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Spatial learning and memory deficits in young adult mice exposed to a brief intense noise at postnatal age

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Abstract

Noise pollution is a major hazardous factor to human health and is likely harmful for vulnerable groups such as pre-term infants under life-support system in an intensive care unit. Previous studies have suggested that noise exposure impairs children's learning ability and cognitive performance and cognitive functions in animal models in which the effect is mainly attributed to the oxidant stress of noise on the cognitive brain. The potential role of noise induced hearing loss (NIHL), rather than the oxidant stress, has also been indicated by a depression of neurogenesis in the hippocampus long after a brief noise exposure, which produces only a tentative oxidant stress. It is not clear if noise exposure and NIHL during early development exerts a long term impact on cognitive function and neurogenesis towards adulthood. In the present study, a brief noise exposure at high sound level was performed in neonatal C57BL/6J mice (15 days after birth) to produce a significant amount of permanent hearing loss as proved 2 months after the noise. At this age, the noise-exposed animals showed deteriorated spatial learning and memory abilities and a reduction of hippocampal neurogenesis as compared with the control. The averaged hearing threshold was found to be strongly correlated with the scores for spatial learning and memory. We consider the effects observed are largely due to the loss of hearing sensitivity, rather than the oxidant stress, due to the long interval between noise exposure and the observations.

Keywords: Noise induced hearing loss; Neonatal mice; Learning; Memory; Neurogenesis

1. Introduction

Hearing loss is one of the most common sensory disorders affecting 10% of the general population (Audiology.org, 2011; ASHA, 2011), and approximately 1.4 per 1000 of newborn babies (CDC, 2014). Noise exposure is one of the major causes for acquired hearing loss in adults (Nelson et al., 2005) and children (Niskar et al., 2001; National Institute on Deafness, 2008; National Institute on Dea, 2007). The damaging effect of noise, however, is not limited in the auditory system, but extended to many other systems (Basner et al., 2014). Recent studies have warned of noise-related impairment of learning ability and cognitive performance (Cheng et al., 2011; Cui et al., 2009; Jauregui-Huerta et al., 2011; Wright et al., 2014). Soldiers who were exposed to excessive noise levels including explosions and blast waves revealed severe noise induced hearing loss (NIHL) and tinnitus (Helfer et al., 2011; Cave et al., 2007), as well as cognitive deficits and memory impairment (Belanger et al., 2009).

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The mechanisms underlying cognitive function decline after noise exposure are not entirely clear. However, animal studies have provided clues as to what might be happening. Noise exposure is likely to impair cognitive functions through two different but closely related approaches. One is related to the oxidative reaction initiated by noise exposure. Increased oxidative stress has been reported in many studies as the cause of neuronal degeneration seen in many auditory nuclei as well as in the brain regions critical for cognitive functions (Cheng et al., 2011; Cui et al., 2009; Chengzhi et al., 2011; Hirano et al., 2006). The other approach is the due to the change of auditory input to the cognitive brain after hearing loss induced by noise. This approach is not investigated intensively in the past, but the possibility has been supported by the connection between the auditory brain and cognitive brain (Kraus et al., 2012) and demonstrated by the hippocampal degeneration and deteriorated spatial memory in C57BL/6J mice with age related hearing loss (Yu et al., 2011) and the suppression of hippocampal neurogenesis in the rat after noise-induced unilateral hearing loss (Kraus et al., 2010).

Most of the studies reviewed above are performed on adult subjects. However, the impact of noise exposure during early development on cognitive functions has been suggested by some studies (Xu et al., 2010; Kim et al., 2006). It is important to determine if noise exposure and NIHL at an early stage of an individual's development can produce a long term effect on cognitive function. Exposure to harmful noise exposure is a true risk for new born babies, especially those who are preterm and immature at birth and have to rely on life support systems in an intensive care unit, where the noise level can go beyond 100 dBA (Slevin et al., 2000; Chang et al., 2001; Blackburn, 1998; Lahav et al., 2014). Noise exposure at such levels for a significant period of time is expected to cause oxidative stress and/or NIHL, which may then affect the physical and neurobehavioral development of those babies, resulting in cognitive deficits as they mature (Blackburn, 1998). Exposure to environmental noise has been reported to impair the cognitive function in children (Stansfeld et al., 2005). Animal studies have also demonstrated that hearing impairment during early development can produce long term impacts on behavior and cognitive functions (Jauregui-Huerta et al., 2011; Sun et al., 2011), suggesting that the auditory system and brain are more vulnerable during neonatal age.

