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Research Report

Noise exposure of immature rats can induce different age-dependent extra-auditory alterations that can be partially restored by rearing animals in an enriched environment

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ABSTRACT

It has been previously shown that different extra-auditory alterations can be induced in animals exposed to noise at 15 days. However, data regarding exposure of younger animals, that do not have a functional auditory system, have not been obtained yet. Besides, the possibility to find a helpful strategy to restore these changes has not been explored so far. Therefore, the aims of the present work were to test age-related differences in diverse hippocampal-dependent behavioral measurements that might be affected in noise-exposed rats, as well as to evaluate the effectiveness of a potential neuroprotective strategy, the enriched environment (EE), on noise-induced behavioral alterations. Male Wistar rats of 7 and 15 days were exposed to moderate levels of noise for two hours. At weaning, animals were separated and reared either in standard or in EE cages for one week. At 28 days of age, different hippocampal-dependent behavioral assessments were performed. Results show that rats exposed to noise at 7 and 15 days were differentially affected. Moreover, EE was effective in restoring all altered variables when animals were exposed at 7 days, while a few were restored in rats exposed at 15 days. The present findings suggest that noise exposure was capable to trigger significant hippocampal-related behavioral alterations that were differentially affected, depending on the age of exposure. In addition, it could be proposed that hearing structures did not seem to be necessarily involved in the generation of noise-induced hippocampal-related behaviors, as they were observed even in animals with an immature auditory pathway. Finally, it could be hypothesized that the differential restoration achieved by EE rearing might also depend on the degree of maturation at the time of exposure and the variable evaluated, being younger animals more susceptible to environmental manipulations.

Abbreviations: HC, Hippocampus; Noise7d/Noise15d, Rats exposed to noise at 7 or 15 days of age; Ct7d/Ct15d, Control rats of Noise7d/15d, respectively; CNS, Central Nervous System; PND, Postnatal Day; EE, Enriched environment cages; St, Standard cages; OF, Open Field; EPM, Elevated plus maze; IA, Inhibitory avoidance

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1. Introduction

Noise can be defined as an unpleasant sound, in general of high intensity. As a result of exposure to noise, physiological functions such as those involving structures of the auditory and non-auditory systems might be damaged (Gannouni et al., 2013).

Noise is formed by a wide range of frequencies and differs from natural sounds or music. Prolonged noise exposure at high intensities can interfere with the performance of humans` work activities and might produce temporary or permanent damage to the auditory system, which can lead to significant hearing loss (Frenzilli et al., 2004; Gourévitch et al., 2014).

People working in heavy manufacturing (>105 dBA for 1 h) or those that handle firearms (>130 dBA for a few seconds) are commonly affected by permanent hearing loss. Likewise, a temporary hearing loss for a few hours is often experienced by people attending concerts or nightclubs, where elevated noise levels ranging between 90 dBA and 105 dBA for 2 hours or more can be usually found (Trapanotto et al., 2004). In contrast, safer noise levels, below 80 dBA, have been considered harmless for the auditory system (NIOSH, 1998).

Luckily, the environmental noise experienced during daily life such as traffic noise is, in general, of mild intensity. Nevertheless, the negative effects that might be induced by continuous noise exposure of moderate intensity on the auditory and non-auditory systems are largely unknown. Moreover, although the effects of noise in living organisms are typically reversible in the short term, some can cause long-lasting or even permanent damage (Manikandan et al., 2006; Goble et al., 2009; Pienkowski and Eggermont, 2012). However, the consequences of noise impact are largely underestimated by the public health setting, and little is known about possible strategies for counteracting noise-induce damage.

Unfortunately, noise is potentially hazardous for millions of people working in noisy places. However, people that live in a noisy environment without being exposed to noise in their daily work-related activities, may also be at risk (Gourévitch et al., 2014). Importantly, little attention has been paid in the study of noise-induced extra-auditory effects. For this reason, scarce publications can be found on this subject (Lenzi et al., 2003; Turner et al., 2005; Rabat, 2007). Further, few data are available using developing animals exposed to noise.

Previous results from our laboratory and from others (Manikandan et al., 2006; Uran et al., 2010, 2012; Cui et al., 2013) showed that the Central Nervous System (CNS) might be one extra-auditory target for noise-induced damage. In particular, much remains unknown regarding the effect of noise on CNS structures, beyond the classical auditory pathway. Specifically, several behavioral and biochemical alterations were observed in noise-exposed animals. Interestingly, it has been shown that chronic and/or intense exposure to noise can impair hippocampal-dependent memory (Manikandan, et al., 2006; Rabat, 2007; Uran et al., 2010, 2012, 2014) and reduce the number of hippocampal neurons and their ramifications (Jáuregui-Huerta et al., 2011). As an acoustic stimulus, noise can be transmitted through the lemniscal ascending path via the inferior colliculus, then to the auditory cortex and finally to the CA3 region of the hippocampus (HC), suggesting that hippocampal function may be affected by noise exposure (Xi et al., 1994; Sakurai, 2002; Kraus et al., 2010; Cheng et al., 2011). However, it should not be discarded that noise might directly affect HC as suggested by Säljö et al (2011), who concluded that the scalp, skull bone and cerebrospinal fluid, which separate the brain from the surrounding air, do not constitute an appreciable protection for the brain against noise, allowing the impact of noise vibrations that might produce undesirable alterations.

