

Role of sound stimulation in reprogramming brain connectivity

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Sensory stimulation has a critical role to play in the development of an individual. Environmental factors tend to modify the inputs received by the sensory pathway. The developing brain is most vulnerable to these alterations and interacts with the environment to modify its neural circuitry. In addition to other sensory stimuli, auditory stimulation can also act as external stimuli to provide enrichment during the perinatal period. There is evidence that suggests that enriched environment in the form of auditory stimulation can play a substantial role in modulating plasticity during the prenatal period. This review focuses on the emerging role of prenatal auditory stimulation in the development of higher brain functions such as learning and memory in birds and mammals. The molecular mechanisms of various changes in the hippocampus following sound stimulation to effect neurogenesis, learning and memory are described. Sound stimulation can also modify neural connectivity in the early postnatal life to enhance higher cognitive function or even repair the secondary damages in various neurological and psychiatric disorders. Thus, it becomes imperative to examine in detail the possible ameliorating effects of prenatal sound stimulation in existing animal models of various psychiatric disorders, such as autism.

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1. Introduction

Sound has been an integral part of ancient human civilizations. Traditionally, various kinds of sound have been used first as signals and later as a form of entertainment, music. Sound at an optimum level for a short period may act as an auditory stimulus to trigger various brain functions. Gottlieb (1963, 1965) established that the auditory stimuli play a major role in shaping perceptual learning in birds. He also showed that auditory stimulation in altering visual preferences in birds (Johnston and Gottlieb 1981). Morphological and biochemical alterations have been demonstrated in the auditory pathway of chick following prenatal sound stimulation (Wadhwa *et al.* 1999; Panicker *et al.* 2002; Alladi *et al.* 2002, 2005a, b). In 2002 Lickliter *et al.* were able to

show for the first time that bird embryos are receptive to sound stimulation which helps improve their learning abilities. Later, Lickliter and his group published a series of articles depicting the influence of pre and postnatal sensory stimulation on the development of perceptual and cognitive learning (Honeycutt and Lickliter 2002; Harshaw and Lickliter 2010, 2011). The role of bimodal sensory stimulation (auditory and visual) and the importance in various learning behaviour was emphasized (Lickliter and Stoumbos 1991; Sleigh and Lickliter 1995). Thus, his pioneering work helped in understanding the importance of different sensory stimulation (especially role of auditory stimulation) in altering the behaviour of birds. However, auditory stimulation did not receive much attention among the scientists in terms of its ability to act as environmental stimuli that can modify the morphological

Keywords. Auditory pathway; avian; brain; sound stimulation; synaptic plasticity

Abbreviations used: BDNF, brain-derived neurotrophic factor; CaBPs, calcium-binding proteins; CREB, cAMP response element-binding; PV, parvalbumin; SPL, sound pressure level

and biochemical development of the avian brain. In this article, we review the role of auditory stimulation as sensory stimuli in shaping various brain functions especially learning and memory during the prenatal period of birds, which parallels similar functions of the mammalian brain.

