Listening to Mom: How the Early Auditory Experience Sculpts the Auditory Cortex of the Brain

Patrick O. Kanold

Introduction

Our ability to understand a language is shaped by how we experience speech as a child. However, when auditory experience is important and how auditory experience acts on the different parts of the brain have been unresolved. In particular, our experience with sounds starts before we are born, and many expecting parents wonder if early exposure to music or other stimuli can influence their developing child. Underlying our ability to hear is the precise wiring or circuitry between neurons in the brain. Auditory processing involves many interconnected structures, including the most complex auditory part of the brain, the auditory cortex. This is the region of the brain that is essential for the processing of complex sounds such as speech and music (Wang, 2018). Results from animal studies have started to reveal the influence of early sound exposure on circuits in the auditory cortex (Meng et al., 2021). These studies indicate that early sound experience, which in humans occurs in the womb starting around midgestation, already has the potential to shape auditory cortical circuits.

Thus, early sound experience or lack of sound experience, for example, in deafness, can potentially impact the brain before birth. Moreover, early insults to the developing brain (e.g., due to injury or exposure to drugs) might interfere with the early wiring processes, resulting in altered development. Moreover, these considerations are relevant for the care of prematurely born infants who are suddenly exposed to a different auditory environment in the neonatal intensive care unit (NICU).

Effects of the Auditory Experience

To show how early experience can shape hearing, I trace the steps occurring in the early development of the auditory system and the influences of an early sensory experience on circuits in the auditory cortex. Hearing, or audition, is central to our ability to communicate. Underlying the ability to identify and distinguish sounds, such as phonemes in languages or the identity of speakers, is the precise wiring between neurons in the auditory system. Hearing is shaped by the experience with sounds, and the effect of this experience is the largest in early childhood. This is illustrated by the ease with which a second language can be learned in childhood versus in adulthood as those of us who learned a second or third language have experienced. Therefore, early exposure to the sounds of a particular language is crucial for perceiving subtle differences between words in that language. From this, it seems to follow that an enhanced auditory experience might be beneficial to the brain. Indeed, playing music or speaking during pregnancy has been popular; however, benefits of such enrichment are unknown. The critical questions to ask are when does the effect of sound experience start and which neurons and which brain circuits are influenced by the experience of sound?

Auditory processing in humans starts in utero, but the effects of fetal sound experience has long been debated. Many parents wonder if playing music or singing to their unborn child will enhance brain function. A variety of studies suggest that a sound experience shapes the fetal brain because fetuses or premature infants can distinguish speech sounds from nonspeech sounds and respond to maternal voices before term (40 gestational weeks [GWs]). For example, 35-GW-old fetuses have been shown to discriminate language (Minai et al., 2017) and newborns have a preference for the voice of their mother (DeCasper and Fifer, 1980) but not the father

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(DeCasper and Prescott, 1984). Newborns also have cry melodies reminiscent of their maternal language (Mampe et al., 2009).

Because of their specificity, for example, of the maternal language, all of these abilities are not likely to be hardwired by genetic programs. Consequently, these experiments point to a fundamental effect of the fetus being exposed to the mother's voice and suggest that complex auditory processing is possible in humans before term birth. Moreover, the selectivity of the responses to the maternal voices indicate that a significant amount of circuit plasticity has occurred in the auditory pathway before birth to create neuronal circuits that allow the developing brain to distinguish the mother's voice from other voices. What has been unclear, however, is how such early sound exposure shapes the auditory pathway and which neurons and circuits are being influenced.

