Spatial object recognition memory formation under acute stress

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Funding information
Agencia Nacional de Promoción Científica y Tecnológica, Grant/Award Number: PICT 2012-1035; Consejo Nacional de Investigaciones Científicas y Técnicas, Grant/Award Number: PIP 00366

Abstract
Stress is known to have a critical impact on memory processes. In the present work, we focus on the effects of an acute stress event closely associated to an unrelated learning task. Here, we show that acute stress (elevated platform [EP] session) experienced 1 hr after a weak spatial object recognition (SOR) training, which only induces a short-term memory (STM), promoted the formation of SOR-long term memory (SOR-LTM) in rats. The effect induced by stress was dependent on the activation of glucocorticoid- and mineralocorticoid-receptors, brain-derived neurotrophic factor (BDNF) and protein synthesis in the dorsal hippocampus. In contrast, EP after a strong SOR impaired SOR-LTM probably by interfering with the use of necessary resources. Moreover, we show that the EP session before training induced anterograde interference, which it was not reversed by a subsequent exposure to an open field. Our findings provide novel insights into the impact of stress on LTM formation in rodents and they are discussed under the behavioral analogue of the synaptic tagging and capture hypothesis.

KEYWORDS
elevated platform, hippocampus, long-term memory, spatial object recognition, synaptic tagging

1 | INTRODUCTION

Our daily lives are full of emotionally arousing experiences. Collectively, the potential threats of our bodily homeostasis are referred to as stress (Levine, 2005). Stressors triggers hypothalamic–pituitary–adrenocortical axis activation leading to glucocorticoid release from the adrenal glands, accompanied by rapid sympathetic physiological responses, that influences neural structures that control emotion and cognition (Joëls, Pu, Wieght, Otzl, & Krugers, 2006). When a situation is perceived as stressful, specific brain regions are activated, including hippocampus, amygdala and prefrontal cortex which are enriched with glucocorticoid receptors (Deppermann, Storchak, Faggatt, & Ehlis, 2014). These areas are also crucial in the formation of spatial memories and are involved in learning from stressful events and their surrounding context which is an essential mechanism to respond adaptively to similar demands in the future (Sandi & Pinelo-Nava, 2007).

Long-term memory (LTM) formation is a gradual process that requires new protein synthesis (McGaugh, 2000; Schafe, Nadel, Sullivan, Harris, & LeDoux, 1999). Learning tasks can induce the synthesis of proteins, if they are strong enough, or they can also use the proteins induced by other events close in time to them. However, synaptic plasticity and learning and memory require input specificity for the encoding and storage of the information. In analogy to synaptic tagging and capture hypothesis (Frey & Morris, 1997) we postulated the behavioral tagging (BT) hypothesis (Moncada & Viola, 2007) proposing that a learning session sets a learning-tag indicating the place where the proteins will be captured to establish LTM (Redondo & Morris, 2011; Viola, Ballarini, Martínez, & Moncada, 2014). In previous studies, we showed that the proteins provided by the exposure to a novel open field (OF) promote the formation of LTM of different learning tasks (Ballarini, Moncada, Martínez, Alen, & Viola, 2009; Moncada, Ballarini, Martínez, Frey, & Viola, 2011). Then, several groups reproduced and extended our findings...
in rodents (for review see Moncada, Ballarini, & Viola, 2015). Moreover, there are findings suggesting the existence of a similar process operating in LTM formation in humans (Ballarini et al., 2013; Dunsmoor, Murty, Davachi, & Phelps, 2015). Besides OF, other experiences such as objects’ exploration in a novel arena, a novel taste, a Morris water maze session, a contextual fear conditioning reminder session, contextual fear conditioning extinction session or a rewarded T-maze task were further described as protein supplier events that promote unrelated memories (Ballarini et al., 2009; Cassini et al., 2013; Dong et al., 2012; Salvetti, Morris, & Wang, 2014). Considering the plethora of data about the modulatory effect on memory processes caused by stress or by the administration of glucocorticoids (Cadle & Zoladz, 2015; Joëls et al., 2006; Sandi & Pinelo-Nava, 2007) we considered that a stressful event could influence unrelated memory formation by providing or competing for protein resources.