Using small rodents (such as rats and mice) to address the developmental impact of noise-induced stress and NIHL on cognitive function is attractive due in part to at least two major reasons. Firstly, this approach allows certain observations, such as neuronal morphology, that are not ethical to perform in human subjects. Secondly, the auditory organs of those rodents are not mature at birth and therefore will mimic the development of preterm human babies (Walters et al., 2013; Kikkawa et al., 2012; Ahituv et al., 2000; Freeman et al., 1999; Sohmer et al., 1995).

In the present study, we observed the impact of a brief noise exposure given at 15 postnatal days (P15d) on the learning/memory function of C57BL/6J mice in young adulthood (2.5 months of age). The noise exposure was at a high level (123 dB SPL) and produced a permanent hearing loss of moderate degree. The changes in hippocampus related learning and memory functions were correlated with the degree of hearing loss.

2. Materials and methods

2.1. Subjects and experimental outline

Pregnant C57BL/6J mice were obtained from the Experimental Animal Center of Jiangsu University, Nanjing, Jiangsu, China. A total of 42 neonatal mice were recruited from 8 litters and were randomly divided into 2 groups with equal sample size ($n = 21$ in each): the control and the noise groups. At P15d, the animals in the noise group were exposed to a broadband (white) noise at 123 dB SPL for 2 h, while the animals in the control group accepted the sham exposure (environmental change). All baby mice were taken back to their mothers after treatment. Two months after the noise exposure (at the age of 2.5 months), all animals were examined for hearing threshold by frequency specific auditory brainstem response (ABR). The capabilities of spatial learning and memory were measured by means of a Morris water maze test prior to the ABR test to avoid the stress impact of anesthesia during ABR. Immediately after the functional test, the hippocampus were harvested for the observation of neurogenesis. All animal procedures were approved by the University Committee for Laboratory Animals of Southeast University, China (Permit number: SCXK2011-0003).

2.2. Noise exposure

The animals in the noise group were treated with an exposure to a broadband noise at 123 dB SPL for 2 h when they were awake. They were unrestrained in a cage 60 cm below the horns of two loudspeakers; one was a low frequency woofer and the other was a high frequency tweeter. Electrical Gaussian noise was delivered to the speakers after power amplification. The acoustic spectrum of the sound was distributed mainly below 20 kHz as reported previously (Wang et al., 2011). The noise level was monitored using a ¼-inch microphone linked to a sound level meter (microphone: 2520, sound level meter: 824, from Larson Davis, Depew, NY, USA).

2.3. ABR test

For ABR recordings, the animal was anesthetized with pentobarbital (80 mg/kg, i.p.) and the body temperature maintained at 37.5–38 °C with a thermostatic heating pad. Three subdermal needle electrodes were used to record ABRs. The non-inverting electrode was inserted at the vertex in the middle point between the two eyes, the reference and the grounding electrodes were on the two earlobes.

TDT hardware and software (BioSig and SigGen) were used for stimulus generation and bio-signal acquisition. The stimuli were played through a broadband speaker (MF1 from TDT, USA), which was placed 10 cm in front of the animal's head. The evoked responses were amplified 20 times and

digitized with a sampling rate of 25 kHz with a TDT pre-amplifier (RA16PA). The responses were averaged 1000 times. ABR thresholds were measures across the frequencies from 2 to 32 kHz with tone bursts presented at the rate of 21.1/s. At each frequency, the test was performed in a descending sequence, starting from 90 dB SPL and descending in 5-dB steps until the ABR response disappeared. The threshold was determined as the lowest level at which a repeatable wave III response could be obtained.

