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REVIEWS

Development of the Human Auditory System

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Abstract | Sound is one of the first stimuli from the external environment to reach and be perceived by the human foetus as early as the fifth month in utero [approximately 25–26 gestation weeks (GW)]. Thus, auditory input may sculpt developing auditory pathways as well as those important for perceiving speech sounds even prior to birth. Detailed anatomical studies on postmortem human brains and a battery of functional studies such as the auditory brainstem response (ABR), magnetoencephalography (MEG) and fMRI (functional magnetic resonance imaging) have revealed that the cochlea and auditory brainstem are well-developed by the third trimester and adult-like in terms of structure by 6 postnatal months, followed by functional maturation. However, earlier studies have found that neurofilament proteins which form the cytoskeleton of axons and act as a marker for maturity in the nervous system (in terms of axonal conduction) are present only in Layer I of the human auditory cortex from 22 GW to 3 postnatal years. These studies have further demonstrated that the neural circuits in all other layers of the auditory cortex have a protracted period of maturation (between 1–12 postnatal years) in terms of neurofilament expression, suggesting a gradual increase in the ability to process sounds. Contrary to these neuroanatomical findings, other studies have shown that third trimester foetuses respond to complex auditory stimuli (including speech sounds) and the auditory cortex is activated by sound as early as 33 GW. In the present review, I have discussed structural and functional data relating to the maturation of the human auditory cortex. In addition to these studies, I have discussed recent results showing that axons in the human auditory cortex may mature before birth, which can be better correlated with the fairly well-developed auditory processing capabilities of the third trimester human foetus.

1 Sound Transduction and the Auditory Pathways

Sound consist of oscillations of air pressure that vary rapidly with time, often thousands of times per second. It is characterized by frequency or the number of oscillations per second (measured in hertz) perceived as pitch and intensity or amplitude (measured in decibels), perceived as loudness. The range of sound frequencies that the human ear can perceive is 20 Hz–20,000 Hz. Additionally, the human ear responds to sound levels from 0 dB (the threshold of hearing) to 120–140 dB, at which level sound is perceived as painful. The external ear or pinna focuses sound into the internal auditory meatus (auditory canal). Sound then strikes the ear drum or tympanum and sets it into vibrations. These vibrations are amplified by a series of small bones or ossicles, the malleus, incus and stapes (which resemble a hammer, anvil and stirrup, respectively) and are present in the middle ear cavity. The ossicles collectively amplify sound travelling to the inner ear by approximately 20-fold. The foot plate of the third bone in the chain, the stapes, covers the oval window of the cochlea

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which is present in the internal ear. The cochlea consists of a spiral tube coiled two and a half times around a bony core called the modiolus. It is divided into three fluid-filled compartments (the scala vestibuli, scala media and scala tympani) by the Reissner's membrane and basilar membrane. Whereas the scala media contains endolymph, the scala vestibuli and tympani contain perilymph. The scala media contains the organ of Corti which is made up of rows of inner and outer hair cells specialized for perceiving sound. The tips of the hair or stereocilia present on the apical surface of hair cells are embedded in the tectorial membrane which is attached to the modiolus. When the vibrations of the tympanic membrane are transmitted to the fluid in the cochlea, the tectorial membrane also begins to vibrate, forcing the stereocilia of the inner hair cells (IHC) to bend. These movements of the stereocilia are converted into electrical signals and are transmitted to the cochlear nerve fibers which synapse at the base of the IHC. Both attributes of sound (frequency and intensity) are encoded at the level of the cochlea itself. The cochlea is organized tonotopically such that high frequencies stimulate the base of the cochlea and low frequencies stimulate the apex whereas the number of IHCs which are stimulated by a sound determines its perceived loudness. The cochlear nerve (also tonotopically organized) relays sound to the medullary cochlear nuclei. The cochlear nuclei process neural information on timing, onset, duration and periodicity,[1] (Fig. 1). The cochlear nuclei in turn project to the superior olivary nuclei in medulla (which is important for sound localization) and nuclei of the lateral lemniscus in the pons wherein sound is processed further. These nuclei project to the inferior colliculus in the midbrain which integrates visual and auditory stimuli.[1] The inferior colliculus projects to the medial geniculate nucleus of the thalamus. Different subdivisions of the medial geniculate nucleus project to primary and non-primary auditory cortical areas located in the superior temporal gyrus of the temporal lobe. Not only does the auditory cortex analyze and perceive complex sounds including speech, it is also important for localizing and identifying sounds. The superior temporal gyrus sends projections to other cortical