The hypothesis of “emotional tagging” (Richter-Levin & Akirav, 2003) was introduced to characterize the relevance of affective factors in determining memory outcomes. It focuses on amygdala activation, resulting in modulation of neural plasticity in other brain regions involved in the emotional memory formation. Recently, it was proposed that stress enhances memory for other experiences using a mechanism of synaptic tagging and capture (Bergado, Lucas, & Richter-Levin, 2011). However, a detailed protocol to demonstrate that proposal still remains to be done.

Here, we show that acute stress experienced 1 hr after a weak spatial object recognition (wSOR) training, that only induces STM, promotes the formation of SOR-LTM in rats. This effect is impaired by drugs that antagonize the glucocorticoid receptors (GR) and mineralocorticoid receptors (MR), that inhibit protein synthesis, or that block BDNF function, which were administered into the dorsal hippocampus before the stressful event took place. However, the effect of 1 hr post-training stress depends on the strength of the learning session. If rats are trained in strong SOR (sSOR) task, the stressful experience impairs the SOR-LTM formation, probably by interfering with the use of the plasticity-related proteins (PRPs). Also, we show that acute stress before sSOR training impairs its LTM formation. Our findings suggest that a stressful event affects LTM formation of an unrelated memory, and they are discussed under the conceptual framework of BT hypothesis.

2 | MATERIALS AND METHODS

2.1 | Animals

Male adult Wistar rats (40–60-day-old, 200–350 g), from Faculty of Exact and Naturals Sciences of Buenos Aires, were housed in groups of five per cage at 21 °C under 12 hr light/dark cycle. All rats had food and water available ad libitum. Animals were handled for 2 min for two consecutive days before the experiment. All procedures complied with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publications No. 80-23, revised 1996) and were approved by the Animal Care and Use Committee of the University of Buenos Aires.

2.2 | Drugs

All drugs used were purchased from Sigma, St. Louis, MO. The protein synthesis inhibitors used were anisomycin (aniso, 80 μg/0.8 μL) and emetine (emet, 50 μg/μL). Aniso was dissolved in HCl, diluted in saline and adjusted to pH 7 with NaOH. Emet was dissolved in saline to reach the appropriate concentration. The MR antagonist spironolactone (spiro, 75 ng/μL) and GR antagonist mifepristone (mife, 20 ng/μL) was dissolved in DMSO and diluted in saline for a final concentration of DMSO 5%. The doses were determined from published studies (Korte, Boer, Kloet, & Bohus, 1995; Moncada et al., 2011; Xing et al., 2014) and pilots experiments in our lab. The function-blocking anti-BDNF antibodies (Chemicon, Temecula, CA; AB1513P) were diluted to working concentration (0.5 μg/0.8 μL) with saline (Slipczuk et al., 2009).

2.3 | Surgery and drugs administration

For the implantation of cannulas, rats were deeply anesthetized (70 mg/kg ketamine; 7 mg/kg xylazine). Cannulas were stereotaxically aimed to CA1 region of the dorsal hippocampus at coordinates A: −3.9 mm, L: ±3.0 mm, D: −3.0 mm, from Bregma (Paxinos & Watson, 2007) and they were cemented to the skull with dental acrylic. To prevent clogging, a needle was placed in the cannula. During surgery, the analgesic meloxicam (0.2 mg/kg) and the antibiotic gentamicin (3 mg/kg) were ip administered. Animals were allowed to recover from surgery at least for 4 days before the experiment.

To infuse the drugs, a 30-gauge needle with its tip protruding 1.0 mm beyond that of the guide was used. The infusion needles were linked by an acrylic tube to a Hamilton microsyringe. Drugs were infused 15 min before EP session. Rats were manually restrained during bilateral drug infusions delivered over 2 min. The needle was left in place for an additional minute after infusion to allow diffusion and to prevent reflux.

2.4 | Histology

Histological examination of the cannulas’ placement was performed after the experiments by the infusion of 0.8 μL of 4% methylene blue in saline solution (Figure 1b). Animals were killed by decapitation 15 min after and their brains were removed and sliced to check the infusion area (maximum spread of about 1.5 mm²) (Villar, Martinez, Lopes da Cunha, Ballarini, & Viola, 2016). Only data from animals with correct cannulas implants (95% of the rats) was included in statistical analyses.