2.4. Behavioral test

The Morris water maze (MWM) used in this study was a plastic, circular pool as described in detail previously (Mendez-Couz et al., 2014; Bonaccorsi et al., 2013). The pool was filled to a depth of 14-cm (0.5-cm over the platform) with tap water 22–24 °C. The water was made opaque with the addition of 100-mL of non-toxic white liquid tempura paint. The MWM test consisted of two phases. The spatial acquisition phase had five training days, each had four training trials with inter-trial interval of 10 min. In the first training day, mice were given an acclimatization session in the MWM as described previously (Vorhees et al., 2006). In this session, each mouse was allowed to freely swim in the pool for 60 s. In each day of five-day training session, the training consisted of 4 trials. In each trial, the animal was released randomly from the four compass locations (NE, NW, SW, and SE). The animal was controlled to enter the water with its head facing the pool wall and allowed to swim and search for the hidden platform for 60 s. If the animal was able to locate the platform and stay steadily on it for more than 5 s the timer is stopped and the mouse was allowed to stay on the platform for 10 s to allow the animal to view the spatial cues in environment. Then, the animal was picked up and returned to the container. If the platform was not found within 60 s, the animal would be guided to it and allowed to stay on it for 15 s. The time needed to reach the platform was recorded as the escaping latency. The next day to the final training day, a single probe trial was given in which the platform was removed. Each mouse was allowed to swim for 60 s in the pool. The number of times the mouse went across the location of the platform during this probe session was recorded as the index of memory of the platform.

2.5. Neurogenesis

Hippocampal neurogenesis was quantified by counting the newly generated neurons using a marker specific to immature neurons (doublecortin, DCX). In each group, the observation was performed successfully in the brains of 6 mice. The animal was deeply anesthetized with pentobarbital (120 mg/kg, i.p.) and fixed with open-chest cardiovascular perfusion of 4% paraformaldehyde in PBS buffer, followed by a post-fixation in the same fixative at 4 °C for 24 h. The brain tissue block was then immersed in 30% sucrose, dehydrated at 4 °C until it sunk to the bottom. The blocks of tissue were then dehydrated and embedded in OCT compound and then frozen in −80 °C freezer. The frozen block was sliced into 25 um thick sections using a microtome (Leica Cryostat Microtome 1900, Germany). One section from every 10 was chosen for further process. The selected sections were permeabilized with 0.1% Triton X-100 in PBS for 30 min, incubated for 30 min in 10% donkey serum in PBS and then incubated in the primary antibody (1:300, goat polyclonal anti-DCX, sc-8066, Santa Cruz, America) overnight at 4 °C. This was followed by treatment with secondary antibodies (1:500, Donkey Anti Goat IgG-H&L Cy3®, ab6949, Abcam, England) for 1 h at room temperature. All antibodies used were diluted in 10% donkey serum in PBS. The number of DCX positive cells in DG region were counted under a fluorescence microscope (OLYMPUS BX53, Japan) and multiplied by 10 to yield the total number of DCX-positive cells in the whole DG region in each animal brain. To avoid the influence of uncontrolled variables in the above procedures, the samples from the control and experimental groups were paired and processed together under the same conditions.

2.6. Statistical analysis

All data are expressed as means ± SEM and *post hoc* (Tukey method) multiple comparisons were performed following ANOVAs.

3. Results

3.1. Noise induced hearing loss

ABR audiograms were obtained at the age of 2.5 months and compared between the normal control group and the noise-exposed group to determine differences in hearing sensitivity. Fig. 1A shows that the ABR thresholds were much higher in the noise group at every frequency tested. Therefore, the noise exposure in the neonatal C57BL/6J mice (15 days after birth) resulted in a large permanent hearing loss as tested in young adulthood. Since a ceiling effect was seen at 32 kHz (as limited by the 90 dB SPL, the highest sound level for ABR testing), we calculated the frequency average across 2–16 kHz as the index of hearing sensitivity (Fig. 1B). The averaged ABR threshold is 42.02 ± 0.6872 dB SPL for the control group, which is significantly lower than the value of 70.07 ± 2.122 dB SPL in the noise group (Student *t* test, $t_{40} = 15.26$, $p < 0.0001$).

