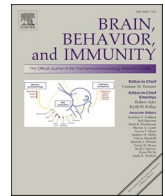


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Chronic low-grade hippocampal inflammation blunts exercise-induced neurogenesis and alters the exercise-induced microglia transcriptome in the rat hippocampus

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ABSTRACT

Chronic low-grade neuroinflammation contributes to *inflammaging* by compromising hippocampal plasticity, with interleukin-1 β (IL-1 β) as a key mediator. The extent to which sustained hippocampal inflammation can interfere with the potential beneficial effects of exercise on plasticity and hippocampus-related behaviour remains unclear. Here we combined bilateral hippocampal IL-1 β overexpression (IL-1 β -OE), to mimic chronic low-grade neuroinflammation with voluntary wheel running, to mimic human exercise training, in adult male Sprague-Dawley rats. We assessed effects on multiple dorsal hippocampal-related behaviours, adult hippocampal neurogenesis, microglial reactivity, and immune cell infiltration. Hippocampal IL-1 β -OE impaired pattern separation, independent of exercise training, and attenuated exercise-induced increases in neurogenesis in the dorsal hippocampus. Hippocampal IL-1 β -OE promoted microglial lipid-droplet accumulation, which exercise paradoxically exacerbated. Transcriptomic profiling revealed that exercise in combination with hippocampal IL-1 β -OE enriched immune and leukocyte trafficking pathways in microglia, while hippocampal IL-1 β -OE alone increased hippocampal CD8⁺ T cell infiltration. These findings indicate that chronic hippocampal inflammation alters microglial and neurogenic responses to exercise, suggesting that inflammatory status critically influences exercise efficacy in supporting hippocampal plasticity.

1. Introduction

A chronic, low-grade inflammatory state called “*inflammaging*” (Franceschi et al., 2018) contributes to the vulnerability of the ageing brain, to the development of neurodegenerative disease (Heneka et al., 2014) and to psychiatric disorders such as depression (Dantzer et al., 2008; Troubat et al., 2021; Zunszain et al., 2013). The hippocampus, a brain region critical for learning, memory and emotion regulation, is particularly sensitive to inflammatory changes (Ekdahl et al., 2003; Monje et al., 2003).

Among the key mediators of neuroinflammation and “*inflammaging*”

is the cytokine interleukin-1 β (IL-1 β), which is increased in the aged rat brain (Martin et al., 2002). Elevated IL-1 β can disrupt the balance between neuroplasticity and neurodegeneration, thereby altering brain function (Goshen et al., 2007; Hueston et al., 2018; Kohman and Rhodes, 2013; Pawley et al., 2020). While physiological levels of IL-1 β are required for hippocampal-dependent cognition (Yirmiya et al., 2002), chronic elevation has been shown to induce deficits in hippocampal-dependent behaviours (Belloy et al., 2025; Goshen et al., 2007; Hueston et al., 2018) and long-term potentiation (LTP) (Bellinger et al., 1993; Kelly et al., 2001; Murray and Lynch, 1998) in rodents. Besides changes in synaptic physiology, IL-1 β also reshapes the neurogenic niche. Long-

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term hippocampal overexpression of IL-1 β in rodents reduces adult hippocampal neurogenesis (AHN) (Hueston et al., 2018; Pawley et al., 2020; Wu et al., 2012). This unique form of plasticity throughout life, is critical for several hippocampal functions, including for pattern separation, the capacity to distinguishing between similar memories (Clelland et al., 2009; Sahay et al., 2011). Notably, chronic low-grade IL-1 β impairs pattern separation, but not other hippocampal-dependent behaviours (Hueston et al., 2018), suggesting that neurogenesis-associated tasks may be more sensitive to inflammatory manipulations than other cognitive tests.

In the healthy brain, microglia are key players in the resolution of inflammation as they serve as immune surveillants (Nimmerjahn et al., 2005) by regulating circuit refinement through synaptic pruning (Paolicelli et al., 2011; Schafer et al., 2012), supporting plasticity (Parkhurst et al., 2013), and maintaining the neurogenic niche by phagocytosing excess newborn neurons (Diaz-Aparicio et al., 2020; Sierra et al., 2010). With age and chronic inflammation, microglia can adopt dysfunctional states (Costa et al., 2021), including lipid-droplet-accumulating microglia (LDAM), which are characterized by impaired phagocytosis and increased pro-inflammatory output (Marschallinger et al., 2020). Microglial alterations are poised to disrupt the neurogenic niche and may disrupt the pro-neurogenic impact of modifiable lifestyle factors such as exercise (Abbink et al., 2017; Naylor et al., 2008).

Physical exercise is a potent, non-pharmacological modulator of brain plasticity. In rodents, voluntary running enhances AHN and memory (O'Leary et al., 2019; Van Praag et al., 1999), while in humans, aerobic exercise increases hippocampal volume and improves memory, effects that are more evident in elderly subjects (Firth et al., 2018; Kaiser et al., 2021; Kandola et al., 2016). Exercise-induced increases in AHN are often most pronounced in the dorsal hippocampus, where newly generated granule cells preferentially contribute to cognitive processes such as pattern separation (Clelland et al., 2009; Sahay et al., 2011; Snyder et al., 2009). This may be due to the functional specialization along the hippocampal longitudinal axis where the dorsal hippocampus primarily mediates spatial learning and cognition, whereas the ventral hippocampus is more prominently involved in anxiety-related and affective behaviours (Bannerman et al., 2004; Fanselow and Dong, 2010; Huckleberry et al., 2018; Levine et al., 2021). Mechanistically, exercise stimulates the release of circulating factors known as 'exerkines', bioactive molecules produced in response to physical activity that can influence brain function (Chow et al., 2022). However, the beneficial effects of exercise are not absolute and may depend on an individual's inflammatory status. For example, in certain (neuro)inflammatory conditions such as long COVID in humans (Appelman et al., 2024), exercise may even exacerbate symptoms. This highlights the complex interaction between exercise and neuroinflammation.

Despite extensive evidence that exercise promotes hippocampal plasticity, it remains unclear whether benefits persist when the hippocampus itself harbours a sustained, low-grade inflammatory state, as opposed to the acute or systemic inflammation modelled in earlier work (Littlefield et al., 2015; Wu et al., 2007). To address this gap with translational relevance, we administered bilateral lentiviral overexpression of full-length murine IL-1 β in the dorsal hippocampus of adult male rats (IL-1 β –OE) and concurrently allowed them voluntary access to running wheels. We investigated whether chronic hippocampal inflammation reshapes (i) hippocampus-dependent behaviour with a particular focus on neurogenesis-sensitive tasks such as pattern separation, (ii) adult hippocampal neurogenesis along the dorso-ventral axis, (iii) microglial morphology and lipid-droplet accumulation, (iv) the hippocampal microglia-specific transcriptome obtained from CD11b⁺-sorted cells, and (v) hippocampal CD8⁺ T-cell infiltration. This integrated approach tests the hypothesis that the efficacy of exercise depends on the neuroinflammatory state.

2. Methods

2.1. Animals and experimental design

All animal procedures were performed under authorizations (#AE19130/P149) issued by the Health Products Regulatory Authority (HPRA, Ireland), in accordance with the European Communities Council Directive (2010/63/EU) and approved by the Animal Experimentation Ethics Committee of University College Cork. Young-adult (8-week-old) male Sprague-Dawley rats were purchased from Janvier (France) and maintained on a 12-h:12-h light:dark cycle (lights on at 07:00 h) at 22 $\pm$ 1°C, with *ad libitum* access to standard chow (Teklad 2018, protein 18.4%, Fat 6%, 3.1 kcal/g) and water. All procedures started after a 2-week acclimatization period. Two independent cohorts of 10-week-old Sprague Dawley rats received bilateral stereotaxic injection of FLAG-tagged lentivirus to overexpress IL-1 β (LV^{IL-1 β}), or a scrambled control (LV^{SCR}) into the dorsal hippocampus. One week later, rats were allowed access to a vertical stainless-steel running wheel (Activity wheel 33 cm $\varnothing$, Tecniplast, UK), or not. Rats were pair-housed and randomly assigned to an experimental group as follows: sedentary and LV^{SCR} "Sed. Scr", sedentary and LV^{IL-1 β} "Sed.IL-1 β ", voluntary running and LV^{SCR} "Ex.Scr", and voluntary running and LV^{IL-1 β} "Ex.IL-1 β " (Fig. 1A; 2A). The first cohort of rats [Scr (n = 10), IL-1 β (n = 12), Ex.Scr (n = 10), Ex.IL-1 β (n = 12)] underwent behavioural testing to assess anxiety- and depression-related behaviours. The second cohort [Scr (n = 10), IL-1 β (n = 12), Ex.Scr (n = 10), Ex.IL-1 β (n = 12)] underwent behavioural testing to assess cognition-related behaviours.