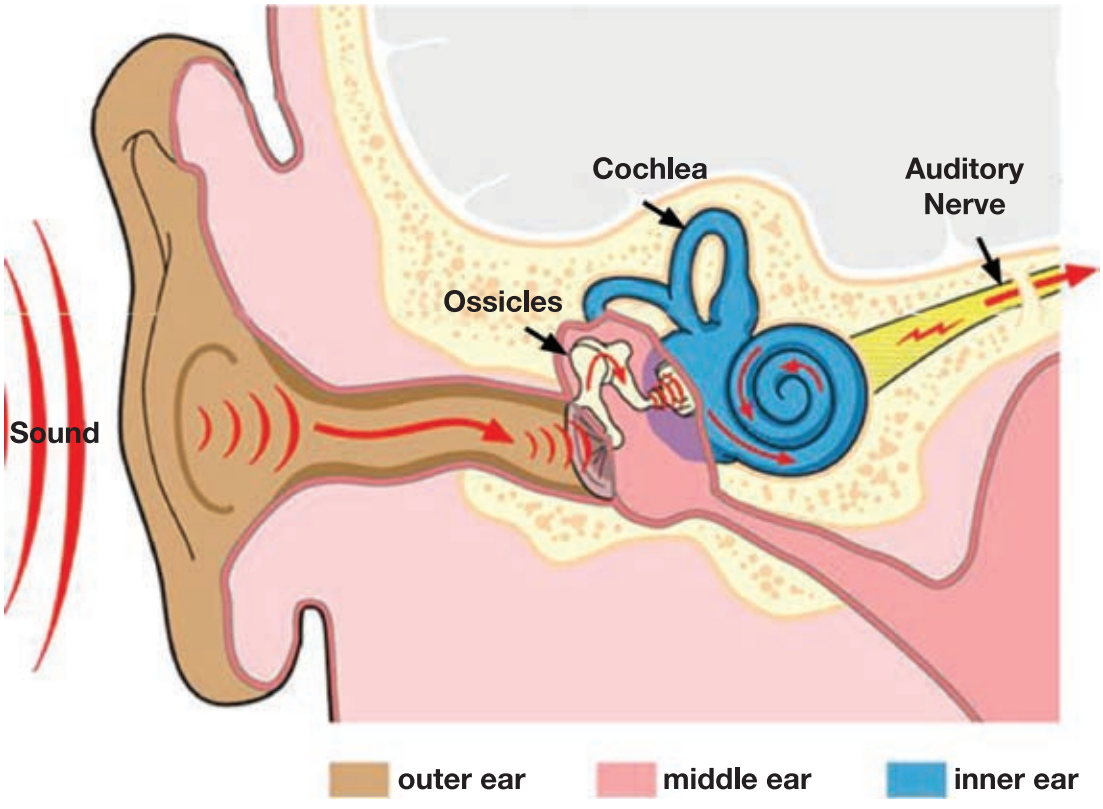

Figure 1: Sound (red arrow) forces the ear drum into vibrations which are conveyed to the ossicles in the middle ear cavity. These vibrations are further conveyed to the cochlea in the inner ear which transduces sound into electrical signals conveyed to the central auditory system through the auditory nerve.
Source: http://www.positscience.com/brain-resources/image-gallery/auditory-images

