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Differential effects of prenatal music versus noise exposure on posnatal auditory cortex development: A systematic review

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Abstract. Loud noise exposure during critical gestation periods may increase implantation failure risks and placentation dysregulation or decrease uterine blood flow. Here, this study review published studies on associations between exposure to various prenatal sound types and reproductive outcomes in chicks and speculate the relevance of these studies to prenatal occupational and environmental noise exposure. PubMed Central, Cochrane, and our local library electronic databases were screened for papers published between 1979 and October 2014. Ten experimental studies on chronic prenatal auditory exposure of domestic chicks to music and various artificial and species-specific sounds were included. Prenatal exposure to auditory stimuli that are rhythmic, patterned, and in the frequency range of species-specific calls are beneficial to neural development, metabolism, and behavior, whereas simple sounds of the same intensity are beneficial or deleterious. Prenatal auditory exposure can substantially influence development and postnatal function of the auditory network and hippocampus. Few occupational and epidemiological studies have been conducted in humans; however, there is suggestive evidence for adverse outcomes, such as low birth weight and poor brain development of environmental noise.

1. Introduction

Pregnant women are often exposed to high-decibel music as well as environmental noise. This exposure may influence the developing fetus and subsequently influence postnatal cognitive abilities. Studies on the effects of prenatal sound stimulation, especially high-decibel sound, on fetal development and neural function are ethically problematic, so the domestic chick (Gallus gallus domesticus) has been widely employed and was chosen as the experimental model in the present review. Advantages of this species include responses to air-borne sound during the embryonic period, a fairly well-developed auditory system at birth, and well-described embryonic auditory pathways [3,10]. In the basilar cochlear papillae of the chick, the afferent synapses appear on the hair cells by embryonic day (E)8–E11 [1] and cells in auditory field L (the highest level of auditory processing in chicks) start differentiating at E8 [2]. Evoked potentials to intense auditory stimuli can be recorded in the brainstem by E11–E12 [3]. Therefore, in the included studies, auditory stimulation was provided
from E10 onward, immediately before functional development of the peripheral auditory areas and brainstem auditory nuclei.

2. Methods
All published studies were searched in PubMed/Medline and Cochrane library using the terms “prenatal auditory stimulation,” “prenatal sound stimulation,” “prenatal chronic loud,” “prenatal ultrasound,” “prenatal noise,” “prenatal supersound” AND Chick, Rat, Mouse, Monkey, Cat, Pig NOT Humans, without time restriction. In addition, relevant existing articles in our personal library (http://www.lib.ui.ac.id, http://eprints.ums.ac.id) were added. Inclusion criteria were in vivo studies that used music (and in some cases other sound patterns as well) as prenatal sound stimuli published in English or the Indonesian language. The studies were grouped according types of characteristics of prenatal sound stimuli, stimulation protocols, and experimental procedures.

3. Results
The search retrieved 28 articles. However, some of the articles did not use music as one type of prenatal auditory stimulation, and others examined postnatal exposure. Therefore, only 10 articles met the inclusion criteria [3–10]. The stimuli examined, protocol details, methodologies, main results, and primary conclusions are summarized in the Table 1.

