SUPPLEMENTARY MATERIAL AND APPENDICES A-B

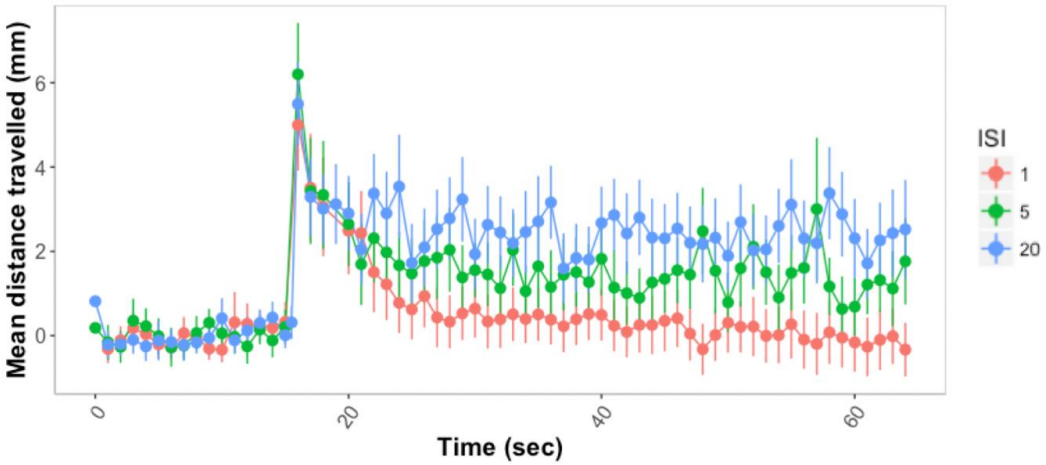

Figure S1. Response and habituation to startle stimuli test with different interstimulus intervals (ISI) in wild type zebrafish larvae. The first stimulus is given at second 15.

Figure S2. Tank used for novel tank diving assay.

Appendix A:

Effects of acute exposure to three different concentrations of JWH-018 on larval behavior.

Over the course of the experiment, time [$\chi2(1)=32.59$, $p<0.0001$] and JWH-018 dose [$\chi2(2)=57.92$, $p<0.0001$] were significantly associated with the distance travelled by larvae (Figure S3).

Treatment with 3 μM JWH-018 impaired larvae locomotion, which was especially noticeable during dark periods [$\chi2(2)=86.65$, $p<0.0001$].

During baseline, 3 μM JWH-018 treated larvae moved significantly less (M=0.26, SE=0.05) than controls (M=0.79, SE=0.05), suggesting that the effects of the drug were independent of exposure to stressful stimuli (such as light). There were no differences between DMSO and 0.03 μM JWH-018 treated larvae during dark1 and dark2.

During light, the distances travelled plunged, reducing the differences across treatment groups. Results for the linear mixed model reported no main effect of dose ($p\geq0.83$), but a significant dose by time interaction [$\chi2(2)=73.55$, $p<0.0001$]. The interaction effect was caused by the impairment in recovery due to JWH-018 exposure: Whereas control fish steadily increased the distances travelled during ligh, larvae treated with 3 μM JWH-018 were unable to show signs of recovery. Slopes for larvae treated with 0.03 μM JWH-018 were lower (Light1: M=0.02, SE=0.011, Light2: M=0.04, SE=0.014) than those for control larvae (Light1: M=0.053, SE=0.011, Light2: M=0.081, SE=0.014), suggesting impairment in recovery, however differences were not statistically significant ($p\geq0.05$).

