



HAL
open science

Specific Hippocampal Interneurons Shape Consolidation of Recognition Memory

Jose F. Oliveira da Cruz, Arnau Busquets-Garcia, Zhe Zhao, Marjorie Varilh, Gianluca Lavanco, Luigi Bellocchio, Laurie Robin, Astrid Cannich, Francisca Julio-Kalajzić, Thierry Lesté-Lasserre, et al.

► **To cite this version:**

Jose F. Oliveira da Cruz, Arnau Busquets-Garcia, Zhe Zhao, Marjorie Varilh, Gianluca Lavanco, et al.. Specific Hippocampal Interneurons Shape Consolidation of Recognition Memory. *Cell Reports*, 2020, 32, pp.108046 -. 10.1016/j.celrep.2020.108046 . hal-03492405

HAL Id: hal-03492405

<https://hal.science/hal-03492405v1>

Submitted on 22 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **SUMMARY**

2

3 A complex array of inhibitory interneurons tightly controls hippocampal activity,
4 but how such diversity specifically impacts on memory processes is scanty
5 known. We find that a small subclass of type-1 cannabinoid receptor (CB₁R)-
6 expressing hippocampal interneurons determines episodic-like memory
7 consolidation by linking dopamine D₁ receptor (D₁R) signaling to GABAergic
8 transmission.

9 Mice lacking CB₁R in D₁-positive cells (D₁-CB₁-KO) display impairment in long-
10 term, but not short-term, novel object recognition memory (NOR). Re-
11 expression of CB₁R in hippocampal D₁R-positive cells rescues this NOR deficit.
12 Learning induces an enhancement of *in vivo* hippocampal long-term
13 potentiation (LTP), which is absent in mutant mice. The CB₁R-mediated NOR
14 and associated LTP facilitation involve the local control of GABAergic inhibition
15 in a D₁-dependent manner.

16 This study reveals that hippocampal CB₁R-/D₁R-expressing interneurons
17 control NOR memory, thereby identifying a mechanism linking the diversity of
18 hippocampal interneurons to specific behavioral outcomes.

19 **KEYWORDS:** CB₁ receptor, novel object recognition memory,
20 hippocampus, interneurons, dopamine, D₁ receptor, GABA.

21

1 INTRODUCTION

2
3 The formation of episodic memory is a multistep brain process that
4 requires the activity of the medial temporal lobe (Squire et al., 2007). In
5 particular, the hippocampus participates in the long-term storage of recently
6 acquired events. Hippocampal circuits are regulated by a large variety of local
7 inhibitory interneurons that are controlled by neuromodulatory systems ensuring
8 their coordinated functions to shape behavioral responses (Klausberger and
9 Somogyi, 2008), whose identities and functions are unclear (Harris et al., 2018;
10 Pelkey et al., 2017; Parra et al., 1998).

11 The endocannabinoid system is a brain modulatory signaling hub mainly
12 formed by type-1 cannabinoid receptors (CB₁R), their endogenous ligands
13 (endocannabinoids), and the enzymes for their synthesis and degradation. In
14 the hippocampus, CB₁R are present in principal neurons and astroglial cells
15 (Busquets-Garcia et al., 2015; Oliveira da Cruz et al., 2016). However, the
16 largest expression of CB₁R resides in GABAergic interneurons (Marsicano and
17 Kuner, 2008; Katona and Freund, 2012), where they modulate local inhibition of
18 hippocampal circuits. Particularly, the largest amount of CB₁R is expressed in
19 cholecystokinin (CCK)-positive interneurons, which are characterized by
20 asynchronous neurotransmitter release (Harris et al., 2018; Katona et al., 1999;
21 Marsicano and Lutz, 1999).

22 Hippocampal CB₁R control episodic-like memory processes and synaptic
23 plasticity (Robin et al., 2018; Hebert-Chatelain et al., 2016; Puighermanal et al.,
24 2009). However, the specific locations where these receptors participate in the
25 mechanisms underlying hippocampal-dependent memory are only partially
26 known.

27 Activity-dependent long-term changes in hippocampal synaptic
28 transmission are considered cellular correlates of memory consolidation (Nicoll,
29 2017; Whitlock et al., 2006), which involves local D₁R signaling (Lisman et al.,
30 2011; Yamasaki and Takeuchi, 2017). The exposure to hippocampal-dependent
31 behavioral tasks induces changes in long-term potentiation (LTP) of synaptic

1 transmission that require the activation of D₁-like receptors (Frey et al., 1990;
2 Granado et al., 2008; Li et al., 2003; Lemon and Manahan-Vaughan, 2006). A
3 novel subpopulation of hippocampal CB₁R/CCK-positive interneurons
4 containing D₁R was recently described (Puighermanal et al., 2017; Gangarossa
5 et al., 2012). However, the potential interactions between D₁R and CB₁R in
6 regulating learning-induced plasticity, activity of hippocampal circuits, and
7 memory processes remain unexplored.

8 Here we assessed the role of D₁R/CB₁R-positive cells in the regulation of
9 episodic-like novel object recognition (NOR) memory. We found that, involving
10 GABAergic transmission, conditional deletion of the *CB₁R* gene in hippocampal
11 D₁R-positive cells impairs long- but not short-term NOR memory and learning-
12 induced LTP enhancement. These intriguing results suggest that CB₁R
13 signaling provides a functional link between hippocampal dopaminergic and
14 GABAergic control of synaptic plasticity and memory consolidation.

15

1 RESULTS

2 CB₁R IN HIPPOCAMPAL D₁R-POSITIVE NEURONS ARE NECESSARY FOR 3 THE CONSOLIDATION OF NOR MEMORY

4 Mutant mice bearing a deletion of the *CB₁R* gene in cells expressing D₁R
5 (D₁-*CB₁R*-KO mice; Monory et al., 2007) displayed no phenotype in the short-
6 term version (3h post-training) of a NOR task (**Figure 1A,B**; Puighermanal et
7 al., 2009; Busquets-Garcia et al., 2011; Robin et al., 2018). Conversely, they
8 showed a strong impairment in long-term (24h) memory as compared to their
9 wild-type (WT) littermates (**Figure 1C**), with no changes in total exploration time
10 (**Figure S1A-S1D**).

11 The majority of CB₁R in D₁R-positive neurons has been previously
12 characterized in striatonigral circuits (Monory et al., 2007). Considering the
13 involvement of these circuits in NOR memory (Darvas and Palmiter, 2009), we
14 tested the role of striatal CB₁R. We infused an adeno-associated virus carrying
15 a Cre-dependent expression of CB₁R (pAAV-CAG-DIO-*CB₁R*) into the striatum of
16 D₁-*CB₁R*-KO mice to obtain re-expression of CB₁R in cells where Cre is present
17 (hereafter called D₁R-positive) in this brain region (STR-*CB₁R*-RS mice, **Figure**
18 **1D and 1E**) as revealed by the immunodetection of a myc-tagged version of
19 CB₁R (CB₁R-myc, see Methods, **Figure 1E**). This re-expression was not
20 sufficient to rescue the phenotype of D₁-*CB₁R*-KO mice in long-term NOR
21 (**Figure 1F, S1E and S1F**), suggesting that CB₁R in striatal D₁R-positive cells
22 do not participate to this type of memory. Anatomical data indicate that a subset
23 of hippocampal neurons contain D₁R (Gangarossa et al., 2012), likely co-
24 expressing CB₁R protein (Puighermanal et al., 2017). Thus, we re-express the
25 *CB₁R* gene in the hippocampus of D₁-*CB₁R*-KO mice to obtain HPC-*CB₁R*-RS mice
26 (**Figure 1D and 1G**). This manipulation fully rescued the phenotype of the
27 mutant mice (**Figure 1F, S1E and S1F**), indicating that hippocampal CB₁R
28 expressed in D₁R-positive cells are required for NOR memory.

29 We recently reported that deletion of CB₁R in hippocampal glial acidic
30 fibrillary protein (GFAP)-positive cells (i.e. mainly astrocytes, GFAP-*CB₁R*-KO
31 mice) also impaired NOR memory (Robin et al., 2018). Indeed, GFAP-*CB₁R*-KO
32 mice were impaired in NOR (**Figure S1G-S1I**; Robin et al., 2018) but, in

1 contrast to D₁-CB₁-KO mice, this phenotype extended to short-term NOR
2 memory (**Figure S1J-S1L**). This difference suggests that CB₁R expressed in
3 hippocampal astrocytes or D₁R-positive cells might control distinct phases of
4 NOR memory consolidation.

5 The primary function of CB₁R activation in neurons is to decrease
6 neurotransmitter release (Castillo et al., 2012, Busquets-Garcia et al., 2017).
7 Accordingly, the deletion of CB₁R from neurons often results in excessive
8 neurotransmission. Thus, we reasoned that inhibition of hippocampal D₁R-
9 positive neurons during NOR consolidation should be able to rescue the
10 memory impairment of D₁-CB₁-KO mice. Viral vectors carrying Cre-dependent
11 expression of an inhibitory Designer Receptor Exclusively Activated by
12 Designer Drugs (DIO-hM4DGi, DREADD-Gi; Robinson and Adelman, 2015) or
13 control mCherry protein were infused into the hippocampi of D₁-CB₁-KO mice
14 and WT littermates (**Figure 1H**). Post-training CNO injections did not affect the
15 NOR performance of D₁-CB₁-KO and WT mice injected with either DREADD-Gi
16 or mCherry, indicating that the drug or its metabolites had no effect *per se*
17 [(Gomez et al., 2017), **Figure 1I, S1M and S1N**]. Conversely, post-acquisition
18 CNO treatment fully rescued the NOR impairment of D₁-CB₁-KO mice
19 expressing DREADD-Gi (**Figure 1I, S1M and S1N**). This strongly suggests that
20 excessive activity of D₁R-positive neurons during the consolidation process is
21 responsible for the memory impairment observed in D₁-CB₁-KO mice.

22 **CB₁R IN HIPPOCAMPAL D₁R-POSITIVE NEURONS CONTROL LEARNING- 23 INDUCED CHANGES OF LTP IN VIVO**

24 Cellular and molecular mechanisms underlying activity-dependent
25 changes in synaptic plasticity are proposed to underlie long-term memory
26 (Aggleton and Morris, 2018). Previous studies showed that conditional and
27 global deletion of CB₁R in neuronal and glial cell populations induces deficits in
28 learning and associated synaptic plasticity (Busquets-Garcia et al., 2017; Robin
29 et al., 2018). To address the role of CB₁R in hippocampal D₁R-positive neurons
30 in the modulation of synaptic plasticity, we recorded *in vivo* evoked field
31 excitatory postsynaptic potentials (fEPSPs) in the hippocampal CA3-CA1
32 pathway of anesthetized mice. High Frequency Stimulation (HFS) induced
33 similar long-lasting LTP of synaptic fEPSPs in both D₁-CB₁-KO and WT

1 littermates (**Figure 2A and 2B**), indicating that hippocampal D₁R/CB₁R-positive
2 neurons are dispensable for the expression of LTP in naïve animals.

