Stress Can Alter Brain, Lead to Psychopathology

BY DAMIAN McNAMARA
Miami Bureau

SAN JUAN, P.R. — Stress can cause structural remodeling of the brain that can have short-term advantages, but if left unchecked, the changes can contribute to psychopathology, according to a presentation by a neuroendocrinologist at the annual meeting of the American College of Psychiatrists.

"The brain is capable of a lot of structural remodeling. The amygdala, hippocampus, and prefrontal cortex show remodeling that may be coordinated among these areas via neural connections," said Bruce S. McEwen, Ph.D. Many mediators play a role, including insulin, glucose, and cytokines, neuroendocrinology studies show.

"Neuroscientists tended to think from the neck up, and endocrinologists tend to think from the neck down. So for a long time I was in between. But there is a growing appreciation of the mind-body connection [regarding stress]," said Dr. McEwen, Alfred E. Mirsky professor and head of the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, Rockefeller University, N.Y.

The downside of stress is well known. Dr. McEwen defined it as "the general process through which environmental demands result in outcomes deleterious to health." Less appreciated are the positive aspects of stress, he said. For example, the stress response is how the body adapts in the face of a real or imagined threat to homeostasis. "Many people think of stress as a bad word with damaging effect on the body. The other side is stress is a challenge, and without our stress response hormones, we would not live long," Dr. McEwen said. "A challenge can be invigorating as long as we can feel in command of the situation." Dr. McEwen's insights come in part from his animal studies and in part from his work on humans in his neuroendocrinology lab.

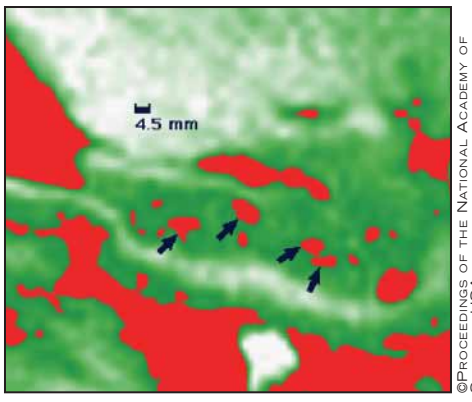
Glucocorticoids such as cortisol can have beneficial and damaging effects, depending on the timing and duration of their release. For example, during acute stress, cortisol enhances immunity, memory, energy replenishment, and cardiovascular function, Dr. McEwen said. However, everything changes when chronic stress induces chronically high levels of cortisol. In this setting, cortisol suppresses immune function and memory, promotes bone mineral loss and muscle wasting, and increases long-term risks for metabolic syndrome and cardiovascular disease.

The body releases stress hormones in an attempt to return to homeostasis after an acutely stressful event. Chronic stress, however, can cause the body to maintain a different baseline state, called allostasis, Dr. McEwen said. Many elements—together called the "allostatic load"—can contribute to this altered state. Sleep deprivation, for example, is a common chronic stressor. People who are sleep deprived have increased blood pressure; elevated evening cortisol, glucose, and insulin levels; elevated inflammatory cytokine levels; increased appetite; depressed mood; and impaired cognitive function.

The adverse effects are many. "When you are 'stressed out,' you feel overwhelmed, out of control, exhausted, anxious, frustrated, or angry," Dr. McEwen said. "Often you lose sleep, eat too much of the wrong things, drink excess alcohol, smoke, and neglect regular, moderate exercise." The stress response spurs activation of many other mediators besides cortisol. Examples include the autonomic nervous system, prolactin, thyroid hormone, inflammatory cytokines, and other components of the neuroendocrine system and immune system.

"We have to recognize that the body works in this nonlinear fashion," Dr. McEwen said.

He and his associates study "social neuroscience," or how a person's social environment can have profound effects on brain function. Influences include daily stressors at home and work as well as major life events. "The brain's response determines not only the physiologic response to stress that leads to allostasis, but [also] the healthy behavioral responses, such as exercising, or detrimental responses, such as overeating or smoking, that can lead to allostatic overload."



This sagittal view of a hippocampus illustrates atrophy (see arrows) in a patient with recurrent depression.

