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MATURATION OF HUMAN AUDITORY CORTEX: IMPLICATIONS FOR SPEECH PERCEPTION

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This project traced the maturation of the human auditory cortex from midgestation to young adulthood, using immunostaining of axonal neurofilaments to determine the time of onset of rapid conduction. The study identified 3 developmental periods, each characterized by maturation of a different axonal system. During the perinatal period (3rd trimester to 4th postnatal month), neurofilament expression occurs only in axons of the marginal layer. These axons drive the structural and functional development of cells in the deeper cortical layers, but do not relay external stimuli. In early childhood (6 months to 5 years), maturing thalamocortical afferents to the deeper cortical layers are the first source of input to the auditory cortex from lower levels of the auditory system. During later childhood (5 to 12 years), maturation of commissural and association axons in the superficial cortical layers allows communication between different subdivisions of the auditory cortex, thus forming a basis for more complex cortical processing of auditory stimuli.

KEY WORDS — auditory cortex, development, neurofilament, thalamocortical axon.

In choosing the time for intervention with a prosthetic device in a hearing-impaired child, it should be useful to have some idea of the stage of maturation of the child's auditory system. In particular, we would like to know something of the status of higher levels of the central auditory system in which acoustic information is made relevant to behavior, including language. In the past decade, the Department of Neuroanatomy at the House Ear Institute has carried out studies of the structural development of the human central auditory system. This paper briefly reviews what we have learned about the maturation of the human auditory cortex and the implications of these findings for the development of speech perception.

The developmental work in the neuroanatomical laboratory was carried out in human postmortem brain tissue collected at the University of Southern California–Los Angeles County Hospital during neuropathologic autopsy. Tissue was collected for an age series extending from the 16th gestational week to 27 years, ie, through the fetal period, infancy, childhood, and young adulthood. In our laboratory, the tissue samples were embedded in celloidin, sectioned on a microtome, and used for a variety of histologic and immunohistochemical procedures. From each tissue sample, one series of every eighth section was stained for cells by Nissl's method, and the intervening sections were immunostained with antibodies that link to different structural elements of neurons and glial cells.

One type of immunostaining that was particularly useful in tracing development was an antibody to axonal filaments. Neurons form their axons quite early in development, and the newly generated axons are extremely thin; they contain very little in the way of axoplasm or cytoskeletal (cell framework) elements. There are shifting ionic currents, but no rapid action potentials flow down the length of the immature axons. When the time arrives for axons to begin to function, they undergo a transformation in which they increase in size, create a framework of neurofilaments within their axoplasm, and induce surrounding glial cells to encircle the axons with a myelin sheath. Once this has occurred, the axons begin to transmit information by rapid conduction. Because neurofilament proliferation within an axon immediately precedes myelination and rapid conduction, immunolabeling of axonal neurofilaments is a useful marker of the onset of function in any neuronal system.

The usefulness of neurofilament immunostaining as a marker of onset of function was illustrated in our previous studies of the development of the human brain stem auditory pathway. Brain stem auditory axons develop an adult-like content of neurofilaments between the 16th and 28th fetal weeks.[1] Myelination of the axons first occurs between the 26th and 28th weeks of development,[2] and by the 29th fetal week, the presence of click-evoked brain stem auditory potentials indicates that rapid synchronous conduction is occurring in brain stem pathways.[3] These findings indicate that the onset of information conduction through the brain stem occurs around the 26th to 28th fetal weeks, at the beginning of the third trimester of development. A rapid increase in axonal conduction velocity and synaptic transmission time