2. Environmental factors as stimulators of brain development

Brain development is a complex phenomenon that includes an interaction between genes and the external environment. Any alterations or manipulations in this interaction can lead to modifications in the neural circuitry. Experience-dependent modifications in the neural connectivity become more predominant if changes are induced from early life. This could lead to long-term plasticity, which allows fine tuning to adapt even when animals are exposed to adverse conditions such as stress (Guilarte *et al.* 2003; Leal-Galicia *et al.* 2008; Reynolds *et al.* 2010). Wistar rats exposed to enriched housing show improved behaviour in the open field and spatial memory abilities in the water maze, reduction in the deficits caused by neonatal anoxia and increase in the expression of Ca²⁺-binding protein (CaBP) – parvalbumin (PV) in hippocampal CA1, CA3 and dentate gyrus regions, indicating the status of cytosolic Ca²⁺ stimulation (Iuvone *et al.* 1996). Environmental enrichment results in increased levels of brain-derived neurotrophic factor (BDNF) in visual cortex, which plays a critical role in neural plasticity during development (Cancedda *et al.* 2004; Sale *et al.* 2004). Enriched environment in early phases of life is able to decrease serum corticosterone levels and thus eases anxiety and irritability in rats (Ma *et al.* 2011). Further, environmental enrichment with objects designed to encourage spatial exploration accelerates the development of spatial learning in northern bobwhite (*Colinus virginianus*) neonatal chicks (Lazic *et al.* 2007). The early influence of sensory or social enrichment is extremely important in psychological development whereas studies in humans and primates demonstrate that social deprivation has long-term consequences on emotion and social behaviour (Champoux *et al.* 1997; Chugani *et al.* 2001; Cirulli *et al.* 2010). In addition to this, there is an effect of visual and tactile stimulation in the development of perceptual responsiveness in chicks (Foushée and Lickliter 2002; Honeycutt and Lickliter 2003). Thus, it is important to understand the role of positive environmental stimuli on the developmental pattern of different brain regions related to learning and memory as this will help in understanding the role of environment factors in shaping an individual's behavioural response. Further, it is to be noted that most studies are largely concentrated on rodents; it is necessary to examine other vertebrates and invertebrates in order to understand the global role of genes–environment interaction in the

prenatal period of development, which is well known for its immense potential for plasticity.

3. Sound as a sensory stimulus

Sensory stimuli in the form of vision, olfaction, touch and sound are the factors that can influence the brain. The visual stimuli, both during early developmental phase and adulthood, has been most commonly used environmental factor to study changes in neural connectivity (Rose and Stewart 1978; Bartoletti *et al.* 2004; Ricciardi *et al.* 2007; Sale *et al.* 2004; Mitchell and Sengpiel 2009). Sound has been shown to produce physiological effects on blood pressure, heart beat and respiration (Knight and Rickard 2001). An increased level of oxygenated haemoglobin in the circulatory blood in the prefrontal and temporal cortices was observed in autism spectrum disorders following sound stimulation (Funabiki *et al.* 2012). It is proposed that listening to music facilitates hippocampal neurogenesis, the regeneration and repair of nerves by adjusting the secretion of steroid hormones, ultimately leading to cerebral plasticity (Fukui and Toyoshima 2008). Birds and mammals generally show a similar pattern of preference to a known stimulus, prenatal auditory experience can modify the development of species-specific auditory perception (Lickliter and Stoumbos 1992; Jain *et al.* 2004). Experiments conducted by Dmitrieva and Gottlieb (1994) showed the importance of perinatal auditory stimulation in the development and maintenance of species-typical perceptual preference by devocalization of mallard and wood ducklings. Mother's vocalization can alter the adverse emotional experience in brush-tailed rat, *Octodon degus* (Ziabreva *et al.* 2003). Therefore, there is a possibility that auditory stimulation can influence by neural plasticity during the pre- and perinatal period. Other than the auditory pathway, sound simulation has profound effects on several brain regions during adulthood including activating emotional signals in amygdala (Wallentin *et al.* 2011), altering the hippocampal neurogenesis (Jáuregui-Huerta *et al.* 2011) and reducing noise correlation in rats prefrontal cortex (Ghim *et al.* 2011). Further, more studies are required to provide direct and strong experimental evidence for the mechanisms of these manipulations. Therefore, it is necessary to explore the influence of auditory stimulation on various neural functions during the prenatal period, when the brain wiring still undergoes continuous pruning.

