

# Effects of long-term tactile deprivation on anxiety-like behavior and c-Fos expression in elderly mice

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**Abstract:** Sensory impairments have been associated with cognitive decline and behavioral changes in aging populations. Early whisker removal in mice is a valuable model for studying tactile deprivation, as it relates to a primary sensory function of this species that parallels the loss of a primary sensory function in humans. While studies have explored the effects of auditory, visual, and olfactory deprivation, the impact of long-term tactile deprivation (LTD) on cognitive and emotional function in aging remains poorly understood. This study aimed to investigate the effects of LTD on anxiety-like behavior and neuronal activity in aged mice. Six-month-old male CD1 mice underwent permanent tactile deprivation by infraorbital nerve sectioning (LTD group) or simulated surgery (Sham group). Six months later, anxiety-like behaviors were assessed using the open field test and elevated plus maze. Following the behavioral testing, immunohistochemical analysis of c-Fos expression was performed in key regions involved in emotional and cognitive processing, including the basolateral amygdala (BLA), central amygdala (CeA), and hippocampal regions (CA1, CA3, and dentate gyrus). LTD mice exhibited increased anxiety-like behavior in the open field test. Additionally, LTD mice exhibit increased c-Fos expression in the amygdala and hippocampal subregions analyzed, indicating increased neuronal activation in these regions. These findings suggest that sensory deprivation may contribute to emotional dysregulation in aging.

**Keywords:** Whiskers; Aging; Amygdala; Hippocampus; Neuronal activity

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## 1.0 INTRODUCTION

Research indicates a significant association between sensory impairments and cognitive decline in older adults, with anxiety and depression being key mediating psychological factors in this relationship (Garnefski & Kraaij, 2012). Dual sensory impairment (DSI) is linked to increased odds of multiple-domain mild cognitive impairment (MCI) and reduced processing speed (Hu *et al.*, 2022), but also to a higher prevalence of emotional

problems, particularly symptoms of anxiety and depression (Liu *et al.*, 2023). Sensory processing abnormalities are common in individuals with MCI or dementia, potentially contributing to behavioral symptoms (Rhodus *et al.*, 2022). Notably, this correlation between sensory and cognitive function increases with age (Badache *et al.*, 2024). Anxiety and depression are among the most common yet frequently overlooked psychological health problems in older

adults, and are themselves strongly related to cognitive decline in this population ([Mao et al., 2025](#)). This relationship is often mediated by sensory impairment, as studies in humans have shown that auditory, visual, and dual sensory loss are all significantly associated with an increased risk of depressive and anxiety symptoms ([Simning et al., 2019](#)).

Sensory impairments, particularly in hearing, vision, and olfaction, are associated with cognitive decline and MCI in older adults. Olfactory dysfunction appears to be an early marker of cognitive decline ([MacDonald et al., 2018](#); [Schubert et al., 2017](#)), likely linked to neurodegeneration in participants with olfactory impairment who had lower volumes in the parahippocampal gyrus, orbitofrontal cortex, and entorhinal cortex ([Dintica et al., 2019](#)). Visual and hearing impairments are also linked to poorer cognitive performance, with dual sensory impairment showing a stronger association with multiple-domain MCI ([Schubert et al., 2017](#)). In auditory areas, evidence shows that hearing impairment is significantly associated with cognitive decline and lower volumes of the temporal cortex, hippocampus, amygdala, and orbitofrontal cortex. Additionally, an increase in the levels of the CSF t-tau protein has been observed ([Wang et al., 2022](#)).

Recent research suggests that reduced tactile sensitivity is related to MCI ([Löffler et al., 2024](#)). Sensory impairments in midlife are linked to subtle cognitive deficits, potentially indicating early brain aging ([Schubert et al., 2017](#)). A strong association between sensory impairment and cognitive decline has been observed in both human and animal studies. Hearing and vision loss are linked to accelerated cognitive decline, an increased risk of dementia, and earlier onset of neurodegenerative phenotypes in animal models ([Paciello et al., 2021](#); [2023](#)), exacerbating cognitive decline and involving areas such as the hippocampus.