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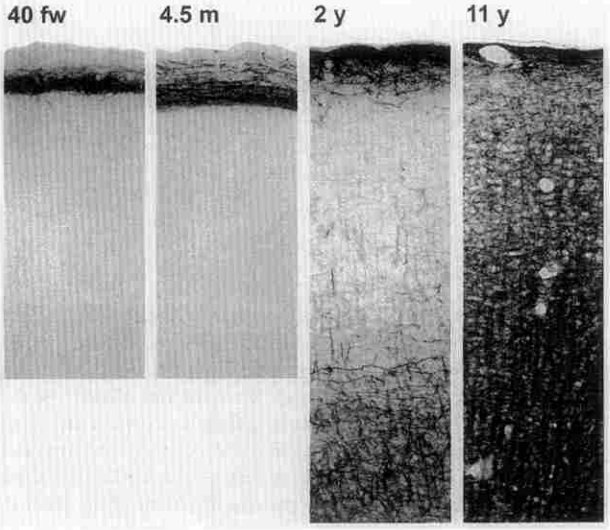

Fig 1. Neurofilament-immunostained sections of cortical tissue. At 40th fetal week (fw) and at 4.5 months' postnatal age, mature axons are present only in marginal layer. By 2 years of age, mature neurofilament-expressing axons are entering deeper cortical layers. By 11 years, mature axons are present with adult-like density in all cortical layers.

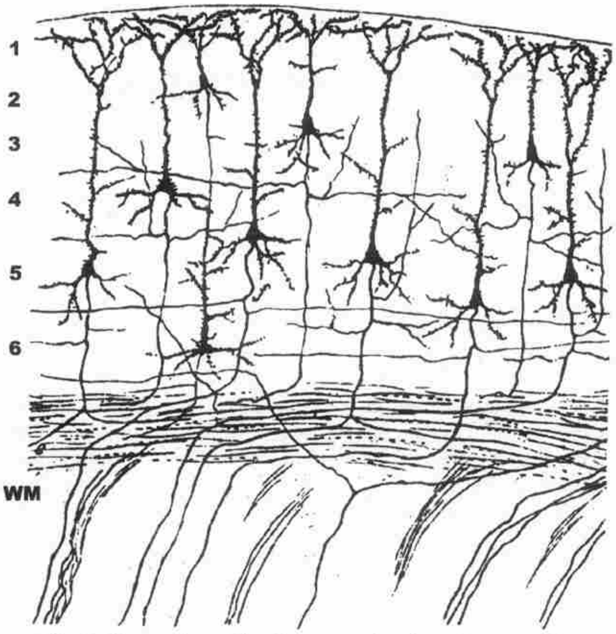

Fig 2. Illustration of laminar organization of cortex. Numerals 1 to 6 indicate cortical layers. WM — deep white matter. Adapted from Ramon y Cajal.[6]

occurs in brain stem pathways during the perinatal period.[3,4] These findings demonstrate that the brain stem auditory pathway is relatively mature at the time of term birth and is functioning in a very adult manner in the first year of life. However, our studies of the cortex produced a very different picture of development, one that extends considerably beyond the perinatal period.[5] With neurofilament immunostaining, we observed 3 periods of cortical development, each characterized by the maturation of a different axonal system.

PERINATAL PERIOD

From the third trimester of gestation to the fourth postnatal month, mature axons are present only in the most superficial layer of the cortex, the marginal layer. This superficial band of neurofilament-expressing axons is present at the 40th fetal week, ie, at the time of term birth, and is still prominent at 4.5 months after birth (Fig 1). The marginal layer, also called layer 1, consists of axons that run parallel to the cortical surface for long distances, often as far as several millimeters. In their course, the axons contact large numbers of apical dendritic tufts, the branched tips of upwardly extending dendrites of neurons lying in the deeper layers of the cortex (Fig 2[6]). Through these apical dendrites, marginal layer axons drive the activity of the deeper cells and are believed to promote their structural and functional maturation.[7] Although marginal layer axons undoubtedly have an important stimulatory role in the rapidly developing cortex of the late fetal period and first year of life, they constitute an intracortical system that carries little or no information on external auditory stimuli.

