NEWS

Lack of corpus callosum yields insights into autism

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A rare birth defect may offer a unique perspective on the **connectivity theory** of autism, which holds that the brains of people with autism have defective long-range connections.

Up to one-third of those missing all or part of the corpus callosum, a thick tract of nerve fibers connecting the left and right brain hemispheres, meet the diagnostic criteria for autism, several recent studies suggest.

“One of the most consistent findings in autism is **diminishment of size of the corpus callosum**,” says **Elliott Sherr**, associate professor of neurology at the University of California, San Francisco, School of Medicine.

About 1 in every 4,000 people lack part or all of the corpus callosum. The condition, increasingly diagnosed before birth, is formally known as agenesis of the corpus callosum (AgCC).

“When we’re talking about autism these days, we’re often talking about it as a disorder of long-range connectivity — and AgCC is the ultimate disconnection model,” says **Elysa Marco**, assistant professor of clinical neurology at the University of California, San Francisco, School of Medicine.

It’s often not clear what causes the abnormality, which strikes early in brain development. But a growing number of brain imaging studies are shedding new light on the extent and details of the condition. Some people are missing the entire corpus callosum; in others, a fragment of the structure remains. Structural damage can be limited to the corpus callosum (dubbed ‘isolated’ AgCC) or spread across the brain.

As in autism, symptoms of AgCC can vary widely. Some people with the defect may have severe **epilepsy**, cerebral palsy or developmental delay. Others, primarily those with isolated AgCC, are able to attend college, hold down a job and raise a family.

In fact, they do so well that “some people think that callosal agenesis has no impact on

functioning," says **Lynn Paul**, senior research scientist at the Caltech Emotion and Social Cognition Laboratory in Pasadena, California. But Paul and others say that even those who are most successful usually have subtle language and social impairments.

Social disconnect:

Previous research has shown that adults with AgCC and normal intelligence quotients (IQ) have trouble with meta-linguistics, or the secondary meanings of language[1]. They struggle to understand things like jokes, sarcasm and figures of speech.

According to unpublished data presented in April at an informal scientific meeting on AgCC in San Francisco, people with this condition also have deficits in **theory of mind,** the ability to infer what others think or feel.

In the study, participants watched animated cartoons featuring shapes that move randomly, 'chase' each other or travel in a way that implies social interactions such as teasing or greeting. Those with AgCC are unable to describe the shapes' intentions as well as controls can, says lead investigator **Warren Brown**, professor of psychology at the Fuller Graduate School of Psychology in Pasadena, California.

Brown says he is reanalyzing these data, separating those with AgCC who meet criteria for autism from those who do not.

"This [approach] can also help us better understand what are the compensatory mechanisms," says Paul, who collaborates with Brown. "What's helping those who don't end up with the [autism] profile — how do they overcome it?"

According to unpublished data Paul presented at the conference, 8 of 26 adults with normal IQ and isolated AgCC qualify for an autism diagnosis based on the Autism Diagnostic Observation Schedule, a gold-standard instrument for identifying the disorder.

The findings are broadly similar to those reported last year by another group of researchers[2]. In that study, researchers administered the Autism Spectrum Quotient, a screening instrument, to 106 people with AgCC or, in the case of children under age 16, their parents. The researchers found that 45 percent of children, 35 percent of adolescents and 18 percent of adults with AgCC **reach the threshold for an autism diagnosis**.

The decline in older age groups "may simply reflect an artifact of the tool," says Marco, who led the study. "Or it may tell us something about accommodations people make as they get older."

Broken links:

Some researchers are using both brain imaging and genetics to probe the mechanisms underlying the social and language impairments characteristic of AgCC.

In a study last year, researchers scanned the brains of 7 people with AgCC and 11 controls using a new technique called high angular resolution diffusion imaging. This technique traces the pathways of white matter, the bundles of nerve fibers that connect different regions of the brain. In contrast to earlier methods, it allows researchers to visualize where fibers that run in different directions cross each other[3].

Using mathematical modeling, the researchers then **mapped the 'connectome,'** the structural links between 82 brain regions, for each study participant.

As a group, people with AgCC have more variable connectomes compared with controls, says study co-leader **Pratik Mukherjee**, associate professor of radiology at the University of California, San Francisco. What's more, their connectomes are different from those of controls even when connections through the corpus callosum are excluded from the analysis.

These results suggest that the brain of a person with AgCC isn't simply missing certain connections but is somehow fundamentally — and unpredictably — rewired.

However, the researchers didn't include information about whether the participants also have autism. And Sherr, who co-led the study, says the numbers are too small to look for correlations between behavior and the degree of rewiring outside the corpus callosum.

The researchers plan to look for correlations, having now scanned a few dozen people with AgCC. Sherr says they hope to have preliminary results by the end of the summer.

Genetic studies of links between AgCC and autism show mixed results. In the most direct investigation so far, Sherr and his colleagues analyzed the genomes of BTBR mice, a strain that shows social deficits reminiscent of autism[4]. Tantalizingly, BTBR mice also lack a corpus callosum.

"We were hoping that we would see correlations between the two," says Sherr. However, the researchers found that the chromosomal regions linked to AgCC in the mice are not the same as those linked to social deficits.

Looking for these genetic links in people may be more fruitful. A 2007 study implicated the chromosomal region 1q44 and identified one gene in the region, AKT3, as a likely key player in AgCC[5].

AKT3 is part of the mTOR pathway, which is involved in cell growth and protein synthesis, and has been **implicated in autism-linked conditions** such as tuberous sclerosis complex and **fragile X syndrome**.

Most recently, Sherr and his colleagues have compared the genomes of people with autism and those with AgCC and have found some chromosomal regions that appear to play a role in both. “We saw a highly significant association between the two,” Sherr reported at the meeting, noting that the data are not yet published.

Sherr says he suspects the BTBR mouse study did not turn up any links because the behavioral tests used may not capture the subtle, complex social and language problems seen in people with AgCC. “There’s no way that you could model meta-linguistic reasoning in the mouse,” he says.

References:

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