The mechanism involving sensory deprivation, anxiety, and cognitive decline remains unclear. In this regard, it is necessary to explore this connection in the context of long-term deprivation. Early whisker removal in rats induces reorganization of thalamic receptive fields that disrupts normal thalamic development ([Nicolelis et al., 1997](#)). These changes persist into adulthood, with deprived animals showing abnormal receptive fields, a reduced ability to discriminate tactile stimuli ([Nicolelis et al., 1997](#)), and increased anxiety-like behaviors ([Ibarra-Castaneda et al., 2025](#)). On the other hand, positive tactile stimulation during development can

enhance neuroplasticity in the prefrontal cortex and amygdala ([Richards et al., 2012](#)), which are regions implicated in emotional regulation and anxiety.

Anxiety-like behaviors have emerged as a potential predictor of cognitive decline in murine models ([Samaey et al., 2019](#)), as they are associated with structural and functional changes in brain regions such as the prefrontal cortex, hippocampus, and amygdala ([Leuner & Shors, 2013](#)). Despite these findings, the mechanisms underlying tactile deprivation in older mice, particularly its impact on anxiety-like behaviors and cognitive decline, remain largely unexplored. This study aims to evaluate the effects of long-term tactile deprivation on anxiety-like behaviors and c-Fos expression in the amygdala and hippocampus of aging mouse brains. This research is essential for advancing the understanding of the relationship between sensory deprivation, cognitive decline, and anxiety-like behaviors in aging populations using a preclinical rodent model. These findings could inform the development of early diagnostic tools and targeted interventions to reduce the impact of sensory loss on cognitive health and emotional well-being.

## 2.0 MATERIALS AND METHODS

### 2.1 Animals

Six-month-old CD1 male mice were randomly assigned to either the control (sham-operated) or tactile-deprived (TD) group and subjected to the sectioning of the infraorbital nerve. All mice were housed under standard laboratory conditions, including polycarbonate cages (28 x 12 x 15 cm) at room temperature (24 ± 1°C) with relative humidity (40%-60%). All experimental procedures adhered to the legal regulations for the care of laboratory animals (Mexican Official Norm 062-ZOO-1999) and were approved by the Committee of Animal Care and Use at the University of Colima.

### 2.2 Tactile deprivation

On day P180 (**Figure 1B**), permanent tactile deprivation was done by sectioning the infraorbital nerve, which transmits vibrissal information to the brain ([Ibarra-Castañeda et al., 2022](#)). Mice were anesthetized via intraperitoneal injection with ketamine (80 mg/kg; Anesket, PiSA) and xylazine (10 mg/kg; Procin, PiSA). In the absence of a stimulus response, a 5-mm incision was made between the eye and the vibrissal pad, followed by the dissection of the facial muscles layer by layer until the infraorbital nerve was located. The nerves were transected transversely, and the proximal and distal stumps were retracted. A 3mm-thick piece of Gelfoam™ (Pfizer, #31201) was placed between the stumps to

prevent reconnection. Finally, the surgical wound was closed using Vetbond3M™ (Minnesota, USA, #1469C), and the rodent was placed in a thermal recovery chamber. The procedure was conducted under a surgical microscope (OPMI Vario/S88, Carl Zeiss, Germany). Sham-operated animals underwent a similar surgical procedure without the sectioning of the infraorbital nerve (**Figure 1B**).

### 2.3 Open-field test

Six months after tactile deprivation, we employed the open-field test (OFT) for evaluating anxiety-like behaviors (**Figure 1A**) ([Seibenhener & Wooten, 2015](#)), which consists of a polycarbonate chamber with dimensions of 40 × 40 × 40 cm (length, width, height), illuminated centrally by a bright light. Each mouse was introduced to the center of the arena and allowed to explore freely for 5 minutes. Behavioral data were captured and analyzed automatically using a video image motion analysis system (Ethovision, Noldus Technology, USA), measuring total distance traveled (cm), mobility time (s), and locomotor speed (cm/s).