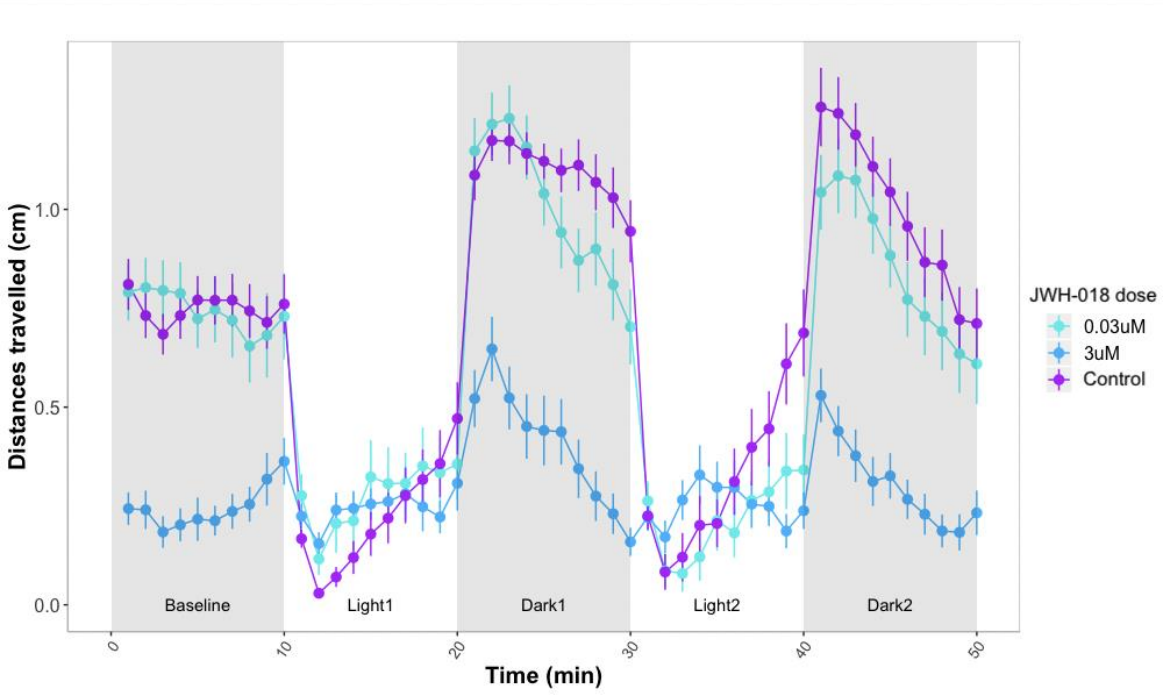

Figure S3. Forced Light-Dark test in 5dpf wildtype zebrafish larvae after acute exposure to JWH-018 (Drug exposure: 3-4 hours prior experiment). Sample sizes n=40 per experimental group. Error bars represent standard error of the mean.

Effects of acute exposure to three different concentrations of THC on larval behavior.

Analysis of the 50 minutes experiment showed that time [$\chi2(1)=99.91$, $p<0.0001$] and dose [$\chi2(2)=19.13$, $p<0.0001$] had a significant effect on distance travelled (Figure S4).

Five dpf larvae treated with 2 μM THC travelled shorter distances over the course of the experiment. This difference was more pronounced during dark periods, where fish treated with 2 μM THC were not able to increase their locomotor activity to the same magnitude as control or 0.05 μM THC treated larvae [$\chi2(2)=14.241$, $p=0.0008$].

During light, all the larvae reduced their locomotion to ~0.5 cm average distance travelled during one minute. Treatment with THC affected the 'recovery' of larvae during the light phase. For the first light period there were no significant differences in the slopes across THC dose groups. However, during the second light period, slopes for fish treated with 2 μM THC were significant lower (M=0.009, SE=0.007) than for fish treated with 0.05 μM THC (M=0.01, SE=0.007) or 0.1% MeOH Control (M=0.04, SE=0.007) [$F(2)=4.418$, $p=0.0138$].