Table 1. Summary of exposure protocols and outcomes from the included studies

| Types of exposure | Exposure protocol | Experimental Techniques | Outcomes |
|-------------------|-------------------|-------------------------|----------|
| [3] Rhythmic sitar music | Frequency range: 100–4000 Hz | 110 dB sound pressure level (SPL) music or noise for 15 min every hour from E10 until hatching | Comprehensive metabolic profiling of chick AuL using H NMR spectroscopy identified 48 sound-modulated metabolites Glx (glutamate+glutamine), lactate, myoinositol, choline, GABA, taurine, NAA, aspartate, and βHB were the most influential metabolites. Minimum effective exposure duration was 6 days Glucose, βHB, NAD, and ATP were reduced by both stimuli, indicating increased energy demand Depletion of major energy metabolites can significantly affect neuronal activity in AuL Loud noise but not music reduced neuromodulatory metabolites such as aspartate and taurine, which may alter glutamatergic and GABAergic activity Noise alters metabolite profiles in AuL, which could disrupt proper function in neonatal and adult stages |
| Arrhythmic vehicle horn sound | Frequency range: 30–3000 Hz Peak: 2700 Hz (simple pattern) | H NMR spectroscopy | |
| [4] Rhythmic sitar music | Frequency range: 100–4000 Hz | Chronic rhythmic music or arrhythmic noise at 110-dB SPL | Immuno-histochemistry (IHC), Western blotting, Quantitative PCR, and H NMR spectroscopy at P1 | Noise exposure (1) Reduced synaptophysin expression, which can alter synaptogenesis (2) Decreased expression of PSD-95, which can alter the excitatory postsynaptic complex, dendritic spine morphology, synaptogenesis, and AMPAR function |
| Vehicle horn sound | Frequency range: 30–3000 Hz | | |
### Table 1. Continue

| Types of exposure | Exposure protocol | Experimental Techniques | Outcomes |
|-------------------|-------------------|-------------------------|----------|
| Recorded environment noise or music at 110 dB | Group I = no stimulation Group II = Rhythmic sitar music at 100–4000 Hz Group III = Arrhythmic noise at 30–3000 Hz | Collection of blood plasma and Plasma corticosterone and noradrenaline levels IHC | Both stimuli increased expression of synaptophysin beginning on E12 as well as synapsin 1 and PSD-95 expression starting on E16 Results suggest these stimuli facilitate early maturation of excitatory synapses Both stimuli improved spatial learning |
| Species-specific sound | Frequency range: 100–6300 Hz Rhythmic sitar music | Frequency range: 100–4000 Hz | A significant increase in volume at E20 was noted only in the music-stimulated group Both auditory-stimulated groups showed a significant increase in the proportion of neurons immunopositive for calbindin D-28K (CaB) and parvalbumin (Pv) The increase in CaB/Pv+ neurons during development in the sound-enriched groups suggests an activity-dependent increase in Ca$^{2+}$ influx, resulting in improved synaptic plasticity and memory |
| Rhythmic sitar music | Frequency range: 100–4000 Hz | Chronic rhythmic music or arrhythmic noise at 110-dB SPL | IHC, Western blotting, Quantitative PCR, H NMR spectroscopy at P1 Hippocampal volume, neuronal nuclear size, and total number of neurons increased significantly in the music-stimulated group compared to the species-specific sound-stimulated and control groups. |
Table 1. Continue

