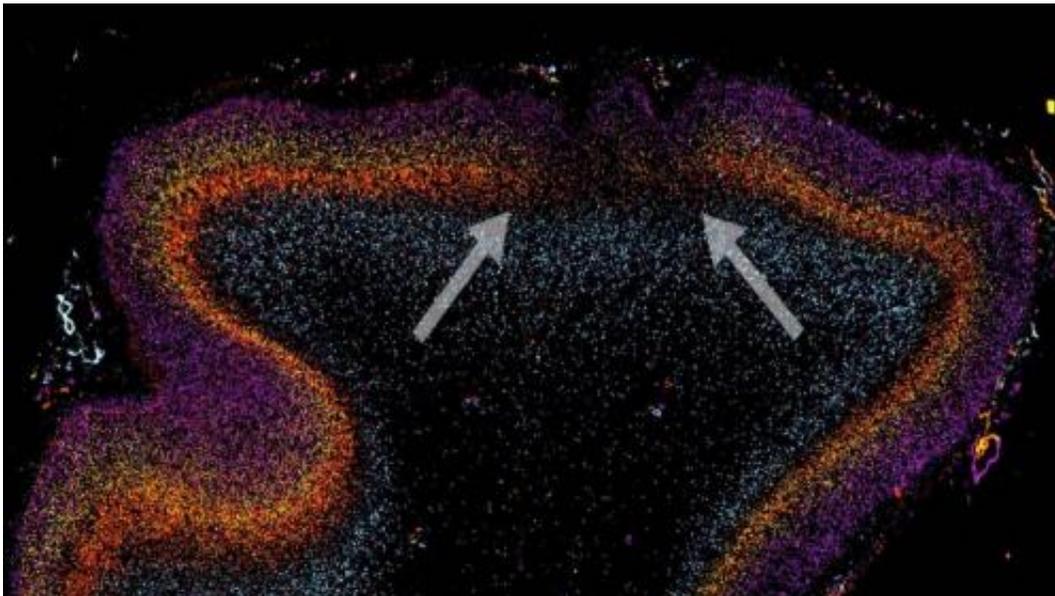


# Patches of cortical layers disrupted during early brain development in autism

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Postmortem analysis of autistic brain tissue revealed patch-like areas of disorganized neurons. Arrows show a patch of decreased or absent expression of genetic markers across multiple layers of the dorsolateral prefrontal cortex. Credit: Rich Stoner, Ph.D., University of California, San Diego

Researchers at the University of California, San Diego School of Medicine and the Allen Institute for Brain Science have published a study that gives clear and direct new evidence that autism begins during pregnancy.

The study will be published in the March 27 online edition of the *New*

*England Journal of Medicine.*

The researchers – Eric Courchesne, PhD, professor of neurosciences and director of the Autism Center of Excellence at UC San Diego, Ed S. Lein, PhD, of the Allen Institute for Brain Science in Seattle, and first author Rich Stoner, PhD, of the UC San Diego Autism Center of Excellence – analyzed 25 genes in post-mortem brain tissue of children with and without [autism](#). These included genes that serve as biomarkers for brain cell types in different layers of the cortex, genes implicated in autism and several control genes.

"Building a baby's brain during pregnancy involves creating a cortex that contains six layers," Courchesne said. "We discovered focal patches of disrupted development of these cortical layers in the majority of children with autism." Stoner created the first three-dimensional model visualizing brain locations where patches of cortex had failed to develop the normal cell-layering pattern.

"The most surprising finding was the similar early developmental pathology across nearly all of the autistic brains, especially given the diversity of symptoms in patients with autism, as well as the extremely complex genetics behind the disorder," explained Lein.

During early brain development, each cortical layer develops its own specific types of [brain cells](#), each with specific patterns of brain connectivity that perform unique and important roles in processing information. As a brain cell develops into a specific type in a specific layer with specific connections, it acquires a distinct genetic signature or "marker" that can be observed.

The study found that in the brains of children with autism, key genetic markers were absent in brain cells in multiple layers. "This defect," Courchesne said, "indicates that the crucial early developmental step of

creating six distinct layers with specific types of brain cells – something that begins in prenatal life – had been disrupted."

Equally important, said the scientists, these early developmental defects were present in focal patches of cortex, suggesting the defect is not uniform throughout the cortex. The brain regions most affected by focal patches of absent gene markers were the frontal and the [temporal cortex](#), possibly illuminating why different functional systems are impacted across individuals with the disorder.

The [frontal cortex](#) is associated with higher-order brain function, such as complex communication and comprehension of social cues. The temporal cortex is associated with language. The disruptions of frontal and temporal cortical layers seen in the study may underlie symptoms most often displayed in autistic spectrum disorders. The visual cortex – an area of the brain associated with perception that tends to be spared in autism – displayed no abnormalities.

"The fact that we were able to find these patches is remarkable, given that the cortex is roughly the size of the surface of a basketball, and we only examined pieces of tissue the size of a pencil eraser," said Lein. "This suggests that these abnormalities are quite pervasive across the surface of the cortex."

Data collected for the Allen Brain Atlas, as well as the BrainSpan Atlas of the Developing Human Brain was developed by a consortium of partners and funded by the National Institute of Mental Health. It allowed scientists to identify specific genes in the developing human brain that could be used as biomarkers for the different layer cell types.

Researching the origins of autism is challenging because it typically relies upon studying adult brains and attempting to extrapolate backwards. "In this case," Lein noted, "we were able to study autistic and

control cases at a young age, giving us a unique insight into how autism presents in the developing brain."

"The finding that these defects occur in patches rather than across the entirety of [cortex](#) gives hope as well as insight about the nature of autism," added Courchesne.

According to the scientists, such patchy defects, as opposed to uniform cortical pathology, may help explain why many toddlers with autism show clinical improvement with early treatment and over time. The findings support the idea that in children with autism the [brain](#) can sometimes rewire connections to circumvent early focal defects, raising hope that understanding these patches may eventually open new avenues to explore how that improvement occurs.

**More information:** Patches of disorganization in the neocortex of children with autism. Stoner R, Chow ML, Boyle MP, Sunkin SM, Mouton PR, Roy S, Wynshaw-Boris A, Colamarino SA, Lein ES, Courchesne E. *NEJM*, March 27, 2014.

Provided by University of California - San Diego

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