3.1 Development of auditory pathway and sound stimulation in birds

The auditory system in chicken matures earlier than other sensory systems. The development of the chick auditory pathway begins around embryonic day E8–E10. This is evident from the observation that in the basilar cochlear

papillae of chick, the afferent synapses appear on the hair cells by about embryonic day E8 to E11 (Cohen and Fermin 1978). The morphological differentiation of the hair cells and cochlear nucleus of the medulla is completed by the E12 or E13 (Knowlton 1967). This is the stage that corresponds to the origin of evoked potentials in the brainstem auditory nuclei in response to intense sound stimulation (Saunders *et al.* 1973). The central processing of auditory information also begins at this time (Jackson *et al.* 1982; Sanes and Walsh 1998). Synaptic contacts between hair cells and primary afferents appear by about E8 to E12 (Cohen and Fermin 1978; Whitehead and Morest 1985a, b) and central synapses between primary afferents and second order cells of NM are functional by about E12 (Jackson *et al.* 1982; Pettigrew *et al.* 1988). Spontaneous electrical activity was recorded from the nucleus magnocellularis (NM) and nucleus laminaris (NL), the second- and third-order nuclei, respectively, in the chick brainstem auditory system, between E14 and E 19 (Lippe 1994) and the behavioural responses to hearing are evident around E15–E17 (Jackson and Rubel 1978). All these studies confirm that the auditory system in chick becomes functional before birth and thus they can perceive external sounds in the prenatal period. A number of studies from our laboratory have shown that the auditory pathway of chicks is plastic and undergoes modifications following prenatal sound stimulation (Wadhwa *et al.* 1999; Alladi *et al.* 2005a, 2005b). Prenatal auditory stimulation in the form of species-specific sound or music stimulation increases the size of neurons and volume of the brainstem auditory nuclei (NM and NL) as well as medio-rostral nidopallium hyperpallium ventrale (MNH; an auditory imprinting area) in chicks (Wadhwa *et al.* 1999; Panicker *et al.* 2002). Also, significant up-regulation of the various synaptic proteins (Alladi *et al.* 2002) and immediate early gene, *c-fos* (Alladi *et al.* 2005a) was observed in the brainstem auditory nuclei as consequent to prenatal acoustic stimulation. CaBPs were also significantly increased in the MNH following prenatal sound stimulation indicating responsiveness of the regions by Ca^{2+} -mediated neural activity (Panicker *et al.* 2002). Moreover, behavioural studies show an enhanced preference of the neonatal chicks towards their maternal voice even stimulated with either species-specific sound or complex sound like sitar music. This suggests that patterned sound at optimal level can influence the auditory perceptual ability of the neonatal chicks (Jain *et al.* 2004). Thus, auditory manipulations by prenatal sound stimulation as early as E10 in chicks results in increase in levels of various activity-dependent markers and size of cochlear nucleus (NM and NL) as well auditory imprinting area (MNH), which explains the remarkable ability of the developing brain to respond to any sensory stimulation by sound.

4. Importance of sound in humans

Hearing is an important function in its own right and also contributes to the ability to speak, which further helps in developing communication skills. In humans, hearing is established *in utero* by the third trimester and there is increase in fetal cortical brain activity in response to species-typical sound (Birnholtz and Benacerraf 1983; Blum *et al.* 1985; Hykin *et al.* 1999). Thus, infants show preferences to some sound stimuli with respect to others, and this selectivity may contribute towards memory consolidation and preference to speech (Harlow and Harlow 1966; Skeels 1966). Crude localization of sound sources is also possible by a newborn (Muir and Field 1979), and its accuracy improves progressively until the age of 18 months (Morrongiello and Rocca 1987). An improved motor ability and autonomic stability is observed in newborn babies when exposed to music during pregnancy (Lind 1980; Chen *et al.* 1994). The above-mentioned studies indicate the preferential response to sounds that develops prenatally and suggest a positive influence of pre- and postnatal auditory stimuli in shaping social and emotional behaviour through modulation of the auditory system. Leng and Shaw (1991) proposed that musical activity can modulate firing patterns and enhance the ability of the cortex to accomplish functions like spatial reasoning. Indeed, there is a strong relationship of music with spatial task performance (Rauscher *et al.* 1993, 1997; Rauscher *et al.* 1995). Musical training in adult humans leads to functional plasticity in the hippocampus (Herdener *et al.* 2010). Functional MRI studies in humans show that the activation of the hippocampus and parahippocampal regions following pleasant music in contrast to the response of unpleasant music (Koelsch *et al.* 2006). Music is shown to facilitate general intelligence tasks (Cockerton *et al.* 1997) as well as arithmetic and examination performances in children (Schreiber 1988; Abikoff *et al.* 1996; Hallam *et al.* 2002). It is found that background music significantly improves cognitive performance in mild to moderate mentally challenged students (Stainback *et al.* 1973) as well as in healthy undergraduate students, older adults and Alzheimer's patients (Cockerton *et al.* 1997; Thompson *et al.* 2005). The spatial performance also gets better with complex music exposure in students and Alzheimer's patients (Johnson *et al.* 2002; Ivanov and Geake 2003). For such acoustic responsiveness, parameters like sound pressure level (SPL), bandwidth, intensity and frequency of the sound stimulus appear to be important.

