Biochemical Pharmacology 245 (2026) 117632

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Time-specific perturbation of the serotonergic system differentially modulates the transcriptional landscape of hippocampal subregions in female rats

Maria Teresa Gallo [a], Alessia Golinelli [a], Camilla Rizzi [a], Fabio Fumagalli [a], Judith R. Homberg [b], Paola Brivio [a,*], Francesca Calabrese [a]

[a] Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", Università degli Studi di Milano, Milan, Italy
[b] Department of Medical Neuroscience, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Centre, Nijmegen, the Netherlands

ARTICLE INFO

Keywords:
Neuroplasticity
Microglia
Fluoxetine
Dorsal hippocampus
Ventral hippocampus
Development

ABSTRACT

Serotonin (5-HT) is implicated in the pathophysiology of psychiatric disorders, and genetic alterations in the serotonin transporter (5-HTT) are identified as risk factors for increased vulnerability. Beyond its role as a neurotransmitter in the adult brain, 5-HT exerts fundamental functions during early development guiding neuronal maturation and network assembly. Perturbations of serotonergic signaling in these sensitive windows have been associated with long-term changes in brain circuitry and increased susceptibility to psychiatric conditions.

The present study aimed to further investigate how the timing of 5-HTT manipulation during perinatal development influences the molecular response, by comparing the effects of transient pharmacological inhibition at specific stages to those seen in constitutive 5-HTT knockout rats.

We analyzed transcriptional profiles in the dorsal (dHip) and ventral hippocampus (vHip) of adult females, focusing on pathways relevant to neuroplasticity, microglial activation, microglia-neuron interaction, peri-neuronal nets, GABAergic signaling, antioxidant and mitochondrial function, and autophagy.

Our findings show that both constitutive deletion and pharmacological inhibition of 5-HTT induce long-lasting molecular alterations in the hippocampus, with partly overlapping but also distinct signatures depending on the timing of exposure and the hippocampal subregion.

In conclusion, constitutive and time-specific early-life perturbations of serotonergic signaling converge on persistent deficits in hippocampal plasticity, but differ in region- and timing-dependent molecular outcomes. These findings provide a framework to further dissect the mechanisms through which early life serotonergic perturbations shape long-term brain function, offering insights that could guide future research toward more targeted therapeutic approaches.

1. Introduction

Serotonin (5-HT) plays a pleiotropic role as a neuromodulatory transmitter, growth factor and neurohormone [1]. Within the central nervous system, it is implicated in a wide range of cognitive, emotional, and vegetative processes, regulating key functions such as learning and memory, social interactions, stress reactivity, mood, and circadian rhythms [1,2]. Beyond its involvement in adult brain physiology, 5-HT plays a pivotal role during neurodevelopment, where it contributes to cell division, neuronal migration, cell differentiation, synaptogenesis [3,4] and the assembly of neural networks [5]. Perturbations of 5-HT availability during these critical developmental windows can interfere with circuit formation, producing long-lasting consequences on brain function. Thus, 5-HT assumes a dual role across the lifespan: a developmental organizer in early life and a functional modulator in the mature brain. Given this broad temporal range of influence on brain function, the mechanisms regulating serotonergic signaling are of critical importance. Among these, the serotonin transporter (5-HTT,

* Corresponding author at: Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", Università degli Studi di Milano, Via Balzaretti 9, 20133 Milan, Italy.
E-mail address: paola.brivio@unimi.it (P. Brivio).

https://doi.org/10.1016/j.bcp.2025.117632
Received 23 September 2025; Received in revised form 2 December 2025; Accepted 11 December 2025
Available online 12 December 2025

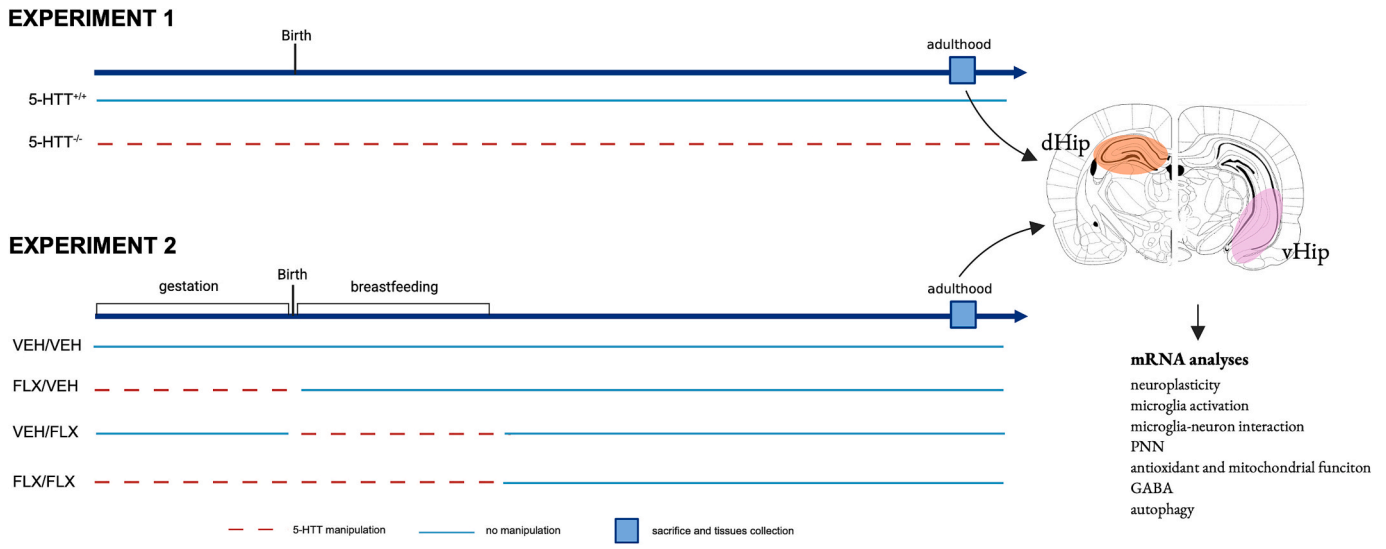

Fig. 1. Schematic representation of the experimental design. Experiment 1 included two groups based on serotonin transporter (5-HTT) genotype: wild-type (5-HTT$^{+/+}$) and knock-out (5-HTT$^{-/-}$). Experiment 2 included four groups: VEH/VEH, in which animals were exposed to vehicle (VEH) during both gestation and breastfeeding; FLX/VEH, exposed to fluoxetine (FLX) during gestation and VEH during breastfeeding; VEH/FLX, exposed to VEH during gestation and FLX during breastfeeding; and FLX/FLX, exposed to FLX during both gestation and breastfeeding. mRNA analyses were conducted in the dorsal and ventral hippocampus (dHip and vHip respectively) of adult female rats to assess the expression level of genes grouped according to their functional roles, including neuroplasticity, microglia activation, microglia–neuron interaction, perineuronal nets (PNN), antioxidant and mitochondrial function, GABAergic signaling, and autophagy.

encoded by the SLC6A4 gene) plays a central role by mediating synaptic reuptake of 5-HT and representing the primary pharmacological target of selective serotonin reuptake inhibitors (SSRIs). Genetic variation at the 5-HTT promoter, particularly the short allele of 5-HTTLPR, has been associated with heightened stress sensitivity and increased vulnerability to psychiatric disorders in absence of positive support [6,7].

Animal models have been instrumental in elucidating the neurobiological consequences of altered serotonergic signaling. Among these, serotonin transporter knockout (5-HTT$^{-/-}$) rodents display anxiety- and depression-like phenotypes [8]. We and others have demonstrated that 5-HTT deletion impairs BDNF-related neuroplasticity and reduces markers of synaptic integrity, including dendritic spines and GABAergic components [9–18].

Since these changes appear during early developmental stages and remain stable thereafter, they strengthen the view that the timing of serotonergic modulation is critical for establishing long-lasting effects on brain circuits and function. In line, transient inhibition of 5-HTT throughout early development by perinatal exposure to the SSRI antidepressant drug fluoxetine (FLX) produces abnormal emotional behaviors in adult mice, an effect that mimics the behavioral phenotype of rodents with a constitutive genetic deletion of 5-HTT [19].

Extending these findings, our recent work showed that perinatal FLX induces age- and sex-dependent behavioral outcomes, with prenatal exposure driving anhedonic-like behavior in adult male rats, whereas postnatal exposure causes cognitive deficits in adult females [20]. These behavioral phenotypes were paralleled by molecular biomarkers detectable in both peripheral blood and brain [20]. A subsequent follow-up study showed that prenatal FLX priming induces early dysfunction of the hypothalamic–pituitary–adrenal axis, already evident in adolescence, thus preceding the emergence of maladaptive behavioral phenotypes [21]. Additionally, we recently observed that perinatal FLX exposure modulates the dynamics of sensitive periods by altering PNNs, parvalbumin-positive interneurons, and genes involved in their opening and closure. These effects were evident in the prefrontal cortex and dorsal hippocampus (dHip) and varied according to exposure timing, brain region, and sex [22]. Specifically, prenatal-FLX anticipated the sensitive period in the dHip of male rats, whereas postnatal exposure postponed it in females. Notably, these developmental effects seem to have an opposite effect in the mature brain, where FLX treatment can transiently "reopen" plasticity windows by enhancing BDNF signaling and reducing PNNs density [23,24].

Here, we hypothesize that brain development is differently affected by the timing and duration of 5-HT system disruption. To address this aim, we compared the effects of a constitutive 5-HTT deletion with those induced by FLX exposure during distinct perinatal periods.

In order to provide a high-resolution characterization of female region- and time-specific molecular signatures, and because their persistent underrepresentation in preclinical research, we focused exclusively on female rats [25]. Acknowledging this bias, as even in our own earlier work with SERT animals the focus had historically been on males [9,11,14,26], we have recently begun including females in our studies [20,22]. As expected, we found that males and females respond to the same early-life manipulations with strikingly different behavioral and molecular profiles, sometimes emerging at different developmental time windows. These observations strongly indicate that pooling sexes, or extrapolating findings across them, can mask meaningful sex-specific patterns.

Moreover, the dorsal and ventral subregions of the hippocampus were examined separately, given their distinct roles in mediating cognitive and emotional functions: dHip in spatial and episodic memory and ventral hippocampus (vHip) in emotional behavior. Our analyses targeted gene clusters commonly implicated in psychiatric conditions, including those related to neuroplasticity [18,27], microglial activity [28], perineuronal nets [29], antioxidant and mitochondrial function [30,31], GABAergic signaling [26], and autophagic processes [32].

The findings herein reported indicate that constitutive deletion and perinatal pharmacological inhibition of 5-HTT induce specific transcriptional changes in the dorsal and ventral hippocampus.

2. Material and methods

2.1. Animals and experimental design

As represented in Fig. 1, we conducted two experiments using distinct rat models to compare the effects of genetic deletion of the 5-HTT, with those resulting from pharmacological inhibition of the 5-HTT during specific early-life periods (gestation, breastfeeding, or both) via administration of FLX.