3 Hippocampal-dependent memory-related processes such as LTP are
4 sensitive to pharmacological and genetic modulation of hippocampal D₁R,
5 particularly after learning (Li et al., 2003, Lemon and Manahan-Vaughan, 2006,
6 Takeuchi et al., 2016, Yamasaki and Takeuchi, 2017). Thus, we hypothesized
7 that CB₁R in D₁R-positive neurons may modulate learning-dependent
8 hippocampal synaptic plasticity. To explore whether acquisition of the NOR task
9 modulates *in vivo* LTP; we recorded fEPSP from C57Bl6/NRj mice after NOR
10 task (**Figure 2C**). The HFS induced stronger LTP in animals exposed to NOR
11 acquisition than in control mice (**Figure 2D and 2E**), showing that the training
12 modulates hippocampal synaptic plasticity. Strikingly, D₁-CB₁-KO mice lacked
13 this learning-induced enhancement of LTP (**Figure 2F and 2G**). Thus,
14 physiological activation of CB₁R in hippocampal D₁R-positive neurons is
15 required for learning-dependent facilitation of LTP.

16 **CB₁R IN HIPPOCAMPAL D₁R-POSITIVE NEURONS MODULATE NOR** 17 **MEMORY CONSOLIDATION THROUGH A GABAERGIC-DEPENDENT** 18 **MECHANISM**

19 D₁R are expressed in different hippocampal cells, including subsets of
20 GABAergic and glutamatergic neurons (Gangarossa et al., 2012). Considering
21 that CB₁R signaling decreases the activity of both hippocampal neurons
22 (Busquets-Garcia et al., 2017, Castillo et al., 2012), we asked whether
23 excessive glutamatergic or GABAergic neurotransmission might underlie the
24 phenotype of D₁-CB₁-KO mice. Thus, we injected non-amnesic doses
25 (Puighermanal et al., 2009) of the NMDA receptor blocker MK-801, the
26 AMPA/kainate receptor antagonist NBQX (**Figure S2A**) or of the GABA_A
27 receptor antagonist Bicuculline in D₁-CB₁-KO and WT littermates immediately
28 after the NOR training. MK-801 or NBQX did neither alter memory performance
29 in WT mice nor did it rescue the amnesic phenotype of D₁-CB₁-KO littermates
30 (**Figure 3A, S2B and S2C**). Conversely, Bicuculline completely reversed the
31 memory impairment of D₁-CB₁-KO mice when injected immediately after
32 training or 1h later, without affecting WT littermates' performance (**Figure 3A,**
33 **S2B and S2C**).

1 These data indicate that excessive GABAergic, but not glutamatergic,
2 ionotropic receptor activity is involved in the phenotype of D₁-CB₁-KO mice. A
3 large proportion of GABAergic hippocampal interneurons contain CB₁R mRNA,
4 which is expressed at different levels [high CB₁R- and low CB₁R-expressing
5 cells; (Marsicano and Lutz, 1999)]. Conversely, D₁R mRNA is expressed at very
6 low levels in the hippocampus ([http://mouse.brain-
7 map.org/experiment/show/35](http://mouse.brain-map.org/experiment/show/35), data not shown), which makes it difficult to
8 accurately quantify its expression above background. Therefore, in order to
9 pinpoint which CB₁R-positive interneurons in the hippocampus contain D₁R, we
10 combined fluorescence *in situ* hybridization for CB₁R mRNA in D₁-Cre and D₁-
11 CB₁-KO mice carrying viral Cre-dependent expression of mCherry (see
12 methods and **Figure 3B**). As described (Marsicano and Lutz, 1999), detectable
13 levels of CB₁R mRNA were present throughout the hippocampus both in
14 pyramidal neurons and in GABAergic interneurons (**Figure S2D**). The
15 distribution of mCherry-tagged D₁-positive neurons in the dorsal CA1 region of
16 D₁-Cre mice was similar to previous findings (Puighermanal et al., 2017,
17 Gangarossa et al., 2012). Double staining revealed that virtually no high CB₁R-
18 expressing interneurons in *strata oriens*, *pyramidale*, *radiatum* or *lacunosum*
19 *moleculare* contain D₁R (**Figure 3C-3F and S2D**). Conversely, D₁R is present
20 in a small subpopulation of low CB₁R-expressing interneurons along the
21 different hippocampal layers (**Figure 3C and 3F**). Importantly, this co-
22 expression was virtually abolished in hippocampi of D₁-CB₁-KO mice (**Figure**
23 **3C, 3D and 3F**).

24 Altogether, these data indicate that CB₁R-dependent modulation of a
25 small subpopulation of D₁R-positive GABAergic interneurons is required during
26 NOR memory consolidation.

27 **SYNAPTIC MECHANISMS UNDERLYING NOR MEMORY CONSOLIDATION** 28 **AND ASSOCIATED HIPPOCAMPAL PLASTICITY**

29 The data collected so far show that reduction of GABAergic signaling
30 prevents the deficits of D₁-CB₁-KO mice in NOR consolidation. Therefore, we
31 tested whether inhibition of GABA_A receptors could rescue the lack of learning-
32 induced LTP enhancement observed in D₁-CB₁-KO mice. Trained mice
33 received Bicuculline or vehicle before testing LTP induction in hippocampal

1 circuits. In vehicle-treated animals, D₁-CB₁-KO mice showed no training-
2 induced LTP enhancement (**Figure 4A-4C**). Strikingly, whereas Bicuculline did
3 not affect LTP in WT animals, it rescued the training-induced LTP of D₁-CB₁-KO
4 mice (**Figure 4A-4C**).

5 Recent data suggest that hippocampal D₁R-like receptors participate in
6 memory formation, but little is known concerning the cell types involved (Lisman
7 et al., 2011, Yamasaki and Takeuchi, 2017). Our data indicate that CB₁R-
8 dependent control of GABAergic transmission from a low number of
9 hippocampal interneurons expressing D₁R is required to guarantee late
10 consolidation of NOR memory. Therefore, it is possible that endocannabinoid
11 actions are secondary to an activation of D₁R in these cells. To address this
12 issue, we first reasoned that partial inhibition of D₁R should "replace" the lack of
13 CB₁R-dependent control of neurotransmission in D₁-CB₁-KO mice. Thus, we
14 administered a sub-effective dose of the D_{1/5}R antagonist SCH-23390 (**Figure**
15 **S3A-S3C**) to D₁-CB₁-KO mice and WT littermates after NOR acquisition and we
16 analyzed the training-induced enhancement of *in vivo* LTP. This treatment
17 slightly reduced the late phase of LTP in WT animals (**Figure 4A-4C**). However,
18 the antagonist abolished the differences between D₁-CB₁-KO mice and WT
19 littermates (**Figure 4A-4C**), indicating that reducing D₁R activity counteracts the
20 absence of CB₁R in the mutants. If LTP is mechanistically linked to NOR
21 consolidation, the same treatment should rescue the memory impairment of D₁-
22 CB₁-KO mice. The administration of SCH-23390 did not alter the behavior of
23 WT mice (**Figure 4D, S3D and S3E**) but, strikingly, it fully rescued the memory
24 impairment of D₁-CB₁-KO littermates (**Figure 4D, S3D and S3E**).

25 Altogether, these results indicate that endocannabinoid-dependent
26 regulation of hippocampal D₁R-positive interneurons represents a necessary
27 step in the dopaminergic control of NOR memory consolidation and associated
28 synaptic plasticity.

1 **DISCUSSION**

2 The present study reveals that a specific subpopulation of hippocampal
3 D₁R/CB₁R-positive neurons controls late consolidation of NOR memory and
4 associated synaptic plasticity by moderating local inhibitory GABAergic activity
5 in the hippocampus. Specifically, CB₁R expressed in D₁R-positive interneurons
6 participate in learning-induced facilitation of *in vivo* LTP and are required for
7 consolidation of NOR memory. Moreover, CB₁R in D₁R-positive neurons are
8 necessary for physiological D₁R-dependent modulation of memory processes,
9 suggesting that cannabinoid signaling is part of a complex modulatory circuit
10 regulated by dopamine transmission in the hippocampus. By determining
11 cellular and behavioral functions of a specific CB₁R-expressing interneuron
12 subpopulation, these data uncover an unforeseen role of CB₁R in the D₁R-
13 dependent control of long-term memory.

14 The endocannabinoid system regulates episodic-like recognition memory
15 processes *via* CB₁R-dependent control of different cell types within the
16 hippocampus (Busquets-Garcia et al., 2017; Soria-Gomez et al., 2017;
17 Busquets-Garcia et al., 2016; Puighermanal et al., 2009; Robin et al., 2018). In
18 the present study we observed that the transition from short- to long-term
19 memory processes is controlled by a functional interaction between D₁R and
20 CB₁R receptors in a specific subpopulation of hippocampal interneurons. In
21 contrast, CB₁R receptor deletion from all body cells or in all forebrain
22 GABAergic neurons does not reproduce the phenotype of D₁-CB₁-KO mice
23 (Puighermanal et al., 2009; Hebert-Chatelain et al., 2016). These apparently
24 contrasting observations can be explained by different possibilities. Long-term
25 deletion of the *CB₁R* gene starting from early developmental stages both in
26 *CB₁R*-KO and *GABA-CB₁R*-KO mice might induce compensatory mechanisms (El-
27 Brolosy et al., 2019; El-Brolosy and Stainier, 2017) masking the functional role
28 of the CB₁R in NOR memory. An alternative or complementary explanation
29 might point to the presence of different subpopulations of brain cells expressing
30 CB₁R and exerting opposite effects on memory processes. For instance,
31 endocannabinoid signaling might promote or inhibit memory formation when
32 acting at D₁R-positive cells or at other neuronal subpopulations, respectively.
33 We have previously shown that astroglial CB₁R are necessary for consolidation

1 of NOR memory by allowing D-Serine availability at glutamatergic synapses
2 (Robin et al., 2018). We cannot fully exclude that deletion of CB₁R in D₁R-
3 positive cells does not involve also astrocytes (Nagatomo et al., 2017).
4 However, no conclusive anatomical evidence so far has been presented for the
5 expression of D₁R in hippocampal astrocytes [(Chai et al., 2017; Zhang et al.,
6 2014), but see (Jennings et al., 2017) for D_{1/5}R pharmacological experiments].
7 Moreover, our current and past results suggest that endocannabinoid control of
8 astrocytes is likely involved in the initial phases of memory formation, whereas
9 the CB₁R-dependent inhibition of D₁R-positive hippocampal interneurons
10 determines later phases of NOR memory consolidation. The time-course effects
11 of pharmacological treatments indicate that D-serine can rescue memory
12 performance of GFAP-CB₁-KO mice only when administered immediately after
13 learning (Robin et al., 2018). This idea is reinforced by the fact that these
14 mutants do not express *in vivo* LTP even in basal "home-cage" conditions
15 (Robin et al., 2018), whereas D₁-CB₁-KO mice only lack the specific facilitation
16 of LTP induced by learning. Altogether, these observations allow speculating
17 that at least two distinct temporal windows exist in the CB₁R-dependent control
18 of NOR. First, astroglial CB₁R are necessary for the plastic processes to initiate
19 the memory. Later, the endocannabinoid-dependent regulation of D₁R-positive
20 interneurons is required to maintain the memory trace for longer periods.

