Behavioural Brain Research 232 (2012) 400–405

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

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

Short communication

Hippocampal c-Fos activation in normal and LPA_1-null mice after two object recognition tasks with different memory demands

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ARTICLE INFO

Article history:
Received 4 February 2012
Received in revised form 3 April 2012
Accepted 10 April 2012
Available online 17 April 2012

Keywords:
Early immediate gene
Knockout
Medial prefrontal cortex
Temporal order memory
Episodic-like memory

ABSTRACT

Normal and LPA_1-null mice, that have well reported hippocampal deficits, were assessed in an episodic-like what-when-where memory task or in a comparable task designed to test memory for familiar objects and locations by discriminating them from novels. Both genotypes performed the novelty recognition task but failed to learn the what-when-where task. However, normal mice showed what-when memory that was impaired in nulls. Each task elicited a different pattern of c-Fos expression. In normal mice, the what-when-where task induced more hippocampal c-Fos activation in the CA1 area than the novelty-based task, correlating with the what-when memory. LPA_1-null mice displayed a basal c-Fos hyperactivity in the hippocampus and in the medial prefrontal cortex, which was regulated differently by the two behavioural tasks employed. Both tasks were matched in exploratory behaviour and c-Fos activation in stress-related brain areas for both genotypes. This study shows that the what-when-where memory task differs from a comparable novelty-based task in both the learning demands and the neuronal correlates. Moreover, results also stress the role of the LPA_1 receptor in hippocampal functioning.

Episodic memory is a complex form of declarative memory that allows learning to happen in association with a particular time and a particular place, allowing to remember life's experiences. In rodents, several procedures have been proposed to study episodic-like memory based on object recognition paradigms. Dere et al. [1] have recently developed a three-trial object recognition task to assess memory of a familiar object ('what'), the temporal order ('when') and the location of its occurrence ('where'). The integrated memory of these three components and their retrieval at once, during the test phase of the task, is a crucial event that would define the memory for an episode. It is important to keep in mind, however, that several concerns have been reported when object recognition tasks are used to research episodic-like memory, because these paradigms may assess simpler forms of memory instead [2]. Despite this, neurobiological studies have demonstrated that the memory components involved in episodic-like object recognition tasks require the integrity of the hippocampus [3], which has been proposed as critical for episodic-like memory [4].

On the other hand, the role of the lysophosphatidic acid (LPA, 1-acyl-2-*sn*-glycerol-3-phosphate) pathway in the hippocampus has been studied recently. LPA acts through six G-protein-coupled receptors, of which the LPA_1 is critically involved in the normal hippocampus development, plasticity and function. The LPA_1 receptor is expressed in the developing and adult brain [5–7], mainly in glial cells [7] but also in hippocampal neurons where it promotes synaptic formation [8]. The relevance of this receptor for hippocampal plasticity has been further evidenced in studies with mice lacking the LPA_1 receptor (LPA_1-nulls), which show defective adult hippocampal neurogenesis, an abnormal regulation of neurotrophic factors, increased vulnerability to chronic stress-effects and altered neurotransmission in the hippocampus [9–12]. These deficits occur in addition to structural abnormalities, such as reduced volume in the CA3 and CA1 areas [10], which are likely due to neurodevelopmental deficits caused by the absence of LPA_1 [13]. To date, spatial and contextual memory impairments have been described in LPA_1-nulls [9,14,15], but the role of the

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http://dx.doi.org/10.1016/j.bbr.2012.04.018

LPA_1 receptor in other forms of hippocampal-dependent memory, such as episodic-like memory, remains to be tested.

We study normal and LPA_1-null mice, a model of hippocampal pathology, in the episodic-like what-when-where memory task (Www-Task) developed by Dere et al. [1] or in a comparable novelty recognition task (Nov-Task) based on the developed by Ennaceur and Delacour [16]. The assessment of mice in the Nov-Task will rule out the existence of short-term memory deficits for objects and locations that could be mistaken for episodic-like memory impairments, because both object and location memories are necessary to solve the more complex Www-Task [2]. On the other hand, the performance of LPA_1-nulls would also allow to assess the relative hippocampal dependence of the two tasks employed, considering the hippocampal dysfunction of these mice. Neuronal activation was compared in both genotypes and tasks by studying the expression of the immediate early gene c-*fos* in the hippocampus and the medial prefrontal cortex (mFPC), which is directly connected to the hippocampus so their interaction is required to solve the Www-task [17]. In addition, the basolateral amygdala (BLA) and the paraventricular hypothalamic nucleus (PVN) were assessed as stress-related areas for which the behavioural tasks were not expected to promote differences.