| Types of exposure | Exposure protocol | Experimental Techniques | Outcomes |
|-------------------|-------------------|-------------------------|----------|
| Vehicle horn sound (simple pattern) | Frequency range: 30–3000 Hz | | |
| [12] Species-specific sound or sitar music Frequency range: 100–6300 Hz | 65 dB SPL music or noise for 15 min every hour from E10 until hatching. | IHC, Western blotting, Quantitative PCR, H NMR spectroscopy at P1 | A peak percentage of apoptotic (TUNEL-positive) cells was noted in the auditory nuclei at E12 than reduced at E16. Prenatal extra-acoustic stimulation appears to alter Bcl-2 and Bax expression to support cell survival and differentiation. |
| [14] Species-specific calls or sitar music at 65 dB | 65 dB SPL music or species-specific call for 15 min every hour from E10 until hatching. | IHC, estimation of total neuron number, estimation of volume, western blotting | In all three groups studied, syntaxin-immunoreactivity surged at E12, followed by a decline at E16 and subsequent stabilization. The stimulated groups continually expressed higher amounts of syntaxin 1. |
| [15] Species-specific calls or sitar music Frequency range: 100–6300 Hz | E10 for 15 min every hour Group I= no sound stimulation Group II= Maternal calls (100–1600 Hz) and hatching calls (100–6300 Hz) Group III= sitar music (100–4000 Hz) | TUNEL staining, IHC, western blotting, quantification of immunoreactivity, quantification of immunoblots | These observations indicate a positive influence of prenatal sound stimulation. The auditory-stimulated groups also demonstrated an increased proportion of PV+ and CaBP+ neurons. Immunostained cells of both the auditory-stimulated groups did not show a significant change in size. The influx of Ca²⁺ ions is essential for long-term potentiation, a phenomenon important for learning and memory. |
| [16] Species-specific calls or sitar musical notes Frequency range: 100–6300 Hz | E10 for 15 min every hour Group I= no sound stimulation Group II= Maternal calls (100–1600 Hz) and hatching calls (100–6300 Hz) Group III= Sitar music (100–4000 Hz) | IHC, estimation of total number neuron, estimation of volume, western blotting | At E8, synaptophysin and syntaxin 1 immunoreactivity was present in the auditory nerve afferent fibers approaching the nucleus magnocellularis (NM). |
| [19] Bobwhite chick calls on cassette recorder at 65 dB | Embryos were stimulated for 40 min each hour with bobwhite contentment vocalization during the last 24 h prior to hatching | Wilcoxon match | Increased preference for species-specific bobwhite maternal calls. |
4. Discussion
A systematic review of studies was conducted to compare the effects of different prenatal auditory exposure protocols, mainly music and (or) species-specific calls versus arrhythmic noise [3–5], on various neurodevelopmental, neurophysiological, biochemical, and behavioral outcomes in the postnatal period. These studies employed a variety of exposure protocols (different sound frequency ranges and intensities) and experimental techniques (including immunohistochemical labeling, electron microscopy, metabolic profiling, and behavioral tests) to demonstrate these differential outcomes. To facilitate comparison, only studies using fertilized chick eggs were included. Several of these studies used moderate sound intensity [6–10], and some of them used high sound intensity [3–5]. The music was generally played on the sitar. The typical phrases and scales used for raga elaboration (a melodic structure for improvisation) in a Alhajia-Bilawal performance are mnDP, RGPmG, NDNS, DnDP, GRGP, DG, and SRGmPDrNS, respectively [5,6,7]. A complex sound waveform of stimulus music with variations in wavelength is called rhythm, which has repetition of certain patterns. In some studies, music rhythmicity triggered physiological responses that enhanced cognitive function [5]. Early exposure to species-specific sound also influenced brain development and behavior, and this finding has been extended to humans [5]. In fact, the utility of Gallus gallus domesticus as a model for prenatal music exposures has been confirmed in some studies [3,4]. It is noteworthy that both chicks and humans hear extraneous sounds during embryonic/fetal development, and the ability to memorize auditory cues is well developed in avians as in humans [8]. In their natural environment, chicks are attracted to auditory stimuli that are segmented, repetitive, and have short component notes, so the ability to perceive music is quite similar to humans, and their ability to distinguish different styles and rhythms is well refined and sophisticated, which suggests that there is great similarity in the way the birds and humans hear music [4,5].

The fertilized chicken egg provides an excellent model to study the effects of prenatal acoustic exposure. All of the studies included in this review used fertilized eggs (E0) of healthy white leghorn domestic chicks weighing 50–60 g (grade A) to evaluate the effects of sound exposure on neuronal morphology, synaptic density, neurochemistry, and behavior [4,5,7,8]. In addition to maintaining genetic similarity, conditions during development can be tightly controlled for a large number of samples. All studies used a double insulated incubator to precisely control acoustic stimulation as well as temperature (37 ± 1 °C) and humidity 70% ± 2% [3–15,17]. Tilting of eggs 4 times a day was automatically controlled, and a photoperiodicity of 12:12 h day and night cycle was maintained for the entire 21 day incubation period. The incubator used for these studies has an aeration system that is activated 2 or 3 times in an hour and is audible, albeit at a constant 40 dB. Although this background sound cannot be eliminated, it did not have a substantial impact on total SPL according to \[\Sigma_{10} = 10 \times \log_{10}(10L1/10 + 10L2/10)\) dB.