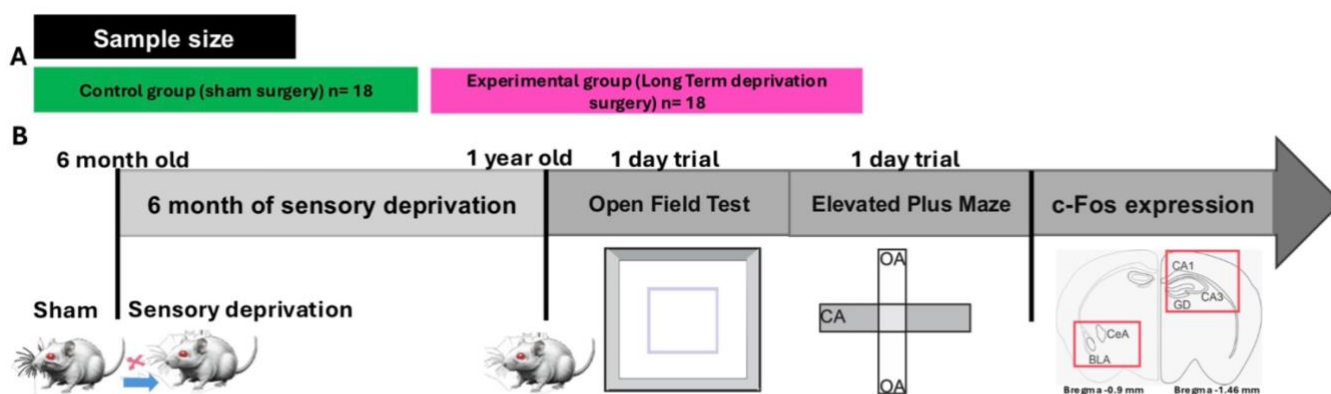
### 2.4 Elevated plus maze

Six months after tactile deprivation, we used the elevated plus maze (EPM), which is a widely utilized behavioral assay for assessing rodent anxiety-like behaviors ([Komada et al., 2008](#)). This apparatus has two

open arms (35 × 5 cm), illuminated with a cold-light source set at 250 lux, intersecting perpendicularly with two enclosed arms (35 × 5 × 16 cm) at a central square platform (5 × 5 cm). Rodents were acclimated to the testing room for 30 minutes, then placed on the central platform, facing one of the closed arms, and allowed to explore freely for 5 minutes. Data were analyzed using EthoVision, and the parameters assessed included the percentage of entries into the open arms relative to the total number of arm entries and the time spent in the open arms. Increased time spent in the open arms indicates lower anxiety levels ([Komada et al., 2008](#)).

### 2.5 Tissue processing

The animals were sacrificed on day P360. Before euthanasia, mice were anesthetized by intraperitoneal injection with sodium pentobarbital (50 mg/kg). Transcardial perfusion was performed with 0.9% NaCl, followed by 4% paraformaldehyde in 0.1 M phosphate buffer (PBS), with overnight post-fixation and storage in 0.1 M PBS plus 0.01% sodium azide at 4°C. Then, 30- $\mu$ m-thick coronal sections were obtained using a vibratome, spanning anterior-posterior coordinates from -0.94 to 1.70 mm relative to Bregma for the central Basolateral Amygdala (CeA) of the amygdala and -3.08 to 3.40 mm for the dorsal hippocampus ([Paxinos & Franklin, 2001](#)). For systematic sampling, sections were serially collected at 200- $\mu$ m intervals across the entire brain.



**Figure 1: Experimental design and timeline.** (A) Random assignment of experimental groups: Sham (green) and LTD (pink). (B) Timeline diagram: Surgery for sensory deprivation was conducted early in the life of the mice (within the first six months). Behavioral testing—specifically the Open Field Test (OFT) and the Elevated Plus Maze (EPM)—was performed in a single session when the animals reached one year of age (six months post-surgery). Following the behavior assessment, c-Fos expression was quantified in the hippocampus and amygdala.

## 2.6 Immunohistochemistry

We processed the brain tissues to label c-Fos. Brain sections were processed in parallel for each immunostaining procedure to ensure consistency. The sections were rinsed thrice for 10 minutes each in 0.1 M PBS. Endogenous peroxidase activity was quenched by incubating the sections in 3% hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) for 30 minutes, then rinsing with 0.1M PBS. The sections were then incubated for 1 hour at room temperature in 0.1 M PBS containing 0.1% Triton X-100 and 10% fetal bovine serum. Subsequently, sections were incubated overnight at 4°C with a primary rabbit IgG anti-c-Fos antibody (1:800, Cell Signaling Technology, #2250S) in a blocking solution. The following day, sections were rinsed and incubated for 60 minutes at room temperature with secondary biotinylated antibody (1:200, goat anti-rabbit, AbD Serotec, #401008). The sections were rinsed and incubated for 45 minutes with avidin-biotin complex (Vectastain Elite ABC Kit, Vector Laboratories, USA, #PK-6101). Immunoreactivity was visualized at room temperature in a 0.03% diaminobenzidine (DAB) solution containing 0.05% nickel ammonium sulfate (Sigma-Aldrich, #261890 and #574988). Brain sections were mounted on glass slides and covered with DPX mounting medium (Aldrich, #06522).

