**Specific Aims**

Animals rely on sensory cues in the environment for appropriate behavioral decision-making. However, information conveyed by sensory cues is context-dependent, e.g. the meaning of a given sensory cue can change depending on the location at which it is presented. Framed in the opposite way, a given location can become associated with a different behavioral strategy depending on the preceding sensory cue. Thus, the integration of sensory and contextual information is a fundamental computation critical for learned behaviors. Recent advances in neurophysiology have revealed core principles for information processing along sensory pathways. However, how sensory information is used in a context-specific manner to drive behavioral decisions remains poorly understood.

The olfactory system has emerged as an ideal model to understand neural circuit mechanisms for sensory-context integration, due to its importance for animal behavior and concise neural circuit architecture. Odors are detected by olfactory sensory neurons in the periphery and represented as spatiotemporal patterns of glomerular activity in the olfactory bulb. Olfactory bulb mitral and tufted cells then transmit odor information to multiple cortical structures, including the piriform and lateral entorhinal cortex. The hippocampus, on the other hand, is essential for experience-dependent encoding of contextual and spatial information – and has been hypothesized to play a role in binding stimulus and context information through auto-associative learning. Hippocampus and LEC exhibit strong, direct, reciprocal connections.

Our overall hypothesis is that the piriform cortex, LEC, and hippocampus form a core neural network essential for computing odor-place associations critical for olfactory navigation. Preliminary *in vivo* calcium imaging experiments in mice suggest that information about odor and place is differentially encoded along the piriform-LEC-hippocampal axis. Furthermore, we have developed a novel behavioral task in which mice must integrate odor and spatial information to identify the location of a reward. We here propose complementary computational and experimental approaches to determine the neural circuit mechanisms supporting context-dependent odor information processing critical for olfactory navigation.

**Aim 1: to quantify and compare olfactory and spatial information coding in piriform, LEC and hippocampus.** The joint distribution of olfactory and spatial representations across piriform, LEC and hippocampus are not well-characterized. Furthermore, it is unknown whether olfactory and spatial information is encoded in distinct, segregated subpopulations of neurons or integrated at the cellular level. We will perform two-color mini-endoscope imaging along with projection-specific fluorescent labeling in neurons in piriform, LEC and hippocampus, in freely moving mice sampling odors at different odor port locations. We predict that odor and place information is represented in opposing gradients along the piriform-LEC-hippocampal axis, and that conjunctive encoding of odor-place information is most robust in LEC neurons.

**Aim 2: to determine the behavioral strategies of mice solving an odor-place association task.** For an odor cue to predict reward location, olfactory and spatial information must be integrated. We will train mice to predict reward location based on the odor presented at a given odor port. We will then change the location of the odor port consistently or inconsistently with contextual (visual and tactile) cues, and we will determine the behavioral strategies employed by mice to identify the reward location. We predict that odors in the presence of robust contextual cues support allocentric behavioral strategies, while odors in the absence of contextual cues support egocentric behavioral strategies.

**Aim 3: to determine the computations that transform representations between piriform, LEC, and hippocampus.** To gain insight into how the brain might transform olfactory inputs and spatial representations into the sorts of conjunctive representations useful for learning adaptive behavioral policies, we will build a set of reinforcement learning models capable of solving the tasks proposed in Aims 1&2. This will include testing various forms of spatial representations observed experimentally (e.g., place cells, and mixed selectivity neurons with odor and place conjunctive representation) in the context of both allocentric and egocentric navigation tasks to see how well they can capture the observed behavioral variability and what types of representations within the models are most useful for generating adaptive behavior. After examining the contributions of different candidate representations to learned behavior, we will extend the model to learn representations from scratch using a feedforward neural network model. We will then compare the observed representations in the hidden layers of the neural network and the population activity in piriform, LEC, and hippocampus, with the goal of mapping the transformation from raw sensory and spatial information to conjunctive codes onto anatomical regions in the odor-place association circuit.

**Recent literature:**

[Spatial maps in piriform cortex during olfactory navigation.](https://pubmed.ncbi.nlm.nih.gov/34937941/)

Poo C, Agarwal G, Bonacchi N, Mainen ZF. Nature. 2022

[Olfactory landmarks and path integration converge to form a cognitive spatial map.](https://pubmed.ncbi.nlm.nih.gov/34710366/)

Fischler-Ruiz W, Clark DG, Joshi NR, Devi-Chou V, Kitch L, Schnitzer M, Abbott LF, Axel R. Neuron. 2021

[Rapid odor processing by layer 2 subcircuits in lateral entorhinal cortex.](https://pubmed.ncbi.nlm.nih.gov/35129439/)

Bitzenhofer SH, Westeinde EA, Zhang HB, Isaacson JS. Elife. 2022

[Dopamine facilitates associative memory encoding in the entorhinal cortex.](https://pubmed.ncbi.nlm.nih.gov/34552245/)

Lee JY, Jun H, Soma S, Nakazono T, Shiraiwa K, Dasgupta A, Nakagawa T, Xie JL, Chavez J, Romo R, Yungblut S, Hagihara M, Murata K, Igarashi KM. Nature. 2021

[Coordination of entorhinal-hippocampal ensemble activity during associative learning.](https://pubmed.ncbi.nlm.nih.gov/24739966/)

Igarashi KM, Lu L, Colgin LL, Moser MB, Moser EI. Nature. 2014

**Notes:**

**Causality**

To test the role of conjunctive odor-place encoding LEC neurons for behavior, we will optogenetically silence LEC.

Problem: silencing LEC interferes with odor discrimination, independent from place associations (Bitzenhofer et al., 2022, Lee et al., 2021).

Silence by projection pattern?

**Learning**

Something about the emergence of conjunctive coding with learning?

**Synchrony?**