5. The hippocampus and its connectivity with the auditory pathway

The avian brain has remarkable similarities with mammalian or human brain for performance of cognitive tasks. With an

old nomenclature developed on the basis of the work of Ludwig Edinger (19th century), the father of comparative neuroanatomy, it was believed that there were differences in the avian and mammalian brains. However, Jarvis *et al.* (2005) along with other scientists modified the nomenclature of various brain regions of birds to be more comparable to mammalian brain system in terms of its structure and function. The avian and mammalian brain regions are also comparable in their genetic and biochemical machinery (Gibbs 2008). Birds such as owls that use nocturnal hunting have a highly sophisticated capacity for sound localization, which is similar to humans and is acquired through learning (Knudsen 2002). Another species of bird, scrub-jays, show episodic memory to recall events that take place at a specific time or place parallel to humans (Clayton and Dickinson 1998). The same species also alter their food-storing locations accordingly to prevent future stealing of food by other birds, thereby exhibiting a behaviour that would qualify as theory-of-mind (Emery and Clayton 2001). The avian hippocampus is homologous to the mammalian hippocampus on the basis of topography, developmental origin (Kallen 1962) and its role in processing spatial memory (Puelles *et al.* 2000; Siegel *et al.* 2002). The morphology (Molla *et al.* 1986; figure 1A), afferent and efferent connectivity (Trottier *et al.* 1995) as well neurotransmitter distributions (Erichsen *et al.* 1994; figure 1B), are also similar in avian hippocampus, compared to the mammalian hippocampus. The existence of retino-thalamo-hippocampal pathway in pigeons was also observed using intraocular injection and the retrograde axonal transport of various other fluorescent tracers (Trottier *et al.* 1995). Similar to its mammalian counterpart, sound stimulation could modulate the neural circuitry of the avian hippocampus due to the presence of a direct and indirect anatomical connectivity with the auditory pathway (Wild *et al.* 1993; Metzger *et al.* 1998; Braun *et al.* 1999; figure 2). In addition, the auditory information processed by the inferior colliculus is transmitted to the

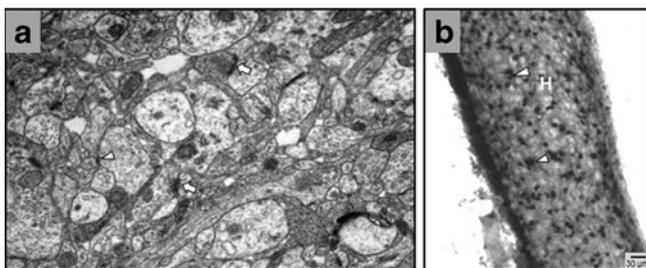


Figure 1. (A) Electron micrograph shows the spine (→) and shaft (↔) synapse in post hatch day 1 chick hippocampus. (B) Photomicrograph shows the distribution of GABA positive cells (↔) in E16 chick hippocampus. H – hippocampus. Scale bar 0.5 μm (A) and 30 μm (B).

