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Review

Developmental programming of auditory learning

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Abstract

The basic structures involved in the development of auditory function and consequently in language acquisition are directed by genetic code, but the expression of individual genes may be altered by exposure to environmental factors, which if favorable, orient it in the proper direction, leading its development towards normality, if unfavorable, they deviate it from its physiological course.

Early sensorial experience during the foetal period (i.e. intrauterine noise floor, sounds coming from the outside and attenuated by the uterine filter, particularly mother's voice) and modifications induced by it at the cochlear level represent the first example of programming in one of the earliest critical periods in development of the auditory system.

This review will examine the factors that influence the developmental programming of auditory learning from the womb to the infancy. In particular it focuses on the following points:

- the prenatal auditory experience and the plastic phenomena presumably induced by it in the auditory system from the basilar membrane to the cortex;
- the involvement of these phenomena on language acquisition and on the perception of language communicative intention after birth;
- the consequences of auditory deprivation in critical periods of auditory development (i.e. premature interruption of foetal life).

Keywords

Auditory, experience, learning, deprivation, prosodic, voice processing, NICU.

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Introduction

As is the case with other sensory systems, the auditory system is capable of shaping structurally and functionally the neuronal systems at its base, following a temporal scale in the life of each individual. Although this capacity for shaping, which represents an adaptation of the organism to different environmental situations, continues into adulthood, it is at its maximum in the foetus and during the first postnatal months with the emerging of the neuronal circuits able to control the subsequent plastic phenomena. Following these critical periods, the auditory system has only to be refined during infancy and adolescence to be ready for new environmental adaptations.

Foetal perception of increasingly higher sound frequencies proceeds with hair cell (HC) tuning inside the cochlea and makes the uterine environment optimal for auditory maturation and for development of the proper connections with the cortex, necessary for language acquisition.

It is understandable how dangerous the auditory deprivation (due to lack of sensorial stimuli or exposure to nociceptive ones) can be: this is what happens with the premature interruption of foetal life mainly at a very low gestational age: it deprives the neonate of the auditory experiences (especially the mother's voice) that it would have had if the pregnancy had arrived at term, and at the same time causes the passage from the low-pass filtered intrauterine environment, to the chaotic one of the neonatal intensive care unit (NICU).

Ototoxic injuries caused by intense background noise may be amplified by those induced by the drugs used in NICUs, in particular the aminoglycosides and loop diuretics. The result is functional repercussions of various gravity (slight problems of language discrimination, incapacity to discriminate frequencies, deafness of different degrees).

Moreover the premature interruption of foetal life may compromise the occurrence of the first cognitive processes of foetal learning (auditory discrimination, preference for prosodic components of sounds and for mother's voice), probably linked to recognition of the communicative intention following birth, in particular for bonding to the mother and language learning.

Developmental programming of foetal auditory learning

The beginning of the foetus's auditory function goes back to about 20 weeks' gestational age (GA) and follows that of other systems (somesthesic, proprioceptive, chemosensorial, kinesthesic, vestibular) which are functionally and structurally active prior to 20 weeks' GA [1]. The earliest evidence of auditory evoked responce is at 16 weeks' GA [2]: it shows the occurrence of the connection of the inner hair cells (IHCs) to the encephalic trunk through the spiral ganglion cells [3].

Many of the changes that take place in the cochlea from 10 to 30 weeks' GA, when it is supposed to have reached more or less complete development, involve the ciliate cells proceeding from the base to the apex and in the radial direction.

IHCs, charged with transformation of sound stimuli into nerve impulses, are the true auditory sensorial cells since they activate the afferent nerve fibres that transport sensorial information to the central nervous system. The appearance of afferent fibres takes place quite early, when the HCs are not yet distinguishable. At 13-14 weeks' GA they abound at the base of the HCs and at 20 to 22 more than 90% of the spiral ganglion cells innervate the IHCs: each axon innervates a single IHC which in turn sends the afferents to 10 axons.

A few afferent axons provide innervations of outer hair cells (OHCs), which act as sound amplifiers and modulators, while efferent ones from pons and brainstem largely innervate them.

IHCs complete their differentiation earlier than OHCs, being the former relatively mature from the functional standpoint at 15 weeks' GA, the latter five to seven weeks later [3].