21 Hippocampal D₁R were previously shown to be mainly on GABAergic
22 interneurons, but lower levels were also detected on glutamatergic neurons
23 (Gangarossa et al., 2012; Puighermanal et al., 2017; [http://celltypes.brain-
24 map.org/rnaseq/mouse_ctx-hip_smart-seq](http://celltypes.brain-map.org/rnaseq/mouse_ctx-hip_smart-seq)). Our data show that the D₁-Cre
25 mouse line used in the present study (Lemberger et al., 2007) induces
26 recombination in a small sub-fraction of hippocampal interneurons containing
27 low levels of CB₁R mRNA, but also in pyramidal neurons and mossy cells.
28 Therefore, we cannot fully exclude that other cell types than hippocampal
29 interneurons might participate in the D₁R/CB₁R-dependent control of memory
30 consolidation. However, our data show that partial blockade of GABA_A
31 receptors, but not of AMPA/Kainate or NMDA glutamatergic ones, reverse the
32 memory impairment of D₁-CB₁-KO mice. Therefore, our findings strongly
33 suggest that CB₁R-control of GABA release from D₁R-positive interneurons

1 regulates late consolidation of NOR memory. However, recent data using
2 emerging technologies suggest that hippocampal cells are more diverse and
3 functionally segregated than previously thought (Harris et al., 2018; Soltesz and
4 Losonczy, 2018). By identifying specific markers, future studies will extend our
5 genetic and pharmacological evidence that a specific subpopulation of
6 D₁R/CB₁R-positive hippocampal interneurons regulates consolidation of NOR
7 memory.

8 LTP at the CA3-CA1 pathway represents a potential molecular and
9 cellular mechanism underlying the behavioral expression of episodic-like
10 memory processes (Morris, 2013). Interestingly, whereas deletion of CB₁R from
11 D₁R-positive cells impairs NOR memory, the same manipulation does not
12 impair *in vivo* LTP of hippocampal synaptic transmission in naïve animals. In
13 agreement with previous evidence in other experimental conditions (Li et al.,
14 2003; Lemon and Manahan-Vaughan, 2006), WT mice exposed to the NOR
15 learning task display a facilitation of *in vivo* LTP as compared to animals
16 exposed to the same environment without any learning. Importantly, this
17 facilitation is absent in D₁-CB₁-KO mice, suggesting that the endocannabinoid
18 control of D₁R-positive hippocampal interneurons is recruited only after learning.
19 The facilitation might be due to a "real" stronger synaptic transmission after
20 learning or to a decrease of baseline synaptic activity (Lisman, 2017), which
21 might be occluded in D₁-CB₁-KO mice. The fact that partial blockade of GABA_A
22 receptors in trained WT mice does not alter the LTP facilitation, suggests that
23 this phenomenon is due to a genuine increase of LTP. In addition, our data
24 indicate that reducing GABAergic transmission in D₁R-positive neurons is
25 required for this form of learning-induced synaptic plasticity. These results
26 reinforce the idea that, in order to reveal relevant mechanisms, investigations
27 on synaptic plasticity associated to memory processes should include not only
28 naïve animals, but also behaviorally challenged ones (Lisman et al., 2011).

29 D₁R activity in the hippocampus is necessary for long-term memory,
30 synaptic plasticity and network dynamics (Lisman et al., 2011, Yamasaki and
31 Takeuchi, 2017; Kaufman et al., 2020; Bethus et al., 2010). Consistently, our
32 results show that high-doses of the D_{1/5}R antagonist SCH23390 impair memory
33 performance in the NOR task. In addition, our data suggest that D₁R/CB₁R-

1 positive hippocampal interneurons are one of the targets of the dopaminergic
2 control of learning and memory processes. Interestingly, it has been shown that
3 parvalbumin (PV)-expressing interneurons require D₁R activity for late phases
4 of memory consolidation through the coordinate control of the activity of
5 hippocampal pyramidal neurons (Karunakaran et al., 2016). Particularly, the
6 authors describe that this D₁R activity modulates hippocampal network
7 oscillations (i.e. sharp-wave ripples), which is a proposed correlate for synaptic
8 plasticity and memory consolidation (Buzsaki, 2015). In addition, previous
9 studies have shown that PV/CB₁R-negative and CCK/CB₁R-positive
10 interneurons have complementary roles in ensuring such high oscillatory ripple
11 events with consequent capacity to modulate synaptic plasticity (Klausberger et
12 al., 2005; Buzsaki, 2015). Therefore, we speculate that the subpopulation of
13 D₁R/CB₁R-positive interneurons described in our work could play a
14 complementary role in maintaining proper excitation/inhibition balance in the
15 hippocampal network activity required for memory consolidation.

16 While the complete elucidation of the complex microcircuitry requires
17 further characterization, our findings support the hypothesis that D₁R/CB₁R-
18 positive hippocampal interneurons belong to a broader circuit participating in
19 the dopaminergic control of memory (Yamasaki and Takeuchi, 2017). Our data
20 are compatible with a scenario where D₁R activation during the
21 learning/consolidation process potentiates GABAergic transmission. However,
22 this D₁R-dependent increase of inhibition is kept within adequate limits by the
23 activation of CB₁R, thereby allowing a proper flow of information. In this sense,
24 in the absence of CB₁R-dependent control of D₁R/CB₁R-positive interneurons
25 (i.e. D₁-CB₁-KO mice), a partial inhibition of either D₁-like or GABA_A receptors
26 rescues the phenotype. In other words, whereas activation of D₁R in
27 interneurons seems to be necessary for the memory process, their abnormally
28 high activity (e.g. in the absence of CB₁R) impairs such functions. In this
29 context, an interesting question relates to the functional link between the
30 endogenous activation of D₁R and CB₁R. Our results allow speculating about
31 two potential scenarios, based on autocrine or paracrine modes of action of
32 endocannabinoid signaling (Busquets-García et al., 2017): (i) General D₁R-
33 dependent dopaminergic signaling in the hippocampus might activate pyramidal

1 neurons (Roggenhofs et al., 2013; Shivarama-Shetty et al., 2018) targeted by
2 D₁R/CB₁R-positive interneurons. This depolarization of pyramidal neurons
3 would, in turn, induce the canonical endocannabinoid-dependent retrograde
4 inhibition of GABAergic release (Castillo et al., 2012), thereby moderating,
5 amongst others, the activation of D₁R/CB₁R-positive interneurons. (ii) Following
6 D₁R activation and consequent interneuron depolarization (Anastasiades et al.,
7 2019; Gorelova et al., 2002), endocannabinoids might be mobilized locally and
8 act in an autocrine manner to decrease the membrane potential and thereby
9 moderate the activity of the neuron (Bacci et al., 2004). These two possibilities
10 are not mutually exclusive and they might reflect the impact of the mechanisms
11 described on general network activity and/or on specific plastic cellular
12 processes, respectively. Future studies will investigate these intriguing
13 scenarios using adapted experimental approaches.

14 Altogether, these data reveal that functionally distinct cell types are present in
15 the general population of hippocampal GABAergic interneurons expressing
16 CB₁R. In particular, D₁R/CB₁R-positive interneurons provide specific behavioral
17 and hippocampal synaptic mechanisms sustaining the fine-tuned regulation of
18 memory processes. The close interaction of CB₁R and D₁R in modulating
19 recognition memory might provide novel therapeutic frameworks for the
20 treatment of cognitive diseases characterized by alterations of both or either
21 endocannabinoid and dopaminergic systems.

22

1 **ACKNOWLEDGMENTS**

2 We thank Delphine Gonzales, Nathalie Aubailly and all the personnel of the
3 Animal Facilities of the NeuroCentre Magendie for mouse care. We thank the
4 Biochemistry Platform of Bordeaux NeuroCampus, and all the members of
5 Marsicano's lab for useful discussions. This work was funded by: INSERM,
6 European Research Council (Endofood, ERC-2010-StG-260515 and
7 CannaPreg, ERC-2014-PoC-640923, MiCaBra, ERC-2017-AdG-786467, to
8 G.M.), Fondation pour la Recherche Medicale (FRM, DRM20101220445 to
9 G.M.; DT20160435664 to J.F.O.d.C.), the Human Frontiers Science Program,
10 Region Aquitaine, Agence Nationale de la Recherche (ANR, NeuroNutriSens
11 ANR-13-BSV4-0006, ORUPS ANR-16-CE37-0010-01, CaCoVi ANR-18-CE16-
12 0001-02, to G.M.) and BRAIN ANR-10-LABX-0043, to GM; NIH/NIDA
13 (1R21DA037678-01), European Regional Development Fund, European
14 Union's Horizon 2020 Research and Innovation Programme (Grant Agreement
15 686009); French State/Agence Nationale de la Recherche/IdEx (ANR-10-IDEX-
16 03-02) and Eu-Fp7 (FP7-PEOPLE-2013-IEF-623638), and from MINECO/AEI
17 (RYC-2017-21776), to A.B-G; FRM (ARF20140129235), to L.B; Ikerbasque
18 (The Basque Foundation for Science), MINECO (Ministerio de Economía y
19 Competitividad) PGC2018-093990-A-I00 (MICIU/AEI/FEDER, UE), to E.S-G.

20 **AUTHOR CONTRIBUTIONS**

21 JFOdC, AB-G, GM and ES-G conceived and supervised the whole
22 project. JFOdC performed and analyzed *in vivo* electrophysiology and
23 behavioral experiments. AB-G and ES-G performed and analyzed behavioral
24 experiments. LB and AC contributed to experiments using viral vectors. LR and
25 GL contributed to behavioral experiments. MV, FJ-K, TLL and MM performed
26 cytochemical experiments. ZZ, MV helped with the analysis of the data. JFOdC,
27 AB-G, GM and ES-G wrote the manuscript. FD contributed to the writing. All
28 authors edited and approved the manuscript.

29

1 **DECLARATION OF INTERESTS**

2 The authors declare no competing interests.

3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

FIGURE 1. HIPPOCAMPAL CB₁R IN D₁R-POSITIVE CELLS ARE NECESSARY FOR LATE, BUT NOT EARLY, CONSOLIDATION OF NOR

(A) Schematic representation of NOR Memory task.

(B) Short-term (3 hours) NOR memory performance of D₁-CB₁-WT mice (n = 10) and D₁-CB₁-KO littermates (n = 7).

(C) Long-term NOR (24 hours) memory performance of D₁-CB₁-WT mice (n = 9) and D₁-CB₁-KO littermates (n = 8).

(D) Schematic representation of the experiment using viral re-expression of the CB₁R gene in the striatum (STR) or the hippocampus (HPC) of D₁-CB₁-WT mice and D₁-CB₁-KO littermates.

(E) Representative images of Cre-expressing D₁-CB₁-KO mice injected with CB₁R-myc in the STR using the same procedure as described in (D) (see methods). Scale bar = 2mm.

(F) NOR memory performance of mice with re-expression of the CB₁R gene in striatum (STR) or hippocampus (HPC). Control [n(D₁-CB₁-WT)=17 and n(D₁-CB₁-KO)=5], STR-CB₁-RS [n(D₁-CB₁-KO)=6] or HPC-CB₁-RS [n(D₁-CB₁-KO)=9].

(G) Immunofluorescence of cells expressing CB₁R-myc in the hippocampus. Scale bar = 500 μm.

(H) Schematic representation of the experiment using viral expression of the Gi-DREADDs or mCherry in the hippocampus of D₁-CB₁-WT mice and D₁-CB₁-KO littermates. Clozapine N-oxide (CNO, 2mg/kg) injections take place after the Training phase of the NOR task.

(I) NOR memory performance of D₁-CB₁-WT mice intra-hippocampally injected with hM4D(Gi) virus or mCherry [n(VEH)=16 and n(CNO)=21], D₁-CB₁-KO mice injected with mCherry [n(VEH)=6 and n(CNO)=7] and D₁-CB₁-KO mice intra-hippocampally injected with hM4D(Gi) [n(VEH)=11 and n(CNO)=14].

Data, mean ± SEM. *p < 0.05, ***p < 0.001, ****p < 0.0001, ns=not significant.

See also **Figure S1** and **Table S1**.