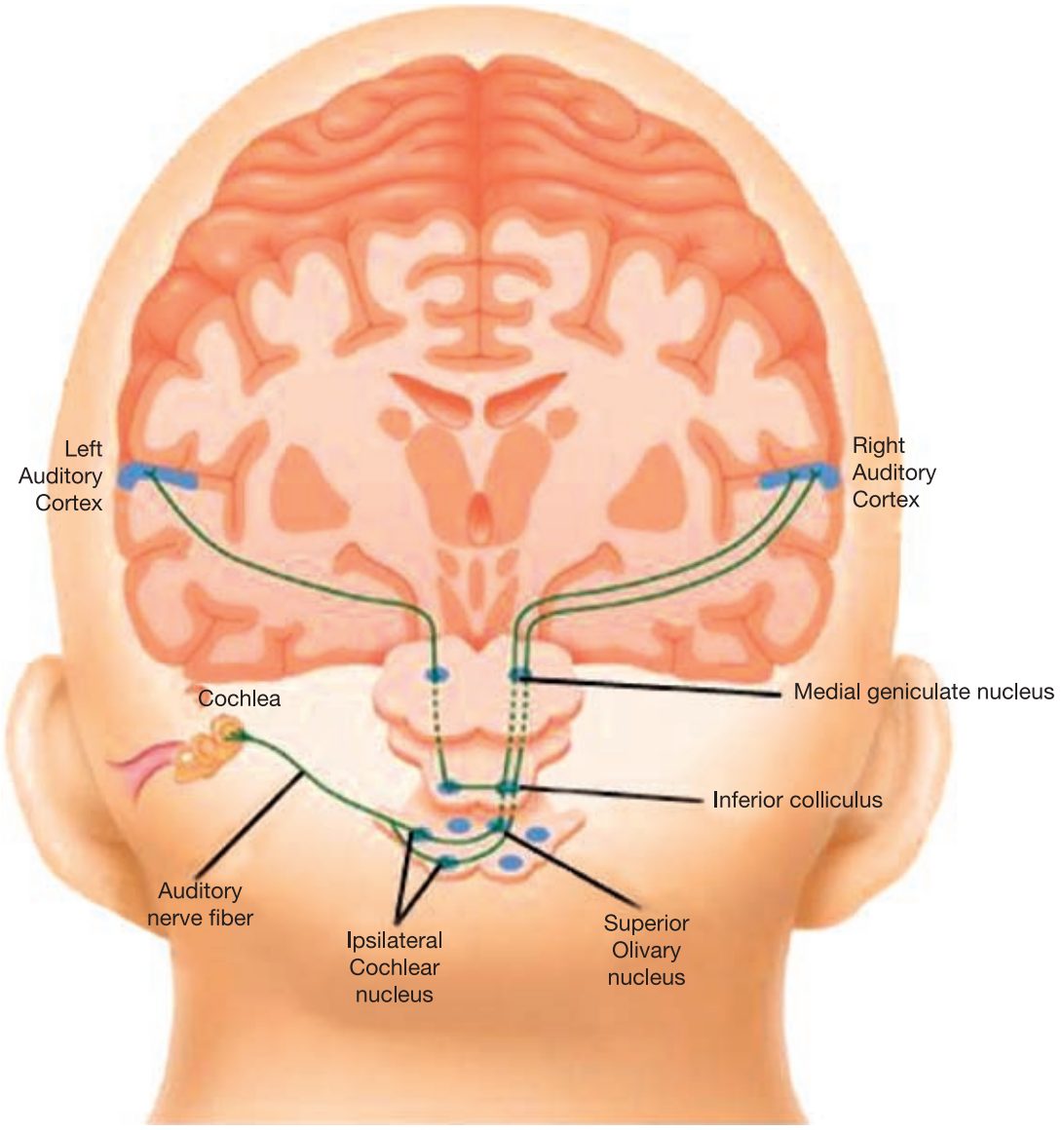

Figure 2: Sound is transduced into electrical impulses which are conveyed to the cochlear nuclei in the brainstem via the auditory nerve (8th cranial nerve). After being processed in the cochlear nuclei, sound is then conveyed to the inferior colliculus which then relays this information to the medial geniculate nucleus (MGN). The MGN sends projections to the temporal lobe wherein the auditory cortex is located for analysing and perceiving complex sounds such as speech and for sound localization.
Source: http://www.positscience.com/brain-resources/image-gallery/auditory-images

areas as well as the hippocampus and is also connected to the limbic system which is important for emotions[2] (Fig. 2).

2 Development of the Auditory Brainstem

The formation of the cochlea, cochlear nerve, brainstem nuclei and pathways as well as the cortical plate begins during the embryonic period of human development [1–13 gestation weeks (GW)].[3] The epidermis on either side of the embryonic head thickens to form a structure called the otic placode which then develops into a hollow sphere or vesicle. Further differentiation of this vesicle leads to the development of the cochlea and the vestibular system (including the utricle, saccule and semicircular canals).[4,5] The primitive cochlea forms a tubular structure or the cochlear duct which begins to lengthen, finally coiling to form two and half turns around the modiolus. The organ of Corti appears in the cochlear duct at 9 GW as a ridge of cells which have microvilli on their surface. These microvilli are replaced by stereocilia during the next three

weeks of development.[6,7] The organ of Corti and the tectorial membrane form simultaneously between 9–13 GW. The tectorial membrane which is attached to the modiolus covers the organ of Corti and the tips of the stereocilia of the hair cells are embedded within it. A layer of cartilage is laid down around the cochlea by 11–12 GW. A group of cells which separates from the otic vesicle differentiates into the statoacoustic ganglion or the spiral ganglion.[8] The peripheral processes of cells of the spiral ganglion synapse on the hair cells of the organ of Corti (9 GW) whereas the central processes of these cells synapse on the cochlear nuclei of the brainstem (5–6 GW), forming the cochlear nerve. All nuclei (cochlear nuclei, lateral and medial superior olive and inferior colliculus) and auditory pathways of the brainstem can be identified by 7–8 GW[8] and the medial geniculate nucleus of the thalamus also begins to develop by 8 GW.[9,10]

During the second trimester (14–26 GW), the cochlea and cochlear nerve mature and neuronal growth, axonal maturation and development of the efferent system takes place. The fluid-filled spaces of the cochlea, the scala tympani and scala vestibuli can be clearly discerned. The inner hair cells of the organ of Corti also develop further and myelination begins by 22 GW in the cochlea. Groups of oligodendrocytes accumulate around fibers of the cochlear nerve and begin to myelinate it by 24 GW. Cells of all brainstem nuclei begin to mature further and produce dendrites which begin to arborize by 24–25 GW.

By 26 GW (end of the second trimester), neurofilament proteins are expressed at adult levels in the brainstem, cochlear nerve and brainstem central pathways.[11] This subfamily of phosphorylated proteins consists of NF-L (low molecular weight), NF-M (medium molecular weight) and NF-H (high molecular weight)[12–15] intermediate filaments which form the axonal cytoskeleton. Interestingly, NF-L is present in the developing brain prior to the expression of NF-M and NF-H in rats[16] and humans.[17,18] The accumulation of NF-M and NF-H in axons leads to an increase in their diameter, which along with an increase in myelination is concomitant with an increase in their conduction velocity;[11,19,20] cf.).[21] The expression of neurofilament proteins can therefore be used as a marker of maturity of neural circuitry during the development of the nervous system.

