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Environmental Noise Affects Auditory Temporal Processing Development and NMDA-2B Receptor Expression in Auditory Cortex

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Abstract

Auditory temporal processing is essential for sound discrimination and speech comprehension. Under normal developmental conditions, temporal processing acuity improves with age. As recent animal studies have shown that the functional development of the auditory cortex (AC) is impaired by early life exposure to environmental noise (i.e., continuous, moderate-level, white noise), here we investigated whether the normal age-related improvement in temporal processing acuity is sensitive to delayed development of the AC. We used a behavioral paradigm, the gap-induced prepulse inhibition of the acoustic startle reflex, to assess the gap detection threshold, and provide a comparison of temporal processing acuity between environmental noise-reared rats and age-matched controls. Moreover, because age-related changes normally occur in the relative expression of different N-methyl-D-aspartate (NMDA) receptor subunits, we assessed the level of protein expression of NMDA-2A and 2B receptors (NR2A and NR2B respectively) in the AC after environmental noise-rearing. As hypothesized, rats reared in environmental noise showed 1) poor temporal processing acuity as adults (i.e., gap detection threshold remained elevated at a juvenile-like level), and 2) an increased level of NR2B protein expression compared to age-matched controls. This poor temporal processing acuity represented delayed development rather than permanent impairment, as moving these environmental noise-reared rats to normal acoustic conditions improved their gap detection threshold to an age-appropriate level. Furthermore, housing normally-reared, adult rats in environmental noise for two months did not affect their already-mature gap detection threshold. Thus, masking normal sound inputs with environmental noise during early life, but not adulthood, impairs temporal processing acuity as assessed with the gap detection threshold.

Keywords

environmental noise; acoustic startle reflex; gap detection; auditory cortex; development; NMDA

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1. Introduction

During normal development neurons in the mammalian auditory cortex (AC) undergo a progressive refinement of their excitatory response properties [1–2] which coincides with a maturation of inhibitory neurotransmission [3–5]. In addition, normal development is marked by a reduction in the degree to which AC neurons demonstrate experience-dependent synaptic plasticity [6]. This greater resistance to plasticity in the adult brain may result from age-related changes in the relative expression of different subunits of N-methyl-D-aspartate (NMDA) receptors (e.g., NR2A and NR2B) [7]. Juvenile brains have a relatively greater level of NR2B subunit expression [8], which is thought to facilitate plasticity and long-term potentiation (LTP) induction [9].

It is well established that brief exposure to intense noise during early development can result in impaired neural processing in the central auditory system in adulthood [10–12], and that the normal maturation of the AC can be dramatically delayed by prolonged exposure to an abnormal sound environment during the formative developmental epoch, termed the critical period [1,6,13]. For example, rearing rats, whose critical period normally extends ~50 days after birth, in environmental noise (i.e., continuous, moderate-level, white noise) results in poor spatial tuning in AC neurons [14], as well as an overall lack of tonotopic refinement [13] and enhancement of NR2B-dependent LTP in the AC [9]. Furthermore, young rats exposed to moderate-level interrupted white noise for 8 h/day for 2 weeks during their critical period showed impaired sound level processing in AC neurons [15] and deficits in sound localization behavior as adults [16]. Ultimately, it has been suggested that environmental noise may contribute to language-related developmental delays in children [13].

Language processing requires the central auditory system to detect rapid changes of speech sounds in temporal and spectral domains [17–18]. Proper maturation of a child's temporal processing ability is essential for their speech comprehension and language development [19–20]. In both humans and laboratory animals, temporal processing acuity can be monitored with a behavioral assessment of the subject's ability to detect short gaps in sound [21]. Under normal developmental conditions, temporal processing acuity improves such that the gap detection threshold in adults is shorter than that for infants (5.2 vs. 11 ms, respectively) [22]. At present, it is uncertain whether this normal age-related improvement in temporal processing acuity is sensitive to delayed development of the AC.