For the Experiment 1, 5-HTT knockout rats (5-HTT$^{-/-}$, Slc6a41Hubr) were developed on a Wistar background by N-ethyl-N-nitrosurea (ENU)-induced mutagenesis [33] and originated from crossing heterozygous 5-HTT$^{+/-}$ rats that were outcrossed for more than 12 generations with wild-type (5-HTT$^{+/+}$) Wistar rats obtained from Harlan Laboratories (Horst, The Netherlands). Ear punches were taken at PND21 for genotyping, which was done by Kbiosciences (Hoddesdon, United Kingdom). Fourteen adult 5-HTT$^{-/-}$ (n = 7) and 5-HTT$^{+/+}$ (n = 7) female rats were used for this study. The animals were maintained under standardized conditions with a 12-h light–dark cycle, room temperature of 22 °C, and 80 % humidity, with free access to food and water.

The animals were sacrificed in adulthood for molecular analyses. All experimental procedures were approved by the Central Committee on Animal Experiments (Centrale Commissie Dierproeven, CCD, The Hague, The Netherlands) and conducted in compliance with European guidelines (Directive 2010/63/EU). All efforts were made to minimize animal suffering and to reduce the number of animals used.

For the Experiment 2, adult female and male Wistar rats (Charles River, Germany) were housed in the animal facility for one month before the experimental procedures began. Each female was paired with a male, and timed pregnancies were recorded upon detection of a vaginal plug designated as gestational day (GD) 0. Following plug detection, male rats were returned to their original cages, while females were individually housed and provided with nesting material. At the weaning (postnatal day (PND) 21) pups were separated by sex and placed in groups of 2–4 animals per cage. For this study, analyses were conducted in twenty-two adult female offspring.

Each dam was assigned to an experimental group just after the plug detection: the FLX/VEH group was exposed to FLX during gestation (from GD0 to PND0) and vehicle (VEH, water) during breastfeeding (PND0 to PND21); the VEH/FLX group was administered with VEH during gestation and FLX during breastfeeding; the FLX/FLX group received FLX during both the gestational and breastfeeding periods, and the VEH/VEH group received vehicle throughout both periods.

FLX was administered via drinking water at a dosage of 15 mg/kg/day, and the drug solution was prepared in excess based on the expected daily water intake of the animals. Indeed, to ensure accurate dosing, we tracked water intake in single-housed females before starting FLX exposure to determine the appropriate dilution. Throughout the drug exposure periods, the solution was freshly prepared each day to adjust the drug concentration adjusting for changes in body weight and water consumption occurring during pregnancy and lactation. At the end of the pharmacological manipulation, all animals were left undisturbed in their home cages. Female offspring were sacrificed in adulthood for molecular analyses (VEH/VEH = 6, FLX/VEH = 4, VEH/FLX = 8, and FLX/FLX = 4). Animals had *ad libitum* access to food and water, and the environment was maintained a consistent 12-hour light/dark cycle, with a temperature of 22 ± 2°C and humidity at 50 ± 5 %. All procedures in the Experiment 2 were conducted in accordance with authorization n° 472/2021-PR approved by the Italian Health Ministry in line with the Italian legislation in animal experimentation (DL 26/2014) and conformed to the European Communities Council Directive of September 2010 (2010/63/EU). All efforts were made to minimize animal suffering and to reduce the number of animals used.

3. Tissues collection

All rats were decapitated at adulthood..

In Experiments 1 and 2, the dHip and vHip were dissected following the stereotaxic coordinates of the Paxinos and Watson atlas (Paxinos and Watson, 2007). Specifically, the dHip corresponds to plates 43–72 and the vHip to plates 73–84.

Table 1
Clustering of genes within the selected gene clusters.

Gene cluster	Gene	References
Neuroplasticity	Total *Bdnf*	[36–39]
	Bdnf isoform IV	[40,41]
	Bdnf isoform VI	[42,43]
	Mmp9	[44–46]
	TrkB	[47–49]
	Dlg4	[50,51]
	Nptx2	[52,53]
Microglia activation	*Iba1*	[54,55]
	CD68	[54,56]
	CD86	[57,58]
Microglia-neuron interaction	*Cx3cr1*	[59,60]
	Cx3cl1	[59,60]
Perineuronal nets	*Ncan*	[61–63]
	Bcan	[63,64]
	Hapln1	[65,66]
	Sem3a	[67,68]
Antioxidant and mitochondrial function	*Cox3*	[69]
	Gpx1	[70]
	Pgc1α	[71,72]
GABAergic signaling	*Gad65*	[73–75]
	Gad67	[75,76]
	Pvalb	[77,78]
Autophagy	*Ulk1*	[79,80]
	Map1lc3	[81,82]
	Becn1	[83,84]
	Lamp1	[85,86]
	Ctsb	[87]

4. RNA preparation and gene expression analysis by quantitative real-time PCR

Total RNA was isolated from the frozen brain tissues by single-step guanidinium isothiocyanate/phenol extraction using PureZol RNA isolation reagent (Bio-Rad Laboratories, Segrate, Italy) and quantified by spectrophotometric analysis as previously described [34]. Samples were treated with DNase (ThermoFisher Scientific) to avoid DNA contamination.

Real-time polymerase chain reaction (q-PCR) was performed to measure total *Bdnf, Bdnf* isoform IV, *Bdnf* isoform VI, *Mmp9, TrkB, Dlg4, Nptx2, Iba1, CD68, CD86, Cx3cr1, Cx3cl1, Ncan, Bcan, Hapln1, Sem3a, Cox3, Gpx1, Pgc1α, Gad65, Gad67, Pvalb, Ulk1,* Map*1lc3, Becn1, Lamp1* and *Ctsb* mRNA levels belonging to seven clusters as summarized in Table 1. Primer sequences used were purchased from Eurofins MWG-Operon (Ebersberg, Germany) and Life Technologies (Italy) (Tables 2 and 3). mRNA was analyzed by Taqman qRT-PCR instrument CFX Opus 384 real-time PCR system, Bio-Rad Laboratories S.r.L., Segrate MI, Italy) using the iScriptTM one-step RT-PCR kit for probes (Bio-Rad Laboratories, Segrate, Italy) (see [35] for details). Samples were run in 384 well formats in triplicate as multiplexed reactions with normalizing internal control *36b4*.

5. Z-score

Z score for each gene was calculated in the single animals according to the formula: Z-score $=\frac{X-\mu}{\sigma}$. X represents the individual gene expression data of each animal, while μ and σ represent the mean and the standard deviation, respectively, of the corresponding control group (5-HTT$^{+/+}$or VEH/VEH).

To obtain a composite z-score for each functional gene cluster, the z-scores of all genes within the same cluster were averaged for each animal.

6. Statistical analysis

GraphPad Prism software version 10.4 (GraphPad Software Inc., CA, USA) was employed to analyze all the data.

Table 2
Sequences of forward and reverse primers and probes used in real-time PCR analyses and purchased form Eurofins MWG-Operon.

Gene	Forward Primer	Reverse Primer	Probe
Total *Bdnf*	AAGTCTGCATTACATTCCTCGA	GTTTTCTGAAAGAGGGACAGTTTAT	TGTGGTTTGTTGCCGTTGCCAAG
Gad65	TGAGGGAAATCATTGGCTGG	TCCCCTTTTCCTTGACTTCTG	TGCCATCTCCAACATGTACGCCA
Gad67	ATACTTGGTGTGGCGTAGC	AGGAAAGCAGGTTCTTGGAG	AAAACTGGGCCTGAAGATCTGTGGT
Pvalb	CTGGACAAAGACAAAAGTGGC	GACAAGTCTCTGGCATCTGAG	CCTTCAGAATGGACCCCAGCTCA
36b4	TCAGTGCCTCACTCCATCAT	AGGAAGGCCTTGACCTTTTC	TGGATACAAAAGGGTCCTGG

Table 3
Probes purchased form Life Technologies which did not disclose the sequence.

Gene	Accession number	Assay ID
Bdnf isoform IV	EF125679	Rn01484927_m1
Bdnf isoform VI	EF125680	Rn01484928_m1
Mmp9	U24441.1	Rn00579162_m1
TrkB	AY265419.1	Rn01441749_m1
Dlg4	M96853.1	Rn00571479_m1
Nptx2	CB578587.1	Rn01756377_m1
Iba1	AF299328.1	Rn03993468_g1
Cd68	BC098931.1	Rn01495634_g1
Cd86	D50558.1	Rn00571654_m1
Cx3cr1	U04808.1	Rn02134446_s1
Cx3cl1	AF030358.2	Rn00593186_m1
Ncan	AF060879.1	Rn00581331_m1
Bcan	AI535159.1	Rn00563814_m1
Hapln1	BC128740.1	Rn00569884_m1
Sem3a	HAAF01008759.1	Rn00436469_m1
Cox3	NC_001665.COX3.0	Rn03296820_s1
Gpx1	BC058438.1	Rn00577994_g1
Pgc1α	AB025784.1	Rn00580241_m1
Ulk1	XM_006249565.2	Rn02108711_s1
Map1lc3	BC083556.1	Rn02132764_s1
Becn1	BC074011.1	Rn00586976_m1
Lamp1	FQ221686.1	Rn00689219_m1
Ctsb	BC072490.1	Rn00575030_m1

Gene expression and z-score results were analyzed using the unpaired *t*-test comparing each experimental group to its control group (5-HTT$^{+/+}$ or VEH/VEH). The normality of residuals was assessed using the Shapiro-Wilk test, and no discernible variation in homogeneity was discovered.

Statistical significance for all the tests was assumed for $p < 0.05$.

7. Results

7.1. Transcriptional impact of constitutive deletion and perinatal pharmacological manipulation of 5-HTT in the dorsal hippocampus

Based on the molecular pathways listed in Table 1, which are commonly dysregulated in psychiatric disorders, we calculated cumulative z-scores from gene cluster expression to quantify the overall transcriptional shifts within each experimental group. As shown in the donut charts in Fig. 2 A-D, the different types of 5-HTT manipulations affect distinct domains. Notably, 5-HTT$^{-/-}$ rats exhibited marked alterations in neuroplasticity, microglial activation markers, and PNN components compared to 5-HTT$^{+/+}$ counterparts (Fig. 2A). Interestingly, prenatal FLX exposure in the FLX/VEH group led to changes in neuroplasticity z-scores comparable in magnitude to those observed in 5-HTT$^{-/-}$ rats (Fig. 2B). Moreover, microglial activation was similarly altered in 5-HTT$^{-/-}$ and in FLX/FLX rats relative to their respective controls (Fig. 2D). Postnatal FLX exposure predominantly impacted antioxidant and mitochondrial function (Fig. 2C) and altered microglia–neuron interaction, a disruption also evident in the FLX/FLX group compared to VEH/VEH controls (Fig. 2D). Additionally, the FLX/FLX group showed significant changes in the PNNs and GABAergic signaling clusters (Fig. 2D).

A more detailed breakdown of *z*-score distributions across functional gene clusters is shown in Fig. 2 panels E–K. These plots represent the deviation from control expression levels for each experimental group, enabling a direct comparison of the extent to which the different 5-HTT manipulations impact specific molecular pathways.

