NEWS

Analysis of mouse brains maps subgroups of autism

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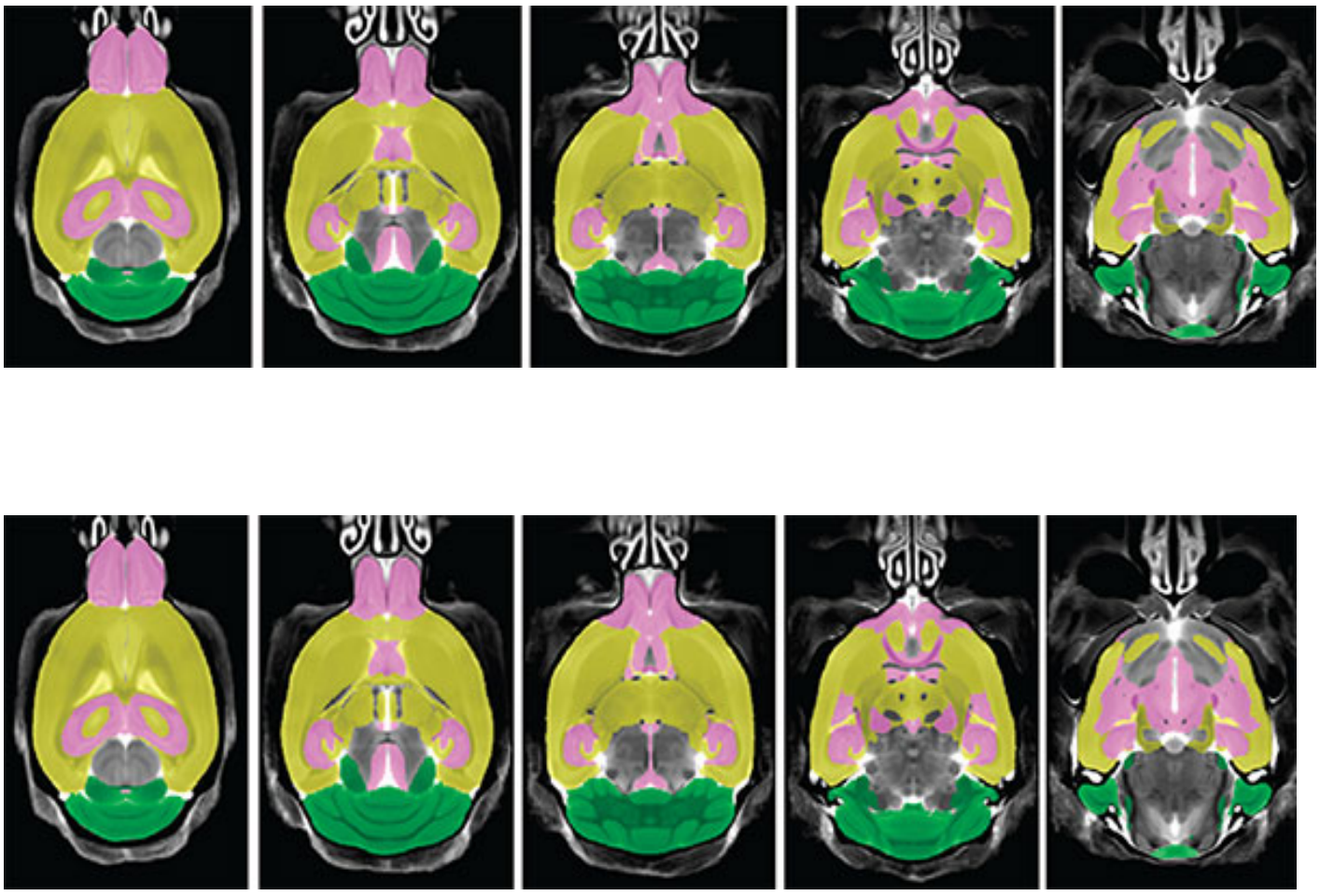

Hot spots: The brains of 26 mouse models of autism are abnormal in tracts that connect different regions (yellow) and in regions that modulate social skills (pink) or movement (green).

