

NARSAD Grants Supporting Breakthroughs: A Recent Update

On April 19th, the *New York Times Magazine* featured an incisive synopsis of the progression of treatments for depression. In a piece titled *Post-Prozac Nation*, Siddhartha Mukherjee outlines the evolutionary nature of research, with a particular emphasis on the brain research that is helping treat depression. He calls attention to the specific contributions of NARSAD-Grant funded researchers.

Current day antidepressants, including Prozac and Paxil, were developed on the theory that depression is caused by a chemical imbalance, or a deficient level of serotonin in the brain. This theory is increasingly being challenged and redefined, with the latest research showing that while serotonin is linked to mood, it is not as simple as having an insufficient amount of it that causes depression.

In the late 1980s, Brain & Behavior Research Foundation Scientific Council Member, Fred H. Gage, Ph.D. began to ask a different question that proved to relate to depression: Does the adult human brain produce new nerve cells? Gage and other scientists revisited old findings and discovered that adult mice, rats and humans did experience the birth of new neurons in the hippocampus, the area in the brain that controls memories and is functionally linked to parts of the brain that regulate emotion. With this discovery, Gage and his collaborators began to study stressed mice exhibiting symptoms similar to human depression. They found that in these mice, the burst of nerve cells in the hippocampus was diminished. Conversely, when mice were housed in an 'enriched' environment — typically containing mazes, nesting materials and toys — they became more active and adventurous. Gage found that more neurons were being born in the hippocampus of the brain of these mice.

René Hen, Ph.D., who has had the support of four NARSAD Grants, was intrigued by Gage's studies and asked another different question: What is the link between Prozac and nerve growth? Using mice in animal models, Hen found that Prozac's positive effects depended on the birth of nerve cells in the hippocampi of the mice rather than solely the level of serotonin. In 2011, he and colleagues repeated the studies with depressed primates and found that neuron birth in the hippocampi of the depressed monkeys was low. When they gave the monkeys antidepressants, the depressed symptoms abated and neuron birth resumed. Blocking the growth of nerve cells made Prozac ineffective.

These discoveries have profound implications for treating depression. Antidepressants like Prozac and Zoloft, Hen suggests, may transiently increase serotonin in the brain, but their effect is seen only when new neurons are born. Might depression be precipitated by the death of neurons in certain parts of the brain rather than by a deficiency of serotonin?

These questions may be answered by the work of Brain & Behavior Research Foundation Scientific Council Member Helen S. Mayberg, M.D. Mayberg used her first NARSAD Young Investigator Grant 20 years ago to investigate brain changes in depressed patients using functional neuroimaging (fMRI). With the help of a

NARSAD Independent Investigator Grant, she went on to identify the subcallosal cingulate--Brodmann Area 25--as not only a key conduit of neural traffic that gives rise to emotion, but also as an area that appears overactive in depressed people. This area is particularly rich in nerve cells that are sensitive to serotonin. In 2002, with a NARSAD Distinguished Investigator Grant, she led breakthrough research when she piloted the use of deep brain stimulation (DBS) to target 'Area 25'.

The results of Mayberg's DBS treatment are remarkable: about 75 percent of treatment-resistant patients experience powerful changes in their moods during testing. And the link to serotonin is still important: researchers found that if they blocked the serotonin signal in the brains of depressed rats, DBS is no longer effective.

In time, these progressive discoveries will most likely lead to new antidepressants that directly initiate nerve growth in the hippocampus or stimulate the subcallosal cingulate. This synopsis of the remarkable journey-to-date to effectively treat depression demonstrates how research discoveries build upon each other. We are proud of the contributions of NARSAD-Grant funded research and thank you for your continued support on the journey to understand the brain and effectively treat its illnesses.