Zebrafish: Development of automated behavioral test paradigms

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Due to the arsenal of genetic techniques developed and the amount of genetic information accumulated for zebrafish over the past three decades, this species has been becoming popular in several disciplines of biology including behavioral neuroscience. The prolific nature, small size, and ease of maintenance of zebrafish make this species a potentially excellent organism for high throughput mutation or drug screening. However, compared to classical rodent species, we know much less about the behavioral characteristics of zebrafish and thus we often do not have appropriate behavioral test paradigms. In the present talk, I will show a range of simple behavioral applications with which we study social behavior, learning and memory, and alcohol induced behavioral changes in zebrafish.

We have developed a custom software application with which we quantify the distances among members of the zebrafish shoal. We discovered that although distances among adult zebrafish remain fairly constant over extended periods of observation time, shoal cohesion fluctuates with a characteristic amplitude and fast (5-10 sec) frequency. We also discovered that shoaling tendencies change during development with a characteristic increase of shoal cohesion between 20-40 days after hatching. We have also conducted numerous learning paradigms to analyze mnemonic and cognitive characteristics of zebrafish. We confirm that similarly to other cyprinids, zebrafish are capable of acquiring simple associative learning tasks (association between two stimuli) and more complex spatial learning tasks (association between reinforcement and a set of diffuse external cues). In addition, we have tested different reinforcers and found that the sight of conspecifics may be an excellent reward for zebrafish and may motivate fish in classical as well as instrumental conditioning paradigms. Based on this, we developed the first pilot paradigm with which we can test learning performance in an automated manner. In this task zebrafish are shown animated images of a group of zebrafish on one side of the tank for a short period of time. The images disappear and remain hidden during the inter-stimulus interval after which they reappear but on the opposite side of the test tank. The experimental zebrafish are expected to learn this presentation pattern and swim to the opposite side after the disappearance of the stimulus fish. Given that both stimulus delivery (zebrafish images are presented by the computer) as well as response quantification (the location of the experimental zebrafish measured by tracking software) is computer automated, the paradigm can be run in a massively parallel manner and thus is appropriate for high throughput applications. Last, in a series of studies we have discovered significant strain differences among zebrafish populations in the way they respond to acute alcohol treatment and we are currently analyzing the effect of chronic alcohol treatment on these strains using the above tests and others. These studies also utilize computer animated images as well as computer aided automated quantification of behavior.

Given the increasingly successful application of zebrafish in behavioral neuroscience research in our and other laboratories and the feasibility of automated behavioral paradigms, we suggest that drug or mutation screening is within our reach with zebrafish and that this species will be an excellent model organism with which the pharmacology and genetics of complex brain function may be analyzed.