

Visualizing and interpreting drug-evoked anxiety behaviors in zebrafish

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Zebrafish (*Danio rerio*) represent a rapidly emerging animal model for high-throughput behavioral analysis. Common in biomedical research, the zebrafish is favored due to physiological similarities to mammals. The corticosteroid axis in zebrafish is highly sensitive to environmental stress, providing opportunity to measure the effects of various anxiolytic and anxiogenic agents on cortisol fluctuation. As in other species, exposure to a novel environment induces robust anxious-like responses. When placed in a novel tank, fish dive to the bottom, maintaining maximum depth until ready to explore. The Novel Tank exploits diving and other behaviors as measures of anxiety, effectively quantifying behavioral parameters such as latency to enter the upper half of a visibly sectioned tank, transitions to the upper half, erratic movements, bouts of locomotor freezing and freezing bout duration. To extend the reliability, endpoint coverage, and throughput of the Novel Tank model, we adopted a video tracking system for automated analysis. Zebrafish chronically exposed to ethanol spent more time in the upper area of the novel tank, in total and per entry. Acute (15 min) exposure to ethanol similarly produced an increase in total top entries and average entry duration, demonstrating an anxiolytic effect. Chronic (21 day) exposure to fluoxetine induced shorter latency to enter the top and significantly longer average entry duration. Treated zebrafish entered the top half more frequently and exhibited significantly lower levels of cortisol, suggesting a robust anxiolytic effect. Zebrafish acutely exposed (15 min) to morphine showed greater average time in the top half, as well as higher average entry duration and fewer erratic movements, indicating acute anxiolysis. Exposure to an extract of Kratom (containing the drug 7-OH-mitragynine) induced acute sedation, as indicated by reduced average velocity. Acute (5 min) exposure to caffeine induced an increase in anxious-like behaviors. Exposed cohorts made significantly fewer top entries and showed reduced average distance and velocity throughout testing. These results demonstrate the reliability of the video tracking system in producing behavioral data consistent with previously observed drug effects and physiological measures.

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