A brain imaging study of 26 mouse models of autism reveals a broad range of structural abnormalities. The models cluster into groups with similar features, reports a study published 9 September in *Molecular Psychiatry.*

The results point to key brain circuits linked to autism, including those involved in movement and brain connectivity.

The researchers chose models with mutations in well-known autism genes or chromosomal regions — such as **CNTNAP2**, **NLGN3**, **SHANK3** and **16p11.2** — as well as inbred strains, such as **BTBR**, that show behaviors reminiscent of autism

They divided the mouse brain into 62 segments that encompass a range of brain regions, such as the amygdala, and tracts of neurons, such as the corpus callosum. They then used magnetic resonance imaging to compare these regions in the mouse models with those of control mice of the same genetic backgrounds.

The models fall into three groups overall: The mice in the first group have mostly larger brain regions than the controls do, whereas those in the second group have mostly smaller brain regions. The third group shows about an even mix of larger and smaller brain regions.

For example, mice with mutations in FMR1, **NRXN1** or **SHANK3** tend to have an abnormally large corpus callosum, which connects the brain's hemispheres. By contrast, the corpus callosum is smaller in BTBR mice and **NLGN3** mutants than in controls.

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The fact that NLGN3 and NRXN1 mutations have divergent effects is surprising because both genes function at neuronal junctions, or **synapses**, says lead researcher **Jason Lerch**, a scientist at the Hospital for Sick Children in Toronto. "We were surprised by the extent of the heterogeneity," he says.

The study is intriguing because it suggests brain imaging may similarly help identify subgroups of individuals with autism.

"It makes me want to go look at the human data and see if we can find a similar approach to classifying participants," says **Kevin Pelphrey**, director of the Child Neuroscience Laboratory at Yale University, who was not involved with the study. "This notion of taking the variability seriously is becoming more and more important in human imaging."

Diverse groups:

The researchers began the project more than five years ago, hoping to characterize autism-related changes in the brains of mice lacking the **fragile X syndrome** gene **FMR1**.

“We came into this somewhat naively,” says **Jacob Ellegood**, a research associate at the Hospital for Sick children in Toronto. “We dismissed that pretty quickly once we realized there are many, many models out there with heterogeneous genetics and behavior.”

The team then collaborated with 34 researchers from 16 institutions — as many as would give them mice to analyze.

Ellegood presented **preliminary findings** from the mice at the **2013 Society for Neuroscience annual meeting** in San Diego, suggesting that the mice cluster into subgroups based on their brain anatomy. The new study details the three clusters and the types of brain regions involved.

The researchers did not find any single brain region that is affected in all the models. Instead, their findings converge on brain structures involved in three main functions related to autism: social skills, movement, and connectivity among brain regions.

“Having different models that come at this from different perspectives is a strength of the study,” says **Ted Abel**, professor of biology at the University of Pennsylvania, who was not involved in the work.

However, some of the diversity may have as much to do with the mice’s genetic makeup as with the autism-linked mutation they carry. To control for any effects from the mice’s genetic background, the researchers directly compared each mutant with a control mouse with an identical background. Even so, they found that mice with the same mutation in the SLC64 gene, but of different backgrounds, fall into different clusters.

It’s also unclear whether the clusters relate to sets of symptoms seen in the mice.

The researchers tried to categorize the mice based on symptoms, but were limited by the type of behavioral data available for each model. Scientists at different labs tend to rely on **widely variable behavioral assays**. And even with the same assay, small differences in technique can **lead to inconsistent results**.

But being able to link the brain changes seen in the study to particular behaviors — for example, defects in connectivity with **repetitive behavior** — would help the field understand what might underlie autism symptoms, says Abel. “That will be the most interesting thing going forward.”

In the meantime, the researchers plan to test whether the subgroups of mice respond differently to

drugs. They are screening a large number of compounds in at least two mouse models from each cluster. “The hypothesis of this paper is that by using anatomy we can predict who will respond [to treatment] and who will not,” says Lerch.

This is likely to be much more difficult to accomplish in people because the human brain changes drastically with age. “The datasets we need in humans are going to be longitudinal, allowing us to classify changes over time,” says Pelphrey.

References:

1: Ellegood J. *et al. Mol. Psychiatry* Epub ahead of print (2014) **PubMed**