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Short communication

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Sarah Delcourte [a,1], Amel Bouloufa [a,1], Renaud Rovera [a], Cécile Bétry [a], Erika Abrial [a], Ouria Dkhissi-Benyahya [a], Christophe Heinrich [a], Guillaume Marcy [a], Olivier Raineteau [a], Nasser Haddjeri [a,*,1], Guillaume Lucas [b,1], Adeline Etiévant [c,1]

[a] Univ Lyon, Université Claude Bernard Lyon 1, Inserm, Stem Cell and Brain Research Institute U1208, Bron, France
[b] Université de Bordeaux, CNRS UMR 5287, INCIA, P3TN, Bordeaux F-33000, France
[c] Integrative and Clinical Neurosciences EA481, University of Bourgogne Franche-Comté, Besançon, France

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ABSTRACT

Prefrontal cortex (PFC) inputs to the hippocampus are supposed to be critical in memory processes. Astrocytes are involved in several brain functions, such as homeostasis, neurotransmission, synaptogenesis. However, their role in PFC-mediated modulation of memory has yet to be studied. The present study aims at uncovering the role of PFC astroglia in memory performance and synaptic plasticity in the hippocampus. Using chemogenetic and lesions approaches of infralimbic PFC (IL-PFC) astrocytes, we evaluated memory performance in the novel object recognition task (NOR) and dorsal hippocampus synaptic plasticity. We uncovered a surprising role of PFC astroglia in modulating object recognition memory. In opposition to the astroglia PFC lesion, we show that chemogenetic activation of IL-PFC astrocytes increased memory performance in the novel object recognition task and facilitated in vivo dorsal hippocampus synaptic metaplasticity. These results redefine the involvement of PFC in recognition mnemonic processing, uncovering an important role of PFC astroglia.

1. Introduction

The neural circuit of recognition memory was shown to involve mainly the hippocampus, perirhinal cortex and medial prefrontal cortex (mPFC) triumvirate [1]. While the involvement of mPFC is well defined in fear memory [2], its role in single-item recognition memory is still in debate [3]. Nevertheless, several studies emphasize interactions between the hippocampus and the PFC in episodic-like memory [1,4]. In rodent, the novel object recognition (NOR) task is increasingly used as an experimental tool in assessing drug effects on episodic-like memory [5], and is traditionally considered as a *neuronal* hippocampal-dependent and PFC-independent behavioral task. Interestingly, several studies point out previously unrecognized functions for *astrocytes*, including regulation of synaptic formation, transmission and plasticity, all of which are considered as the infrastructure for information processing and memory formation and stabilization [6–8]. Conversely, astrocytic dysfunction was observed in several brain disorders and was shown to involve the PFC and be associated with cognitive impairments. Still, although a lesion of mPFC-astroglia has been revealed to alter some processes of working memory [9] and the in vivo hippocampal synaptic plasticity [10], the influence of this brain component on episodic memory remains unknown. Here we provide evidence, using the NOR task in rats, that selective activations of glial infralimbic (IL)-PFC produced an improvement of performance in an episodic-like memory associated with a facilitation of the hippocampal synaptic plasticity.

2. Material and methods

2.1. Animals

All animal procedures were in strict accordance with current national and international regulations on animal care, housing, breeding, and experimentation, performed in compliance with the ARRIVE guidelines, approved by the regional ethics committee CELYNE (C2EA42–13–02–0402–005) and performed in compliance with the

* Correspondence to: Institut Cellule Souche et Cerveau, INSERM U1208, Université Claude Bernard Lyon 1, 18, Avenue Doyen Lépine, 69500 Bron, France.
E-mail address: nasser.haddjeri@inserm.fr (N. Haddjeri).
[1] These authors contributed equally

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European Communities Council (86/609 ECC, still in use at the time the experiments started) for the care and use of laboratory animals. All efforts were made to minimize suffering. The experiments have been carried out in male Sprague-Dawley OFA rats (Charles Rivers, France) at least one week after their arrival and weighing from 260 to 320 g at the day of the experiment. Animals were kept under standard laboratory conditions (12:12 light-dark cycle with free access to food and water). After acclimatization to the environment for one week, rats were randomly assigned to each groups and tested during the light phase of the cycle.

2.2. Infralimbic PFC infusions

The L-alpha-aminoadipic acid (L-AAA) (20 μg/μl), a specific gliotoxin for astrocytes, was dissolved in NaOH 1 N and Ringer's solution (pH between 6.9 and 7.2). The L-AAA was infused bilaterally into the IL-PFC through 30-gauge stainless-steel cannulas stereotaxically implanted (in mm: 3.2 anterior and ±0.5 lateral from bregma, depth between −5 and −5.5) in chloral hydrate (0.4 g/kg, i.p.) anesthetized rats. Infusions were intermittently delivered at a rate of 1 μl/min with 1 min delay, 5 times, corresponding to a final dose of 100 μg/μl of L-AAA for each hemisphere [10] through infusion cannulas attached by a Tygon® tubing to a 50 μl Hamilton syringe with an infusion pump (Harvard apparatus). At the end of the infusion, cannulas were removed and rats were replaced to their home cages. Control group received the same surgery and were infused with vehicle. The experiments were carried out 48 h after the L-AAA infusion because of the glial-lesion reversibility, the maximum effect occurring 48 h after the infusion [10].