## 2.7 Quantification

We utilized 40X magnification (field area = 0.15 mm<sup>2</sup>) to examine c-Fos expression in the amygdala and the cornu ammonis region 1 (CA1), region 3 (CA3), and dentate gyrus (DG) of the hippocampus. We analyzed ten consecutive 30- $\mu$ m brain sections, selected in series interspaced at 200- $\mu$ m intervals, from each subject (n = 5 animals per group). These sections span from anterior-posterior coordinates -0.9 to -1.94 mm relative to Bregma. This approach was utilized for cell counting in the basolateral (BLA), central amygdala (CeA), and hippocampus (CA1, CA3, and DG). We quantified only the immunolabeled cells present within the same focal plane. The focal plane was established at the midpoint of each tissue section using the microscope's computerized Z-axis positioning function. All imaging and histological analyses were conducted with a Zeiss Axio-Observer D1 microscope (Göttingen, Germany) and Axio-Vision 4.8.1 imaging software (Göttingen, Germany) by a researcher blinded to group assignments.

## 2.8 Statistical analysis

The normality of the data distribution was assessed using the Shapiro-Wilk test, while heteroscedasticity was evaluated with the F-test for unequal variances. We

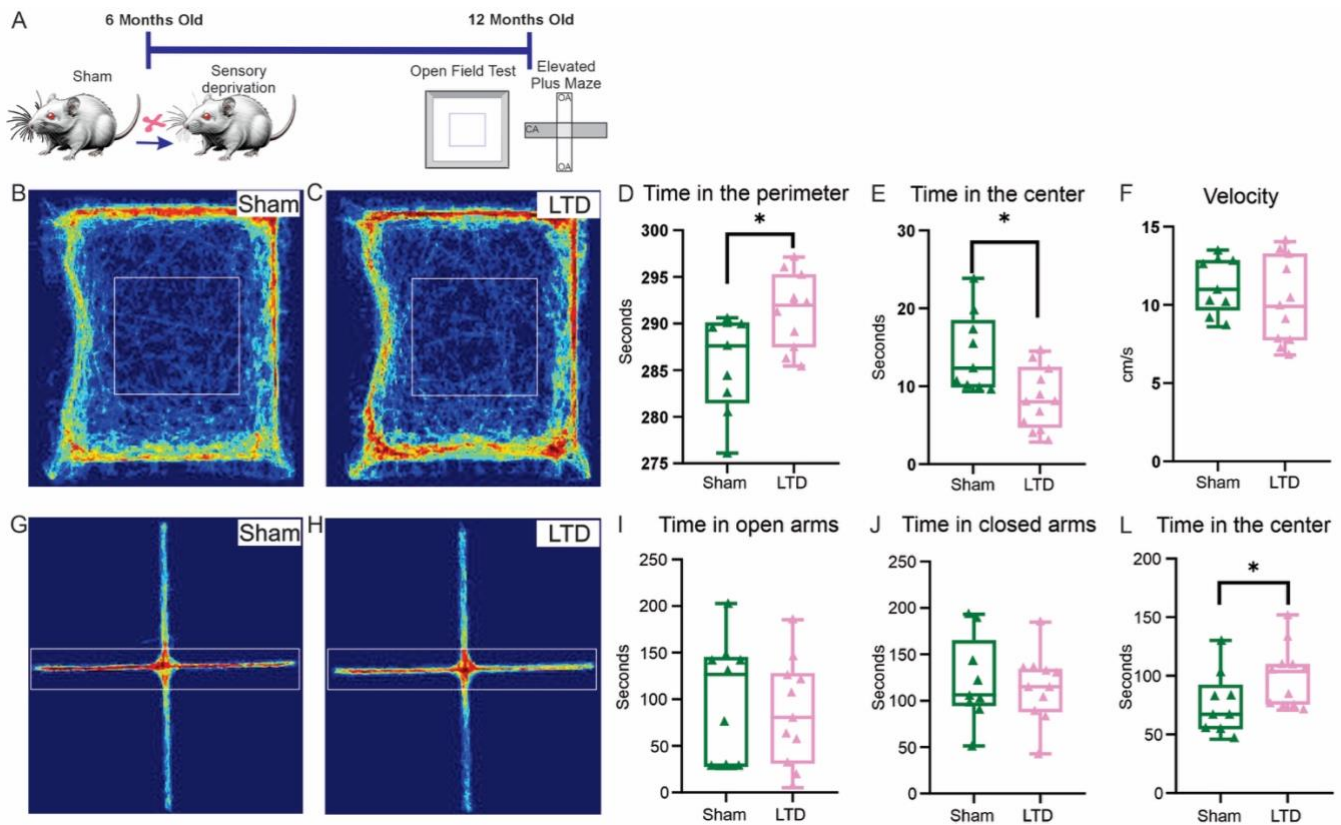
found that the data are not normally distributed; therefore, the data are presented as the median (Md) and interquartile range (IQR). The Mann-Whitney U test was employed to determine statistically significant differences between groups. A confidence level of 95% ( $p \leq 0.05$ ) was used to determine statistical significance. Prism V8 (GraphPad) software was used for data analysis and graph plotting.