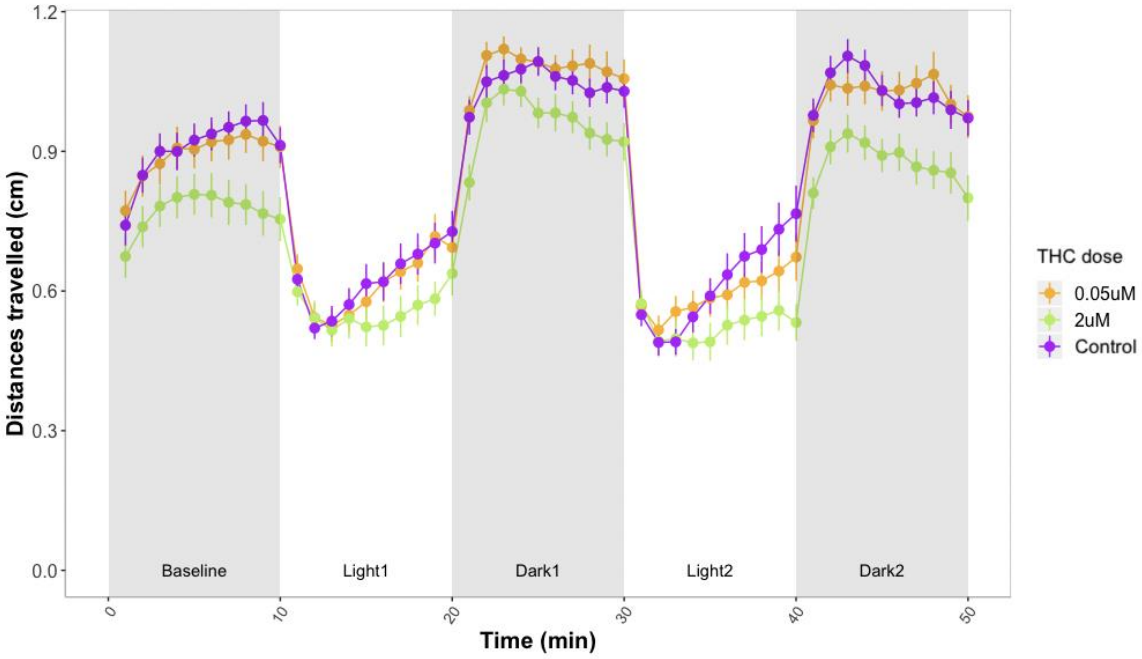

Figure S4. Forced Light-Dark test in 5 dpf wildtype zebrafish larvae after acute exposure to THC (Drug exposure: 3-4 hours prior experiment). Sample sizes n=48 per experimental group. Error bars represent standard error of the mean.

Developmental exposure to 0.15 μM nicotine from two to seven dpf led to an increase in nicotine preference when fish were adults (~four months old) and conditioned to 5 μM nicotine.

Drug-induced reinforcement of behavior, that reflects the hedonic value of drugs of abuse including nicotine, is highly conserved in both mammalian and non-mammalian species [51–54]. Conditioned place preference (CPP), where drug exposure is paired with specific environmental cues, is commonly used as a measure of drug-induced reinforcement and reward [55]. Previous studies have shown that zebrafish show a robust CPP to nicotine [32,56–58].

Here, we show developmental exposure to 0.15 μM nicotine leads to altered sensitivity of the drug-induced reinforcement and reward as measured in CPP (See [32] for methodology on the CPP assay). Fish that were not developmentally treated with nicotine showed a small increase in preference when conditioned with 5 μM nicotine. By contrast, fish exposed to 0.15 μM nicotine from two to seven days showed an increased change in preference [Interaction between CPP condition and developmental exposure: $F(1,73)=4.482$, $p=0.038$] (Figure S5).