The vector, containing the virus, was dissolved in PBS + MgCl2 + KCl at a concentration of $6{,}0.10^{12}$ vg/mL. Rats were anesthetized with Chloral Hydrate (0,4 g/kg, i.p.; SIGMA) and implanted with cannulas for the virus microinjections. Briefly, 1 μl of ssAAV-5/2-hGFAP-hM3D(Gq)-mCherry-WPRE-hGHp(A) (GFAP-Gq-DREADD; Viral vector Facility-Zurich University) was infused bilaterally into the IL-PFC (AP + 3.2 mm; mL ± 0.5; DV + 5.5 mm from bregma) using 25 gauge injectors at a rate of 0.1 μl/min. Control group received the same surgery and were infused with vehicle. The experiments were carried out 10 days' post-surgeries.

2.3. Novel object recognition test

For behavioral experiments: GFAP-Gq-DREADD virus was injected in IL-PFC and IL-PFC glial lesion was performed with L-AAA gliotoxin. To determine the putative effects of IL-PFC glial activation and lesion on cognitive capacities in the NOR task, 4 different groups were evaluated: sham and sham-CNO animals, IL-PFC- glial DREADDed and IL-PFC-L-AAA groups. Sham rats were exposed to the same surgery without virus/L-AAA injection.

The present study investigated the ability of IL-PFC astroglia activation to enhance episodic memory and the impairment of retention induced by a glial lesion. The novel object recognition (NOR) task was performed in a plexiglass Y-maze apparatus (45 × 15 × 33 cm) [11]. The Y-maze was placed in a room illuminated by 2 halogen lamps giving a uniform dim light in the apparatus (60 lx). The apparatus and the objects were washed with ethanol 10 % after each trial. The NOR test is based on the natural propensity of rats to explore novelty in their environment. More specifically, rodents are able to discriminate between a novel and a previously seen (i.e. familiar) object. The objects are different in shape, color and texture. They are made of plastic (green) and metal (brown), around 17 cm high and were too heavy to be displaced by rats. Objects were previously tested for absence of spontaneous preference for one object. Rats were placed in the experimental room for at least 30 min before testing. After a habituation session to the apparatus and test room environment during which animals were allowed to explore freely the apparatus during 6 min, rats were exposed to two identical objects during the first trial (T1). Animals were placed in the apparatus containing 2 identical objects for the amount of time necessary to spend a total of 15–20 s exploring these 2 objects. Any rat not exploring the objects for 15–20 s within a cut-off time of 4 min was excluded from the experiments. Exploration is defined as the animal having its head within 2 cm of the object while looking at, sniffing or touching it. Then, after an inter-trial interval (ITI) of 2 or 24 h, one of the previously explored objects now familiar was presented with a novel object during the second trial. At short ITIs, rats can discriminate between the two objects, spending more time exploring the novel object than the familiar one while, with longer ITI (24 h), animals are unable to discriminate between the familiar and the novel object, spending the same amount of time with the two objects [5]. The present study was aimed to evaluate if IL-PFC glial activation is able to enhance memory performance using 24 h ITI. In the second trial (T2) which lasted 3 min, animals were exposed to an identical copy of the objects previously seen during the first trial and a novel object. Animals with low level of object exploration (novel + familiar < 5 s) were excluded from data analysis. A video camera recorded rat's behaviors during each trial and scoring was performed by blinded experimenters. Results were presented as time (s) spent in active exploration of the familiar (F) or novel (N) object during T2 ± SEM. Recognition memory was estimated using a recognition index (RI): [(N – F) / (N + F)] x 100.

For DREADDed animals, CNO (3 mg/kg, i.p.) was administrated 90 and 30 min before T1 in sham and IL-PFC GFAP-Gq-DREADDed rats.

Aricept (donepezil hydrochloride monohydrate, Sigma Aldrich, France) a reference acetylcholinesterase inhibitor, was administered (1 mg/kg, i.p.) 1 h before T1 session to validate our experimental condition. In fact, Aricept was used as a positive reference considering its memory facilitating effect in animal models and Alzheimer patients.

