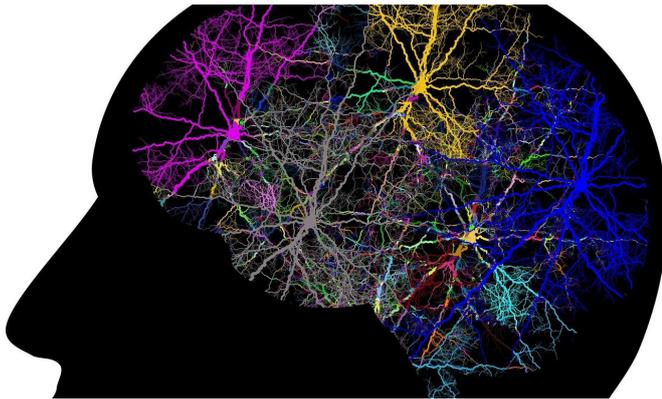


Study suggests sounds influence the developing brain earlier than previously thought

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Scientists have yet to answer the age-old question of whether or how sound shapes the minds of fetuses in the womb, and expectant mothers often wonder about the benefits of such activities as playing music during pregnancy. Now, in experiments in newborn mice, scientists at Johns Hopkins report that sounds appear to change "wiring" patterns in areas of the brain that process sound earlier than scientists assumed and even before the ear canal opens.

The current experiments involve newborn [mice](#), which have ear canals that open 11 days after birth. In human fetuses, the ear canal opens prenatally, at about 20 weeks gestation.

The findings, published online Feb. 12 in *Science Advances*, may eventually help scientists identify ways to detect and intervene in abnormal wiring in the [brain](#) that may cause hearing or other sensory problems.

"As scientists, we are looking for answers to basic questions about how we become who we are,"

says Patrick Kanold, Ph.D., professor of biomedical engineering at The Johns Hopkins University and School of Medicine. "Specifically, I am looking at how our sensory environment shapes us and how early in fetal development this starts happening."

Kanold started his career in [electrical engineering](#), working with microprocessors, a natural conduit for his shift to science and studying the circuitry of the brain.

His research focus is the outermost part of the brain, the [cortex](#), which is responsible for many functions, including sensory perception. Below the cortex is the white brain matter that in adults contains connections between [neurons](#).

In development, the white matter also contains so-called subplate neurons, some of the first to develop in the brain—at about 12 weeks gestation for humans and the second embryonic week in mice. Anatomist Mark Molliver of Johns Hopkins is credited with describing some of the first connections between neurons formed in white matter, and he coined the term subplate neurons in 1973.

These primordial subplate neurons eventually die off during development in mammals, including mice. In humans, this happens shortly before birth through the first few months of life. But before they die off, they make connections between a key gateway in the brain for all sensory information, the thalamus, and the middle layers of the cortex.

"The thalamus is the intermediary of information from the eyes, ears and skin into the cortex," says Kanold. "When things go wrong in the thalamus or its connections with the cortex, neurodevelopmental problems occur." In adults, the neurons in the thalamus stretch out and project

long, armlike structures called axons to the middle layers of the cortex, but in [fetal development](#), subplate neurons sit between the thalamus and cortex, acting as a bridge. At the end of the axons is a nexus for communication between neurons called synapses. Working in ferrets and mice, Kanold previously mapped the circuitry of subplate neurons. Kanold also previously found that subplate neurons can receive [electrical signals](#) related to sound before any other cortical neurons did.

The current research, which Kanold began at his previous position at the University of Maryland, addresses two questions, he says: When sound signals get to the subplate neurons, does anything happen, and can a change in sound signals change the brain circuits at these young ages?

First, the scientists used genetically engineered mice that lack a protein on hair cells in the inner ear. The protein is integral for transforming sound into an electric pulse that goes to the brain; from there it is translated into our perception of sound. Without the protein, the brain does not get the signal.

In the deaf, 1-week-old mice, the researchers saw about 25% - 30% more connections among subplate neurons and other cortex neurons, compared with 1-week-old mice with normal hearing and raised in a normal environment. This suggests that sounds can change brain circuits at a very young age, says Kanold.

In addition, say the researchers, these changes in neural connections were happening about a week earlier than typically seen. Scientists had previously assumed that sensory experience can only alter cortical circuits after neurons in the thalamus reach out to and activate the middle layers of the cortex, which in mice is around the time when their ear canals open (at around 11 days).

"When neurons are deprived of input, such as sound, the neurons reach out to find other neurons, possibly to compensate for the lack of sound," says Kanold. "This is happening a week earlier than we thought it would, and tells us that the lack of sound likely reorganizes connections in the immature

cortex."

In the same way that lack of sound influences brain connections, the scientists thought it was possible that extra sounds could influence early neuron connections in normal hearing mice, as well.

To test this, the scientists put normal hearing, 2-day-old mouse pups in a quiet enclosure with a speaker that sounds a beep or in a quiet enclosure without a speaker. The scientists found that the mouse pups in the quiet enclosure without the beeping sound had stronger connections between subplate and cortical neurons than in the enclosure with the beeping sound. However, the difference between the mice housed in the beeping and quiet enclosures was not as large as between the deaf mice and ones raised in a normal sound environment.

These mice also had more diversity among the types of neural circuits that developed between the subplate and [cortical neurons](#), compared with normal hearing mouse pups raised in a quiet enclosure with no sound. The [normal hearing](#) mice raised in the quiet enclosure also had neuron connectivity in the subplate and cortex regions similar to that of the genetically-engineered deaf mice.

"In these mice we see that the difference in early sound experience leaves a trace in the brain, and this exposure to sound may be important for neurodevelopment," says Kanold.

The research team is planning additional studies to determine how early exposure to sound impacts the brain later in development. Ultimately, they hope to understand how [sound](#) exposure in the womb may be important in human development and how to account for these circuit changes when fitting cochlear implants in children born deaf. They also plan to study brain signatures of premature infants and develop biomarkers for problems involving miswiring of subplate neurons.

More information: Early peripheral activity alters nascent subplate circuits in the auditory cortex, *Science Advances* (2021). [DOI: 10.1126/sciadv.abc9155](#) ,

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