3.2. Impact of NIHL on spatial learning and memory

The spatial learning ability of the mouse was tested in MWM just before the ABR tests to avoid potential impact of anesthesia induced stress on learning and memory. The first stage of the MWM test involved a five-day training period in which the mice learned to find the hidden platform underwater and escape by using spatial cues around the pool. Fig. 2 shows the swimming traces from representative examples of mice in each group. Initially (the first day), the animal took a much longer path before the platform was found. The path length

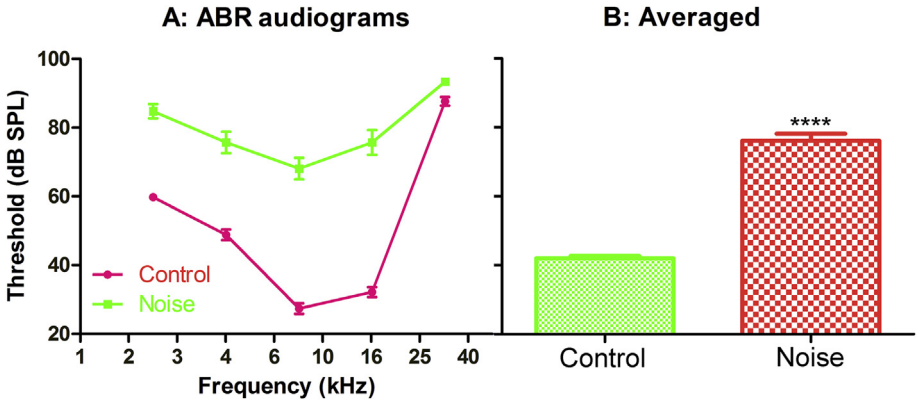

Fig. 1. Comparison of ABR threshold between the control and the noise exposed animals. A: ABR threshold audiogram. B: averaged ABR thresholds across 2–16 kHz (n = 21, ****: $p < 0.0001$).

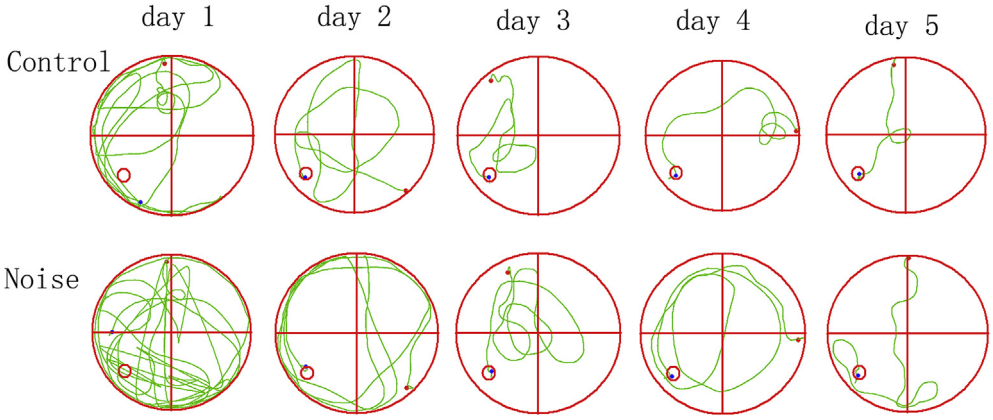

Fig. 2. Representative swimming traces obtained from example mice in both control and noise groups.

was reduced with further training. The decrease in the escape latency (Fig. 3A), defined as the time required for the animal to find the platform, indicates the ability of the animals to learn and use spatial cues. In the noise-exposed group, the decrease with training is less obvious. The averaged escape latency for the control group was 45.16 ± 1.93 s at the first day of the training and dropped to 22.21 ± 2.28 s at the day 5. The corresponding value for the noise group was 46.35 ± 2.165 s at the first day, very close to that of the control. However, the latency was 37.249 ± 2.578 s at day 5, showing a much smaller improvement in escape latency from day 1 to day 5. This indicates that the spatial learning ability is impaired in the noise group. A two way ANOVA was performed against the factors of noise and training. The result shows a significant effects for noise treatment ($F_{1,200} = 24.026$, $p < 0.001$) and training ($F_{4,200} = 11.469$, $p < 0.001$), but not the interaction between both ($F_{4,200} = 2.073$, $p = 0.086$). Under the factor of training, post-hoc parawise comparisons show a significant

