Researchers learn more about interactions in the cortex

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Professor Paola Arlotta (far right) discusses an image of neurons with graduate student Simona Lodato (right to left), Professor of Neurology Kathleen Quest, and Professor of Molecular and Cellular Biology Tako Hensch. The study's findings could potentially help future researchers to better understand the circumstances that lead to errors in the building and functioning of brain circuitry. Credit: Kris Snibbe/Harvard Staff Photographer

To an untrained observer, the electrical storm that takes place over the brain's neural network seems a chaotic flurry of activity. But as neuroscientists understand it, the millions of neurons are actually engaged in a sort of tightly choreographed dance, a tango of excitatory and inhibitory neurons. How is this precise balance that makes normal function possible achieved during development? And how does it go wrong in diseases like epilepsy when brain activity goes out of control?

Focusing on the cerebral cortex, the part of the brain controlling thought, sensory awareness, and motor function, a group of Harvard Stem Cell Institute (HSCI) researchers in the Department of Stem Cell and Regenerative Biology (SCRB), led by Assistant Professor Paola Arlotta, has discovered that excitatory neurons control the positioning of inhibitory neurons in a process that is critically important for generating balanced circuitry and proper cortical response.

Professor Takao Hensch, a collaborator on the study in the Harvard Center for Brain Science, Department of Molecular & Cellular Biology (MCB), had previously shown that the maturation of this circuit balance triggers critical periods of brain development. Certain inhibitory cells appear particularly vulnerable to genetic or environmental factors in early life, contributing to mental illness, such as schizophrenia or autism spectrum disorders.

The findings were published today (Feb. 23) in the journal Neuron. The work shows that “in the cortex, different types of excitatory neurons communicate specifically with only specific types of inhibitory interneurons, guiding them to integrate properly into functional circuitry,” said Simona Lodato, a graduate student in the Arlotta lab and the first author of the study.

In a normal cerebral cortex, inhibitory interneurons prevent excitatory-projection neurons from constantly discharging, the researchers said. Every subtype of excitatory neuron is controlled by its own interneurons, and the two types of cells are arranged together. Complicating the task, however, is the fact that excitatory-projection neurons and inhibitory interneurons are born in different areas of the brain, and must migrate great distances to finally come together within the cortex, a feat now understood to require the guidance of projection neurons.

By eliminating a transcription factor called Fezf2, which controls the

proper development of a defined population of excitatory neurons of the cortex, the researchers were able to study neuronal development in the absence of one class of excitatory neurons. They then observed that the generation of inhibitory interneurons was unaffected, but lacked guidance on how to be sorted in the cortex, and were found to have settled in incorrect locations, unable to contribute to proper electrical brain activity. Hensch and colleagues then functionally confirmed an aberrant spread of activity, which may explain the propensity for seizures that Arlotta observed in these mice.

Intriguingly, in complementary experiments when projection neurons were generated outside the cortex, they were able to attract interneurons of the right type and build a separate micro-network. The two results demonstrate the extent to which the excitatory-projection neurons contribute to the development of neuronal circuitries in this part of the brain. They also shed light on the existence of a developmental “code” that matches neurons of the right type to guarantee normal activity, the scientists found.

Arlotta said her team now plans to test the universality of the new findings by investigating whether excitatory neurons also organize the local inhibitory network in other parts of the nervous system. Additionally, the researchers hope to come to determine the actual mechanisms allowing projection neurons to guide their corresponding interneurons. Given that cell-to-cell interactions typically rely on the expression of complementary sets of molecules by the cells involved, the scientists said it is possible that subtypes of interneurons might express different surface molecules, which enable them to respond differently to projection neurons.

The results of this study shed important light on the intricacies of the developing brain and may help future researchers to better understand the circumstances that lead to errors in the building and functioning of

brain circuitry. Arlotta said she hopes that “understanding the developmental events that regulate the interactions between projection neurons and interneurons in the cerebral cortex will provide further insights into the basic developmental processes that establish local functional circuitry and may inspire tools with which to modulate these circuits in epileptic and psychiatric diseases.”

Provided by Harvard University

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