## 3.0 RESULTS

### 3.1 LTD modulates anxiety-like behaviors

To investigate anxiety-like behavior and changes in neuronal processes after six months of tactile deprivation in old mice (12-month-old), both OFT and the EPM were conducted. Subsequently, the animals were sacrificed, and the number of c-Fos-positive cells in the hippocampus and amygdala was quantified (**Figure 2A**). In the OFT, exploratory behavior and anxiety levels were assessed by measuring the time each mouse spent in the center and periphery (**Figure 2B-F**). The LTD group spent more time in the periphery (**Figure 2D**, LTD group, Md = 292.6s, IQR = 287.5–295.3) than the Sham group (Md = 287.6s, IQR = 281.5–290.1; U = 19; P = 0.02), and less time spent in the center compared to the LTD group (**Figure 2E**, Sham group, Md = 12.35s, IQR = 9.845–18.52 vs. LTD group, Md = 8.010s, IQR = 4.670–12.51; U = 19; P = 0.02). The velocities between groups were not significantly different (**Figure 2F**; Sham group = 10.9 cm/s, IQR = 9.6–12.8; LTD = 9.9 cm/s, IQR = 7.7–13.3, U = 38, P = 0.41).

In the EPM, we assessed anxiety-like behaviors linked to narrow and open spaces. All mice were placed in the center of the maze and allowed to move freely. We quantified the time each mouse spent in each arm and the center (**Figure 2G-L**). The time spent in open arms did not show a significant difference between the LTD and sham group (**Figure 2L**; Sham group; Md = 126.8s, IQR = 27.45–145.5 vs. LTD group Md = 80.58s, IQR = 30.70–128; U = 41; P = 0.5516). Consistently, no statistically significant differences were observed in the closed arms between the groups (**Figure 2J**; Sham group; Md = 106.4s, IQR = 94.33–165.4 vs. LTD group; Md = 115.1s, IQR = 87.58–134.5; U = 48; P = 0.9408). In contrast, the time spent in the center showed significant differences between the groups (**Figure 2L**; Sham; Md = 67.23s, IQR = 54.44–92.51 vs. LTD group, Md = 103.8s, IQR = 75.38–110.3; U = 22; P = 0.03). Altogether, these results suggest that mice with long-term deprivation exhibit increased anxiety-related behaviors and a propensity for risk-taking compared to controls.



**Figure 2: Anxiety-like behaviors were evaluated by the Open Field Maze (OFM) and Elevated Plus Maze (EPM).** (A) Study design showing the timeline of experimental procedures. 6-month-old mice underwent sensory deprivation and were kept for 6 months under housing conditions. After the OFT and EPM were conducted, all mice were sacrificed for tissue processing. (B-C) OFM thermal image processing, the red area represents where the subjects spent more time, and the blue area where the subjects spent less time. (D) Time (s) spent in the perimeter and (E) time (s) spent in the center of the OFM. (F) Median velocity (cm/s) from the sham and LTD groups during the test. (G-H) In thermal image processing in EPM, closed arms of the EPM are enclosed by white rectangles. (I) Time (s) spent in the open arms. (J) Time (s) spent in the closed arms. (K) Time (s) spent in the center. The data are shown as the medians and IQR (1-3). \* $p > 0.05$ ; Mann-Whitney U test.