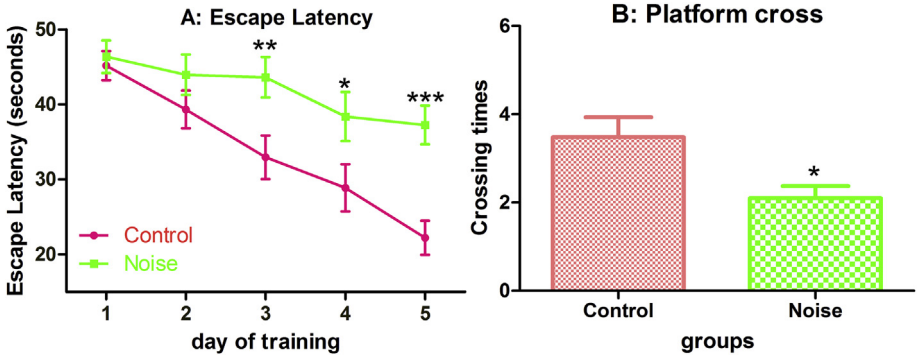

Fig. 3. Comparison of escape latency changes with training in control and noise groups. A: escape latencies against days of training. B: number of platform crosses during 60 s of swimming (the hidden platform was taken off). For all the tests, n = 21, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

difference between the control and the noise groups at day 3 (Tukey method, $p = 0.004$), 4 ($p = 0.011$) and 5 ($p < 0.001$).

The second stage of MWM was the spatial orientation test, in which the hidden platform was removed and the number of crosses through the platform area within 60 s was counted as an index of memory. This number was 2.10 ± 0.28 in the noise group, which is significantly lower than the value of 3.48 ± 0.46 obtained in the control group (Student t test, $t_{40} = 2.594$, $p < 0.05$, Fig. 3B).

3.3. Correlation between NIHL and MWM results

A Pearson correlation was performed to verify if the degree of NIHL is correlated to the outcome of MWM tests. A significant positive correlation was seen between the averaged ABR threshold and the escape latency at day 5 (Fig. 4A, r = 0.607, $p < 0.001$). Since there is no significant difference in the escape latency between the two groups at day 1 of MWM training, the larger values of latency in the noise group indicate a smaller reduction or improvement in the latency with training. Therefore, the positive correlation at the final day of the training suggests a learning deficit in subjects with hearing loss. On the other hand, there is a negative correlation between the averaged ABR thresholds and the platform crossing times in the spatial orientation experiment (r = −0.366, $p < 0.05$), suggesting a memory decline in subjects with NIHL.

3.4. Neurogenesis in hippocampus

The impact of the noise induced hearing loss on neurogenesis was evaluated by counting newly generated hippocampus cells in DG region, identified by an antibody against DCX, a maker specific to newly generated neurons. Fig. 5 shows the representative images take from both control (Fig. 5A) and noise (Fig. 5B) groups. Fig. 6 comparesthe averaged counts of DCX positive cells in the whole DG region in both groups. The average number of DCX positive cells in the noise group was 8038.33 ± 263.69, significantly lower than the value from the control group (9121.67 ± 240.62, n = 6 in each group, Student t test, $t_{10} = 7.434$, $p < 0.0001$).

4. Discussion

In the present study, a brief noise exposure was given to C57 mice at P15d. Although not tested until young adulthood, it is reasonable to assume that NIHL was established immediately after the noise exposure and the ABR threshold differences between the groups represented the long-lasting permanent threshold shifts caused by the noise, which was in the range of a mild to moderate hearing loss across the frequencies tested (Fig. 1).