The experiments were performed on the *Malaga* variant of the LPA_1-null mouse, derived from Contos et al. [18] colony and described in our previous work [13]. Male LPA_1-null mice and their wild-type (WT) littermates were maintained in a C57BL/6J×129X1/SvJ hybrid background and housed individually. Procedures were performed according to the European and Spanish animal research laws (86/609/EEC, 98/81/CEE, 2003/65/CE and 2007/526/EC; Real Decreto 1205/2005 and 178/2004; and Ley 32/2007 and 9/2003). During the first experiment, six animals per genotype were evaluated in the Www-task, as shown in Fig. 1A. The Www-task was performed as described by Dere et al. [1,19]. Mice first received 5 min of habituation to an open-field (40 cm × 40 cm). Sixty min later, they were first exposed to 4 identical objects for 10 min (Sample 1), then after 90 min delay interval they were exposed to a novel set of 4 identical objects for another 10 min (Sample 2). The Test Trial followed after 90 min interval and lasted another 10 min. This test trial consisted of two objects from the second sample ('recent' objects), that were replaced in their respective position, and two objects from the first sample ('old' objects). One of the old objects was placed in the location it occupied previously and the second was placed in a location that was previously occupied by a recent object (Fig. 1A). In this way, the Www-task tested both the 'what and when memory' (the preference for old over recent objects) and the 'what and where memory' (the preference for the old object displaced to another familiar location over the non-displaced old object) (Fig. 1A). During a second experiment, a separate group of six mice per genotype were evaluated in the Nov-Task. This used the same protocol as the Www-task except that objects during Sample 2 were placed in a different arrangement, and that novel objects were substituted for recent objects during the Test Trial (Fig. 1B). These changes allowed the Nov-Task to test object recognition memory (the preference for novel over familiar objects) and object location memory (the preference for objects displaced to new locations over non-displaced objects) (Fig. 1B). The type of object used as 'old', 'recent' or 'novel' was counterbalanced across mice, and objects were replaced by identical copies for each trial. The time spent by the mice exploring each object, as defined by touching it with the nose or forepaws, was analysed observationally, and discrimination ratios were calculated using the formulas depicted in Fig. 1A and B. The total time of object exploration was also calculated. Locomotion (cm travelled) and tigmotaxis (percentage of time spent in the maze periphery, defined as the area within 8 cm of the walls) were analysed with the software Ethovision XT (Noldus, The Netherlands). The threshold for statistical significance was set at $P \leq 0.05$.

For the Www-task, a comparison of genotypes by *t*-tests for independent groups revealed that LPA_1-nulls were impaired in what-when memory (Ratio 1: $t_{(10)} = 2.330$, $P = 0.045$; Ratio 2: $t_{(10)} = 3.659$, $P = 0.004$; Fig. 1A). Accordingly, within-group comparisons of object exploration times revealed a preference for older over more recent objects only in the WT genotype (Table 1). In regard to what-where memory, neither genotype discriminated the old-displaced object from the old-static object (Ratio 3 in Fig. 1A; Table 1). However, the Nov-Task revealed that mice from both genotypes displayed correct object recognition memory (Ratios 4, 5 and 6 in Fig. 1B; Table 1) and also a correct object location memory (Ratios 7, 8 and 9 in Fig. 1B; Table 1). Exploratory measures were compared among genotypes and tasks by two-way ANOVA with repeated measures (genotype × task × trial) followed by post hoc Fisher's least significant difference (LSD). Results showed a reduction of object exploration and locomotion across trials, indicating habituation to the behavioural testing. Differences between genotypes were found by both measures, in

Table 1
Mean (±SEM) object exploration in seconds and within group comparison of exploration times by *t*-test for dependent samples. Objects (capital letters) and memory ratios are named as pictured in Fig. 1A and B. Differences between exploration times.