2.4. Fields EPSP recordings

The amplitude of field excitatory post-synaptic potential (fEPSP: considered as direct measure of pathway connectivity) from CA1 stratum radiatum of the right hippocampal hemisphere were recorded in urethane-anesthetized rats (1.4 g/kg, i.p.) placed in a stereotaxic frame. Unilateral implantations of electrodes were performed using standard stereotaxic procedures. Briefly, a bipolar stimulating electrode (NEX-200, Rhodes Medical Instruments, USA) was positioned in the CA3 area to stimulate the ipsilateral Schaffer collateral-commissural pathway (in mm: 3.0 posterior and 1.5 lateral to bregma; 2.8 ventral from the dura) and a recording single-barrelled glass micropipette (Harvard apparatus) was positioned in the CA1 stratum radiatum of the dorsal hippocampus (in mm: 5.0 posterior and 3 lateral to bregma; 2.3 ventral to the dura). Electrode positions were optimized to record maximal field responses evoked at a frequency of 0.033 Hz following electrophysiological criteria (64): i) the amplitude of evoked potential depends on stimulation intensity (input-output curves), ii) a facilitation of the second pulse occurred when we applied a paired-pulse.

At the beginning of each experiment, input-output curves were used to determine the stimulus intensity that evoked a field EPSP amplitude of 55 % of the maximum used during the experiment. A 30 min baseline was then recorded under low-frequency stimulation (0.033 Hz). LTD was induced by low frequency stimulation (LFS), which consisted on biphasic squares pulses (0.2 ms duration) at 3 Hz during 5 min. After 30 min recordings, LTP was induced by high frequency stimulation (HFS) which consisted on ten trains at 0.5 Hz, each composed of twenty pulses at 200 Hz. Evoked response recorded before and after LTD and LTP induction were stored for analysis of fEPSP amplitude. Values obtained were expressed as a percentage of those measured during baseline. Area under the curves (AUC) was measured during 30 min after LFS and HFS.

To determine whether selective chemogenetic activation of transduced astroglia in IL-PFC modulated in hippocampal synaptic plasticity, clozapine-n-oxide (CNO, 3 mg/kg, i.p.) was administrated 30 min before LFS in sham and IL-PFC GFAP-Gq-DREADDed rats.

Hence, to determine the putative modulation of IL-PFC-induced changes in hippocampal synaptic metaplasticity by glial system, 2

different groups were evaluated: sham-CNO animals and IL-PFC- glial DREADDed groups.

To evaluate whether electrolytic lesion of the IL-PFC could induce changes in hippocampal synaptic transmission, anesthetized rats received direct current delivery of 500 μA for 10 s 15 min after the beginning of baseline recording. Following completion of experiments, their brains were removed, frozen to −40 °C, and sliced at 60 μm intervals in a cryostat. Brain sections were mounted on glass slices and examined with a microscope to verify the correct position of the electrodes for the IL-PFC of the lesioned group.

2.5. Immunohistochemistry and imaging

At the end of experiments, rats were transcardiacally perfused with 4 % paraformaldehyde in phosphate-buffered saline (PBS) and their brains were removed, frozen to −20 °C and sliced at 30 μm intervals in a cryostat. To evaluate the position and the extent of the lesion in the PFC, fluorescent labeling and microscopic examination of slides were assessed. Briefly, post-fixed brains were sectioned (30 μm sections, coordinates 4.7–1.6 mm from bregma) and stored in phosphate-buffered saline (PBS) containing 0.1 % of sodium azide at 4 °C. Free-floating sections were incubated for 30 min in blocking buffer (1 % normal