The behavior test showed that the NIHL we established in the early stages of hearing development exerted a strong influence on the spatial learning ability of these mice as tested in their young adulthood (2.5 months of age, Figs. 2 and 3). This reduction in spatial learning was also accompanied by a depression of neurogenesis in the hippocampus as compared with the control subjects (Figs. 5 and 6). Correspondingly, a significant deterioration in spatial learning and memory was detected in the noise group and found to be significantly correlated with the degree of hearing loss (Fig. 4).

The adverse impact of noise exposure beyond the auditory system has been identified in many previous studies in human subjects and animal models (Basner et al., 2014; Wright et al., 2014). For example, exposures to laboratory and environmental noise were found to impair cognitive function, including learning and memory (Cui et al., 2009; Chengzhi et al., 2011; Kraus et al., 2010; Stansfeld et al., 2005; Manikandan et al., 2006; Cui et al., 2012; Rabat et al., 2006).

As discussed, the adverse impact of noise on learning and memory may occur via at least two different but overlapped approaches: oxidative stress and hearing loss. Previous studies have mostly been focused on the oxidative stress of noise, while the potential impact of the hearing loss by noise was largely ignored. In fact, in most of these studies the cognitive functions and changes in brain morphology and molecular content were observed shortly after or even during the period

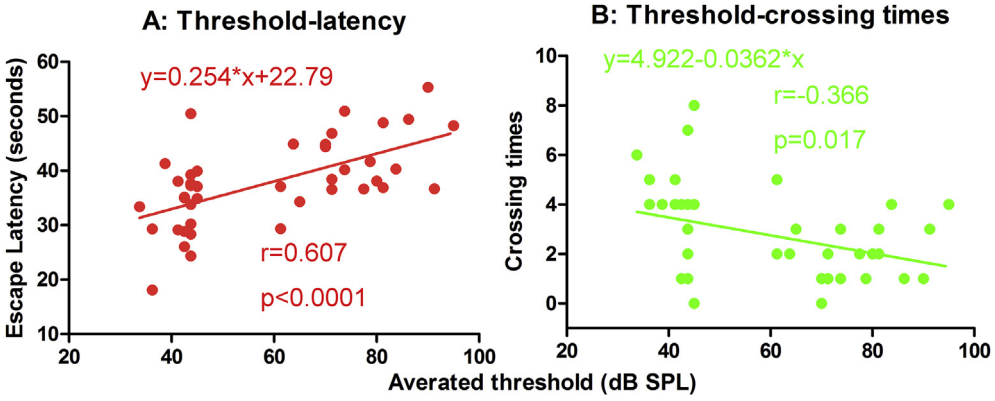

Fig. 4. Correlation and linear regression for averaged ABR thresholds against escape latency in spatial acquisition test (A) and platform crossing times in spatial orientation test (B) respectively.