In the present study, we investigated the effect of environmental noise on 1) the maturation of temporal processing acuity in rats, and 2) the protein expression of NMDA receptor subunits (NR2A and NR2B) in their AC. We used a behavioral paradigm, the gap-induced prepulse inhibition of the acoustic startle reflex (Gap-PPI), to assess the gap detection threshold [23], and provide a comparison of temporal processing acuity between environmental noise-reared rats and controls. In addition, using standard laboratory techniques described in our recent study [24], we compared the level of NR2A and NR2B subunit protein expression in the AC between groups. Because the absence of normal sound input during early life retards the functional development of the AC [1,9,13], we hypothesized that environmental noise-rearing would delay the normal maturation of temporal processing acuity (i.e., gap detection threshold would fail to decrease). Furthermore, based on a previous report [9], we expected the relative level of protein expression of NR2B in the AC to remain elevated in the environmental noise-reared rats, indicative of developmental arrest in an immature state.

2. Experimental Procedures

2.1. Animals and noise environment

A total of 30 male Sprague-Dawley rats (Harlan) were used in this study. All experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of University at Buffalo, and conform to the guidelines issued by the National Institutes of Health. At postnatal day-7, rat pups and their breeding mothers were randomly assigned into one of two groups: an environmental noise-exposed group, or control group. For environmental noise-rearing, rat pups and their mother were housed in a cage installed with a speaker (super tweeter, Radio Shack) which presented continuous white noise for 24 hours per day (70 dB SPL). The environmental noise was produced by a signal generator (RM1, Tucker-Davis Technology, TDT), and the sound level was calibrated using a sound level meter (Larson Davis 824, 1/4 inch microphone). The spectrum of the noise was measured by custom software using a 1/4 inch microphone (The Acoustical Interface, Belmont, CA) which showed a broad spectrum from 4 to 50 kHz (Fig. 1). The rat pups and their mothers that were assigned to the control group were housed in similar cages, but they were not exposed to the environmental noise protocol. Irrespective of group assignment, the pups were weaned at approximately three weeks of age, and the male and female pups were then raised in separate cages. The pups continued to be exposed to either the environmental noise or control conditions according to their initial assignment until the experimental testing was conducted.

2.2. Behavioral testing of temporal processing acuity

Using a behavioral paradigm, the gap-induced prepulse inhibition of the acoustic startle reflex (Gap-PPI), we assessed the gap detection threshold in the control and environmental noise-reared rats. Gap detection is a well-accepted and reliable behavioral measure to assess temporal processing acuity [21]. As described in our recent paper [23], the Gap-PPI paradigm exploits an animal's abrupt motoric response to a sudden, startle-eliciting sound. More specifically, if the rat is able to detect a brief silent gap in an otherwise continuous background noise that precedes the startle-eliciting sound, the magnitude of the startle response is inhibited (i.e., gap prepulse inhibition). By varying the duration of the silent gap and monitoring the level of inhibition of the startle response, we were able to determine each rat's gap detection threshold.

During the Gap-PPI paradigm, the rat was placed in a custom fabricated wire mesh cage that was mounted on a Plexiglas floor, contained within a ~40 cm tall cubic-shaped sound isolation chamber. The size of the wire mesh cage was adjusted to restrict the rat's movement within the calibrated sound field. The startle-eliciting sound, which consisted of a broadband noise burst presented at 100 dB SPL (20 ms duration, 0.1 ms rise/fall time), was generated by a RP2 Real-time Processor (TDT) controlled by custom software, and delivered by a speaker (Fostex FT28D) located ~20 cm above the wire mesh cage. A piezoelectric transducer attached to the bottom of the Plexiglas platform generated a voltage proportional to the magnitude of the startle response. The output of the piezoelectric transducer was connected to a low-pass filter (World Precision Instruments, LPF-300) set at 1000 Hz, and then digitized by an analog-to-digital signal converter (RP2 Real-time Processor, TDT). The root mean square (RMS) amplitude of the first 100 ms of the startle response after the onset of the sound stimulus was measured using custom software.

The startle stimulus was presented in a white noise background (60 dB SPL), which was either continuous, or contained a brief silent gap prior to the startle stimulus. The duration of the silent gap varied from 1–50 ms, and the offset of the silent gap preceded the onset of the startle stimulus by 60 ms. The RMS amplitude of the acoustic startle response was measured

in the presence of continuous noise with no silent gap (STng), or noise containing a silent gap (STg). To determine the level of gap prepulse inhibition, the following formula was used: $\text{Gap-PPI} = (\text{STng-STg})/\text{STng} \times 100\%$. For each of ten gap conditions (0, 1, 2, 4, 6, 8, 10, 15, 25 and 50 ms gap duration), eleven trials were performed. The first trial of each condition was discarded to account for the animal's acclimation to the stimulus paradigm, and the results per gap condition were averaged based on the last ten trials of each condition. The inter-trial interval was 17–23 s, and presentation of the variable gap conditions was randomized. The gap detection threshold was defined as the minimum duration of gap needed to induce a statistically significant inhibition of the startle response.