2.2. Stereotaxic surgery and lentiviral injection

Lentiviral constructs were based on a HIV backbone encoding the full-length murine IL-1 β open reading frame (accession NM_008361.3) or empty control vector, both under a CMV promoter and including a FLAG tag driven by an IRES element. Vectors were purchased from Genecopoeia (LV^{SCR}: #ULP-NEG-Lv101-A00 and LV^{IL-1 β} : #ULP-Mm03282-Lv101-A00), with titres exceeding 1 $\times$ 10¹⁰ TU/mL. All surgical procedures were conducted under aseptic conditions. Rats were anaesthetised with isoflurane/O₂ (2–3% for induction, 1–3% for maintenance), and anaesthetic depth was confirmed by the loss of toe-pinch reflex. Animals were placed in a stereotaxic frame, and local anaesthesia (EMLA cream and 0.5% bupivacaine) was applied to the scalp and ear bars. LV^{SCR} or LV^{IL-1 β} vector were injected bilaterally in the dorsal hippocampus at coordinates: AP – 3.5 mm, ML $\pm$ 2.4 mm, DV – 3.8 mm relative to Bregma. A total volume of 3 μ L at a rate of 1 μ L/min was injected per site, followed by a 5 min diffusion period. The incision was then sutured, and the wound treated with iodine and local anaesthesia. For postoperative analgesia, Meloxicam (Metacam® 1 mg/kg in 5 mg/mL) was administered subcutaneously at the end of the surgery and continuously via drinking water (5 mg/mL) until 3 days post-surgery. Rats were allowed to recover for a week after the surgery, before being placed in their respective experimental condition, with or without a running wheel.

2.3. Behaviours

Rats from both cohorts underwent behavioural testing starting 24 days following initiation of exercise. Rats from cohort 1 (Fig. 1A) underwent the openfield test (OFT), the elevated plus maze (EPM) test, female urine sniffing test (FUST) and the forced swim test (FST). Rats in the cohort 2 (Fig. 2A) were tested in the modified spontaneous location recognition (MSLR) test, the spontaneous alternation in the Y-maze, the novelty suppressed feeding (NSF) test and the Morris water maze (MWM). For each behavioural test, rats were singly housed (the same cage for each rat was used for the duration of the study) and acclimated to the behavioural testing room at least 45 min prior to each test. All behavioural tests were conducted during the light phase (8:30am to

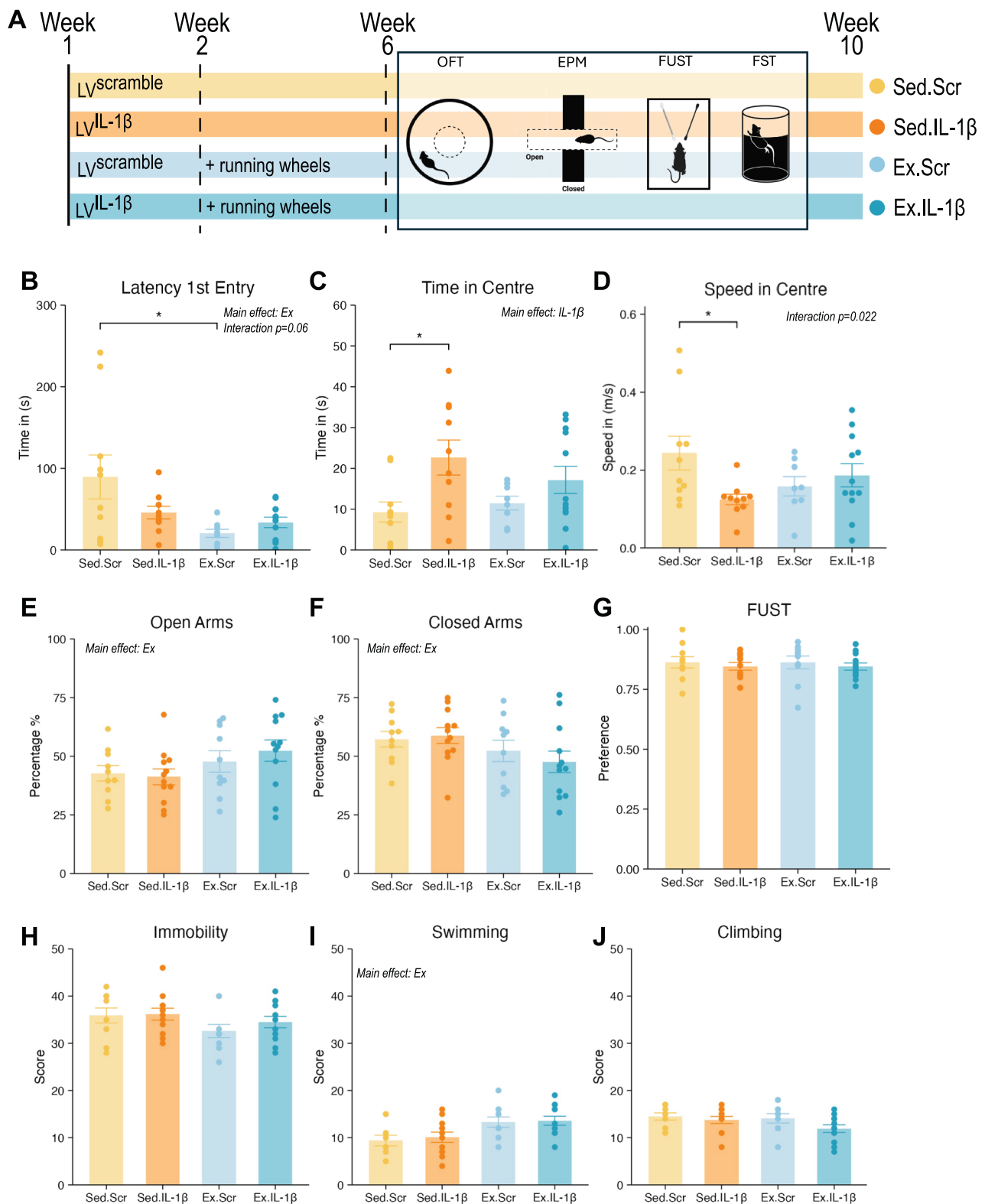


Fig. 1. Differential effect of exercise and IL-1 β on anxiety- and depressive related behaviours A) Experimental timeline. All rats were pair housed and received stereotaxic surgery to overexpress IL-1 β (LVIL-1 β) or not (LVscramble). A week after the recovery from the surgery, rats were separated into 4 experimental groups; sedentary with LVscramble (Sed.Scr), sedentary with LVIL-1 β (Sed.IL-1 β) or had continuous access to a running wheel with LVscramble (Ex.Scr) or exercise with LVIL-1 β (Ex.IL-1 β). Mood-associated behavioural testing commenced after 24 days of exercise. Exercise continued throughout testing for a total of 8 weeks. B) Latency to 1st enter the centre in the OFT. C) Time spent and D) speed in centre of the OFT. Percentage of time spent in E) the open arms and F) the closed arms in the EPM. G) Percentage preference for urine in the FUST. H) Immobility, I) Swimming and J) Climbing scores in the FST. Data are expressed as mean $\pm$ SEM. Following posthoc comparisons all p value < 0.08 are reported, * $p < 0.05$ vs corresponding control.