1 **FIGURE 2. LEARNING-INDUCED FACILITATION OF *IN VIVO* HIPPOCAMPAL**
2 **LTP REQUIRES CB₁R AT D₁R-POSITIVE NEURONS**

3 (A and B) HFS in the dorsal hippocampal CA3 Shaffer-Collateral pathway
4 induces an *in vivo* LTP in dorsal CA1 *stratum radiatum*. (A) Summary plots of
5 recorded evoked fEPSP in anesthetized D₁-CB₁-WT (n=8) and D₁-CB₁-KO
6 (n=8) mice. (B) Bar histograms of normalized fEPSP from (A) representing 30
7 and 60 minutes after HFS.

8 (C) Schematic representation of the experimental setup (see methods).

9 (D and E) Learning modulates *in vivo* LTP. (D) Summary plots of recorded
10 evoked fEPSP from mice expose to Control (n=8) and NOR Training (n=11)
11 conditions. (E) Bar histograms of normalized of evoked fEPSP from (D)
12 representing 30 and 60 minutes after HFS.

13 (F and G) Learning-induced modulation of *in vivo* LTP is impaired in D₁-CB₁-KO
14 mice. (F) Summary plots of recorded fEPSP in anesthetized D₁-CB₁-WT (n=10)
15 and D₁-CB₁-KO (n=10) mice. (G) Bar histograms of normalized of evoked
16 fEPSP from (F) representing 30 and 60 minutes after HFS.

17 Traces on the right side of the summary plots represent 150 superimposed
18 evoked fEPSP before HFS (1, grey), 30 minutes (2, brown) and 60 minutes (3,
19 black) after HFS.

20 Data, mean ± SEM. *p < 0.05, ns=not significant.

21 See also **Table S1**.

22

1 **FIGURE 3. HIPPOCAMPAL CB₁R/D₁R-POSITIVE INTERNEURONS**
2 **MODULATE SYNAPTIC GABAERGIC TRANSMISSION.**

3 (A) NOR memory performance of mutant mice administered with: vehicle [n(D₁-
4 CB₁-WT)=14 and n(D₁-CB₁-KO)=14], MK-801 [0.1 mg/kg, IP; n(D₁-CB₁-WT)=7
5 and n(D₁-CB₁-KO)=7], NBQX [5 mg/kg, IP; n(D₁-CB₁-WT)=8 and n(D₁-CB₁-
6 KO)=5], or Bicuculline immediately after [n(D₁-CB₁-WT)=10 and n(D₁-CB₁-
7 KO)=10] or 1 hour after the training phase [n(D₁-CB₁-WT)=10 and n(D₁-CB₁-
8 KO)=8].

9 (B) Schematic representation of the experimental procedure to detect CB₁R
10 mRNA in D₁R-positive cells.

11 (C and D) Representative images of CB₁R mRNA (in green) and mCherry
12 protein (in red) labeling in the hippocampal CA1 region of D₁-Cre (C) and D₁-
13 CB₁-KO (D) mice. White arrows indicate colocalization between CB₁R-positive
14 and D₁R-positive cell bodies. Scale bar = 150 μm.

15 (E and F) Floating bars indicating the layer specific distribution of the % of cell
16 bodies expressing high (E) and low amounts (F) of CB₁R, which colocalize with
17 mCherry-positive (i.e. D₁R-positive) in D₁-Cre (n=3) and D₁-CB₁-KO (n=3).

18 Data, mean ± SEM. *p < 0.05, **p < 0.01, ns=not significant.

19 See also **Figure S2** and **Table S1**.

1 **FIGURE 4. CELLULAR MECHANISMS LINKING D₁R-SIGNALLING WITH**
2 **GABAERGIC ACTIVITY DURING LEARNING-INDUCED FACILITATION OF *IN***
3 ***VIVO* LTP AND MEMORY CONSOLIDATION**

4 (A) Effects of the GABA_A receptor antagonist Bicuculline, the D_{1/5}R antagonist
5 SCH 23390 on learning-induced modulation of *in vivo* LTP in D₁-CB₁-WT and
6 D₁-CB₁-KO mice. Summary plots of recorded evoked fEPSP in Vehicle [n(D₁-
7 CB₁-WT)=6 and n(D₁-CB₁-KO)=8], Bicuculline [0.5 mg/kg; IP, n(D₁-CB₁-WT)=9
8 and n(D₁-CB₁-KO)=11] and SCH 23390[0.3 mg/kg; IP, n(D₁-CB₁-WT)=6 and
9 n(D₁-CB₁-KO)=6].

10 (B and C) Bar histograms of (A) representing normalized fEPSP from 30 (B)
11 and 60 (C) minutes after HFS.

12 (D) Memory performance D₁-CB₁-WT and D₁-CB₁-KO mice after being injected
13 with vehicle [n(D₁-CB₁-WT)=6 and n(D₁-CB₁-KO)=10] or SCH 23390 [0.3 mg/kg;
14 IP, n(D₁-CB₁-WT)=10 and n(D₁-CB₁-KO)=10]

15 Traces on the right side of the summary plot (A) represent 150 superimposed
16 evoked fEPSP before HFS (1, grey), 30 minutes (2, brown) and 60 minutes (3,
17 black) after HFS.

18 Data, mean ± SEM. *p < 0.05, **p < 0.01, ns=not significant.

19 See also **Figure S3** and **Table S1**.

20
21
22
23
24
25
26
27
28
29
30

1 **STAR METHODS**

2 **RESOURCE AVAILABILITY**

3

4 **LEAD CONTACT**

5

6 Further information and requests for resources and reagents should be directed
7 to and will be fulfilled by the Lead Contact, Giovanni Marsicano
8 (giovanni.marsicano@inserm.fr).

9

10 **MATERIALS AVAILABILITY**

11

12 Mouse lines generated and used in the current study are available from the lead
13 contact upon request. We are glad to share the mouse lines with reasonable
14 compensation by requestor for its processing and shipping.

15

16 **DATA AND CODE AVAILABILITY**

17

18 The data supporting the current study have not been deposited in a public
19 repository but are available from the lead contact on request.

20

1 **EXPERIMENTAL MODEL AND SUBJECT DETAILS**

2 **ANIMAL MODEL**

3 All experimental procedures were approved by the ethical committee of the
4 French Ministry of Higher Education, Research and Innovation (authorization
5 APAFIS#18111). Maximal efforts were made to reduce the suffering of the
6 animals. Male mice were used in this study.

7 D_1 - CB_1 -KO mice were generated as previously described (Monory et al., 2007;
8 Terzian et al., 2011). Briefly, CB_1 floxed mice (Marsicano et al., 2003) were
9 crossed with D_1 -Cre line (Lemberger et al., 2007), in which the Cre
10 recombinase was placed under the control of the D_1 gene (*Drd1a*) regulatory
11 sequences using transgenesis with modified bacterial artificial chromosomes.
12 The pattern of Cre expression recapitulated the expression pattern of the
13 endogenous *Drd1a* (Lemberger et al., 2007). Breeding was performed by
14 mating male Cre-positive D_1 - CB_1 -KO mice with homozygous CB_1 -flox female
15 mice deriving from a separate colony. In order to detect possible germline or
16 ectopic recombination events, genotyping of tail samples from pups (PD10) was
17 performed by genomic PCR using primers suited to identify WT, “floxed” and
18 “recombined” bands. No germline or ectopic recombination was detected. Eight
19 to 14 weeks-old naïve male D_1 - CB_1 -KO and WT littermates were used. 8-14
20 weeks old male C57BL/6Rj mice purchased from Janvier (France). 8-12 weeks-
21 old D_1 -Cre mice breed in the animal facilities of the U1215 we also used.
22 Animals were housed collectively under standard conditions of temperature and
23 humidity in a day/night cycle of 12/12 hours (light on at 7 am). Animals that
24 underwent surgery were kept in individual cages after the procedures to avoid
25 conflict with their littermates. Food and water were provided *ad libitum*. All the
26 experiments were performed during the light phase. Behavioral experiments
27 were performed from 9 am to 3 pm. Electrophysiology experiments were
28 performed from 8 am to 7 pm.

29

1 **METHOD DETAILS**

2

3 **DRUG PREPARATION AND ADMINISTRATION**

4 Bicuculline, MK-801, NBQX and SCH23390 were purchased from Merck
5 (formerly Sigma-Aldrich, France) and were dissolved to their final concentration
6 in physiological saline (NaCl 0.9%). The exogenous DREADD ligand clozapine-
7 N-oxide (CNO, 2 mg/kg) was purchased from Tocris Bioscience (Bristol, UK)
8 and dissolved in saline after gently mixing with a vortex. All drugs were injected
9 intraperitoneally in a volume of 10 ml/kg. Vehicle in all the conditions was
10 composed of physiological saline (NaCl 0.9%) injections.

11 **NOVEL OBJECT RECOGNITION MEMORY**

12 We used the novel object recognition (NOR) memory task in an L-maze
13 (Busquets-Garcia et al., 2013; Busquets-Garcia et al., 2011; Hebert-Chatelain
14 et al., 2016; Puighermanal et al., 2013; Puighermanal et al., 2009; Robin et al.,
15 2018).

16 The task took place in a L-shaped maze made of dark grey polyvinyl chloride
17 made by two identical perpendicular arms (35 cm and 30 cm long respectively
18 for external and internal L walls, 4.5cm wide and 15 cm high walls) placed on a
19 white background (Busquets-Garcia et al., 2011; Puighermanal et al., 2009).
20 The task occurred in a room adjacent to the animal house with a light intensity
21 fixed at 50 lux. The maze was overhung by a video camera allowing the
22 detection and offline scoring of animal's behavior. The task consisted in 3
23 sequential daily trials of 9 minutes each. During the habituation phase (day 1),
24 mice were placed in the center of the maze and allowed to freely explore the
25 arms in the absence of any objects. The training phase (day 2) consisted in
26 placing the mice again in the corner of the maze in the presence of two identical
27 objects positioned at the extremities of each arm and left to freely explore the
28 maze and the objects. The testing phase occurred 24 hours later (day 3): one of
29 the familiar objects was replaced by a novel object different in its shape, color
30 and texture and mice were left to explore both objects. The position of the novel
31 object and the associations of novel and familiar were randomized. All objects

1 were previously tested to avoid biased preference. Memory performance was
2 assessed by the discrimination index (DI). The DI was calculated as the
3 difference between the time spent exploring the novel (TN) and the familiar
4 object (TF) divided by the total exploration time (TN+TF): $DI = [TN - TF] / [TN + TF]$.
5 Memory was also evaluated by directly comparing the exploration time of novel
6 and familiar objects, respectively. Object exploration was defined as the
7 orientation of the nose to the object at less than 2 cm. Experienced
8 investigators evaluating the exploration were blind of treatment and/or genotype
9 of the animals. Pharmacological treatments were immediately administered
10 after the training phase.