In our first series of experiments, the Gap-PPI paradigm was performed on environmental noise-reared rats (n=6) and age-matched controls (n=9). Of the six noise-reared rats, three were tested at 2-months old (P-2m) and three were tested at 3-months old (P-3m). After their initial testing session, the P-2m (n=3) and P-3m (n=3) noise-reared rats were then housed in normal acoustic conditions for an additional 28 and 35 days, respectively. Throughout this period of normal acoustic exposure, the Gap-PPI paradigm was performed on four different days (P-2m: 2, 7, 14 and 28 days; P-3m: 5, 14, 21 and 35 days). In separate series of experiments, we performed Gap-PPI testing on normally-reared, adult rats (n=6) before (at 3-months old) and after they had been housed in environmental noise for 10 days, 1 month and 2 months.

2.3. NR2A and NR2B protein expression in the AC

Following euthanasia (via deep anoxia with CO₂, then decapitation), the AC was collected from 2-month old environmental noise-reared rats (n=6) and control rats (n=3). The location of the AC was identified using stereotaxic landmarks, as described by a previous paper: 3–7 mm caudal to the bregma and 2–6 mm ventral from the top of the cortex [25]. A punch (2 mm diameter) was centered on the AC and inserted down to the white matter to take the sample [26]. A detailed description of the Western blot procedures used in the present study appears in our previous paper [24]. Briefly, the tissue from each animal was homogenized in 1% sodium dodecylsulfate (SDS) sample loading buffer with phosphatase inhibitor (PhosStop, Roche). Protein concentrations of the samples were calculated by measuring the absorbance at 595 nm in a Multiskan Bichromatic plate reader (Lab Systems). The final concentration of sample protein was adjusted to 1 mg/ml. Aliquots of crude lysate containing 50 µg of protein were electrophoresed in NuPage 4–12% Bis-Tris Gel (Invitrogen). The proteins were transferred to nitrocellulose membrane (Schleicher and Schuell), immunolabeled with primary and then the secondary antibodies. Rabbit anti NR2A polyclonal antibody (AB1555P, 180 kDa, Millipore, Billerica, MA), rabbit anti NR2B polyclonal antibody (AB1557P, 180 kDa, Millipore) and a mouse anti-β-actin antibody (MAB1501, 42 kDa, Millipore) were used to quantify the expression of NR2A and NR2B. Quantity-one (Bio-Rad) was used to measure the density of bands in the Western blots.

2.4. Statistical analyses and data presentation

A two-way analysis of variance (ANOVA) was used in the following Gap-PPI% data comparisons: 1) environmental noise-reared rats versus controls; 2) environmental noise-reared rats at the end of noise exposure versus 14 days of normal acoustic experience; and 3) normally-reared, adult rats before versus after two months of environmental noise exposure. A one-way ANOVA was used in the following gap detection threshold data comparisons: 1) environmental noise-reared rats at various times during normal acoustic experience; and 2) normally-reared, adult rats at various times during environmental noise exposure. A Student's t-test was used to compare: 1) the gap detection threshold of environmental noise-reared rats versus age-matched controls; and 2) the ratio density of NR2A/β-actin (or NR2B/β-actin) of environmental noise-reared rats versus age-matched controls. The level of

statistical significance adopted was $P < 0.05$. GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA) was used to perform the statistical analyses and generate the graphs. Results are presented as the mean $\pm$ standard error of the mean.