During the transition to the perinatal period (27 GW–29 GW), myelination begins in the cochlear nerve and in brainstem pathways including the trapezoid body, lateral lemniscus, brainstem commissures and pathways connecting the inferior colliculus to the MGN.[19,22,23] The perinatal period itself (third trimester to 6th postnatal month) is characterized by the maturation of neurons and axonal pathways in the brainstem. The cochlea attains maturity a few weeks before birth[24] and so does the olivocochlear system. Adult-like levels of myelination are achieved in the cochlear nerve and brainstem auditory pathways by 6–12 postnatal months and may underlie the decrease in latency observed in the auditory brainstem response (ABR) peaks between pre- and postnatal months (see below,).[25–36] The development of the Po-Na complex (middle latency response) may result from the myelination of axons from the inferior colliculus to the MGN which becomes well-defined by 33 GW.[29,30,35] By 6 postnatal months, the brainstem is already adult-like, in terms of structure.

3 Structural Development of the Human Auditory Cortex

The forebrain is very primitive at 4 GW and the cerebral hemispheres consist of a thin shell of neurons surrounding the comparatively large lateral ventricular spaces in each hemisphere. By 8 GW, the wall of the cortex begins to thicken as the progenitor cells of the ventricular zone multiply and migrate, forming the cortex.[37] The marginal zone (future Layer I) appears next and contains the processes of the cells which form the ventricular zone. A specialized subset of cells called the Cajal-Retzius (CR) cells also begins to appear in the marginal layer at this time.[38,39] These cells are important for attracting migrating neuroblasts into the underlying cortical plate which gives rise to other layers of the cortex by secreting the chemoattractant protein reelin.[40,41] The formation of the marginal zone is followed by the appearance of the intermediate zone which lies between the ventricular and marginal zones. The next layer to emerge is the subventricular zone which forms between the ventricular and intermediate layers and also consists of progenitor cells. The cortical plate and subplate are the next to form between the marginal zone and the intermediate zone. Layers II–VI of the presumptive cortex arise from the cortical plate whereas the subplate and the intermediate zone transform into the subcortical white matter. The subplate layer is also known to act as a 'waiting compartment' wherein subcortical axons (including thalamic afferents) initially terminate before entering and arborizing within different layers of the cortex.[42]

Krmpotić-Nemanić and colleagues performed a series of studies on the development of the auditory cortex in post-mortem fetal brains[38,43–46]

using a combination of histological techniques (Nissl and Golgi staining), enzyme histochemistry and electron microscopy. They demonstrated that different layers of the developing cortex (marginal zone, cortical plate, intermediate zone, subventricular and ventricular zones) were present in the incipient auditory cortex at 11–12 GW.[43] Differentiating neurons with developing dendritic arborisations could be seen in the three outermost layers, namely the marginal zone, cortical plate and intermediate zone at this stage. The subplate layer which lies below the cortical plate had differentiated from the outer part of the intermediate zone at 12–13.5 GW. Krmpotić-Nemanić et al. (1980, 1983)[44,45] were the first to use enzyme histochemistry for acetylcholine esterase (AChE) to demonstrate that cholinergic afferents reach the human auditory cortex. They found that AChE-positive fibres from the region of the ventral posterior thalamus and basal telencephalon grew towards the incipient auditory cortex as early as 10.5 GW. These fibers entered the marginal zone and subplate layer of the auditory cortex by 20–24 GW and the cortical plate, which is composed of columns of neurons, between 22–28 GW.[43,46] Since synaptogenesis occurs in all layers of the cortical plate (future auditory cortex[47]) during this period, their results suggested that thalamic afferents from the medial geniculate nucleus innervated the auditory cortex by ~25 GW. Further, Moore and Guan (2001[17]) demonstrated that a plexus of neurofilament-positive axons were present in the marginal layer [also demonstrated by[48] at 25 GW], whereas the underlying cortical plate was completely devoid of immunostaining for the neurofilaments. Since the cortical plate did not appear to contain any neurofilament-positive axons, Moore and Linthicum (2007[3]) suggested that the axons in the marginal layer presumably extend from the brainstem reticular formation into the auditory cortex.

During the transition to the perinatal period (27 GW–29 GW), the temporal lobe could be discerned as a distinct part of the cortex. Cortical arousal measured by cortical evoked potentials which could be detected at this time probably resulted from the axonal plexus in the marginal layer.[22,23] In the perinatal period which follows (third trimester to 6th postnatal month), neurons and axonal pathways began to mature in Layer I of the cortex and influence the differentiation of neurons in underlying cortical areas. The cortex continued to enlarge and differentiate further during this period. By 37 GW, there was a clear separation between the medial Heschl's gyrus (also called the transverse temporal gyrus) which contained the primary auditory cortex and the more lateral part of the superior temporal gyrus wherein the secondary or non-primary auditory cortical areas were located.[17] The auditory cortex and the afferent axons from the medial geniculate nucleus matured between 6 months and one year (the transition to childhood). Whereas Layer I of the auditory cortex decreased in thickness, Layers II–VI increased in size. Moore and Linthicum (2007[3]) demonstrated that there was an increase in neurofilament-positive axons in Layers IV–VI during this period. From 2 to 5 years (early childhood), thalamic axons within the auditory cortex continued to mature and their density reached adult levels in Layers IV–VI.[17] Cortical neurons increased in size and there was an increase in their dendritic arbors.[49–51] Myelination began in the auditory cortex by 3 postnatal months[52] and was completed by 6 years of age,[49–51] whereas MGN afferents to the cortex achieved myelination by 4–5 years.[53,54] Moore and Guan (2001[17]) further demonstrated that neurofilament expression reaches adult levels by 12 years and that this maturation included axons from the MGN as well as intrinsic cortical axons (Moore and Linthicum, 2007[3]).