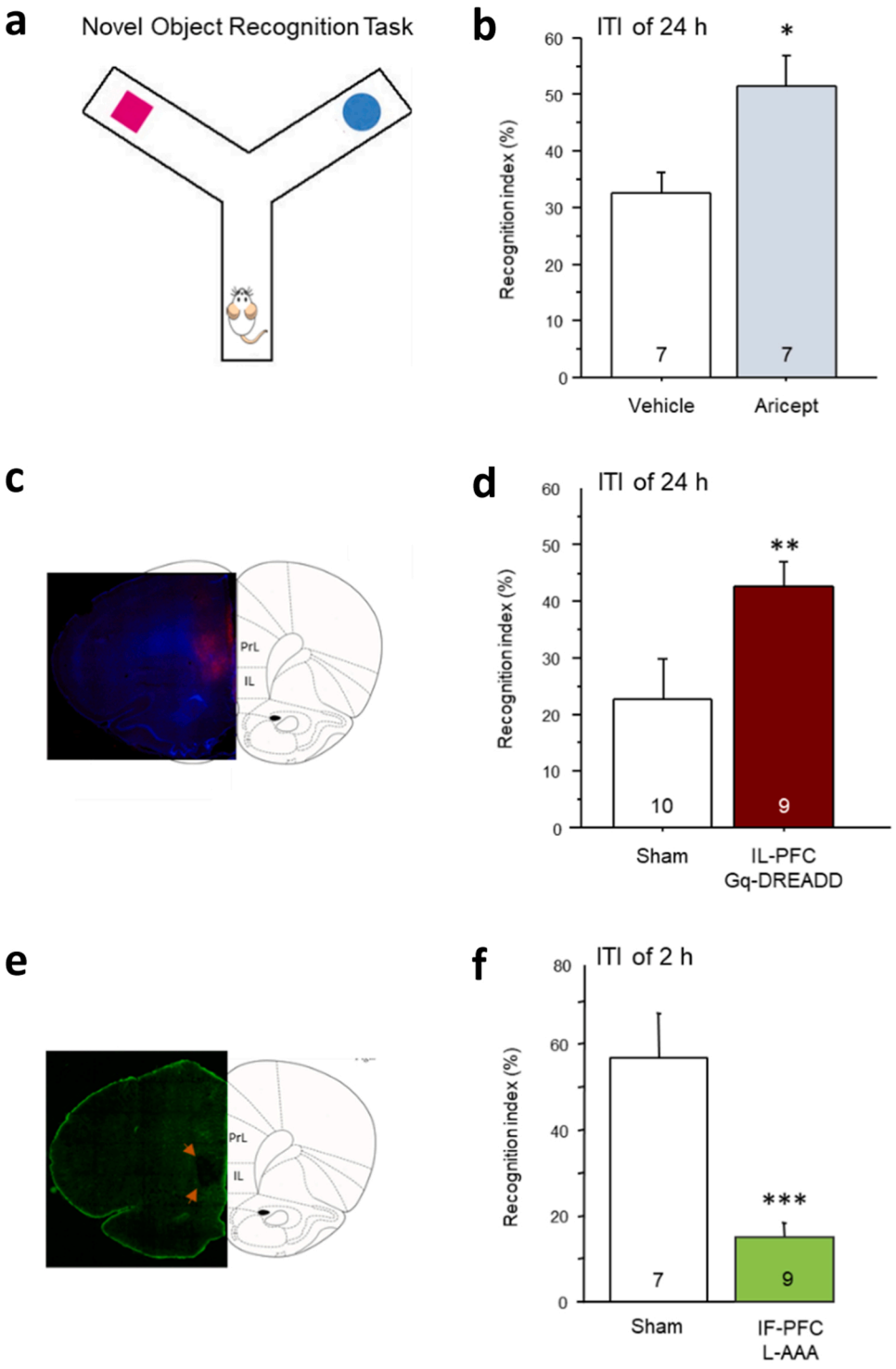

Fig. 1. Effects of astroglia IL-PFC activation and lesion on recognition memory performance (expressed as recognition index: RI) during the second trial of the NOR task and conducted 24 h (**a-d**) or 2 h (**f**) after the first trial. **a**: Illustration of the novel object recognition test as described in methods section. The prototypical pro-cognitive agent donepezil (1 mg/kg; i.p., see results section) increased significantly the time exploring the novel objet than the familiar one (**b**). **c**: Immunohistological image showing virus expression in the IL-PFC. **d**: Similarly, hM3Dq activation of IL-PFC astrocytes enhanced NOR memory as pre-testing CNO injection was shown to increase significantly novel object preference. **e**: Representative micrograph of GFAP immunostained section showing the effects of L-AAA. **f**: Conversely, L-AAA-induced glial lesion in IL-PFC reduced significantly the time exploring the novel objet than the familiar one. Results are expressed as mean ± SEM. *$p < 0.05$ and **$p < 0.01$. Numbers at the bottom of the columns represent the number of rats per group.

goat serum in 0.5 % Triton X-100, PBS) and exposed overnight (4 °C) to rabbit anti-glial acidic fibrillary protein [1:500; GFAP, DAKO (Trappes, France)] in blocking buffer. After several washing, sections were exposed (1 h) to the antibodies Alexa Fluor 488 goat anti-rabbit (1:500; Invitrogen) in blocking buffer. Finally, sections were incubated during 10 min in 4′,6-Diamidine-2′-phenylindole dihydrochloride [1:200; DAPI; Roche (Meylan, France)] which binds selectively to DNA. Fluorescent immunostaining images were collected employing a fluorescent microscope (Leica DMR-RXA). Loss of GFAP-positive cells was measured on 5–6 sections per animal in ventral PFC using ImageJ software. Drawing the outline of the lesion allowed determining the extent of the lesion (in mm^2 ± S.E.M.). Only animals showing correct location of the lesion in the IL-PFC were included in the study.

To evaluate the localization and extent of the virus infection, post-fixed brains were sectioned (30 μm, coordinates: 4.7 to AP 1.7 mm from bregma) and stored in PBS 0.1 M. Free floating sections were then incubated in a blocking buffer (Tris-NaCL Blocking buffer; 0.4 % Triton (TNBTx) overnight at 4 °C. Following, sections were incubated with primary rabbit antibody anti-GFAP (Dako, 1:1000) and mouse anti-NeuN (Millipore, 1:500) overnight at 4 °C with continuous agitation in PB 0.1 M, 0.4 % Triton (PBTx) + 10 % TNB buffer. After several washes in PBTx, brain sections were exposed (4 h, room temperature) to secondary antibodies: Alexa 488 (Donkey,anti-Rabbit, Jackson 1:500) and Alexa 647 (Goat,anti-mouse, Invitrogen 1:500) overnight at 4 °C in PB 0.1 M 0.4 % Triton (PBTx) +10 % TNB buffer. Finally, sections were incubated in DAPI (1:10000) during five minutes in PB 0.1 M. Images were obtained with a Leica SPE confocal (Leica Microsystems).

