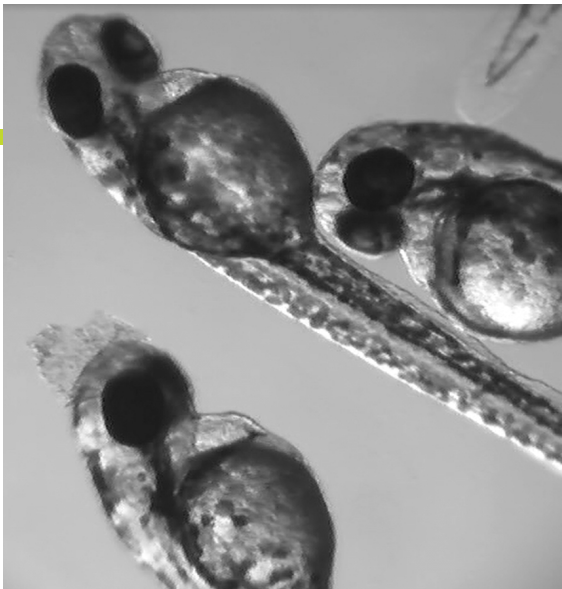




Zebrafish larvae activity

A study of locomotive behavior with DanioVision by Rob Willemsen and Herma van der Linde.