4 Electrophysiological Correlates of the Development of the Auditory System

Responses of the 8th nerve and different components of the auditory brainstem (cochlear nuclei, inferior colliculus and MGN) to sound can be recorded from the scalp are of short latency (<10 ms) and are collectively called the auditory brainstem response or ABR (reviewed in).[55,56] Typical ABRs consist of a series of 7 waves which represent compound action potentials of different parts of auditory brainstem circuitry in response to sound. Wave I and II represent the response of the distal and proximal parts of the cochlear nerve, respectively, as this nerve exits the internal ear and enters the brainstem to terminate on cochlear neurons in the medulla and pons. Wave III arises from second-order neurons in the cochlear nuclei whose axons terminate in the inferior colliculus. The cochlear nuclei also project to the superior olivary complex (important for sound localization and for detecting sound intensity) which further projects to the inferior colliculus. Wave IV is thought to arise from axonal connections between these latter nuclei (that is, superior olives and inferior colliculi). Auditory evoked potentials in the axons of the inferior colliculus neurons are thought to contribute to Wave V, whereas projections of

the neurons forming the medial geniculate nuclei of the thalamus to the cortex may contribute to Wave VI and VII. A number of studies[23,57,32] have demonstrated that the ABR can be demonstrated in 28–29 conceptional age (CA) premature infants and waves I, III and V become clearly detectable at 35 CA.[35,57] Since auditory input is first perceived by the cochlea, cochlear maturity would influence ABR in all other ABR generators, that is, the cochlear nuclei, superior olivary complex, inferior colliculus and medial geniculate nucleus. Although the cochlea is almost adult-like by approximately 26–27 GW, it attains complete maturity a few months after birth.[24] Ponton et al (1992[57]) have demonstrated that the latency difference between waves I and V (which represents the brainstem conduction time) mature to adult levels by 1.5–2 years after birth.

Another set of auditory evoked responses which mature alongside the ABR responses are the middle latency responses (MLR, 10–50 ms[58,59]), consisting of five waves (N0, P0, Na, Pa and Nb). The Po-Na waves represent auditory transmission in the neural circuitry connecting the inferior colliculus and medial geniculate nucleus.[60] Whereas the Po waves are barely discernable at 25–27 GW, they become well-defined by 33 GW and develop further by birth.[29,30,35] Further, the Na peak achieves adult levels (18 ms) by the 3rd postnatal month.[61]

The third set of auditory evoked responses are referred to as long latency auditory evoked responses (LLAEPs) or auditory late responses (ALPs) which occur 50–300 ms after stimulus onset originate mainly from the auditory cortex.[62,63] In adults, LLAEPs consist of four waves, P1 (a small positive peak, 50 ms post-stimulus onset) followed by a well-defined negative peak N1 (90–150 ms post-stimulus onset) and P2, a broad positive peak which occurs 175–200 ms after the onset of the auditory stimulus.[64,65] Since the LLAEPs are generated by the auditory cortex, they are also called cortical auditory evoked potentials (CAEPs) and are thought to be correlates of perception.[62,63] The CAEPs can be categorized as discriminative or obligatory.[64,65]

Discriminative or endogenous CAEPs include MMN (mismatch negativity) and P300.[64] When a certain set of similar stimuli (acoustic, phonetic or contextual) are being presented and a deviant stimulus is introduced randomly, the auditory cortex responds to this odd-ball stimulus with a larger event-related response (ERP), called MMN. MMN indicates pre-attentive processes at work in the brain, since these suggest that the individual is paying attention to and detecting a change in a uniform set of stimuli. Since event-related responses in infants are largely positive (as opposed to those in adults), MMN is referred to as MMR (mismatch response) in infants to differentiate them from MMN seen in adults. MMR is first observed in the fronto-central part of the cortex at birth and in the temporal region by 1–2 postnatal months, becoming clearly discernable by 3 postnatal months.[66] Interestingly, Draganova et al. (2005, 2007[67,68]) have used magnetoencephalography to demonstrate MMR in 28 GW fetuses. Trainor et al. (2003[69]) have demonstrated that the transition from positive to adult-like negative cortical evoked potentials takes place at 6 postnatal months.