Unpaired *t*-test revealed a statistically significant reduction in neuroplasticity-related *z*-scores in 5-HTT$^{-/-}$ rats compared to their wild-type counterparts ($p < 0.05$ vs 5-HTT$^{+/+}$), and a similar decrease observed in the FLX/VEH group ($p < 0.01$ vs VEH/VEH; Fig. 2E). Furthermore, 5-HTT$^{-/-}$ rats displayed a marked downregulation in genes related to microglial activation ($p < 0.01$ vs 5-HTT$^{+/+}$), a pattern that was mirrored in the FLX/FLX group ($p < 0.001$ vs VEH/VEH; Fig. 2F). Furthermore, microglia–neuron interaction was significantly disrupted in both VEH/FLX ($p < 0.001$ vs VEH/VEH) and FLX/FLX groups ($p < 0.001$ vs VEH/VEH, Fig. 2G).

Interestingly, some effects depend on the timing of the 5-HTT manipulation. Indeed, PNN ($p < 0.05$ vs VEH/VEH; Fig. 2H) and GABAergic signaling ($p < 0.05$ vs VEH/VEH; Fig. 2J) were significantly reduced only in the FLX/FLX group, whereas mitochondrial funtion-related z-score was selectively increased in the VEH/FLX group ($p < 0.05$ vs VEH/VEH; Fig. 2I).

By considering the specific genes measured belonging to each of the seven functional clusters (Fig. 2L), we were able to dissect the previously described effects in more detail. Indeed, in the 5-HTT$^{-/-}$ group, impaired neuroplasticity was primarily associated with a marked downregulation of the expression of total *Bdnf* expression (–23 % $p < 0.05$ vs 5-HTT$^{+/+}$), *Bdnf* isoform VI (−24 % $p < 0.05$ vs 5-HTT$^{+/+}$), the high affinity Bdnf receptor *TrkB* (−13 % $p < 0.05$ vs 5-HTT$^{+/+}$), and *Dlg4* (−11 % $p < 0.05$ vs 5-HTT$^{+/+}$). Similarly, prenatal FLX exposure (FLX/VEH) resulted in reduced expression of total *Bdnf* (−21 % $p < 0.01$ vs VEH/VEH), *Bdnf* isoform IV (−31 % $p < 0.01$ vs VEH/VEH), and *Bdnf* isoform VI (−24 % $p < 0.05$ vs VEH/VEH).

For the microglial activation cluster, mRNA levels of *Iba1*, *CD68*, and *CD86* were assessed. *Iba1* and *CD68* were significantly reduced in 5-HTT$^{-/-}$ rats (*Iba1*: −12 % $p < 0.05$; CD68: −12 % $p < 0.05$ vs 5-HTT$^{+/+}$) compared to controls. Notably, *Iba1* expression was also decreased in the FLX/VEH (−12 % $p < 0.05$ vs VEH/VEH), VEH/FLX (−10 % $p < 0.05$ vs VEH/VEH), and FLX/FLX (−24 % $p < 0.05$ vs VEH/VEH) groups, while *CD68* was significantly downregulated in the FLX/FLX (−35 % $p < 0.001$ vs VEH/VEH).

In the 5-HTT$^{-/-}$ group we found an opposite effect on the expression of *Cx3cr1* and *Cx3cl1* (+22 % $p < 0.001$ vs 5-HTT$^{+/+}$ and − 30 % $p < 0.001$ vs 5-HTT$^{+/+}$, respectively), underlying the non-significant change in the z-score of the gene cluster “microglia-neuron interaction”.

Importantly, *Cx3cl1* expression was also significantly reduced in the FLX/VEH (−43 % $p < 0.001$ vs VEH/VEH), VEH/FLX (−37 % $p < 0.001$ vs VEH/VEH), and FLX/FLX (−52 % $p < 0.001$ vs VEH/VEH).

Within the PNN-related genes, *Sem3a* expression was increased in the 5-HTT$^{-/-}$ group (+38 % $p < 0.01$ vs 5-HTT$^{+/+}$), a pattern also observed in the VEH/FLX group (+65 % $p < 0.05$ vs VEH/VEH), while in the FLX/FLX group, *Sem3a* was instead downregulated (−30 % $p < 0.001$ vs VEH/VEH).

Concerning antioxidant and mitochondrial function, *Gpx1* expression was significantly reduced in 5-HTT$^{-/-}$ animals (−15 % $p < 0.05$ vs 5-HTT$^{+/+}$) compared to 5-HTT$^{+/+}$ rats, whereas it was upregulated in the VEH/FLX group (+27 % $p < 0.05$ vs VEH/VEH).

Interestingly, some genes were selectively affected by pharmacological manipulation of 5-HTT but not by the genetic deletion.

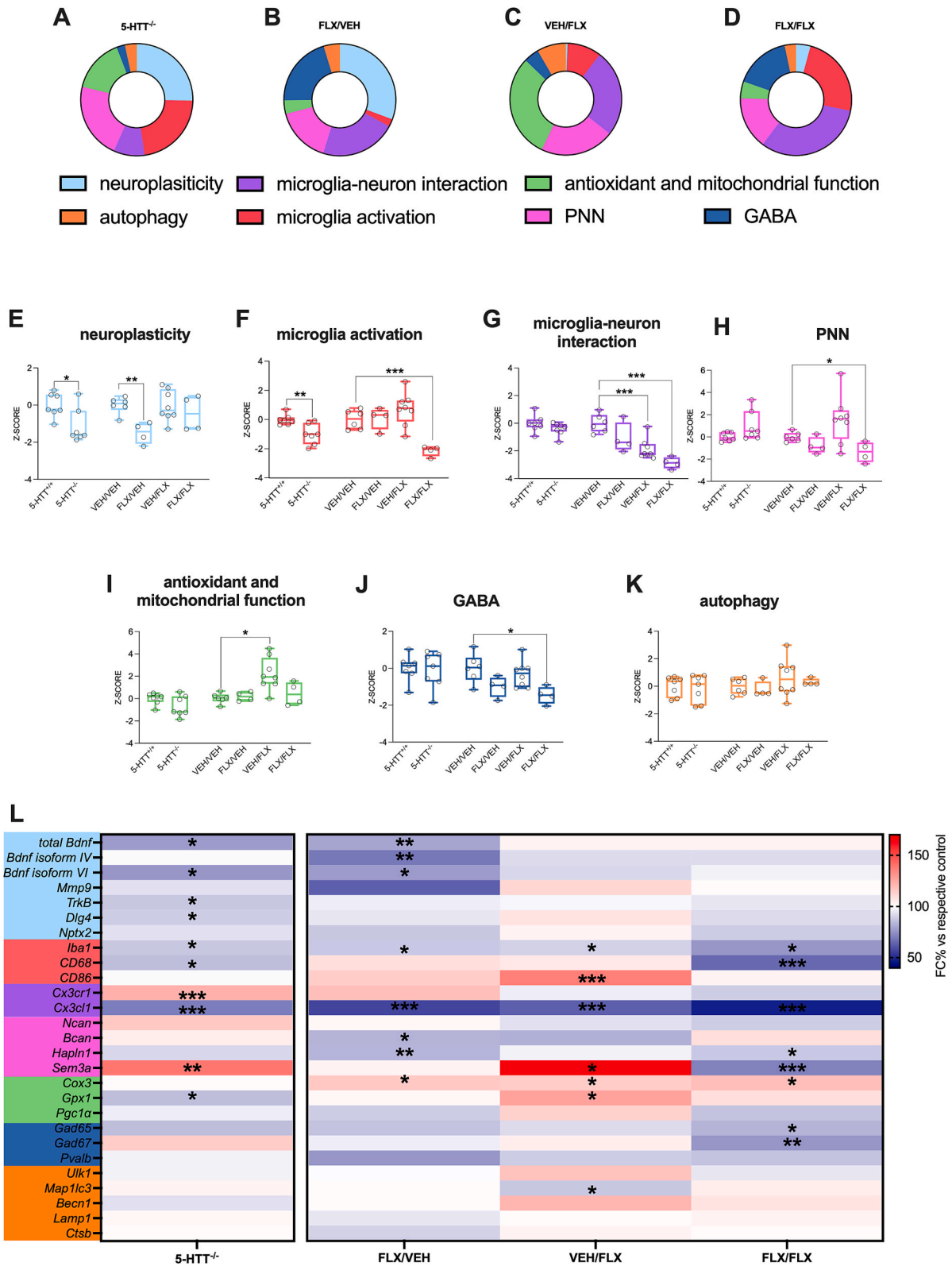

Fig. 2. Gene expression analysis in the dorsal hippocampus of adult female rats across experimental conditions. **(A-D)** Donut charts showing the proportional representation of different gene functional categories regulation in each experimental group compared to respective control group (5-HTT$^{+/+}$ or VEH/VEH). Each functional gene class is labelled by a color: neuroplasticity (light blue), microglia activation (red), microglia–neuron interaction (purple), perineuronal nets (PNN; pink), antioxidant and mitochondrial function (green), GABAergic signaling (blue), and autophagy (orange). **(E-K)** *Z*-score distribution of gene expression grouped by functional category: neuroplasticity **(E)**, microglial activation **(F),** microglia–neuron interaction **(G)**, PNN **(H)**, antioxidant and mitochondrial function **(I),** GABAergic signaling **(J),** autophagy **(K).** Data are presented as box and whiskers with horizontal lines representing the median. The whiskers go down to the smallest value and up to the largest. *p < 0.05, **p < 0.01, ***p < 0.001 (unpaired *t*-test vs respective control group). **(L)** Heatmap representing fold changes (FC%) in mRNA expression levels of genes categorized by function. Each column represents a different experimental group: 5-HTT$^{-/-}$, FLX/VEH, VEH/FLX, and FLX/FLX. Color scale indicates fold changes (blue = downregulated, red = upregulated) relative to respective controls. *p < 0.05, **p < 0.01, ***p < 0.001 (unpaired *t*-test).

