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Researchers uncover novel mechanism that balances the sizes of functional areas in the brain

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In the cerebral cortex, the brain's powerful central processing unit responsible for higher functions, specialized subdivisions known as areas are laid out like a map, but little is known about the genetic forces that shape the geography of our brains.

In this week's advance online edition of *Nature Neuroscience*, an international collaboration between researchers at the Salk Institute for Biological Studies and the Telethon Institute of Genetics and Medicine in Italy reports the discovery of a novel function for a factor that negotiates the borders between areas and balances their sizes and positions relative to each other.

The factor, COUP-TF1, ensures that the frontal areas don't claim too much cortical real estate. Without COUP-TF1 keeping the frontal areas in check, they undergo massive expansion squeezing and pushing neighboring sensory areas literally to the back of the brain.

The findings show how the cortex is properly parceled into "frontal" areas that control higher functions related to emotions and the movements of our bodies versus areas that interpret our sensory environment and allow us to see, hear and feel. Because primary areas in humans differ by two-fold or more in the normal population, these findings may explain these size differences, which appear to account, at least in part, for differences between individuals in behavior and skills.

“Until now, there has been only one other gene, Emx2, that everybody agrees on directly controls area patterning,” explains co-senior author Dennis O’Leary, Ph.D., professor in the Molecular Neurobiology Laboratory at the Salk Institute. “Our current understanding of this process is the proverbial tip of the iceberg. We are only beginning to define the mechanisms that determine the area identity of neurons in the cortex.”

The back of the cortex is predominantly specialized to process vision, whereas the front of the cortex handles motor functions and controls voluntary movement, as well as having a central role in higher cognitive functions. The area right above the ear trades in sounds and speech, while the somatosensory area located in the middle top of the head interprets information about touch and pain.

In previous studies, the O’Leary lab discovered that Emx2, a gene common to mice and men as is COUP-TF1, instructs progenitor cells to develop into visual neurons. “Emx2 is the gold standard for genes that impart area identity to cortical neurons,” says O’Leary. “When we increased the amount of Emx2, the visual area expanded at the expense of the frontal and somatosensory areas and vice versa.”

Just like the Emx2 gene, COUP-TF1 is normally most active in the back of the cortex, with its activity gradually tapering off toward the front. Both genes code for transcription factors — which operate by controlling a cascade of other genes — hinting at a possible role for COUP-TF1 in area patterning as well.

Completely eliminating the gene in lab mice through genetic engineering – a mainstay of scientists trying to figure out the function of a particular gene – did not clarify the roles of COUP-TF1. “Mice without COUP-TF1 have many defects and die a few days after birth before functional areas can be defined,” explains co-first author Shen-Ju Chou, a

postdoctoral researcher in the O'Leary lab.

So O'Leary and his team collaborated with Italian researchers, led by Dr. Michele Studer, who is co-senior author with O'Leary of the study, to develop mice in which COUP-TF1 can be selectively removed from progenitor cells in the cortex just before they start generating cortical neurons. The mice survive to be adults and appear quite normal. Their cortical landscape, however, is a different matter.

"We were surprised by what we saw," Chou says. "The frontal areas took over most of the cortex, while the sensory areas were drastically reduced in size and relegated to a small domain at the back of the brain." The overall size of the cortex stayed the same.

"Our findings imply that Emx2 and COUP-TF1 work in opposing ways," says O'Leary. "While Emx2 works in a positive manner to specify the area identity of visual neurons, the presence of COUP-TF1 prevents progenitor cells from taking on a motor area identity."

Although the mice lacking COUP-TF1 in their cortex do not have any obvious sensory or motor problems, the researchers believe that a closer look will reveal substantial deficits. Their prediction is based on a study published by O'Leary and his colleagues earlier this year. They found that individual areas must be the right size relative to each other or mice will underperform in tests of their skills at the relevant behaviors.

Source: Salk Institute

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