3. Results

3.1. Behavioral testing of temporal processing acuity

To determine the effect of masking normal sound inputs on temporal processing acuity development, the Gap-PPI paradigm was performed on the environmental noise-exposed rats and age-matched controls. Compared to the control group, rats reared in the environmental noise showed much lower Gap-PPI% at 2-months old (P-2m, Fig. 2A, significant, two-way ANOVA, $F(8, 45) = 15$, $P < 0.0001$) and 3-months old (P-3m, Fig. 2B, significant, two-way ANOVA, $F(9, 60) = 11.3$, $P < 0.0001$), indicative of impaired temporal processing acuity. Furthermore, the averaged gap detection threshold of the control group at 2-months old was significantly lower than that of the environmental noise-reared group (6 ± 2 ms vs. 16.6 ± 7 ms; Student's t-test, $P = 0.02$; Fig. 2C). This group difference in gap detection threshold persisted in 3-month old rats; the average gap detection threshold was 3.4 ± 1.9 ms for the control group versus 8.6 ± 1.1 ms for the environmental noise-reared group (Student's t-test, $P = 0.005$; Fig. 2C).

To determine whether the environmental noise-induced changes in gap detection threshold represented a delayed development or permanent impairment, the environmental noise exposure was ceased at either P-2m or P-3m and the rats were housed in normal acoustic conditions for up to 28 or 35 days, respectively. As shown in Fig. 3A, following 14 days of normal acoustic experience, rats that had been reared in environmental noise until 2-months old demonstrated an increase in Gap-PPI% (two-way ANOVA, $F(1, 18) = 14.55$, $P = 0.001$). This improvement in temporal processing acuity occurred rapidly following the cessation of environmental noise, as evidenced by significant decrease in the average gap detection threshold (one-way ANOVA, $F(1, 14) = 5.46$, $P = 0.02$) (Fig. 3B). Although there was a trend for the average gap detection threshold to decrease in the 35 days after environmental noise exposure had ceased (Fig. 3D), the Gap-PPI% did not statistically improve (two-way ANOVA, $P > 0.05$) after 14 days of normal acoustic experience for rats reared in environmental noise until 3-months old (Fig. 3C).

Finally, we investigated whether housing normally-reared, adult rats in environmental noise for 2 months would affect their temporal processing acuity. Adult rats were housed in environmental noise starting at 3-months of age, and the Gap-PPI paradigm was performed three times during the exposure: 10 days, 1 month and 2 months. There was no significant difference in Gap-PPI% before and during environmental noise exposure in these adult rats (two-way ANOVA, $P > 0.05$; Fig. 4A). The averaged gap detection threshold remained stable throughout 2 months of environmental noise exposure (one-way ANOVA, $P > 0.05$; Fig. 4B). Thus, the continuous, moderate-level, white noise did not affect temporal processing acuity in normally-reared, adult rats.

3.2. NR2A and NR2B protein expression in the AC

The protein expression of NR2A and NR2B subunits in the AC in the 2-month old control rats ($n = 3$) and environmental noise-reared rats ($n = 6$) was examined using the Western blotting technique. The Western blotting bands of NR2A are shown in Fig. 5A. The molecular weight of the NR2A band was about 180 kDa (sample 1–3 were from control group, sample 4–9 were from noise-reared rats, the scale band was shown on the left). The Western blotting bands of NR2B are shown in Fig. 5C which molecular weights was about 180 kDa (sample 1–3 were from control group, sample 4–9 were from noise-reared rats, the

scale band was shown on the left). To quantify the changes of NR2A and NR2B expression, the ratio of the relative density of NR2A or NR2B compared to the β -actin expression was calculated. Fig. 5B shows the density ratio of NR2A/ β -actin expression in the control group ($n = 3$, animal 1–3) and the environmental noise group ($n = 6$, animal 4–9). There was no significant difference between in NR2A expression between the groups (Fig. 5B, Student's t -test, $P > 0.05$). In contrast, the NR2B/ β -actin density ratio in the environmental noise group was ~4-fold greater than the control group (Student's t -test, $F = 10.8$, $P < 0.001$, Fig. 5D).

4. Discussion

The present study provides an investigation of the effect of environmental noise-rearing (i.e., continuous, moderate-level, white noise) on 1) temporal processing acuity assessed behaviorally, and 2) NMDA receptor subunit (NR2A and NR2B) protein expression in the AC. As hypothesized, rats exposed to environmental noise during early postnatal life (from 7-days to 2- or 3-months old) showed poor temporal processing acuity as adults (i.e., gap detection threshold remained elevated at a juvenile-like level), as well as an increased level of NR2B protein expression compared to age-matched controls. Additional testing revealed that this poor temporal processing acuity represented delayed development rather than permanent impairment, as moving these environmental noise-reared rats to normal acoustic conditions improved their gap detection threshold to an age-appropriate level. Furthermore, housing normally-reared, adult rats (3-months old) in environmental noise for 2 months did not affect their already-mature gap detection threshold. Collectively, our results suggest that masking normal sound inputs with environmental noise during early life, but not adulthood, impairs temporal processing acuity as assessed with the gap detection threshold.

