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How our unique brain takes shape during mid-pregnancy

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About four or five months after conception, a burst of synaptic growth begins in the prefrontal cortex (PFC) of the human fetus. And within this tangled mass of connections, the developing brain acquires the

unique properties that make humans capable of abstract thought, language, and complex social interactions.

But what are the molecular ingredients necessary for this flowering of synapses to occur and that lead to such profound changes in the brain? In two papers published Sept. 29 in the journal *Nature*, Yale researchers have identified key changes in gene expression and structure in the developing human brain that makes it unique among all animal species.

These insights could have profound implications for understanding common developmental or brain disorders, researchers say.

"It is surprising and somewhat disappointing that we still don't know what makes the human brain different from the brains of other closely related species," said Nenad Sestan, the Harvey and Kate Cushing Professor of Neuroscience at Yale, professor of comparative medicine, of genetics and of psychiatry, and senior author of both papers. "Knowing this is not just an intellectual curiosity to explain who we are as a species—it may also help us better understand neuropsychiatric disorders such as schizophrenia and autism."

For the studies, Sestan's lab team conducted an extensive analysis of gene expressions that occur in the prefrontal cortexes of humans, macaque monkeys, and mice midway through fetal development and then identified both similarities and differences between the species.

A critical factor in determining both similarities and differences observed in the developing brain of these species, they found, is the concentration of retinoic acid, or RA, a byproduct of Vitamin A. Retinoic acid, which is essential for the development of every organ, is tightly regulated in all animals. Too much or too little RA can lead to developmental abnormalities.

In the first paper, a research team led by Mikihito Shibata and Kartik Pattabiraman, both from Yale School of Medicine, found that RA is increased in the PFC during the second trimester, the most crucial time for formation of neural circuitry and connections. This increase in RA at this stage was also found in mice and macaques.

When researchers blocked RA signals in the prefrontal cortex of mice, the animals failed to develop the specific circuits and connectivity in areas of the brain that in humans are essential for working memory and cognition. In humans, this same pathway is also disrupted during development in patients with schizophrenia and autism spectrum disorders, suggesting these disorders may share similar roots during development.

However, a close examination of the genes which both synthesize and turn off RA in the prefrontal cortex revealed important differences between mice and primates. For instance, in mice the gene CYP26B1 limits activity of RA beyond the animal's tiny prefrontal cortex. However, when researchers blocked this gene in the mice, areas of their brains associated with sensory and motor skills came to resemble synaptic wiring of the prefrontal cortex. This finding further affirms the crucial role played by RA in the expansion of the prefrontal cortex—and in promoting ever greater brain complexity—in humans and other primates.

"RA is the first domino to fall, which sets in motion the complex gene networks which lead to development of brain areas associated with human thought," said Pattabiraman, a clinical fellow in the Yale Child Study Center and co-author of both papers.

Researchers then asked how retinoic acid works this magic.

The development of the human brain is marked by the burst of synaptic

growth during the second trimester. These connections start in the PFC but gradually diminish as they approach sensory and motor neurons towards the rear of the brain.

To better understand why that is, Shibata and Pattabiraman in the second study focused on the gene CBLN2, which is enriched in the PFC and plays a key role in forming these connections. The gene is also directly regulated by RA. They found that CBLN2 is switched on earlier in the front of the developing human brain than in other parts of the brain. Furthermore, they found that the gene is expressed longer and over a wider area of the human brain than in the macaque or mouse, suggesting a central role of the PFC in the emergence of human-specific properties.

The researchers also identified small genomic deletion near the CBLN2 gene which have been conserved in the evolution of human and chimpanzees but not in other animals. To see whether these deletions played a role in growth of PFC connections, they introduced the deletions into the mouse genome. Mice possessing these deletions showed a human-like expansion of CBLN2 and a 30% increase of connections in the adult mouse PFC.

Taken together, the two papers show that the path to understanding the genetic mechanisms underlying advanced cognitive ability starts with the localized production of RA, which then activates various downstream genes, including CBLN2. This dictates where and when these crucial brain connections are formed.

"The prefrontal cortex integrates the information from other parts of the central nervous system and provides top-down control of attention, thought, emotions and actions," Sestan said. "It is also central to dysfunctions in many neuropsychiatric disorders. The subtle changes in the connections that create the human mind may make it sick as well."

More information: Hominini-specific regulation of CBLN2 increases prefrontal spinogenesis, *Nature* (2021). DOI: 10.1038/s41586-021-03952-y , www.nature.com/articles/s41586-021-03952-y

Regulation of prefrontal patterning and connectivity by retinoic acid, *Nature* (2021). DOI: 10.1038/s41586-021-03953-x , www.nature.com/articles/s41586-021-03953-x

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