	Object exploration				Within group comparison of object exploration times		
					'old' vs 'recent'		'old-displaced' vs 'old-static'
	A	B	C	D	RATIO 1	RATIO 2	RATIO 3
WT	10.76 ± 1.86	18.77 ± 2.66	17.67 ± 2.66	10.69 ± 2.82	$t_{(5)} = 3.329$, $P = 0.015^{*}$	$t_{(5)} = -8.041$, $P = 0.000^{**}$	$t_{(5)} = 0.352$, $P = 0.739$
Null	16.43 ± 2.18	20.03 ± 3.73	21.57 ± 1.43	27.33 ± 3.75	$t_{(5)} = 3.317$, $P = 0.764$	$t_{(5)} = -0.528$, $P = 0.620$	$t_{(5)} = -0.317$, $P = 0.764$

					'novel' vs 'old'			'displaced (new location)' vs 'static'		
	E	F	G	H	RATIO 4	RATIO 5	RATIO 6	RATIO 7	RATIO 8	RATIO 9
WT	37.01 ± 1.62	16.68 ± 1.91	12.33 ± 1.70	17.06 ± 1.69	$t_{(5)} = 6.380$, $P = 0.001^{*}$	$t_{(5)} = 3.086$, $P = 0.027^{*}$	$t_{(5)} = 4.958$, $P = 0.004^{*}$	$t_{(5)} = 8.763$, $P = 0.000^{**}$	$t_{(5)} = -8.763$, $P = 0.034^{*}$	$t_{(5)} = 8.237$, $P = 0.000^{**}$
Null	29.23 ± 4.31	19.78 ± 4.74	13.65 ± 3.37	17.90 ± 3.24	$t_{(5)} = 3.755$, $P = 0.013^{*}$	$t_{(5)} = -2.884$, $P = 0.034^{*}$	$t_{(5)} = 4.423$, $P = 0.007^{*}$	$t_{(5)} = 3.860$, $P = 0.012^{*}$	$t_{(5)} = -2.758$, $P = 0.040^{*}$	$t_{(5)} = 3.932$, $P = 0.011^{*}$

* $P < 0.05$.
** $P < 0.001$.