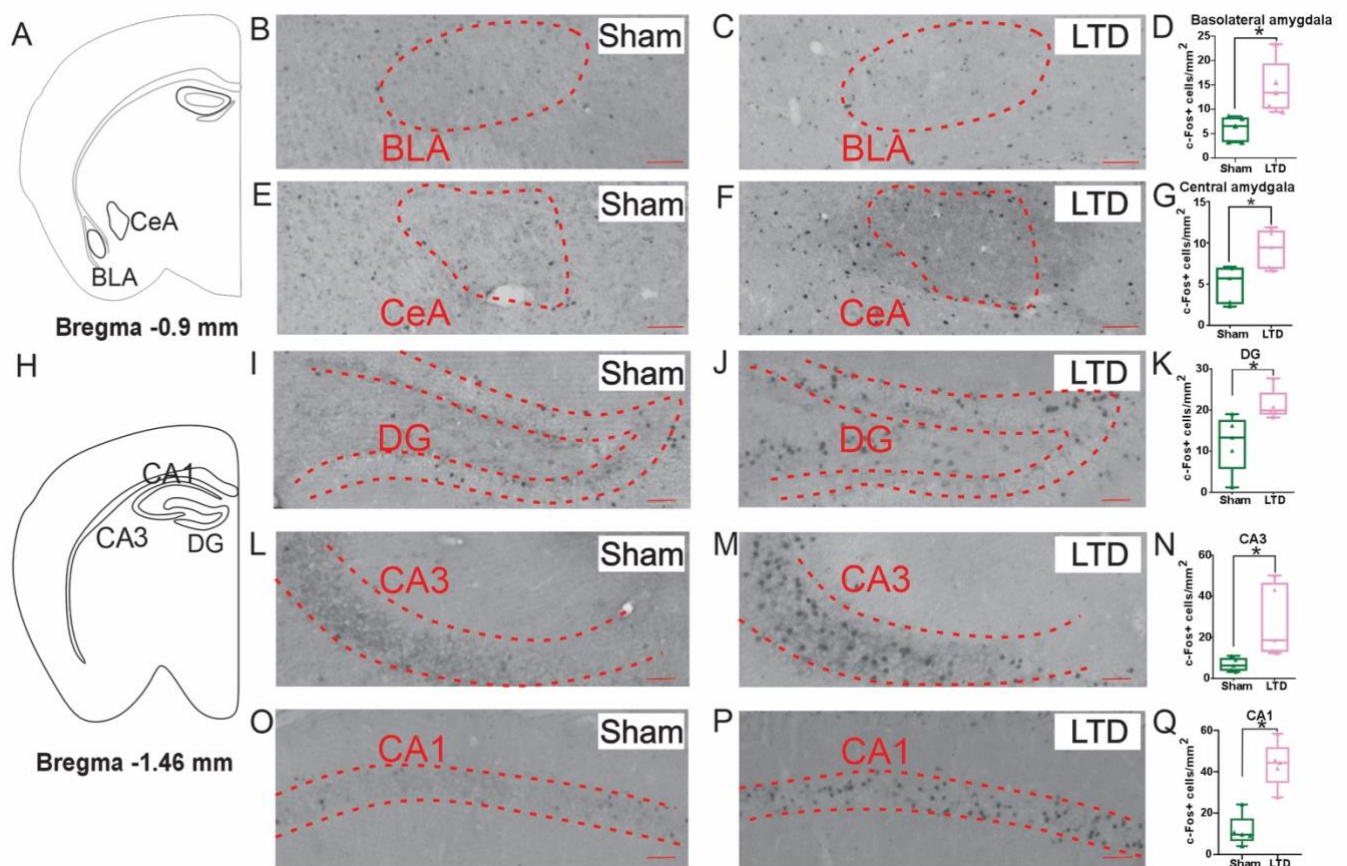
### 3.2 LTD modulates c-Fos expression in cognitive and emotional processing brain areas

Then, the effects of tactile deprivation on anxiety-related mechanisms in older mice were further investigated by examining c-Fos expression in brain structures associated with cognitive and emotional processing, specifically the hippocampus and amygdala. The c-Fos expression in the basolateral amygdala (BLA) was quantified. Surprisingly, the LTD has more c-Fos+ cells (Figure 3A-D; Md = 13.4 cells, IQR = 10.06-19.44) than the control group (Md = 6.5 cells, IQR = 3.2-8.3,  $U = 0$ ,  $P = 0.007$ ).