The second type of CAEPs includes obligatory or exogenous evoked potentials (OEPs). Since the OEPs depend solely on external auditory stimuli and the integrity of the central auditory pathways, they are less affected by factors such as attention and memory. They can therefore be recorded reliably to assess auditory cortical function at different age groups including infants and children.[65] In adults, OEPs consist of two main positive peaks (P1 and P2) and one main negative peak (N1[64]) interspersed between them. A smaller negative peak N2 follows P2. Whereas N1 reflects the activity of at least four neural generators, P2 is thought to represent activity in the primary auditory cortex.[65]

Results from different studies[30,35,70,71] have shown that obligatory evoked potentials can be recorded from the cortex in 24 week preterm babies. At 24 GW, OEPs consist of a large negative wave with a latency of 200 ms and a positive wave with a peak latency of 600 ms. By 30 GW, the latency of the positive wave decreases to 300 ms and it increases in amplitude. Only the positive wave (peak latency 250 ms) remains at birth (40 GW), which is present until 5 postnatal months. At this time, a new negative wave appears (peak latency 400 ms) and the positive wave increases to 400 ms. Further, there is a decrease in the latencies of the three main waves P2, N2 and P3[70,72] such that by 5 yrs, the OEPs consist of a positive wave (peak latency 100 ms) followed by negative wave (peak latency 200 ms) and a positive wave (peak latency 350 ms[73,74]). In adulthood, the OEP complex consists of four waves, P1-N1-P2-N2 (with latencies of 50, 100, 150 and 200 ms, respectively), which is first seen between 14–16 years. Whereas P1 becomes adult-like early during development, N1 attains adult levels by 9 yrs.[74] Additionally, both P2 and N2 mature early, both achieving adult-like values by 2–3 years.[74,75]

5 Correlation between Anatomical and Electrophysiological Changes During Development of the Human Auditory System

In one of the most extensive reviews to date on structure-function correlates of the development of the human auditory system, Eggermont and Moore (2012[55]) have divided audition into discrimination and perception. Whereas discrimination refers to the 'ability to recognize different auditory stimuli', perception represents the 'linking of a stimulus to its meaning or significance.[55] These authors suggest that whereas the physical attributes of sound are analysed by the brainstem, the reticular activating system (RAS) and thalamic inputs to Layer I which occurs during fetal development mediates attention to sound (cf.[3]). Further, they suggest that discrimination of sound begins before birth (GW) and continues during the first few postnatal months.

Eggermont et al. (1996[24]) have shown that the cochlea and cochlear nerve are mature by 3 postnatal months, followed by the maturation of the brainstem (in terms of neural circuitry) by 1.5 years, including the projection from the inferior colliculus to the medial geniculate nucleus (MGN). Eggermont and Moore (2012[55]) have identified the neurofilament-positive fibers described by Moore and Guan (2001[17], reviewed in[3]) which innervate Layer I as RAS fibers. Further, they have attributed the early auditory discriminatory capabilities of the human fetus to the RAS pathway since the MGN and thalamocortical fibers as well as neural circuitry within the auditory cortex does not mature until adulthood (20 years, cf.).

According to Eggermont and Moore (2012[55]), the cochlea is important for spectrally analysing sound which is followed by a more detailed analysis of various parameters of sound by the brainstem. The cochlea develops first, followed by the gradual maturation of other auditory components of the brainstem (the cochlear nuclei, inferior colliculi, olivary complex and medial geniculate nucleus of the thalamus). The presence of biphasic ABR waves in the brainstem during the third trimester represents an increased neural activity in the auditory neural circuits which can be correlated with an increase in myelination in these pathways. The last component of the auditory brainstem (projections of the inferior colliculus to the MGN) matures by 3 postnatal months and can be correlated with the maturation of the Po-Na complex of ABR.

As mentioned above, Eggermont and Moore (2012[55]) suggest that the only input to the auditory cortex at term and during the months immediately following birth consists of the RAS which consists of thin, slowly conducting neurofilament-positive axons in Layer I (cf.[17]). Since Cajal-Retzius (CR) cells are also present in Layer I during this period,[38,39] they suggest that the axons of the RAS which terminate in Layer I as well as the axons of CR neurons are the only components of cortical auditory neural circuitry capable of generating neural activity. Since P2 and MMR as well as wave V of ABR are present at birth and mature soon thereafter, they can be attributed to Layer I of the auditory cortex. By 6 postnatal months, the CR neurons disappear and thalamic axons from the MGN enters Layer I of the auditory cortex, which also coincides with the MMR (positive) changing to MMN (negative) which is characteristic of adulthood. Between 6 postnatal months and 1 year of development, Layer I of the auditory cortex decreased in thickness and Layers II-VI increased in size. Moore and Linthicum (2007[3]) demonstrated that there was an increase in neurofilament-positive axons in Layers IV–VI during this period. Other studies[74,77] have demonstrated that this period coincides with the emergence of long latency cortical evoked responses (MMN or mismatch negativity and the N2 wave, see below) takes place at this time. Moore and Linthicum (2007) have also attributed the response of ~6 month old infants to phonemes of their native languages, discrimination of speech sounds[78,79] and the decrease in their ability to discriminate between phonemes of a non-native language[80,81] to the neural circuitry within Layers I, IV, V and VI.