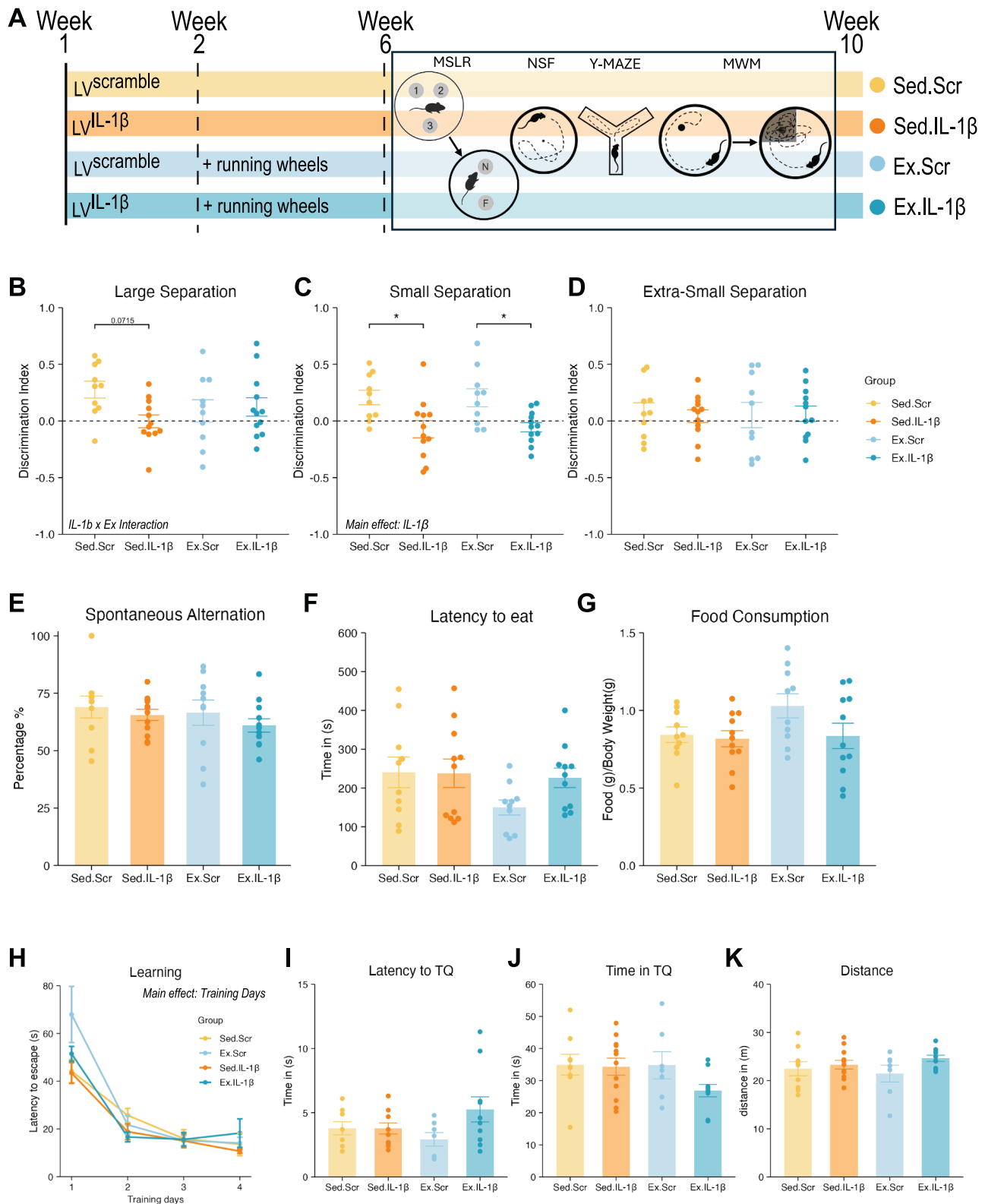


Fig. 2. IL-1 β overexpression induced an impairment in pattern separation, while exercise had no effect. A) Experimental timeline. All rats were pair housed and received a lentivirus overexpressing IL-1 β (LVIL-1 β) or not (LVscramble). A week after surgery, rats were separated into 4 experimental groups; sedentary with LVscramble (Sed.Scr), sedentary with LVIL-1 β (Sed.IL-1 β) or had continuous access to a running wheel with LVscramble (Ex.Scr) or exercise with LVIL-1 β (Ex.IL-1 β). Cognitive associated behavioural testing commenced after 24 days of exercise. Exercise continued throughout testing for a total of 8 weeks. Discrimination ratio in the B) large separation, C) small separation and D) extra-small separation tasks of the MSLR. E) Spontaneous alternation in the Y-Maze. F) Latency to eat in the NSF and G) Food consumption 30 min post NSF test. H) Learning in the MWM measured as latency to escape over the 4 training days. I) Latency to the target quadrant (TQ), J) Time spent swimming in TQ and K) distance swam during the probe trial of MWM. Data are presented as mean $\pm$ SEM. Following posthoc comparisons all p value < 0.08 are reported, * $p < 0.05$ vs corresponding control.

5:30 pm). All apparatus and objects were cleaned with an ethanol (70% and 30% respectively) solution between exposure of each animal to remove odour cues. Behaviours were scored live in a blinded fashion or by using automated software (AnyMaze Stoelting, Europe). Detailed methods for each behavioural test are described in the [supplementary material](#) section.

2.4. Tissue collection and post-mortem analysis

At week 10, rats were euthanized (between 9:30am–1 pm) with an injection of pentobarbital (150 mg/kg; i.p.); blood was collected by cardiac puncture; spleen and adipose tissue dissected; and rats were transcardially perfused either with ice-cold Hanks' Balanced Salt Solution (HBSS) without calcium and magnesium (Sigma #H6648) supplemented with 1 mM ethylene-diamine tetra-acetic acid (EDTA) (ThermoFisher Scientific #AM9261) for microglial magnetic sorting, or with saline followed by 4% (v/v) paraformaldehyde (#30525-89-4; Fisher) for immunohistochemical (IHC) analysis. Blood samples were collected into EDTA tubes and centrifuged (15 min, 5000 rpm).

2.5. Isolation of hippocampal microglia

Microglial cells were isolated from rat hippocampus using a slightly modified protocol from (Bordt et al., 2020). After HBSS perfusion, hippocampi were rapidly dissected, weighed and minced with sterile razor blades on ice, and enzymatically digested in 5 mL of HBSS containing 2 mg/mL Collagenase A (Sigma #COLLA-RO), 28 U/mL DNase I (Millipore Sigma #10104159001), 10 mM HEPES (Thermo Fisher Scientific #15630080) and 5% foetal bovine serum (Sigma #F9665) for 15 min at 37°C. Tissue was mechanically dissociated to a single-cell suspension using a glass pasteur pipette. The suspension was next filtered through 70 µm nylon cell strainers (Miltenyi Biotec #130-098-462), centrifuged (300g, 10 min, 4°C), and debris was removed using Debris Removal Solution (Miltenyi Biotec #130-109-398). Cells were resuspended in 900 µL of cold Debris Removal Solution and overlaid with 4 mL of ice-cold PBS to create a visible gradient, followed by centrifugation at $\geq 3000g$ for 10 min at 4°C. After removing the upper layers, cells were washed in PBS and centrifuged (1,000g, 10 min, 4°C). The pellet was then incubated with CD11b Rat MicroBeads (Miltenyi Biotec #130-105-634) in MACS buffer (PBS with 1 mM EDTA and 1% BSA), and CD11b⁺ microglia were isolated using magnetic LS columns (Miltenyi Biotec #130-042-401) and a QuadroMACS separator (Miltenyi Biotec #30-090-976). Isolated microglia were centrifuged and a fraction was saved for cell quantification. Cells were then washed and subsequently used for RNA extraction.

2.6. RNA extraction and RNA sequencing of hippocampal microglia

2.6.1. RNA preparation and sequencing

RNA was extracted from magnetic sorted microglia using RNeasy Micro Kit (Qiagen #74004) following manufacturer instructions. PolyA⁺ RNA was sequenced by Illumina NovaSeq 150 bp paired-end sequencing at a depth of 20–30 million reads (Genewiz, Azenta Life Sciences, Germany).

2.6.2. RNAseq analysis

See [supplementary materials](#) for detailed methods on the bioinformatics analysis of the RNAseq data.

2.7. Immunohistochemistry

After PFA perfusion, brains were extracted and postfixed for 24 h in 4% PFA, cryoprotected in 30% sucrose and subsequently flash frozen. Brains were coronally sectioned (40 µm) in a 1:12 series through the hippocampus and preserved in an anti-freeze solution at –20°C before processing. For each analysis, an average of 8–10 sections were stained

per rat (approximately 5–6 dorsal and 3–4 ventral sections). The dorsal hippocampus was defined as AP: Bregma – 2.2 to – 5.2 and ventral hippocampus as AP: – 5.2 to – 6.7. All sections were brought to room temperature for 15 min and washed 3 times in PBS before staining. See [supplementary material](#) and methods for details on staining, imaging and quantification.

2.8. Statistical analysis

All statistical analyses were performed in R studio (Version 2025.05.1 + 513). All the statistical results are compiled in [Supplementary table 1](#). Data were first tested for outliers using the Grubbs-outlier test and normality using the Shapiro–Wilk test. For normally distributed data a two-way ANOVA was conducted with Exercise and IL-1β as main factors. When a significant main effect or interaction was detected, Tukey post-hoc test was used for pairwise comparisons. For non-normally distributed data, a Kruskal–Wallis test was performed, followed by Dunn's multiple comparisons test with Bonferroni correction for multiple testing. Spatial learning in the MWM and running distance were analysed using a repeated measures ANOVA with Time as the within-subject factor, and Group as the between-subject factor. All data are presented as individual datapoints and as mean ± SEM unless indicated otherwise. A significance threshold of $p < 0.05$ was applied for all analyses, with trends reported for $p < 0.08$. Data were graphed using the Tidyplot package on R (Engler, 2025).

3. Results

3.1. Differential effects of hippocampal IL-1β-OE and exercise on anxiety- and depression-related behaviours

Increased IL-1β expression in the hippocampus was confirmed after IL-1β-OE with lentivirus ([Supp Fig. 1](#)). Running distance was reduced by IL-1β-OE ($F(1,20) = 8.63$, $p = 0.008$) from week 3 onwards ([Supp Fig. 2A](#)). We next assessed anxiety-like and depression-like behaviours in the OFT, EPM, FUST and FST ([Fig. 1A](#)). In the OFT, there was no effect of hippocampal IL-1β-OE but exercise significantly affected the latency to enter the centre ($F(1,36) = 7.21$, $p = 0.011$), and a trend toward an exercise × IL-1β interaction ($F(1,36) = 3.76$, $p = 0.06$) was observed. Post-hoc analysis showed that Ex.Scr rats entered the centre zone faster than Sed.Scr rats ($p = 0.016$, [Fig. 1B](#)). For the time spent in the centre, a main effect of IL-1β ($F(1,36) = 8.50$, $p = 0.006$) was observed, with Sed. IL-1β rats spending more time in the centre than Sed.Scr rats ($p = 0.031$, [Fig. 1C](#)). The speed of rats in the centre zone was not affected by exercise or IL-1β but there was a significant exercise × IL-1β interaction ($F(1,36) = 5.686$, $p = 0.022$). Posthoc analysis showed that Sed.IL-1β rats moved significantly slower in the centre than Sed.Scr ($p = 0.043$, [Fig. 1D](#)). The total distance travelled and speed in the whole apparatus did not differ between groups ([Supp Fig. 3A–B](#)). In the EPM, two-way ANOVA analysis revealed a main effect of exercise on overall exploration of the maze. Exercised rats spent significantly more time in the open arms than sedentary one ($F(1,40) = 4.34$, $p = 0.044$). In contrast, IL-1β-OE and the exercise × IL-1β interaction had no significant effect on open-arm exploration ([Fig. 1E](#)). A similar pattern was observed for percent time spent in the closed arms, where exercise again showed a significant main effect ($F(1,40) = 4.34$, $p = 0.044$) but neither IL-1β nor the interaction reached significance ([Fig. 1F](#)). In the FUST, no effects of exercise nor IL-1β were found on the preference for female urine odour, indicating no changes in hedonic behaviour ([Fig. 1G](#)). In the FST, no main effects of IL-1β were observed on immobility and swimming behaviours. However, there was a trend toward a main effect of exercise on immobility ($F(1,40) = 3.19$, $p = 0.08$), with exercising rats tending to be less immobile ([Fig. 1H](#)). Similarly, exercise significantly increased swimming behaviour ($F(1,40) = 12.02$, $p = 0.001$). Post-hoc comparisons revealed a tendency toward increased swimming in both Ex.Scr and Ex.IL-1β rats compared with their sedentary counterparts (both $p = 0.08$, [Fig. 1I](#)).

