

A UNIFIED THEORY OF DEPRESSION

Antidepressants may work by providing a rosier lens through which to see the world

For decades two very different treatments of depression have existed side by side. Medications act on molecules, cells and synapses in the brain. Psychological therapies focus on cognition and behavior, trying to alter negatively biased thinking. Now a new theory suggests that these interventions may work in more similar ways than anyone realized, providing an opportunity to better integrate the two approaches. More important, it may help provide patients faster, more reliable relief from this crippling condition.

Antidepressant drugs increase the levels of certain chemical messengers in the brain, such as serotonin and norepinephrine. Yet exactly how these neurotransmitters affect mood is unknown. “There was a missing link between the cellular, molecular and synaptic bases of these drugs, on the one hand, and what they affect in humans, which is their experiences, perceptions, memories and feelings,” says Catherine Harmer, a neuroscientist at the University of Oxford.

The psychological explanation, meanwhile, describes depression in terms of distorted information processing. Depressed people are thought to process perceptions, experiences and memories with a negative bias. Many studies confirm that depressed individuals show increased sensitivity to sad faces, greater memory for negative material and reduced responsiveness to rewards as compared with healthy people. Successful therapies teach patients how to correct for this clouded vision.

Harmer now believes that antidepressants may also work by altering this negative emotional processing. About a decade ago she and her colleagues tested the effects of commonly prescribed antidepressants on healthy volunteers and found that many of the drugs skewed emotional processing to the positive. Previous research had shown that antidepressants also change these measures in depressed people, but studies included only patients who had been on medication for six to eight weeks because the drugs were assumed to take that long to kick in. Why antidepressants take so long to work “has been a puzzle in psychiatry for a really long time,” says Jonathan Roiser of the Institute of Cognitive Neuroscience at University College

London. Some patients spend months, or even years, trying one drug after another, with no way of knowing in advance which might work.

But in 2009 Harmer and her colleagues showed that a single dose of a common antidepressant altered emotional processing in depressed patients within a matter of hours. Initially, depressed people showed less sensitivity to happy faces, took longer to respond to positive descriptors of themselves and remembered fewer positive words than healthy volunteers. A dose of reboxetine—but not a placebo—returned all these measures to normal levels within three hours. Another study Harmer published in 2012 showed that the amygdala of depressed patients became less hyperactive in response to fearful faces after a seven-day course of escitalopram (Lexapro). In both studies, the emotion-processing changes happened well in advance of any improvement in mood.

If antidepressants provide a rosier lens through which to experience the world, the puzzle of their delayed action might finally be solved. A patient presumably needs time to become acquainted with the world that their new, more positive perspective unveils. This experiential learning might also explain why outcomes vary so widely with drugs. “You need to have enough opportunities to pick up on this more positive mode of processing,” Harmer says. She hopes to study whether patients who get out more are indeed the ones who do better. If so, doctors could identify people who need extra help coming out of their shell and reengaging with the world. “It’s a new perspective on how you might best combine pharmacological and psychological treatment,” she says.

Yet perhaps the most exciting aspect of this research is the possibility of predicting early how effective a treatment will be—both for individuals and in the development of new drugs. Initial indications are encouraging. A 2009 study found that patients who had been on antidepressants for two weeks showed increased accuracy in recognizing certain facial emotions, including happiness. Those whose accuracy changed the most also showed the most clinical improvement after six weeks, suggesting that these early processing changes might predict later outcomes.

Ultimately Harmer’s research may even enable us to stop seeing biology and psychology as competing explanations. “Her work provides us with the ability to bridge between those different levels of explanation,” Roiser says. “That’s very powerful.”

—Simon Makin

