My New Scientist

Memory implants: Chips to fix broken brains

04 June 2014 by Sally Adee
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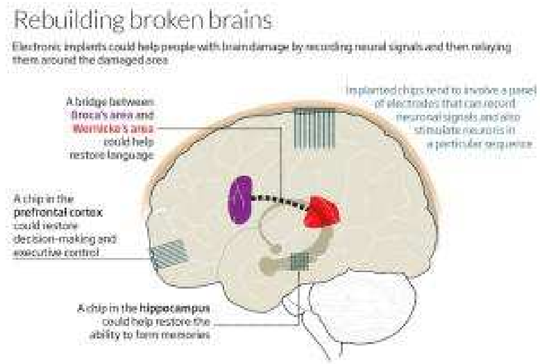

Rebuilding broken brains

Enlarge image

Bridging the brain gaps *(Image: Raymond Beisinger)*

Transplanted memories and mind-controlled wheelchairs are real – now implants are on the horizon that will repair brain damage and maybe even patch dementia

SAM DEADWYLER's work sounded a little too much like something from *The Matrix* – and that was a big problem. In the same way that Neo downloads a kung fu master's skills, Deadwyler had wired up the brain of a rat with electronics that transplanted memories derived from 30 rats into its brain, allowing it to draw on training that it had never personally experienced. The study had the potential to be a landmark finding – but "everyone thought it was science fiction", he says. "I thought, 'no one's going to believe this unless I do a hundred control experiments'."

So he did just that. Last December – 10 years after the original experiment – the paper was published at last. Instant kung fu is still the stuff of Hollywood blockbusters, but this research could nevertheless have a huge impact on many people living with brain damage. Ultimately, the same kind of neural implants that allowed memories to be "donated" from many rats into another individual could restore lost brain function after an accident, a stroke or Alzheimer's disease.

For a lot of people with memory loss, damaged parts of the brain are failing to pass information from one area to another. If you could create electronics that interpret the signals from one area, circumvent the damaged parts, and write them into the second area, you could help people regain the ability to form new memories, or even gain access to precious old ones. Such a chip would act as a kind of brain bypass.

Getting there won't be easy: such an implant requires neuroscience that is only now beginning to be understood. More than that, however, these new technologies raise ethical questions that were once the reserve of science fiction. Our memories define us, so preserving them from damage could save our identity – but when your memory is a computer algorithm, are you still the same person? It's almost time to find out: the first human studies will begin within five years.

Our ability to communicate directly with the brain has accelerated rapidly over the past two decades. The technology – known as brain-machine interfaces – has restored hearing and sight in the form of cochlear and retinal implants. It has also helped people control prosthetic limbs: one robotic arm, connected to the motor cortex, has such sensitivity that amputees can hold a cup of coffee, pick individual grapes and even play the guitar.

Impressive as they are, however, these devices have a limited job. "The prosthetic limbs are mainly about output – we read one area of the brain and use it to control a device," says Robert Hampson, who works on cognitive implants with Deadwyler at Wake Forest Baptist Medical Center in North Carolina. "And the retinal and cochlear implants are input devices. We take output from a machine and input it to one part of the brain."

When translating between two areas of the brain, however, you need a device that can do both: record activity from one set of neurons and then electrically stimulate another set of neurons to replay it whenever it is needed. Needless to say, it's an endeavour rife with challenges. "To make a cognitive device, we first have to know what a memory looks like," says Hampson. The search for a memory trace in the brain has been complicated by the fact that there are many different kinds of memories: there's the short-term "working memory" that helps you to remember a phone number before you dial, sense memories that might include the echo of what someone's just said, and long-term memories of facts, skills and experiences. It is this long-term recall, and how it emerges from working memory, that Deadwyler and Hampson are interested in.

Although each memory trace is different, all long-term memories begin life in a region called the hippocampus, the brain's "printing press". Place an implant here and it might be possible to record memories as they form. The next step is to figure out the neural code that represents a particular memory. The key is thought to lie in the exact firing pattern of interconnected neurons; one synchrony of neurons might translate to your idea of the Eiffel tower, for instance, while another, perhaps overlapping, network might represent Paris more generally.

Quietly, over the past couple of decades, neuroscientists have begun to find ways to crack that code. Early steps were made in the 1990s by Theodore Berger at the University of Southern California, who turned to a technique called multi-input/multi-output. MIMO is more typically used to tease signal from noise in wireless communications, but Berger realised he could apply the same principle to pick out meaningful signals from the noise of millions of neurons firing. The quest didn't endear him to sceptics. "People called him crazy for a long, long time," says Eric Leuthardt, a neurosurgeon at the University of Washington in St Louis, Missouri.