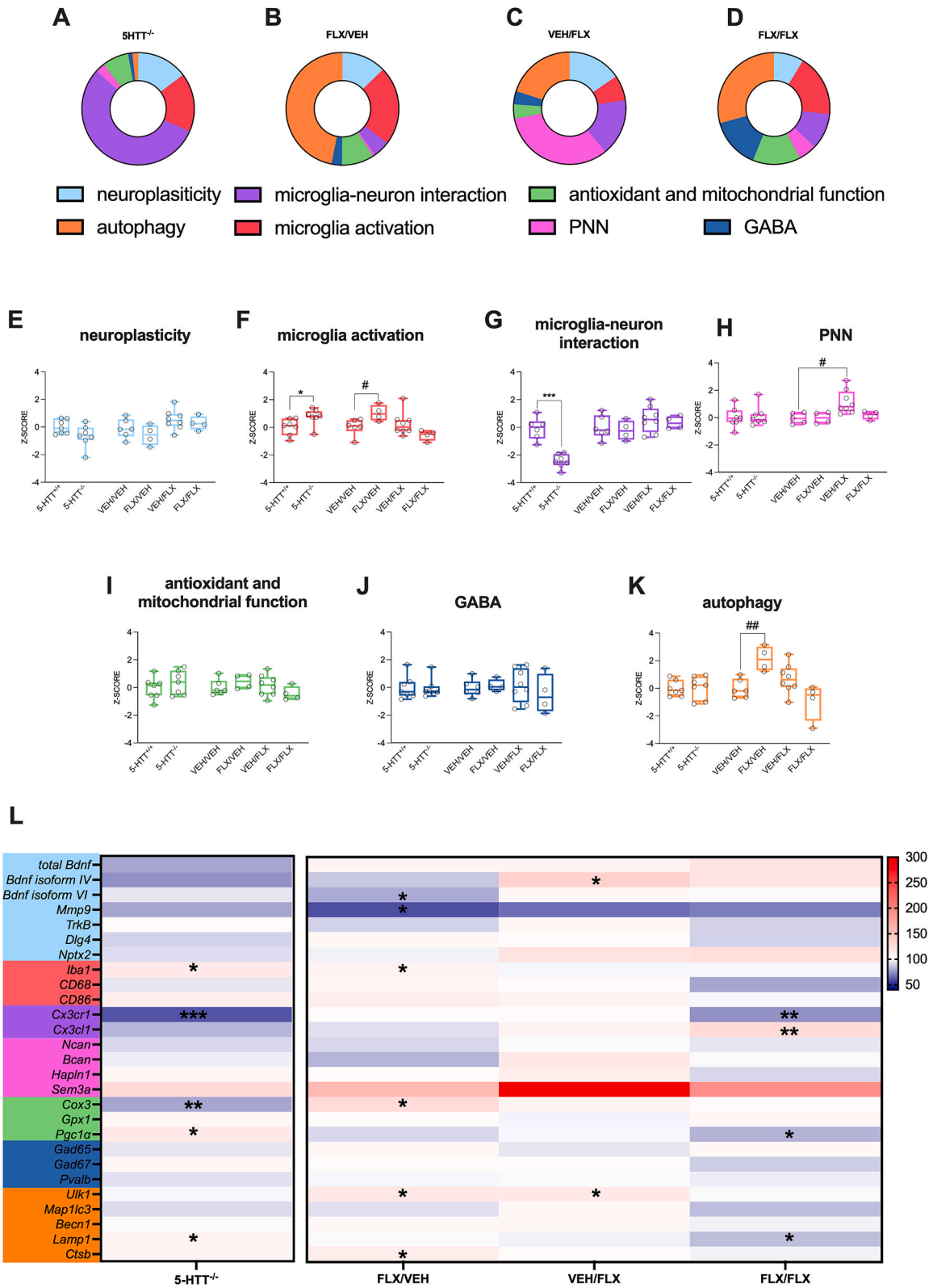

Fig. 3. Gene expression analysis in the ventral hippocampus of adult female rats across experimental conditions. **(A-D)** Donut charts showing the proportional representation of different gene functional categories regulation in each experimental group compared to respective control group (5-HTT$^{+/+}$ or VEH/VEH). Each functional gene class is labelled by a color: neuroplasticity (light blue), microglia activation (red), microglia–neuron interaction (purple), perineuronal nets (PNN; pink), antioxidant and mitochondrial function (green), GABAergic signaling (blue), and autophagy (orange). **(E-K)** Z-score distribution of gene expression grouped by functional category: neuroplasticity **(E),** microglial activation **(F),** microglia–neuron interaction **(G),** PNN **(H),** antioxidant and mitochondrial function **(I),** GABAergic signaling **(J),** autophagy **(K).** Data are presented as box and whiskers with horizontal lines representing the median. The whiskers go down to the smallest value and up to the largest. *p < 0.05, **p < 0.01, ***p < 0.001 (unpaired *t*-test vs respective control group). **(L)** Heatmap representing fold changes (FC%) in mRNA expression levels of genes categorized by function. Each column represents a different experimental group: 5-HTT$^{-/-}$, FLX/VEH, VEH/FLX, and FLX/FLX. Color scale indicates fold changes (blue = downregulated, red = upregulated) relative to respective controls. *p < 0.05, **p < 0.01, ***p < 0.001 (unpaired *t*-test).

Specifically, in the FLX/VEH group, we observed reduced expression of *Bcan* (−18 % $p < 0.05$ vs VEH/VEH) and *Hapln1* (−17 % $p < 0.01$ vs VEH/VEH), two PNN components. *Hapln1* was also downregulated in the FLX/FLX group (−12 % $p < 0.05$ vs VEH/VEH). In addition, *Cox3*, an antioxidant and mitochondrial function marker, was upregulated in FLX/VEH (+15 % $p < 0.05$ vs VEH/VEH), VEH/FLX (+15 % $p < 0.05$ vs VEH/VEH), and FLX/FLX (+19 % $p < 0.05$ vs VEH/VEH) groups.

Differently, in the VEH/FLX group *CD86* was significantly increased (+37 % $p < 0.001$ vs VEH/VEH), while Map*1lc3*, a gene involved in autophagy, was selectively downregulated (−13 % $p < 0.05$ vs VEH/VEH).

Lastly, *Gad65* and *Gad67*, key GABAergic markers, were selectively downregulated in the FLX/FLX group (*Gad65*: −17 % $p < 0.05$; *Gad67*: −24 % $p < 0.01$ vs VEH/VEH).

7.2. Transcriptional impact of constitutive deletion and perinatal pharmacological manipulation of 5-HTT in the ventral hippocampus

In the vHip, as illustrated in the donut charts (Fig. 3A-D), the genetic deletion of 5-HTT (Fig. 3A) was associated with prominent alterations in microglia activation and microglia–neuron interaction. Notably, changes in microglial activation were also detected in the FLX/VEH group (Fig. 3B). Other alterations appeared to be specific to each experimental group: VEH/FLX showed a disrupted z-score profile related to perineuronal nets (PNNs; Fig. 3C), while FLX/VEH exhibited changes in the autophagy-related gene cluster.

Quantitatively (Fig. 3E-K), both 5-HTT$^{-/-}$ ($p < 0.05$ vs 5-HTT$^{+/+}$) and FLX/VEH ($p < 0.05$ vs VEH/VEH) groups exhibited a significant increase in microglia activation-related *z*-scores (Fig. 3F) while a selective reduction in microglia–neuron interaction was observed exclusively in the 5-HTT$^{-/-}$ group ($p < 0.001$ vs 5-HTT$^{+/+}$; Fig. 3G). Differently, VEH/FLX animals showed elevated PNN-related *z*-scores ($p < 0.05$ vs VEH/VEH; Fig. 3H), and the FLX/VEH group exhibited a significant upregulation of autophagy-associated genes ($p < 0.01$ vs VEH/VEH; Fig. 3K).

Looking at the expression of the individual genes (Fig. 3L), we found increased mRNA levels of *Iba1* in both 5-HTT$^{-/-}$ (+17 %, $p < 0.05$ vs 5-HTT$^{+/+}$) and FLX/VEH animals (+11 %, $p < 0.05$ vs VEH/VEH). Differently, *Cx3cr1* expression was decreased in 5-HTT$^{-/-}$ rats (–40 %, $p < 0.001$ vs 5-HTT$^{+/+}$) and in the FLX/FLX group (–26 %, $p < 0.01$ vs VEH/VEH).

Although the *z*-scores for antioxidant and mitochondrial function and autophagy-related pathways were not significantly altered overall, 5-HTT$^{-/-}$ animals displayed reduced *Cox3* expression (–21 %, $p < 0.01$ vs 5-HTT$^{+/+}$), along with increased levels of *Pgc1α* (+17 %, $p < 0.05$ vs 5-HTT$^{+/+}$) and *Lamp1* (+10 %, $p < 0.05$ vs 5-HTT$^{+/+}$). Moreover, in the FLX/VEH group we observed reduced expression of *Bdnf* isoform VI (−20 %, $p < 0.05$ vs VEH/VEH) and *Mmp9* (−41 %, $p < 0.05$ vs VEH/VEH), while *Cox3* (+28 %, $p < 0.05$ vs VEH/VEH), *Ulk1* (+20 %, $p < 0.05$ vs VEH/VEH), and *Ctsb* (+15 %, $p < 0.05$ vs VEH/VEH) were upregulated.

Differently, postnatal FLX exposure (VEH/FLX group) led to increased expression of *Bdnf* isoform IV (+36 %, $p < 0.05$ vs VEH/VEH) and *Ulk1* (+16 %, $p < 0.05$ vs VEH/VEH).

Finally, in the FLX/FLX group, *Cx3cl1* expression was increased (+30 %, $p < 0.01$ vs VEH/VEH), accompanied by reduced levels of *Pgc1α* (−18 %, $p < 0.05$ vs VEH/VEH) and *Lamp1* (−15 %, $p < 0.05$ vs VEH/VEH).

8. Discussion

This study provides a comprehensive view of the long-term molecular consequences of 5-HTT manipulations across dorsal and ventral hippocampal subregions, highlighting how the timing and length of serotonergic perturbation shapes distinct outcomes.

Our data show that some processes are similarly altered in the genetic model and in the pharmacological ones, while others are modulated only under specific conditions.

In particular, both the removal of 5-HTT and the prenatal-FLX exposure led to comparable reductions in neuroplasticity markers in the dHip indicating that serotonergic disruption during gestation is sufficient to cause persistent deficits in adult dHip plasticity. This is consistent with previous evidence showing that constitutive 5-HTT deletion reduces *Bdnf* levels in the adult hippocampus of male rats [26,88,89] and that prenatal FLX exposure induces long-lasting alterations in neuroplasticity detectable at adulthood [90].

Additionally, in dHip, microglial activation was reduced both in 5-HTT$^{-/-}$ and in FLX/FLX rats suggesting that the transient prenatal or postnatal FLX exposure alone is not sufficient to impact microglial activation, while manipulations spanning both developmental windows, as in FLX/FLX animals, reproduce the effect of constitutive 5-HTT loss.

Looking in more detail, we observed that, although *Iba1* expression was decreased across all experimental groups, genetic deletion and extended perinatal FLX exposure (FLX/FLX) also led to a reduced *CD68* expression indicating a shift toward a less active, hypofunctional microglial state, potentially limiting synaptic remodeling and trophic support. These findings support previous studies showing that both 5-HTT mutant animals and rodents exposed to perinatal FLX exhibit disrupted inflammation-related processes in the hippocampus [91,92].

Conversely, in vHip, 5-HTT constitutive deletion increased microglial activation by upregulating *Iba1* expression, a result also observed in the FLX/VEH group, emphasizing that early gestational 5-HTergic disruption is sufficient and necessary to induce persistent immune-related changes in this subregion.

