Depression stems from miscommunication between brain cells, study shows

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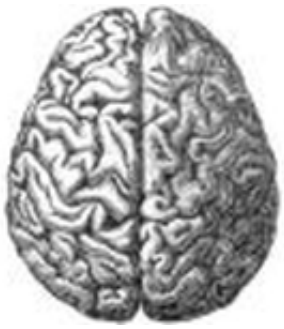

A new study from the University of Maryland School of Medicine suggests that depression results from a disturbance in the ability of brain cells to communicate with each other. The study indicates a major shift in our understanding of how depression is caused and how it should be treated. Instead of focusing on the levels of hormone-like chemicals in the brain, such as serotonin, the scientists found that the transmission of excitatory signals between cells becomes abnormal in depression. The research, by senior author Scott M. Thompson, Ph.D., Professor and Interim Chair of the Department of Physiology at the University of Maryland School of Medicine, was published online in the March 17 issue of *Nature Neuroscience*.

According to the Centers for Disease Control and Prevention, between 2005 and 2008, approximately one in 10 Americans were treated for

depression, with women more than twice as likely as men to become depressed. The most common antidepressant medications, such as Prozac, Zoloft and Celexa, work by preventing brain cells from absorbing serotonin, resulting in an increase in its concentration in the brain. Unfortunately, these medications are effective in only about half of patients. Because elevation of serotonin makes some depressed patients feel better, it has been thought for over 50 years that the cause of depression must therefore be an insufficient level of serotonin. The new University of Maryland study challenges that long-standing explanation.

"Dr. Thompson's groundbreaking research could alter the field of psychiatric medicine, changing how we understand the crippling public health problem of depression and other mental illness," says E. Albert Reece, M.D., Ph.D., M.B.A., Vice President for Medical Affairs at the University of Maryland and John Z. and Akiko K. Bowers Distinguished Professor and Dean at the University of Maryland School of Medicine. "This is the type of cutting-edge science that we strive toward at the University of Maryland, where discoveries made in the laboratory can impact the clinical practice of medicine."

Depression affects more than a quarter of all U.S. adults at some point in their lives, and the World Health Organization predicts that by 2020 it will be the second leading cause of disability worldwide. Depression is also the leading risk factor for suicide, which causes twice as many deaths as murder, and is the third leading cause of death for 15-24 year olds.

The first major finding of the study was the discovery that serotonin has a previously unknown ability to strengthen the communication between brain cells. "Like speaking louder to your companion at a noisy cocktail party, serotonin amplifies excitatory interactions in brain regions important for emotional and cognitive function and apparently helps to

make sure that crucial conversations between neurons get heard," says Dr. Thompson. "Then we asked, does this action of serotonin play any role in the therapeutic action of drugs like Prozac?"

To understand what might be wrong in the brains of patients with depression and how elevating serotonin might relieve their symptoms, the study team examined the brains of rats and mice that had been repeatedly exposed to various mildly stressful conditions, comparable to the types of psychological stressors that can trigger depression in people.

The researchers could tell that their animals became depressed because they lost their preference for things that are normally pleasurable. For example, normal animals given a choice of drinking plain water or sugar water strongly prefer the sugary solution. Study animals exposed to repeated stress, however, lost their preference for the sugar water, indicating that they no longer found it rewarding. This depression-like behavior strongly mimics one hallmark of human depression, called anhedonia, in which patients no longer feel rewarded by the pleasures of a nice meal or a good movie, the love of their friends and family, and countless other daily interactions.

A comparison of the activity of the animals' brain cells in normal and stressed rats revealed that stress had no effect on the levels of serotonin in the 'depressed' brains. Instead, it was the excitatory connections that responded to serotonin in strikingly different manner. These changes could be reversed by treating the stressed animals with antidepressants until their normal behavior was restored.

"In the depressed brain, serotonin appears to be trying hard to amplify that cocktail party conversation, but the message still doesn't get through," says Dr. Thompson. Using specially engineered mice created by collaborators at Johns Hopkins University School of Medicine, the study also revealed that the ability of serotonin to strengthen excitatory

connections was required for drugs like antidepressants to work.

Sustained enhancement of communication between brain cells is considered one of the major processes underlying memory and learning. The team's observations that excitatory brain cell function is altered in models of depression could explain why people with depression often have difficulty concentrating, remembering details, or making decisions. Additionally, the findings suggest that the search for new and better antidepressant compounds should be shifted from drugs that elevate serotonin to drugs that strengthen excitatory connections.

"Although more work is needed, we believe that a malfunction of excitatory connections is fundamental to the origins of depression and that restoring normal communication in the brain, something that serotonin apparently does in successfully treated patients, is critical to relieving the symptoms of this devastating disease," Dr. Thompson explains.

Provided by University of Maryland