2.6. Statistics

All results were expressed as means and standard errors of the mean (S.E.M). Data were analyzed using a student t-test when two groups were compared and one-way or two-way analyses of variance (ANOVA), followed by a Fisher post hoc comparison, when multiple comparison was needed. F values are reported only when significant ($p < 0.05$). Statistical significance was set at $p < 0.05$.

3. Results

3.1. The effect of IL-PFC astroglia activation on recognition memory

To assess the effects of the activation and lesion of IL-PFC astroglia on the object recognition memory, we have used a Y maze apparatus in order to acquire a good and stable level of exploration [11] (Fig. 1a) with a time-fixed of 15–20 s of total object exploration of familiar objects [5]. Indeed, as previously observed in young animals [12], when the total object exploration time of familiar objects was superior to 20 s, control animals were able to recognize familiar objects 24 h (RI = 65.5 ± 8.3 %; n = 7) and even 72 h later (RI=72.3 ± 15.8 %; n = 3) making the evaluation of a pro-cognitive effect virtually impossible. Also, we found that donepezil (Aricept), used as a positive reference compound to validate our experimental conditions, presented a solid recognition memory facilitating action (Fig. 1b, RI=51.7 ± 5 %, $p < 0.05$ vs vehicle RI=32.4 ± 4 %; Table 1). To selectively stimulate astroglia, we employed adeno-associated virus transduction in the IL-PFC to express the hM3D (Gq) designer receptor exclusively activated by a designer drug (DREADD) [13] under control of the GFAP promoter. Stimulating Gq-coupled DREADDs with clozapine N-oxide (CNO) was previously shown to increase inositol 1,4,5-triphosphate signaling, which increases release of intracellular Ca2 + and glutamate release [13]. The NOR test was secondly used in sham and IL-PFC glial DREADDed rats with an inter-trial interval of 24 h (Fig. 1c). Significantly, we found that the systemic administration of CNO (3 mg/kg, i.p.) in GFAP-Gq-DREADD transfected animals increased their recognition performance in the NOR task (RI= 42.8 ± 4 %, $p < 0.05$ vs vehicle control RI=22.8 ± 7 %; Table 1). Accordingly, Gq-DREADD expression was consistently found in the GFAP expressing astroglia at the site of virus microinjection (Fig. 4). Finally, the NOR task was conducted in infused rats with the astrocyte specific toxin L-α-aminoadipic acid [10] (L-AAA) with an inter-trial interval of 2 h (Fig. 1e). As expected, sham control rats spent

Table 1
Statistical analysis.

Figure 1

Student's *t* Test	1b: Vehicle vs Aricept (1 mg/kg)	1d: sham vs IL-PFC Gq-DREADD	1f: sham vs IL-PFC L-AAA
Recognition Index	T_{14}=-2,836 P=0,0132	T_{17}=-2,356 P=0,0307	T_{14}: 3,985 P=0,0014

Figure 2

Student's *t* Test	2d: Sham vs Gq-DREADD Post LFS	2d: Sham vs Gq-DREADD Post HFS	2d: Sham vs Gq-DREADD Post LFS+ HFS
AUC	T_6=-4,436 P=0,0044	T_6=-1,517 P=0,1810	T_6: -2,592 P=0,0411

Figure 3

Student's t Test	3 (insert): Pre vs Post electrolytic lesion
AUC	T_8=5,564 P=0,0005