11 ***IN VIVO* ELECTROPHYSIOLOGY IN ANESTHETIZED MICE**

12 Experiments were performed as described in (Robin et al., 2018). Mice were
13 anesthetized in a box containing 5% Isoflurane (Virbac, France) before being
14 placed in a stereotaxic frame (Model 900, Kopf instruments, CA, USA) in which
15 1.0% to 1.5% of Isoflurane was continuously supplied via an anesthetic mask
16 during the whole duration of the experiment. The body temperature was
17 maintained at $\pm 36.5^{\circ}\text{C}$ using a homoeothermic system (model 50-7087-F,
18 Harvard Apparatus, MA, USA) and the state of anesthesia was assessed by
19 mild tail pinch. Before surgery, 100 μl of the local anesthetic lurocaine
20 (vetoquinol, France) was injected in the scalp region. Surgical procedure started
21 with a longitudinal incision of 1.5 cm in length aimed to expose Bregma and
22 Lambda. After ensuring the correct alignment of the head, two holes were
23 drilled in the skull for electrode placement. Glass recording electrodes were
24 inserted in the CA1 stratum radiatum, and a concentric stimulating bipolar
25 electrode (Model CBARC50, FHC, ME, USA) placed in the CA3 region.
26 Coordinates were as follows: CA1 stratum radiatum: A/P 1.5, M/L 1.0, DV 1.20;
27 CA3: A/P 2.2, M/L 2.8, D/V 1.3 (20 insertion angle). The recording electrode (tip
28 diameter = 1–2 mm, 2–4 M Ω) was filled with a 2% pontamine sky blue solution
29 in 0.5M sodium acetate. At first the recording electrode was placed by hand
30 until it reached the surface of the brain and then to the final depth using a
31 hydraulic micropositioner (Model 2650, KOPF instruments, CA, USA). The
32 stimulation electrode was placed in the correct area using a standard
33 manipulator. Both electrodes were adjusted to find the area with maximum

1 response. *In vivo* recordings of evoked field excitatory postsynaptic potentials
2 (fEPSPs) were amplified 1000 times and filtered (low-pass at 1Hz and high-
3 pass 3000Hz) by a DAGAN 2400A amplifier (DAGAN Corporation, MN, USA).
4 fEPSPs were digitized and collected on-line using a laboratory interface and
5 software (CED 1401, SPIKE 2; Cambridge Electronic Design, Cambridge, UK).
6 Test pulses were generated through an Isolated Constant Current Stimulator
7 (DS3, Digitimer, Hertfordshire, UK) triggered by the SPIKE 2 output sequencer
8 via CED 1401 and collected every 2 s at a 10 kHz sampling frequency and then
9 averaged every 180 s. Test pulse intensities were typically between 40-250 μ A
10 with a duration of 50 ms. Basal stimulation intensity was adjusted to 30%–50%
11 of the current intensity that evoked a maximum field response. All responses
12 were expressed as percent from the average responses recorded during the 15
13 min before high frequency stimulation (HFS). HFS was induced by applying 3
14 trains of 100 Hz (1 s each), separated by 20 s interval. fEPSP were then
15 recorded for a period of 60 min. C57BL6/NRj mice underwent this *in vivo*
16 electrophysiology procedure after the training phase of NOR task. Also, where
17 specified, D₁-CB₁-KO and D₁-CB₁-WT received an injection of Bicuculine (0.5
18 mg/kg, intraperitoneal) or SCH 23390 (0.3 mg/kg, intraperitoneal) or vehicle
19 immediately after undergoing training in NORT and before being subjected to
20 the *in vivo* electrophysiology procedure. At the end the experiment, the position
21 of the electrodes was marked (recording area: iontophoretic infusion of the
22 recording solution during 180 s at 20mA; stimulation area: continuous current
23 discharge over 20 s at +20mA) and histological verification was performed *ex*
24 *vivo*.

25

1 SURGERY AND VIRAL ADMINISTRATION

2 Mice were anesthetized in a box containing 5% Isoflurane (Virbac, France)
3 before being placed in a stereotaxic frame (Model 900, Kopf instruments, CA,
4 USA) in which 1.0% to 1.5% of Isoflurane was continuously supplied via an
5 anesthetic mask during the whole duration of the experiment. For viral intra-
6 HPC AAV delivery, mice were submitted to stereotaxic surgery (as above) and
7 AAV vectors were injected with the help of a microsyringe (0.25 ml Hamilton
8 syringe with a 30-gauge beveled needle) attached to a pump (UMP3-1, World
9 Precision Instruments, FL, USA). Where specified, D₁-CB₁-WT and D₁-CB₁-KO
10 mice were injected directly into the hippocampus (HPC) or striatum (STR) (0.5
11 µl per injection site at a rate of 0.5 µl per min), with the following coordinates:
12 HPC, AP -1.8; ML ±1; DV -2.0 and -1.5; Striatum: AP -1.34; ML ±2.8; DV -1.84.
13 Following virus delivery, the syringe was left in place for 1 minute before being
14 slowly withdrawn from the brain. CB₁ *floxed* mice were injected with rAAV-CAG-
15 DIO (empty control vector), AAV-CAG-DIO-CB₁ or AAV-CAG-DIO-CB₁-myc to
16 induce re-expression of the CB₁ receptor gene in hippocampal or striatal D₁-
17 positive cells. To generate the aforementioned rAAVs, mouse CB₁ receptor
18 coding sequence (either native or fused to myc-tag at the C term) was cloned in
19 rAAV-CAG-DIO vector using standard molecular cloning technology. The
20 coding sequence was cloned inverted in orientation to allow Cre-dependent
21 expression of CB₁ receptors (Atasoy et al., 2008). In another experiment, and
22 using the same procedure as described as above, D₁-CB₁-WT and D₁-CB₁-KO
23 mice were injected intra hippocampally (AP -1.8; ML ±1; DV -2.0 and -1.5), with
24 pAAV-hSyn-DIO-hM4D(Gi)-mCherry or pAAV-hSyn-DIO-mCherry (addgene,
25 USA). For anatomical experiments and using the same procedure as above, D₁-
26 Cre and D₁-CB₁-KO were injected intra hippocampally with pAAV-hSyn-DIO-
27 mCherry. In this specific experiment, expression was allowed to take place for 2
28 weeks. For the remaining experiments, animals were used around 4-5 weeks
29 after local infusions. Mice were weighed daily and individuals that failed to
30 regain the pre-surgery body weight were excluded from the following
31 experiments.

32

1 **IMMUNOHISTOCHEMISTRY ON FREE-FLOATING SECTIONS.**

2 Mice were anesthetized with pentobarbital (Exagon, Axience SAS, 400 mg/kg
3 body weight), transcardially perfused with phosphate-buffered solution (PBS
4 0.1M, pH 7.4) before being fixed with 4% formaldehyde (Sigma-Aldrich). The
5 The brains were extracted and incubated overnight at 4°C in the same fixative,
6 then embedded with sucrose 30% for 3 days and finally frozen in 2-
7 methylbutane (Sigma-Aldrich) at -80°C. Free-floating frozen coronal sections
8 (40 µm) were cut out with a cryostat (Microm HM 500M Microm Microtech),
9 collected collected in an antifreeze solution and conserved at -20°C. Sections
10 were permeabilized in a blocking solution (in PBS: 10% donkey serum, 0.3%
11 Triton X-100) for 1 hour at room temperature (RT). Then, sections were
12 incubated with a rabbit primary antibody against the C-myc epitope tag (1:1000,
13 BioLegend) overnight at 4°C. After several washes with PBS, slices were
14 incubated for 2 hours with a secondary antibody goat anti-rabbit Alexa Fluor
15 488 (1:500, Fisher Scientific) and then washed in PBS at RT. Finally, sections
16 were incubated with 4',6-diamidino-2-phenylindole (DAPI 1:20000, Fisher
17 Scientific) diluted in PBS for 5 minutes to visualize cell nuclei and then were
18 washed, mounted and coverslipped. All the antibodies were diluted in blocking
19 solution. The sections were imagedimaged with a slides scanner Hamamatsu
20 Nanozoomer 2.0 HT.

21 **COMBINED FLUORESCENT *IN SITU* HYBRIDIZATION (FISH)/**
22 **IMMUNOHISTOCHEMISTRY (IHC) ON FREE-FLOATING FROZEN SECTIONS**

23 Mice were anesthetized with pentobarbital (Exagon, Axience SAS, 400 mg/kg
24 body weight), transcardially perfused with PBS (0.1M, pH 7.4) before being
25 fixed with 4% formaldehyde (Sigma-Aldrich). The brains were extracted and
26 incubated overnight at 4°C in the same fixative, then embedded with sucrose
27 30% for 3 days and finally frozen in 2-methylbutane (Sigma-Aldrich) at -80°C.
28 Free-floating frozen coronal sections were cut out with a cryostat (30 µm,
29 Microm HM 500M Microm Microtech) and collected in an antifreeze solution and
30 conserved at -20°C.

31 Section were washed several times with PBS with diethyl pyrocarbonate (PBS-
32 DEPC) to wash out the antifreeze solution. The endogenous peroxidases were

1 inactivated by incubating the free-floating sections with 3% H₂O₂ in PBS-DEPC
2 for 30 minutes. All endogenous biotin, biotin receptors, and avidin binding sites
3 present in the tissue were blocked by using the Avidin/Biotin Blocking Kit
4 (Vector Labs, USA). Then, the slices were incubated overnight at RT with a
5 rabbit polyclonal primary antibody against DsRed (1:1000, Takara Bio) diluted in
6 a blocking solution (0.3% Triton X-100 diluted in PBS-DEPC). The following
7 day, after several washes, the sections were incubated with a secondary
8 antibody goat anti-rabbit conjugated to a horseradish peroxidase (HRP) (1:500,
9 Cell Signaling Technology) during 2 hours at RT followed by TSA Biotin System
10 (Biotin TSA 1:100, PerkinElmer) for 10 minutes at RT. After several washes, the
11 slices were fixed with 4% of formaldehyde (Sigma Aldrich) for 10 minutes and
12 blocked with 0.2M HCl for 20 minutes at RT. Then, the section were acetylated
13 in 0.1 M Triethanolamine, 0.25% Acetic Anhydride for 10 minutes. This step
14 was performed to reduce non-specific probe binding. Sections were hybridized
15 overnight at 60°C with Digoxigenin (DIG)-labeled riboprobe against mouse CB₁
16 receptor (1:1000, prepared as described in (Marsicano and Lutz, 1999). After
17 hybridization, the slices were washed with different stringency wash buffers at
18 65°C. Then, the sections were incubated with 3% of H₂O₂ for 30 minutes at RT
19 and blocked 1 hour with NEN blocking buffer prepared according to the
20 manufacturer's protocol (PerkinElmer). Anti-DIG antibody conjugated to HRP
21 (1:2000, Roche) was applied for 2 hours at RT. The signal of CB₁ receptor
22 hybridization was revealed by a TSA reaction using fluorescein isothiocyanate
23 (FITC)-labeled tyramide (1:80 for 12 minutes, Perkin Elmer). After several
24 washes, the free-floating slices were incubated overnight at 4°C with
25 Streptavidin-Texas Red (1:400, PerkinElmer). Finally, the slices were incubated
26 with DAPI (1:20000; Fisher Scientific) diluted in PBS, following by several
27 washes, to finally be mounted, cover slipped and imaged with an
28 epifluorescence Leica DM 6000 microscope (Leica, Germany).

29

30

31

1 **QUANTIFICATION AND STATISTICAL ANALYSIS**

2 **DATA COLLECTION**

3 No statistical methods were used to pre-determine sample sizes, but they are
4 similar to those reported in previous publications. All data collection and/or
5 analysis were performed blind to the conditions of the experimenter except for
6 the *in vivo* electrophysiological experiments. All mice were assigned randomly
7 to the different experimental conditions.

8 **FLUORESCENCE QUANTIFICATIONS**

9 Cells expressing mRNAs were quantified in the different layers (*stratum oriens*,
10 *stratum pyramidale*, *stratum radiatum* and *stratum lacunosum moleculare*) of
11 the dorsal hippocampus. CB₁ receptor positive cells were classified according to
12 the level of transcript visualized by the intensity of fluorescence (Marsicano and
13 Lutz, 1999; Terral et al., 2019). “High-CB₁” cells were considered to be round-
14 shaped and intense staining covering the entire nucleus whereas “Low-CB₁”
15 cells were defined with discontinuous shape and lowest intensity of
16 fluorescence allowing the discrimination of grains of staining.