2.5 | Spatial object recognition

Spatial object recognition (SOR) memory is the ability to detect the spatial displacement of previously encountered objects. If a familiar and a novel location of objects already encountered are presented to a rat, it will spend more time exploring the spatially displaced object (novel location) relative to the stationary one (Dere, Huston, & Souza Silva, 2005).

The objects were located in a 60 cm wide x 40 cm long x 50 cm high acrylic box. The frontal wall of the box is transparent and the
back wall is hatched, while laterals walls are white with different visual clues. On the training day (TR), two identical objects (aluminum, glass or plastic objects of similar dimensions) were included in the arena in two adjacent corners and animals were left to explore the arena for 5 min in a weak training (wSOR) or 10 min in case of strong one (sSOR). The room where SOR training took place was dimly lighted.
Exploration time for each object, defined as sniffing or touching it with the nose or forepaws, was measured using a hand stopwatch. Rats were excluded from the analysis if they explore one of the objects more than 65% of the total objects-exploration time during TR. In the test session (TS), performed 30 min later (STM) or 24 hr later (LTM), one of the objects was switched to a new position and exploration time was recorded again. Animals were allowed to explore for 2 min and those with total objects-exploration time lower than 10 s were excluded. Results are expressed as a preference index: [Exploration time of new location (Tn)-Exploration time of familiar location (Tf)]/[Tn + Tf]. A positive and significantly different to zero score indicates memory. A representative mean ± SEM of the total exploration time during wSOR was 51.04 ± 1.80 s and during TS was 17.63 ± 0.59 s.

From rat to rat, the familiar or new position of the object in TS was counterbalanced. The box and the objects were thoroughly cleaned between trials.

2.6 | Elevated platform

Behavioral stress was evoked by placing the rat on an elevated platform (EP) made of white acrylic (20 x 20 x 80 cm above ground level) for 30 min in a brightly lit room (Degroot et al., 2004). During this period, the animals show behavioral signs of stress (freezing immobility, piloerection, urination, and defecation). We performed radioimmunoassay for measuring corticosterone plasma levels 5 min after EP and we confirmed high amount of this hormone (control: 34.43 ± 7.25 ng/mL, n = 5; EP: 822.0 ± 77.30 ng/mL, n = 6; p < .001 Student’s t-test).

2.7 | Open field

The OF consisted of a square box of 50 x 50 x 39 cm, with black walls and floor, which is divided into nine quadrants by white stripes. Animals were left to explore for 5 min under normal lighting of the room (Moncada & Viola, 2007). Rats did not show any freezing signs; in contrast they displayed a typical spontaneous exploratory behavior. A representative mean ± SEM (n = 21) for the number of quadrant crossings was 98.38 ± 3.11 and for the number of rearings was 49.19 ± 2.27.

2.8 | Data analysis

Statistical analysis of behavioral data was performed using Graph Pad Prism® software. Differences between the groups were determined using non-paired Student t-test or one-way ANOVA. Post hoc comparisons were made using Newman-Keuls or Dunnett comparison test.

3 | RESULTS

3.1 | Acute stress 1 hr after a weak SOR, that only induces STM, promotes SOR-LTM

We trained rats to explore two identical objects inside a context (wSOR). In the test session, one of the objects was placed in a novel location in the same context and we measured the exploration to both objects. Figure 1a shows that the group of rats trained with wSOR and tested 30 min later showed SOR-STM; however, a parallel group of rats trained with the same wSOR but tested 24 hr later did not show SOR-LTM (p < .01 vs STM group). In contrast, when animals experienced a stressful event (30 min exposure in EP) 60 min after wSOR, SOR-LTM was established (p < .05 vs LTM group).

3.2 | The promoting effect of stress depends on the activity of MR and GR, BDNF and protein synthesis in the dorsal hippocampus