The hippocampus is a target for stress hormones. Structural changes are mostly seen in depression, he said. Patients with depression are more likely to have atrophy of the hippocampus and prefrontal cortex. Glucose, insulin, insulinlike growth factor 1, lipopolysaccharide, proinflammatory cytokines, and sex hormones are external factors that affect the hippocampus. "All of these may have an influence on mood and memory," he said. "Recent evidence suggests [that the] hippocampus plays a bigger role than we thought in mood." ■

Chronic Tics Did Not Worsen For Patients on Levodopa

BY DOUG BRUNK
San Diego Bureau

LA JOLLA, CALIF. — Children and adults with chronic tic disorders who were treated with levodopa did not experience a worsening of tics, Dr. Mollie Gordon reported during a poster session at the annual meeting of the American Neuropsychiatric Association.

Treated patients did experience significant improvements in attention and hyperactivity symptoms.

"I think this challenges the way we think about the dopamine pathways in the brain," Dr. Gordon, of the department of psychiatry at Washington University School of Medicine, St. Louis, said in an interview. "We've always thought of Tourette as being in a sense an excess of dopamine that affects children with movement disorders and causes them to tic and have other sequelae. So when we block the dopamine, these patients do better. What we've shown here is that if we give them dopamine, we would expect them to get worse, since the medicines we've been using block dopamine. But they don't."

In an 8-week pilot study, Dr. Gordon and her associates randomly assigned 12 children and 18 adults with Tourette syndrome or chronic tic disorder to receive 12.5 mg of carbidopa, 50 mg of levodopa, or matched placebo capsules. The researchers recorded tic severity, clinical status, and side effects at baseline, 4 weeks, and 8 weeks. Instruments used included the Yale Global Tic Severity scale, video recordings of tics, the Clinical Global Impressions scale, the Global Assessment of Functioning scale, and various questionnaires.

The researchers found that tic severity did not increase in patients who took levodopa. Patients who took levodopa also experienced improvements in attention and hyperreactivity symptoms (a 17% improvement vs. no improvement for those on placebo), and the drug was not associated with any significant side effects.

Limitations of the study as stated in the poster include the fact that serum prolactin did not decrease appreciably in patients who took levodopa and that the "limited number of subjects may have reduced statistical significance of any effect."

Dr. Gordon hopes that future studies will shed more light on the pathophysiology of dopamine regulation. "We know that these patients have a dopamine abnormality in the brain," she said. "If it's not a matter of being too much or too little [dopamine], the question is, how do we figure out what's wrong? Do these drugs affect auto inhibitory receptors? Is there something going on in the brain that has to do with the dopamine dysregulation? If we [have] more information about the pathophysiology of these diseases, then we can figure out the best management."

The study was funded in part by the Tourette Syndrome Association. ■

Suicide Risks Higher After DBS Among Parkinson's Patients

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — Parkinson's disease patients who have undergone subthalamic nucleus deep brain stimulation have higher rates of completed and attempted suicide than do others with the disease, Dr. Valerie Voon reported at the annual meeting of the American Academy of Neurology.

The rate of completed suicides following deep brain stimulation (DBS) for Parkinson's disease was found to be 0.4% and the rate of attempted suicides 0.9% in the largest multicenter study of its kind, said Dr. Voon, a psychiatrist with the National Institute of Neurological Disorders and Stroke, Bethesda, Md.

The researchers noted that the suicide rate among Parkinson's patients within the first year after undergoing subthalamic DBS was 11- 37 times higher than the suicide rate in the general population, based on World Health Organization data. The rate was 4-13 times higher in postoperative year 2 and dropped to baseline in postoperative years 3 and 4.

The rate of suicide is 10 times lower in Parkinson's disease patients who have not undergone DBS, when compared with the World Health Organization's general population data, she said.

Dr. Voon and her associates surveyed 75 movement disorders centers in North America and Europe to locate Parkinson's patients who underwent subthalamic nucleus DBS and subsequently attempted or completed suicide. Participating centers had published medical literature on DBS and had operated on more than 100 DBS patients.

Of the 75 centers, 55 responded and provided data on 5,255 Parkinson's disease patients who underwent subthalamic nucleus DBS. After DBS, 22 of the patients completed suicide (0.4%) between 1 month and 4 years.

The researchers also found that 47 patients attempted suicide (0.9%). The attempted suicides took place between approximately 1 week and 8 years following DBS.

Preoperatively, three completed and three attempted suicides were reported. These patients were on DBS wait lists. "The highest risk period is in the first 10 months to 1.5 years" after DBS, she said. "At 10 months time, 50% of the events had already occurred. At 17 months, 75% of the events had occurred."

Logistic regression analysis based on a study of 70 controls showed that these factors were independently associated with an increased risk of suicide: past history of impulse control disorder or substance abuse, being single, or having postoperative depression.

Suicide is potentially preventable, so patients and families should be aware of this risk, Dr. Voon said. ■