



A CHANGE OF MIND

Cognitive behavioural therapy is the best-studied form of psychotherapy. But researchers are still struggling to understand why it works.

Anna's life began to unravel in 2005 when her husband of 30 years announced that he had fallen in love with another woman. "It had never even occurred to me that my marriage could ever end," recalls Anna, a retired lawyer then living in Philadelphia, Pennsylvania. "It was pretty shocking."

Over the course of several months, Anna stopped wanting to get up in the morning. She felt tired all the time, and consumed by negative thoughts. "I'm worthless. I messed up everything. It's all my fault." She needed help, but her first therapist bored her and antidepressants only made her more tired. Then she found Cory Newman, director of the Center for Cognitive Therapy at the University of Pennsylvania, who started her on a different kind of therapy. Anna learned how to obsess less over her setbacks and give herself more credit for her triumphs. "It was so helpful to talk to someone who steered me to more positive ways of thinking," says Anna, whose name has been changed at her request.

BY EMILY ANTHES

Cognitive therapy, commonly known as cognitive behavioural therapy (CBT), aims to help people to identify and change negative, self-destructive thought patterns. And although it does not work for everyone with depression, data have been accumulating in its favour. "CBT is one of the clear success stories in psychotherapy," says Stefan Hofmann, a psychologist at Boston University in Massachusetts.

Antidepressant drugs are usually the first-line treatment for depression. They are seen as a quick, inexpensive fix — but clinical trials reveal that only 22–40% of patients emerge from depression with drugs alone. Although there are various approaches to psychotherapy, CBT is the most widely studied; a meta-analysis¹

published this year revealed that, depending on how scientists measure outcomes, between 42% and 66% of patients no longer meet the criteria for depression after therapy.

But no one knows exactly how CBT helps. Depression is a complex disorder that manifests in many different ways, and CBT is multifaceted, involving a series of talking sessions whose precise content differs from one therapist and patient to another. Working out exactly how it affects the brain requires studies that are difficult to conduct and to fund. Still, researchers are beginning to piece together answers using a combination of clinical psychology and neuroimaging experiments. Learning more about how CBT works — and why it does not work for everyone — could ultimately help doctors to deliver better care.

"If we don't understand the active ingredients, it's going to be hard to improve the treatment," says Daniel Strunk, a psychologist at Ohio State University in Columbus. "In understanding the mechanism, we might ▶

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► understand that that's more relevant to some patients than others."

CBT encompasses a range of psychotherapies, all based on the premise that people with depression have excessively negative, and often inaccurate, beliefs about themselves and the world. It is designed to equip patients with the skills they need to "become their own therapists", says Strunk, by critically examining those negative beliefs. Correct a person's way of thinking, and the depression will lift, according to the theory.

On the face of it, this seems to be supported by results. "There are dozens of studies that show that people after being treated with cognitive therapy — and after being less depressed — show less negative thinking," says Robert DeRubeis, a psychologist at the University of Pennsylvania. "That's as easy to demonstrate as it is that gravity exists."

What scientists debate is the mechanism. People treated with antidepressants and other kinds of psychotherapy also show more positive thinking after recovering from depression. So does changing someone's thought patterns actually cause their depression to lift? Or does the therapy relieve depression in a different way — by helping people to form a bond with a therapist, for example — so that the positive thinking is merely a consequence of their improved mental health?

UNRAVELLING MECHANISMS

To get at this question, researchers have attempted to show that the change in thinking precedes and predicts the gains in mental health. "By the end of treatment, lots of things will be better," Strunk says. "And so what you really want to do is get inside the moment or moments when someone has a positive therapeutic change and try to understand what's shifting in just those moments."

Research by DeRubeis and his colleagues has revealed^{2,3} that many depressed adults undergoing CBT experienced 'sudden gains', in which their symptoms lessened significantly between two therapeutic sessions. These rapid changes accounted for more than half of the patients' total improvement over the course of treatment.

Recordings of the therapy session just before a sudden gain reveal that a person's way of thinking changes more in that session than in others. "Patients are beginning to speak about changing their minds about many of the negative, exaggerated ways in which they've seen their lives," says DeRubeis. The fact that they begin demonstrating these cognitive changes just before their symptoms improve suggests that altering a person's thinking style may indeed lead to recovery.