Because SOR is a hippocampus-dependent task (Ballarini et al., 2009; Mumby, Gaskin, Glenn, Schramek, & Lehmann, 2002), we wondered if the promoting effect of stress on SOR-LTM formation would be blocked by the administration of GR or MR antagonists in the CA1 of the dorsal hippocampus. Rats were trained with a wSOR and an EP stress session was given 60 min after. Animals received hippocampal infusions 15 min before EP, with vehicle, mifepristone or spironolactone (Figure 1b shows a representative schema of the infusion area). SOR-LTM was registered 24 h after training. Figure 1c shows that rats infused with veh expressed SOR-LTM (p < .01 vs CTR); in contrast, rats infused with mife or spiro did not express it (p < .01 vs veh). Moreover, the promotion of SOR-LTM formation induced by stress after wSOR (p < .001 vs CTR), was blocked by the intra-hippocampal administration of the protein synthesis inhibitors anisomycin (p < .01 vs veh) or emetine (p < .05 vs veh), 15 min before EP exposure (Figure 1d). Because one effector protein with memory-enhancing action induced by GR activation is BDNF (Chen, Bambah-Mukku, Pollonini, & Alberini, 2012; Revest et al., 2014), here we blocked BDNF function by infusing anti-BDNF antibodies into the dorsal hippocampus 15 min before EP. We found that SOR-LTM promotion was blocked (p < .01 vs veh, Figure 1e).

3.3 | There is a narrow time window of efficacy of acute stress on SOR-LTM formation

Next, we studied if the acute stress could have effects when it was experienced at other times around wSOR. Rats were exposed to EP 60 or 30 min before wSOR, or 30, 60, or 90 min after it. As expected stress 60 min after wSOR promoted the formation of SOR-LTM (p < .05 vs CTR, Figure 2). However, no other time interval either before or after wSOR was successful to induce SOR-LTM.

3.4 | Stress 1 hr before SOR training has a detrimental effect on SOR-LTM

Given that the EP exposure before wSOR did not induce the formation of SOR-LTM, we decided to expose rats to an OF session, an event widely demonstrated to promote LTM for different learning tasks by inducing protein synthesis (Moncada, Ballarini, Martinez, & Viola, 2014). Figure 3a shows that OF 60 min after wSOR induce SOR-LTM (p < .05 vs CTR); however, in a parallel group of rats which
also experienced EP session 60 min before wSOR, the SOR-LTM formation was prevented (p < .05 vs OF). Moreover, rats trained in sSOR expressed SOR-LTM, but rats exposed to an EP 60 min before sSOR were amnesic (p < .05 vs CTR), and this effect could not be reverted by the OF experienced 60 min after sSOR (p < .05 vs CTR, Figure 3b). SOR-LTM was not affected by exposing rats to an OF 60 min after sSOR (preference index mean (±SEM): OF: 0.23 ± 0.07 (n = 11) vs CTR: 0.21 ± 0.05 (n = 14), p > .05 after t-test). Finally, we wondered if this negative effect of acute stress specifically affects SOR-LTM formation. To study this issue, rats were exposed to the EP 60 min before sSOR and SOR-STM was registered 30 min later. Figure 3c shows that animals can encode information and express STM (p > .05 vs CTR), suggesting that the effect of EP is selective on memory consolidation.

3.5 | Stress 1 hr after strong SOR training interfered with SOR-LTM formation

In Figure 4, we observed that sSOR induced SOR-LTM in rats; however, EP 60 min after sSOR impaired SOR-LTM expression (p < .05 vs CTR). This amnesia was prevented by exposing animals to an OF session 60 min before sSOR (p < .05 vs STR + 60). OF session experienced 60 min before sSOR did not affect SOR-LTM formation (preference index mean (±SEM): OF: 0.17 ± 0.06 (n = 19) vs CTR: 0.26 ± 0.06 (n = 14), p > .05 after t-test). Therefore, EP 60 min after wSOR promoted SOR-LTM, but EP 60 min after sSOR blocks SOR-LTM, probably by providing or competing for resources, respectively.

4 | DISCUSSION

Most studies describe the effect of stress when it is intrinsic to a learning task, highlighting its involvement in memory consolidation (Lalumiere, McGaugh, & McIntyre, 2017; McGaugh, 2013). Also, increasing the stress intensity at training accelerates systems consolidation and memory generalization in a process triggered by glucocorticoid and noradrenaline released into the hippocampus (Pedraza, Sierra, Boos, Quillfeldt, & Alvares, 2016). However, an extrinsic stress experience affects the memory of any incidental learning temporally associated with it, and its impact depends on factors such as the intensity and the duration of the stress situation, the moment at which it was experienced and the type of the learning task involved (Joëls & Baram, 2009). A unifying theory states that stress acting around the time of the event to be remembered exerts its action on some overlapping circuits and facilitates learning and memory process (Joëls et al., 2006). Stress influences the acquisition of unrelated information in a time-dependent fashion, having an enhancing effect when is near to learning and an impairing one when it is temporally separated from it (Cadle & Zoladz, 2015).