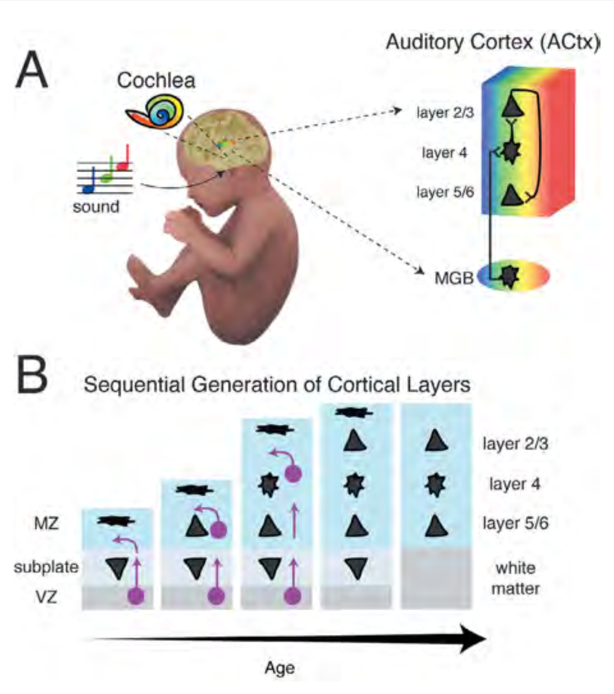
Functional Organization of the Auditory System

The auditory system is organized in a hierarchical manner starting from the conversion of sound into neural impulses in the ear up to the complex analysis or the evoked neuronal activity patterns in central brain structures. Sound is transmitted through the ear canal and middle ear and then enters the inner ear, the cochlea, where it is converted into neural activity. Sound-evoked neural activity then propagates through a series of different brainstem and midbrain structures before reaching the auditory thalamus (medial geniculate body [MGB]) and finally the auditory cortex (ACtx; **Figure 1A**) (Budinger and Kanold, 2018). The ACtx is a key sound-processing region for many higher order processes such as the processing of complex stimuli like speech and music (Wang, 2018). The ACtx itself is composed of six layers of morphologically different neurons that are highly interconnected and are thought to perform the hierarchical processing of sounds (Budinger and Kanold, 2018).

One of the hallmarks of the functional organization of sensory cortices in the adult is the orderly organization of neurons responding to sensory features such as sound frequency across the cortical surface in that they form "maps" of the sensory space (Kaas, 2000). In the auditory system, cells respond selectively to a particular sound frequency and the orderly organization means that neighboring cells share frequency selectivity and that there is an orderly progression of frequency preference across the cortex (Schreiner and Winer, 2007).

Thus cells preferring low-frequency sounds (**Figure 1A**, *blue*) are located at one end of the ACtx, whereas cells that prefer high-frequency sounds (**Figure 1A**, *red*) are located at the other end of the ACtx, with cells that prefer midfrequency sounds (**Figure 1A**, *green*) in-between. The resulting map of sound frequency is called a "tonotopic map," and the orderly organization is thought to be important for normal brain function (Kaas, 1997). The tonotopic organization of the auditory system originates in the cochlea and requires precisely ordered projections

Figure 1. ***A:*** *hierarchical processing of sound from cochlea to auditory cortex (ACtx). The cochlea transduces sounds into neural impulses that are relayed to the auditory cortex via brainstem nuclei and the auditory thalamus (medial geniculate body [MGB]). Different parts of the cochlea respond selectively to different sound frequencies (**colors**). The orderly frequency map is preserved up to the ACtx. The ACtx contains different interconnected layers. Inputs to the ACtx from the MGB arrive in layer 4.* ***B:*** *sequential generation of cortical layers. Subplate neurons and cells in the marginal zone (MZ) are born before the permanent cortical layers. Newborn neurons in the ventricular zone (VZ; **purple**) migrate radially to their target layer and differentiate.*



between the different processing stages (Hackett et al., 2011). For example, cells in the low-frequency region of the MGB (**Figure 1A**, *blue*) project to one end of the ACtx (**Figure 1A**, *blue*) while cells in the high-frequency region of the MGB (**Figure 1A**, *red*) project to the other end of the ACtx (**Figure 1A**, *red*).

The Development of "Hearing"

The development of the auditory system, and especially the ACtx, is a protracted process starting prenatally. Extensive work in animals has shown that the developmental process requires a complex interplay of genetic programs, spontaneous and sensory-driven neural activity; so both "nature" and "nurture" are heavily involved (Goodrich and Kanold, 2020).