17 **STATISTICAL ANALYSES**

18 Data were expressed as mean ± SEM or single data points and were analyzed
19 with Prism 6.0 (Graphpad Software), using two-tails *t*-test (paired, unpaired) or
20 one-way ANOVA (Dunnett’s), two-way ANOVA (sidak’s). Sample sizes and p-
21 values can be found in figure legends and Table S1.

22

23

1 REFERENCES

- 2 AGGLETON, J. P. & MORRIS, R. G. M. 2018. Memory: Looking back and
3 looking forward. *Brain and Neuroscience Advances*, 2,
4 2398212818794830.
- 5 ANASTASIADES, P.G., BOADA, C., AND CARTER, A.G. 2019. Cell-Type-
6 Specific D1 Dopamine Receptor Modulation of Projection Neurons and
7 Interneurons in the Prefrontal Cortex. *Cerebral Cortex* 29, 3224–3242.
- 8 ATASOY, D., APONTE, Y., SU, H. H. & STERNSON, S. M. 2008. A FLEX
9 switch targets Channelrhodopsin-2 to multiple cell types for imaging and
10 long-range circuit mapping. *J Neurosci*, 28, 7025-30.
- 11 BACCI, A., HUGUENARD, J.R., AND PRINCE, D.A. 2004. Long-lasting self-
12 inhibition of neocortical interneurons mediated by endocannabinoids.
13 *Nature* 431, 312-316.
- 14 BETHUS, I., TSE, D., AND MORRIS, R.G. 2010. Dopamine and memory:
15 modulation of the persistence of memory for novel hippocampal NMDA
16 receptor-dependent paired associates. *The Journal of neuroscience : the*
17 *official journal of the Society for Neuroscience* 30, 1610-1618.
- 18
- 19 BUSQUETS-GARCIA, A., BAINS, J. & MARSICANO, G. 2017. CB1 Receptors
20 Signaling in the Brain: Extracting Specificity from Ubiquity.
21 *Neuropsychopharmacology*.
- 22 BUSQUETS-GARCIA, A., DESPREZ, T., METNA-LAURENT, M.,
23 BELLOCCHIO, L., MARSICANO, G. & SORIA-GOMEZ, E. 2015.
24 Dissecting the cannabinergic control of behavior: The where matters.
25 *Bioessays*, 37, 1215-25.
- 26 BUSQUETS-GARCIA, A., GOMIS-GONZALEZ, M., GUEGAN, T., AGUSTIN-
27 PAVON, C., PASTOR, A., MATO, S., PEREZ-SAMARTIN, A., MATUTE,
28 C., DE LA TORRE, R., DIERSSEN, M., MALDONADO, R. & OZAITA, A.
29 2013. Targeting the endocannabinoid system in the treatment of fragile X
30 syndrome. *Nature medicine*, 19, 603-7.
- 31 BUSQUETS-GARCIA, A., GOMIS-GONZALEZ, M., SRIVASTAVA, R. K.,
32 CUTANDO, L., ORTEGA-ALVARO, A., RUEHLE, S., REMMERS, F.,
33 BINDILA, L., BELLOCCHIO, L., MARSICANO, G., LUTZ, B.,
34 MALDONADO, R. & OZAITA, A. 2016. Peripheral and central CB1
35 cannabinoid receptors control stress-induced impairment of memory
36 consolidation. *Proc Natl Acad Sci U S A*, 113, 9904-9.
- 37 BUSQUETS-GARCIA, A., PUIGHERMANAL, E., PASTOR, A., DE LA TORRE,
38 R., MALDONADO, R. & OZAITA, A. 2011. Differential role of
39 anandamide and 2-arachidonoylglycerol in memory and anxiety-like
40 responses. *Biological psychiatry*, 70, 479-86.
- 41 BUSQUETS GARCIA, A., SORIA-GOMEZ, E., BELLOCCHIO, L., AND
42 MARSICANO, G. 2016. Cannabinoid receptor type-1: breaking the
43 dogmas. *F1000Res* 5.
- 44 BUZSAKI, G. 2015. Hippocampal sharp wave-ripple: A cognitive biomarker for
45 episodic memory and planning. *Hippocampus* 25, 1073-1188.
- 46

- 1 CASTILLO, P. E., YOUNTS, T. J., CHAVEZ, A. E. & HASHIMOTODANI, Y.
2 2012. Endocannabinoid signaling and synaptic function. *Neuron*, 76, 70-
3 81.
- 4 CHAI, H., DIAZ-CASTRO, B., SHIGETOMI, E., MONTE, E., OCTEAU, J. C.,
5 YU, X., COHN, W., RAJENDRAN, P. S., VONDRISKA, T. M.,
6 WHITELEGGE, J. P., COPPOLA, G. & KHAKH, B. S. 2017. Neural
7 Circuit-Specialized Astrocytes: Transcriptomic, Proteomic,
8 Morphological, and Functional Evidence. *Neuron*.
- 9 DARVAS, M. & PALMITER, R. D. 2009. Restriction of dopamine signaling to the
10 dorsolateral striatum is sufficient for many cognitive behaviors. *Proc Natl*
11 *Acad Sci U S A*, 106, 14664-9.
- 12 EL-BROLOS, M. A., KONTARAKIS, Z., ROSSI, A., KUENNE, C., GUNTHER,
13 S., FUKUDA, N., KIKHI, K., BOEZIO, G. L. M., TAKACS, C. M., LAI, S.
14 L., FUKUDA, R., GERRI, C., GIRALDEZ, A. J. & STAINIER, D. Y. R.
15 2019. Genetic compensation triggered by mutant mRNA degradation.
16 *Nature*, 568, 193-197.
- 17 EL-BROLOS, M. A. & STAINIER, D. Y. R. 2017. Genetic compensation: A
18 phenomenon in search of mechanisms. *PLoS Genet*, 13, e1006780.
- 19 FREY, U., SCHROEDER, H. & MATTHIES, H. R. 1990. Dopaminergic
20 antagonists prevent long-term maintenance of posttetanic LTP in the
21 CA1 region of rat hippocampal slices. *Brain Research*, 522, 69-75.
- 22 GANGAROSSA, G., LONGUEVILLE, S., DE BUNDEL, D., PERROY, J.,
23 HERVE, D., GIRAULT, J. A. & VALJENT, E. 2012. Characterization of
24 dopamine D1 and D2 receptor-expressing neurons in the mouse
25 hippocampus. *Hippocampus*, 22, 2199-207.
- 26 GOMEZ, J. L., BONAVENTURA, J., LESNIAK, W., MATHEWS, W. B., SYSA-
27 SHAH, P., RODRIGUEZ, L. A., ELLIS, R. J., RICHIE, C. T., HARVEY, B.
28 K., DANNALS, R. F., POMPER, M. G., BONCI, A. & MICHAELIDES, M.
29 2017. Chemogenetics revealed: DREADD occupancy and activation via
30 converted clozapine. *Science*, 357, 503-507.
- 31 GORELOVA, N., SEAMANS, J.K., AND YANG, C.R. 2002. Mechanisms of
32 dopamine activation of fast-spiking interneurons that exert inhibition in rat
33 prefrontal cortex. *J Neurophysiol* 88, 3150-3166.
- 34 GRANADO, N., ORTIZ, O., SUAREZ, L. M., MARTIN, E. D., CENA, V., SOLIS,
35 J. M. & MORATALLA, R. 2008. D1 but not D5 dopamine receptors are
36 critical for LTP, spatial learning, and LTP-Induced arc and zif268
37 expression in the hippocampus. *Cereb Cortex*, 18, 1-12.
- 38 HARRIS, K. D., HOCHGERNER, H., SKENE, N. G., MAGNO, L., KATONA, L.,
39 BENGTTSSON GONZALES, C., SOMOGYI, P., KESSARIS, N.,
40 LINNARSSON, S. & HJERLING-LEFFLER, J. 2018. Classes and
41 continua of hippocampal CA1 inhibitory neurons revealed by single-cell
42 transcriptomics. *PLoS Biol*, 16, e2006387.
- 43 HEBERT-CHATELAIN, E., DESPREZ, T., SERRAT, R., BELLOCCHIO, L.,
44 SORIA-GOMEZ, E., BUSQUETS-GARCIA, A., PAGANO ZOTTOLA, A.
45 C., DELAMARRE, A., CANNICH, A., VINCENT, P., VARILH, M., ROBIN,
46 L. M., TERRAL, G., GARCIA-FERNANDEZ, M. D., COLAVITA, M.,
47 MAZIER, W., DRAGO, F., PUENTE, N., REGUERO, L., ELEZGARAI, I.,
48 DUPUY, J. W., COTA, D., LOPEZ-RODRIGUEZ, M. L., BARREDA-
49 GOMEZ, G., MASSA, F., GRANDES, P., BENARD, G. & MARSICANO,

- 1 G. 2016. A cannabinoid link between mitochondria and memory. *Nature*,
2 539, 555-559.
- 3 JENNINGS, A., TYURIKOVA, O., BARD, L., ZHENG, K., SEMYANOV, A.,
4 HENNEBERGER, C. & RUSAKOV, D. A. 2017. Dopamine elevates and
5 lowers astroglial Ca(2+) through distinct pathways depending on local
6 synaptic circuitry. *Glia*, 65, 447-459.
- 7 KARUNAKARAN, S., CHOWDHURY, A., DONATO, F., QUAIRIAUX, C.,
8 MICHEL, C. M. & CARONI, P. 2016. PV plasticity sustained through
9 D1/5 dopamine signaling required for long-term memory consolidation.
10 *Nat Neurosci*, 19, 454-64.
- 11 KATONA, I. & FREUND, T. F. 2012. Multiple functions of endocannabinoid
12 signaling in the brain. *Annual review of neuroscience*, 35, 529-58.
- 13 KATONA, I., SPERLAGH, B., SIK, A., KAFALVI, A., VIZI, E. S., MACKIE, K. &
14 FREUND, T. F. 1999. Presynaptically located CB1 cannabinoid receptors
15 regulate GABA release from axon terminals of specific hippocampal
16 interneurons. *J Neurosci*, 19, 4544-58.
- 17 KAUFMAN, A.M., GEILLER, T., AND LOSONCZY, A. 2020. A Role for the
18 Locus Coeruleus in Hippocampal CA1 Place Cell Reorganization during
19 Spatial Reward Learning. *Neuron* 105, 1018-1026 e1014.
- 20 KLAUSBERGER, T., MARTON, L.F., O'NEILL, J., HUCK, J.H., DALEZIOS, Y.,
21 FUENTEALBA, P., SUEN, W.Y., PAPP, E., KANEKO, T., WATANABE,
22 M., ET AL. 2005. Complementary roles of cholecystinin- and
23 parvalbumin-expressing GABAergic neurons in hippocampal network
24 oscillations. *The Journal of neuroscience : the official journal of the*
25 *Society for Neuroscience* 25, 9782-9793.
- 26 KLAUSBERGER, T. & SOMOGYI, P. 2008. Neuronal diversity and temporal
27 dynamics: the unity of hippocampal circuit operations. *Science*, 321, 53-
28 7.
- 29 LEMBERGER, T., PARLATO, R., DASSESSE, D., WESTPHAL, M.,
30 CASANOVA, E., TURIAULT, M., TRONCHE, F., SCHIFFMANN, S.N.,
31 AND SCHUTZ, G. 2007. Expression of Cre recombinase in
32 dopaminergic neurons. *BMC Neurosci* 8, 4.
- 33 LEMON, N. & MANAHAN-VAUGHAN, D. 2006. Dopamine D1/D5 receptors
34 gate the acquisition of novel information through hippocampal long-term
35 potentiation and long-term depression. *J Neurosci*, 26, 7723-9.
- 36 LI, S., CULLEN, W. K., ANWYL, R. & ROWAN, M. J. 2003. Dopamine-
37 dependent facilitation of LTP induction in hippocampal CA1 by exposure
38 to spatial novelty. *Nat Neurosci*, 6, 526-31.
- 39 LISMAN, J. 2017. Criteria for identifying the molecular basis of the engram
40 (CaMKII, PKMzeta). *Mol Brain*, 10, 55.
- 41 LISMAN, J., GRACE, A. A. & DUZEL, E. 2011. A neoHebbian framework for
42 episodic memory; role of dopamine-dependent late LTP. *Trends*
43 *Neurosci*, 34, 536-47.
- 44 MARSICANO, G., GOODENOUGH, S., MONORY, K., HERMANN, H., EDER,
45 M., CANNICH, A., AZAD, S.C., CASCIO, M.G., GUTIERREZ, S.O., VAN
46 DER STELT, M., ET AL. 2003. CB1 cannabinoid receptors and on-
47 demand defense against excitotoxicity. *Science* 302, 84-88.
- 48 MARSICANO, G. & KUNER, R. 2008. Anatomical distribution of receptors,
49 ligands and enzymes in the brain and the spinal cord: circuitries and

