NEWS IN FOCUS

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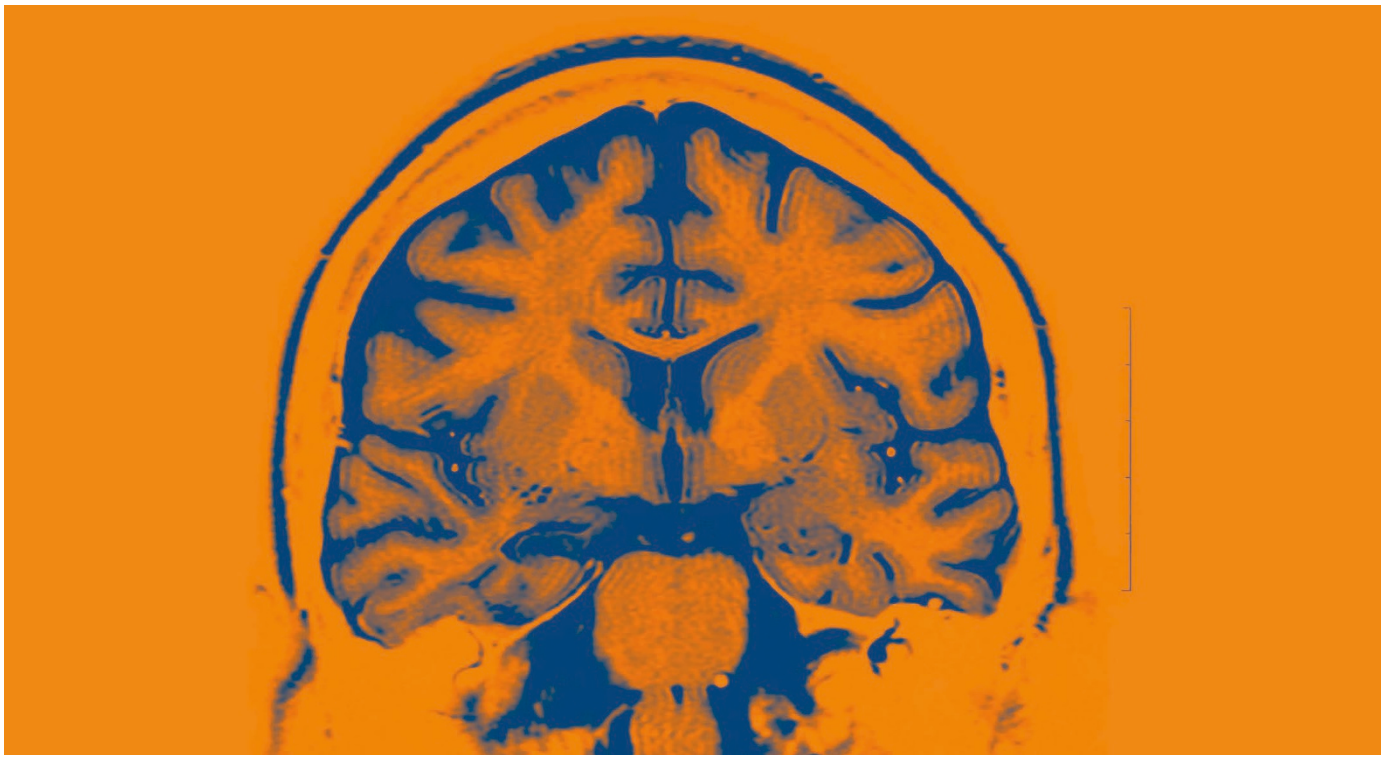

Brain implants are used to treat epilepsy and movement disorders.

NEUROSCIENCE

Brain implants for mood disorders tested in people

AI-controlled appliances record neural activity and automatically stimulate the brain.

BY SARA REARDON

Brain implants that deliver electrical pulses tuned to a person's feelings and behaviour are being tested in people for the first time. Two teams funded by the US military's research arm, the Defense Advanced Research Projects Agency (DARPA), have begun preliminary trials of 'closed-loop' brain implants that use algorithms to detect patterns associated with mood disorders. These devices can shock the brain back to a healthy state without input from a physician.

The work, presented this month at the Society for Neuroscience (SfN) meeting in Washington DC, could eventually provide a way to treat severe mental illnesses that resist current therapies. But it also raises thorny ethical concerns, not least because the technique could give researchers a degree of access to a person's inner feelings in real time.

The general approach — using a device implanted in the brain to deliver electric pulses that alter neural activity — is known as deep-brain stimulation. It is used to treat movement disorders, but has been less successful against mood disorders. Early evidence suggested that constant stimulation of certain brain regions could ease chronic depression, but a major study involving 90 people with depression found no improvement after a year (P. E. Holtzheimer *et al. Lancet Psychiatry* **4,** 839–849; 2017).

The scientists behind the DARPA-funded projects say that their work might succeed where earlier attempts failed, because they have designed their brain implants specifically to treat mental illness — and to switch on only when needed. "We've learned a lot about ▶

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the limitations of our current technology," says Edward Chang, a neuroscientist at the University of California, San Francisco (UCSF), who is leading one of the projects.