During early mammalian life, the CNS undergoes progressive structural and functional development and may be more susceptible to potential damage induced by a variety of environmental factors like noise. In fact, developing brain is considered more plastic than the adult brain; therefore, disruption of the normal developmental time-course can be induced after a relatively short noise exposure period and with more lasting effects when compared with noise-exposed adult individuals (Wang, 2004; Kujawa and Liberman, 2006).

Interestingly, it is known that the critical period in the development of rat auditory system extends from about postnatal days 11–13 (De Villers-Sidani et al., 2008). Therefore, it could be of interest to investigate if rats of 7 days, that do not have a functional auditory pathway yet, can anyway be affected by noise exposure.

Since different tissues could be affected by the vibration provoked by noise, it should not be discarded that noise might impact the HC through a direct mechanism, besides the already known indirect pathway (Säljö et al., 2011).

Finally, the possibility of restoring noise-induced damage has not been evaluated in our experimental model yet. A non-pharmacological neuroprotective strategy, the enriched environment (EE, Laviola et al., 2008; Petrosini et al., 2009), has shown to be an effective protective tool against different CNS injuries (Lores-Arnaiz et al., 2006; Baldini et al., 2013). It consists in accommodating the animals in cages larger than the standard, which contains different toys, ramps and wheels. Unfortunately, few reports about the success of enriched environment strategy as an approach to counteract the effects of different injuries in developing animals, including noise, have been published (Baldini et al., 2013; Jiang et al., 2015).

Thus, the aims of the present work were to test the existence of age-related differences in extra-auditory hippocampal-dependent behavioral measurements that might be affected in noise-exposed rats as well as to evaluate the effectiveness of a non-pharmacological potential neuroprotective strategy, the EE, on noise-induced behavioral alterations.

2. Results

2.1. *Open field (OF) parameters*

2.1.1. *Vertical exploration (rearing and climbing in the first session)*

Two way ANOVA analysis shows significant differences in the time spent rearing and climbing in the first session of the OF,

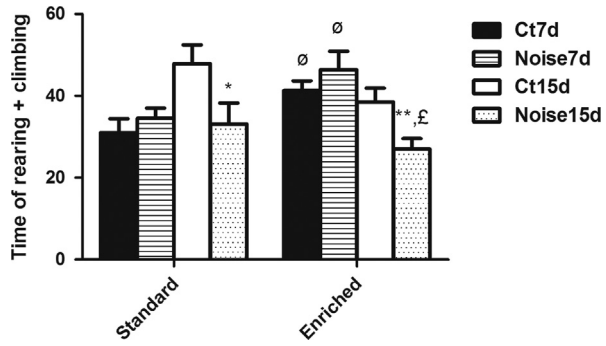

Fig. 1 – Time of rearing and climbing in the OF task (vertical exploratory activity) made by control and noise-exposed rats, reared in standard and enriched conditions. Filled bars: Control animals sham-exposed at 7 days (Ct7d); stripped bars: Noise exposed animals at 7 days (Noise7d); open bars: Control animals sham-exposed at 15 days (Ct15d); dotted bars: Noise exposed animals at 15 days (Noise15d). Standard: Animals housed in standard cages; Enriched: Animals housed in enriched cages. A significant decrease in the time of rearing+climbing was found in Noise15d rats when compared with Ct15d rats, both in Standard and in enriched cages. No changes were found in Noise7d animals when compared with Ct7d rats, neither in standard nor in enriched cages. A significant decrease in the time of rearing and climbing of Noise15d rats reared in EE was found when compared with Noise7d animals reared in EE. Significant increases were observed between 7-days-old animals reared in EE when compared with their standard cages counterparts. Data are mean ± SEM of the time of rearing and climbing; $n=6$ for each group. *, **$p<0.05$ and 0.01, respectively, when compared with the respective control animals. ø, $p<0.05$, when compared with the standard cage counterpart. £, $p<0.05$, when compared with the same group and housing condition, but of a different age.

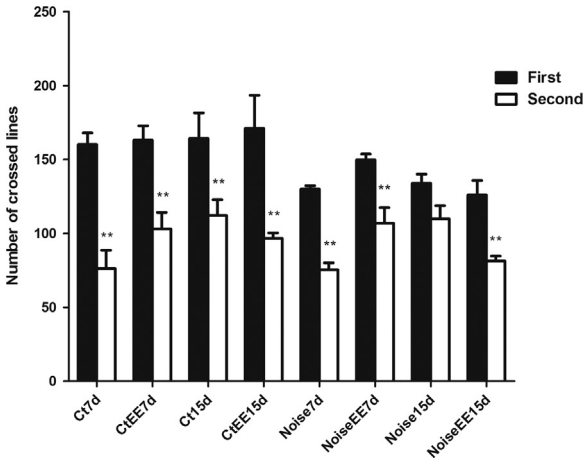

Fig. 2 – Number of lines crossed in the OF task by control and noise-exposed rats, reared in standard and enriched conditions, in the first and second sessions. Filled bars: first session (First); open bars: second session (Second).Groups: control animals sham-exposed at 7 days: standard cage, Ct7d; enriched cage, Ct7dEE; Noise exposed animals at 7 days: standard cage, Noise7d; enriched cage, Noise7dEE; control animals sham-exposed at 15 days: standard cage, Ct15d; enriched cage, Ct15dEE; Noise exposed animals at 15 days: standard cage, Noise15d; enriched cage, Noise15dEE. Although most groups showed significant differences in the number of lines crossed in the first and the second session of the OF, no significant differences were found between the number of lines crossed in the first vs the second session in Noise15d rats reared in standard cages. Data are mean ± SEM of the lines crossed in the OF; $n=6$ for each group. **, $p<0.01$, when compared with the first session.

