SUPPLEMENTARY INFORMATION

Experimental protocol

Experiment 1: 5-HT turnover was assessed in the prefrontal cortex, hippocampus and brainstem of naïve Htr3a KO and WT mice using HPLC.

Experiment 2: 5-HT_{1A} receptors coupling capacity to G-protein was assessed in the dorsal raphe nucleus (DRN) of naïve Htr3a KO and WT mice by measuring [^{35}S]GTP-γ-S binding after stimulation with a 5-HT_{1A}R agonist.

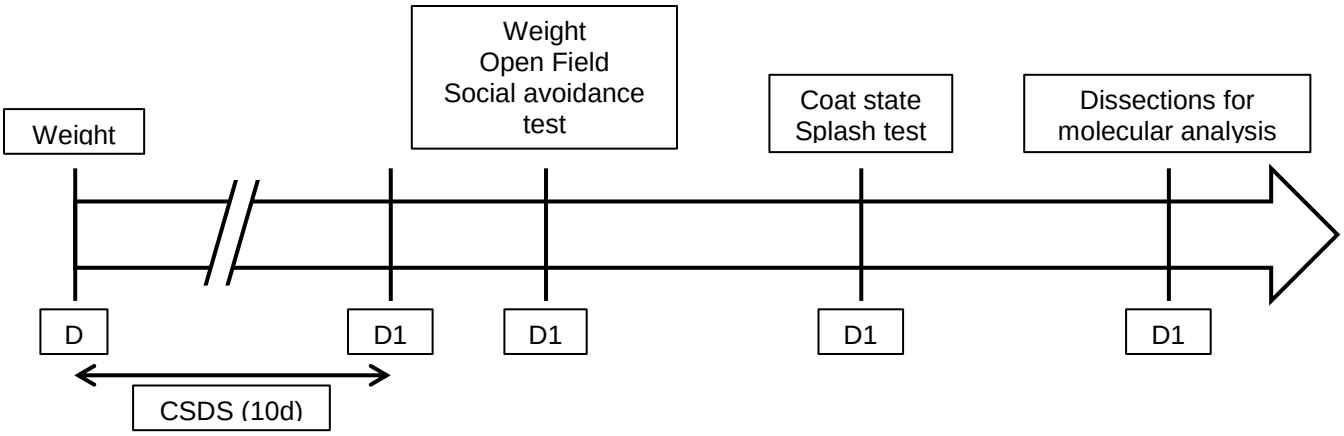
Experiment 3: Expression of 5-HT_{1A}R mRNA (*Htr1A*) was quantified by qRT-PCR in the prefrontal cortex, hippocampus and raphe of naïve Htr3a KO and WT mice.

Experiment 4: Behaviour of naïve Htr3a KO and WT mice was assessed in the elevated plus maze.

Experiment 5: Behaviour of naïve Htr3a KO and WT mice was assessed in the social interaction test.

Experiment 6: Behaviour of naïve, saline-, citalopram- (2.5 or 5.0 mg/kg) and fluoxetine-acutely treated Htr3a KO and WT mice was assessed in the forced swim test.

Experiment 7: Naïve Htr3a KO and WT mice were subjected to the CSDS paradigm for 10 days, and their behaviours related to anxiety and depression were assessed the following days:



Experiment 8: Using *in vitro* electrophysiological recordings, DRN 5-HT neurons basal firing rate and its response to stimulation with ipsapirone 50 nM were assessed in naïve Htr3a KO and WT mice, and in animals of both genotype treated with saline or citalopram (5 or 20 mg/kg/day) for 14 days.

All experiments were performed using separated (n=6-14 per group) male Htr3a KO and WT mice.

SUPPLEMENTARY TABLE

	Time in interaction zone with target present (s)	
	Control	*Stressed*
Htr3a WT mice	7.33 ± 1.80	5.92 ± 1.73
Htr3a KO mice	15.44 ± 4.23*	10.02 ± 2.58*

Table S1: Social avoidance test

In the social avoidance test, there were no differences in terms of time interacting with the target between stressed and control animals. However, non-stressed and stressed Htr3a KO mice spent significantly more time than paired WT mice in the interaction zone when the target was present. Each value was the mean ± S.E.M. of n = n = 11 Control WT, 12 Stressed WT, 11 Control KO and 15 Stressed KO mice. * $p < 0.05$, effect of genotype, 2-way ANOVA.