According to Eggermont and Moore (2012[55]), the perception of auditory stimuli (speech) which begins from 6 postnatal months onwards and continues into the teenage years depends on the maturation of neural circuits connecting the thalamus and the auditory cortex. Moore and Guan (2001) have shown that axons in the proximal part of the MGN-auditory cortex circuit begin to express neurofilaments soon after birth and these axons become myelinated between 4 postnatal months and 4 years after birth. Moore and Guan (2001[17]) had demonstrated that neurofilament expression in the axon terminals of MGN neurons in the infragranular layers of the auditory cortex extends over the period from 6 postnatal months to 5–6 years. The formation of synapses between thalamic axons and Layer IV of the auditory cortex coincide with the maturation of the Pa-Nb/ complex of ABR by age 5. The P1 wave which represents perception also matures by 5–6 years and may be generated by Layer III or IV of the cortex which receive input from the MGN. The

maturation of the Pa (peak 25–30 msec[61]) and P1 waves[74,82–84] to adult levels coincides with the completion of myelination in the MGN afferents to the cortex by 4–5 years[53,54] and the auditory cortex by 6 years of age.[49–51]

Moore and Guan's (2001[17]) study reveals that neurofilament expression reaches adult levels in the auditory cortex by 12 postnatal years and there is maturation of intrinsic cortical axons.[3,17] The delayed period of maturation of the auditory cortex can be correlated with the appearance of the N1 wave in 9 year-olds.[85,86] The generator of this wave is thought to be Layers II and III of the auditory cortex, which are important for intracortical processing. The input to these layers matures between 6–12 years, which correlates well with increased perceptual abilities in late childhood, such as the discrimination of speech in a noisy background[87] and the discrimination of masked and degraded speech,[88–94] cf.[55]).

6 Does the Neural Circuitry of the Human Auditory Cortex Actually Develop Over a Protracted Duration?

In contrast to Moore and Guan's (2001[17]) findings, Ulfig and Chan (2002[95]) used immunohistochemistry to demonstrate that neurofilament expression can be seen in the intermediate zone and subplate of the temporal lobe at 25 GW in the human fetus. Further, Pujol et al. (2006[52]) have demonstrated that myelination in the human auditory cortex begins at 3 postnatal months. These findings are at odds with Moore and Guan's (2001[17]) finding showing that neurofilament positivity increases by the end of the first postnatal year, since myelination is known to be concurrent with or following the increase in neurofilament expression. Further, Kostović et al. (2002[96]) and Judas et al. (2005[97]) have used a combination of magnetic resonance imaging and histology on the human fetal brain to demonstrate that in general, thalamocortical axons innervate the subplate by 23 GW and the cortical plate by 32 GW in humans and callosal and cortico-cortical pathways appear between 33 and 35 GW (reviewed in[98] and[99]). A recent paper[48] has used RT-PCR to show that mRNA for both heavy and medium chain neurofilaments are expressed in the human superior temporal gyrus as early as 15 GW onwards. They have also used immunohistochemistry to demonstrate that a plexus of neurofilament-positive fibers is present in the deepest layers of the cortical plate (presumptive Layers V and VI) in fetuses at 25 GW (Fig. 3). Interestingly, some of the neurofilament-positive fibers also extended into Layer I, where they may form synapses. Since varicosities could be seen along the length of axons forming the plexus in the infragranular layers at 25 GW, it is possible that synaptic contacts were present within Layers V and VI at this stage of development. Pundir et al. (2011[48]) have further demonstrated that neurofilament-positive axons extend into Layer IV and the overlying Layer III between 32 and 40 GW, in an inside-out manner. In contrast to Moore and Guan's (2001[17]) findings which demonstrate that axons within the human auditory cortex become adult-like (in terms of neurofilament expression) by 12 postnatal years, Pundir et al. (2011[48]) have shown that there is a very intricate and dense plexus of neurofilament-positive axons through all layers of the auditory cortex by 9 postnatal months. Since neurofilament expression is a hallmark of axonal maturity, these results suggest that neural circuitry within the human auditory cortex may be more mature than earlier thought. However, in the absence of tract-tracing studies, the identity of the neurofilament-positive axons in the developing auditory cortex is still not known. It is possible that these axons are cortical afferents from the reticular activating system, as suggested by Moore and Linthicum (2007[17]) and Eggermont and Moore (2012[55]). It is also possible that these axons may be thalamocortical and originate from the medial geniculate nucleus and/or within the cortex (cortico-cortical) at birth and during early postnatal development (9 months). If indeed these axons emerge from the MGN, the time-line for development of subcortical connections with the human auditory cortex would be similar to that of the visual cortex wherein tract-tracing tracing studies have revealed that axons from the lateral geniculate nucleus enter the subplate by ~22 GW and begin to arborize soon after. Further, cortico-cortical connections between different areas of the primary and non-primary visual areas are established in the human fetus by ~37 GW, prior to birth.[100,101]

What are the implications of a neurofilament-positive network of axons being present in different layers of the developing auditory cortex before 6 postnatal months as suggested earlier?[3,17,55] Earlier studies have used ultrasound, electroencephalography and recorded auditory evoked fields, respectively, to show that human fetuses can respond to various complex vibroacoustic stimuli as early as 26 GW[102–104] and human speech sounds at ~37 GW.[105–107] It is therefore not surprising that neonates preferentially process speech