depending on the age of exposure (7 or 15 days), rearing condition-standard (St) or enriched (EE) cages- and type of treatment–Noise or Control (Ct)-(main effect: $F_{7,67}=4,07$, $p<0.01$, Fig. 1). As the interaction between rearing condition and treatment was statistically significant ($F_{3,67}=4,46$, $p<0.01$), simple effects analysis was performed (St: $F_{3,32}=3,6$, $p<0.05$; EE: $F_{3,34}=5,6$, $p<0.01$). Whereas no significant differences in the time spent rearing and climbing in the first session of the OF were observed in animals exposed to noise at 7 days when compared with the respective controls in both rearing conditions, animals of 15 days exposed to noise spent significantly less time in rearing and climbing than their respective controls, both in St and EE conditions, as suggested by post-hoc comparisons (St: Noise15d vs Ct15d, $t_{12}=2,1$, $p<0.05$; EE: Noise15d vs Ct15d, $t_{11}=2,76$, $p<0.01$). Moreover, both Noise7d animals and their respective control (Ct7d) reared in EE made significantly more rearing and climbing than their counterparts housed in standard cages (Noise7d (St vs EE): $t_{14}=2,31$, $p<0.05$; Ct7d (St vs EE): $t_{23}=2,54$, $p<0.05$). Finally, a significant difference was found between Noise7d and Noise15d animals reared in EE ($t_{13}=3,6$, $p<0.01$).

2.1.2. *Habituation (number of lines crossed in the first and second sessions)*

Repeated measures two way ANOVA analysis shows overall significant differences in the lines crossed in the first and second sessions of the OF ($F_{15,95}=9,4$, $p<0.01$, Fig. 2). Post-hoc comparisons showed that animals exposed to noise at 7 days and their respective controls, reared in St or EE conditions, crossed significantly fewer lines in the second session of the OF than in the first session (St: Ct7d (first vs second), $t_6=5,7$, $p<0.01$; Noise7d (first vs second), $t_6=4$, $p<0.01$; EE: Ct7d (first vs second), $t_{10}=5,7$, $p<0.01$; Noise7d (first vs second), $t_{12}=4$, $p<0.01$). In addition, control animals sham-exposed at 15 days showed a significant difference between sessions, reared both in St or EE conditions (St: Ct15d (first vs second), $t_8=4,2$, $p<0.01$; EE: Ct15d (first vs second), $t_8=5,9$, $p<0.01$). However, whereas no differences between the number of lines crossed in both sessions of the OF were found in Noise15d rats reared in standard cages (first vs second, $t_{10}=1,7$, NS), Noise15d animals reared in EE showed a significantly decreased locomotor activity in the second when compared with the first session of the OF (first vs second, $t_{10}=3,3$, $p<0.01$).

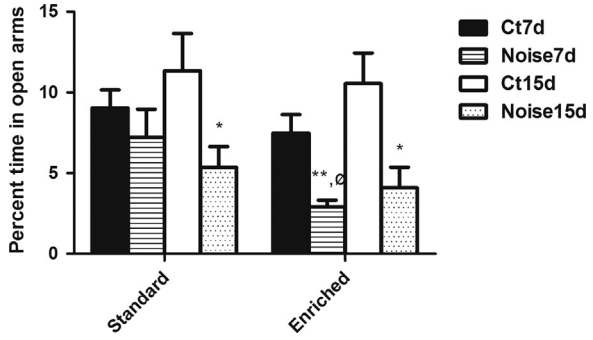

Fig. 3 – Percent time spent in open arms in the EPM task by control and noise-exposed rats. Filled bars: Control animals sham-exposed at 7 days (Ct7d); stripped bars: Noise exposed animals at 7 days (Noise7d); open bars: Control animals sham-exposed at 15 days (Ct15d); dotted bars: Noise exposed animals at 15 days (Noise15d). Standard: Animals housed in standard cages; Enriched: animals housed in enriched cages.A significant decrease in the percent time spent in open arms was observed in Noise15d animals, reared both in standard and in enriched cages. A significant decrease was observed in Noise7d animals when compared with Ct7d, only when animals were reared in EE. Data are mean ± SEM of the percent time spent in open arms of the EPM; $n=6$ for each group. *, **, $p<0.05$ and $p<0.01$, respectively, when compared with the respective controls. ø, $p<0.05$, when compared with the standard cage counterpart.

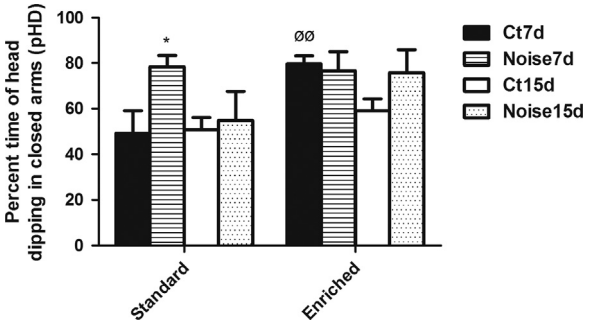

Fig. 4 – Percent time of head dipping made in closed (protected) arms (percent time pHD) in the EPM task by control and noise-exposed rats.Filled bars: Control animals sham-exposed at 7 days (Ct7d); stripped bars: Noise exposed animals at 7 days (Noise7d); open bars: Control animals sham-exposed at 15 days (Ct15d); dotted bars: Noise exposed animals at 15 days (Noise15d). Standard: Animals housed in standard cages; Enriched: animals housed in enriched cages. A significant increase in the percent time of pHD was found in Noise7d rats reared in standard cages when compared with Ct7d rats. No changes were found in percent time of pHD when these animals were reared in EE. Data are mean ± SEM of the percent time of head dipping in the closed arms of the EPM; $n=6$ for each group. *, $p<0.05$, when compared with the respective controls. øø, $p<0.01$, when compared with the standard cage counterpart.