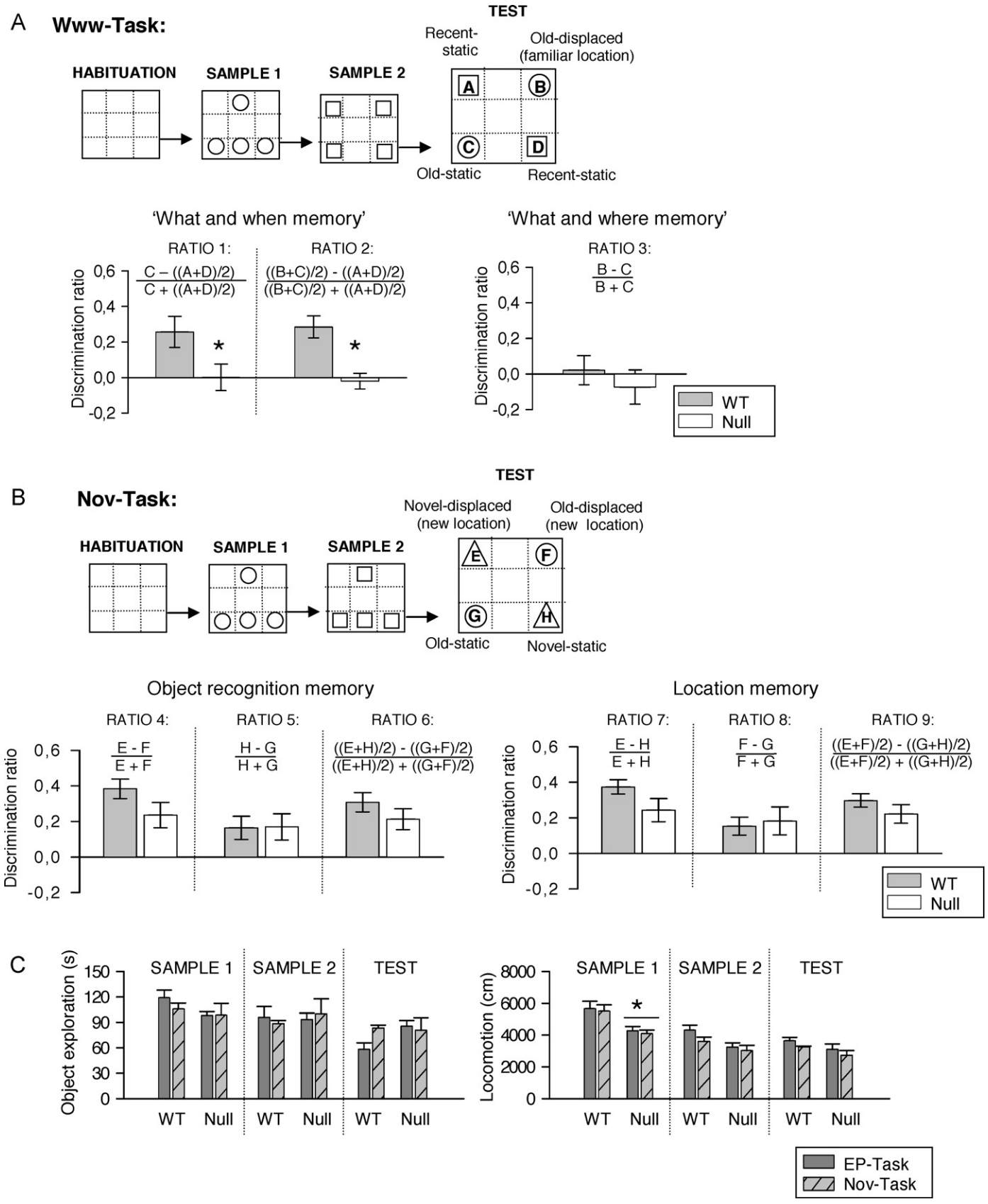

Fig. 1. Behavioral protocol and memory measures in the Www-task (A) and the Nov-Task (B). Each symbol (circle, square or triangle) represents one type of object. Discrimination ratios were calculated as stated in the formulas, in which capital letters refer to the time the mice spent exploring the object named by that letter. (C) Both tasks did not differ in exploratory parameters. Means ± SEM. Differences between genotypes, $^{*}P < 0.05$.

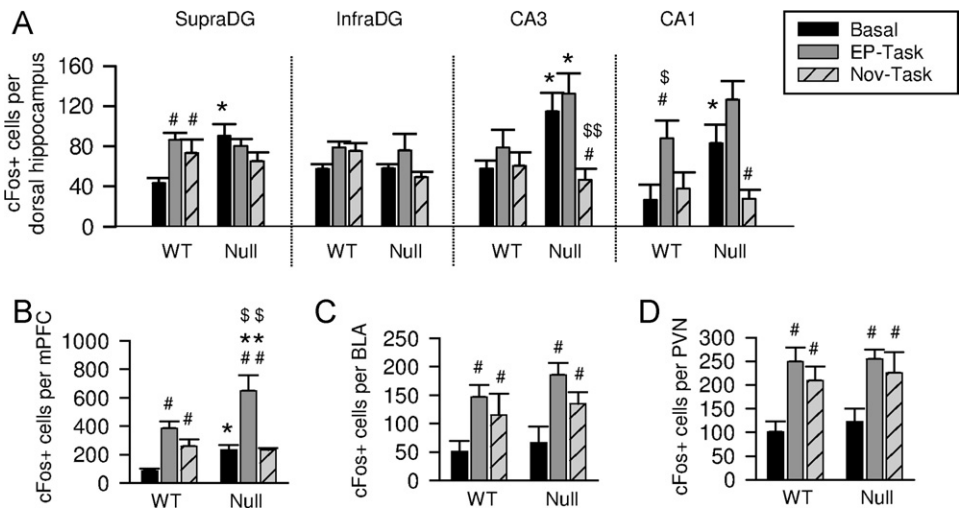

Fig. 2. Total cFos expression (means ± SEM) in the left hemisphere in WT and LPA_1-null mice under basal conditions and after performing the Www-task or the Nov-Task. LSD: difference between WT and LPA_1-nulls with the same treatment, $^*P < 0.05$, $^{**}P < 0.001$; difference compared with the basal condition, $\#P < 0.05$, $\#\#P < 0.001$; difference between tasks within the same genotype, $\$P < 0.05$, $\$\$P < 0.001$.