Researchers have also shown that learning mental coping skills may be the most important kind of cognitive change during CBT. "The cardinal skill is catching your thoughts in a moment where your mood takes a turn for the worse and thinking through the accuracy

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of your thoughts in that moment," says Strunk.

In CBT, therapists will often ask patients to monitor their own thoughts. Anna, for example, had been doing volunteer teaching when she started therapy, and she often found herself comparing her abilities with those of another teacher, which made her feel inadequate. Anna's therapist asked her to describe what she and the other teacher did during classes. "It was perfectly obvious once you started thinking about it that the other teacher and I both had good moments and bad moments," Anna recalls. "I had begun to focus on every possible negative about what I did, and every possible positive about someone else."

Anna is no longer in therapy, but when such thoughts return, she can now identify them and examine them to determine whether she is drawing unrealistic conclusions. "It's not that I never have sweeping negative thoughts," she says, "but I'm not so much a victim of them."

Strunk and his colleagues have found⁴ that gaining new cognitive coping skills correlates with an improvement in depressive symptoms, even if negative beliefs remain. And once people have learned these skills, they can use them for the rest of their lives, which may explain why the benefits of CBT last even after the treatment has ended — something that has not proved true for antidepressants. There are not many data on whether other forms of psychotherapy have a similarly protective effect.

Some researchers have looked to neuroimaging to understand more about the mechanisms of CBT. People with depression tend to have detectable differences in two primary brain systems: the prefrontal cortex, which is responsible for complex mental tasks such as self-control and planning, and the limbic system — including the amygdala — which is involved in emotional processing. In healthy people, the prefrontal cortex can inhibit amygdala activity, keeping emotions in check. But imaging shows that in many people with depression, the prefrontal cortex seems to be less active. "Depressed people have what you might think of as a trigger-happy amygdala,"

says Greg Siegle, a neuroscientist at the University of Pittsburgh in Pennsylvania.

There is some evidence that CBT can correct these problems. In a study⁵ published in 2007, Siegle used functional magnetic resonance imaging (fMRI) to show that depressed adults had increased levels of activity in the amygdala when performing an emotional task and reduced levels of activity in the dorsolateral prefrontal cortex when performing a cognitive task. When he followed up 9 of the trial participants, Siegle found⁶ that a 14-week course of cognitive therapy had almost completely reversed the situation.

"The imaging data have been really encouraging," says Timothy Strauman, a psychologist at Duke University in Durham, North Carolina, who has generated similar results⁷. "We do find evidence for the kinds of changes that you would expect."

Researchers speculate that CBT — with its focus on controlling thoughts — re-engages the underactive prefrontal cortex, which, in turn, helps to quieten the hyperactive limbic system (see 'Desired behaviour'). "Cognitive therapy teaches you to step in and use your prefrontal cortex rather than letting your emotions run away with you," says Siegle.

Still, there are caveats. The prefrontal cortex and the amygdala are not the only brain areas that behave differently in depression; nor are they the only areas that therapy affects. The studies have been small and they occasionally contradict each other. "I'm always cautious, because there haven't been enough studies," says Cynthia Fu, a neuroscientist at the University of East London, UK. She estimates that there have been three to four times as many neuroimaging studies of antidepressant use as of psychotherapy. "It's a new field, and people use different tasks, they scan people at different times, and that can lead to quite different results."

TOUGH QUESTIONS, TOUGH ANSWERS

As with the changes in negative thinking, it is not yet clear whether these neurological changes are a cause or a consequence of recovery. To answer that, scientists will need to image patients repeatedly throughout the course of CBT to track the changes and determine whether they predict improvement.

Such studies are expensive, time-consuming and burdensome for patients. And in general, scientists say, it can be harder to study CBT than antidepressants: there are more confounding factors, because therapists and sessions can vary widely. And it is difficult to administer a placebo. Researchers can compare participants receiving CBT with others who are randomly assigned to receive drugs or pharmacological placebos, or are put on a waiting list for treatment; they can also use a control group made up of patients who receive general counselling, but it is impossible to blind the study properly, because the therapists will know which participants are receiving which treatments. Another

challenge is finding funding. “It’s a David-and-Goliath-type comparison,” says Strunk. “There are pharmaceutical companies that make antidepressants, so there’s a lot of financial backing there. The amount of money is just different scales.”