2.2. *Elevated plus maze parameters (EPM)*

2.2.1. *Anxiety-like behavior (time spent in the open arms of the EPM, less time means increased anxiety-like behavior)*

Fig. 3 shows a significant main effect of the time spent in the open arms of the EPM (two way ANOVA, $F_{7,46}=4{,}1$, $p<0.01$). Post-hoc comparisons showed that whereas the time spent in the open arms of the EPM was unchanged in Noise7d rats when compared with their respective controls when reared in standard cages (St: Noise7d vs Ct7d, $t_{10}=0{,}8$, NS), a significant decrease in the time spent in the open arms was observed when Noise7d animals were reared in an EE, when compared with their respective controls (EE: Noise7d vs Ct7d: $t_{10}=3{,}1$, $p<0.01$). On the other hand, a significant decrease in the time spent in the open arms of the EPM was observed in Noise15d animals in both rearing conditions when compared with their respective controls (St: Noise15d vs Ct15d, $t_{11}=2{,}2$, $p<0.05$; EE: Noise15d vs Ct15d, $t_{10}=2{,}6$, $p<0.05$). In addition, the time spent in open arms of the EPM by Noise7d animals was significantly lower in rats reared in EE than in those reared in standard cages (Noise7d (St) vs Noise 7d (EE), $t_9=2{,}1$, $p<0.05$).

2.2.2. *Risk assessment behavior (percent time and number of head dipping in the closed (protected) arm)*

Two way ANOVA analysis shows statistically significant main effects in the percent time and number of head dipping made in the closed (protected) arms (percent time of pHD: $F_{7,47}=2{,}53$, $p<0.05$; percent number of pHD: $F_{7,45}=4{,}83$, $p<0.01$, Figs. 4 and 5, respectively). Post-hoc comparisons showed a significant increase in the percent time and number of pHD in Noise7d rats reared in standard cages when compared with their respective controls (St: percent time of pHD of Noise7d vs Ct7d: $t_7=2{,}5$, $p<0.05$; percent number of pHD of Noise7d vs Ct7d: $t_7=3{,}1$, $p<0.05$). In contrast, when Noise7d rats were reared in an EE, no differences were found in percent time and number of pHD when compared with their respective controls (EE: percent time of pHD of Noise7d vs Ct7d: $t_{10}=0{,}4$, NS; percent number of pHD of Noise7d vs Ct7d: $t_{10}=0{,}6$, NS). Moreover, no significant changes in the percent time and number of pHD were observed in Noise15d animals, neither in standard nor in enriched cages, when compared with their respective controls (St: percent time of pHD of Noise15d vs Ct15d: $t_{12}=0{,}3$, NS; percent number of pHD of Noise15d vs Ct15d: $t_{10}=1{,}19$, NS; EE: percent time of pHD of Noise15d vs Ct15d: $t_{11}=1{,}53$, NS; percent number of pHD of Noise15d vs Ct15d: $t_{10}=0{,}72$, NS). Further, a significant increase in the percent time of pHD was observed when Ct7d animals were reared in EE when compared with those control animals reared in standard cages (Ct7d in EE: 79.6 ± 3.5; Ct7d in St: 49.27 ± 9.8, $t_{10}=3{,}3$, $p<0.01$). Finally, a significant increase in percent number of pHD was observed in Ct7d, Ct15d and Noise15d reared in EE when compared with their respective counterparts reared in standard conditions, whereas no differences between Noise7d reared in EE were observed when compared with Noise7d animals reared in standard cages (Ct7d in EE: 70.91 ± 6.36; Ct7d in St: 46.64 ± 7.52, $t_{10}=3{,}8$, $p<0.01$; Ct15d in EE: 60.48 ± 6.87; Ct15d in St: 41.34 ± 6.36, $t_{11}=2{,}8$, $p<0.05$; Noise 7d in EE: 74.44 ± 7.52; Noise 7d in St: 66.84 ± 7.52, $t_8=0{,}64$, NS;

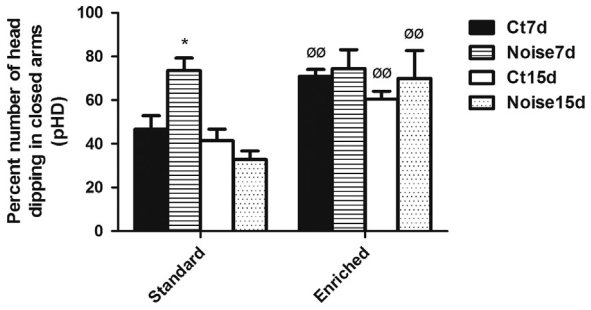

Fig. 5 – Percent number of HD made by control and noise-exposed animals in the closed (protected) arms (percent number of pHD).Filled bars: Control animals sham-exposed at 7 days (Ct7d); stripped bars: Noise exposed animals at 7 days (Noise7d); open bars: Control animals sham-exposed at 15 days (Ct15d); dotted bars: Noise exposed animals at 15 days (Noise15d). Standard: Animals housed in standard cages; Enriched: animals housed in enriched cages. A significant increase in the percent number of pHD was found in Noise7d rats reared in standard cages when compared with Ct7d rats, without changes when these animals were reared in EE. No significant changes were observed in 15d animals reared in both conditions. Data are mean ± SEM of the number of HD made in the closed arms of the EPM; $n=6$ for each group. *, $p<0.05$, when compared with the respective controls. øø, p< 0,05, when compared with the standard cage counterpart.