Of note, we observed reduced expression of microglia–neuron interaction markers only in the vHip of 5-HTT$^{-/-}$ rats, suggesting that this phenotype is probably due to an early and stable alterations of the serotonergic system, while perinatal transient alterations are not enough to perturb it in the long term. In particular, we observed a marked reduction of *Cx3cr1* mRNA levels without changes in *Cx3cl1*, suggesting a clear dysregulation of neuron-microglia signaling. Interestingly, genetic variants in the *Cx3cr1* gene have been previously associated with psychiatric conditions [93]. The parallel increase in microglial activation (mainly driven by *Iba1* upregulation) and reduction of microglia-neuron interaction (selectively due to decreased *Cx3cr1* expression, with unaltered *Cx3cl1*) suggest that microglia become more active but less responsive to neuronal regulatory signals. This imbalance might suggest an alteration of the homeostatic neuron–microglia crosstalk, potentially leading to a primed microglial state that may affect synaptic refinement and long-term network stability. Moreover, disruption in the microglia-neuron signaling has been previously shown to contribute to neurodevelopmental and neuropsychiatric disorders [94].

Additionally, *Cx3cr1* was also reduced in FLX/FLX animals, alongside the increase of *Cx3cl1* potentially balancing the overall cluster effect. This pattern suggests that perinatal 5-HTT disruption is sufficient to drive long-term *Cx3cr1* reduction, but the restoration of 5-HTT function after FLX discontinuation may trigger compensatory increases in *Cx3cl1*.

In contrast we found less overlap in the dHip between the genetic and the pharmacological manipulation.

Here, microglia-neuron interaction was specifically reduced both in FLX/FLX and in VEH/FLX groups, indicating that postnatal FLX exposure alone is sufficient and necessary to produce this effect. Notably, *Cx3cl1* expression was lowered in all experimental groups, while 5-HTT constitutive deletion resulted in increased *Cx3cr1* levels, pointing to disrupted neuron–microglia signaling, with more receptors but reduced neuronal signaling.

Consistent with our recent evidence demonstrating that early FLX exposure affects parvalbumin-positive GABAergic interneurons, contributing to the disruption of sensitive period timing in the dHip and leading to an imbalance in excitatory/inhibitory signaling as well as alterations in PNN composition [22], we observed a reduction of *Gad65*, *Gad67*, together with a downregulation of PNN components (*Hapln1*, *Sem3a*) in the dHip of FLX/FLX rats.

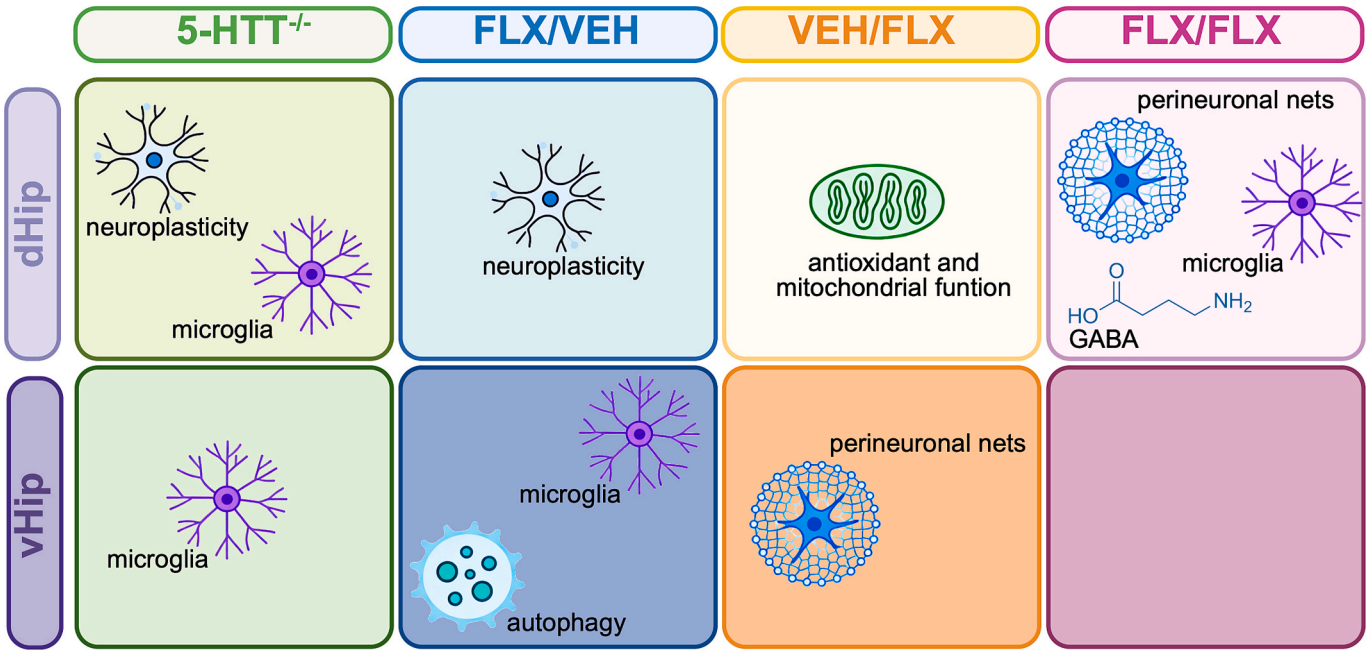

Fig. 4. Molecular effects of constitutive 5-HTT deletion and pharmacological 5-HTT inhibition during specific early-life time windows in the dorsal and ventral hippocampus of adult female rats**.** Each box represents the gene clusters impaired in each experimental condition specifically in the dorsal (dHip) and ventral (vHip) hippocampal subregions.

Postnatal-FLX exposure also enhanced antioxidant and mitochondrial function in dHip, as reflected by the upregulation of *Gpx1* and *Cox3*, indicating that 5-HTergic perturbations restricted to the lactation period selectively target distinct metabolic pathways, which remain unaffected by prenatal or constitutive manipulations. Consistent with this observation, altered mitochondrial bioenergetics have previously been reported after postnatal exposure to FLX [95].

Differently, when 5-HTT manipulation was limited to gestation (FLX/VEH), we observed an upregulation of autophagy-related genes (*Ulk1*, *Ctsb*) in the vHip, suggesting that even transient gestational interventions are sufficient to recruit this pathway. Interestingly, other perinatal manipulations, such as maternal separation have also been shown to induce long-lasting alterations in autophagic processes [96].

Since several studies performed on SERT male rats have shown that both pharmacological or non-pharmacological approaches can ameliorate behavioral and molecular deficits (e.g. [14,26,89,97–101]), future studies will investigate whether similar interventions may also be effective in female SERT rats and in animals exposed to FLX early in life.

The differences between the dorsal and ventral hippocampi may depend on the marked heterogeneity of serotonergic signaling across these two subregions. This heterogeneity spans multiple dimensions, including patterns of innervation, receptor subtype distribution, 5-HTT abundance, and developmental sensitivity to 5-HT signaling (for details see [102]).

Finally, we acknowledge that estrous-related variability in hippocampal molecular markers may have contributed to within-group variance and represents a limitation to be addressed in future studies.

In conclusion, this study demonstrates that constitutive 5-HTT deletion and pharmacological manipulations during defined perinatal windows can cause partially overlapping molecular outcomes although through distinct pathways and in a fashion which depends upon the timing of the perturbation. Serotonergic manipulations restricted to prenatal or postnatal stages elicited unique signatures, highlighting that the developmental phase in which serotonergic signaling is perturbed critically determines the nature and persistence of hippocampal outcomes. Thus, while genetic and pharmacological disruptions share common endpoints, their consequences cannot be fully equated, as they differentially shape hippocampal maturation in a stage-dependent manner (Fig. 4).

These findings provide a framework to further dissect the mechanisms through which serotonergic perturbations shape long-term brain function, offering insights that could guide future research toward more targeted therapeutic approaches.

CRediT authorship contribution statement

Maria Teresa Gallo: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Alessia Golinelli:** Methodology, Investigation, Formal analysis. **Camilla Rizzi:** Methodology, Investigation, Data curation. **Fabio Fumagalli:** Writing – review & editing. **Judith R. Homberg:** . **Paola Brivio:** Writing – review & editing, Formal analysis, Data curation. **Francesca Calabrese:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by a grant from the Italian Ministry of University and Research (PRIN2022-2022P45ZSZ), by a grant from the Ministry of Health (PNRR-MCNT1-2023-12378320) to FC and from MIUR Progetto Eccellenza (2023-2027) to the Department of Pharmacological and Biomolecular Sciences “Rodolfo Paoletti”, Università degli Studi di Milano, Milan, Italy, and by the European Community’s Horizon 2020 Program (H2020- MSCA-ITN-2020) under grant agreement no 953327 (SEROTONIN and BEYOND to Judith R. Homberg).

Data availability

Data will be made available on request.

References

[1] J. Bacqué-Cazenave, R. Bharatiya, G. Barrière, J.-P. Delbecque, N. Bouguiyoud, G. Di Giovanni, D. Cattaert, P. De Deurwaerdère, Serotonin in animal cognition and behavior, Int. J. Mol. Sci. 21 (2020) 1649, https://doi.org/10.3390/ijms21051649.

[2] M. Kanova, P. Kohout, Serotonin—its synthesis and roles in the healthy and the critically Ill, Int. J. Mol. Sci. 22 (2021) 4837, https://doi.org/10.3390/ijms22094837.

[3] P.M. Whitaker-Azmitia, Serotonin and brain development: role in human developmental diseases, Brain Res. Bull. 56 (2001) 479–485, https://doi.org/10.1016/S0361-9230(01)00615-3.

[4] P. Gaspar, O. Cases, L. Maroteaux, The developmental role of serotonin: news from mouse molecular genetics, Nat. Rev. Neurosci. 4 (2003) 1002–1012, https://doi.org/10.1038/nrn1256.

[5] E.A. Daubert, B.G. Condron, Serotonin: a regulator of neuronal morphology and circuitry, Trends Neurosci. 33 (2010) 424–434, https://doi.org/10.1016/j.tins.2010.05.005.

[6] A. Caspi, K. Sugden, T.E. Moffitt, A. Taylor, I.W. Craig, H. Harrington, J. McClay, J. Mill, J. Martin, A. Braithwaite, R. Poulton, Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene, Science 301 (2003) (1979) 386–389, https://doi.org/10.1126/science.1083968.

[7] J.R. Homberg, J. Jagiellowicz, A neural model of vulnerability and resilience to stress-related disorders linked to differential susceptibility, Mol. Psychiatry 27 (2022) 514–524, https://doi.org/10.1038/s41380-021-01047-8.

[8] A.V. Kalueff, J.D.A. Olivier, L.J.P. Nonkes, J.R. Homberg, Conserved role for the serotonin transporter gene in rat and mouse neurobehavioral endophenotypes, Neurosci. Biobehav. Rev. 34 (2010) 373–386, https://doi.org/10.1016/j.neubiorev.2009.08.003.

[9] P. Brivio, J.R. Homberg, M.A. Riva, F. Calabrese, Alterations of glutamatergic markers in the prefrontal cortex of serotonin transporter knockout rats: a developmental timeline, Cell. Mol. Neurobiol. 39 (2019) 715–720, https://doi.org/10.1007/s10571-019-00673-9.

