor, K. *et al.* Persistent Structural Plasticity Optimizes Sensory Information Processing in the Olfactory Bulb. *Neuron* **91,** 384–396 (2016).

5. Sailor, K., Schinder, A. F. & Lledo, P.-M. Adult neurogenesis beyond the niche: its potential for driving brain plasticity. *Current Opinion in Neurobiology* **42,** 111–117 (2017).

6. Wiechert, M. T., Judkewitz, B., Riecke, H. & Friedrich, R. W. Mechanisms of pattern decorrelation by recurrent neuronal circuits. *Nature Neuroscience* **13,** 1003–1010 (2010).

7. Mouret, A., Murray, K. & Lledo, P.-M. Centrifugal drive onto local inhibitory interneurons of the olfactory bulb. *Annals of the New York Academy of Sciences* **1170,** 239–254 (2009).

Expected profile of the candidate (optional):

The PPU candidate would be responsible for performing experiments, data collection, data processing and computational modeling, therefore we seek one who is highly technically trained and independent. The candidate must have a strong background in programming in Matlab, Python or other program languages and have experience in hardware interfaces. Preferably the candidate will also have a strong background in neuroscience.

Contact:

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