The general sequence of processing stages between the ear and the ACtx is also present in development (Goodrich and Kanold, 2020), with one important exception. In early development, there is an additional specialized population of neurons, subplate neurons, that are present in the ACtx in early development before the MGB is connected to the ACtx (**Figure 1B**). These subplate neurons form early relay circuits connecting the MGB with the input layer of the ACtx (layer 4) and form a specialized developmental structure that provides a functional scaffold for the permanent wiring of the cortex. This review focuses on these specialized circuits, the events that can shape their function, and ways by which these circuits can influence later ACtx function.

In humans, physiological or neural responses to sound emerge around the end of the second trimester. A fundamental concept to define is the onset of hearing. Hearing has both sensory-processing and cognitive components because attention-based mechanisms can amplify or suppress sound-evoked responses, such as when ignoring background noises or attending to a particular instrument in an orchestra. For the purposes of this review, hearing means the onset of auditory processing and does not cover the cognitive aspects.

Auditory-processing development starts with the maturation of the cochlea and requires the neural transmission of sound-evoked neural activity to the brainstem and more central structures such as the ACtx. External sounds can be transmitted to the fetus but are attenuated by the womb, whereas sounds generated by the mother can be enhanced by conduction from the larynx to the body (Richards et al., 1992). Accordingly, the fetal environment is rich in potential auditory stimuli. Fetal movements in response to externally generated low-sound frequencies can be detected midgestation, at about the 19th GW, whereas responses to higher frequencies emerge later (Hepper and Shahidullah, 1994). Consequently, it can be reasoned that the human inner ear and, at least, the brainstem circuits must be functional at these ages, albeit likely not mature.

The more detailed development of auditory processing has been studied in animal models such as mice and ferrets that are born in a more immature state (altricial). Much of the development that happens in the womb in humans happens after birth in altricial animals. Furthermore, altricial animals undergo a major transition in their hearing in that they are born with closed ear canals that attenuate sounds and that open postnatally. Moreover, a major difference between altricial animals and humans is that the early sound environment in humans will be dominated by maternal sounds, whereas maternal sounds will be attenuated in altricial animals.

Indeed, although ear opening in altricial animals is sometimes called the "onset of hearing," data from multiple altricial species such as ferrets (Wess et al., 2017) and mice (Meng et al., 2020) show that auditory responses are present even at the level of ACtx at time periods when the ears are closed. Although sound-evoked responses can be recorded, it should be emphasized that these responses are not mature, and therefore neurons in young animals do encode sensory stimuli as robustly as the adult does. Together, these studies give us rough estimates of when peripheral sounds drive neural activity in the auditory system, but due to experimental limitations, it is possible that even earlier responses exist.

Formation of the Auditory Cortex and Its Connections

The ACtx consists of six layers of neurons that are distinguished by differences in neuronal cell shape and connectivity (**Figure 1A**) (Budinger and Kanold, 2018). The major group of cortical neurons, excitatory neurons, are generated in the bottom of the cortex, and with each round of cell generation, a different layer is built (**Figure 1B**). Newborn neurons will move past older mature neurons and stack on top of each other; therefore, the cortex is built from the bottom up.

Subplate neurons are the earliest born cortical excitatory neurons and reside at the bottom of the cortex (Kostovic and Rakic, 1980). Moreover, subplate neurons, in contrast to other cortical neurons, mostly disappear during development (Luskin and Shatz, 1985) and form a transient population of deep neurons.

There is also another group of early-generated transient neurons on the outer margin of the cortex; hence, although the adult cortex contains six layers, the developing cortex contains additional largely transient neuronal layers at its deeper and outer margins (Molnár et al., 2020). The sequential generation of neurons is important for understanding the varying effects of developmental insults and injuries. Insults at younger ages will most directly affect early-born deep neurons, whereas insults at later ages will influence both superficial and deep neurons. This means that because deep and superficial neurons perform different functions, the same insults at different times can have distinct functional consequences.