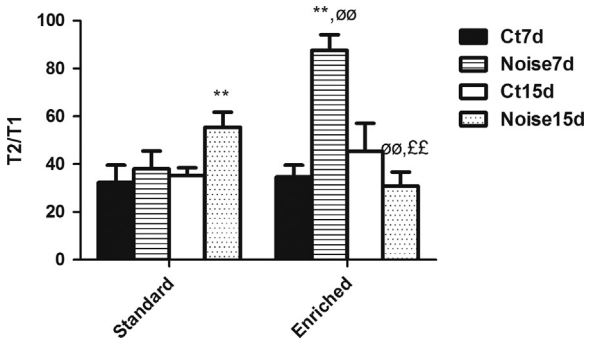

Fig. 6 – Latency to enter the dark compartment in both sessions (ratio T2/T1) of control and noise-exposed animals in the IA task, reared in standard and enriched conditions. Filled bars: Control animals sham-exposed at 7 days (Ct7d); stripped bars: Noise exposed animals at 7 days (Noise7d); open bars: Control animals sham-exposed at 15 days (Ct15d); dotted bars: Noise exposed animals at 15 days (Noise15d). Standard: Animals housed in standard cages; Enriched: animals housed in enriched cages.A significant increase was observed in T2/T1 ratio of Noise15d rats reared in standard cages when compared with Ct15d animals. No differences were found between Noise15d animals and Ct15d animals reared in EE. A significant increase was observed in T2/T1 ratio of Noise7d rats reared in enriched cages when compared with Ct7d animals. Significant differences were observed between noise-exposed animals reared in enriched cages and their standard cages counterparts. Data are mean ± SEM of the T2/T1 ratio measured in the IA task; $n=6$ for each group. **, $p<0.01$, when compared with the respective controls. øø, $p<0.01$, when compared with the standard cage counterpart. ff, $p<0.01$, when compared with animals of the same group and housing condition, but of other age.

Noise 15d in EE: 69.98±6.87; Noise15d in St: 32.79±7.52, $t_9=2,56$, $p<0.05$, Fig. 5).

2.3. *Inhibitory avoidance parameters*

2.3.1. *Associative memory (ratio between the latency to enter the dark compartment in retention and training sessions, T2/T1)*

Two way ANOVA analysis shows a significant main effect of the T2/T1 ratio in the IA task ($F_{7,62}=5,7$, $p<0.01$). As a significant interaction of session × treatment was found, simple effects analysis of each rearing condition was made. Although a significant simple effect in standard cages was found ($F_{3,36}=2,8$, $p<0.05$), post-hoc comparisons showed no significant changes in the T2/T1 ratio in the IA task in Noise7d rats reared in standard cages when compared with their respective control animals (St: Noise7d vs Ct7d: $t_{10}=0,5$, NS). In contrast, a significant simple effect of enriched cages was observed ($F_{3,26}=6,2$, $p<0.01$) and Noise7d rats that were reared in an EE showed a better performance on this task than their respective controls (EE: post-hoc comparisons for Noise7d vs Ct7d: $t_{10}=6,7$, $p<0.01$). On the other hand, a significant increase in T2/T1 ratio was observed in Noise15d rats reared in standard cages when compared with their respective controls (St: Noise15d vs Ct15d: $t_{23}=2,1$, $p<0.05$, Fig. 6), whereas the T2/T1 ratio of Noise15d animals reared in enriched cages did not differ significantly from their respective controls (EE: Noise15d vs Ct15d: $t_{12}=1,2$, NS). Moreover, a significant difference was observed in T2/T1 ratio of Noise7d and Noise15d animals reared in EE when compared with their counterparts reared in standard cages (Noise7d St vs EE: $t_9=4,3$, $p<0.01$; Noise15d St vs EE: $t_{10}=3,9$, $p<0.01$). Finally, a significant difference was found between the T2/T1 ratio of Noise7d and Noise15d reared in EE (EE: Noise7d vs Noise15d: $t_{11}=6,2$, $p<0.01$).

3. Discussion

Present results show that exposure of 7 and 15-days-old animals to moderate levels of white noise (95–97 dB SPL, 2 h) was capable to trigger significant hippocampal-related behavioral alterations that were differentially affected, depending on the age of exposure.

The finding of noise-induced behavioral changes, even in animals with an immature auditory pathway, could suggest that hearing structures might not be necessarily involved in the generation of hippocampal-related behaviors. However, given that rats of 15 days have an already developed auditory system at the age of exposure and showed more noise-related alterations than those observed in rats exposed at 7 days, it should not be ruled out that noise-induced damage to the auditory pathway could indirectly contribute to the observed alterations (De Villers-Sidani et al., 2008; Kraus et al., 2010; Uran et al., 2014). These data are supported by Säljö et al. (2011), who reported that an electromagnetic field

could be formed after noise-blast exposure, and that a direct transmission of the blast wave to the brain through the skull might directly affect different central structures, independently form auditory input.