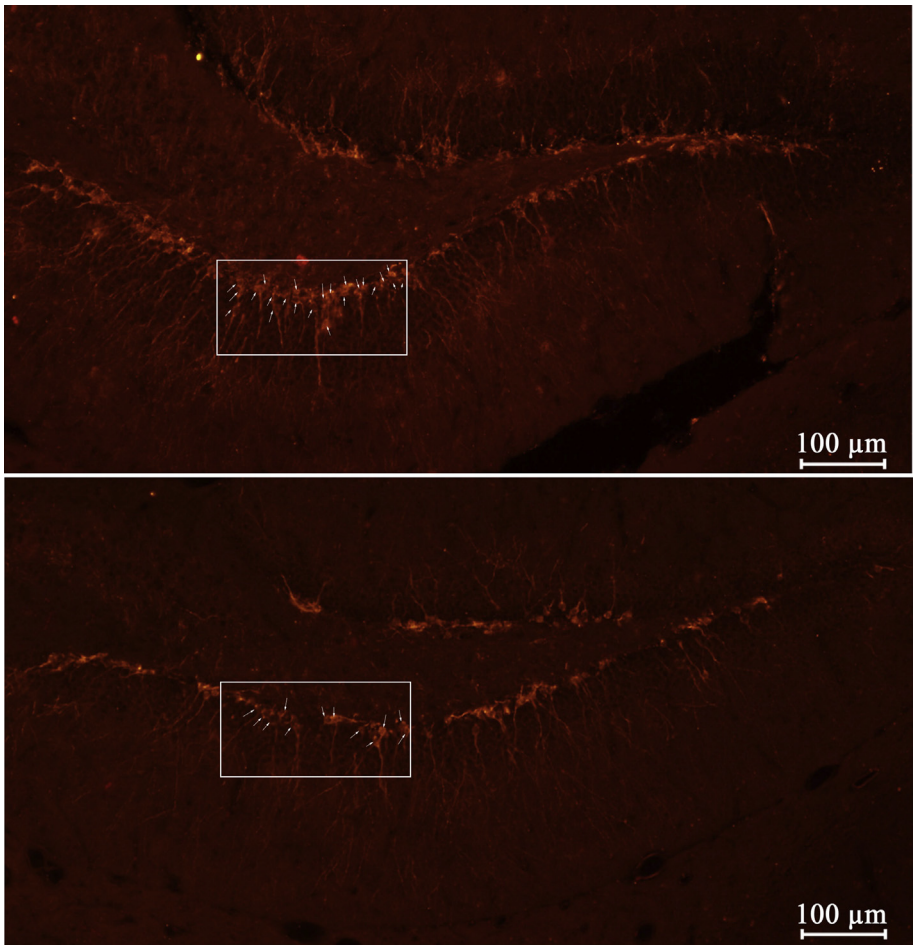

Fig. 5. Representative images of DCX staining of hippocampal DG regions. A: control and B: noise group. The white arrows point to the individual DCX neurons identified under 40× magnification.

of noise exposure. In many studies, the noise level was so low that a hearing loss, in terms of changes in hearing sensitivity, was not expected and therefore not even documented. For example, impaired learning and memory capabilities were found in mice after exposure to white noise at 80 dB SPL, 2 h per day for a 6-week period, and the deterioration in the learning and memory by this noise exposure was attributed to the increased level of malondialdehyde (MDA) and superoxide dismutase (SOD) detected in the inferior colliculus, auditory cortex and the hippocampus (Cheng et al., 2011). Similar

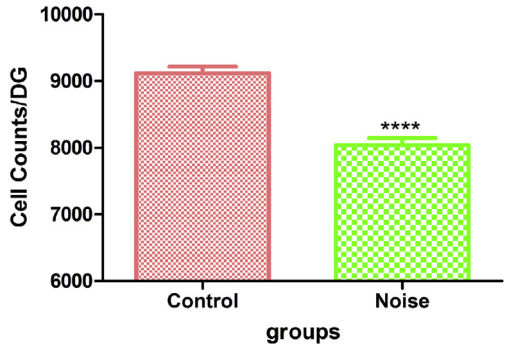

Fig. 6. Comparison on the number of DCX positive cells in DG between groups. ****: $p < 0.0001$.

results were reported in other studies using noise exposure at higher levels (100 dBA for 4 h daily for 30 days) (Manikandan et al., 2006).

While the role of noise induced stress is widely recognized, the independent effect of NIHL should not be ignored, especially in cases of brief noise exposure. With very short noise exposures the induced oxidative stress quickly disappears with time (Sarah Hayes et al., 2011) while the NIHL remains.

The possible impact of NIHL (rather than oxidative stress) on cognitive function is first supported by recent recognition of hearing loss in general as an independent risk factor of dementia (Lin et al., 2011a, 2011b, 2013; Lin, 2011). However, exactly how hearing loss promotes the development of dementia remains to be investigated. Nevertheless, a strong anatomical and functional connection between the brain regions for auditory functions and cognitive functions exists. The hippocampus receives auditory input through the lemniscal ascending pathway, which transmits acoustic stimuli from the inferior colliculus to the auditory cortex and then to the hippocampus (Moxon et al., 1999). Furthermore, the hippocampus projects indirectly to the auditory cortex (O'Mara, 2005). The auditory association cortex has both direct and indirect pathways to the hippocampus and receives indirect input from it in turn. These connections enable the formation of long-term auditory memories and facilitate the

processing of linguistic and musical input (Kraus et al., 2012). Reduced auditory input resulted from hearing loss has been found to cause hippocampal degeneration and impaired memory function. For example, C57BL/6J mice with age related HL demonstrated hippocampal degeneration and had reduced spatial memory tested in the Morris water maze (Yu et al., 2011).