[10] P. Schipper, P. Brivio, D. de Leest, L. Madder, B. Asrar, F. Rebuglio, M.M. M. Verheij, T. Kozicz, M.A. Riva, F. Calabrese, M.J.A.G. Henckens, J.R. Homberg, Impaired fear extinction recall in serotonin transporter knockout rats is transiently alleviated during adolescence, Brain Sci. 9 (2019) 118, https://doi.org/10.3390/brainsci9050118.

[11] F. Calabrese, G. Guidotti, A. Middelman, G. Racagni, J. Homberg, M.A. Riva, Lack of serotonin transporter alters bdnf expression in the rat brain during early postnatal development, Mol. Neurobiol. 48 (2013) 244–256, https://doi.org/10.1007/s12035-013-8449-z.

[12] F. Crestani, M. Lorez, K. Baer, C. Essrich, D. Benke, J.P. Laurent, C. Belzung, J.-M. Fritschy, B. Lüscher, H. Mohler, Decreased GABAA-receptor clustering results in enhanced anxiety and a bias for threat cues, Nat. Neurosci. 2 (1999) 833–839, https://doi.org/10.1038/12207.

[13] A.L. De Blas, Brain GABAA receptors studied with subunit-specific antibodies, Mol. Neurobiol. 12 (1996) 55–71, https://doi.org/10.1007/BF02740747.

[14] G. Guidotti, F. Calabrese, F. Auletta, J. Olivier, G. Racagni, J. Homberg, M. A. Riva, Developmental influence of the serotonin transporter on the expression of Npas4 and GABAergic markers: modulation by antidepressant treatment, Neuropsychopharmacology 37 (2012) 746–758, https://doi.org/10.1038/npp.2011.252.

[15] G. Sbrini, P. Brivio, P.M. Peeva, M. Todiras, M. Bader, N. Alenina, F. Calabrese, The absence of serotonin in the brain alters acute stress responsiveness by interfering with the genomic function of the glucocorticoid receptors, Front. Cell. Neurosci. 14 (2020), https://doi.org/10.3389/fncel.2020.00128.

[16] M. Toledo-Rodriguez, P. Goodman, M. Illic, C. Wu, H. Markram, Neuropeptide and calcium-binding protein gene expression profiles predict neuronal anatomical type in the juvenile rat, J. Physiol. 567 (2005) 401–413, https://doi.org/10.1113/jphysiol.2005.089250.

[17] D.J. Houwing, L. Staal, J.M. Swart, A.S. Ramsteijn, M. Wöhr, S.F. de Boer, J.D. A. Olivier, Subjecting dams to early life stress and perinatal fluoxetine treatment differentially alters social behavior in young and adult rat offspring, Front. Neurosci. 13 (2019), https://doi.org/10.3389/fnins.2019.00229.

[18] J.R. Homberg, R. Molteni, F. Calabrese, M.A. Riva, The serotonin–BDNF duo: Developmental implications for the vulnerability to psychopathology, Neurosci. Biobehav. Rev. 43 (2014) 35–47, https://doi.org/10.1016/j.neubiorev.2014.03.012.

[19] M.S. Ansorge, M. Zhou, A. Lira, R. Hen, J.A. Gingrich, Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice, Science 306 (2004) (1979) 879–881, https://doi.org/10.1126/science.1101678.

[20] M.T. Gallo, P. Brivio, B. Dolci, F. Fumagalli, F. Calabrese, Perinatal serotonergic manipulation shapes anhedonic and cognitive behaviors in a sex- and age-dependent manner: Identification of related biological functions at central and peripheral level, Brain Behav. Immun. 114 (2023) 118–130, https://doi.org/10.1016/j.bbi.2023.08.016.

[21] M.T. Gallo, B. Dolci, F. Fumagalli, P. Brivio, F. Calabrese, Prenatal fluoxetine exposure influences glucocorticoid receptor-mediated activity in the prefrontal cortex of adolescent rats exposed to acute stress, ACS Chem. Neurosci. 15 (2024) 1560–1569, https://doi.org/10.1021/acschemneuro.3c00856.

[22] M.T. Gallo, A. Virenque, A. Golinelli, F. Fumagalli, E. Castrén, P. Brivio, F. Calabrese, From early-life fluoxetine exposure to lifelong, sex-specific behavioral changes: decoding the dynamics of sensitive periods, Mol. Psychiatry (2025), https://doi.org/10.1038/s41380-025-03223-6.

[23] J. Umemori, F. Winkel, G. Didio, M. Llach Pou, E., Castrén, iPlasticity: Induced juvenile-like plasticity in the adult brain as a mechanism of antidepressants, Psychiatry Clin. Neurosci. 72 (2018) 633–653, https://doi.org/10.1111/pcn.12683.

[24] J.F. Maya Vetencourt, A. Sale, A. Viegi, L. Baroncelli, R. De Pasquale, O.F. O'Leary, E. Castrén, L. Maffei, The antidepressant fluoxetine restores plasticity in the adult visual cortex, Science 320 (2008), doi: 10.1126/science.1150516 385 388.

[25] M. DuMont, A. Agostinis, K. Singh, E. Swan, Y. Buttle, D. Tropea, Sex representation in neurodegenerative and psychiatric disorders' preclinical and clinical studies, Neurobiol. Dis. 184 (2023) 106214, https://doi.org/10.1016/j.nbd.2023.106214.

[26] G. Sbrini, P. Brivio, K. Bosch, J.R. Homberg, F. Calabrese, Enrichment environment positively influences depression- and anxiety-like behavior in serotonin transporter knockout rats through the modulation of neuroplasticity, spine, and GABAergic markers, Genes (Basel) 11 (2020) 1248, https://doi.org/10.3390/genes11111248.

[27] R.B. Price, R. Duman, Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model, Mol. Psychiatry 25 (2020) 530–543, https://doi.org/10.1038/s41380-019-0615-x.

[28] H. Wang, Y. He, Z. Sun, S. Ren, M. Liu, G. Wang, J. Yang, Microglia in depression: an overview of microglia in the pathogenesis and treatment of depression, J. Neuroinflammation 19 (2022) 132, https://doi.org/10.1186/s12974-022-02492-0.

[29] S. Spijker, M.-K. Koskinen, D. Riga, Incubation of depression: ECM assembly and parvalbumin interneurons after stress, Neurosci. Biobehav. Rev. 118 (2020) 65–79, https://doi.org/10.1016/j.neubiorev.2020.07.015.

[30] P. Brivio, M.T. Gallo, P. Karel, G. Cogi, F. Fumagalli, J.R. Homberg, F. Calabrese, Alterations of mitochondrial dynamics in serotonin transporter knockout rats: a possible role in the fear extinction recall mechanisms, Front. Behav. Neurosci. 16 (2022), https://doi.org/10.3389/fnbeh.2022.957702.

[31] P. Brivio, M. Audano, M.T. Gallo, P. Gruca, M. Lason, E. Litwa, F. Fumagalli, M. Papp, N. Mitro, F. Calabrese, Metabolomic signature and mitochondrial dynamics outline the difference between vulnerability and resilience to chronic stress, Transl. Psychiatry 12 (2022) 87, https://doi.org/10.1038/s41398-022-01856-7.

[32] N.C. Gassen, T. Rein, Is there a role of autophagy in depression and antidepressant action? Front. Psychiatry 10 (2019) https://doi.org/10.3389/fpsyt.2019.00337.

[33] B.M.G. Smits, J.B. Mudde, J. van de Belt, M. Verheul, J. Olivier, J. Homberg, V. Guryev, A.R. Cools, B.A. Ellenbroek, R.H.A. Plasterk, E. Cuppen, Generation of gene knockouts and mutant models in the laboratory rat by ENU-driven target-selected mutagenesis, Pharmacogenet. Genomics 16 (2006) 159–169, https://doi.org/10.1097/01.fpc.0000184960.82903.8f.

[34] P. Brivio, M.T. Gallo, P. Gruca, M. Lason, E. Litwa, F. Fumagalli, M. Papp, F. Calabrese, Resilience to chronic mild stress-induced anhedonia preserves the ability of the ventral hippocampus to respond to an acute challenge, Eur. Arch. Psychiatry Clin. Neurosci. 273 (2023) 1041–1050, https://doi.org/10.1007/s00406-022-01470-0.

[35] P. Brivio, M.T. Gallo, P. Gruca, M. Lason, E. Litwa, F. Fumagalli, M. Papp, F. Calabrese, Chronic N-acetyl-cysteine treatment enhances the expression of the immediate early gene Nr4a1 in response to an acute challenge in male rats: comparison with the antidepressant venlafaxine, Int. J. Mol. Sci. 24 (2023) 7321, https://doi.org/10.3390/ijms24087321.

[36] E. Sangiovanni, P. Brivio, M. Dell'Agli, F. Calabrese, Botanicals as modulators of neuroplasticity: focus on BDNF, Neural Plast. 2017 (2017) 1–19, https://doi.org/10.1155/2017/5965371.

[37] C.S. Wang, E.T. Kavalali, L.M. Monteggia, BDNF signaling in context: from synaptic regulation to psychiatric disorders, Cell 185 (2022) 62–76, https://doi.org/10.1016/j.cell.2021.12.003.

[38] B. Lu, G. Nagappan, Y. Lu, BDNF and Synaptic Plasticity, Cognitive Function, and Dysfunction, in (2014:) 223–250, https://doi.org/10.1007/978-3-642-45106-5_9.

[39] T. Yang, Z. Nie, H. Shu, Y. Kuang, X. Chen, J. Cheng, S. Yu, H. Liu, The role of BDNF on neural plasticity in depression, Front. Cell. Neurosci. 14 (2020), https://doi.org/10.3389/fncel.2020.00082.

[40] K. Sakata, N.H. Woo, K. Martinowich, J.S. Greene, R.J. Schloesser, L. Shen, B. Lu, Critical role of promoter IV-driven BDNF transcription in GABAergic transmission and synaptic plasticity in the prefrontal cortex, in: Proceedings of the National Academy of Sciences 106, 2009, pp. 5942–5947, https://doi.org/10.1073/pnas.0811431106.

[41] F. Zheng, H. Wang, NMDA-mediated and self-induced bdnf exon IV transcriptions are differentially regulated in cultured cortical neurons, Neurochem. Int. 54 (2009) 385–392, https://doi.org/10.1016/j.neuint.2009.01.006.

[42] W. Singer, M. Manthey, R. Panford-Walsh, L. Matt, H.-S. Geisler, E. Passeri, G. Baj, E. Tongiorgi, G. Leal, C.B. Duarte, I.L. Salazar, P. Eckert, K. Rohbock, J. Hu, J. Strotmann, P. Ruth, U. Zimmermann, L. Rüttiger, T. Ott, T. Schimmang, M. Knipper, BDNF-Live-Exon-Visualization (BLEV) allows differential detection of bdnf transcripts in vitro and in vivo, Front. Mol. Neurosci. 11 (2018), https://doi.org/10.3389/fnmol.2018.00325.