Interestingly, an environmental challenge such as EE might improve (PND7 rats) or impair (PND15 rats) behavioral performances of noise-exposed animals, which confirm the different susceptibility to environmental manipulations in these age groups. It could be postulated that visual, social and physical stimulation during the peri-adolescence period, attained by rearing the rats in EE, might modify the changes induced by a previous exposure to a physical agent -such as noise- by generating a restoration of several emotional and behavioral parameters (Lores-Arnaiz et al., 2006). It is worth mentioning that just short periods of rearing in an enriched environment appeared to be sufficient to produce brain-related changes in peri-adolescent rats, but not in adults, suggesting that adolescence in the mouse and rat species is a highly sensitive period likely to be modified by environmental challenges (Heim and Nemeroff, 1999; Spear, 2000). Likewise, the use of just one week of EE in the present experimental model, in contrast with longer periods used in adult animals, supports this hypothesis.

Exposed rats reared in enriched conditions showed an age-dependent disparate restoration of the various parameters altered, that seems to depend on the degree of rat maturation at the time of exposure and on the variable tested. Inasmuch as in noise-exposed PND7 animals a restoration of all affected behavioral measurements was observed after EE rearing, in contrast to the restoration of only some of the altered factors observed in PND15 animals, it could be suggested that the response of younger animals to an injury would be more likely to be modified by environmental manipulations.

Significant differences in noise-induced changes were found between Noise7d and Noise15d rats reared in standard cages. First, noise induced a decrease in exploratory activity in OF task only in Noise15d rats and the time spent in open arms of the EPM, which may reflect increased anxiety-like behavior, as suggested by Kalouda and Pitsikas (2015). Second, noise was able to induce a deficit in habituation and associative memory only in rats exposed at 15 days of age, without changes at 7 days, suggesting that more immature animals could be refractory to the damaging effects of noise on different types of memories and emotional behaviors, probably due to the impossibility of noise to accede to the Central Nervous System through a functional auditory system. Therefore, it could be suggested that an increase in anxiety-like behavior was induced only when animals were exposed to noise at a more mature age and that a functional auditory system is required to get into Central Nervous System to induce significant damage (Sakurai, 2002; Uran et al., 2014). However, it should not be discarded that a direct injury, independent from the auditory pathway, might be induced in noise-exposed animals, given that animals with a rudimentary auditory system (e.g., 7-days-old) can be actually be damaged. In fact, noise was capable to increase risk assessment behaviors (RABs) only when animals were exposed at 7 days, which might suggest that, at least in part, noise could generate hippocampal-related behavioral alterations through a mechanism independent from the auditory pathway (De Villers-Sidani et al., 2008; Säljö et al., 2011).

With a focus on RABs, it could be stated that defensive behavior in mammals refers to any behavior which reduces the chances of an animal being harmed and is closely related to fear/anxiety. Its biological function is to inform behavioral strategies in potentially dangerous situations (Carobreza and Bertoglio, 2005). The increase in RABs parameters (percent time and number of pHD) observed in Noise7d rats suggests that at this early developmental age noise exposure was able to make these animals more aware against potential dangers, such as an open environment (Rodgers and Cole, 1993). As EE has shown *per se* to increase RABs in Ct7d, Ct15d and Noise15d rats when compared with the respective age and treatment groups reared in standard conditions, it could be suggested that these ethological measures might be susceptible to be altered through an environmental challenge, supporting results of Pietropaolo et al. (2004) using a mice model of environmental enrichment. An interesting finding was that noise-induced increases in RABs observed in Noise7d animals were effectively avoided after rearing animals in EE, suggesting that threatening behaviors in animals exposed at early ages could be handled through the modification of rearing conditions. In contrast, Noise15d animals reared in standard cages showed unchanged RABs parameters, suggesting that age of exposure is crucial to guide this emotional output.

EE failed to restore both the impaired exploratory activity and the decreased percent time in open arms observed in Noise15d animals, variables related to emotional behavior. It should be mentioned that sometimes EE rearing fails to rescue individuals from damage, as suggested by Cotel et al. (2012) in a mice model of Alzheimer disease. In contrast, rearing in EE was capable of counteracting the remaining noise-related changes induced in Noise15d animals (habituation and associative memory alterations), restoring them to control values. This discrepancy might be associated with the different pathways involved either in emotional behavior and/or in the different types of memories studied, that can be differently damaged by noise (Izquierdo and Medina, 1997).

In addition, although no changes in anxiety-like behavior were observed when animals were exposed at a less mature age (e.g., 7 days), an environmental manipulation was able to unmask a noise-induced increase in anxiety-like behavior. Therefore, it could be suggested that enrichment might induce adaptation of animals exposed at a more immature stage in order to guarantee defensive tools aimed to avoid a potential damage through the increase in anxiety-like behavior, resembling noise-induced effects observed when animals were exposed at 15 days (Kujawa and Liberman, 2006; Chengzhi et al., 2011).

It is important to highlight that in our experimental model, animals were evaluated only at 28 days of age; long-lasting behavioral effects (e.g., in adulthood) were not assessed. Therefore, although previous results showed that noise effects were reverted in adult animals (90-days-old) exposed to noise at 15 days of age (Uran et al, 2014), further experiments will be made to find out if the behavioral

alterations observed in adolescent animals exposed to noise at 7 days were retained over time.