- 1 neurochemistry. In: KOFALVI, A. (ed.) *Cannabinoids and the brain*. New
2 York: Springer.
- 3 MARSICANO, G. & LUTZ, B. 1999. Expression of the cannabinoid receptor
4 CB1 in distinct neuronal subpopulations in the adult mouse forebrain. *Eur*
5 *J Neurosci*, 11, 4213-25.
- 6 MONORY, K., BLAUDZUN, H., MASSA, F., KAISER, N., LEMBERGER, T.,
7 SCHUTZ, G., WOTJAK, C. T., LUTZ, B. & MARSICANO, G. 2007.
8 Genetic dissection of behavioural and autonomic effects of Delta(9)-
9 tetrahydrocannabinol in mice. *PLoS Biol*, 5, e269.
- 10 MORRIS, R. G. 2013. NMDA receptors and memory encoding.
11 *Neuropharmacology*, 74, 32-40.
- 12 NAGATOMO, K., SUGA, S., SAITOH, M., KOGAWA, M., KOBAYASHI, K.,
13 YAMAMOTO, Y. & YAMADA, K. 2017. Dopamine D1 Receptor
14 Immunoreactivity on Fine Processes of GFAP-Positive Astrocytes in the
15 Substantia Nigra Pars Reticulata of Adult Mouse. *Front Neuroanat*, 11, 3.
- 16 NICOLL, R. A. 2017. A Brief History of Long-Term Potentiation. *Neuron*, 93,
17 281-290.
- 18 OLIVEIRA DA CRUZ, J. F., ROBIN, L. M., DRAGO, F., MARSICANO, G. &
19 METNA-LAURENT, M. 2016. Astroglial type-1 cannabinoid receptor
20 (CB1): A new player in the tripartite synapse. *Neuroscience*, 323, 35-42.
- 21 PARRA, P., GULYÁS, A. I. & MILES, R. 1998. How Many Subtypes of Inhibitory
22 Cells in the Hippocampus? *Neuron*, 20, 983-993.
- 23 PELKEY, K. A., CHITTAJALLU, R., CRAIG, M. T., TRICOIRE, L., WESTER, J.
24 C. & MCBAIN, C. J. 2017. Hippocampal GABAergic Inhibitory
25 Interneurons. *Physiol Rev*, 97, 1619-1747.
- 26 PUIGHERMANAL, E., BUSQUETS-GARCIA, A., GOMIS-GONZALEZ, M.,
27 MARSICANO, G., MALDONADO, R. & OZAITA, A. 2013. Dissociation of
28 the pharmacological effects of THC by mTOR blockade.
29 *Neuropsychopharmacology*, 38, 1334-43.
- 30 PUIGHERMANAL, E., CUTANDO, L., BOUBAKER-VITRE, J., HONORE, E.,
31 LONGUEVILLE, S., HERVE, D. & VALJENT, E. 2017. Anatomical and
32 molecular characterization of dopamine D1 receptor-expressing neurons
33 of the mouse CA1 dorsal hippocampus. *Brain Struct Funct*, 222, 1897-
34 1911.
- 35 PUIGHERMANAL, E., MARSICANO, G., BUSQUETS-GARCIA, A., LUTZ, B.,
36 MALDONADO, R. & OZAITA, A. 2009. Cannabinoid modulation of
37 hippocampal long-term memory is mediated by mTOR signaling. *Nat*
38 *Neurosci*, 12, 1152-8.
- 39 ROBIN, L. M., OLIVEIRA DA CRUZ, J. F., LANGLAIS, V. C., MARTIN-
40 FERNANDEZ, M., METNA-LAURENT, M., BUSQUETS-GARCIA, A.,
41 BELLOCCHIO, L., SORIA-GOMEZ, E., PAPOUIN, T., VARILH, M.,
42 SHERWOOD, M. W., BELLUOMO, I., BALCELLS, G., MATIAS, I.,
43 BOSIER, B., DRAGO, F., VAN EECKHAUT, A., SMOLDERS, I.,
44 GEORGES, F., ARAQUE, A., PANATIER, A., OLIET, S. H. R. &
45 MARSICANO, G. 2018. Astroglial CB1 Receptors Determine Synaptic D-
46 Serine Availability to Enable Recognition Memory. *Neuron*, 98, 935-944
47 e5.
- 48 ROBINSON, S. & ADELMAN, J. S. 2015. A Method for Remotely Silencing
49 Neural Activity in Rodents During Discrete Phases of Learning. *J Vis*
50 *Exp*, e52859.

- 1 ROGGENHOFE, E., FIDZINSKI, P., SHOR, E., AND BEHR, J. 2013. Reduced
2 Threshold for Induction of LTP by Activation of Dopamine D1/D5
3 Receptors at Hippocampal CA1–Subiculum Synapses. *PLOS One* 8,
4 e62520.
5
- 6 SHIVARAMA-SHETTY, M., GOPINADHAM, S., AND SAJIKUMAR, S. 2018.
7 Dopamine D1/D5 receptor signaling regulates synaptic cooperation and
8 competition in hippocampal CA1 pyramidal neurons via sustained
9 ERK1/2 activation. *Hippocampus* 26, 137-150.
10
- 11 SOLTESZ, I., AND LOSONCZY, A. 2018. CA1 pyramidal cell diversity enabling
12 parallel information processing in the hippocampus. *Nature neuroscience*
13 21, 484-493.
14
- 15 SORIA - GOMEZ, E., METNA, M., BELLOCCHIO, L., BUSQUETS - GARCIA,
16 A. & MARSICANO, G. 2017. Handbook of Neurobehavioral Genetics and
17 Phenotyping. 323-355.
- 18 SQUIRE, L. R., WIXTED, J. T. & CLARK, R. E. 2007. Recognition memory and
19 the medial temporal lobe: a new perspective. *Nat Rev Neurosci*, 8, 872-
20 83.
- 21 TAKEUCHI, T., DUSZKIEWICZ, A. J., SONNEBORN, A., SPOONER, P. A.,
22 YAMASAKI, M., WATANABE, M., SMITH, C. C., FERNANDEZ, G.,
23 DEISSEROTH, K., GREENE, R. W. & MORRIS, R. G. 2016. Locus
24 coeruleus and dopaminergic consolidation of everyday memory. *Nature*,
25 537, 357-362.
- 26 TERRAL, G., BUSQUETS-GARCÍA, A., VARILH, M., ACHICALLENDE, S.,
27 CANNICH, A., BELLOCCHIO, L., BONILLA-DEL RÍO, I., MASSA, F.,
28 PUENTE, N., SORIA-GÓMEZ, E., GRANDES, P., FERREIRA, G. &
29 MARSICANO, G. 2019. CB1 receptors in the anterior piriform cortex
30 control odor preference memory. *Curr Biol*, 29, 2455-64.
- 31 TERZIAN, A.L., DRAGO, F., WOTJAK, C.T., AND MICALE, V. 2011. The
32 Dopamine and Cannabinoid Interaction in the Modulation of Emotions
33 and Cognition: Assessing the Role of Cannabinoid CB1 Receptor in
34 Neurons Expressing Dopamine D1 Receptors. *Frontiers in behavioral*
35 *neuroscience* 5, 49.
- 36 WHITLOCK, J. R., HEYNEN, A. J., SHULER, M. G. & BEAR, M. F. 2006.
37 Learning induces long-term potentiation in the hippocampus. *Science*,
38 313, 1093-7.
- 39 WU, C., YAN, R., ZHANG, R., BAI, F., YANG, Y., WU, Z. & WU, A. 2013.
40 Comparative pharmacokinetics and bioavailability of four alkaloids in
41 different formulations from *Corydalis decumbens*. *J Ethnopharmacol*,
42 149, 55-61.
- 43 YAMASAKI, M. & TAKEUCHI, T. 2017. Locus Coeruleus and Dopamine-
44 Dependent Memory Consolidation. *Neural Plast*, 2017, 8602690.
- 45 YOON, B. E. & LEE, C. J. 2014. GABA as a rising gliotransmitter. *Front Neural*
46 *Circuits*, 8, 141.
- 47 ZHANG, Y., CHEN, K., SLOAN, S. A., BENNETT, M. L., SCHOLZE, A. R.,
48 O'KEEFFE, S., PHATNANI, H. P., GUARNIERI, P., CANEDA, C.,
49 RUDERISCH, N., DENG, S., LIDDELOW, S. A., ZHANG, C., DANEMAN,
50 R., MANIATIS, T., BARRES, B. A. & WU, J. Q. 2014. An RNA-

1 sequencing transcriptome and splicing database of glia, neurons, and
2 vascular cells of the cerebral cortex. *J Neurosci*, 34, 11929-47.