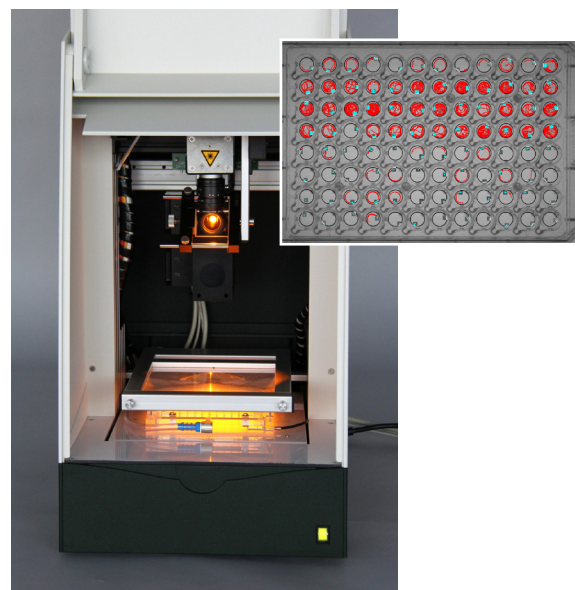
INTRODUCTION

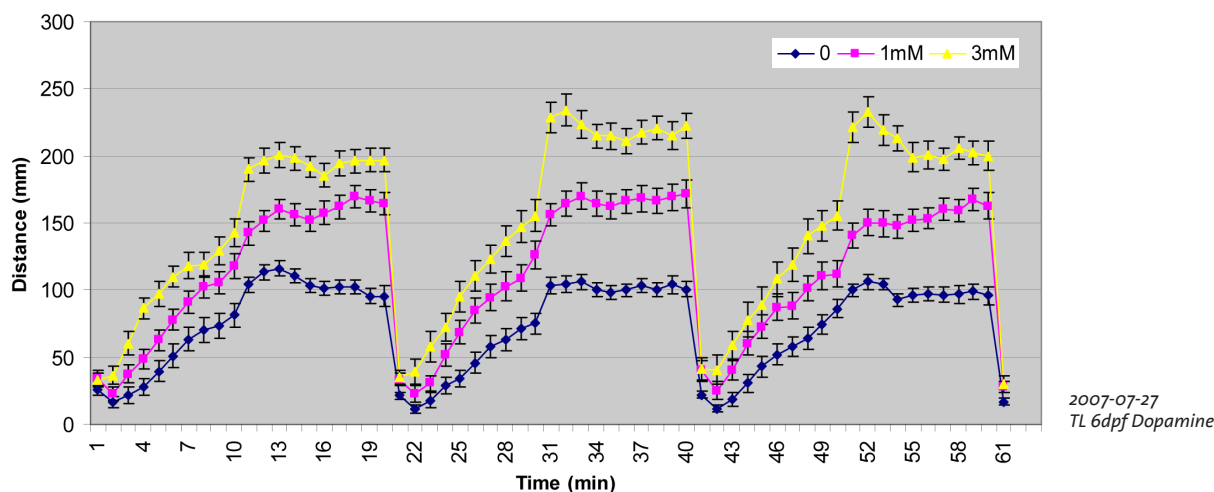
Parkinson's Disease (PD) is the second most common human neurodegenerative disorder after Alzheimer disease. PD patients present aberrant motor activity with resting tremor, muscular rigidity, bradykinesia and postural imbalance^[1,2]. The cause of these symptoms is loss of dopaminergic neurons in the substantia nigra, pars compacta. PD patients display a beneficial response to dopamine-replacement therapy. About 85-90% of the PD cases are sporadic with a complex aetiology. In 10-15% of the PD patients, a familial predisposition can be found. Our research focuses on the leucine-rich repeat kinase 2 (LRRK2) gene. Mutations in the LRRK2 gene are the most frequent known cause of PD^[3]. The major aim of our research is understanding the molecular mechanisms underlying PD by generating animal models of PD using zebrafish, *Danio rerio*. Further characterization of these genetically modified zebrafish includes swimming behavior as a readout for aberrant motor activity. Larval zebrafish represent an excellent model to study locomotive behavior. Zebrafish larvae show a robust locomotor activity, such as swimming, at day 6-7 post fertilization (dpf)^[4]. In addition, we are interested in the development of high-throughput screens of small molecules to investigate novel therapeutic approaches for PD using transgenic LRRK2 (normal and mutant) zebrafish. The zebrafish has become an important vertebrate model organism for pre-clinical drug discovery applications as well. Larvae behavioral assays, using 96-well plate, are now well established as a meaningful whole organism tool to model human disease. Importantly, larval zebrafish show the ability to absorb compounds through the water.

In the present study we used DanioVision™ an automated high-throughput tracking system of zebrafish larvae from Noldus Information Technology (Wageningen, the Netherlands), including control of light and dark conditions, to study the effect of several doses of dopamine on locomotor activity of wild type larvae of zebrafish.

MATERIAL & METHODS

Wild type zebrafish of the TL strain were maintained at 28°C under standard conditions in compliance with the local animal welfare legislation. Embryos were collected after natural spawning and raised in embryo medium containing methylene blue. Larval zebrafish were tested for behavioral consequences of dopamine treatment by measuring swimming behavior at 6 dpf.





Dopamine treatment was performed at two different concentrations; 1 mM and 3 mM. Larvae were arrayed 1 per well in a 96-well plate containing 150 microliter of embryo medium and were allowed to acclimate for 15 minutes before beginning the experiment. For each concentration of dopamine we analyzed 32 individual larvae.

Zebrafish larvae activity monitoring was carried out with DanioVision at 25 frames s⁻¹ (gray-scaling) at 28°C using Ethovision® XT. We set up a trial protocol with 10 minutes white light on and 10 minutes dark (3X) inside the DanioVision Observation Chamber. The acquired track files were analyzed for total distance moved per minute using Ethovision XT. Minimal distance moved filter was used to filter out system noise.

MAIN RESULTS

We found that zebrafish wild type larvae show elevated locomotor activity after exposure to dopamine compared to untreated wild type larvae. The effect was dosagedependent, that is, higher concentrations of dopamine result in higher locomotor activity. In addition, we observed gradually elevated locomotor activity during periods of bright illumination that was unrelated to the treatment. At the start of the light period the larvae showed for a very short moment almost total lack of locomotor activity.

DISCUSSION

DanioVision, the automated high-throughput tracking system of zebrafish larvae as described here, has proven to be very successful. This behavioral test assess zebrafish locomotor activity under different conditions, including exposure of larvae to different concentrations of dopamine combined with the use of light-dark conditions using an in vivo vertebrate organism. Ultimately, this set up will enable us to screen for compounds that will hopefully be used in PD therapeutics. Importantly, we will reduce costs and increase efficacy in drug discovery for new therapeutics for PD.

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