It's not that memory signatures have been invisible to other scientists. There has been some evidence to suggest that people have extremely specialised neurons that fire in response to a single concept, such as their grandmother or Jennifer Aniston.

However, these so-called grandmother cells encode a narrow range of ideas, whereas Berger was chasing the ability to encode any memory. Slowly but surely he has shown that the MIMO algorithm can do this – by using it to isolate the specific signal behind the memory of an action, and then replaying that exact sequence.

In one groundbreaking experiment, Berger – now working with Deadwyler and Hampson – implanted a chip containing electrodes into the hippocampus of rats. Then they used the MIMO algorithm to isolate and record the relevant neural code as trained animals pressed one of two levers to receive a treat. After drugging the rats to impair their ability to remember which lever gave the treat, the team then used the same electrodes to deliver the same firing pattern back to the neurons. Despite its amnesia, the rodent knew which lever to push. In other words, the algorithm had helped to restore the rat's lost memory.

It was a triumph, demonstrating that electronics can crack the neural code and potentially replace damaged areas of the brain – acting as an artificial hippocampus to treat amnesia, for instance.

One key question raised by Deadwyler's research was whether we each have a different neural code, or whether there is a more generalised language shared by everyone. This is where Deadwyler and Hampson's attempts to transplant memories between rats comes in. Their experiments typically involved two sets of rats trained to run between two arenas, pressing a series of levers in a certain order. Importantly, one set was trained to delay their actions – they had to pause for up to 30 seconds before they were able to press one of the levers – while the second set was not. Presented with the unexpected delay, the second set of rats lost the plot – they could not remember which lever they had been taught to press. But when Deadwyler and Hampson used MIMO to record the brain activity for this task in the first group and replayed it in the second using electrodes, those rats began to act as if they had taken the alternative form of training, choosing the correct lever even after a long pause, even though that had not been part of their previous experiences. "Our model lets us establish a memory that has not been used before," Hampson says.

Was the set-up really this good? Or could their success be explained by some other cause? Deadwyler and Hampson embarked on an enormous number of control experiments to rule out every other explanation, including the possibility that it was just an unintentional artefact of electronically tickling the brain, or some general improvement caused by electrical stimulation. Finally, in December the paper was published: it really is possible to plant a general signature of a memory in the brain (*Journal of Neural Engineering*, vol 10, p 066013).

If that could be replicated in humans, a chip could come with ready made code that could give people a head start on relearning general skills such as brushing your teeth or driving a car, say – actions that are often lost after brain damage. "Before we can get someone with brain damage back to work, we want to return their capability to form those fundamental declarative memories," says Justin Sanchez, who is in charge of neuroprosthetics research at the University of Miami in Florida.

Wired up

Further developments should allow these neural chips to tackle more sophisticated problems than simple skill learning. "Think of the guy coming back from war who can't remember his wife's face," says Sanchez. For that kind of recognition, the brain breaks down the person, place or object into specific features – such as the colour of their hair or their height – and encodes them separately.

Using MIMO to replicate that process is an ambitious challenge that Deadwyler and Hampson have begun to explore more recently. For instance, they trained macaques to remember the position and shape of a picture on a screen, and then choose the same image from a much larger selection nearly a minute later. All the while the algorithm, via electrodes in the macaques' brains, recorded the neural signals that formed in the prefrontal cortex and hippocampus. Then they drugged the monkeys to disrupt their ability to form new long-term memories, before getting them to perform the task again. When they electrically stimulated neurons with the same signals that they had recorded on successful trials, those monkeys performed a lot better. By injecting the code, they had stimulated the hippocampus and the prefrontal cortex to reproduce the "correct" memories.

Intriguingly, Deadwyler and Hampson had found patterns that corresponded not to the exact images the monkeys were looking at, but to more universal features in them, such as whether they contained the colour blue, or a human face. "This is how we think memory works," says Deadwyler: instead of wastefully creating separate neural signatures for every new person, place or thing you encounter, the brain breaks the incoming information down into features. "Then to remember a specific item, you don't need to remember everything about it," he says. Rather than the fine details, it's the combination of features that help bring the item in question back to mind.

The monkeys' own brain plasticity may have given the algorithm a helping hand, says Daofen Chen at the National Institutes of Health in Bethesda, Maryland. "The brain tries to meet the machine halfway," he says. "It is an adaptive process. Give the brain enough – even imperfect – information, and it can translate it into something it finds useful." This phenomenon has already been robustly demonstrated for cochlear implants, and it could be a powerful aid to any brain-injured people hoping to use future cognitive implants.