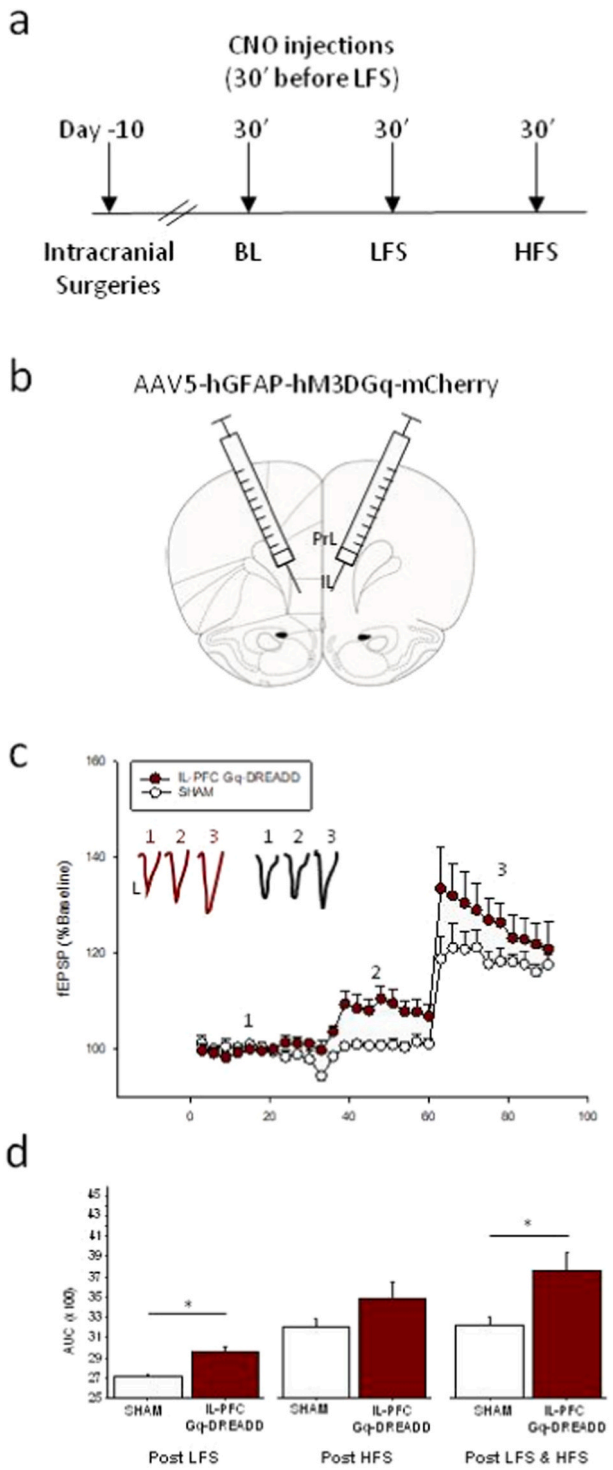

Fig. 2. Astroglial IL-PFC-induced facilitating effect on hippocampal synaptic plasticity. **a**: Experimental timeline used for the electrophysiological experiments in sham and DREADDed rats. **b**: Localization of AAV-GFAP-Gq-m-cherry virus in the IL-PFC. **c**: Time-course responses illustrate changes induced by CNO injections in DREADDed and sham rats showing the effects of glial chemogenetic activation on hipocampal synaptic plasticity. Inserts show typical field EPSPs recorded before and after low and high frequency stimulations; calibration vertical bar, 0.5 mV; horizontal bar, 5 ms. **d**: Histograms illustrate changes (area under the curve) induced after LFS or HFS by IL-PFC glial chemogenetic activation after CNO systemic injections. Results are expressed as mean ± SEM. Numbers at the bottom of the columns represent the number of rats per group. **p < 0.01 and ***p < 0.001 significantly different from sham; ##p < 0.01 and ###p < 0.001 significantly different from PFC-treated rats.

more time exploring the novel objet than the familiar one (recognition index (RI) = 56.6 ± 10 %; Fig. 1e). Remarkably, the RI of L-AAA infused rats was significantly decreased compared to control rats (RI=15.6 ± 4 %; $p < 0.001$, L-AAA vs control), demonstrating a memory performance deficit, in agreement with data observed in mice after neuronal chemogenetic inactivation of the mPFC [15].

3.2. The effect of IL-PFC astroglia on hippocampal synaptic plasticity

Hereafter, the modulation of dorsal hippocampus synaptic metaplasticity by glial IL-PFC activation was examined in vivo by application of low and high frequency stimulations (LFS and HFS) on Schaffer's collateral pathway to induce LTD or LTP, respectively, in dorsal hippocampal CA1 area [10] (Fig. 2a). Strikingly, electrolytic lesion within the IL-PFC was shown to decrease fEPSP amplitude of hippocampal CA1 synapses (by 8 %, $p < 0.001$), revealing the presence of an undescribed excitatory tone from the IL-PFC to dorsal hippocampus (Fig. 3; Table 1). As expected in vivo [10,14] in the dorsal hippocampus of control rats, LFS failed to induce a LTD whereas HFS produced a stable LTP of ≈ 20 % (Fig. 2c). Importantly, we found that the systemic administration of CNO (3 mg/kg, i.p.) in GFAP-Gq-DREADD transfected animals induced a LTP-like of ≈ 10 % after LFS and by 28 % after HFS (Fig. 2d). A two-way ANOVA conducted on AUC values normalized to baseline obtained after LFS revealed an effect of IL-PFC glial DREADD activation ($p = 0.0044$). A secondary analysis indicated that IL-PFC chemogenetic glial activation significantly increased fEPSP after HFS by ≈ 14 % when compared to baseline values ($p < 0.041$; Table 1).