In the foetus the sound stimulus, through vibration of the head induced by the sound field resulted in the amniotic liquid, is transmitted (after attenuation in the passage through tissues and fluids of pregnancy) to the basilar membrane which performs its first accurate analysis. By vibrating differently depending on the sound frequency, it tunes each point to a characteristic frequency and at the same time plans the response of the single HCs that respond each one only to the frequencies present in the original sound [4].

The tuning of frequencies along the pathway of the IHCs corresponds to that along the spiral ganglion whose neurons respond to the frequencies of the cells, which they are connected to. As is the case of the HCs, each axon has a characteristic frequency to which it is more sensitive. This tonotopic organization, proceeding from the bottom to the top in different critical periods of postnatal life [2, 4], is mirrored at first in the cochlear nerve fibres and afterwards in the trunk nuclei and in the auditory cortex. Thus prenatal experience and the plastic phenomena induced by it, starting from the basilar membrane, have a controlling function over later cerebral plasticity.

The first studies on foetal responses to external sounds would agree with previous observations.

In 1983 Birnholz and Benacerraf [2] observed in their case histories of 236 foetuses the appearance of the cochleopalpebral reflex between 16 and 32 weeks' GA for acoustic vibratory stimuli of 500-1,000 Hz, with a significant increase in the frequency of the evoked responses after 26 weeks' GA. Ten years later, Hepper and Shahidullah, observing 450 foetuses with ultrasounds, saw that only one responded to 500 Hz tones at 19 weeks, while the response to 250-500 Hz was present in almost all cases at 27 weeks; from 29 to 31 weeks there was the beginning of perception of frequencies of 1-3 kHz to which 100% responded between 33 and 35 weeks' GA [5]. Foetal perception of increasingly higher sound frequencies proceeds hand in hand with HC tuning inside the cochlea and makes the uterine environment optimal for auditory maturation owing to its action as a high frequency filter [6].

Starting from the 27 weeks' GA, the possibility of perceiving low-frequency sounds coming from the outside and attenuated by the uterine filter is accompanied by the capacity to discriminate sounds at different frequencies through phenomena of habituation and dishabituation: these represent one of the first and simplest cognitive functions correlated with language acquisition [7].

Cortical foetal responses to sounds of different frequencies reflect cortical synaptic activity. Starting from 24 weeks' GA, rapid dendritic and synaptic development conditioned the increasing thickness of the cortical plate. At 27 weeks' GA the temporal lobe can be observed as a distinct structure and between 30 weeks' GA and the first two months synapse addition reaches the maximum [8]: recording trough magnetoencephalography, an imaging technique for measuring the magnetic fields produced by the brain's electrical activity, is objective proof of their presence in the foetus [9].

But following observation of foetal movements and measurement of cardiac frequency, other interesting discriminative foetal capabilities have emerged; among these the most sensational concerns the foetus's preference for the mother's voice over that of other female voices documented for the first time in 1980s by de Casper et al. [10]. Recently this preference has been documented through digital recording of the foetal heart rate (FHR) in response to listening to a story told by the mother or by another unknown female voice. Foetuses (33 to 40 weeks' GA) spoken by a foreign female responded with an increase in FHR only on hearing the mother's voice. The same response was observed in Chinese and Canadian foetuses whose mothers read in Mandarin and English respectively. A heart rate increase similar to that shown with the mother's voice was observed in response to a story recited in a foreign language (but not in the native) by an unknown female voice: so foetuses were able to discriminate their native from a foreign language. In authors' opinion the foetus presumably recognized the mother' s voice on the basis of its acoustic properties and native language on the basis of its prosodic properties present in part in the mother's voice which it was familiar with [11].

The discovery that prosodic characteristics are conserved after filtration of the high frequencies by the mother's uterus was made in studies of the ovine model in which sound transmission takes place almost in the same way as in the human model [12]. The use of uterine sensors has documented that, despite the deformation of the high frequencies by the filter effect, sounds from the outside (voices in particular) maintain their prosodic properties, including in their low-frequency component. On the contrary, they partly lose the linguistic properties (for example the distinction of phonemes) included in the high frequencies. Of the voices in a conversation, the mother's voice is the least deformed, and even less so in song or recitation; singing or reciting voices better maintain rhythm, intonation and musicality and for this reason are preferred by the foetus.

The results of these and other studies lead to speculation on the importance of prosodic information that the foetus is capable of acquiring. It would be an essential cognitive process for learning in the foetal period and for recognition of the communicative intention of language following birth, in particular for bonding to the mother. Foetal exposure to sound stimuli, especially to the mother's voice, is probably the premise for the creation of the neuronal circuits involved in language acquisition following birth.