accordance with the exploratory impairment reported in nulls [14]. The ANOVA results for object exploration are as follows: 'trial' $F_{(2,40)} = 21.095$, $P = 0.000$; 'genotype × trial' $F_{(2,40)} = 4.777$, $P = 0.014$; and 'genotype × task × trial' $F_{(2,40)} = 4.064$, $P = 0.025$. The ANOVA results for locomotion are as follows: 'genotype' $F_{(1,20)} = 10.291$, $P = 0.004$; 'trial' $F_{(2,40)} = 76.243$, $P = 0.000$; and 'genotype × trial' $F_{(2,40)} = 4.537$, $P = 0.017$; LSD is shown in Fig. 1C. Tigmotaxis remained high and unchanged throughout the testing (means ranged from 75 to 88% for both tasks for both genotypes). The consistency of the tigmotaxis measure was likely due to the fact that the location of objects within the maze's periphery promoted peripheral exploration. Finally, the habituation trial was analysed to confirm that animals had no initial spatial preference for any of the four maze corners where objects were later located in the test trial (data not shown).

Ninety min after the completion of the Www-task or the Nov-Task, mice were intracardially perfused to assess c-Fos expression. Additionally, six mice per genotype were taken directly from their home cage and used to assess basal c-Fos immunoreactivity. Free-floating immunohistochemistry was performed on every fourth coronal vibratome section (50 μm) from the left hemisphere, using rabbit anti-c-Fos (1:2500; Santa Cruz Biotech. sc-52, USA) and mouse anti-rabbit biotinylated (1:500, Dako, Danmark) antibodies and the peroxidase-conjugated extravidin method with diaminobenzidine as the cromogen. Histological and cell quantification procedures are detailed in Castilla-Ortega et al. [10]. Quantification was carried out in the dorsal hippocampus (from −1.22 to −2.54 mm from bregma) in the suprapyramidal and infrapyramidal blades of the dentate gyrus (SupraDG, InfraDG), the CA3 and the CA1 areas [20]. Infralimbic and prelimbic cortices within the mFPC, the BLA and the PVN were also quantified for c-Fos expression. Analyses were made by factorial ANOVA (genotype × treatment, where the treatment was basal, Www-task or Nov-Task) followed by LSD. For WT mice, both tasks increased c-Fos activity in the SupraDG and in the mPFC, while only the Www-task increased activation in CA1 (Fig. 2A and B). LPA_1-null mice showed increased c-Fos in the SupraDG, CA3, CA1 and mPFC areas under basal conditions. This basal hyperactivity was reduced in CA3 and CA1 after the Nov-Task but not after the Www-task, which in turn induced a notable c-Fos increase in the mPFC of nulls (Fig. 2A and B). Both behavioural tasks increased c-Fos expression in the BLA and PVN equally for both genotypes (Fig. 2C and D). The ANOVA results for SupraDG are as follows: 'genotype × treatment' $F_{(2,30)} = 4.133$, $P = 0.026$; CA3 'genotype': $F_{(1,30)} = 5.611$, $P = 0.024$; and 'treatment' $F_{(2,30)} = 4.773$, $P = 0.015$. The ANOVA results for CA1 are as follows: 'genotype' $F_{(1,30)} = 3.879$, $P = 0.050$; and 'treatment' $F_{(2,30)} = 6.389$, $P = 0.005$. The ANOVA results for mPFC are as follows: 'genotype' $F_{(1,30)} = 10.896$, $P = 0.002$; 'treatment' $F_{(2,30)} = 320.159$, $P = 0.000$; and 'genotype × treatment' $F_{(2,30)} = 4.686$, $P = 0.017$. The ANOVA results for BLA are as follows: 'treatment' $F_{(2,30)} = 9.414$, $P = 0.001$. The ANOVA results for PVN are as follows 'treatment' $F_{(2,30)} = 10.562$, $P = 0.000$. LSD is shown in Fig. 2. Pearson's correlation analyses revealed significant relationships among the memory ratios (Fig. 1A and B) and c-Fos expression. Overall, in the Www-task, hippocampal c-Fos correlated positively with 'what and when memory' in both genotypes, whereas in the Nov-Task it correlated with object location memory (positively in WTs but negatively in nulls). Correlations were found as follows: for WT in the Www-task, Ratio1-CA1 = 0.977 and Ratio2-CA1 = 0.906; for Nulls in the Www-task, Ratio1-SupraDG = 0.854, Ratio1-CA3 = 0.886, Ratio1-CA1 = 0.804, Ratio1-BLA = 0.891, Ratio2-SupraDG = 0.908, and Ratio3-CA1 = −0.862; for WT in Nov-Task, Ratio7-BLA = 0.836, Ratio9-CA3 = 0.785, Ratio9-CA1 = 0.766, and Ratio9-BLA = 0.878; and for Nulls in Nov-Task, Ratio7-SupraDG = −0.909, Ratio7-mPFC = −0.795, Ratio9-SupraDG = −0.802, Ratio9-CA1 = −0.883, and Ratio9-mPFC = −0.809; $P < 0.05$ in all cases.