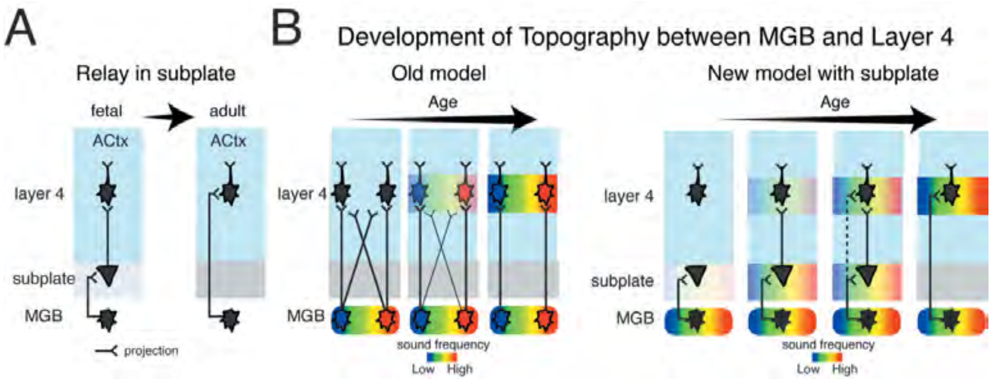
Subplate Neurons Are the First Cortical Cells to Respond to Sounds and the Substrate of Early Topography

Neurons grow projections, called axons, and communicate via specialized structures called synapses, thereby forming neural circuits. The earliest generated transient neuronal layers are also the site of the early establishment of cortical synapses (Kostovic and Molliver, 1974). In adults, the input layer of the ACtx, layer 4, receives direct synaptic inputs from the MGB (**Figure 2A**) (Budinger and Kanold, 2018). This direct pathway is crucial for transmitting sound-evoked activity from the inner ear to the ACtx and thus is essential for auditory processing. In early development, this direct connection does not exist. Instead, MGB neurons first form synapses with subplate neurons (Kanold and Luhmann, 2010), and MGB axons remain constricted to the subplate for a period before growing to their eventual target in layer 4. Consistent with the early MGB inputs to the subplate, recordings in young animals have shown that subplate neurons respond to sound before ACtx layer 4 neurons (Wess et al., 2017).

During this time period, subplate neurons themselves project to the ACtx layer 4 (Zhao et al., 2009); thus subplate neurons form an essential relay for sound information to reach layer 4 and beyond (**Figure 2A**) (Wess et al., 2017). The direct transmission between the MGB and the ACtx layer 4 and thus the adult-like pattern emerge after ear opening (Barkat et al., 2011) and subplate neurons disappear during subsequent development (Kanold and Luhmann, 2010). These results also suggest that the early sound-evoked responses detected in human babies are due to subplate activation.

Although the ACtx contains the tonotopic map in adults, in early development, there is no map (**Figures 1A** and **2B**).

Figure 2. ***A:*** *subplate neurons relay ascending MGB activity to layer 4 in development, whereas in adults, the MGB directly activates layer 4.* ***B:*** *model of topographic mapping of frequency preference (**colors**) by ordered projections from the MGB to ACtx layer 4.* ***Left:*** *old model suggests that the adult pattern emerges from initially unordered and unrefined projections to layer 4.* ***Right:*** *new model suggests that topographic organization emerges first by projections to the subplate and later in layer 4.* ***Dashed line****, maturing connection.*



Classic experiments in the visual system have shown that topographic order emerges during development because of a refinement process of the thalamic projections to cortical layer 4 (LeVay et al., 1978). The development from the MGB to layer 4 of the ACtx is also thought to undergo such refinement (**Figure 2B**, *left*) (Razak et al., 2009). However, recordings in young animals showed a topographic organization of sound-evoked responses in the subplate at ages before layer 4 neurons responded to sound (Wess et al., 2017). Thus, topographic maps emerge in the subplate and not in layer 4 and also earlier than previously appreciated (Wess et al., 2017).