3

4

5

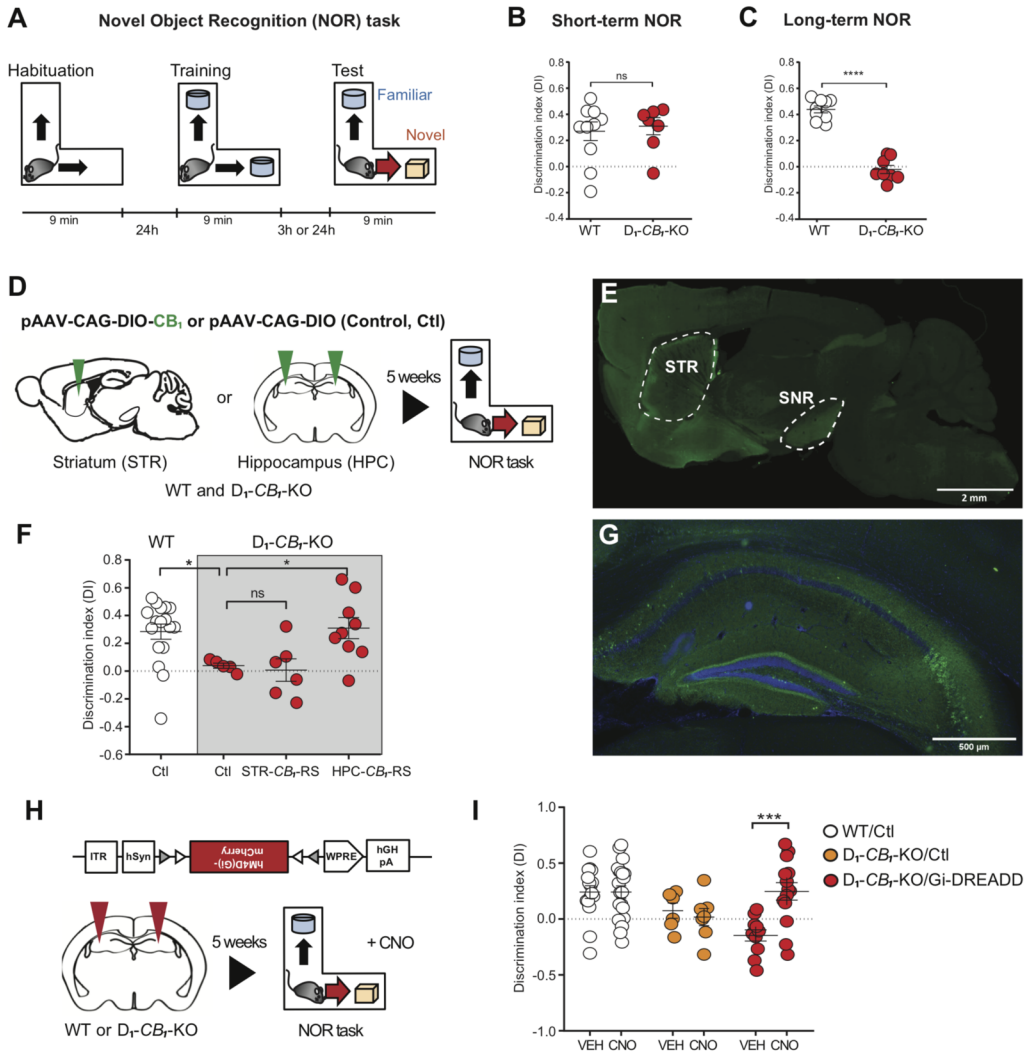
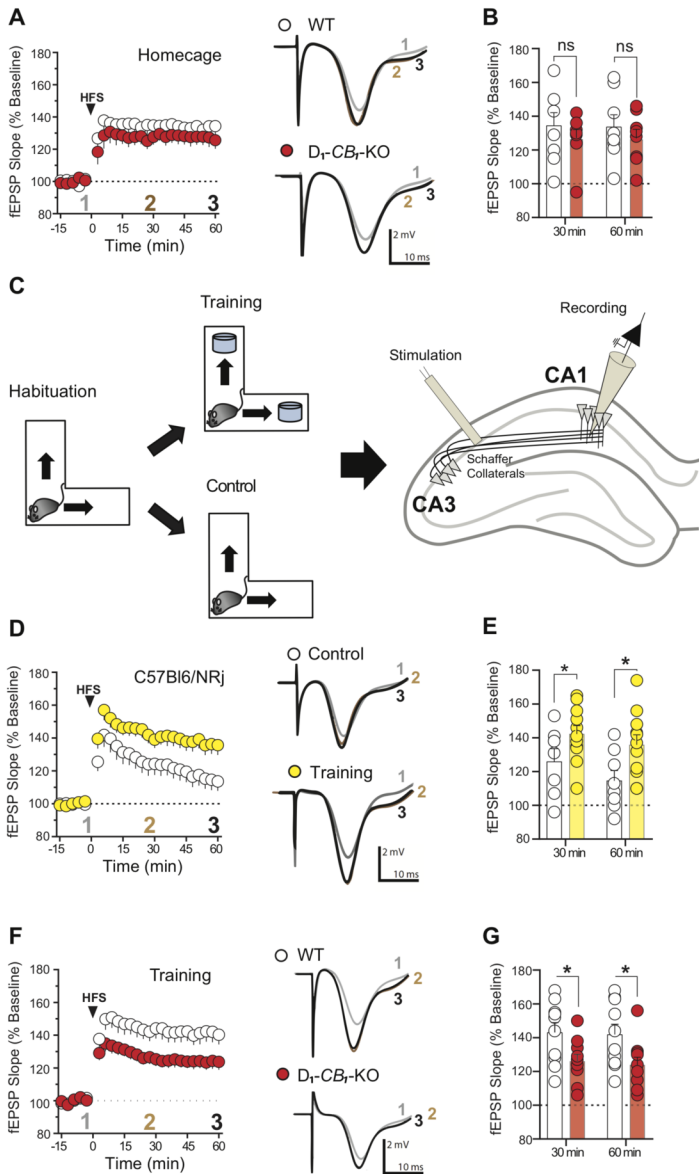
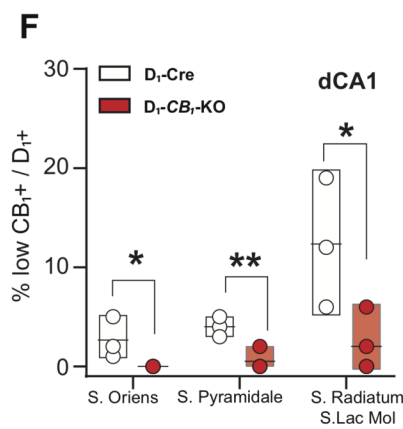
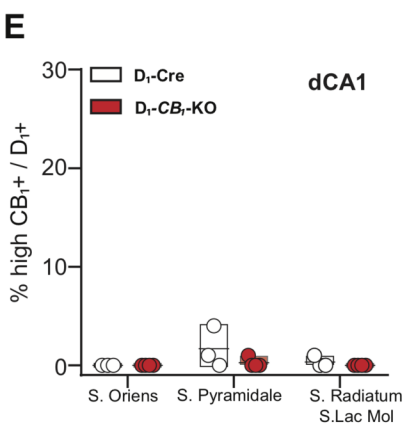
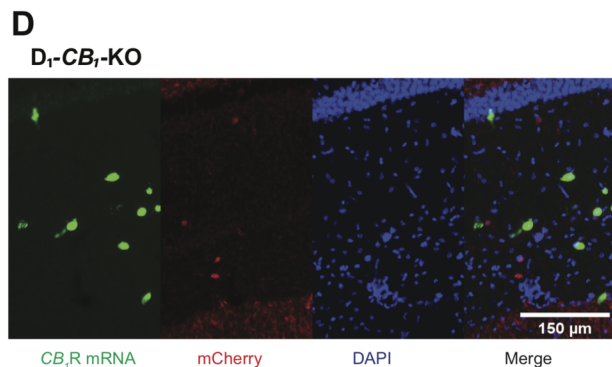
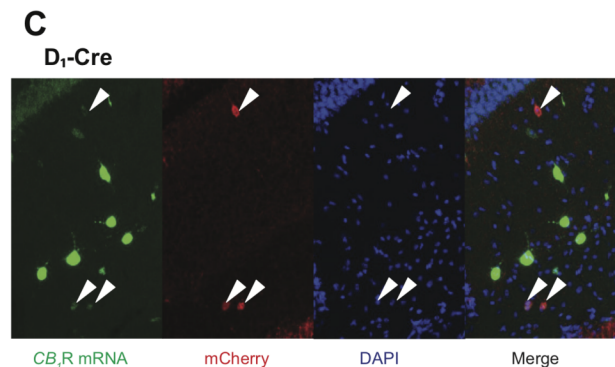
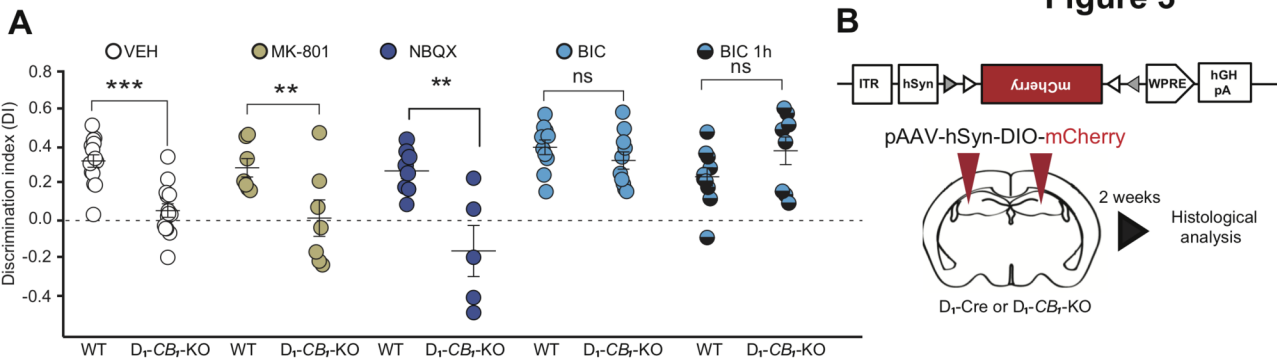
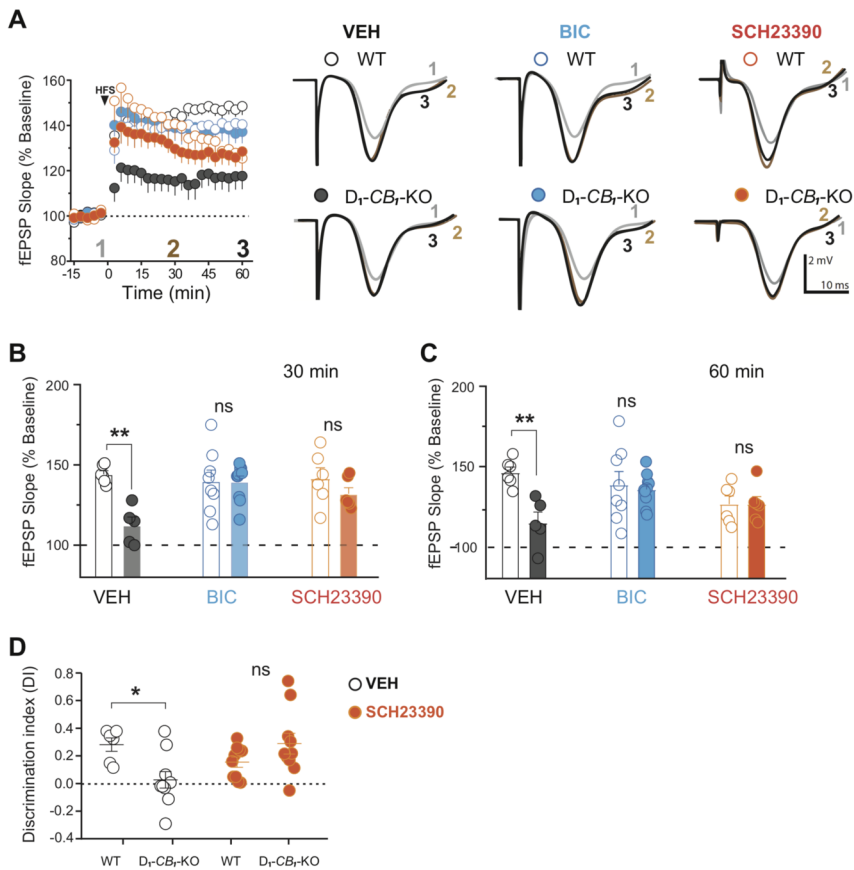


Figure 2







Hippocampal Circuits