There may even exist a more advanced form of learning conditioned by experiences and the time at which they occur in relation to maturation of the nervous system: at 37 weeks' GA the foetus not only shows a preference for lullabies recorded by the mother and heard once a day from 33 to 37 weeks' GA compared with those never heard [11], but if reciting of the rhyme begins between 28 and

32 weeks' GA it shows this preference already at 34 weeks and even before if it begins to hear them at 28 weeks [13].

The developmental origins of the cortical organization underlying voice and emotional prosody processing in the human brain remain unknown.

In the adult fMRI (functional Magnetic Resonance Imaging) has allowed to localize the cerebral processing of vocal sounds in the temporal voice areas (TVAs) placed in the superior temporal sulcus (STS) and in the right lower frontal region [14]. The STS seems to be manly involved in speech perception, more anterior region in speaker recognition and in the acknowledgement of speech affective intention [15].

An innovative fMRI procedure, designed to examine foetal brain activation to sounds might be clarify the localization of neural responses to voice in foetal cortex. This method was able to demonstrate left temporal lobe activation to sound stimuli applied in the abdomen of pregnant women at 3rd trimester of gestation [16].

Even more interesting appears in a following study in foetuses older than 33 weeks' GA, the involving of two distinct regions in perceiving mother's voice (lower bank of temporal lobe) and unfamiliar voices (upper bank) [17]. These results, as the specific involvement of left temporal lobe in foetal period, must be confirmed due the small sample size.

Developmental programming of transnatal auditory learning

As mentioned previously, the prenatal capacity to discriminate specific sounds in the uterus appears to be the origin of postnatal language acquisition [18].

Listening to the mother's voice before birth gradually leads the newborn to turn its attention to other voices as well [19]: following birth, the preference for an unknown female voice rather than silence may be proof of this [20]. The discovery that already at two days from birth [21] the newborn is capable of activating one auditory recording rather than another through modifications of the intervals between non-nutritive sucking, has made it possible to observe the preference for the mother's voice over the voices of other women, for the language used by the mother during pregnancy (rather than a foreign language), for the mother's normal adult voice rather than "motherese" (the special tone of voice that mothers often use with their children only after birth), which the foetus has not become familiar with in its prenatal life [22].

Moreover, the newborn appears to pay attention to particular prosodic elements such as timbre, rhythm and accent [23], features well represented in recordings made with intrauterine hydrophones. In this regard it is not surprising that the "filtered" mother's voice is preferred to the unfiltered natural voice [24], as well as recordings of melodies or lullabies rich in musicality and rhythm which the foetus is familiar with, or even the sound tracks of television programmes followed by the mother during pregnancy. All these familiar sounds have proved themselves also capable of calming crying newborns [25].

Although these studies leave no doubt as to the newborn's behaviour in response to auditory stimuli rich in prosodic elements, little is known about the mechanism underlying this ability.

Concerning this, a study [26] in which near-infrared spectroscopy (NIRS) was used to examine the newborn's response to a female voice produced using speech synthesis software, reciting a story for children, is quite interesting. The stories were recorded using a monotone voice (with no prosodic elements) and a variably toned voice (rich in prosodic elements). An increase in cerebral blood flow in the cortex of both frontal lobes (considered the site of perception of emotional elements in adult language), documented by means of the increase in O_2Hb, followed the varying voice but not the monotone one. Although the voices were produced artificially by the PC, the newborns (aged 1 to 9 days) were capable of perceiving not only the physical differences but also the emotional elements of the tone stimuli: which is to say it may detect the emotional intention of the speaker on the basis of the prosodic features of the sentences.

Recently, NIRS was used for the purpose of locating the areas involved in perceiving the voice in its different expressions (vocal and prosodic) and in understanding the evolution from early infancy to adulthood [27]. In the first experiment on children of 4 to 7 months, in whom response to the voice was compared to other sounds, at 7 but not at 4 months the areas activated by the voice were distinguishable from those activated by other sounds. They were located in the posterior part of the temporal lobe in both hemispheres, but more extensively on the right.