4. Discussion

The present study shows that chemogenetic activation of IL-PFC astroglia induced a heterosynaptic facilitation of the hippocampal synaptic metaplasticity that is accompanied by an improvement of memory performance in the NOR task.

Memory depends on activity-dependent changes in the strength of synapses [16] and hebbian plasticity, as represented by LTP and LTD of synapses which are the most influential hypothesis to account for encoding of memories [17]. Whereas the ventral hippocampus was repeatedly shown to project to the mPFC [18], a direct projection from the mPFC to the hippocampus in rodents was described only recently. Indeed, Deisseroth's group was the first to define a monosynaptic mPFC to dorsal hippocampus projection in mice, and to find that optogenetic manipulation of this projection is capable of eliciting contextual memory retrieval [19]. It is tempting to propose that astroglial IL-PFC modulation observed in our study takes the path of the projection from mPFC to dorsal hippocampus. The anatomical organization of the mPFC is optimally suited for a structure involved in forming plans to achieve goals, as highly processed inputs, and information regarding motivational value, can be readily linked to the early stages of motor output [20]. The rodent mPFC is subdivided into the anterior cingulate cortex, the prelimbic, the IL and the dorsal peduncular cortex and glutamatergic connections within each mPFC sub-region are highly recurrent, and the mPFC sub-regions are interconnected via glutamatergic and GABAergic projections, enabling crosstalk between them [20,21]. Here we show that, after the chemogenetic activation of IL-PFC astroglia, the LFS of Schaeffer's collaterals induced a LTP-like plasticity, while the LTP elicited by HFS was enhanced. Moreover, electrolytic lesions of IL-PFC decreased hippocampal-CA1 fEPSP amplitude, revealing the presence of an excitatory tone from IL-PFC to dorsal hippocampus. Noteworthy, using the same chemogenetic paradigm, Scofield et al. [13] have elegantly shown that administration of CNO in GFAP-hM3D-DREADD transfected animals increased ventral striatum extracellular glutamate levels in vivo. Thus, one may assume that the facilitation of hippocampal LTP induced by CNO in dreaded-rats could be due to an mPFC astroglial-dependent release of glutamate within the hippocampus. This top-down synaptic mechanism would, in turn, favor

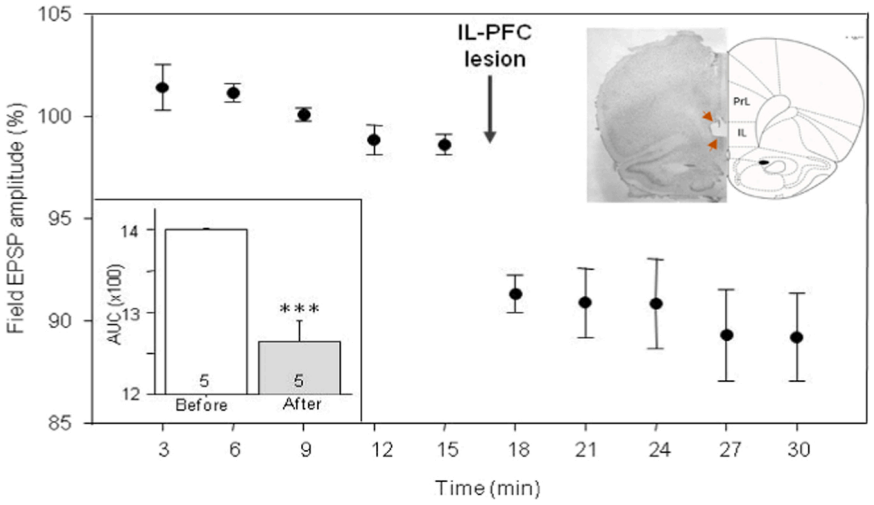

Fig. 3. Effect of an electrolytic lesion of the IL-PFC on fEPSP recorded in dorsal hippocampus. Time-course responses illustrate changes induced by an electrolytic lesion into the IL-PFC on field EPSP amplitude recorded in CA1 area of dorsal hippocampus. Insert: AUC histograms illustrated changes induced by electrolytic lesion. Results are expressed as mean ± SEM. ***$p < 0.0001$ using paired t-test.