In conclusion, present results suggest that noise exposure might induce different behavioral effects, depending on the age of exposure, being older animals more susceptible to the damage, probably due to the different degree of maturity of the auditory system.

The age-dependent restoration achieved by EE rearing seemed to depend on the degree of maturation at the time of exposure and the variable tested, being younger animals more susceptible to be affected by environmental manipulations.

4. Experimental procedures

4.1. Animals

Healthy male and female albino Wistar rats were obtained from the animal facilities of the Biochemistry and Pharmacy School, University of Buenos Aires, Argentina. A total of 20 females and 10 males were used for mating procedures. Pregnant rats were isolated and left undisturbed until delivery. The day of birth was designated as postnatal day (PND) 0. In average, 10 pups per litter were delivered and only male rats (in average, 4–6 per litter) were used for the different experimental procedures.

PND7 and PND15 littermates were randomly assigned to the different experimental groups, being the litter the experimental unit, so that not more than one male from each litter was attributed to each variable to be measured, and were divided into four groups: control at PND7 (Ct7d), control at PND15 (Ct15d), noise exposed at PND7 (Noise7d) and noise exposed at PND15 (Noise15d). In turn, within each group, animals were divided into two groups: one was reared in standard cages (St) and the other one in enriched cages (EE).

Six animals per experimental group and per behavioral task were used, being a subset of rats (n=48) exposed to noise (Noise7d and Noise15d). Another subset of animals – the Ct7d and Ct15d, sham-exposed rats (n=48) – was placed in the same box as noise-exposed rats, but without noise emission. In addition, within each experimental group, a subgroup (24 animals) was reared in standard cages and the other 24 in enriched cages. Some animals were tested in both OF and EPM tasks, whereas others were evaluated only in the IA task. Total of animals used: 96.

All groups were kept with their dams until weaning, at 21 days of age. Then, rats were separated and maintained 3–4 per cage (standard or enriched) for one week with food and water *ad libitum*, on 12 h light-dark cycles (lights on at 7 A.M.) at 21±2 °C and wood shavings for bedding.

Animals were handled and sacrificed according to the Institutional Committee for the Use and Care of Laboratory Animal rules (CICUAL, School of Medicine, University of Buenos Aires, Argentina). This Committee, under resolution 503/10, approved the present experimental protocol. The CICUAL adheres to the rules of the "Guide for the Care and Use of Laboratory Animals" (NIH) (2011 revision) and to the EC Directive 86/609/EEC (2010 revision) for animal experiments.

To avoid circadian rhythm alterations, noise exposures were performed in the intermediate phase of the light cycle, between 10 A.M. and 2 P.M. Moreover, behavioral tests were performed at the same time in each session. Behavioral tests were performed at PND 28.

4.2. Noise exposure

Animals were kept in their home cages (dimensions: 40 cm × 25 cm × 16 cm) and the entire litter was assigned to the same group, so that they were not handled throughout exposure period. The mother was removed and the home cage with the pups was introduced into an "ad hoc" wooden sound chamber of 1 m × 1 m × 1 m fitted with a ventilated top as reported by Cui et al. (2009). Four-six rats per cage, depending on the litter size, were exposed simultaneously.

Computer software TrueRTA was chosen to produce white noise, using a bandwidth from 20 Hz to 20,000 Hz in octave bands. For sound amplification, an active 2 way monitor (SKP, SK150A, 40 W RMS per channel) was used, located 30 cm above the animal cage placed in the sound chamber. Noise intensity was measured by using an omnidirectional measurement condenser microphone (Behringer ECM 8000) prior to animal exposure, by positioning the microphone in the sound chamber at several locations, and taking an average of the different readings.

PND7 and PND15 animals were exposed to white noise at 95–97 dB SPL (20–20,000 Hz), 2 h, in a single exposure (Noise7d and Noise15d). Ct7d and Ct15d animals were placed in the same box of noise-exposed animals for the same period of time, but without noise emission (sham-exposure). Background noise level ranged between 50 and 55 dB SPL, being within the interval suggested by the WHO guidelines (NIOSH, 1998) and by other authors (Campeau et al., 2002; Sasse et al., 2008). Lighting was provided by a 20 W lamp located in the upper left corner of the sound chamber. In addition, the chamber was provided with a sound attenuation system made with Celotex™.

4.3. Enriched environment (EE)

A subset of animals of all groups was reared in an EE and 3–4 animals were housed together. Whereas the standard cages are stainless steel conventional top-wired rectangular cages of 40 cm × 25 cm × 16 cm, EE cages consisted of 54 cm × 40 cm × 41 cm plastic cages with two levels, containing two connecting ramps. Different plastic toys and tunnels, as well as a running wheel, were placed in the cage. A palatable food, such as Froot Loops®, was added regularly in addition to the conventional balanced food. The objects were changed each two days to ensure continued novelty. Rats were maintained in their housing condition (St or EE) for one week prior to behavioral studies.

4.4. Behavioral assessment

PND28 animals were used for all behavioral experiments.

