

Steps in the development of the brain's cellular geography revealed by new studies

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Two new studies of the developing human brain are helping researchers

reconcile a long-held debate over how the brain forms. The research appears Oct. 6 in a special issue of *Nature* highlighting studies that contribute to a cell census, or "parts list," of the brain.

The UC San Francisco papers shed light on how the developing cerebral cortex—the outermost layer of the brain, associated with high-level processing—develops its characteristic map, which is common across human beings and critical to our functioning.

The work also validates a new approach for predicting what kinds of cells early human neurons may become and provides an expansive dataset for researchers working to clarify the links between brain development and psychiatric and neurological illnesses.

"Understanding how the human brain develops—how cells mature and connect across regions—remains a huge problem," says Arnold Kriegstein, MD, Ph.D., a professor of Neurology and member of the UCSF Weill Institute for Neurosciences and former director for the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research. "Today there is a global effort to use new technology to understand the developing brain at a molecular and cellular level in a way that's never been possible before."

A special kind of map

The brain's intricate topography sets it apart from other organs in the body. In the kidney or liver, removing a chunk will likely have similar effects whether it's from the organ's top or the bottom. But in the brain, damage can have wildly different consequences depending on the location. Brain damage toward the back of the skull will likely impact vision, for example, whereas damage on the side might cause problems moving or sensing touch. While neuroscientists know this map and its importance well, they've long debated just how it comes to be.

For years researchers have wondered whether the early tissue of the brain might hold a pre-set map that simply gets transferred to the cortex as it develops—an idea dubbed the protomap hypothesis. Others favored the competing protocortex hypothesis, which supposes that all early neurons have the potential to become any part of the brain and that it's their ongoing interactions with each other that helps each neuron figure out its ultimate destination within the growing brain map.

"Our new findings say it's a little bit of both," Kriegstein said.

Applying cutting-edge methodology, Kriegstein and his team analyzed the genetic expression profiles of hundreds of thousands of developing brain cells. They found that cells in the prefrontal cortex, an area in the front of the brain associated with cognition, and V1, a back-of-the-brain region important for vision, expressed genes linked to their respective regions at a very early stage. Developing cells between the two brain poles, however, took much longer to begin showing gene expression patterns that destined them to specific locations.

"What we see is that early on there are just two basic areas of the cerebral cortex that differ clearly—the front and the back," says Kriegstein. "But later on, the areas in between start to become subdivided, possibly as ongoing interactions influence cellular identities in those areas."

In other words, the unfolding organization of the [cerebral cortex](#) seems to kick off with a pre-determined protomap that establishes the brain's poles, but quickly switch to a protocortex model as cells in the middle help direct each other's identities.

Predicting identity earlier

In a parallel study, UCSF researchers took an additional step towards

understanding brain development in more detail by establishing a new method for predicting the eventual fate of early neural cells. Instead of identifying individual cells by looking at gene expression in the form of mRNA transcripts—molecular work-orders that tell cellular machinery which proteins to build—the researchers wondered if cell identity could be determined by looking at the structure of the genetic material itself. By turning their sights on chromatin—the mess of DNA strands and proteins uniquely packaged in each cell, they found that the fate of a cell's lineage could be predicted even before the stage when it could be called a neuron. That means the chromatin state may reveal key information about developing cells that cannot be captured in gene expression alone.

That may be because mRNA is short-lived within the cell, the researchers say, as it functions to simply deliver instructions from one part of the cell to another. But the structure created by how DNA is wound around various proteins—the cell's "chromatin state"—is more stable and directly determines which instructions are sent out. Pieces of DNA that are tightly wrapped around proteins have their genes tucked away—closed for business, so to speak—while genes poking out away from proteins are open. Thus, it makes sense that examining the chromatin's state can tell researchers a good deal about what's going on inside a cell.

A resource for all

The work of Kriegstein and colleagues goes far beyond the questions asked in their current studies, however. In mapping gene expression and chromatin states across the developing brain, the team has created a unique database—freely available [here](#)—where scientists can scrutinize the behavior of genes they already know to be implicated with disease. Scientists know that conditions from Parkinson's to schizophrenia to neurodevelopmental disorders seem to involve very specific cell types or

very specific time points during the brain's life. But scientists know little about how or when neural cells run into trouble and whether anything might be done to protect them.

"The location and the identities of the [cells](#) have a lot to do with whether they're vulnerable to specific diseases," Kriegstein says. "Our dataset is very rich in the expression of genes that other people have already identified as being associated with quite a range of diseases. It could give us an idea of where and when some of these diseases begin to emerge."

More information: Bhaduri, A., Sandoval-Espinosa, C., Otero-Garcia, M. et al. An atlas of cortical arealization identifies dynamic molecular signatures. *Nature* 598, 200–204 (2021).
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