The results of the first experiment indicate that voice processing takes place at 7 months in the posterior part of the temporal lobe, as in the adult [14, 15], although in the child the site appears to be farther behind: in any case, there is continuity in the development of the TVAs from the age of 7 months to adulthood, corresponding to a progressive specialization of this area [28, 29]. Myelinisation of acoustic radiation, essential for the beginning of voice processing, starts to become visible around the sixth month of life, in agreement with the results of the study in which at 7 months, but not at 4, the initial signs of the process were evident [30].

With the fMRI it was possible to observe that in primates there is an area corresponding to the STS (although much less developed) which is thought to be specialized in a primitive form of voice processing, activated by species-specific vocalization, thanks to which animals succeed in recognizing other individuals of the same species [31]. The more posterior localization of the area, called the "what pathway", compared to the adult, reflects what was described by Grossmann in children of 7 months [27] and makes it possible to provide voice processing with a phylogenetic as well as ontogenetic interpretation (progressive extension of the TVA area and its increasingly more frontal localization in the passage from the monkey to Homo Sapiens and from the infant to the adult) [32].

The importance of species-specific vocalization not correlated with spoken language represents further proof of the role of environmental auditory experience in the development of cortical areas devoted to vocal recognition. In other animals it assumes a meaning different from recognition of individuals of the same species, but one that is just as important from the social standpoint: for example, in bats the vocalizations emitted in flight, which have the characteristic of frequency-modulated sweeps, are essential for their orientation in space. If the animals are devocalized at an early age, the cortical areas for recognition of the sweeps lose their selectivity and the bats lose their sense of orientation [33].

In the second experiment, involving only children of 7 months, the cortical responses to neutral sentences were compared to those spoken with happy or angry prosody: the emotional prosody (more pronounced with the angry voice) but not the neutral prosody, evoked an increased response not only in the posterior part of the temporal lobe (only on the right) but also in the right lower frontal cortex: this region was prevalently involved in the response to the happy prosody.

The results of the second study, in which the temporal response to angry prosody is more evident, lead to the belief that the signals inducing fear have a greater impact in voice processing, which in such a way acquire a defensive meaning as well as recognition [34]. The involvement of the lower right frontal cortex in happy prosody appears to indicate that vocal expressions with a positive tonality are further processed in the frontal cortex after being examined in the temporal cortex [35].

Infant-directed speech (motherese), quite pleasing to babies and by many considered an element favouring language acquisition [36] may be placed in the same category as happy prosody. Characteristically rich in positive prosodic elements [37], motherese may be processed in the frontal area where happy prosody is found.

Developmental programming of auditory impairment

As in other organs, the cerebral structures involved in language acquisition, genetically planned, are also shaped by environmental conditions which, if favourable, orient gene expressiveness in the proper direction, leading its development towards normality, if unfavourable, they deviate it from its physiological course.

From this viewpoint it is understandable how dangerous the premature interruption of foetal life can be, especially at a very low gestational age: it deprives the neonate of the auditory experiences (especially the mother's voice) that it would have had if the pregnancy had arrived at term, and at the same time causes the passage from a low-pass filtered environment, which is that within the uterus, to the chaotic one of the NICU [38].

Experimental studies confirm these observations. For example, exposure of newborn rats to single-tone stimuli increased the representation of the primary cortex area corresponding to that frequency [39]; on the contrary, a continuous noise that masks environmental sounds interrupted maturation of the cortex, an effect reversible with a return to exposure to a normal environmental situation [40, 41].

Preterm birth determines the passage of the foetus from an environment that acts as a low-pass filter, in which sounds below 100 Hz with a maximum intensity of 60 dB dominate, to one in which high frequencies and intensities above 60 dB prevail. The more intense the background noise level in neonatal intensive care units, especially for low frequencies, the lesser will be the newborn's ability to continue tuning the HCs (which occurs mostly between 28 weeks' GA and the first 2 months of life) [7, 42] and discriminate environmental sounds. It is assumed that the period of greatest sensitivity to noise in the foetus is between 28 weeks' GA and birth: this corresponds to the final stage of tectorial membrane development, when its fusion with the cilia of the OHCs takes place. Their deflection modulates and amplifies sounds through modulation of the electrical potential of the cell. It is thus likely that these mechanical aspects inherent in the function of the cochlea are the ones involved in sensitivity to noises [2].