On E9.5, a part of the eggshell approximately 2–5 mm size is removed at the animal pole over the air sac without damaging the membrane to facilitate sound transfer. All studies also used a similar delivery system, two speakers affixed to the opposite walls of the incubating chamber connected to a sound system with auto-reverse facility. Music exposure in all studies was for 15 min per hour (a total of 6 h per day) from E10 until hatching [3–10].

Some of these studies employed exposure protocols with sequential modulation of sound properties based on known changes in embryonic chick response characteristics during development, such as the change in peak response to intense sound from moderate frequency until E17 and to higher frequencies from E17 until hatching. Such protocols included species-specific sound at 100–1,600 Hz from E10 to E14 followed by 1,600–6,300 Hz from E15 until hatching, and slow sitar music (100–1,600 Hz) from E10 to E14 followed by fast sitar music (100–4,000 Hz) from E15 until hatching [6–10].

To replicate the occupational or recreational exposure times experience in daily life (6–8 h per day, 100–120 dB SPL), chick embryos were exposed to noise or music at 110 dB SPL for 15 min per hour throughout the day (total 6 h per day). Behavioral responses of chick embryos to external stimuli including sound is evident around E15–17. Therefore, in the included studies, sound exposure started
at E10 and continued until hatching to examine effects over the major period of auditory system development. Details of the audio system settings inside the incubator and acoustic profiles of sound used were described in a previous publication. Briefly, the frequency of the music stimulus ranged between 100 and 4000 Hz and that of the noise stimulus between 30 to 3000 Hz with a peak at 2.7 kHz [8].

The noise sound consisted of simple waves with a constant wavelength, whereas the sitar music had a complex waveform. Variations of sound energy with frequency and time imparted a rhythmic pattern to the music stimuli, whereas the noise stimuli had a relatively continuous and arrhythmic pattern. Noise with peak energy near 2.7 kHz has been used on the basis of the fact that most hearing loss occurs in this range, which why 2, 3, and 4 kHz frequencies are included in the damage-risk formulas of most studies. In the study by Alladi et al [9], music and noise were matched for weighted output (110 ± 3 dB SPL) as confirmed using a Class-I sound level meter [9].

In precocial organisms like humans and chicks, ACx neurons in early development are tuned to specific intensities and frequencies of sound. This tuning depends on a precise balance between excitatory and inhibitory inputs (E/I balance). Several of the studies found that prenatal sound exposure altered tuning by influencing the balance between glutamatergic and GABAAergic synaptogenesis or synaptic function. For instance, one study revealed effects of prenatal chronic exposure to noise and music at 110 dB SPL on the expression of excitatory and inhibitory circuit-associated molecules in the AuL at E16, E18, and P1 [5].

Prenatal music and sound stimulation also influence the individual size and total number of neurons in the hippocampus and increase expression levels of the calcium-binding proteins calbindin D-28K and parvalbumin [11]. Sleigh and Lickliter suggested that long-term potentiation and short-term memory may be facilitated by the greater Ca2+ influx permissible in the presence of high calcium buffering capacity. Indeed, sound exposure increased spatial memory, a major function of the hippocampus [7]. Further, the enhanced calcium buffering capacity may also enhance cell survival [10].

The effects of prenatal auditory stimulation on synaptic density and mean synaptic height were also examined by transmission electron microscopy. Mean synaptic density increased with no alteration in the mean synaptic height following both types of auditory stimulation in the dorsal as well as ventral part of the hippocampus. This finding suggests that prenatal sound improves hippocampal function by increasing circuit complexity, transmission, and plasticity [9]. These changes appear to depend at least in part on the transcription factor CREB and brain-derived neurotrophic factor (BDNF), a major regulator of synaptic plasticity in the hippocampus. Prenatal music exposure altered expression of CREB mRNA, CREB phosphorylation (required for transactivation), and BDNF expression, with a decline in CREB mRNA and p-CREB during the early period, following by increases at E12 and a subsequent increase in BDNF at E16 [8]. Prenatal auditory stimulation also modulated the expression of critical synaptic proteins. In both groups exposed to prenatal auditory stimuli (music or noise), expression of the presynaptic protein synaptophysin increased starting from E12, whereas synapsin 1 and the postsynaptic protein PSD-95 increased starting at E16, and both groups exhibited improved spatial learning [7]. Surprising, prenatal complex rhythmic music exposure in chick facilitated postnatal spatial learning but transiently impaired memory. In both groups, total plasma corticosterone levels were reduced compared to unexposed controls [6].