As the technology improves, brain chips that incorporate electrodes and algorithms like MIMO may be able to translate extremely fine details of an experience. Ranulfo Romo at the University of Mexico has shown that his chips can pick up the signals that capture very subtle changes in sensory perceptions, such as a certain frequency of vibrations against the skin. As a proof of principle, he even used the set-up to implant one monkey's ongoing sensations into another's brain, as if they were telepathic. "The monkeys integrated the false perception as their own working memory," says Romo.

The work is an important sign of the recent progress, says John Donoghue of Brown University in Providence, Rhode Island, whose work on brain-machine interfaces inspired current neuroengineering. "The monkey had to make a sophisticated perceptual distinction," he says. "Romo showed that not only do you detect the information, but you can use it as if it were real," he says.

Such fine-tuned decoding of sensory information could have important applications beyond restoring perceptual information to memories. For instance, sometimes people lose the ability to speak thanks to damage in the brain between Wernicke's area and Broca's area. A chip capable of picking up on those detailed sensory signals and translating them between the two regions might therefore return their speech (see diagram).

Despite these advances, the biggest unknown is the quality of the experiences. "For an animal, you can't ask them 'what is your perception of a memory?'," says Sanchez. That could soon change. The Restoring Active Memory project, run by Sanchez for the US Defense Advanced Research Projects Agency (DARPA), is pushing the research into human trials. It is due to select researchers for funding at the end of this month, and one of the first steps will be to understand how the experience of a new memory translates into electrical code in the human brain.

Prying into the hippocampus is already a familiar undertaking, thanks mostly to experiments on people with intractable epilepsy, whose doctors eavesdrop on their brain signals using deep penetrating electrodes to better understand their condition (see "Source code"). MIMO, Sanchez says, is only one of several contenders for processing these signals. After the competing algorithms and electronics have been tested and refined on volunteers like these, prototype chips will enter clinical trials. These studies will require the approval of the US Food and Drug Administration and informed consent of the volunteers. If deemed sufficiently safe by the FDA, a chip will be cleared for use. DARPA hopes to use the resulting implants to help soldiers who return from war with traumatic brain injuries.

Several neuroengineering researchers envision similar chips for people with Alzheimer's disease and stroke, depending on the extent of the damage. In more severe cases of brain damage, Hampson imagines a device worn on the belt, with buttons that help you remember specific locations and their meanings. "Let's say I'm in the kitchen – I need to remember where the silverware is," he says. The patient would press the right button "and the memory pops up because we've stored the code".

As the target population for such implants widens, the obvious ethical questions centre around issues of informed consent. After all, for most experimental procedures, consent requires a sound mind, and memory chips are specific interventions for people whose minds have been damaged. Both Deadwyler and Sanchez say this issue is more straightforward than it appears: procedures have long been in place to allow close relatives of people in comas or with illnesses such as Alzheimer's to make decisions for them.

The deeper questions about memory modification were familiar staples in the arts long before Neo uploaded kung fu. As Luis Bunuel, arguably the father of surrealist film, put it: "Our memory is our coherence, our reason, our feeling, even our action. Without it, we are nothing." If you change those memories artificially, are you still you?

Deadwyler and Hampson's rat experiments highlight one possible concern: your memories may no longer be your own. "Activate the right circuits, and you generate the illusion that you are recalling something," says Romo. What kind of controls could ensure that every implanted memory reflected the reality of that person's environment? And whether or not those memories are your own, sparking neurons related to memory will eventually lead, directly or not, to changes in your decisions – so who is responsible for the consequences of those decisions?

There is also the chance that such chips could regurgitate long-buried events. Not all of those recollections will be wanted – one of the brain's biggest talents is to forget, as well as to remember. But perhaps it's a small price to pay for a lifetime of new memories to come.

This article appeared in print under the headline "The memory fix"

Source code

We've come a long way in our ability to decode the meaning of the brain's signals – far enough to allow people to control wheelchairs with their thoughts and perhaps even restore their ability to form new memories (see main feature).

But before you can tease out what the brain's signals might mean, you first need a high-fidelity signal. There are many ways to eavesdrop on the brain's electrical communications, and they're all about trade-offs. Think of it as a night at a concert. Non-invasive electrodes on the scalp can listen to the entire orchestra. You can zero in on the string section by getting a little more invasive with electrocorticography, which involves placing a sheet of electrodes on the surface of the brain. But if you want to listen to an individual violin, you have no choice but make direct contact with individual neurons.

Such high precision requires inserting deep-penetrating electrodes – which come with several caveats. Their insertion can rip and slice the surrounding neurons, causing oedema and scarring, and the brain's immune response forms scars that wall off the invading object. Soon, the electrodes can no longer read any meaningful information.