We found that pretraining stress specifically impaired SOR-LTM without affecting SOR-STM. This effect was independent of the training strength and could not be reverted by OF exposure. In contrast, the effect of post-training stress was training strength-dependent. Thus, stress impaired SOR-LTM when the training was strong but promoted SOR-LTM when the training was weak. Such promoting effect was blocked by protein synthesis inhibitors, antibodies against BDNF and GR’s and MR’s antagonist, infused into the dorsal hippocampus before EP. Our findings are consistent with previous studies showing that post-training EP impaired a consolidated recognition LTM but it promoted SOR-LTM when rats were subjected to a weak training through a mechanism involving GR in the amygdala (Maroun & Akirav 2008; Segev, Ramot, & Akirav, 2012). Also in line with our results, recent findings demonstrated that anisomycin-induced amnesia of SOR was reverted by infusing BDNF into the dorsal hippocampus, suggesting an important role of BDNF as a product of protein synthesis required for the consolidation for this task (Aarse, Herlitze, & Manahan-vaughan, 2016; Ozawa, Yamada, & Ichitani, 2014). Here, we proposed that GC secreted by stress could be involved in the synthesis of PRPs in the hippocampus. It was reported that stress-increased GC secretion induces the expression of pro-BDNF and tissue-plasminogen activator proteins that allows further proteolytic processing of pro-BDNF into BDNF (Revest et al., 2014). Also, the experience of a short-time stress induced a significant increase in BDNF mRNA levels in the whole rat hippocampus, followed by an augmented BDNF protein level, probably due to glucocorticoids effects on glutamate release into the hippocampus (Marmigère, Givalois,
Moreover, several molecular pathways are proposed to be induced by GR activation in hippocampus including the release of glutamate, increases in synaptic GluA1 expression, phosphorylation of CaMKII, TrkB, and CREB (Finsterwald & Alberini, 2014). Thus, given the effects of pCREB on gene transcription which include the increase of mRNA for BDNF and Arc (Barco et al., 2005; Ying et al., 2002) and the transcriptional and translational effects of GR and MR in the hippocampus (Datson, Perk, Kloet, & Vreugdenhil, 2001; Roozendaal et al., 2010), we suggest that stress could increase the expression of protein synthesis.

We have previously described that a novel OF exposure, 60 min before or after a wSOR, promoted SOR-LTM by protein synthesis-dependent mechanisms (Ballarini et al., 2009). Thus, either novel OF exposure as well as EP session 60 min post wSOR promoted SOR-LTM formation. In contrast, an EP experienced 60 min before a SOR had impairing effects on the SOR-LTM, which is consistent with previous findings using different stressors on spatial water maze LTM (Kim, Koo, Lee, & Han, 2005; Park, Zoladz, Conrad, Fleshner, & Diamond, 2008). We observed that this negative effect of stress before learning on the formation of SOR-LTM considers the priming or preconditioning: a first synaptic plasticity primes or modifies a subsequent synaptic plasticity. This is referred as metaplasticity (Abraham & Bear, 1996). While metaplasticity was initially defined and studied at synaptic and cellular level, it was also useful to describe plasticity changes on a more global level referring as “behavioral metaplasticity” (Schmidt, Abraham, Maroun, Stork, & Richter-Levin, 2013). Therefore, we suggest that the synaptic changes induced by exposure to EP could affect the following synaptic changes induced by SOR leading to the impairment in SOR-LTM formation.