These observations suggested a new model of the development of cortical topographic maps; maps might be established in the subplate and these maps might later be transferred into layer 4 by the projections from the subplate to layer 4 (**Figure 2B**, *right*). Although the development of MGB projections to the subplate and then to layer 4 is sequential, this sequential nature is not a general rule across the auditory-processing hierarchy. Hence, one can speculate that the initial period when MGB fibers are present in the subplate serves a particular developmental purpose, namely, developing a functional scaffold aiding the development of cortical organization. In this model, building an initial sketch, or scaffold, of the topographic map in parallel with the generation of the cortical layers could enable faster development of sensory cortical function than serial layer generation and map development.

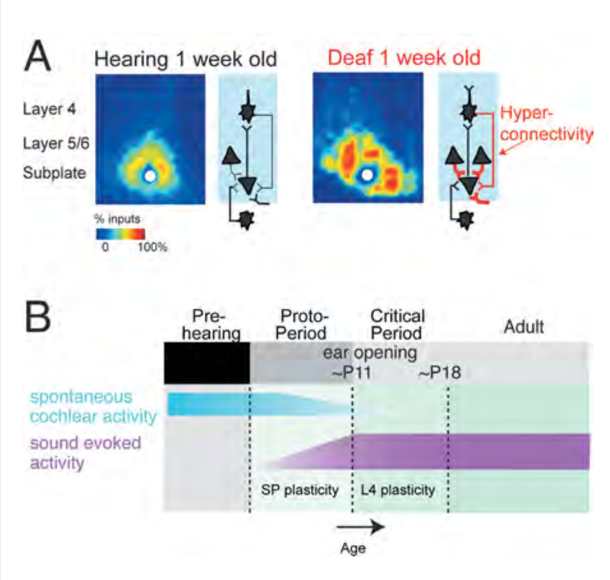
The Role of Neural Activity and Early Sensory Experience on Cortical Development

Neural activity plays a big role in shaping brain circuits. However, the origin of this activity and its nature change during development. At the earliest stages of development, a large part of the neural activity observed in the brain appears to be overtly "spontaneous," meaning not occurring in response to an external sensory stimulus (Khazipov and Luhmann, 2006). Later in development, neural activity driven by sensory stimuli such as sounds becomes dominant. One important source of early spontaneous activity is the cochlea (Tritsch et al., 2007), which produces spontaneous activity before the onset of sensory transduction and ear opening, although it wanes after ear opening. Work in developing rodents has shown that cochlea-generated spontaneous activity propagates all the way to the ACtx (Babola et al., 2018). The peripheral generated spontaneous activity patterns can be thought of as test patterns that prime the downstream circuits for the onset of the sensory experience and play a key role in sculpting nascent circuits before the onset of sensory functions.

The effects of the sensory experience during the periods where peripheral spontaneous activity is present have only recently been started to be studied. This is because it had been assumed that animals did not hear before ear opening. But because the ACtx can show sound-evoked responses before the ears open (Wess et al., 2017); this indicated the potential for an effect of the sound experience on ACtx circuits.

Subplate neurons also receive inputs from the developing cortical neurons (Viswanathan et al., 2012). The topology of these circuits can be studied in rodent brain slice preparations (**Figure 3A**) and allows for the study of circuit changes after manipulations. Studies in genetically deaf mice, for example, such as those deficient in mechanotransduction (Meng et al., 2021) or synaptic function (Mukherjee et al., 2021), revealed that their subplate neurons receive inputs

Figure 3. ***A:*** *subplate neurons receive intracortical inputs, and early deafness leads to hyperconnectivity of subplate neurons. Images show the density of inputs from each cortical location to subplate in mice. In deaf mice, connections to subplate neurons arise from more neurons. Adapted from Meng et al. (2021).* ***B:*** *the 3 phases of early auditory development.* ***Gray****, stages of hearing. SP, subplate; P11 and P18, postnatal days 11 and 18, respectively.*



from more cortical neurons (called hyperconnectivity), even when examined before ear opening. This suggests that the lack of sound inputs even before ear opening had caused circuit changes (**Figure 3A**).