Scientists are eager to know why CBT works for only some people, and to be able to identify those who will respond. “There’s a lot of trial and error,” says Lena Quilty, a psychologist at the Centre for Addiction and Mental Health in Toronto, Canada. But every failed treatment can extend a person’s suffering and add to the cost of medical care.

Certain clinical and demographic factors

seem to predict whether a person will respond to drugs or CBT. Those with personality disorders in addition to depression, for instance, tend to do better with antidepressant medications than with cognitive therapy, and married people seem to benefit more from cognitive therapy than from medication.

Researchers have now begun searching for patterns of brain activity that can identify how well someone will respond to CBT. In a study⁸ published last year, neurologist Helen Mayberg of Emory University in Atlanta, Georgia, and her colleagues used positron emission tomography (PET) to measure glucose metabolism in the brains of 82 adults with depression. They

then randomly assigned each participant to receive 12 weeks of treatment with either CBT or a commonly prescribed antidepressant from the selective serotonin reuptake inhibitor class. People with high activity in the right anterior insula, a brain region that communicates with both the amygdala and the prefrontal cortex, tended to respond well to the drug. Those with an underactive insula were more likely to improve with CBT.

It is not yet clear why. “Fundamentally, one has to think about the network in the brain that goes wrong in depression as being dynamic,” says Mayberg. “Those systems are broken differently in people who respond to different treatments.” Cognitive therapy may be able to repair some problems, whereas drugs may be better at patching up others.

Neuroimaging is not yet a practical tool for identifying the best course of treatment, so researchers are working on other approaches. In 2011, Siegle and his colleagues demonstrated⁹ that clinicians might be able to use the pupil of the eye as a window on the brain. Depressed adults were shown negative words; those whose pupils did not dilate much had reduced activity in some areas of the prefrontal cortex and were more likely to benefit from cognitive therapy than those whose pupils dilated more.

In practice, clinicians hoping to tailor treatments may need to consider many factors, including a person’s marital status, brain activity and genetics; a small body of research indicates that people with certain genetic sequences are more likely than others to respond to CBT.

And scientists may need to get a better handle on depression itself — in all its forms and manifestations — before they can understand how CBT alleviates it and who is likely to benefit. Strauman is optimistic about the growing number of collaborations that he is seeing between neuroscientists and clinical psychologists who are willing to tackle the problem. “I think we’re finally at the point,” he says, “where the complexity of our thinking is a match for the complexity of the disorder.” ■

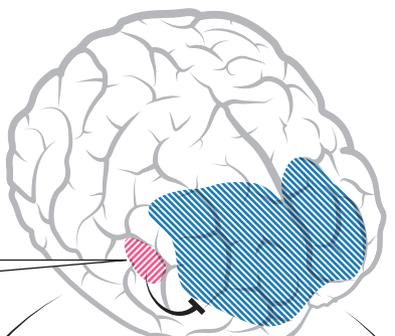
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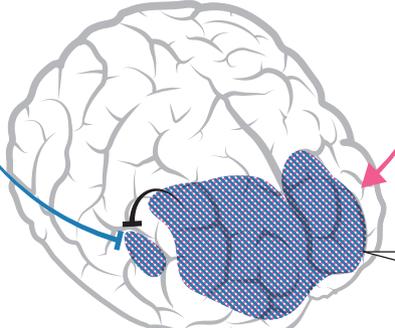
DESIRED BEHAVIOUR

Depressed individuals often have an overactive (pink) amygdala and a less-active (blue) prefrontal cortex compared to healthy people.

1 Activity in the amygdala, which is associated with emotional responses, may repress activity in the prefrontal cortex, which is involved in executive function.



2 Some researchers suspect that antidepressant medication quiets activity in the amygdala, whereas cognitive behavioural therapy (CBT) increases activity in the prefrontal cortex.



3 Although the two approaches work in different ways, they both seem to restore stability in these areas of the brain.

LONG-TERM BENEFITS

Studies have shown that people who completed a course of CBT had a lower rate of relapse than people who stopped taking antidepressant medication.