Climbing behaviour was not affected by either of the interventions (Fig. 1J). Taken together, these results suggest that exercise exerts modest anxiolytic in the OFT and EPM while IL-1 β -OE primarily affects locomotor activity rather than anxiety or depressive-like behaviours.

3.2. Hippocampal IL-1 β -OE, but not exercise, impairs pattern separation

Both hippocampal neurogenesis-dependent and -independent behaviours were assessed for cognitive function (Fig. 2A). In the large separation paradigm of the MSLR, which assesses spatial location memory with a low cognitive load, no main effects of exercise or IL-1 β -OE were observed but a trend toward an exercise $\times$ IL-1 β interaction ($F(1,40) = 4.04, p = 0.051$) was evident. Post-hoc analysis showed that Sed.IL-1 β rats had a reduced discrimination performance compared to Sed.Scr ($p = 0.07$, Fig. 2B). In the small separation condition, which

assesses pattern separation and has a higher cognitive load, IL-1 β but not exercise or their interaction significantly affected rats performance ($F(1,40) = 16.45, p = 0.0002$). IL-1 β -OE significantly reduced the discrimination index in both Sed.IL-1 β ($p = 0.025$) and Ex.IL-1 β ($p = 0.042$) rats (Fig. 2C). In the extra-small separation condition which has the highest cognitive load, no main effect of either intervention nor their interaction was observed (Fig. 2D). In the Y-maze, neither IL-1 β -OE nor exercise significantly affected spontaneous alternation behaviour (Fig. 2E). Similarly, in the NSF, neither exercise nor IL-1 β significantly influenced the latency to feed and subsequent food consumption (Fig. 2F-G). In the MWM, repeated-measures ANOVA revealed a main effect of training day ($F(3,102) = 67.95, p < 0.0001$), confirming successful learning during the acquisition phase (Fig. 2H). In the probe test, no significant effects of exercise, IL-1 β nor their interaction were found for latency to enter or time spent in the target quadrant (Fig. 2I-J).

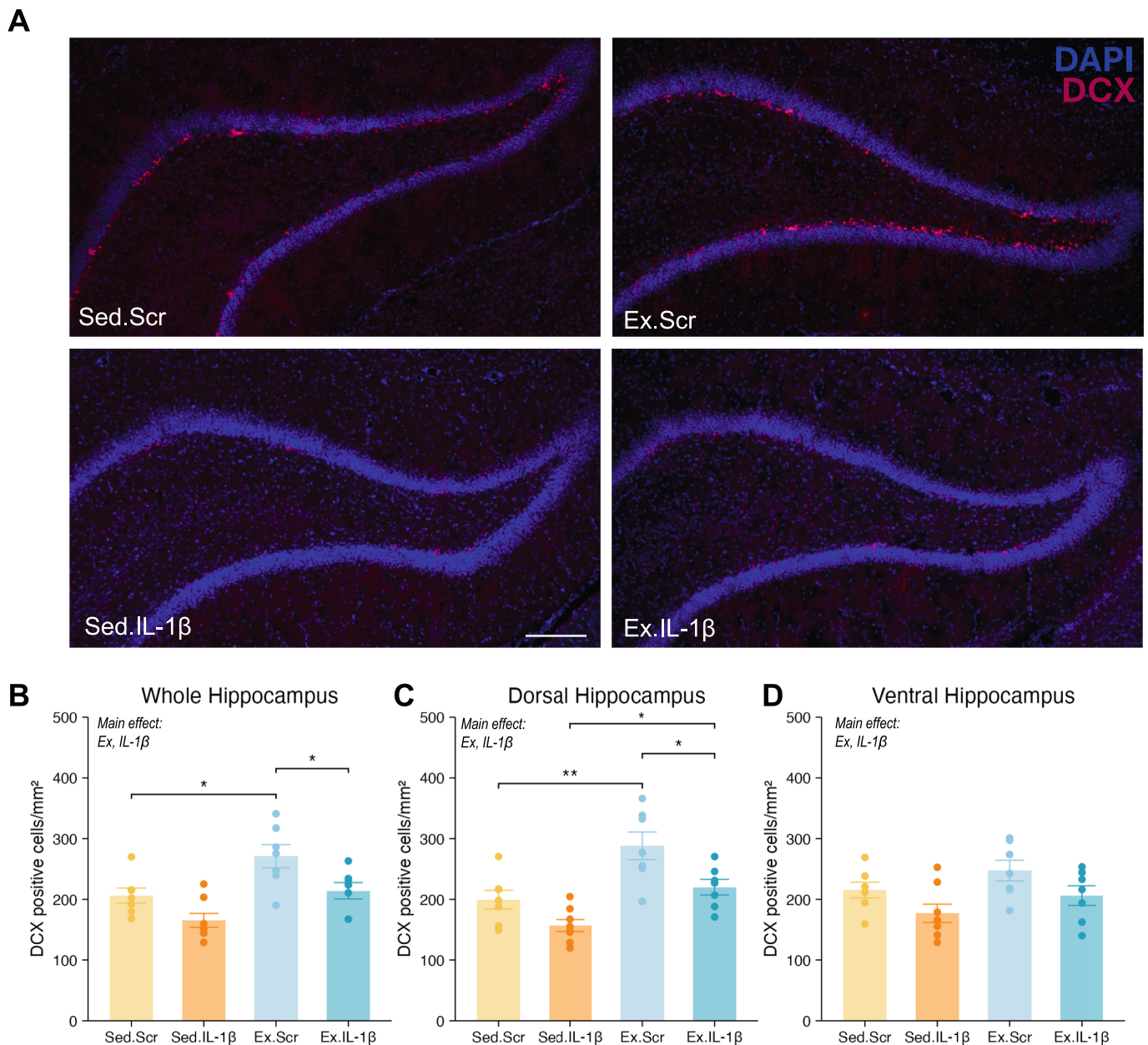


Fig. 3. IL-1 β overexpression attenuates exercise-induced hippocampal neurogenesis A) Representative images (10X) of DCX + staining in the dentate gyrus of the hippocampus. Scale bar = 200 μ m. Immunohistochemical measurement of newly born immature neurons (DCX + cells per mm^2) through B) the whole, C) dorsal and D) ventral hippocampus. Data are presented as mean $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$ vs corresponding control.

During the probe trial, the total distance swam did not differ between groups, indicating that rats did not differ in their swimming ability (Fig. 2K). Together, these results indicate that hippocampal IL-1 β -OE selectively impairs pattern separation without affecting spatial learning, and that voluntary exercise had no effect on hippocampal-dependent cognitive behaviours.

3.3. IL-1 β overexpression attenuates exercise-induced hippocampal neurogenesis

Because of the effects of IL-1 β -OE on neurogenesis-associated behaviour we quantified immature newly born neurons in the dentate gyrus across the longitudinal axis of the hippocampus by staining DCX + cells (Fig. 3A). In the whole hippocampus (wHi), two-way ANOVA revealed significant main effects of both exercise ($F(1,25) = 16.61$, $p = 0.0004$) and IL-1 β ($F(1,25) = 11.59$, $p = 0.002$), with no significant interaction between the two factors. Post-hoc analysis indicated a significant increase in the number of DCX-positive cells in Ex.Scr ($p = 0.02$), but not in Ex.IL-1 β ($p = 0.093$) compared to their sedentary counterparts. Interestingly, Ex.IL-1 β rats had a reduced number of DCX-positive cells compared to Ex.Scr ($p = 0.0473$, Fig. 3B). The effects observed in the wHi appear to be driven by changes in the dorsal hippocampus (dHi). Specifically, exercise ($F(1,25) = 24.53$, $p < 0.0001$) and IL-1 β ($F(1,25) = 12.32$, $p = 0.002$), but not their interaction, significantly affected the number of DCX + cells in the dHi. Exercise increased DCX + cell numbers in Ex.Scr ($p = 0.003$) and Ex.IL-1 β animals ($p = 0.036$), but to a lesser extent. The number of DCX-positive cells were significantly lower in Ex.IL-1 β compared to Ex.Scr ($p = 0.027$) rats, indicating that IL-1 β attenuated the pro-neurogenic effects of exercise (Fig. 3C). In the ventral hippocampus (vHi), both exercise ($F(1,25) = 4.28$, $p = 0.049$) and IL-1 β ($F(1,25) = 6.61$, $p = 0.017$) exerted significant main effects on the number of DCX + cells, but no statistically significant interaction nor post hoc comparisons were found (Fig. 3D).