SUPPLEMENTARY FIGURES

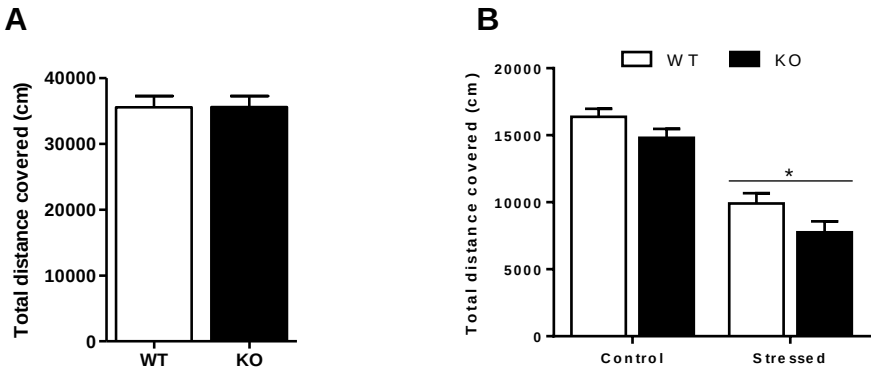


Figure S1

A: Locomotor activity in the elevated plus maze. Animals from both genotypes displayed a similar locomotion in the EPM. Each bar was the mean ± S.E.M. of n = 8 WT and 6 KO mice.

B. Locomotion of Htr3a KO and WT mice submitted to CSDS in the open field. Both stressed mutant and wild-type animals displayed a similar hypolocomotion in the open field. Each bar was the mean ± S.E.M. of n = 11 Control WT, 12 Stressed WT, 11 Control KO and 15 Stressed KO mice. *p < 0.05, effect of stress, 2-way ANOVA.

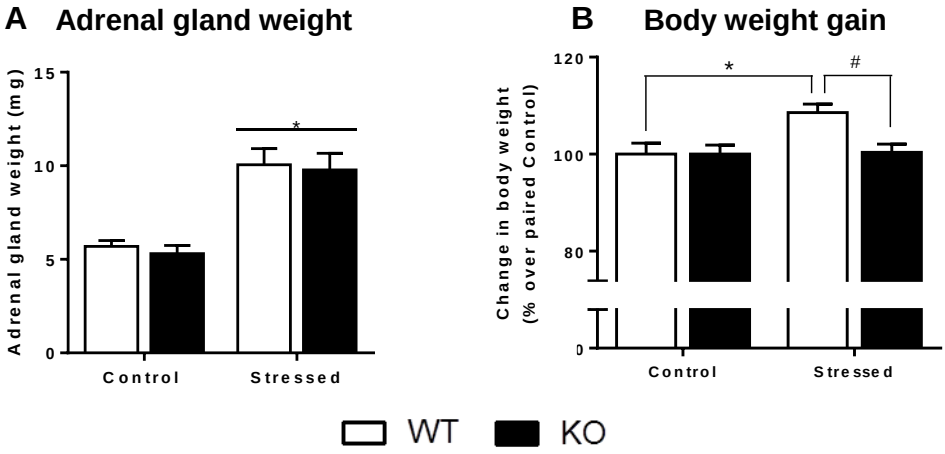


Figure S2. Effect of CSDS on body and adrenal weight

(A) Effect of stress on adrenal gland weight. Stress similarly increased adrenal gland weight in both genotypes. There was no effect of genotype nor an interaction between the stress and genotype factors. Each bar was the mean ± S.E.M. of n = 11 Control WT, 12 Stressed WT, 11 Control KO and 15 Stressed KO mice. * p<0.05, effect of stress (two-way ANOVA).

(B) Body weight gain was higher in stressed WT compared to non-stressed paired mice. Stress had no effect in Htr3a KO mice. Each bar was the mean ± S.E.M. of n = 11 Control WT, 12 Stressed WT, 11 Control KO and 15 Stressed KO mice. * p < 0.05, "Control WT" vs "Stressed WT", # p < 0.05, "Stressed WT" vs "Stressed KO", 2-way ANOVA followed by Bonferroni post-hoc test.