Prenatal noise and music have different effect on physiological arousal, synaptogenesis, and spatial behavior. In one study, the music group exhibited increased synaptophysin and PSD-95 expression in hippocampus, whereas the noise groups exhibited a decrease. Further, these stimuli had differential effects on arousal as indicated by plasma noradrenaline level. Together, these changes may differentially affect postnatal behavior. Indeed, the noise group demonstrated impaired spatial memory [5]. Chronic prenatal high-decibel noise and music exposure also have differential effects on synapses in ACx, likely due to opposite effects on expression of synaptophysin, PSD-95, and gephyrin, proteins important for synaptic stability, and thus ACx development and maturation [4]. Finally, prenatal
chronic loud music and noise were demonstrated to have aberrant effects on tissue metabolite profiles that could reduce general neural function and specifically glutamatergic and GABAergic transmission.

Outcome comparisons among all included studies imply that prenatal music exposure benefits brain development and function, particularly in the ACx and hippocampus, as evidenced by morphological, biochemical, and behavior analyses. For instance, the study by Panickers et al. [11] provides evidence for a positive influence of prenatal sound stimulation on the mediorostral neostriatum/hyperstriatum ventral region of the chick forebrain. Others demonstrated increased expression of parvalbumin and calbindin D28K, which may protect neurons from stressors such as excessive calcium influx. Such neurons could therefore display high electrical activity without calcium overload. Prenatal auditory enrichment was also reported to increase the synthesis of synaptic proteins such as synaptophysin and syntaxin 1 in chick brainstem auditory nuclei [4]. Increases in both neuron number and synaptic density may underlie the enhanced auditory imprinting and learning observed in chicks exposed to music or moderate intensity sound during embryonic development [5].

Prenatal music exposure also induced the expression of the immediate early transcription factors c-Fos and c-Jun in chick brainstem. Under normal conditions, c-Fos and c-Jun expression in nucleus magnocellularis and nucleus laminaris are developmentally upregulated and expression of both remains high during the period of cell death. In stimulated groups, however, c-Fos expression was elevated, whereas c-Jun showed an earlier reduction compared with controls. This opposing pattern of c-Fos and c-Jun expressions in response to sound stimulation may indicate enhanced cell survival [5]. Consistent with this notion, another study reported that prenatal auditory enrichment altered programmed cell death in developing chick brainstem by modulating pro- and anti-apoptotic protein expression. In controls, TUNEL-positive cells peaked at E12 and were reduced by E16. Expression of anti-apoptotic Bcl 2 which higher than controls, whereas pro-apoptotic Bax expression was reduced compared with controls consistent with other studies showing increased neuronal number [6].

5. Conclusions
Further studies are needed to explain how prenatal auditory stimulation alters the development and function of the auditory cortex and hippocampus. Collectively, these findings suggest that narrow-frequency dominant arrhythmic loud noise (spectrally degraded sound) exposure during the embryonic period disturbs the expression of synaptic stability proteins, leading to developmental delays that impair auditory-associated behavior. In contrast, rhythmic and spectrally rich music exposure (in a frequency range similar to species-specific sounds) at high SPL maintains the synaptic excitatory/inhibitory balance required for fine tuning of ACx neuron responses. We conclude that controlled prenatal auditory stimulation has a positive effect on development and augments the role of spontaneous activity in the development of the auditory system. The optimum frequency for auditory exposure is about 2700 Hz.

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