The central amygdala (CeA) is critical for fear learning and modulates passive and active defensive responses. The majority of CeA neurons project to brainstem and hypothalamic structures, mediating endocrine, autonomic, motor, and emotional responses. In this area, similar results were observed (Figure 3E-G); the

LTD group has more c-Fos+ cells (Md = 9.4 cells, IQR = 6.8-11.5) than the sham group (Md = 5.7 cells, IQR = 2.5-6.9,  $U = 2.5$ ,  $P = 0.03$ ).

In the hippocampal region, a key structure for long-term memory consolidation, spatial memory formation, and navigation, the dentate gyrus showed a significant increase in c-Fos cells in the LTD group (Figure 3H-K; Md = 19.9 cells, IQR = 18.8-24.2) compared to the Sham group (Md = 13.3 cells, IQR = 5.6-17.6,  $U = 1$ ,  $P = 0.01$ ). Similarly, in the CA3 region, the LTD group exhibited higher c-Fos expression (Figure 3L-N; Md = 18.6 cells, IQR = 12.9-46.6) compared to the control group (Md = 6.3 cells, IQR = 3.7-10,  $U = 0$ ,  $P = 0.00$ ). In the CA1 region, the LTD group also showed significantly higher values (Figure 3O-Q; Md = 44.3 cells, IQR = 34.6-51.9) compared to the Sham group (Md = 9.6 cells, IQR = 6.5-17.4;  $U = 0$ ;  $P = 0.0079$ ).



**Figure 3: c-Fos expressing cells in the basolateral (BLA), central amygdala (CeA), and dentate gyrus (DG), CA3, and CA1 regions of the hippocampus.** (A) Representative coronal section of the basolateral amygdala (CeA) area squared in red. (B-C) Immunostaining for c-Fos (black dots) in the BLA and the (D) median number of c-Fos+ cells. (E) Representative coronal section of the central amygdala (CeA), squared in red. (F-G) Immunostaining for C-Fos (Black dots) in the CeA and the median number of c-Fos + cells. (H) Representative coronal section of the DG region of the hippocampus. (I-J) Immunostaining for c-Fos in the DG of the Sham and LTD groups. (K) Quantification of c-Fos + cells in the DG. (L-M) Immunostaining for c-Fos in CA3. (N) Quantification of C-Fos + cells in CA3. (O-P) Immunostaining for c-Fos in the CA1 of the Sham and LTD groups. (Q) Quantification of c-Fos+ cells in the CA1. Scale bars = 50µm. The data are shown as the medians and IQR (1-3). \*p > 0.05; Mann-Whitney U test.

#### 4.0 DISCUSSION

This study investigated the age-related changes upon long-term tactile deprivation and its effects on anxiety and c-Fos expression. Older mice with tactile LTD exhibited more anxiety-like behavior in the open field test. While no significant differences were found between open and closed arms in the EPM, the group spent more time in the center than the sham group. Surprisingly, the LTD group showed more c-Fos protein expression in the hippocampus and amygdala.

Aging is associated with a wide range of cognitive and learning deficits in both humans and nonhuman animals. The OFT is commonly used to assess locomotor activity and anxiety-like behaviors in aging mice

(Figueiredo Cerqueira et al., 2023). A previous study reported age-related decreases in the OFT activity across different mouse strains (Liao et al., 2024; Shoji et al., 2016; Shoji & Miyakawa, 2019). In our study, the LTD group spent significantly less time in the center of the arena, an indicator of anxiety, while spending more time in the periphery, which may indicate a preference for safer, less exposed areas (Seibenhener & Wooten, 2015). Several mechanisms may motivate this exploratory behavior, including reactions to novelty, surprise, and curiosity (Prut & Belzung, 2003). An alternative explanation for this type of behavior is that the OFT is a stressful environment for the animal where its escape is prevented by surrounding walls, or, in the

case of the tactile LTD, maybe the mice feel safe due to the contact with the body of the walls.

