CROSS TALK

Autism lesion or artifact? Experts discuss new find

BY **GREG BOUSTEAD**

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In early April, we reported on a study that found **distinct areas of seemingly immature neurons** in the brains of children with autism. The study analyzed gene expression in postmortem brain tissue and identified patches of disorganized cells in the brain's cortex, or outer layer.

The results suggest that autism arises *in utero* while the cortex is still developing. The study garnered **widespread coverage** in the **popular press** and spurred debate in the research community about its methods, the significance of the findings and how best to confirm them.

We asked experts who study brain pathology and development for their perspectives on the study.

What do you think? Share your reactions and follow-up questions in the comments section below.

Flora Vaccarino

Professor,Yale University

Findings leave process unclear

Harris Professor, Child Study Center, Yale University
Higher-order hints: “This new study adds more meat to the emerging evidence that crucial aspects of embryonic brain development are disrupted in autism. Their suggestion is that the morphogenesis of cortical layers, a process that occurs in the first trimester of gestation in humans, is fundamentally disorganized.
“Other reports (that is, from the labs of **Manuel Casanova** and **Daniel Geschwind**) have suggested that there are area-specific cortical disruptions of gene expression in the disorder, again

pointing to subtle alterations in fundamental processes governing the way the brain is initially built. In this new paper, gene expression was disrupted in the patches in a coordinated fashion (that is, for more than one gene and in more than one layer), suggesting that some kind of higher-order process is disrupted, rather than its being a problem with isolated gene expression."

Too soon: "I consider this report preliminary because I would have expected to see parallel evidence in the tissue analysis of disrupted layers in the cortex, as commonly is seen in disorders of neuron migration. Cortical layers are each formed by specific neuron types, each with a typical shape, size and connectivity, specified by programs of interacting genes expressed in their progenitor cells.

"Assuming that the neurons are abnormal, and that this is not due to some artifact altering RNA levels in these patches, the paper leaves unclear the process that is disrupted in these brains: Are the neurons mis-specified to a non-cortical, non-layer neuron type? Or is their migration altered, such that the cortical neurons are there, but their position is altered?"

Robert Hevner

Professor,Seattle Children's Research Institute - Seattle Children's Hospital

Needs confirmation

Professor of Neurological Surgery, Seattle Children's Research Institute, University of Washington

Compelling statistic: "The 'patches' of disorganization in this study were found in 10 out of 11 brains with autism, but only 1 out of 11 control brains, suggesting that the patches are, if not specific, at least highly enriched in most autism brains — which is surprising given the etiological, genetic and phenotypic heterogeneity of the disorder. Indeed, despite the small, explorative nature of the study, this statistical difference is its most compelling aspect, because the significance of such molecular patches is otherwise completely unknown."

Important caveats: "First, it is notable that neurons migrated to the correct layer and grew to the correct size and shape, but presumably failed to then express the correct layer-specific molecular profile. Second, there is as yet no evidence that the observed molecular defects had any impact on neural connectivity or physiology, or that they relate in any way to autism phenotypes. Third, no mechanism that would lead to the formation of patches during development is apparent."

Handle with care: "Finally, the possibility that the patches are mere artifacts arising focally in the tissue after death is far from excluded. In fact, it is well known that RNA degrades rapidly in postmortem tissue. The authors tried to address this possibility by also studying the expression of genes specific for interneurons and glia, which were seen to be mostly intact in patches (although

there were exceptions). However, because projection neurons exhibit selective vulnerability to many pathological insults, they may also be more vulnerable to artifact, given their large size and unique membrane properties. Even gentle handling can cause anomalies in the cellular architecture of the cortex, and might conceivably disrupt cells in subtle ways that accelerate molecular degradation."

Random differences? "Why would such artifacts be more prevalent in the brains of individuals with autism than in those of controls? Here, it is important to remember that the number of cases was small and differences could arise randomly. In addition, it is likely that the autism brains were simply subjected to more handling during the postmortem examination and sampling."

"Overall, this work demonstrates a new type of possible lesion that may have tremendous importance in autism, but should be viewed with caution until independent confirmation is obtained and the possibility of experimental artifacts is excluded."

Margaret Esiri

Fellow of the Royal College of Pathologists, Professor of Neuropathology,Oxford University

Highlighting a research bottleneck

Professor of Neuropathology, University of Oxford; Former Director, UK Brain Bank for Autism and Related Developmental Research

Still early: "This is an interesting paper but one whose significance is hard to assess. The technique is a relatively novel one that has been used very little so far on human postmortem material. Although the researchers have made efforts to ensure that their results are not influenced by the nature of the material studied, it will take more research before it's clear just what this study is telling us."

It takes brains: "There is a major difficulty in having this study independently replicated because there is **a shortage of postmortem brains** donated for research from young people with autism or controls. There needs to be more awareness of the tremendous value that **postmortem brain donation** has for research. Studies of the brain based on imaging in life have produced much important new information. But imaging is unable to take us down to the level of detail that can inform us about patterns of gene expression and protein composition at the cellular and molecular levels."

Watch this space: "This is the type of information that can lead to new understanding, and that has the potential to assist in developing interventions to help people with autism and other developmental disorders. For the time being, though, it is a matter of 'watch this space.'"