Behavioral studies on both humans and rats have shown that temporal processing acuity improves during normal development, such that both adult humans [22] and rats [21,23] demonstrate a gap detection threshold of ~5 ms. The results from our adult control rats are consistent with this age-related decrease in gap detection threshold (P-2m: 6 ± 2 ms; P-3m: 3.4 ± 1.9 ms). In contrast, rats reared in environmental noise for 2 months had a gap detection threshold of ~17 ms, which is comparable to that of juvenile rats (15-days old) reared in a normal acoustic environment [21]. Thus, the masking of salient sound inputs with environmental noise during early postnatal life prevented the normal maturation of temporal processing acuity. Of the multiple regions within the central auditory pathway that contribute to temporal processing acuity, previous studies have highlighted the critical importance of the AC. For example, cortical insults, such as transient deactivation [27] and surgical ablation of the AC [28], as well as developmental cortical malformation (e.g., microgyria) [29] have been shown to disrupt temporal processing acuity as assessed by the Gap-PPI paradigm. These findings, coupled with the present results and those of other studies (discussed below), lead us to suggest that the poor temporal processing acuity caused by environmental noise-rearing is associated with a delayed development of the AC.

Normal maturation of the AC is characterized by a progressive refinement of the spectral and temporal response properties of its constituent neurons. For example, electrophysiological studies on developing rats have revealed that the progression to adulthood is marked by an increased frequency-selectivity of neurons in the primary AC (i.e., neurons become more narrowly-tuned) [30] and an increased cortical ability to respond to high-rate acoustic stimuli, suggestive of improved temporal processing [1]. Exposing juvenile rats to environmental noise causes neurons in their AC to have sluggish temporal response properties [1]. However, similar to the present study in which gap detection threshold improved when the environmental noise-reared rats were moved to normal acoustic conditions (Fig. 3B and 3D), AC neurons showed an improved ability to respond to high-rate acoustic stimuli after environmental noise exposure ceased [1]. These “rescue”

experiments suggest that the poor temporal processing caused by environmental noise represents a developmental delay, not an irreversible impairment. Further support for this suggestion is based on our finding that temporal processing acuity was not impaired in rats exposed to environmental noise as adults. Instead, the already-matured gap detection threshold of the adult rats remained at a normal level following 2 months of environmental noise exposure (i.e., ~5 ms; Fig. 4B). Taken together, our results suggest that the functional maturation of temporal processing acuity can be delayed by masking normal sound inputs with environmental noise during early life.

In addition to the delayed development of temporal processing acuity (present findings) and excitatory response properties of AC neurons [1], environmental noise-rearing preserves the heightened, juvenile-like plasticity properties of the AC. For example, compared to adult controls, rats raised in environmental noise until adulthood demonstrated elevated levels of LTP induced by thalamocortical activation [9,31]. This LTP enhancement was critically-dependent on NR2B subunit activation, as local application of NR2B subunit antagonists blocked the effect [9]. Consequently, the authors proposed that environmental noise-induced changes in the subunit composition of NMDA receptors, such as the possible maintenance of higher NR2B subunit levels, attenuation of the increase in NR2A subunit levels, or a combination of these two factors, could underlie the increased plasticity they observed [9]. In the present study, the environmental noise-reared rats had an elevated level of NR2B subunit protein expression in the AC compared to age-matched controls (Fig. 5D), despite no difference in NR2A subunit levels (Fig. 5B). Thus, our results suggest that the heightened AC plasticity associated with early life exposure to environmental noise may be mediated by the maintenance of juvenile-like levels of NR2B subunit expression. In contrast, during the preparation of our manuscript, Xu et al. reported that rearing rats in environmental noise had no effect on the expression levels of NMDA receptors [14]. We are uncertain if differences in the experimental procedures, such as tissue preparation, animal age, or antibody sensitivity, contributed to the conflicting results between the two studies. Interestingly, consistent with the suggestion that environmental noise rearing prevents the maturation of the AC, Xu et al. [14] found that early environmental noise exposure altered the expression of subunits of the GABA-A receptor, indicative of a return to its juvenile form.