Many studies attest to the auditory discrimination abilities of perinatal infants. Infants in the first months of life can accurately distinguish speech sounds that differ in a variety of acoustic characteristics[8-13] and vary across different speakers.[14,15] In addition to distinguishing individual speech sounds, infants at 2 to 4 months of age detect differences in the segmentation of multisyllable phrases[16] and changes in the word order of sentences.[17] Previously heard stimuli are retained for as long as 24 hours,[18] and stimulus retention is enchanced by syllable organization[19] and prosodic linkage.[20] This precise processing of stimulus parameters in the first months of life is accomplished by infants with a very mature cochlea and brain stem, but a cortex with mature axons only in layer 1. Given that there is no route for transmission of auditory information to the cortex at this stage of development, it seems likely that the accurate stimulus discrimination evidenced by infants younger than 5 to 6 months reflects the analytical abilities of the brain stem.

EARLY CHILDHOOD

Between 4.5 months and 1 year of age, neurofilament-expressing axons first appear in the white matter core of the temporal lobe, with axons radiating up into the deeper layers 4, 5, and 6. By 2 years of age, a light plexus of vertical and horizontal axons is apparent in the deeper cortical layers (Fig 1), and this plexus becomes progressively denser by 3 to 5 years. The course and termination of these axons clearly identifies them as thalamocortical afferents, and thus as axons that carry input from the lower levels of the auditory system. The developmental course of this system of axons indicates that cortical processing of auditory information conveyed from the ear and brain stem begins between 4.5 months and 1 year of age. The increasing axonal density up to at least 5 years of age implies that maturation of this system continues through the early childhood years.

The idea that these deep axons relay auditory information to the cortex is supported by the behavioral transition in speech sound discrimination that occurs in the second half of the first year of life. Although infants between birth and 4 months of age discriminate speech sounds equally well in their environmental language and one to which they are not exposed,[21] at 6 months of age infants begin to differentially discriminate prototype and variant versions of native and non-native speech sounds.[22] Between 6 and 9 months of age, infants begin to listen significantly longer to monosyllables that have a high probability of occurrence in their ambient language[23] and to words that have the stress pattern of that language.[24,25] At the same time, there is reduced discrimination of sounds of a foreign language. American infants at 6 to 8 months respond to differences in Hindi speech sounds, but show little response to the same contrasts at 10 to 12 months.[26] Similarly, Japanese infants distinguish the consonants /r/ and /l/ at 6 to 8 months of age, but not at 10 to 12 months.[27] In another study, evoked responses showed a similar transition, in that between 6 and 12 months of age the amplitude of the mismatch negativity increased to contrasts in native (Finnish) phonemes, but decreased to contrasts between non-native (Estonian) phonemes.[28] It seems likely that the shift to a stronger focus on sounds of the environmental language that occurs in infants between 6 and 12 months of age is a reflection of maturation in thalamocortical afferents and an incipient participation of the deeper cortical layers in the process of auditory perception. Overall, the time of development of this deep axonal system, from 6 months to 5 years, coincides with the onset and development of perceptual language.

LATE CHILDHOOD

At 5 years of age, neurofilament expression is still confined to the deeper cortical layers. After 5 years of age, mature axons begin to appear in cortical layers 2 and 3, and by 11 to 12 years of age their density is equivalent to that of young adults (Fig 1). These axons represent corticocortical connections, such as commissural axons, which interconnect the cerebral hemispheres and allow the two halves of the brain to work together. They also include association fibers, which interconnect different areas of cortex within the same hemisphere. These intrahemispheric and interhemispheric axons form the morphological basis for greater complexity in cortical processing of auditory input.

Studies of auditory perceptual skills during late childhood support the notion of increasing complexity in cortical information processing. Studies of perception of sound in noise[29] and speech in noise[30,31] indicate that this ability improves steadily across late childhood and the teen years. In addition, the performance of children in perception of speech distorted by binaural switching, interruption, filtering, or spectral degradation improves markedly between 4 to 5 years and 11 to 12 years.[32-34] Thus, the time course of maturation of perception of masked and degraded auditory stimuli, which makes greater demands on intracortical processing, matures in parallel with the superficial layers and the corticocortical connections they generate. These intrinsic cortical connections should mediate the improvement in perceptual skills that occurs between 5 and 12 years of age, and their development represents the final stage in the maturation of the human auditory cortex.

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