Our results suggest that cellular and molecular mechanisms triggered by stress and SOR interact in the dorsal hippocampus and they may result in SOR-LTM. These results could be analyzed under the BT hypothesis, which postulates that a two-step cellular process is required to form a LTM: the setting of a tag induced by learning and the supply of PRPs. Under this view, stress post wSOR could positively affect this unrelated memory within specific time-lapse, providing PRPs to transient sites tagged by learning. It is interesting to highlight that BDNF receptor TrkB was postulated as a potential component of the behavioral tag, while BDNF is a good candidate for being one of the PRPs (Lu et al., 2011). In addition, there are results suggesting the role of Arc, GluA1 and Homer-1a as other molecules acting as PRPs (see Moncada et al., 2015 for revision). Moreover, our results also suggest the presence of a SOR learning-tag. We think that EP previous to SOR could prevent this tag setting impairing the formation of SOR-LTM, and it is why OF exposure, a PRPs provider
event (Ballarini et al., 2009), did not rescue this impairment. An important aspect of the postulated learning-tag is its transient duration; so, if PRPs arrive when the tag has already decayed, the capture mechanism should not work (Viola et al., 2014). That is probably why EP 90 min after a wSOR did not promote SOR-LTM. Finally, the BT hypothesis predicts that the tags set by different tasks localized in a common population of neurons could compete for capturing the available PRPs (Moncada et al., 2015). In that sense, retroactive interference was observed when an event was experienced after a strong learning task (Martínez, Alen, Ballarini, Moncada, & Viola, 2012; Martínez, Villar, Ballarini, & Viola, 2014; Villar et al., 2016). We suggest that this is the case for the impairing effect of the EP experienced 60 min post sSOR, which is compatible with the fact that a source of PRPs, like OF 60 min before sSOR, prevents this impairing effect.

Taken as a whole, BT hypothesis offers a conceptual framework to analyze our present findings. However, we want to highlight that non-synaptic mechanisms, like changes in neuronal intrinsic excitability, were recently proposed as an alternative model (Korz, 2018). Moreover, although in our work we studied the effects of stress on a spatial memory focusing on the role of dorsal hippocampal area, this is a partial view of the complex phenomenon of memory formation that, in fact, involves the activation of other brain regions. Among them, the multiple effects of stress on amygdala and its impact on several brain areas, including the hippocampus, would affect different synaptic plasticity and memory processes (McGaugh, 2013; Richter-Levin & Maroun, 2010).

In conclusion, our results show that acute stress affects satellite SOR memory formation in rats. Stress 1 hr post SOR training is able to promote LTM if the training session is weak; however, stress impairs SOR-LTM when training is strong. Stress always prevents SOR-LTM when is experienced before a weak or strong SOR session (Figure 5).

![Figure 4](image)

**FIGURE 4** Stress 60 min after strong SOR impairs SOR-LTM formation and this effect is rescued by OF. Control group of rats (CTR, n = 18) was trained with sSOR. A second group was exposed to EP 60 min after training (STR + 60, n = 12) and a different group, besides EP, explored an OF 60 min before training (OF STR + 60, n = 17). SOR-LTM was tested 24 hr after sSOR. All data are expressed as preference index mean (±SEM). Newman–Keuls analysis after one-way ANOVA, $F_{(2,44)} = 3.540; \ast p < .05$

![Figure 5](image)

**FIGURE 5** Effect of stress on unrelated but temporally associated spatial memory: a possible interpretation based on BT hypothesis. Schema summarizes the present results. (a) A weak SOR training (Weak learning, surrounded by a dotted circle) that does not induce per se SOR-LTM, can generate LTM if stress is experienced during a narrow time window. This is compatible with a postulated transient learning-tag setting (induced by SOR training session). (b) This effect of stress on SOR-LTM formation depends on protein synthesis, GR and MR activity and BDNF in the dorsal hippocampus. A main point in BT hypothesis is the requirement of PRPs provided by a strong experience, like stress (c) Stress 60 min after strong SOR training (strong learning, surrounded by continue line circle) impairs SOR-LTM formation, possibly due to the competition for PRPs. (d) Stress 60 min before SOR training also prevents LTM formation, probably due to metaplastic changes that could hinder the setting of a putative learning-tag.
ACKNOWLEDGMENTS
We gratefully acknowledge Dr Jorge Medina for his comments to the manuscript. We thank Nadia Alen, Camila Martinez Calejman and Dr. Cora Cymeryng for plasma corticosterone levels measuring. This work was supported by Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT, PICT 2012-1035) and Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET, PIP 00366) to Haydee Viola.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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How to cite this article: Lopes da Cunha P, Villar ME, Ballarini F, Tintorelli R, Ana Maria Viola H. Spatial object recognition memory formation under acute stress. Hippocampus. 2019;29:491–499. https://doi.org/10.1002/hipo.23037