Aiming for a Multifaceted Approach to Psychiatric Disorders

November 27, 2013

In the search for new ways to prevent and treat mental illnesses, scientists need to refine their understanding of the complex interplay between environmental factors and brain development in these disorders.

Steadily chipping away at this goal is Elaine F. Walker, recipient of the 2013 APS James McKeen Cattell Fellow Award and professor of psychology and neuroscience at Emory University. In her award address at the 25thAPS Annual Convention in Washington, DC, Walker discussed the changing views of mental illness, as well as recent genetic, neuroscientific, and behavioral findings.

Historically, models of psychiatric illness have been overly simplistic or incomplete, said Walker, with theories and assumptions too simple to account for the complexities of the mind and brain.

“In the 1970s and 80s, there were vying accounts about the determinants of human behavior, and often they were argued with zealous commitment to a particular theoretical position,” Walker explained. “Fortunately these are things of the past.”

Today, instead of single determinants of human behavior, psychological scientists work with complex and multivariate models. Walker discussed these multiple levels of study, beginning with potential genetic and epigenetic factors.

Parental Factors

Several studies have shown that older fathers tend to produce more de novo mutations — small genetic alterations in sperm cells — than do younger fathers. In a perfect example of how biology and environment interact, it’s thought that these small changes to DNA can result from the father’s stress levels, poor nutrition, or contaminants. And evidence shows that this phenomenon may have a significant bearing on later mental health in children.

“Paternal age is significantly associated with risk for schizophrenia in offspring,” Walker said. “Not surprisingly given the fluidity of diagnostic boundaries, similar findings have been found for a range of developmental disorders, including autism spectrum disorders.”

While genetic factors may contribute to an abnormal developmental trajectory, they only account for a portion of the overall susceptibility to psychiatric illness. Research on environmental influences in prenatal life has revealed other ways in which a child can be left vulnerable. Viral infections during pregnancy, exposure to drugs and contaminants, and maternal nutritional deficiencies have all been linked to disorders in children.

Maternal stress during pregnancy — as measured by levels of the stress hormone cortisol — turns out to be a significant predictor of impaired cognitive development in children. As Walker described, high levels of cortisol in a mother's blood have a significant bearing on the offspring's psychology and physiology. In an experiment with non-human primates, offspring who had been subjected to maternal stress in either early or late gestation showed higher cortisol levels and were less likely to explore their surroundings. In addition, these offspring failed to produce new neurons in the hippocampus at the typical rate, possibly forecasting memory or spatial reasoning deficits. A similar study found that when pregnant rhesus monkeys were exposed to influenza virus, their offspring tended to have reduced functioning in brain regions involved in in complex cognition, decision making, and social behavior. Data like these, Walker believes, are illustrative of a larger theme.

"Things are more complicated than we had assumed," she said. "There are more determinants of human behavior than we thought, and these factors interact in complex ways."

The Role of Life Events

After birth, the complex interplay between biology and environment continues. Humans normally experience a gradual decline in gray matter during adolescence, but studies have suggested that more stressful life events or risk for psychiatric disorder accelerates this decline, perhaps leading to the onset of mental illness. Thus, because at-risk individuals tend to display higher levels of cortisol release in adolescence and early adulthood, hormonal tests may someday be used as a predictive tool for indicating when early intervention might be most effective.

Walker's most recent research is aimed at doing just that. In collaboration with other scientists, she is studying a developmental period called the "prodrome," or the period of months or years that lead up to the onset of clinical psychiatric disorder. This specific project — the North American Prodrome Longitudinal Study (NAPLS) — aims to enhance our ability to identify at-risk individuals, and also to understand the neural mechanisms that trigger psychosis. To meet these goals, Walker and her team of researchers have performed structured interviews with over 1,000 adolescents and young adults, looking for subclinical manifestations of psychotic disorders — like delusions, perceptual abnormalities, or disorganized thoughts.

The researchers have found that those participants who show some semblance of preclinical symptoms in the interviews are much more likely to develop psychosis later in life. And as Walker points out, stress may be a contributing factor: Young adults who show higher baseline levels of cortisol in the lab are much more likely to develop psychosis, and at-risk adolescents report more stressful life events than controls.

While these correlational data do not establish causality, the fact that they corroborate the experimental findings in non-human primates is encouraging. It means that, unlike clinical research from 30 years ago, we can be more confident that our methods are valid. It also means that we can begin to understand which variables are most significant in leading to mental illness.

"It's going to be easier to find points of leverage for intervention," Walker added. "There are so many processes at work in determining the changes in the brain that trigger the expression of psychosis in at-risk individuals. Our opportunities for intervening and altering those trajectories may be better than we

had assumed.”