3.4. IL-1 β and exercise interactions influence microglial morphology and lipid droplet accumulation

Given that microglia are key mediators of neuroinflammation, we assessed microglial density and morphology in the hippocampus by staining for Iba1 (Fig. 4A). In the wHi, Kruskal–Wallis testing revealed a significant overall difference in microglial numbers between groups ($\chi^2(3) = 10.52$, $p = 0.015$). Post-hoc analysis showed that exercise significantly reduced microglial cell counts in IL-1 β -OE rats ($p = 0.036$) (Fig. 4B). In the dHi, the Kruskal–Wallis test also highlighted significant group differences ($\chi^2(3) = 8.68$, $p = 0.0339$) but *post hoc* testing did not reveal any significant difference between groups (Fig. 4C). In the vHi, two-way ANOVA revealed a main effect of exercise ($F(1,26) = 4.34$, $p = 0.047$), with no significant effect of IL-1 β nor their interaction (Fig. 4D). The Kruskal–Wallis test showed a significant overall effect on microglial soma size in the wHi ($\chi^2(3) = 13.46$, $p = 0.004$). Post-hoc comparisons showed that Sed.IL-1 β rats had larger soma size compared to Sed.Scr ($p = 0.035$, Fig. 4E). In the dHi, a significant overall effect was detected ($\chi^2(3) = 9.76$, $p = 0.021$), with a trend towards enlarged soma in Sed.IL-1 β compared with Sed.Scr rats ($p = 0.069$, Fig. 4F). In the vHi, two-way ANOVA revealed a significant main effect of IL-1 β ($F(1,26) = 9.23$, $p = 0.005$) on soma size, with no significant effect of exercise nor their interaction. Post hoc testing did not reveal any significant difference between groups (Fig. 4G). Microglial lipid droplet (LD) accumulation represents a hallmark of metabolic dysregulation that both reflects and promotes neuroinflammatory states. Thus, we tested whether IL-1 β -OE could promote LD accumulation in microglia (Fig. 4H). In the wHi, two-way ANOVA analysis revealed a significant main effect of IL-1 β ($F(1,26) = 11.54$, $p = 0.002$), but no main effect of exercise nor their interaction. Post-hoc analysis showed a higher percentage of Iba1 $^{+}$ microglia containing lipid droplets per field of view in Ex.IL-1 β rats ($p = 0.006$, Fig. 4I). A similar pattern was observed in the dHi, where IL-1 β exerted a

significant main effect ($F(1,26) = 13.49$, $p = 0.001$), again increasing the percentage of LD-containing-microglia in Ex.IL-1 β rats ($p = 0.0044$, Fig. 4J). In the vHi, there was also a main effect of IL-1 β on lipid droplet accumulation ($F(1,26) = 4.93$, $p = 0.0354$), with a trend toward significance in Ex.IL-1 β rats compared with Ex.Scr ($p = 0.055$, Fig. 4K). These results suggests that IL-1 β -OE promotes microglial reactivity, reflected by increased soma size and lipid accumulation. While exercise reduced microglial number and partially normalised soma size, it paradoxically exacerbated LD-accumulation in IL-1 β rats.

3.5. IL-1 β overexpression blunts the microglial transcriptomic response to exercise

We next analysed the transcriptome landscape of microglia obtained by magnetic-activated cell sorting of CD11b $^{+}$ cells from the hippocampus. The main effect of exercise was evident in six differentially expressed genes (DEGs) at a Benjamini–Hochberg false discovery rate (FDR) < 0.05 (Fig. 5A). This included the up-regulation of *Trem3* ($\beta = 0.97$, FDR = 0.034), a rodent-specific paralogue of the microglial marker *Trem2*. The effect of exercise was dependent on viral vector group, as no DEGs emerged in the IL-1 β group alone (Fig. 5B), while 26 DEGs passed FDR correction in the control (Scr) group (Fig. 5C). In the control group, exercise downregulated *Cxcr3* ($\beta = -1.3$, FDR = 0.034), a chemokine receptor involved in microglial recruitment, and upregulated *Fgf10* ($\beta = 1.6$, FDR = 0.014), which has been reported to inhibit pro-inflammatory microglial signalling (Fig. 5C). This difference in DEGs (Fig. 5B–C) suggests that IL-1 β -driven inflammation may have blunted the transcriptional responsiveness of microglia to exercise at the individual gene level. Interestingly, IL-1 β -OE alone did not yield any significant DEGs when compared with controls (Supp figure S4A), and in exercising conditions (Supp figure S4B). Only two transcripts were differentially expressed in the sedentary control comparison: *Ppp1r13l* ($\beta = -0.32$, FDR = 0.0094), a predicted gene, and *AC124874.1* ($\beta = 0.52$, FDR = 0.0027), which lacks RefSeq annotation (Supp figure S4C). We next assessed whether coordinated transcriptional changes might emerge at the pathway level. To this end, Gene Set Enrichment Analysis (GSEA) was performed using the Gene Ontology (GO) database, applying *p*-value-weighted fold changes for all protein-coding genes. Interestingly, at the pathway levels the main effects of exercise were across both groups (Fig. 5D left panel) contrasting with the effects observed at the gene level (Fig. 5A). Interestingly, exercise in the IL-1 β group produced the strongest enrichment of GO terms (Fig. 5D right panel; Table 1), contrasting with the minimal effects observed at the single-gene level (Fig. 5B). The majority of enriched pathways were associated with immune responses, leukocyte trafficking, cell killing, and ribosomal function. Examination of enrichment score profiles for GO terms containing “cytokine”, “immune”, or “leukocyte” keywords revealed consistent up-regulation by exercise in the IL-1 β group (Fig. 5E), corroborating the overall GSEA findings (Fig. 5D, right panel). Plotting the weighted fold changes for genes within these pathways identified *Trem3* as the top contributor across all immune- and leukocyte-related terms (Fig. 5F). Other recurrently up-regulated genes included *Trem1* and *Chga* (Chromogranin A), the latter known to promote microglial activation. Collectively, these findings suggest that while IL-1 β -OE suppresses exercise-induced transcriptional changes in microglia at the individual gene level, the combination of exercise and IL-1 β is associated with activation of immune and leukocyte-associated molecular programmes in hippocampal microglia.

3.6. IL-1 β overexpression induce CD8 $^{+}$ T cell recruitment in the hippocampus independently of exercise

To determine whether the transcriptomic changes in the microglia reflect increased peripheral immune recruitment, we examined CD8 $^{+}$ T cell infiltration in the hippocampus. CD8 $^{+}$ T cells are regulators of neuroimmune interactions (Reel et al., 2024). Microglia have recently