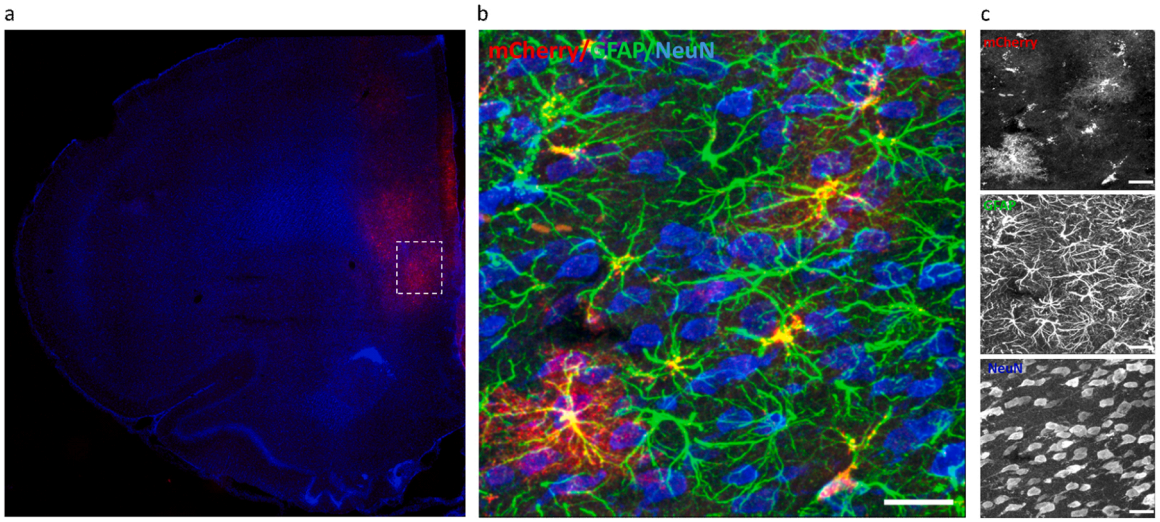

Fig. 4. Localization of AAV-GFAP-Gq-m-cherry virus in the IL-PFC (**a**) Coronal image of brain section showing mCherry labelling (red) in the Il-PFC (white square). (**b,c**) Overview of astroglial and neuronal staining in the IL-PFC Anti-GFAP (green) and anti-NeuN (blue) immunohistochemistry confirming expression of AAV-GFAP-Gq-m-cherry virus in astroglia (yellow) but not in neuron. scale bar (b,c) = 10 μm.

an enhancement of cognitive processes. Indeed, as learning induces LTP in the hippocampus [22], we have then evaluated the putative memory improvement induced by chemogenetic activation of IL-PFC astroglia. Our results show that chemogenetic activation of IL-PFC astroglia improved recognition of the NOR task when it was presented 24 h after the first trial. The role of the hippocampus in object recognition memory processes is still unclear, as conflicting results have been reported after lesion studies, the delay imposed for recognition appearing to constitute a key factor [23]. In the present study, rats were stimulated within the IL-PFC 30–90 min before NOR tests, i.e. by using a kinetic of CNO injection very similar to that chosen for electrophysiological experiments. Thus, our data suggest that the pro-cognitive effect of chemogenetic activation of IL-PFC astroglia may be related to the enhancement of dorsal hippocampus synaptic metaplasticity. Supportively, correlations between mPFC and hippocampal plasticity's have previously been observed in Y maze test [24] and recognition memory consolidation is accompanied by transient potentiation in the hippocampus CA3-CA1 synapses [25]. Conversely, repeated stress causes cognitive decline and decreases the expression of glial fibrillary acidic protein (GFAP)+ astroglial cells in the PFC. The stress-induced alterations in astroglial density and morphology might significantly contribute to cognitive impairments [26]. Hence, our data showed that a glial lesion within the IL-PFC produced a recognition memory performance deficit in agreement with previous studies [9].

5. Conclusion

Collectively, this study demonstrates for the first time that chemogenetic activations of glial IL-PFC induced a hetero-synaptic facilitation of the hippocampal synaptic metaplasticity that is correlated with an improvement of memory performance in the NOR task. In opposition, an IL-PFC glial lesion produced an episodic-like memory performance deficit. We have previously shown that mPFC astroglia play a crucial role in allowing local pyramidal neurons to sustain their activity when stimulated electrically [10]. The present data indicates that the fueling action of astroglia is also required even under resting conditions, in which the mPFC tonically excites the activity of the hippocampus and facilitates its metaplasticity. Also, they confirm the hypothesis that

mPFC astroglia is involved in memory through a modulation of the mPFC-hippocampus circuitry [9], further extending this concept to the NOR test which appears now to constitute a mPFC-dependent behavioral task. These findings may contribute to open new avenues of research in the field of cognition, focused on glial support while minimally acting on mPFC neuronal activity, and able to improve LTP-LTD impairments such as those induced by β-amyloids [27].

Ethics approval

All experiments were approved by the animal care and use committee of Lyon University.

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CRediT authorship contribution statement

A.E., S.D., A.B., G.L. and **N.H.** designed research; **A.E., A.B.** and **S. D.** performed research; **R.R.** and **E.A.** contributed to the behavioral and electrophysiological experiments; **G.M., C.H.** and **O.R.** contributed to the immunochemistry; **A.E., A.B., S.D., C.B., O.D-B, G.L.** and **N.H.** analyzed the data. **A.E., A.B., S.D., G.L.** and **N.H.** wrote the paper. All authors reviewed the manuscript.

Declaration of Competing Interest

There is no conflict of interest in the current research.

Data availability

Data will be made available on request.

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