Ototoxic injuries caused by intense background noise may be amplified by those caused by drugs used in NICUs, in particular the aminoglycosides and loop diuretics. Susceptibility to aminoglycosides appears to begin even earlier, from the sixteenth to the eighteenth week, and includes the final stages of ciliogenesis and maturation of the lower surface of the tectorial membrane: the injury may be of different degrees, going from impairment of fusion of the tectorial membrane with stereocilias to complete destruction of the OHCs. The result is functional repercussions of varying gravity (slight problems of language discrimination, incapacity to discriminate frequencies, deafness of different degrees) [2, 43].

The ototoxic mechanism of furosemide responsible for damage to the external structure of the cochlea, the stria vascularis, is different. Composed of three kinds of cells (marginal, intermediate and basal) and a compact network of capillaries, it plays an important role in production of the endolymph (intermediate cells) and allows maintenance of the endocochlear potentials created by the different ionic composition of the endolymph and perilymph: the former, in which the stereocilia are immersed, is similar to intracellular liquid; the latter, in which the bases of the ciliate cells plunge, to extracellular liquid. Experimental studies indicate that the absence of the intermediate cells (gerbil) causes deafness. Thanks to the melanin contained in the basal and marginal cells, the stria is also capable of re-establishing endocochlear potential during and after exposure to noise. In the presence of a reduced blood flow to the cochlea (neonatal asphyxia) or of electrolytic imbalances (which are caused by the use of loop diuretics), its destruction in the period of the highest development of endocochlear potentials (presumably the first two weeks of life) may induce serious damages to the hearing function [3].

Researching the best clinical procedures to improve NICU environment is a relevant topic for neonatologists.

An acoustic environment similar to that of the third trimester would be the most advantageous, but for the impossibility to duplicate it, efforts should be addressed in the reduction of sound levels and in the enrichment of NICU auditory background with sounds familiar for the infant.

The sound levels in NICUs and infant incubators published in the literature have different degrees but almost all exceed those recommended by international societies [44-47]. Remarkable progress has been made in the production of infant incubators, which are currently highly technological [48] but volume of alarm systems are usually too high as that of telephones, door-rings, towel dispensers and other devices [49, 50].

Noxious acoustic signals should be minimized as much as possible in the NICU: regular sound monitoring should be introduced and when it is allowed by physical spaces, a silent alarm system should be used [38].

Research in the field of manufacturers to reduce noise from medical equipment should be encouraged.

Design and architectural measures can contribute to improve acoustic environment: for instance some NICUs are testing individual rooms, which have proved to be acceptable by parents and staff members [38].

Chaotic NICU environment often depends on a non-coordinate activity of operators whose schedules and talking do not take into account what is happening with the infant. An adequate education of staff members is consequently required: they must be conscious aware of the part who plays in providing an environment that protects infant from adverse effects of noise [50, 51].

Moreover since the risk of noise damage increases if ototoxic drugs are used, blood monitoring is recommended in these case to allow an individualized administration of the drugs [53, 54].

Considerations made before about deprivation of the auditory experiences (especially the mother's voice) in premature infants are increasing the researchers' efforts to find expedients to provide the infant with familiar sounds both when he can be held outside the incubator as when he cannot. In the first case skin-to-skin contact may enable the infant to hear sounds which have familiarized with in the womb, as mother's and father's voices and their heart beats [38]. Vocal music singing by the mother in the form of lullabies, doggerels, ditties might be useful. When infant can't be moved from the incubator or when parents are not present, the transmission trough a special devise of mother's voice recorded with heart beat sounds represents an innovative method whose preliminary results seem to be useful for increasing physiological stability in the neonatal period [55-58]

Conclusions

Despite progress in research into the molecular and genetic mechanisms involved in the development of the auditory pathways, our knowledge is still limited as concerns the interactions between the maturation of term and preterm newborns, the pathological conditions common to these subjects and exposure to noise and ototoxic drugs.

However, it can be stated with certainty that the auditory pathways cannot mature normally in conditions of auditory deprivation caused by lack of sensorial stimuli or exposure to nociceptive ones. Early sensorial experience during the foetal period and modifications induced by it at the cochlear level represent the first example of plasticity in one of the earliest critical periods in development of the auditory system. The gradual exposure to high-frequency sounds also makes it possible for the foetal cochlea to process progressively the components of the human voice, which constitute the stimulus necessary for development of the proper connections with the cortex, fundamental for language acquisition following birth [38].

More efforts can be made to reduce noise in the periods critical for the auditory development and provide the infant with adequate sounds stimuli so that the auditory pathways may continue to mature even outside the uterus.

Declaration of interest

No conflicts of interest exist.

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