Research

Neural circuitry and behavior

An animal's survival depends on its ability to react appropriately to environmental stimuli. The responses can be innate, and can also be modified by experience. The goal of the lab is to gain insight into how neural circuits in the vertebrate brain generate an optimal response. To achieve this, we use the zebrafish and a combination of behavioral assays, high-speed brain imaging and manipulation.

The Alarm Response

A starting point for experiments is the alarm response. In the 1930's Karl von Frisch noticed that injury to a European minnow caused a fright reaction in other members of the fish school. He demonstrated that the skin contained substances, termed Schreckstoff, which act via the olfactory system to trigger a state of fear. The fish change their swimming behavior dramatically - either darting or freezing - in response to this alarm pheromone.

Subsequent experiments by other scientists established that many freshwater fish species have this response. All the classical hallmarks of fear, including physiological changes such as increase in blood cortisol levels, can be triggered by Schreckstoff.

We have used classical biochemical separation to characterize the alarm substance. We find that the substance is a mixture, and one component is a glycan, chondroitin sulfate. Calcium imaging of the olfactory bulb has enabled identification of regions that are activated following detection of the alarm substance. Current experiments are focused on characterization of the receptor neurons, as well as the higher brain regions involved in the response.

The approach that we are taking to identify the circuits mediating innate fear is to image the entire brain, at single cell resolution, in fish that express genetically encoded calcium indicators. Mathematical analysis is then carried to determine how the networks function.

The habenula

One node in information flow from the forebrain to midbrain is the habenula. This evolutionarily conserved structure is involved in the regulation of dopamine, serotonin, norepinephrine and histamine, and receives extensive input from the basal ganglia. The medial habenula has an important role in reward and addiction, while the lateral habenula is involved in learning, especially with regards to aversive stimuli.

The habenula provides an attractive model to investigate how microcircuits regulate behavior. We are able to image activity in all cells in the habenula, as a larval zebrafish is exposed to aversive or attractive stimuli. Additional, neural activity can be manipulated either optically (for example using KillerRed transgenic lines) or by expression of tetanus toxin. Using a larval fear conditioning assay, we have found that the medial habenula modulates fear responses. Current experiments are directed at understanding the basis of this.

Click here to view the Video of **"The scent of danger: A 70-year-old puzzle solved "** .