The EPM is based on the natural aversion of mice to open and elevated spaces, alongside their innate curiosity to explore a novel environment. A reduced time spent and the number of entries into the open arms are used as indices of anxiety ([Komada et al., 2008](#)). In our case, the mice spent more time in the central area. Some studies have suggested that this measure represents impulsivity ([Rico et al., 2017](#)). Recent research has explored its application in aging studies, revealing that the characteristics of the apparatus can significantly influence test outcomes in older mice ([Gaspar et al., 2023](#)). Thus, our findings, supported by previous studies, suggest that anxiety-like behavior tends to decrease with age ([Ferreira et al., 2023](#)). Previous studies indicate that sensory deprivation induced by whisker loss can disrupt emotional processing and promote anxiety responses in rodents ([Ibarra-Castaneda et al., 2025](#)). Together, these data support the hypothesis that long-term deprivation of the whisker system in mice induces a state of increased anxiety and risk-taking behaviors, likely due to altered sensory integration and modulation of neural circuits involved in fear and anxiety. This knowledge could aid in developing more targeted and effective treatments for anxiety and related disorders in older populations.

In this study, we investigated the impact of tactile deprivation on c-Fos expression in key brain regions involved in cognition and emotion, the amygdala and hippocampus, in older mice. Our results show significant increases in c-Fos expression in the basolateral and central amygdala of LTD mice compared with the sham group. These findings suggest that LTD may lead to elevated neuronal activity within the amygdala, potentially contributing to altered emotional processing and anxiety-like behaviors ([Truitt et al., 2009](#)), as well as the fear learning-activated neurons in the anterior BLA that contribute to anxiety-like behaviors ([Hammack et al., 2023](#)).

Furthermore, we observed a significant increase in c-Fos expression in the dentate gyrus, CA3, and CA1 regions of the hippocampus in the LTD group. These findings are consistent with previous studies showing that sensory deprivation can induce significant neuroplastic changes in the hippocampus, affecting both synaptic and intrinsic plasticity. Studies have shown that whisker

deprivation for 9 days in young mice can lead to decreased activity of CA3 pyramidal neurons, altered synaptic facilitation, and changes in AMPA and NMDA receptor expression ([Milshtein-Parush et al., 2017](#)). Whisker trimming at different postnatal ages induced a decrease in dendritic spine density. This reduction was accompanied by a highly significant decrease in dendritic spine head diameter ([Briner et al., 2010](#)). In this context, the brain's adaptive response to sensory loss involves cross-modal plasticity, where deprived areas are recruited by other sensory modalities ([Mohan & Vanneste, 2017](#)).

Aging is a complex process that causes significant structural and physiological changes in the brain, often resulting in behavioral impairments and increased occurrence of neuropsychiatric and neurodegenerative disorders. Our results indicated elevated c-Fos expression in the amygdala and hippocampus of LTD mice, suggesting that these brain regions may be particularly susceptible to the effects of sensory deprivation. These findings have important implications for understanding the impact of sensory limitations on brain function and behavior in aging populations, particularly those experiencing sensory impairments such as vision or hearing loss.

## 5.0 CONCLUSIONS

Long-term tactile deprivation induces anxiety-like behaviors and increases c-Fos expression in the hippocampus and central and basolateral amygdala, brain regions essential for emotional regulation and cognitive function. These findings suggest that sensory deprivation disrupts neural circuitry, contributing to increased anxiety behaviors and altered neuronal activity. Therefore, this study highlights the long-term effects of sensory impairments, such as tactile deprivation, and underscores their potential role in the pathophysiology of mild cognitive decline in aging.

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**Author Contributions:** G.M.A. performed the experiments and analysed the data; G.M.A., D.Z.L., V.L.V. and O.G.P. edited the manuscript; G.M.A. and V.L.V. wrote the original draft; D.Z.L., O.G.P. and V.L.V. reviewed the manuscript; V.L.V. and O.G.P. conceived and designed the experiments.

**Conflict of Interest:** The authors declare no conflict of interest.

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