It has been proposed that environmental factors which preserve the AC in a state of immaturity, such as the masking of salient sound inputs with noise, may potentially contribute to language developmental delays in children [13]. The findings of the present study are consistent with this proposal, as we observed that, in addition to arresting AC development (i.e., an elevated NR2B subunit protein expression), environmental noise-rearing resulted in poor temporal processing acuity, which has been linked to impaired language development. Put simply, children with poor temporal processing acuity are more likely to develop poorer language ability than the children with better temporal processing resolution [20]. Given this relationship, the delayed maturation of temporal processing acuity observed in the present study confirms that environmental noise exposure poses a risk for abnormal child development. Finally, although we found that the cessation of environmental noise exposure yielded a prompt improvement in temporal processing acuity (Fig. 3), the long-term implication of such exposure on language ability remains to be determined.

Abbreviations

AC	auditory cortex
Gap-PPI	gap-induced prepulse inhibition

LTP	long-term potentiation
NMDA	N-methyl-D-aspartate
NR2A	NMDA-2A receptor
NR2B	NMDA-2B receptor
RMS	root mean square

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Figure 1.
The spectrum of the environmental noise used in the experiment.

Figure 2.

Gap-induced prepulse inhibition (Gap-PPI) of the acoustic startle reflex revealed impaired temporal processing acuity in environmental noise-reared rats. (A) The Gap-PPI% measured in rats reared in environmental noise until 2-months old (N-2m) was significantly lower than that of age-matched controls (C-2m) (two-way ANOVA, ***P < 0.0001). (B) At 3-months old, the Gap-PPI% measured in environmental noise-reared rats (N-3m) was also significantly lower than that of a control group (C-3m) (two-way ANOVA, ***P < 0.0001). (C) The gap detection threshold in the environmental noise-reared rats was significantly elevated compared to age-matched controls (N-2m vs. C-2m: Student's t-test, *P = 0.02; N-3m vs. C-3m: Student's t-test, **P = 0.005).

Figure 3.

Temporal processing acuity in environmental noise-reared rats improved after they were housed in a normal acoustic environment. (A) Rats reared in environmental noise until 2-months old demonstrated an increase in Gap-PPI% after an additional 14 days of normal acoustic experience (N-2m+Q14) compared to values recorded immediately after noise-rearing (N-2m) (two-way ANOVA, ** $P = 0.001$). (B) In rats reared in environmental noise until 2-months old, there was a significant decrease in their gap detection threshold after they were moved to normal acoustic conditions (one-way ANOVA, * $P = 0.02$), such that the average gap detection decreased from 16 ± 7 ms to 4 ± 1.2 ms after 28 days of normal acoustic experience. (C-D) In rats reared in environmental noise until 3-months old, there was a trend for the average gap detection threshold to decrease following normal acoustic experience (N-3m: 8.6 ± 0.7 ms; N-3m+Q35: 4.7 ± 0.7 ms); however, the Gap-PPI% did not statistically improve (two-way ANOVA, $P > 0.05$) after 14 days of normal acoustic experience.

Figure 4.

Environmental noise exposure did not affect temporal processing acuity in normally-reared, adult rats. (A) The Gap-PPI% did not change after 3-month old rats (Pre) were housed in environmental noise for an additional two months (N-2m) (two-way ANOVA, $P > 0.05$). (B) The already-mature average gap detection threshold in normally-reared, adult rats (Pre: 5.0 ± 0.7 ms) was unchanged after environmental noise exposure for 10 days (N-10d), one month (N-1m) or 2 months (N-2m) (one-way ANOVA, $P > 0.05$).

Figure 5.

Environmental noise-rearing had a differential effect on NR2A and NR2B protein expression in the auditory cortex (AC). (A and C) Western blotting bands of NR2A (A) and NR2B (C) for six environmental noise-reared rats (band 4–9) and three age-matched controls (band 1–3) (each band represents an individual animal). (B and D) The density ratio of NR2A/ β -actin expression in the control and the environmental noise groups did not differ (Student's t-test, $P > 0.05$; panel B), whereas there was a ~4-fold greater NR2B/ β -actin density ratio in the environmental noise-reared rats compared to the age-matched controls (Student's t-test, $F = 10.8$, $**P < 0.001$; panel D).