[43] K.R. Maynard, J.W. Hobbs, M. Sukumar, A.S. Kardian, D.V. Jimenez, R. J. Schloesser, K. Martinowich, Bdnf mRNA splice variants differentially impact CA1 and CA3 dendrite complexity and spine morphology in the hippocampus, Brain Struct. Funct. 222 (2017) 3295–3307, https://doi.org/10.1007/s00429-017-1405-3.

[44] M.V. Green, T. Pengo, J.D. Raybuck, T. Naqvi, H.M. McMullan, J.E. Hawkinson, E. Marron, Fernandez de Velasco, B.S. Muntean, K.A. Martemyanov, R. Satterfield, S.M. Young, S.A. Thayer, Automated Live-Cell Imaging of Synapses in Rat and Human Neuronal Cultures Front, Cell Neurosci. 13 (2019), doi: 10.3389/fncel.2019.00467.

[45] X. Wang, O. Bozdagi, J.S. Nikitczuk, Z.W. Zhai, Q. Zhou, G.W. Huntley, Extracellular proteolysis by matrix metalloproteinase-9 drives dendritic spine enlargement and long-term potentiation coordinately, in: Proceedings of the National Academy of Sciences 105, 2008, pp. 19520–19525, https://doi.org/10.1073/pnas.0807248105.

[46] V. Nagy, O. Bozdagi, A. Matynia, M. Balcerzyk, P. Okulski, J. Dzwonek, R. M. Costa, A.J. Silva, L. Kaczmarek, G.W. Huntley, Matrix metalloproteinase-9 is required for hippocampal late-phase long-term potentiation and memory, J. Neurosci. 26 (2006) 1923–1934, https://doi.org/10.1523/JNEUROSCI.4359-05.2006.

[47] R. Moliner, M. Girych, C.A. Brunello, V. Kovaleva, C. Biojone, G. Enkavi, L. Antenucci, E.F. Kot, S.A. Goncharuk, K. Kaurinkoski, M. Kuutti, S.M. Fred, L. V. Elsilä, S. Sakson, C. Cannarozzo, C.R.A.F. Diniz, N. Seiffert, A. Rubiolo, H. Haapaniemi, E. Meshi, E. Nagaeva, T. Öhman, T. Róg, E. Kankuri, M. Vilar, M. Varjosalo, E.R. Korpi, P. Permi, K.S. Mineev, M. Saarma, I. Vattulainen, P. C. Casarotto, E. Castrén, Psychedelics promote plasticity by directly binding to BDNF receptor TrkB, Nat. Neurosci. 26 (2023) 1032–1041, https://doi.org/10.1038/s41593-023-01316-5.

[48] E. Jetsonen, G. Didio, F. Winkel, M. Llach Pou, C. Boj, L. Kuczynski-Noyau, V. Võikar, R. Guirado, T. Taira, S.E. Lauri, E. Castrén, J. Umemori, Activation of TrkB in Parvalbumin interneurons is required for the promotion of reversal learning in spatial and fear memory by antidepressants, Neuropsychopharmacology 48 (2023) 1021–1030, https://doi.org/10.1038/s41386-023-01562-y.

[49] L. Minichiello, M. Korte, D. Wolfer, R. Kühn, K. Unsicker, V. Cestari, C. Rossi-Arnaud, H.-P. Lipp, T. Bonhoeffer, R. Klein, Essential role for TrkB receptors in hippocampus-mediated learning, Neuron 24 (1999) 401–414, https://doi.org/10.1016/S0896-6273(00)80853-3.

[50] M.D. Mardones, P.V. Jorquera, A. Herrera-Soto, E. Ampuero, F.J. Bustos, B. van Zundert, L. Varela-Nallar, PSD95 regulates morphological development of adult-born granule neurons in the mouse hippocampus, J. Chem. Neuroanat. 98 (2019) 117–123, https://doi.org/10.1016/j.jchemneu.2019.04.009.

[51] I. Ehrlich, M. Klein, S. Rumpel, R. Malinow, PSD-95 is required for activity-driven synapse stabilization, in: Proceedings of the National Academy of Sciences 104, 2007, pp. 4176–4181, https://doi.org/10.1073/pnas.0609307104.

[52] J. Zhou, S.D. Wade, D. Graykowski, M.-F. Xiao, B. Zhao, L.A.A. Giannini, J. E. Hanson, J.C. van Swieten, M. Sheng, P.F. Worley, B. Dejanovic, The neuronal pentraxin Nptx2 regulates complement activity and restrains microglia-mediated synapse loss in neurodegeneration, Sci. Transl. Med. 15 (2023), https://doi.org/10.1126/scitranslmed.adf0141.

[53] Z. Wang, T. Jin, Q. Le, C. Liu, X. Wang, F. Wang, L. Ma, Retrieval-driven hippocampal NPTX2 plasticity facilitates the extinction of cocaine-associated context memory, Biol. Psychiatry 87 (2020) 979–991, https://doi.org/10.1016/j.biopsych.2019.10.009.

[54] J. Lier, W.J. Streit, I. Bechmann, Beyond activation: characterizing microglial functional phenotypes, Cells 10 (2021) 2236, https://doi.org/10.3390/cells10092236.

[55] Y. Imai, S. Kohsaka, Intracellular signaling in M-CSF-induced microglia activation: Role of Iba1, Glia 40 (2002) 164–174, https://doi.org/10.1002/glia.10149.

[56] M.E.V. Swanson, M. Mrkela, H.C. Murray, M.C. Cao, C. Turner, M.A. Curtis, R.L. M. Faull, A.K. Walker, E.L. Scotter, Microglial CD68 and L-ferritin upregulation in response to phosphorylated-TDP-43 pathology in the amyotrophic lateral sclerosis brain, Acta Neuropathol. Commun. 11 (2023) 69, https://doi.org/10.1186/s40478-023-01561-6.

[57] T. Zhou, Z. Huang, X. Sun, X. Zhu, L. Zhou, M. Li, B. Cheng, X. Liu, C. He, Microglia polarization with M1/M2 phenotype changes in rd1 mouse model of retinal degeneration, Front. Neuroanat. 11 (2017), https://doi.org/10.3389/fnana.2017.00077.

[58] A. Gottlieb, N. Toledano-Furman, K.S. Prabhakara, A. Kumar, H.W. Caplan, S. Bedi, C.S. Cox, S.D. Olson, Time dependent analysis of rat microglial surface markers in traumatic brain injury reveals dynamics of distinct cell subpopulations, Sci. Rep. 12 (2022) 6289, https://doi.org/10.1038/s41598-022-10419-1.

[59] J.-M. Huang, N. Zhao, X.-N. Hao, S.-Y. Li, D. Wei, N. Pu, G.-H. Peng, Y. Tao, CX3CL1/CX3CR1 Signaling mediated neuroglia activation is implicated in the retinal degeneration: a potential therapeutic target to prevent photoreceptor death, Investigative Opthalmology & Visual Science 65 (2024) 29, https://doi.org/10.1167/iovs.65.1.29.

[60] X. Wang, Y. Xie, Y. Niu, B. Wan, Y. Lu, Q. Luo, L. Zhu, CX3CL1/CX3CR1 signal mediates M1-type microglia and accelerates high-altitude-induced forgetting, Front. Cell. Neurosci. 17 (2023), https://doi.org/10.3389/fncel.2023.1189348.

[61] D. Baidoe-Ansah, H. Mirzapourdelavar, S. Aleshin, B.H. Schott, C. Seidenbecher, R. Kaushik, A. Dityatev, Neurocan regulates axon initial segment organization and neuronal activity, Matrix Biol. 136 (2025) 22–35, https://doi.org/10.1016/j.matbio.2025.01.001.

[62] S. Schmidt, T. Arendt, M. Morawski, M. Sonntag, Neurocan contributes to perineuronal net development, Neuroscience 442 (2020) 69–86, https://doi.org/10.1016/j.neuroscience.2020.06.040.

[63] C. Mueller-Buehl, J. Reinhard, L. Roll, V. Bader, K.F. Winklhofer, A. Faissner, Brevican, Neurocan, Tenascin-C, and Tenascin-R Act as Important regulators of the Interplay between Perineuronal Nets, Synaptic Integrity, Inhibitory Interneurons, and Otx2, Front. Cell Dev. Biol. 10 (2022), https://doi.org/10.3389/fcell.2022.886527.

[64] M.F. Hazlett, V.L. Hall, E. Patel, A. Halvorsen, N. Calakos, A.E. West, The perineuronal net protein brevican acts in nucleus accumbens parvalbumin-expressing interneurons of adult mice to regulate excitatory synaptic inputs and motivated behaviors, Biol. Psychiatry 96 (2024) 694–707, https://doi.org/10.1016/j.biopsych.2024.02.003.

[65] S.P. Lemieux, V. Lev-Ram, R.Y. Tsien, M.H. Ellisman, Perineuronal nets and the neuronal extracellular matrix can be imaged by genetically encoded labeling of HAPLN1 *in vitro* and *in vivo*, (2023). https://doi.org/10.1101/2023.11.29.569151.

[66] K.A. Giamanco, M. Morawski, R.T. Matthews, Perineuronal net formation and structure in aggrecan knockout mice, Neuroscience 170 (2010) 1314–1327, https://doi.org/10.1016/j.neuroscience.2010.08.032.

[67] G. Dick, C.L. Tan, J.N. Alves, E.M.E. Ehlert, G.M. Miller, L.C. Hsieh-Wilson, K. Sugahara, A. Oosterhof, T.H. van Kuppevelt, J. Verhaagen, J.W. Fawcett, J.C. F. Kwok, Semaphorin 3A Binds to the perineuronal nets via chondroitin sulfate type E Motifs in rodent brains, J. Biol. Chem. 288 (2013) 27384–27395, https://doi.org/10.1074/jbc.M111.310029.

[68] Y.-X. Mei, H.-S. Chen, Q.-L. Cao, W.-W. Lv, Y. Liu, S.-L. Deng, Q. Zhou, Z.-J. Zhang, F. Wang, Z.-L. Hu, J.-G. Chen, Semaphorin 3A-mediated perineuronal nets formation incubates depressive-like behaviors in male mice via activating parvalbumin-expressing interneurons, Mol. Psychiatry (2025), https://doi.org/10.1038/s41380-025-03239-y.

[69] R.A. Capaldi, Structure and function of cytochrome *c* oxidase, Annu. Rev. Biochem 59 (1990) 569–596, https://doi.org/10.1146/annurev.bi.59.070190.003033.

[70] D.E. Handy, E. Lubos, Y. Yang, J.D. Galbraith, N. Kelly, Y.-Y. Zhang, J.A. Leopold, J. Loscalzo, Glutathione peroxidase-1 regulates mitochondrial function to modulate redox-dependent cellular responses, J. Biol. Chem. 284 (2009) 11913–11921, https://doi.org/10.1074/jbc.M900392200.

[71] J.F. Halling, H. Pilegaard, PGC-1α-mediated regulation of mitochondrial function and physiological implications, Appl. Physiol. Nutr. Metab. 45 (2020) 927–936, https://doi.org/10.1139/apnm-2020-0005.