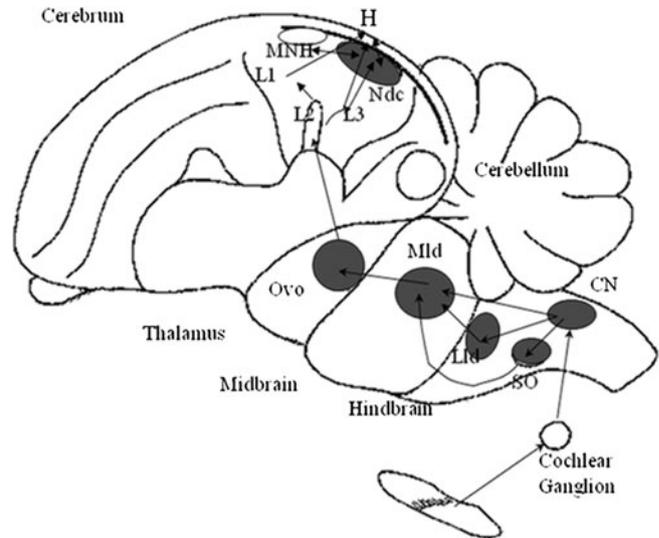


Figure 2. Schematic diagram shows the connectivity of the chick hippocampus with the auditory pathway. MNH – medio-rostral nidopallium/hyperpallium ventral; Field L (L1, L2 and L3) – auditory cortex; H – hippocampus; Ndc – nidopallium dorsocaudale; Ovo – nucleus ovoidalis (thalamic auditory nucleus); CN – cochlear nucleus.

auditory cortex and finally to the CA3 region of the hippocampus (Moxon *et al.* 1999). In rats, damage to the vestibular system results in a long-term impact on the electrophysiological and neurochemical function of the hippocampus (Smith *et al.* 2005). The data further suggest that 6 weeks after noise exposure can progressively impair learning and memory ability of mice, which may result from increased oxidative stress markers, tau hyperphosphorylation and auditory coding alteration (Cheng *et al.* 2011). Thus, auditory stimulation affects areas in the brain other than regions associated with the auditory pathway.

5.1 Alteration in molecular pathway following sound stimulation

Music exposure improves maze learning in adult rats (Rauscher *et al.* 1998) and mice (Aoun *et al.* 2000). In perinatal period, it enhances learning performance by altering BDNF/TrkB signalling in mice (Chikahisa *et al.* 2006). BDNF expression and TrkB mRNA levels also are significantly increased in the prefrontal cortex, amygdala and hippocampus of rat and mice (Angelucci *et al.* 2007; Li *et al.* 2010). Music exposure during gestation period results in increased neurogenesis in the hippocampus and enhanced spatial learning ability in rat pups, whereas exposure to

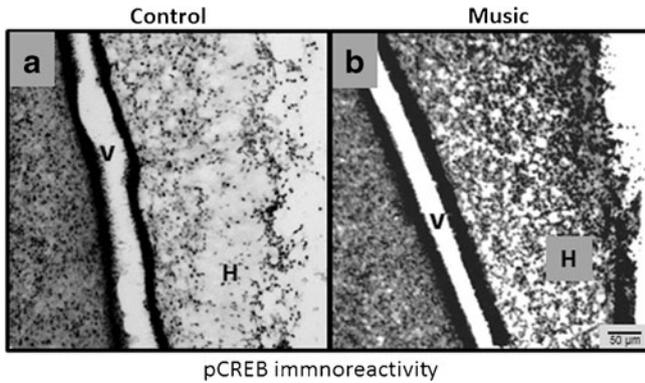


Figure 3. Photomicrograph shows the expression of p-CREB in E12 chick hippocampus in the control (A) and music stimulated (B) group. Note the increased expression levels of p-CREB in the music stimulated group. H – hippocampus, v – lateral ventricle. Scale bar, 50 µm.