As a result, few implants have lasted more than a year or two. "Ideally you want a lifetime implant," says Mohammad Reza Abidian of Pennsylvania State University in University Park. We may soon be able to extend their life expectancy by "up to 10 years". Abidian has surveyed what neuroscientists are exploring for the next generation of electrodes.

1. Shrink

Creating thinner wires mitigates one of the major mechanical issues with brain implants –

the fundamental mismatch between a hard, rigid electrode and a soft, squishy brain. The thinner you make them – and some are now nanofilaments – the more bendy they become and the less they'll irritate the brain.

2. Camouflage

No matter how thin, penetrating electrodes will give themselves away as foreign objects because they are made of silicon with metal tips. Some scientists are looking into biocompatible materials and hydrogels to render the interlopers invisible. Wrapping polymer electrodes in silk is another option, allowing them to easily slide into soft brain tissue. Once inside, the silk dissolves and is absorbed by the brain – without an immune response. But even biocompatible materials won't fool the brain's immune cells all the time.

3. Infiltrate

To really blend in, you need to trick the brain into thinking your implant is alive. To do this, some researchers are looking into organic electrodes, made of materials such as polymers and hydrogels, which are most famously found in contact lenses.

4. Seduce

A perfect implant would not just be tolerated but would entice neurons into embracing the electrodes, growing into and around them. Neuronal connections tend to be insulated with myelin, so researchers at the University of California, San Francisco, have built polymer scaffolds that encourage the brain to lay myelin around implants, which should improve the chances of making a good connection. Others are doping electrodes with neurotransmitters, proteins and nerve growth factors.

Besides listening to neurons, electrodes often need to stimulate them, which can also cause damage if done repeatedly. A left-field technique may minimise the intrusion.

Using a technique called optogenetics, researchers can use pulses of light to switch the genes inside individual neurons on or off. This should make it possible to pinpoint specific parts of the brain, the way only penetrating electrodes can now. There are even indications that it can be done without the fibre-optic cable that is currently necessary to deliver the light into the brain: passing certain wavelengths of light through an intact skull has shown promise.

There's just one catch. To make the cells sensitive to light, you need to insert a gene using gene therapy. Even so, neuroscientist Sam Deadwyler at Wake Forest University in North Carolina thinks that while using optogenetics in humans is a long way off, it's the only way cognitive prostheses will ever be used beyond people with brain injuries and diseases. "It's a technology that doesn't require you to put electrodes in the head," he says. "That would make it possible to adapt for general use."

In other words, if it doesn't require brain surgery, it's something people might use some day simply to improve their memory.

The rise of the silicon brain

It is nearly 150 years since scientists discovered that the brain's neurons can be stimulated with electricity. The hope is that chips doing just this can bypass damaged parts of the brain – restoring lost sight, movement and memory. Progress has been slow, however

1870

Gustav Fritsch and Eduard Hitzig show that electrical stimulation to the brain's motor cortex can control the body's movements

1956

First patent awarded for a retinal implant to restore sight to blind people. It took decades for a working device to be realised

1957

First human trial of cochlear implants, which transmit sound to the brain. Although the technology was crude, it showed that electronics can translate sensory information into the brain's language

1996

Electrodes were implanted in the right and left hemispheres of a monkey's brain, giving it control of a prosthetic arm

2004

A volunteer with quadriplegia tested BrainGate, a device implanted into his brain that allowed him to switch on lights, change channels on a television and manage e-mails using only his thoughts

2008

Another volunteer with quadriplegia performs sophisticated movements with a prosthetic arm, controlled via a chip in his motor cortex that sent commands to the arm

2010

Treatment-resistant depression is mitigated by stimulation with a deep-brain electrode

2011

An electrode array manages to restore a rat's memory after its hippocampus is temporarily disrupted – showing the technique could cure some forms of amnesia

2012

Second Sight, based in California, creates glasses with an integrated camera that converts images into electronic patterns. These are sent to a small patch of electrodes surgically attached to the retina, where they stimulate nerves leading to the brain. A small group of blind volunteers reported that the system let them detect hand movements. Some could even count fingers

2012

A prosthetic arm created at the University of Pittsburgh – directed by two implants in the motor cortex – allowed a 52-year-old woman paralysed from the neck down to eat without assistance for the first time in 10 years

2014

DARPA's Restoring Active Memory project is launched. It aims to begin human trials on memory implants within five years

***Sally Adee** is a features editor at New Scientist*

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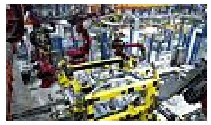

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