4.4.1. *Open field task (OF)*

An open field device was used to analyze habituation memory and exploratory activity, known to depend on the HC (Vianna et al., 2000; Barros et al., 2006). In this task, the repeated exposure to the same environment induces a reduction in locomotor activity that was taken as a measure of preservation of habituation memory (Vianna et al., 2000; Pereira et al., 2011). In addition, the first session in the OF can be used to assess changes in emotionality induced by exposure to a novel environment, so that vertical exploratory activity was quantified by recording the number and time spent doing rearing and climbing in the forelimbs. Activity was recorded using a camcorder. To minimize the olfactory stimulus, the floor of the box was cleaned with a 10% ethanol solution between sessions.

Apparatus: OF device consisted of a 50 cm × 50 cm × 50 cm dimly illuminated wooden box, with a floor divided into 25 equal squares by black lines.

First Session: Prior to exposure, rats were individually placed in the behavioral room and allowed to acclimatize for five minutes, to control for variables that can significantly alter physiological and behavioral indicators of stress (Walf and Frye, 2007). After that, rats were withdrawn from the cage, placed on the center rear quadrant of the OF box and allowed to freely explore the box for five minutes. The number of lines crossed was recorded over the session, as well as the number and time of rearing and climbing.

Second Session: After 1 h inter-trial in their home cages, animals were left to explore the apparatus for another five minutes and the number of lines crossed was recorded again to evaluate habituation to the device (Barros et al., 2006).

4.4.2. *Elevated plus maze (EPM)*

This task is used to evaluate anxiety-related behaviors, dependent on the integrity of the HC (Montgomery, 1955; Brenes et al., 2009; Violle et al., 2009). In addition, some ethologically-related items can be evaluated (Carobreza and Bertoglio, 2005), designated as “risk assessment behaviors” (RABs) because they have been associated to detection and analysis of threats or threatening situations (Rodgers and Cole, 1993). Head dipping (HD) is defined as the stretching of rats' heads over the ledge of an open arm and their bending under the maze floor. HD recording was differentiated as a function of their occurrence in different parts of the maze. Closed arms and center platform were designated as “protected” areas (i.e. offering relative security) and the “protected” scores for head-dipping (percent time of pHD and percent number pHD) were calculated as the percentage of these behaviors displayed in or from the protected areas.

Apparatus: The wooden apparatus consisted of four arms of equal dimensions (50 cm × 10 cm) and raised 50 cm above the floor. Two arms, enclosed by walls 40 cm high, were perpendicular to the two other opposed open arms.

Session: Prior to exposure, rats were individually placed in the behavioral room and allowed to acclimatize for five minutes, to control for variables that can significantly alter physiological and behavioral indicators of stress (Walf and Frye, 2007). After that, rats were placed in one of the closed arms, facing the center of the maze and were recorded for five minutes using a camcorder. The percent of time spent on each arm was scored, as well as the time and number of pHD. Maze was cleaned between sessions with a 10% alcohol solution. Only few rats randomly distributed across experimental groups fell down when walking in the open arms; these animals were excluded from the study.

4.4.3. *Inhibitory avoidance task (IA)*

Inhibitory avoidance task measures the memory of an aversive experience through the simple avoidance of a location in which the unpleasant experience occurred. This task depends heavily on the dorsal HC and measures associative memory (Ennaceur and Delacour, 1988, Izquierdo and Medina, 1997).

Apparatus: We used an inhibitory avoidance apparatus as described by (1999), Roozendaal (2002). It consists of a box (60 cm × 60 cm × 40 cm), divided into two compartments: one is illuminated while the other is equipped with a removable cover to allow it to be dark. A removable partition divided the two compartments. The floor of the dark compartment consisted of a stainless steel grid at the bottom, through which a continuous current could be delivered.

Habituation session: Prior to exposure, rats were individually placed in the behavioral room and allowed to acclimatize for five minutes, to control for variables that can significantly alter physiological and behavioral indicators of stress (Walf and Frye, 2007). After that, the rat was placed into the lit box and allowed to freely explore the apparatus. Either after passing three times to the dark side or after three minutes spent in the dark side, the rat was removed from the apparatus. After ten minutes, the rat was placed again in the lit side and when it entered the dark side, the doors were closed and the rat was retained for ten seconds in this side.

Training session (T1): After 1 h, each rat was placed in the lit compartment, facing away from the dark compartment; the latency to move into the dark compartment was recorded. When the rat stepped with all four paws in the dark compartment, a foot shock (1.2 mA, 2 s) was delivered. The rat was then removed from the apparatus and returned to its home cage.

Retention session (T2): retention was made 1 h after the training session by following a similar procedure, except for the fact that no shock was delivered. The ratio between the latency to move into the dark compartment in the retention and the training sessions (T2 and T1, respectively) was taken as a measure of associative memory retention (T2/T1). To minimize the olfactory stimulus, the box was cleaned with a 10% ethanol solution between sessions.

4.5. *Statistical analysis*

Significant differences between groups were analyzed through two way ANOVA test with Tukey post-hoc comparisons. When interactions were significant, simple effect tests were performed (Infostat/L). Results are expressed as mean values ± SEM. A probability <0.05 was accepted as significant.

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Approval of animal experiments

Animals were handled and sacrificed according to the Institutional Committee for the Use and Care of Laboratory Animal rules (CICUAL, School of Medicine, University of Buenos Aires, Argentina). This Committee, under resolution 503/10, approved the present experimental protocol. The CICUAL adheres to the rules of the "Guide for the Care and Use of Laboratory Animals" (NIH) (2011 revision) and to the EC Directive 86/609/EEC (2010 revision) for animal experiments.

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