This study compared the performance of WT and LPA_1-null mice in two object recognition tasks with different memory demands. Mice from both genotypes performed properly the Nov-Task, displaying a strong preference for both novel and displaced objects over familiar and non-displaced ones. These preferences clearly support the ability of the two genotypes to identify and remember the physical attributes of the objects (novel vs familiar objects) and the previously explored spatial locations (displaced vs non-displaced objects). Therefore, there is no impairment in the capacity to recognize familiar objects and locations that may underlie the reported deficits in the Www-task. The Www-task was designed to study mice's capacity to retrieve the what, when and where components in an integrated way during the test phase (i.e. episodic-like memory). Unfortunately, no conclusions regarding to episodic-like memory can be drawn from this study due to the lack of what-where memory in the WT mice. This unexpected result contrasts with the reported ability of rodents to solve this task [1,3,21,22]. Taking into account that different strains

may display notable differences in brain functioning and memory capacities [23], our divergent results are likely a consequence of the genetic background of the WT mice used (C57BL/6J×129X1/SvJ). In supporting this, differences among mice strains have already been reported in the Www-Task. While C57BL/6J mice were able to perform properly all the components [1,3], C57BL/6J/BomTac mice failed to perform the what-where [24].

The exact nature of the specific deficit for the what-where memory is unclear and not easy to clarify. As reported in the Nov-Task, WT mice had no deficit in the memory of objects or in the discrimination of spatial locations that could explain their what-where impairment in the Www-Task. It is thus possible that the binding of both components in order to remember that a particular object was explored in a particular location (i.e. what-where), involved a more complex process. In agreement, some neurobiological data have shown that the what-where memory requires a greater recruitment of the cortical-hippocampal circuit that underlies the Www-Task [3]. In that study, while the what-when memory is impaired by hippocampal but not by mPFC lesions, the what-where memory required the integrity of both the hippocampus and the mPFC. However, because the what-where memory component of the task is assessed by displacing a familiar object to an already familiar location, we cannot rule out that the exploratory motivation under those conditions was notably reduced as it has been reported in rats [21].

On the other hand, WT mice performed the what-when memory, in which nulls were impaired. The interpretation of this memory component is controversial. Although rodents are capable to form temporal order memories [25], an important issue is that the preference for old over recent stimuli could be established by recency judgments in object recognition tasks. Instead of having an explicit memory of the order of objects presentation, mice could solve the what-when by comparing the relative memory strengths of each object, spending more time with the older objects as they forgot over time about a number of its attributes [2]. Therefore, it is possible that LPA_1-null mice show a problem with recency (i.e. the memory traces for both objects may have equal strength in this genotype) instead of a deficit in temporal order memory. This issue cannot be solved by our data, because the employed task, as most temporal order tasks, neither provide an accurate measure of recency nor of the 'when' component of an episode [2]. While the recency hypothesis cannot be ruled out, the correct object memory of both genotypes tested in the Nov-Task (measured at the same delay after which the old objects had to be remembered in the Www-Task) argues against substantial differences in the short-term memory trace strength that would affect recency discrimination in LPA_1-null mice, so the impairment of a higher cognitive process may underlie nulls' what-when deficit. The fact that the null genotype shows a preserved short-term spatial memory [14,15] also supports this hypothesis.

