How Today's Human Brain Became so Uniquely Human

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What unique processes conspire to create a healthy, functional human brain?

How can we be so genetically similar to, say, chimpanzees, and yet be light-years more sophisticated cognitively and behaviorally?

It may just come down to six cells.

Evolutionary biologists who study the human brain and explore questions about why we're so different from other primates are especially interested in the contrasts between humans and chimpanzees.

"We share more than 99% of our DNA with chimpanzees, yet the human and chimpanzee brains are unique. That difference has always been very fascinating to me," said Soojin Yi, PhD, professor in the Department of Ecology, Evolution, and Marine Biology at the University of California, Santa Barbara.

Yi and colleagues recently published findings in the *Proceedings of the National Academy of Sciences* (*PNAS*) that help deepen scientists' understanding about what's behind our brain differences. They've found that "there is more differential gene expression in human brains," said Yi, referring to the activation of different genes within a single brain cell type that defines that cell's purpose.

What's more, she said, "Different brain cells follow different evolutionary paths depending on their unique roles in the brain."

New Findings

While previous studies have suggested that human brain evolution is linked to accelerated changes in gene expression, Yi said many questions still remain. To explore how genes in different types of human brain cells have evolved compared with those of chimpanzees, the researchers used single-cell human and nonhuman primate (chimpanzee and rhesus macaques) transcriptomic data — messenger RNA transcripts present in a specific cell type — to analyze the unique molecular profiles (the gene activity) of six brain cell types.

Yi said many single-cell research approaches had focused primarily on neurons, with relatively small numbers of nonneuronal cells, so their team aimed for a more diverse approach. "To balance the brain cellular heterogeneity and statistical rigor," she said that in addition to looking at excitatory and inhibitory neurons, they also looked at four glial cell types — astrocytes, microglia, oligodendrocytes, and oligodendrocyte precursor cells.

Each of these cell types plays an important role in brain function and health. For example, excitatory neurons transmit signals between brain regions, inhibitory neurons help control brain activity, oligodendrocytes contribute to the formation of the myelin sheath around nerve fibers, and microglia are the brain's immune cells, always on the prowl for pathogens. Star-shaped astrocytes play a variety of roles, including maintaining the blood-brain barrier and supporting neurons.

What They Learned

"Compared to chimpanzee brains, the human brain showed significant signs of accelerated regulatory evolution across all of the six major cell types in the brain," said Yi, explaining that certain genes in human brain cells have evolved to produce more of certain proteins at a faster rate than in other primates. "It's much more extensive than previously believed," she said.

Of the 25,000 genes involved in their analysis, Yi and colleagues were able to identify differences in the expression of about 5%-10% of the genes. When they considered cell subtypes, differences in expression leapt to 12%-15%.

While the researchers expected to see more regulation than what was seen in previous studies, as well as some kind of cell-type specificity, Yi said, "We didn't expect as much cell-type specificity as we saw."

"What was really interesting to me was that when you compared cell types, genes that are differentially expressed in microglia are very different than genes that are differentially expressed in neurons," said Yi.

The findings support the belief held among many other researchers that there is "a tremendous amount of diversity" among even the same types of brain cells in one part of the brain compared with another, Yi said. "You may have the same cell type [such as a neuron], but it looks a little bit different in terms of transcript profiles depending on where it is located in the brain. I think that we cannot look at the brain from just a molecular perspective. We've got to really appreciate that the brain is an amalgam of many different cell types doing their own things while also working together to do these very complex functions that our brains are capable of," said Yi.

The authors pointed out study limitations, including the fact that data from nonhuman primates came from individuals living in captive facilities, which could affect their transcriptional profiles.

Another Perspective

In André Sousa's lab at the University of Wisconsin-Madison, the assistant professor of neuroscience and his colleagues study human brain development and evolution. "We try to understand the mutations that have accumulated in human DNA after our split from our closest lineage — chimpanzees, bonobos, and gorillas — that can alter gene expression," he said.

Sousa, who was not involved in the *PNAS* study, said the new research adds another piece to the puzzle. "I don't think it's an 'aha moment' in the sense that several studies before this had shown this abundance of genes that are more expressed in the human brain. But most of those studies were done at the bulk tissue level. The brain is very heterogeneous, and in bulk tissue studies, you can be diluting lots of signals," he said.

Because the new study analyzed single cells, he said, "they found way more differentially expressed genes than previous studies. And we need to be a little bit careful because it could be a bias from the methodology because when you are analyzing single cells, you increase your statistical power."

Sousa said the results of the study left him pondering the fact that "in general, more genes are more expressed both in chimpanzees and humans than genes that are lower expressed." And that's interesting.

"I've been thinking about it quite a lot. Why do we see more genes going up than down in all of these species? We still don't know very much about what it means. It's hard to understand what's happening because it's very complex. It can have a lot of justifications, both molecularly, what's happening in the DNA, but also evolutionarily, what are the constraints that allow a gene to be more or less expressed?" he said.

Sousa said he also found it interesting that the researchers subdivided certain cell types into subgroups. "Even within subtypes, they saw accelerated evolution in terms of more upregulated genes in humans and chimpanzees than downregulated ones, and what the interesting thing they see is that the genes that are differentially expressed in each cell tend to be different. So they speculate that that probably reflects functional specialization of these cells in these species. It's a potential explanation. But it's impossible to know for sure from this data set and will require more research," said Sousa.

The authors hope to continue studying differential gene expression at the cellular level in both human and primate brains, especially the brain cell subtypes. But Yi said as scientists continue to piece together clues to what makes today's human brain so uniquely human, all animal brain evolution is fascinating. "There are other species with awesome brains that are doing all these special things, too," she said.

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