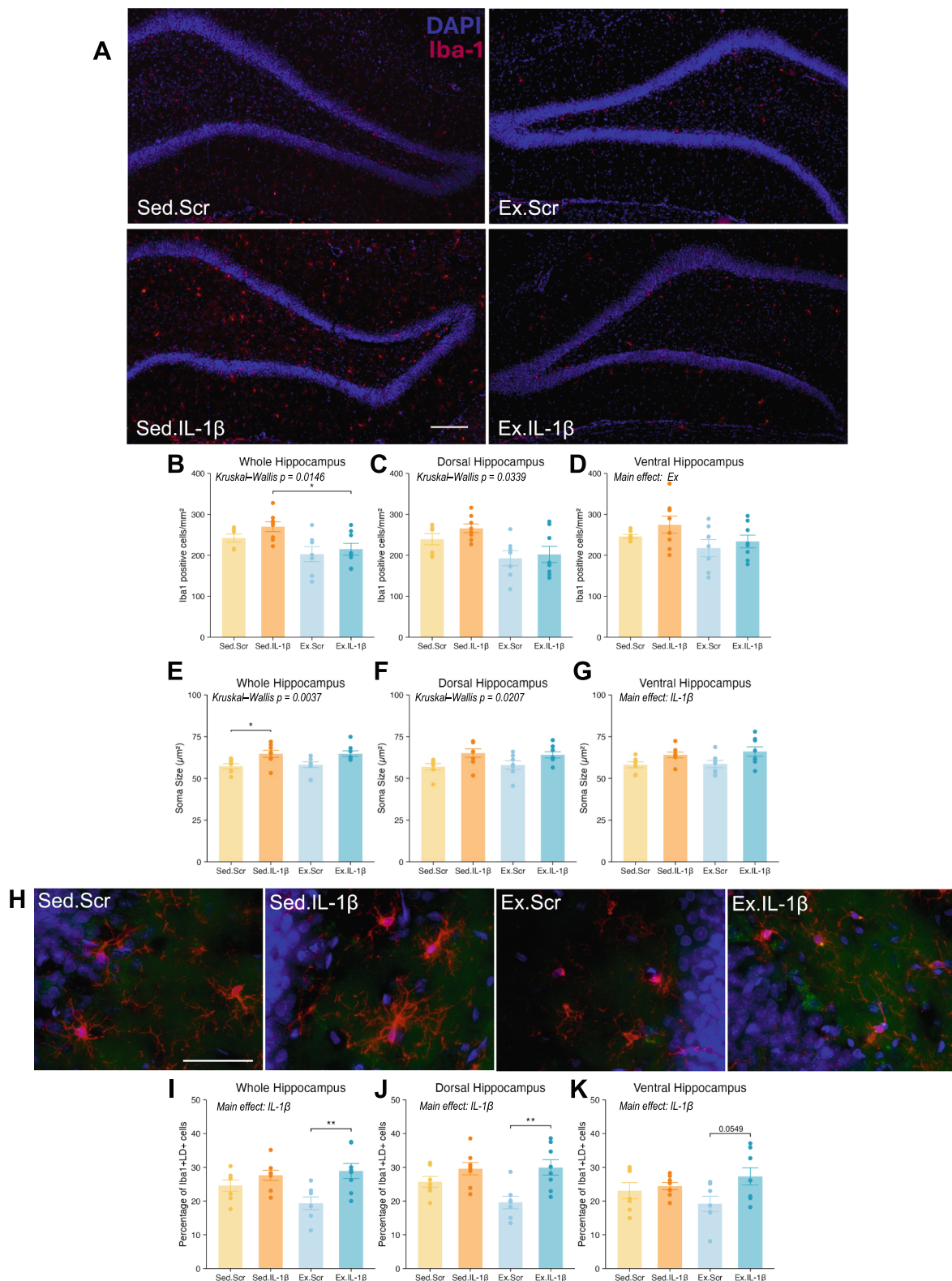


Fig. 4. IL-1 β and exercise interactions influence microglial morphology and lipid droplet accumulation A) Representative images (10X) of Iba1+ staining in the dentate gyrus area of the hippocampus. Scale bar = 200 μ m. Immunohistochemical measurements of microglia (Iba1 + cells per mm²) through B) the whole, C) dorsal and D) ventral hippocampus. Microglia soma size (μ m²) in E) the whole hippocampus and in the F) dorsal and G) ventral regions. H) Representative images (40X) of Iba1+ and lipid droplet staining in the dentate gyrus area. Scale bar = 50 μ m. Percentage of microglia containing lipid droplet per field of view in I) the whole hippocampus and in the J) dorsal and K) ventral regions. Data are presented as mean $\pm$ SEM. All p value < 0.08 are reported, *p < 0.05, **p < 0.01 vs corresponding control.

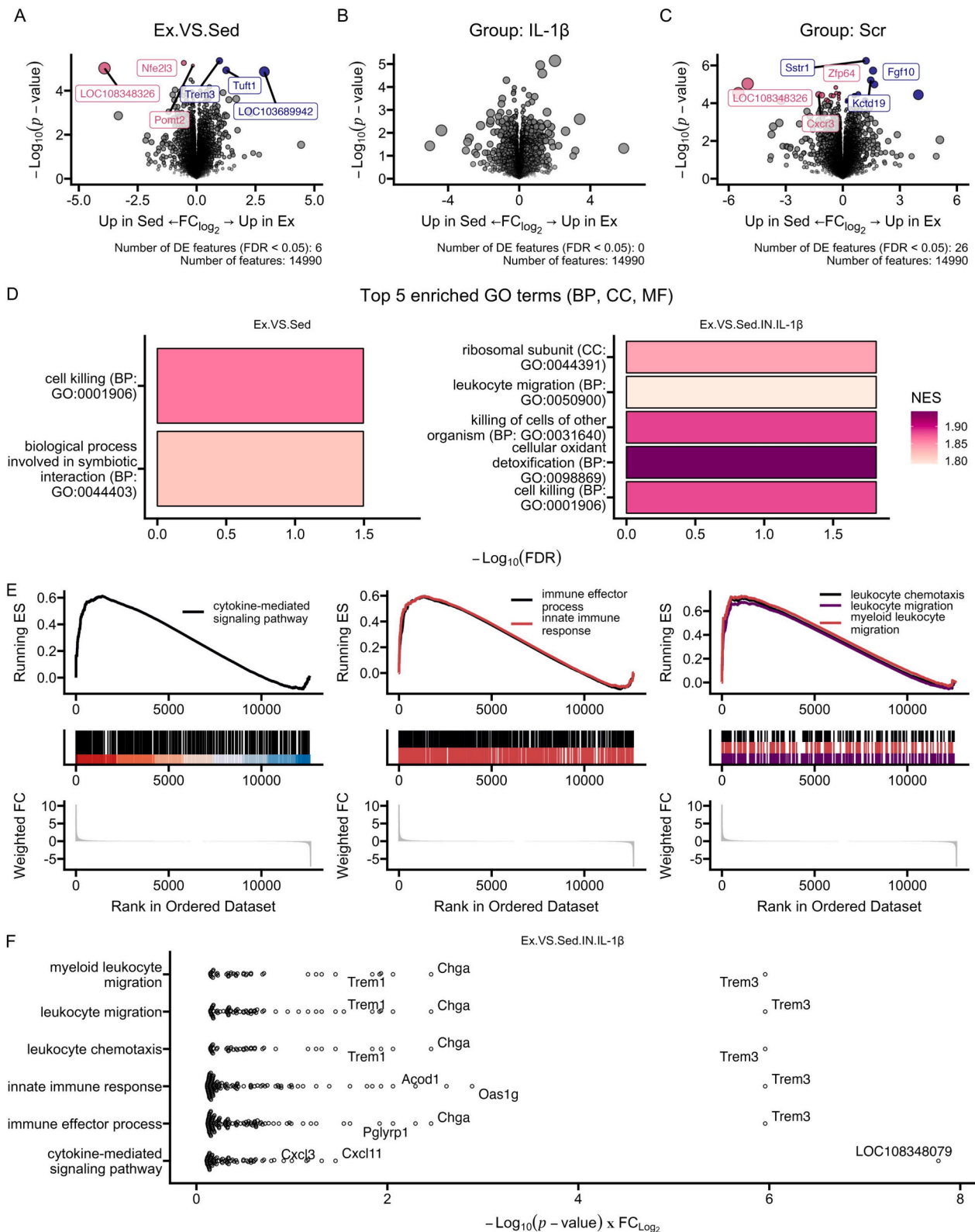


Fig. 5. IL-1 β overexpression blunts microglial transcriptomic response to exercise. A-C) Volcano plots of differential expression analyses of microglial transcriptomics. A) Main effect of exercise. Effect of exercise in the IL-1 β groups (B) and in the scramble groups (C) the top 3 up- and down-regulated (i.e. FDR < 0.05) genes are highlighted. D-F) Gene Set Enrichment Analysis (GSEA) of Gene Ontology (GO) terms. D) Top enriched GO terms per contrast. NES highlight the direction of regulation and correct for differences in gene set size. E) Running GSEA enrichment score (ES) profiles for enriched GO terms relating to “cytokine” (left), “immune” (middle), and “leukocyte” (right) terms in the exercise contrast of the IL-1 β groups. F) Weighted fold changes (FC) of genes mapping to GO terms highlighted in (E). GSEA was performed with p-value-weighted log2 fold changes (FC) from each differential expression analysis contrast. The Gene Ontology (GO) database was used to assess functional enrichment for “biological process” (BP), “cellular compartment” (CC), and “molecular function” (MF) terms. Abbreviations: FC (Fold Change), FDR (False Discovery Rate), NES (Normalized Enrichment Score).

Table 1
Enriched GO terms among nominal DEGs

Ontology ID Description			Set sizeNESpFDR			
Ex.VS.Sed.IN-IL-1β						
BP	GO:0050900	leukocyte migration	303	1.8	3.4e-06	0.015
BP	GO:0098869	cellular oxidant detoxification	83	1.9	7.1e-06	0.015
BP	GO:0001906	cell killing	157	1.9	9.2e-06	0.015
CC	GO:0044391	ribosomal subunit	176	1.8	1.3e-05	0.015
BP	GO:0031640	killing of cells of other organism	42	1.9	1.8e-05	0.015
CC	GO:0005840	ribosome	213	1.8	1.8e-05	0.015
BP	GO:0032496	response to lipopolysaccharide	358	1.7	2.4e-05	0.017
BP	GO:0045087	innate immune response	474	1.6	2.9e-05	0.018
BP	GO:0002252	immune effector process	468	1.6	4.2e-05	0.023
BP	GO:0097529	myeloid leukocyte migration	178	1.8	4.5e-05	0.023
BP	GO:0002237	response to molecule of bacterial origin	373	1.7	5.7e-05	0.026
BP	GO:0060326	cell chemotaxis	242	1.7	8.4e-05	0.034
BP	GO:0030595	leukocyte chemotaxis	183	1.8	9.5e-05	0.034
BP	GO:0071216	cellular response to biotic stimulus	238	1.7	9.7e-05	0.034
BP	GO:0044403	biological process involved in symbiotic interaction	194	1.7	0.00011	0.034
BP	GO:0019221	cytokine-mediated signaling pathway	331	1.6	0.00011	0.034
BP	GO:0071219	cellular response to molecule of bacterial origin	216	1.7	0.00017	0.047
BP	GO:0042742	defense response to bacterium	148	1.8	0.00017	0.047
BP	GO:0031347	regulation of defense response	470	1.6	0.00018	0.047
Ex.VS.Sed						
BP	GO:0001906	cell killing	157	1.9	7e-06	0.032
BP	GO:0044403	biological process involved in symbiotic interaction	194	1.8	1.3e-05	0.032

Abbreviations: Normalized Enrichment Score (NES), False Discovery Rate (FDR).

been associated with CD8⁺ T cells recruitment in aged mice (Groh et al., 2025). Thus, we quantified CD8⁺ T cells across hippocampal subregions (Fig. 6D) to assess whether IL-1 β -OE and exercise modulate immune cells recruitment to the brain. In the wHi, Kruskal–Wallis test revealed a significant overall effect on the number of CD8⁺ T cells ($\chi^2(3) = 11.62$, $p = 0.008$). A trend towards increased CD8⁺ T cell numbers in Ex.IL-1 β compared to Ex.Scr g rats was observed ($p = 0.062$, Fig. 6A). In the dHi, two-way ANOVA revealed a significant main effect of IL-1 β ($F(1,20) = 18.84$, $p = 0.0003$), but not of exercise nor their interaction. Post-hoc analyses revealed significantly higher CD8⁺ T cell counts in both Sed. IL-1 β ($p = 0.03$) and Ex.IL-1 β ($p = 0.027$) rats compared to their respective controls (Fig. 6B). No effects were detected in the vHi, where neither exercise nor IL-1 β influenced CD8⁺ T cell numbers, suggesting a region-specific effect (Fig. 6C). Qualitative observation of the meninges at the 3rd ventricle (Supp Fig. S4) highlighted that in sedentary control and exercising control rats, CD8⁺ T cells were sparse. In contrast, both IL-1 β -overexpressing control and IL-1 β -overexpressing exercising rats

displayed increased CD8⁺ T cells surrounding meningeal structures, with the densest labelling observed in IL-1 β -OE exercising animals. Together, these findings indicate that IL-1 β -OE promotes hippocampal infiltration of CD8⁺ T cells.

