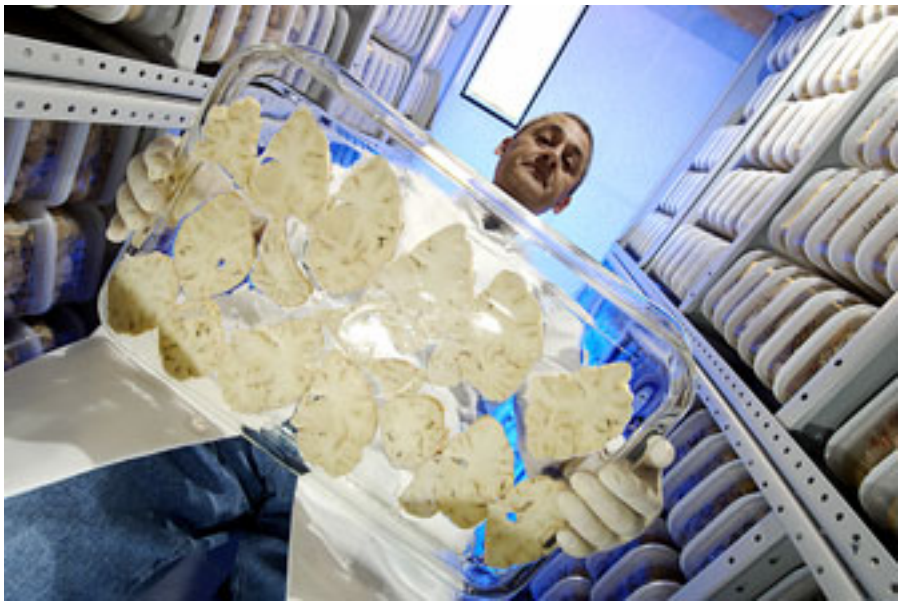
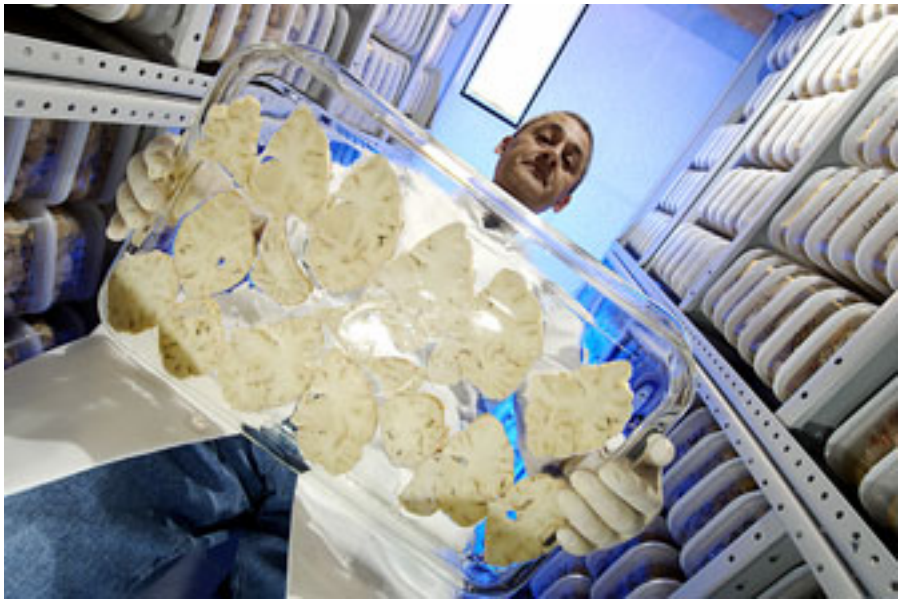
VIEWPOINT

Insights for autism from schizophrenia

BY **DAVID LEWIS, ALLISON A. CURLEY**

13 NOVEMBER 2012





Brain tales: Postmortem samples from well-characterized individuals with autism can help researchers distinguish causes and consequences of the disorder.

A key element in understanding any illness, including autism, is knowledge of the underlying pathology — the cellular and molecular alterations that give rise to symptoms. In fact, for many disorders, the initial description of the illness was based on the relationship between a particular set of symptoms and pathological alterations in a certain organ.

A classic example of this link in a brain illness is Alzheimer's disease. When Alois Alzheimer first described the disorder in 1906, he linked its hallmark pathology — plaques, tangles and cell loss in the brain — with short-term memory loss.

A trained eye is unlikely to miss the distinctive pathology of Alzheimer's disease, but other brain disorders, such as schizophrenia and autism, have more subtle physical characteristics. As a result, the initial descriptions of these disorders were based on the clinical signs alone.

In diseases that affect other organs, researchers can define pathology by examining tissues biopsied from living individuals. But they can only study brain disorders using postmortem samples. These samples are crucial for **helping us understand and treat** disorders such as autism and schizophrenia.

In the case of schizophrenia, interest in studying postmortem brain tissue as an essential research tool has surged over the past two decades, and researchers have made substantial progress in

revealing pathological changes associated with the disorder. For example, there is consistent evidence that genes that regulate interneurons — which dampen brain signals — are expressed differently in the brains of individuals with the disorder than in controls[1].

From these studies, we have learned many lessons that are applicable to research on autism, a disorder for which brain tissue has not been as well studied.

Tissue tales:

First, we have learned the importance of collecting and using only high-quality tissue samples from well-characterized individuals. This provides the greatest confidence that findings actually represent the pathology of the illness.

For example, a number of factors that occur prior to or after death influence the levels of gene products in the brain[2]. It is critical to use robust techniques to quantify these variables and appropriate study designs to account for their effects. Similarly, demographic information (such as age and sex) and clinical variables (such as medication use) can also affect gene expression.

A second lesson from schizophrenia research is that it is important to take into account current knowledge about brain circuits. Because disorders such as autism and schizophrenia typically appear during childhood and adolescence, respectively, understanding **how normal brain circuits develop** over time is especially important.

The human brain undergoes a lengthy period of maturation, and different molecules, brain cells and neural circuits may be particularly vulnerable at different stages of development. Human brain tissue is extremely difficult to obtain, but as an alternative, tissue from nonhuman primates has proven to be an **informative model** of human brain development[3].

Finally, to understand any one factor's potential role in the disorder, researchers must consider the 'four Cs:' cause, consequence, compensation and confound[4].

A given finding may represent a cause — an underlying event in the disease process that leads to symptoms — or a deleterious consequence of a cause. Compensation is the response to either a cause or consequence that attempts to return the brain to a normal state of functioning. The dreaded confound is unrelated to the underlying disease process.

Making these distinctions is critical in a number of respects, including for developing treatments. For example, researchers should ideally design treatments to lower the effects of a cause or consequence, but to increase the effects of compensation.

Differentiating among the four Cs is difficult, but proof-of-concept tests in animal models can help. For example, researchers can identify a treatment confound by using animals to examine the

effects of medications.

Similarly, manipulations in animals that lead to the same abnormalities seen in postmortem human tissue can help distinguish among the 4Cs. For example, people with schizophrenia have low levels of GAD67 and CBR1[5]. Lowering GAD67 expression in mice decreases CBR1 levels, suggesting that the latter is a consequence of the former[6].

As autism research moves forward, application of these lessons from schizophrenia will help to advance the discovery of its pathology and lead to better diagnosis, treatment and prevention.

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