NEWS

Brain scans from dozens of mice may reveal autism subtypes

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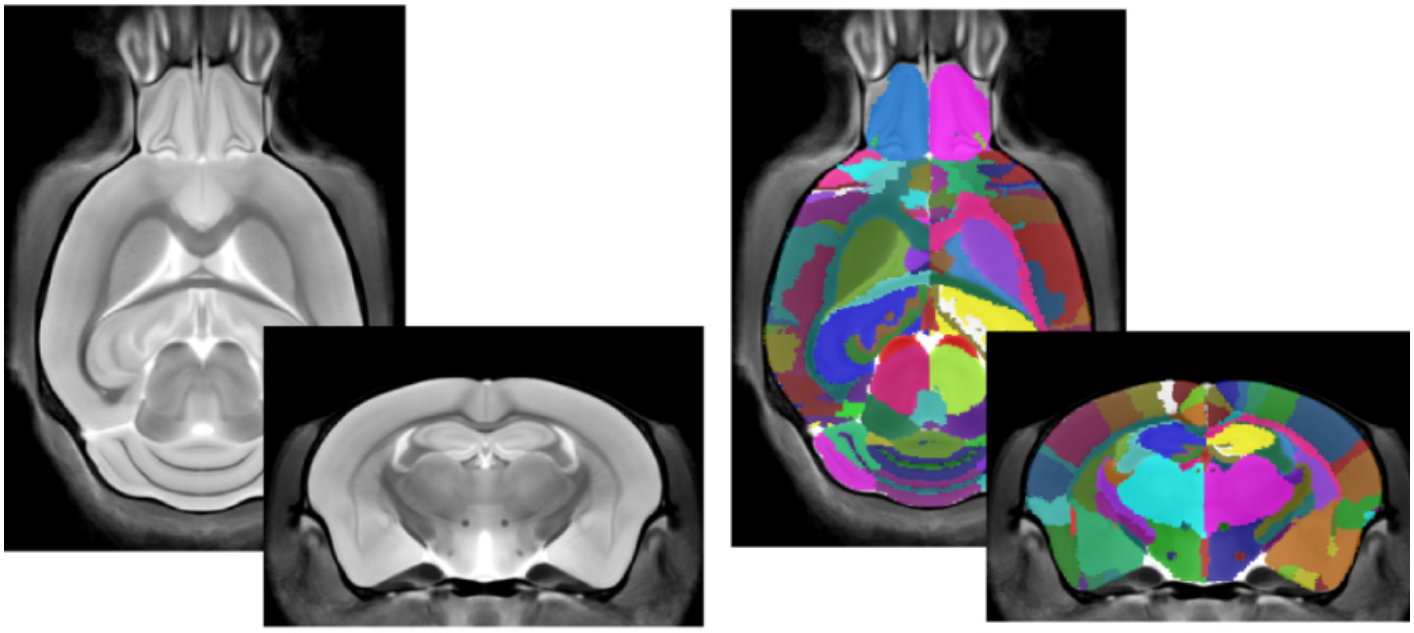

Analyzing large numbers of autism mice, researchers have found that the mice cluster into subtypes based on brain structure and functional connectivity.

In one project, Canadian researchers performed nearly 4,000 structural brain scans in 92 mouse models of autism. They looked for brain regions that are smaller or larger in the mutants than in controls.

The mice cluster into four groups based on similarities in brain structure, the team found. By linking genes in each cluster to cellular pathways, the researchers ascribed potential functions to each group.

In another project, researchers from Switzerland and Italy are looking at brain connectivity in lightly sedated mice. They have so far found three patterns of connectivity within 14 mouse models of autism.

Both teams presented their findings at the **2018 Society for Neuroscience annual meeting** in San Diego, California.

The teams plan to eventually pool resources and compare findings to identify overlap among the structural and functional clusters.

“The idea is to try to understand how many subtypes of autism there are out there and to use objective translatable measures to define them,” says **Alessandro Gozzi**, senior researcher at the Istituto Italiano di Tecnologia in Genova, Italy, one of the leaders of the connectivity study.

All the mouse models:

The structural team previously analyzed 26 mouse models of autism and reported that the models **cluster into three groups**. With almost four times as many mice now, they have found four distinct groups.

One cluster includes three different strains of mice with mutations in the top autism gene, **CHD8**, a duplication of a long stretch of genes called **16p11.2** and the ion channel **SCN1A**. Another includes the genes **NLGN1**, **NLGN2**, **NRXN1** and **SHANK3** — all of which function at **synapses**, the junctions between neurons.

The team first pared the 92 models down to 51, each with a mutation in a unique gene. They then used a database of protein interactions to look for candidates that interact with these 51. They identified 749 genes, which they added to the relevant clusters.

Group theory: Structural brain scans of 92 autism mouse models suggest the mice cluster into four types.

The team then assessed whether any of these expanded clusters contains a disproportionate number of genes involved in pathways associated with autism. Their analysis suggests that genes in the CHD8 cluster are involved in the WNT signaling pathway, for example, whereas genes in the synaptic cluster are involved in stabilizing proteins at synapses.

The project's ultimate goal is to help develop treatments for autism, says **Jacob Ellegood**, a research associate at the **Mouse Imaging Centre** in Toronto. He and his colleagues are conducting clinical trials in autistic children while testing the same drugs in multiple autism mouse models.

If an individual's brain-scan pattern matches that of one of the mouse clusters that responded to the treatment, he says, "then all of a sudden you're off to the races for probably the best option."

The key to the study will be to determine how the mouse data translate to people, says **Cynthia Schumann**, associate professor of psychiatry and behavioral sciences at the University of California, Davis, who was not involved in the work.

"It's in a mouse, but it's really important information we can't get from humans because we aren't able to get enough individuals with different gene mutations," she says. "The next step is to bring it back to the human and see if they're able to reconcile that."

Translational tool:

The connectivity team is using a similar clustering technique for data from 20 autism mouse models. They presented preliminary data from 14 of them on Saturday.

The project has so far revealed three groups that make sense, says **Valerio Zerbi**, group leader at the Neural Control of Movement Lab at ETH Zurich in Switzerland, who presented the findings. For example, **MECP2** and **CDKL5**, both of which lead to a similar syndrome when mutated, are in the same group.

Strikingly, two of the three groups show near-opposite patterns of connectivity. For example, one group shows diminished connectivity in the prefrontal cortex, which is involved in higher-order thought, and hyperconnectivity in the lateral septal nucleus, which plays a role in reward; the other group shows the reverse pattern.

These alterations would average out if you were to combine data from both sets of mice, Gozzi notes. The findings show how autism's heterogeneity may confound brain-imaging scans in people, he says.

Structural data may be less translatable between mice and people than functional connectivity, he says, because mouse brains have a different shape than human brains. In a study published in

May, Gozzi's team showed that functional-connectivity patterns in mice missing the 16p11.2 chromosomal region **match those seen in people** with the same deletion.

"We found exactly the same thing, or pretty much as close as it gets if you consider that these are species that are many million years apart," Gozzi says.

Gozzi aims to use connectivity features from mouse brains to cluster human scans from a **large repository of scans**. Using the mouse data to guide the analysis might reveal true categories of autism, he says.

*For more reports from the 2018 Society for Neuroscience annual meeting, please **click here**.*