4. Discussion

Here, we show that chronic, low-grade hippocampal inflammation selectively impaired pattern separation in adult male rats, but did not affect spatial learning, memory, nor anxiety- or depressive-like behaviours. Exercise did not modulate these cognitive deficits. Exercise increased AHN in healthy control rats, an effect blunted by chronic, low-grade hippocampal inflammation. Combined histological and transcriptomic data further showed that hippocampal inflammation pushed microglia towards a lipid-droplet-accumulating, activated state, and that exercise, during these conditions, amplified lipid-droplet accumulation in microglia. Hippocampal inflammation further increased the number of CD8⁺ T cells in the hippocampus, independent of exercise. Taken together, these findings suggest that the inflammatory context critically shapes microglial and neurogenic responses to exercise.

Consistent with prior work in adult male Sprague Dawley rats (Hueston et al., 2018), IL-1 β -OE selectively impaired performance in the small-separation task of the MSLR test. The absence of IL-1 β -induced deficits in the MWM and spontaneous alternation test suggests that IL-1 β -OE in the dorsal hippocampus differentially affected cognitive processes that relied on adult-born neurons (Clelland et al., 2009) versus those that were not AHN-dependent (Saxe et al., 2006; Temme et al., 2016). Anxiety- and depression-related behavioural changes in our study were modest. While no previous work had explicitly shown that chronic hippocampal IL-1 β affected mood-related behaviours, it had been reported that inflammation (LPS) combined with stress induced behavioural changes (Wang et al., 2011).

Voluntary exercise did not influence cognitive performance, consistent with earlier reports showing that exercise-induced improvements were less pronounced in young adult (Nicolas et al., 2024; Nota et al., 2025) than in aged rats (Caruso et al., 2024; Van Praag et al., 2005). Exercise reduced anxiety like behaviour and increased stress-coping behaviour as reported previously (Nicolas et al., 2024; Nota et al., 2025). Exercise has been shown to exert anxiolytic effects in certain inflammatory stress models (Jung et al., 2023), which persist even when neurogenesis is inhibited (Schoenfeld et al., 2016), and which may explain why exercise induced behavioural changes in IL-1 β rats with reduced neurogenesis in the current study. However, exercise failed to rescue the IL-1 β -induced pattern-separation deficit. This contrasts with other studies that reported a beneficial effect of exercise in neuro-inflammation models (LPS) where both voluntary and forced exercise rescued hippocampal-dependent memory in adult male rats, in a step-down avoidance task (Kim et al., 2013) and in the radial arm maze (Ko and Ko, 2020). Here, it is possible that locally sustained IL-1 β expression in the dorsal hippocampus induces task-dependent effects or a stronger disruption of hippocampal plasticity that is less responsive to exercise-induced plasticity.

IL-1 β -OE markedly reduced the number of DCX⁺ neurons, consistent with reports from lentiviral (Hueston et al., 2018) and transgenic models (Wu et al., 2012). Exercise robustly increased neurogenesis in control rats (as previously described (Nicolas et al., 2024; Van Praag et al., 1999)) but produced only a mild effect in IL-1 β overexpressing animals, indicating that IL-1 β blunted exercise-driven neurogenic capacity. These effects were most prominent in the dorsal dentate gyrus, aligning with our injection site and the dorsal hippocampus role in spatial discrimination (Fanselow and Dong, 2010).

While the neurogenic response after exercise is modulated by specific early life experiences (Abbink et al., 2017; Järlestedt et al., 2013; Naylor et al., 2008), earlier IL-1 β likely suppresses neurogenesis through multiple mechanisms including inhibition of progenitor proliferation, reduced neuronal survival, and/or alterations in the neurogenic

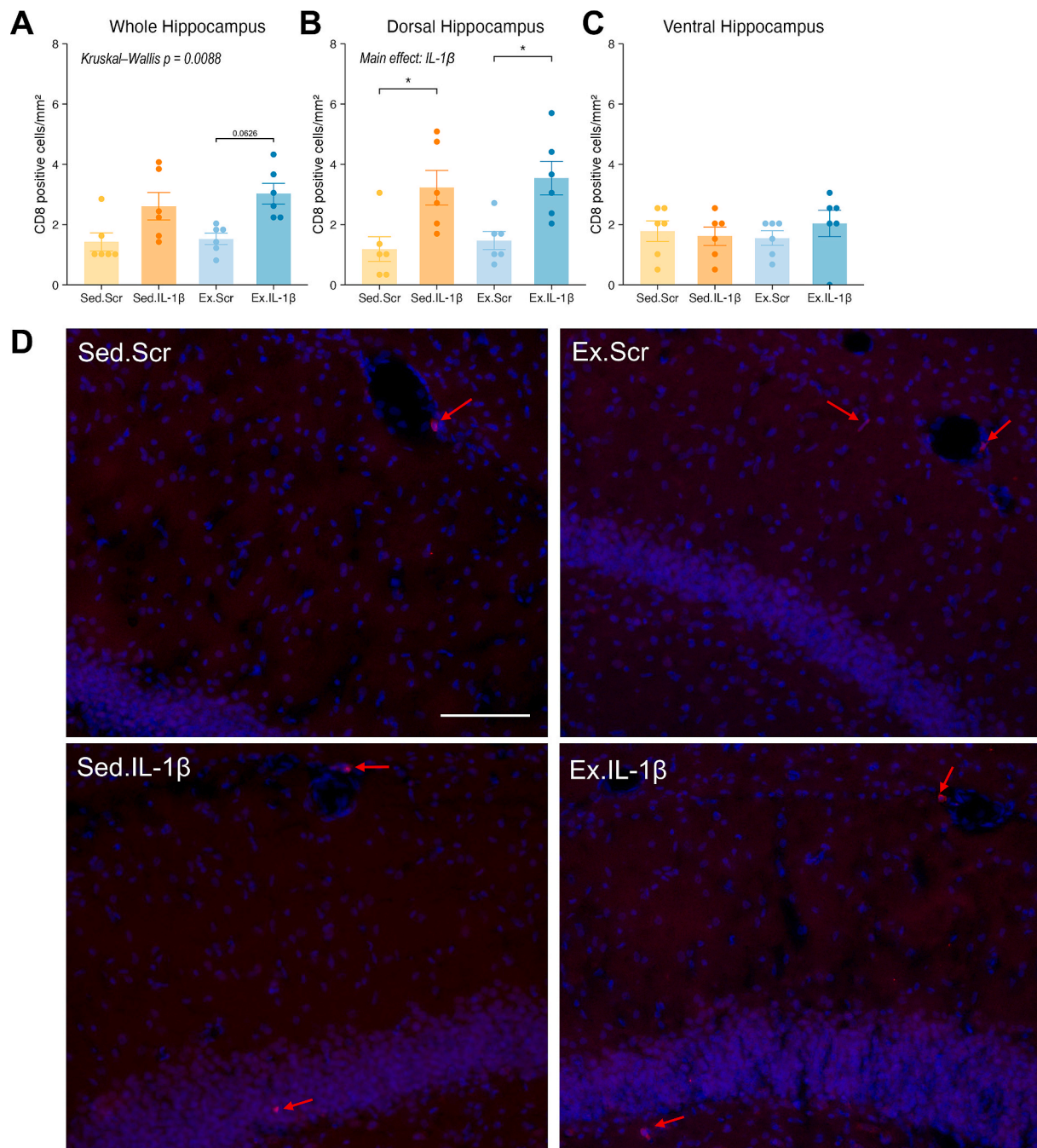


Fig. 6. IL-1 β overexpression induces CD8⁺ T cell recruitment in the hippocampus independently of exercise. Immunohistochemical measurement of CD8⁺ T cells (per mm²) through A) the whole B) dorsal and C) ventral hippocampus. D) Representative images (20X) of CD8 + staining in the dentate gyrus-CA1 area of the hippocampus Scale bar = 100 μ m. Data are presented as mean $\pm$ SEM. All p value < 0.08 are reported, * p < 0.05, ** p < 0.01 vs corresponding control.

microenvironment (Goshen et al., 2007; Monje et al., 2003). The neurogenic niche has recently been highlighted as a critical substrate for neurogenesis to occur (Salta et al., 2023), and it is hence possible that chronically increased IL-1R signalling decreased cell proliferation in the neurogenic niche (Koo and Duman, 2008; Vanderheiden et al., 2024; Zunszain et al., 2012). Clearly, the neurogenic effects of exercise were insufficient to overcome this inhibition. For example, albeit in a different context, it was reported that elevation of IL-1 β in the hippocampus in a SARS-CoV-2 mouse model was associated with loss of hippocampal neurogenesis and memory deficits, which were attenuated by prior vaccination (Vanderheiden et al., 2024), suggesting that a resolution of inflammation is necessary to support hippocampal neurogenesis.