[72] A. Dabrowska, J.L. Venero, R. Iwasawa, M. Hankir, S. Rahman, A. Boobis, N. Hajji, PGC-1α controls mitochondrial biogenesis and dynamics in lead-induced neurotoxicity, Aging 7 (2015) 629–643. https://doi.org/10.18632/aging.100790.

[73] A.B. Walls, E.M. Eyjolfsson, O.B. Smeland, L.H. Nilsen, I. Schousboe, A. Schousboe, U. Sonnewald, H.S. Waagepetersen, Knockout of GAD65 has major impact on synaptic GABA synthesized from astrocyte-derived glutamine, J. Cereb. Blood Flow Metab. 31 (2011) 494–503, https://doi.org/10.1038/jcbfm.2010.115.

[74] M.D. Lange, K. Jüngling, L. Paulukat, M. Vieler, S. Gaburro, L. Sosulina, P. Blaesse, H.K. Sreepathi, F. Ferraguti, H.-C. Pape, Glutamic acid decarboxylase 65: a link between GABAergic synaptic plasticity in the lateral amygdala and conditioned fear generalization, Neuropsychopharmacology 39 (2014) 2211–2220, https://doi.org/10.1038/npp.2014.72.

[75] C.S. Pinal, A.J. Tobin, Uniqueness and redundancy in GABA production., Perspect, Dev. Neurobiol. 5 (1998) 109–118.

[76] B. Chattopadhyaya, G. Di Cristo, C.Z. Wu, G. Knott, S. Kuhlman, Y. Fu, R. D. Palmiter, Z.J. Huang, GAD67-mediated GABA synthesis and signaling regulate inhibitory synaptic innervation in the visual cortex, Neuron 54 (2007) 889–903, https://doi.org/10.1016/j.neuron.2007.05.015.

[77] R. Druga, M. Salaj, A. Al-Redouan, Parvalbumin - positive neurons in the neocortex: a review, Physiol. Res. (2023) S173–S191. https://doi.org/10.33549/physiolres.935005.

[78] C.A. Villalobos, Q. Wu, P.H. Lee, P.J. May, M.A. Basso, Parvalbumin and GABA microcircuits in the mouse superior colliculus, Front. Neural Circuits 12 (2018), https://doi.org/10.3389/fncir.2018.00035.

[79] M. Zachari, I.G. Ganley, The mammalian ULK1 complex and autophagy initiation, Essays Biochem. 61 (2017) 585–596, https://doi.org/10.1042/EBC20170021.

[80] Z. Rong, K. Zheng, J. Chen, X. Jin, Function and regulation of ULK1: from physiology to pathology, Gene 840 (2022) 146772, https://doi.org/10.1016/j.gene.2022.146772.

[81] S.R. Bonam, J. Bayry, M.P. Tschan, S. Muller, Progress and challenges in the use of MAP1LC3 as a legitimate marker for measuring dynamic autophagy in vivo, Cells 9 (2020) 1321, https://doi.org/10.3390/cells9051321.

[82] Y. Chen, H. Yi, S. Liao, J. He, Y. Zhou, Y. Lei, LC3B: a microtubule-associated protein influences disease progression and prognosis, Cytokine Growth Factor Rev. 81 (2025) 16–26, https://doi.org/10.1016/j.cytogfr.2024.11.006.

[83] S. Tran, J. Juliani, T.J. Harris, M. Evangelista, J. Ratcliffe, S.L. Ellis, D. Baloyan, C.M. Reehorst, R. Nightingale, I.Y. Luk, L.J. Jenkins, S. Ghilas, M.H. Yakou, C. Inguanti, C. Johnson, M. Buchert, J.C. Lee, P. De Cruz, K. Duszyc, P.A. Gleeson, B.T. Kile, L.A. Mielke, A.S. Yap, J.M. Mariadason, W.D. Fairlie, E.F. Lee, BECLIN1 is essential for intestinal homeostasis involving autophagy-independent mechanisms through its function in endocytic trafficking, Commun. Biol. 7 (2024) 209, https://doi.org/10.1038/s42003-024-05890-7.

[84] K. Prerna, V.K. Dubey, Beclin1-mediated interplay between autophagy and apoptosis: New understanding, Int. J. Biol. Macromol. 204 (2022) 258–273, https://doi.org/10.1016/j.ijbiomac.2022.02.005.

[85] N. Chaudhry, M. Sica, S. Surabhi, D.S. Hernandez, A. Mesquita, A. Selimovic, A. Riaz, L. Lescat, H. Bai, G.C. MacIntosh, A. Jenny, Lamp1 mediates lipid transport, but is dispensable for autophagy in *Drosophila*, Autophagy 18 (2022) 2443–2458, https://doi.org/10.1080/15548627.2022.2038999.

[86] X.-T. Cheng, Y.-X. Xie, B. Zhou, N. Huang, T. Farfel-Becker, Z.-H. Sheng, Revisiting LAMP1 as a marker for degradative autophagy-lysosomal organelles in the nervous system, Autophagy 14 (2018) 1472–1474, https://doi.org/10.1080/15548627.2018.1482147.
[87] S.M. Man, T.-D. Kanneganti, Regulation of lysosomal dynamics and autophagy by CTSB/cathepsin B, Autophagy 12 (2016) 2504–2505, https://doi.org/10.1080/15548627.2016.1239679.
[88] R. Molteni, A. Cattaneo, F. Calabrese, F. Macchi, J.D.A. Olivier, G. Racagni, B. A. Ellenbroek, M. Gennarelli, M.A. Riva, Reduced function of the serotonin transporter is associated with decreased expression of BDNF in rodents as well as in humans, Neurobiol. Dis. 37 (2010) 747–755, https://doi.org/10.1016/j.nbd.2009.12.014.
[89] F. Calabrese, R. Molteni, A. Cattaneo, F. Macchi, G. Racagni, M. Gennarelli, B. A. Ellenbroek, M.A. Riva, Long-term duloxetine treatment normalizes altered brain-derived neurotrophic factor expression in serotonin transporter knockout rats through the modulation of specific neurotrophin isoforms, Mol. Pharmacol. 77 (2010) 846–853, https://doi.org/10.1124/mol.109.063081.
[90] A.L. Arzuaga, D.D. Edmison, J. Mroczek, J. Larson, M.E. Ragozzino, Prenatal stress and fluoxetine exposure in mice differentially affect repetitive behaviors and synaptic plasticity in adult male and female offspring, Behav. Brain Res. 436 (2023) 114114, https://doi.org/10.1016/j.bbr.2022.114114.
[91] W. Qiu, K.A. Go, Y. Wen, P. Duarte-Guterman, R.S. Eid, L.A.M. Galea, Maternal fluoxetine reduces hippocampal inflammation and neurogenesis in adult offspring with sex-specific effects of periadolescent oxytocin, Brain Behav. Immun. 97 (2021) 394–409, https://doi.org/10.1016/j.bbi.2021.06.012.
[92] F. Macchi, J.R. Homberg, F. Calabrese, C. Zecchillo, G. Racagni, M.A. Riva, R. Molteni, Altered inflammatory responsiveness in serotonin transporter mutant rats, J. Neuroinflammation 10 (2013) 883, https://doi.org/10.1186/1742-2094-10-116.
[93] K. Ishizuka, Y. Fujita, T. Kawabata, H. Kimura, Y. Iwayama, T. Inada, Y. Okahisa, J. Egawa, M. Usami, I. Kushima, Y. Uno, T. Okada, M. Ikeda, B. Aleksic, D. Mori, T. Someya, T. Yoshikawa, N. Iwata, H. Nakamura, T. Yamashita, N. Ozaki, Rare genetic variants in CX3CR1 and their contribution to the increased risk of schizophrenia and autism spectrum disorders, Transl, Psychiatry 7 (2017) e1184–e, https://doi.org/10.1038/tp.2017.173.
[94] Y. Zhan, R.C. Paolicelli, F. Sforazzini, L. Weinhard, G. Bolasco, F. Pagani, A. L. Vyssotski, A. Bifone, A. Gozzi, D. Ragozzino, C.T. Gross, Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior, Nat. Neurosci. 17 (2014) 400–406, https://doi.org/10.1038/nn.3641.
[95] A.I. da Silva, G.R.F. Braz, R. Silva-Filho, A.A. Pedroza, D.S. Ferreira, R. Manhães de Castro, C. Lagranha, Effect of fluoxetine treatment on mitochondrial bioenergetics in central and peripheral rat tissues, Appl. Physiol. Nutr. Metab. 40 (2015) 565–574, https://doi.org/10.1139/apnm-2014-0462.
[96] C. Liu, S. Hao, M. Zhu, Y. Wang, T. Zhang, Z. Yang, Maternal separation induces different autophagic responses in the hippocampus and prefrontal cortex of adult rats, Neuroscience 374 (2018) 287–294, https://doi.org/10.1016/j.neuroscience.2018.01.043.
[97] C. Wilson, J. Rogers, F. Chen, S. Li, P.A. Adlard, A.J. Hannan, T. Renoir, Exercise ameliorates aberrant synaptic plasticity without enhancing adult-born cell survival in the hippocampus of serotonin transporter knockout mice, Brain Struct. Funct. 226 (2021) 1991–1999, https://doi.org/10.1007/s00429-021-02283-y.
[98] C. Wilson, S. Li, A.J. Hannan, T. Renoir, Antidepressant-like effects of ketamine in a mouse model of serotonergic dysfunction, Neuropharmacology 168 (2020) 107998, https://doi.org/10.1016/j.neuropharm.2020.107998.
[99] M. Sadighi, L. Mai, Y. Xu, M. Boillot, G. Targa, F. Mottarlini, P. Brambilla, P. Gass, L. Caffino, F. Fumagalli, J.R. Homberg, Chronic exposure to imipramine induces a switch from depression-like to mania-like behavior in female serotonin transporter knockout rats: Role of BDNF signaling in the infralimbic cortex, J. Affect. Disord. 351 (2024) 128–142, https://doi.org/10.1016/j.jad.2024.01.186.
[100] M. Kuznetsova, C. Wilson, L. Cheng, T. Pang, S. Li, B.R. Roberts, L.C. Lago, H. Tran, A.F. Hill, A.J. Hannan, T. Renoir, Serotonergic-dependent effects of exercise and elevated stress hormone on small non-coding RNA transcriptomics and proteomics in a mouse model of affective disorders, Neuropharmacology 265 (2025) 110240, https://doi.org/10.1016/j.neuropharm.2024.110240.
[101] K. Roversi, C. Buizza, P. Brivio, F. Calabrese, M.M.M. Verheij, C.T.D. Antoniazzi, M.E. Burger, M.A. Riva, J.R. Homberg, Neonatal tactile stimulation alters behaviors in heterozygous serotonin transporter male rats: role of the amygdala, Front. Behav. Neurosci. 14 (2020), https://doi.org/10.3389/fnbeh.2020.00142.
[102] C.L. Kandilakis, C. Papatheodoropoulos, Serotonin modulation of dorsoventral hippocampus in physiology and schizophrenia, Int. J. Mol. Sci. 26 (2025) 7253, https://doi.org/10.3390/ijms26157253.