Conversely, raising mice with background sounds before ear opening showed that the presence of sounds even before ear opening reduces connections to the subplate neurons (Meng et al., 2021). These bidirectional changes indicate that even though sound transmission and neural processing is immature at early ages, the auditory environment can already shape auditory cortical circuits. These experiments suggest that a lack of sound input leads to a compensatory increase in connections to subplate neurons and thereby can potentially alter subsequent developmental processes. Importantly, these experiments show that manipulating the sound experience before the onset of the "classic" critical period, which starts at the ear opening period, can alter the development of ACtx circuits (Meng et al., 2021).

The effects of the sound experience at the next stage of development, such as after ear opening, have been well studied, especially on circuits in layer 4 and beyond. This period starts when MGB fibers contact layer 4 neurons; sensory-evoked neural activity during this later stage of development when the eyes and ears function is pivotal for shaping and fine-tuning brain circuits. Hence, it has been called the "critical period" but might be better labeled as the "L4 critical period." Sound exposures during this time, for example, raising rodents in the presence of noise or tones from just before ear opening (in mice around postanal day 11 [P11]), resulted in altered frequency selectivity of ACtx neurons and abolished (Zhang et al., 2002) or altered (Zhang et al., 2001) tonotopic maps in the ACtx. All these sound exposures were effective during a period lasting less than a week following ear opening and therefore show that there is a limited period when L4 circuits seem to be malleable.

These results force us to rethink the early developmental period during which MGB axons are present in the subplate (Kostovic and Rakic, 1990) and when the cochlea is able to transduce sounds. This period is likely highly dynamic in that it involves circuit refinement and emergence of topographic maps (**Figures 2C** and **3B**). Thus, this period represents a "proto-organizational period" in which an outline of cortical organization develops. Accordingly, we can divide the early developmental process into three distinct phases (**Figure 3B**).

(1) *Prehearing Period:* No sensory evoked activity is present. Only spontaneous activity is present.
(2) *Proto-Organizational Period:* Sound-evoked activity is present and can drive plasticity in the subplate. Because of closed ear canals, sound thresholds are high. Peripheral spontaneous activity is also present but decreasing. Layer 4 is not directly activated by MGB.
(3) *Normal-Hearing Period:* Sound-evoked activity is present. The MGB directly activates layer 4 and sound manipulations can cause layer 4 plasticity. The beginning of this period marks the classic critical period. Because of open ear canals, sound thresholds are low.

Clinical Implications of Early Sensory Effects on Cortical Circuits

Congenital hearing loss is a relatively common condition found in 1 in about 1,000 newborns and is of diverse origin (Chen and Oghalai, 2016). Long-term deafness results in large-scale and fine-scale changes in the ACtx and beyond. For example, adult congenitally deaf cats have a decreased cortical thickness in different auditory cortical regions (Berger et al., 2017), suggesting the atrophy of neurons and/or connections. Similarly, widespread changes in large-scale brain structure are also seen in humans with hearing loss (Manno et al., 2021). However, we now know that deafness already results in brain changes at the younger ages (likely even before birth); thus the adult phenotype might be due to cascading and compounding changes throughout the development of cortical circuits.

The early susceptibility of subplate neurons to sound is important in the case of babies in the NICU where they are exposed to an abnormal sound environment. Care must be taken to adjust the ambient sensory environment as to not overactivate or deprive cortical circuits. Moreover, these considerations are important in other contexts because in many prelingually deaf humans, cochlear implants (CIs) are fitted within the first years to restore hearing. The programming of these devices must consider that auditory cortical processing might already have been altered at time of implantation and is changing during the initial period of use.

What Are Subplate Neurons Listening to?

