

A*STAR study links autism diversity to spatial changes in developing brain

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Researchers used brain organoids, single-cell mapping and computational analysis to show that autism-related developmental changes may occur as distinct spatial mosaics rather than through a uniform process.



Researchers from A*STAR have identified spatial differences in early brain development that could help explain why autism spectrum disorder affects individuals so differently.

The study, conducted by the A*STAR Genome Institute of Singapore in collaboration with the A*STAR Bioinformatics Institute, suggests that autism may arise not only from which genes are affected, but also from where and how developmental changes occur in the growing brain.

Published in Nature Communications, the research used brain organoids generated from induced pluripotent stem cells donated by individuals with and without autism spectrum disorder.

These three-dimensional cellular models reproduce key stages of fetal brain development that cannot be directly studied in humans.

Researchers combined the organoids with single-cell gene activity mapping and advanced computational analysis to identify individual cell types, map their locations and examine how they assemble during brain development.

Organoids from donors without autism formed the orderly cellular layers typically seen in the developing cerebral cortex.

In organoids derived from individuals with autism, however, this layered organisation frequently broke down in distinct patches, while nearby regions developed normally.

The location and extent of these disorganised areas also varied between individuals.

The findings suggest that autism may not develop through a single uniform developmental process, but instead through distinct spatial patterns of brain development that differ from person to person.

Researchers traced these structural differences to radial glial cells, neural stem cells that act as both architects and scaffolding during early brain development.

Normally, radial glial cells remain closely connected while guiding newly formed neurons into their appropriate positions.

In the autism-derived organoids, these connections were disrupted, leading to disorganisation of the underlying scaffold and preventing neurons from forming their normal layered structure.

The abnormalities persisted into later developmental stages, suggesting that early changes in the interaction between neural stem cells may have longer-term effects on how the cerebral cortex is assembled.

“By looking at how brain cells assemble into tissues, we may better understand why autism presents so differently from one person to another,” said Dr Liu Jinyue, Principal Scientist at A*STAR GIS and co-corresponding author of the study.

The research provides a complementary approach to autism studies that have traditionally focused on individual genes and biological pathways.

Rather than examining molecular changes alone, the researchers incorporated spatial information to understand how those changes are organised across developing brain tissue.

The work combined A*STAR GIS expertise in spatial genomics and stem cell biology with A*STAR BII capabilities in computational biology, enabling researchers to reconstruct early brain development at single-cell resolution.

“Understanding biology is not only about which cells are present, but also where they are and how they interact,” said Dr Wan Yue, Executive Director of A*STAR GIS.

“By adding the spatial dimension and combining diverse expertise, we can study not just autism but also other complex human diseases in entirely new ways. This has exciting potential to advance precision health through more accurate disease classification and ultimately, more targeted treatment approaches.”

In the longer term, the researchers said the framework could contribute to improved classification of autism and potentially identify new opportunities for intervention.