DARPA is supporting Chang's group and another at Massachusetts General Hospital (MGH) in Boston, with the eventual goal of treating soldiers and veterans who have depression and post-traumatic stress disorder. Each team hopes to create a system of implanted electrodes to track activity across the brain as the organ is stimulated. The groups are developing their technologies in experiments with people with epilepsy who already have electrodes implanted in their brains to track their seizures.

At the SfN meeting, electrical engineer Omid Sani of the University of Southern California in Los Angeles — who is working with Chang's team — presented the first map of how mood is encoded in the brain over time. He and his colleagues worked with six people with implanted electrodes for epilepsy, tracking their brain activity and moods over one to three weeks. By comparing the two types of information, the researchers could create an algorithm to 'decode' that person's changing moods. Some broad patterns emerged, particularly in brain areas associated with mood.

Chang and his team are ready to test their new single-closed-loop system in a person, Sani says. Chang adds that the group has already tested some closed-loop stimulation in people, but he declined to provide details because the work is preliminary.

The MGH team is taking a different approach. Rather than detecting a particular mood or mental illness, the researchers want to map the brain activity associated with behaviours that are present in multiple disorders — such as difficulties with concentration and empathy. At the SfN meeting, they reported on tests of algorithms that stimulate the brain when a person is distracted from a set task, such as matching images of numbers or identifying emotions on faces.

"You have to do a lot of tuning to get it right."

The researchers found that delivering electrical pulses to areas of the brain involved in decision-making and emotion significantly improved participants' performance. The team also mapped the brain activity that occurred when a person began failing or slowing at a set task because they were forgetful or distracted, and reversed it with stimulation. They are now beginning to test algorithms that use specific patterns of brain activity as a trigger to automatically stimulate the brain.

Wayne Goodman, a psychiatrist at Baylor College of Medicine in Houston, Texas, hopes that closed-loop stimulation will prove a viable long-term treatment for mood disorders — partly because the latest generation of algorithms is more personalized and based on physiological signals, rather than a physician's judgement. "You have to do a lot of tuning to get it right," says Goodman, who is about to launch a small trial of closed-loop stimulation to treat obsessive–compulsive disorder.

One challenge when stimulating areas of the brain associated with mood, he says, is the possibility of creating extreme happiness that overwhelms all other feelings. Other ethical considerations arise because the algorithms used in closed-loop stimulation can tell the researchers about the person's mood, beyond what may be visible from behaviour or facial expressions. "We will have access to activity that encodes their feelings," says Alik Widge, a psychiatrist and engineering director of the MGH team. Like Chang and Goodman's teams, Widge's group is working with neuroethicists to address the ethical concerns surrounding its work.

Still, Chang says, the technologies that his team and others are developing are only a first step towards better treatment for mood disorders. He predicts that data from trials of brain implants could help researchers to develop therapies that stimulate the brain through the skull. "For the first time," he says, "we're going to have a window on the brain where we know what's happening in the brain when someone relapses." ■

BIOLOGY

Cells use 'alien' DNA to make protein

Expanded genetic alphabet could allow for the production of new protein-based drugs.

BY EWEN CALLAWAY

Life has spent the past few billion years working with a narrow alphabet. Now, researchers have broken those rules by adding extra letters to biology's limited lexicon.

Chemist Floyd Romesberg of the Scripps Research Institute in La Jolla, California, and colleagues manipulated *Escherichia coli* bacterial cells to incorporate two types of foreign chemical bases, or letters, into their DNA. The cells used that information to insert unnatural amino acids into a fluorescent protein.

Organisms naturally encode heritable information using just four bases: adenine (A), thymine (T), cytosine (C) and guanine (G). These form pairs that hold together DNA's double helix, and different three-letter sequences code for each of the 20 amino acids that make up proteins in living cells. The latest work, reported in *Nature* on 29 November, is the first to show that unnatural bases can be used to make proteins in a living cell (Y. Zhang *et al. Nature* http://dx.doi.org/10.1038/nature24659; 2017).

The result, Romesberg says, shows that synthetic biology — a field focused on imbuing organisms with new traits — can accomplish its goals by reinventing the most basic facets of life. "There is no biological system so fundamental and more intimately related to what we are than information storage and retrieval," he says. "What we've done is design a new part that functions right alongside the existing parts and can do everything they do."

Several teams are attempting to expand the genetic code. The 4 natural DNA bases can be arranged in 64 different 3-letter combinations, called codons, that specify amino acids. But redundancy in this code — for instance, CGC, CGA, CGG and CGT all stand for the amino acid arginine — means that nearly all proteins needed for life are made of just 20 amino acids.

Some researchers, including geneticist George Church of Harvard Medical School in Boston, Massachusetts, are repurposing redundant codons to specify new amino acids. Romesberg's group is exploring a different strategy: adding an entirely new base pair into DNA. That would vastly increase the number of possible codons, in theory giving cells the ability to exploit more than 100 extra amino acids.

Although Church still thinks that his own approach is more practical for most applications, he describes the new work as a "milestone in exploring the fundamental building blocks of life".

NATURAL FIT

To function in living cells, foreign base pairs need to sit alongside natural bases without disturbing the shape of DNA or disrupting essential tasks, such as the processes that faithfully copy DNA and transcribe it into messenger RNA — an intermediary molecule between DNA and proteins. In 2014, Romesberg's lab

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