Given that sounds can shape the early established circuits, it seems natural to identify which sounds are likely to influence subplate circuits in both humans and altricial animals. In humans, external sounds will be attenuated and filtered by the womb (Gerhardt et al., 1990) and the mother will be the dominant source of sounds. Sources generated by the mother will include breathing, heartbeat, digestive noises, and vocalizations. A distinguishing feature between these sounds is that the first three are ongoing and have relatively constant spectral content, whereas speech is more rare and variable.

Given that developing synapses show high rates of adaptation and that young neurons do not sustain high firing rates, responses to ongoing stimuli likely adapt quickly. In contrast, natural speech has a varying frequency content, is irregular, and is likely to produce less adaptation. Therefore, it is likely that intermittent speech sounds will cause more subplate activity than background sounds. Similarly, external sounds such as other voices or music can be transmitted to the fetus but will be attenuated and filtered. Thus, rare lower frequency sounds will be most effective in activating subplate neurons (Hepper and Shahidullah, 1994).

In animals, the situation is similar, but because the ear canals are closed, maternal vocalizations are attenuated. Moreover, given that pups are outside the womb, other sources of sound are present. Some major potential sound sources are self-generated vocalizations and vocalizations of conspecifics close by in the nest. Thus, it is intriguing to speculate that self-generated sound stimuli could aid in the development of the auditory system in altricial animals. Such a scenario is not too far-fetched because elegant work in ducklings has shown a role for self-vocalizations in auditory development (Gottlieb, 1971).

These considerations also apply to the auditory environment in the NICU because premature infants are suddenly exposed to a very different auditory environment than they had experienced in the womb. High-frequency sounds are not attenuated outside the womb and can potentially drive neural activity. Therefore, care should be taken to replicate the fetal environment by attenuating such sounds. Furthermore, providing rare, speech-like sounds such as recordings of the mother might be of use.

Damage of Subplate Neurons Might Cause Developmental Abnormalities and Sensory Dysfunctions

Given their key location and early development, it should be of no surprise that damage of the subplate neurons due to exposure to drugs or injury leads to developmental abnormalities, including those associated with sensory-processing deficits. For example, lesioning subplate neurons prevents the topographic and functional maturation in layer 4 (Kanold and Luhmann, 2010) and leads to altered large-scale activity changes in the brain (Tolner et al., 2012), suggesting that the altered brain activity observed in infants could be indicative of subplate damage or lesions. Moreover, neonatal hypoxia-ischemia, which in humans is linked to a variety of neurodevelopmental disorders, leads to subplate hyperconnectivity (Sheikh et al., 2019). Subplate abnormalities are also seen in rodent models of autism spectrum disorder (ASD) (Nagode et al., 2017). Thus, sensory-processing deficits in multiple neurodevelopmental disorders could be the consequence of early subplate damage that prevents the maturation of cortical sensory processing.

Outlook

If and how the early sound experience can shape our auditory system has long been debated. Studies of early development of the auditory cortex in animals have shown that sound-evoked activity is present much earlier than previously assumed and that an early sensory experience can leave a long-lasting trace. It remains to be tested if such early exposure can influence the further development of the cortex and could thereby promote language or musical learning at infant ages.

The considerations discussed draw almost exclusively from nonhuman animal studies. The subplate is expanded and more compartmentalized in primates than in rodents (Molnar and Clowry, 2012), indicating that subplate size might scale with brain complexity. It is an open question if humans contain specialized subplate neurons or if human brains are enriched in certain subplate subpopulations.

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About the Author

Patrick O. Kanold
pkanold@jhu.edu
Department of Biomedical Engineering
Johns Hopkins University School of Medicine
733 N. Broadway Avenue, Miller 379
Baltimore, Maryland 21205, USA

Patrick O. Kanold is currently a professor in the Biomedical Engineering Department, Johns Hopkins University, Baltimore, Maryland. He holds a Diplom-Ingenieur (Dipl.-Ing; MSc) from the Technical University Berlin and a PhD from Johns Hopkins University. His laboratory studies the neural circuits in the developing and adult auditory cortex of animals and how sensory experiences shape these circuits using advanced imaging and physiological methods.