non-musical noise causes growth retardation, decreased neurogenesis in the hippocampus, and impaired spatial learning ability in pups (Kim *et al.* 2006). Sound stimulation during the prenatal period leads to an increase in

CaBPs in chick hippocampus, which may trigger activity-dependent Ca^{2+} signalling pathways important for neuronal plasticity, and initiates the early development of hippocampal functions in chicks (Chaudhury *et al.* 2006, 2008). This activated signalling pathway in turn up-regulates cAMP response element-binding (CREB) protein phosphorylation (figure 3), resulting in increased expression of BDNF, a change that may help in neuronal survival, dendritic growth and synaptic plasticity in chick hippocampus (Chaudhury and Wadhwa 2009). Prenatal sound stimulation also causes an increase in synaptic density and synaptic proteins in chick hippocampus, which probably leads to increase in synaptic plasticity in stimulated groups that may influence long-term connectivity (Chaudhury *et al.* 2009, 2010). Prenatal sound stimulation also leads to enhanced spatial learning and perceptual preferences in neonatal chicks (Jain *et al.* 2004; Chaudhury *et al.* 2010; Kausar *et al.* 2011). Thus, sound stimulation could trigger the calcium-dependent signalling pathway, which might trigger the direct and indirect connection in the auditory pathway of the avian brain (figure 4). This may lead to activation of hippocampal neurons, which is connected to the auditory pathway and might play a crucial role in influencing hippocampal functions like learning and memory in chicks.

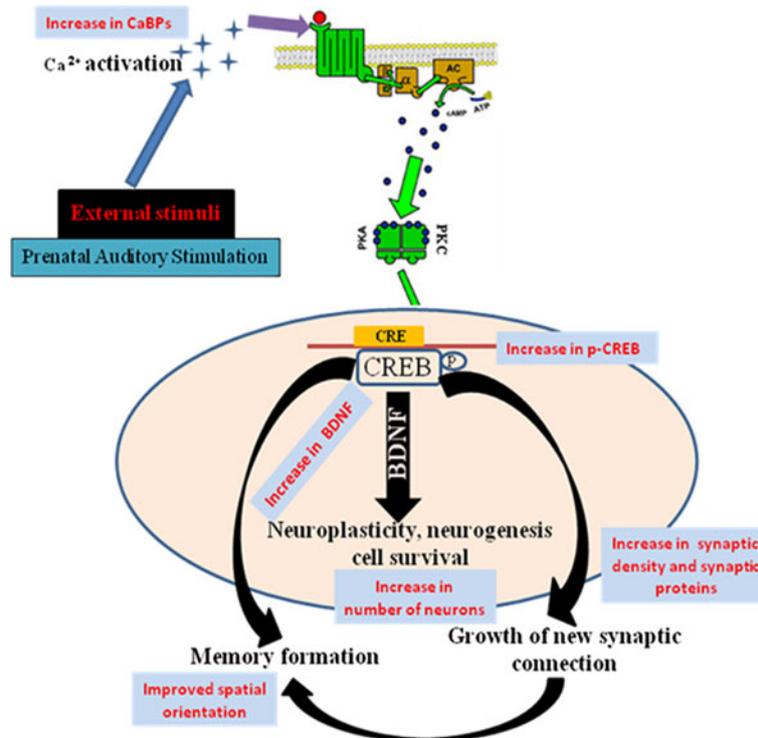


Figure 4. Schematic diagram shows the possible activity-dependent pathway in chick hippocampus following prenatal auditory stimulation. Prenatal sound stimulation in chicks leads to calcium influx which in turn activates the second messenger cascade up-regulating p-CREB, which then increases the levels of BDNF for neurogenesis and neuroplasticity or increases synaptic activity resulting in improved spatial orientation.