The c-Fos study allowed the comparison of the neuronal activation elicited by both tasks in both genotypes. In WT mice, the Www-task induced more hipopocampal c-Fos expression than the Nov-Task, which was selective for the CA1 area and correlated with the what-when memory. Within the hippocampus, the CA1 area could have a specific role in recency/temporal memory, as lesions in CA1, but not in CA3, impair the preference for old over recent objects [26]. The SupraDG and the mFPC were activated after both tasks in the WT genotype. This result could be expected, given the role of the SupraDG in processing spatial information [27] and the interaction of the mPFC with the hippocampus to integrate object-spatial relationships [3], as evidenced by lesion studies. C-Fos studies have also highlighted the role of these structures to process spatial information. The presentation of novel individual visual stimuli does not increase hippocampal c-Fos, but all the hippocampal subfields (DG, CA3, CA1) respond to a novel spatial rearrangement of familiar stimuli [28] and also to spatial tasks, in which the increase of spatial demands (i.e. some spatial cues removed) evokes more c-Fos activity in the hippocampus and mPFC [29]. In regard to the c-Fos immunoreactivity found in the BLA and the PVN, it suggested that both tasks elicited a similar emotional response, although these and other brain areas not assessed here could also be recruited for some cognitive aspects of the tasks.

In the case of LPA_1-nulls, increased basal c-Fos expression was revealed in their hippocampus (SupraDG, CA3 and CA1) and mPFC. Although the mPFC has been less well studied in this genotype, severe neurochemical abnormalities are described in their hippocampus to suggest a strengthening of basal hippocampal glutamatergic transmission. These changes include an increased basal glutamate release [30], altered density and activity of several glutamate receptors [9,12], accumulation of SNARE complexes and increased phosphorylation of the Ca^{2+}/calmodulin-dependent kinase II (CaMKII) [12]. Nevertheless, phosphorylation of the nuclear cAMP responsive element-binding protein (CREB), an important promoter of *c-fos* transcription, is blunted [12], so the augmented basal c-Fos expression in nulls' hippocampus may be accounted for by CREB activity independent of phosphorylation [31] or by other calcium-mediated transcription factors [32]. Interestingly, this basal hyperactivity was regulated differently by the two behavioural tasks to which LPA_1-null mice were submitted. After the Www-task, nulls did not significantly increase hippocampal c-Fos expression from basal levels, which agrees with an impaired responsiveness of their hippocampal glutamatergic system [30]. In contrast, activation of the mPFC increased dramatically, perhaps to compensate for the lack of hippocampal function that seems required to solve both 'where' and 'when' components of this task [3]. It should be noted, however, that changes in c-Fos expression described here may not account for the performance in this task but rather for the subsequent consolidation of information [33] and additional alterations in nulls, as an impaired adult hippocampal neurogenesis [11,34], may also be responsible for their recency/temporal memory deficit. Regarding the Nov-Task in which nulls learned, hippocampal c-Fos immunoreactivity was reduced from basal levels in CA3 and CA1, and the mPFC did not increase its expression. Thus, we may speculate on an adaptive mechanism that allows LPA_1-nulls to successfully complete some tasks in which the hippocampal demands are moderate. Further research employing pharmacological manipulation of the LPA_1 signalling pathway would be useful for investigating its potential modulation of declarative memory.

Acknowledgments

We are grateful to Carmelo Millón Peñuela for his help, to Ana Isabel Gómez Conde and Juan Gómez Repiso for their technical assistance, to University of Málaga for maintenance of mice and to the members of the 'Neuropsicofarmacología de los Transmisores Lipídicos' research group for their valuable support. We are also grateful to the anonymous reviewers for their insightful comments on a previous version of this manuscript. Authors have no conflict of interest to declare.This study is sponsored by University of Málaga; Spanish Ministries of Health and of Science; Red de Trastornos Adictivos, Andalusian Ministry of

Innovation, Science and Enterprise; Grant number: Ayuda para la actividad productiva del PIF, III Plan Propio (to E.C.O.). MEC SEJ2007-61187 -co-funded by ERDF-, MICINN PSI2010-16160 and SEJ-4515 (to L.J.S.). PI07/0629, PI10/02514 -co-funded by ERDF- and CTS643 (to G.E.). RD06/001/0000 and SAF2010-20521 (to F.R.F).

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