Chronic IL-1 β increased soma size and lipid-droplet accumulation of microglia, characteristic of metabolically dysregulated, pro-inflammatory states seen in ageing and neurodegeneration (Marschallinger et al., 2020). The modest IL-1 β -induced effects on microglial numbers and morphology is somewhat surprising given the well-established role of IL-1 β in microglial activation (Pawley et al., 2020; Shaftel et al., 2008; Van Dam et al., 1995). This may reflect the fact that all rats underwent surgery (Scr or IL-1 β), or the possibility that functional changes in microglia can occur due to metabolic and transcriptional changes without strong changes in their number or morphology (Paolicelli et al., 2022). Under control conditions, exercise exerted modest effects on microglial reactivity. In this regard, it is important to note that most of the effects of exercise are observed in

models of inflammatory conditions such as neuroinflammation, neurodegeneration and ageing, in which exercise converts reactive microglia with short, non-ramified processes into more highly ramified cells with reduced expression of pro-inflammatory cytokines (Chauquet et al., 2024; Kodali et al., 2021; Xiao et al., 2021). We observed that exercise, combined with IL-1 β exacerbated lipid-droplet accumulation which may be surprising, but this dissociation supports the hypothesis that morphological normalization does not necessarily reflect restored metabolic competence nor a reactive state (Paolicelli et al., 2022). Microglia containing lipid droplets exhibit impaired phagocytosis and heightened inflammatory output (Ji et al., 2013; Vicedomini et al., 2024), which could contribute to the deleterious environment of the hippocampus and likely has blunted the beneficial effects of exercise on neurogenesis.

Growing evidence indicates that microglial reactivity is not a binary phenomenon but rather encompasses a spectrum of functional states with distinct molecular signatures and functional consequences (Colonna and Butovsky, 2017; Keren-Shaul et al., 2017; Paolicelli et al., 2022). Transcriptomic analysis of isolated microglia from the hippocampus revealed that exercise induced more robust gene-level effects in control than in IL-1 β -OE rats. In the control group, exercise induced a downregulation of the chemokine receptor *Cxcr3*, which is known to mediate microglial recruitment to sites of injury in response to *Cxcl10* signalling (Rappert et al., 2004). When considered with the concomitant upregulation of *Fgf10*, which has been found to inhibit microglial pro-inflammatory signalling in the context of spinal cord injury (Chen et al., 2017), this suggests that exercise had an anti-inflammatory-like effect on the microglial transcriptome in the absence of *prior* inflammation. The lack of pathway enrichment by exercise in the control group implies that the functional response to exercise may be more complex and subtle. On the other hand, in IL-1 β -OE rats, exercise was associated with enrichment of gene sets linked to pro-inflammatory immune responses and leukocyte trafficking, driven by recurring up-regulation of *Trem3*, *Trem1* and *Chga*. Treadmill running has been found to reverse pro-inflammatory microglia phenotypes (determined by gene expression, cytokine profiles, and morphology) in the hippocampus, in a rat model of Alzheimer's disease (Lu et al., 2017) and a mouse model of chronic unpredictable stress (Liu et al., 2024). However, treadmill and voluntary wheel running differ in their motivational, stress, and intensity components, and have been shown to produce different magnitudes of exercise-induced adult hippocampal neurogenesis (Caruso et al., 2026). It is therefore plausible that they likewise engage microglial regulation in distinct ways. In our study, chronic IL-1 β may “prime” microglia such that physiological stimuli, including exercise, may preferentially trigger exaggerated immune programs rather than restorative ones. This may explain why IL-1 β alone produced modest transcriptomic changes, whereas IL-1 β -OE in combination with exercise induced a stronger phenotype.

Among the top genes in the enriched “cytokine-mediated signalling” pathway (Table 1) was *Cxcl11*, which can recruit T cells via the *Cxcr3* receptor (Groom and Luster, 2011). A recent report found that age-related microglia reactivity in mice recruits CD8⁺ T cells through CXCL10-CXCR3 signalling to white matter tracts, leading to their degeneration (Groh et al., 2025). We quantified CD8⁺ T cells in the brain and found that IL-1 β increased hippocampal CD8⁺ T cell numbers, particularly in the dorsal hippocampus. Exercise further increased CD8⁺ infiltration in the whole hippocampus in IL-1 β -OE animals but not in controls. The functional consequences of CD8⁺ T cell infiltration in our study appear to be mostly detrimental, given the negative correlation between T cell and DCX numbers (Supp Fig. 5A). This is consistent with evidence that CD8⁺ T cells can directly suppress neurogenesis (Li et al., 2023). In addition, the positive correlation between numbers of CD8⁺ T cells and LD-rich microglia (Supp Fig. 5B) suggest reciprocal reinforcement between peripheral and central immune states. While some T cell subsets support cognitive function under homeostasis (Kipnis et al., 2004; Zarif et al., 2018), CD8⁺ T cell infiltration has been associated

with neurodegeneration in a mouse model of tauopathy (Chen et al., 2023). Despite IL-1 β -induced reductions in neurogenesis and increases lipid-droplet-accumulating microglia, these two measures did not significantly correlate (Supp Fig. 5C). This dissociation suggests that microglial lipid accumulation is not a direct proxy for impaired neurogenesis. Instead, LD formation may reflect a broader state of microglial metabolic stress that does not linearly track with neurogenic disruption. In this context, LD-rich microglia may contribute to an inflammatory milieu and our data suggest that other immune factors, such as CD8⁺ T cells, may exert more direct control over the neurogenic niche than microglia itself. Future studies should explore whether exercise-induced T cell recruitment in inflammatory conditions accelerates microglial dysfunction or impairs neurogenesis via cytotoxic or inflammatory mechanisms.

IL-1 β -OE reduced voluntary running behaviour (Supp. Fig. 2A), thus exercise itself may have interacted with central IL-1 β signalling, eventually exacerbating fatigue as previously described in mice (Carmichael et al., 2006). Despite reduced running, IL-1 β -OE rats displayed normal exercise-induced changes in physiological measures. Exercise reduced body weight (Supp. Fig. 2B) and adipose tissue mass, independently of IL-1 β (Supp. Fig. 2C). This indicates that the reduced running distance was sufficient to trigger a systemic physiological response. Finally, IL-1 β -OE increased spleen weight (Supp. Fig. 2D), independently of exercise. This enlargement may translate to an enhanced peripheral immune activation, as previously described in rats (Speaker et al., 2014), possibly contributing to hippocampal increases in CD8⁺ T cells numbers.

Overall, our findings challenge the assumption that exercise is universally beneficial for hippocampal plasticity. Instead, exercise efficacy seems to depend on the neuroinflammatory state, with chronic IL-1 β altering microglial and neurogenic responses to running. This may parallel clinical conditions such as chronic fatigue syndrome or long-COVID, where exercise intolerance and symptom exacerbation are thought to arise from maladaptive neuroimmune responses (Tate et al., 2022). Because our results were based on RNA-sequencing from the total microglial population of the hippocampus, we could not resolve microglial states at the single-cell level (Masuda et al., 2020) and future studies should examine how inflammatory priming shapes microglial diversity and their subsequent responsiveness to exercise. Exercise effects may also depend on sex, as shown in a study where aged mice males, but not females, showed increased MHC-II⁺ microglia following exercise (Kohman et al., 2013), though little is known about sex as a moderating factor (Coleborn et al., 2025).

In conclusion, our findings reveal that chronic hippocampal IL-1 β -OE selectively impairs pattern separation and attenuates exercise-induced neurogenesis. Under inflammatory conditions, exercise is associated with enrichment of immune activation and leukocyte trafficking pathways in microglial transcriptional programs, accompanied by increased CD8⁺ T cell infiltration. These findings underscore that pre-existing inflammation fundamentally alters how the brain responds to exercise, suggesting that inflammatory processes may need to be addressed before exercise interventions can effectively support plasticity in ageing and neurodegenerative conditions.

CRedit authorship contribution statement

Sarah Nicolas: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Maria Giovanna Caruso:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Sebastian Dohm-Hansen:** Writing – review & editing, Software, Formal analysis. **Tara Foley:** Methodology, Data curation. **Paul J. Lucassen:** Writing – review & editing, Conceptualization. **Joram D. Mul:** Writing – review & editing, Conceptualization. **Aonghus Lavelle:** Supervision, Software. **Jane E. English:** Supervision, Software. **Olivia F. O’Leary:** Writing – review & editing, Supervision, Project administration,

Conceptualization. **Yvonne M. Nolan:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: YMN is in receipt of research funding from Marigot Limited and has received honoraria from Yakult as an invited speaker. OFO has received research funding from Marigot Limited and Alkermes plc and honoraria as an invited speaker at a meeting organised by Janssen. This support neither influenced nor constrained the contents of this article. All other authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary results and detailed methods to this article can be found online at <https://doi.org/10.1016/j.bbi.2026.106815>. Supplementary results include: validation of hippocampal IL-1 β overexpression, effects of IL-1 β overexpression on voluntary running activity and body weight, exercise- and IL-1 β -dependent changes in adipose tissue and spleen weight, and correlation analyses between DCX, CD8⁺ T cell infiltration, and lipid-droplet-containing microglia. Supplementary methods detail the behavioural paradigms used, immunohistochemical protocols, and the RNA-seq bioinformatics pipeline, including a complete list of R packages used.

Data availability

Data will be made available on request.

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