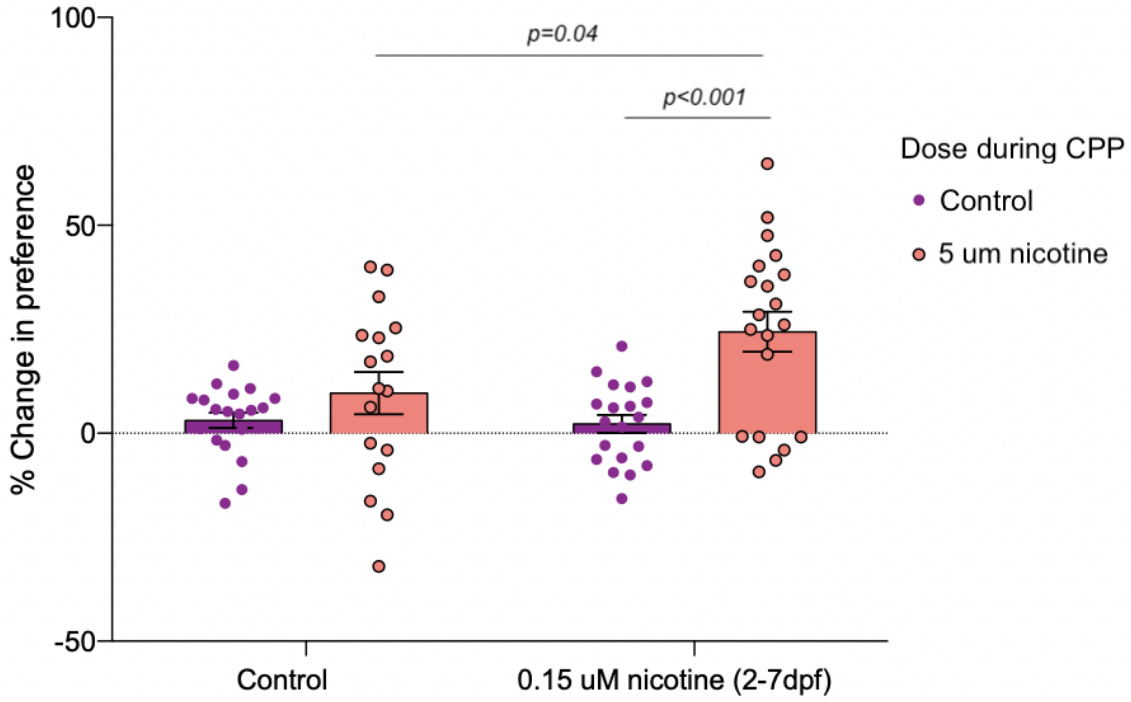

Figure S5. 5 μM nicotine-induced place preference in adult zebrafish is exacerbated by developmental exposure to 0.15 μM nicotine (from 2-7 dpf). n=17 to 20 fish per experimental group.

Appendix B: Behavioral assays data analysis

Data analysis for forced/light Dark test

Firstly, we performed an overall analysis to identify the experimental variables that were significant predictors of distance travelled during the whole duration of the experiment (50 minutes). We fitted the data to a linear mixed model with total distance travelled as response variable, experimental variables (e.g. genotype, dose, time) as fixed effects, and fish ID as random effects.

We then created three subsets of the experiment: baseline, dark, and light periods. We analyzed each subset separately by fitting the data to linear mixed models as previously described. To assess differences between the first and second light periods, and between the first and second dark periods, we added the period number as fixed effect in the linear mixed models.

Linear mixed models were calculated using the R package lme4 [59]. To identify significant fixed effects, we calculated Analysis of Deviance Tables (Type II Wald $\chi 2$ tests) for the models using the R package `car' [60]. Where significant differences were established, we carried out post-hoc Tukey tests with the R package `emmeans' [61] to further characterize the effects.

Larvae usually increased the distance travelled during the course of the light periods, and decreased it during the course of dark periods. To further explore these behaviors, we calculated linear models for each zebrafish at each light and dark period using distance travelled as response variable and time as independent variable. In these linear models, the

β coefficient for time represents the increase (or decrease) in distance travelled over time, and can be interpreted as the larva `recovery rate' from dark-light, or light-dark transitions. We constructed ANOVA models (R function `aov') to assess what variables were significant predictors of such slopes.

Data analysis for Habituation to startle response

We firstly investigated larvae spontaneous locomotion by testing whether distances travelled before the stimuli differed across experimental groups. We then investigated larvae startle responses by testing whether distances travelled during the stimuli differed across experimental groups. In both analyses, we fitted the data to linear mixed models using the R package lme4 [59], with total distance travelled as response variable, experimental variables (e.g. genotype, dose, time) as fixed effects, and fish ID as random effects.

Data analysis for novel tank diving

To analyze genotype and/or treatment differences in the *time that zebrafish spent on the bottom* of the tank, we performed beta regressions using the R package `betareg' [62]. We used beta regression because proportion time spent on the bottom of the tank was used as response variable. Proportion data is bounded by the interval [0, 1] and often exhibits heterogeneity in variance, which violates statistical assumptions used by linear models [62].

To analyze genotype or treatment differences in the *total distance* that zebrafish travelled in the tank, we fitted the data to a linear mixed model with the total distance travelled during one minute as response variable, time, genotype and/or treatment as fixed effects, and fish ID as random effects.

To analyze genotype or treatment differences in the *number of transitions* that zebrafish made between the top and the bottom of the tank, we fitted the data to a generalized linear mixed model with Poisson distribution. The Poisson distributions is commonly used when the response variable is count data [63]. We used the number of transitions to the top-bottom of the tank response variable, time, genotype or/and treatment as fixed effects, and fish ID as random effects.

Experiments were replicated on different days, and data was jointly analyzed afterwards. Mixed models were calculated using the R package lme4 [59]. To identify experimental variables with significant effects, we calculated Analysis of Deviance Tables (Type II Wald $\chi 2$ tests) for the models using the R package `car' [60]. Where significant differences were established, we carried out post-hoc Tukey tests with the R package `emmeans' [61] to further characterize the effects.