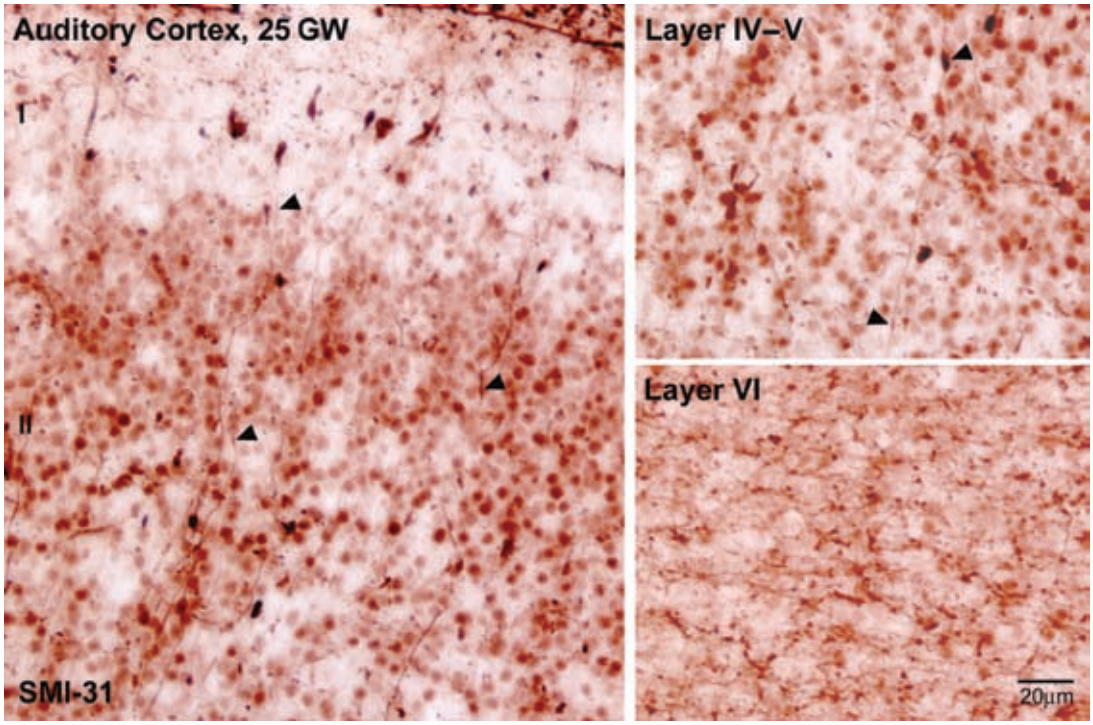

Figure 3: (**Left**) Very fine fibers and axon terminals as well as a small number of axons oriented towards the pial surface can be seen in the deeper part of Layer I just below the dense band of fibers (arrowheads). Large varicosities are also seen along some of the fibers. Layer II consists of densely packed cells, some of which are labelled for SMI-31. (**Layer IV-V**) SMI-31-positive axons (arrowheads) are also present at the junction of Layers IV and V, interspersed between cells. (**Layer VI**) A very dense plexus of vertical and horizontal SMI-31 immunoreactive fibers is present in presumptive Layer VI of HG. Scale bar = 20 µm.

sounds, especially to those spoken in their native languages.[108–111] Draganova et al. (2005; 2007[66,67]) have used magnetoencephalography (MEG) to demonstrate that fetuses respond to differences in the frequency of sounds at 28 GW. Further, Jardri et al. (2008[112]) have used functional magnetic resonance imaging to demonstrate that sound can activate the primary auditory cortex as early as 28–34 GW. Many of these results as well as others [such as the activation of the primary auditory cortex at 3 postnatal months,[113] the generation of long latency potentials[22,29,30,35,70,114–116] and MMN in infants[117–120] have been attributed to the axonal connections between the RAS and Layer I of the auditory cortex. However, recent results[48] demonstrating that neurofilament-positive axons arborize extensively throughout the auditory cortex suggest that the entire thickness of the cortex from Layer I to Layer VI may be activated by sound as early as 32 GW, whatever may be the source of these axons.

The above findings indicate that it is very important to identify the source of the axons which arborize within the developing human auditory cortex. The method of choice would be to inject lipophilic dyes in the MGN and in the auditory cortex (Heschl's gyrus and superior temporal gyrus) of post-mortem brains at different gestational ages. Anterograde label (labelled axon terminals) in the auditory cortex from injections in the MGN and retrograde label (labelled somata) in the MGN from injections in the auditory cortex would suggest that the plexus of axons in the cortex originates in the thalamus. In contrast, if cortical injections of lipophilic tracers give rise to retrograde label in the brainstem reticular formation, these results will suggest that the axons from the reticular activating system invade the auditory cortex prior to the establishment of thalamocortical connections from the MGN. It would also be important to correlate these findings with those of magnetic resonance imaging of the post-mortem fetal human brain (cf.[96,97]).

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