Furthermore, the fact that no hearing loss (in terms of hearing sensitivity change) was documented in most of the previous studies addressing the noise effect on cognitive function should not be considered as evidence against the effect of NIHL on cognitive function. This is largely due to the fact that noise exposure at relatively low doses may not produce a loss of hearing sensitivity, but may instead significantly damage the afferent innervation to cochleae and therefore reduce the output of the cochlea to the brain (Shi et al., 2013; Liu et al., 2012; Kujawa et al., 2009).

Investigating the impact of NIHL during early development on cognitive function is important for at least three reasons. Firstly, exposure to harmful noise is likely to occur in new borns, and especially in preterm babies. Secondly, at an early age of auditory development the cochlea is likely to be more vulnerable to hazardous factors including noise (Hall, 2000; Li et al., 2009; Reeves et al., 2010; Surenthiran et al., 2003; Saunders et al., 1982; Lenoir et al., 1980). Newborn mice have no hearing function. At P15d, their peripheral auditory organs reaches adulthood status (Mikaelian et al., 1964), roughly corresponding to the perinatal period of human subjects. At this moment, their brain is not yet matured (Semple et al., 2013), and is sensitive to abnormal sensory input. Thirdly, hearing loss established during early development has been found to exert long lasting impacts on cognitive function (Pimperton et al., 2012; Papacharalampous et al., 2011; Guzzetta et al., 2011). Recently, an interesting report even showed that a conductive hearing loss established in neonatal rats for a short period of time significantly increased their sensitivity to acoustic seizure in adulthood (Sun et al., 2011).

However, most previous studies of noise effects on cognitive functions were on adult subjects. The study of the long-term cognitive effect of noise exposure during early stage of auditory development is still rare and few reports are available. Continuous exposure to white noise at 65−70 dB SPL between P5d and P56d in rats decreased the number of spatial sensitive neurons in their primary auditory cortex (Xu et al., 2010). Exposure to white noise at 95 dB (A) for one hour per day during the last week of pregnancy was found to cause spatial learning and memory deficit of rat pups 3 weeks after birth, accompanied with depressed hippocampal neurogenesis (Kim et al., 2006). More recently, a similar prenatal noise exposure was reported to impair the spatial memory and hippocampal plasticity of rats tested in young adulthood (P42-50d) (Barzegar et al., 2015). Since no hearing loss was documented in those studies, the deterioration in spatial learning and memory was again attributed to the oxidative stress induced by the noise exposure, which was indicated by an increased serum corticosterone level in the offspring of rats tested long after the noise exposure, as shown in one report involving noise exposure at an early developmental period (Barzegar et al., 2015). This long-lasting effect of prenatal noise exposure on serum corticosterone of the offspring is similar to reports from others using long-term noise exposure (Cheng et al., 2011; Cui et al., 2009; Jauregui-Huerta et al., 2011). In the present study, spatial learning and memory as well as hippocampal neurogenesis were evaluated 2.5 months following a brief noise exposure after which induced oxidative stress changes are expected to be transient (Sarah Hayes et al., 2011; Samson et al., 2008). In our other experiment in adult mice, we found that one week after such a brief noise exposure, no difference could be found in molecules related to oxidative stress (including SOD, MDA, corticosterone etc) between the control and the noise groups (Data not shown).

In conclusion, the present report suggested an independent role of hearing loss induced by noise, rather than its oxidative effect on the cognitive function and hippocampal neurogenesis. The mechanisms of this long term impairment on cognitive function by a brief noise exposure in postnatal age should be further investigated.

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