Appendix C: Adult behavior after developmental exposure to nicotine and THC in wild zebrafish

Developmental exposure to 2μM THC and 0.15 μM did not affect the time spent on the bottom of the tank, the distance travelled nor the number of transitions between the top and bottom area of the tank for wild type zebrafish (Figure S6) ($p>0.05$).

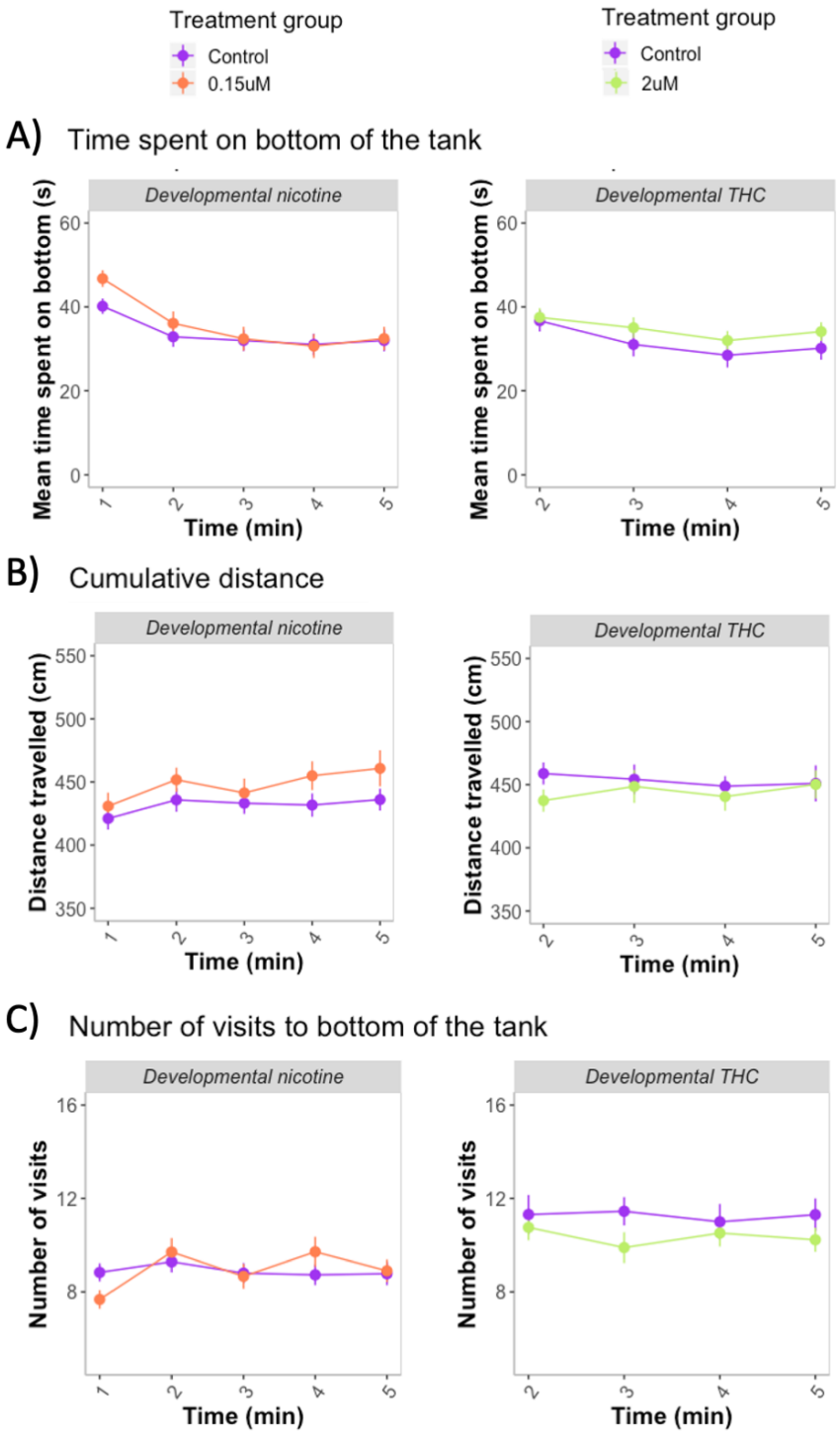

Figure S6. Novel tank diving response in adult wild type zebrafish after developmental exposure to 2μM THC and 0.15 μM nicotine. Sample sizes for each group: control THC: n=30, developmentally exposed to THC: n=40, control nicotine: n=79, developmentally exposed to nicotine: n=53. Error bars represent ±SEM.

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