5.2 Role of sound stimulation in various diseases and effect of sound (noise) stimulation

In recent years, neuroimaging techniques have helped scientists to better understand of the neural correlates of music processing and perception in the brain. Music has a beneficial effect on nausea (Ezzone *et al.* 1998), anxiety and depression (Burns *et al.* 2002; Talwar *et al.* 2006), cerebral ischemia (Noda *et al.* 2004) and even on pain sensation (Siedliecki and Good 2006). It exerts a positive influence on the autistic spectrum disorder, as measured by an improvement in the clinical global impression scale and the Brief Psychiatric Rating Scale (Boso *et al.* 2007). It has been introduced as a treatment modality for the disturbed behaviour caused by Alzheimer's disease (Brotons and Marti 2003), senile dementia (Sung and Chang 2005) and schizophrenia-like disorders (Gold *et al.* 2005). It also leads to increased motor coordination in Parkinson's patients (Bernatzky *et al.* 2004). In rat models of cerebral trauma, an enriched environment in combination with sound stimulation provides greater recovery in comparison to rats exposed to an enriched environment only and/or to standard housing (Maegele *et al.* 2005). In terms of neurochemical mediators, endorphins, endocannabinoids, dopamine and nitric oxide are altered in the musical experience (Boso *et al.* 2006). Auditory enrichment by means of classical music has been shown to be a reliable method for reducing stress levels in several breeds of layer chicks (Dávila *et al.* 2011). Thus, auditory stimulation within the audible range could bring about positive changes in patients suffering from various brain disorders.

On the other hand, sound in the form of noise has detrimental effects on the brain connectivity leading to several pathological conditions. Noise reduces activity in the hippocampus as shown by the fMRI studies in humans (Hirano *et al.* 2006). An increase in the serum corticosterone levels and a long-term reduction of proliferating cells in the hippocampal formation was reported after environmental noise exposure (Jáuregui-Huerta *et al.* 2011). Noise causes a significant impairment in the early spatial memory, possibly by disrupting glutamate-NMDA receptor signalling and triggering aberrant tau hyperphosphorylation in the hippocampus. In long-term noise-stress exposed rats, there is oxidative stress, increased cholinergic activity, reduced dendritic count in the hippocampus and elevated plasma corticosterone level, which can cause impaired spatial memory (Manikandan *et al.* 2006). Even moderate-intensity noise leads to learning and memory impairment in mice (Cheng *et al.* 2011). Thus, both patterned music as well as loud noise stimulation has a capability to modulate the hippocampus, thus causing alterations in the synaptic plasticity. It is evident that the functional development of the brain is dependent on neural activity that is likely to be mediated by a variety of environmental factors including auditory stimulation.

6. Conclusion

Auditory stimulation in the form of a mother's voice or music can trigger mechanisms of brain functions including learning and memory. However, sound can have detrimental effect when played at a high decibel level or in an unpleasant manner, e.g. loud noise. It is important to understand the nature of sound stimulation along with the critical period of development, during which sound influences brain structure and functions across species, because sound stimulation can modify neural connectivity in the early phase of life and thus enhance higher cognitive function or even repair damaged connectivity in various neurological disorders and pathological conditions. In addition, the pleasantness of sound is associated with emotion: it might be a factor that can be effectively used for therapeutic treatment of the secondary illness in many psychiatric conditions. The effect of sound stimulation could be associated with the up-regulation of many neurochemical pathways in the brain. Most prominently, auditory stimulation triggers the BDNF-Trk pathway (Angelucci *et al.* 2007; Wang *et al.* 2011), which is similar to the pathway stimulated by enriched environment (Aguado *et al.* 2003; Rossi *et al.* 2006; Sun *et al.* 2010). This has also been postulated in our studies on the chick hippocampus following prenatal sound stimulation (Chaudhury *et al.* 2009). It would be appropriate to validate prenatal sound stimulation protocols in existing animal models of various psychiatric disorders to determine whether sound stimulation in the form of environmental enrichment could be a non-invasive effective way to influence cell signalling pathways in the brain, and thus to enhance beneficial functions including learning and memory.

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