NATURE|Vol 461|15 October 2009

Small, furry ... and smart

Researchers have engineered more than 30 strains of 'smart mice', revealing possible ways to boost human brains. But, as **Jonah Lehrer** finds, cognitive enhancement may come at a cost.

P. MURPHY

Ten years ago, Joe Tsien eased a brown mouse, tail first, into a pool of opaque water. The animal squirmed at first; mice don't generally like getting wet. But once released, it paddled in a wide circle, orienting itself by the array of coloured shapes hung above the pool. Within seconds, the mouse headed straight for the safety of a small platform hidden just beneath the water's surface.

Most mice require at least six sessions before they can remember the location of the platform in a Morris water maze. But this animal needed just three.

Tsien, based at Princeton University in New Jersey at the time, named his creation Doogie after the teenage genius in the television programme *Doogie Howser, MD*. The work was one of the earliest examples of neuroscientists using genetic engineering to generate cognitively enhanced animals in a bid to understand memory and learning.

PRINCETON UNIV.

"There's something magical about taking a mind and making it work better," says Alcino Silva, a professor of neuroscience at the University of California, Los Angeles, and one of the pioneers in the field of enhanced cognition.

Researchers have now created or identified at least 33 mutant mouse strains that, like Doogie, have enhanced cognitive abilities. The animals tend to learn faster, remember events longer and solve complex mazes better than ordinary mice. And because the molecular pathways used in the brain to form long-term memories are almost identical in humans and rodents, the hope is that the work will inform research into treatments for a wide variety of learning and memory problems, from dyslexia to dementia.

Much of the work involves making an adult brain behave more like a younger, more flexible version of itself by increasing the organ's plasticity. This, in turn, means that some problems, long believed to have been made permanent during development, might actually be reversed.

Moreover, the mice raise a tantalizing possibility that normally functioning human brains could be improved. Already, drugs designed to help with attention deficit and sleep disorders are infiltrating college campuses and workplaces around the world, where they are being used without prescription to enhance cognition. Within the next decade, it might be possible to take a pill that will not only help alleviate the symptoms of learning disorders but also act as an intellectual steroid, pumping up the brain's potential. What the mice have clearly shown, in ways that pill-popping humans have not, is that enhancement could have unexpected trade-offs.

Improving on evolution

It was while Silva was studying mouse models of neurofibromatosis, a genetic disorder characterized by learning disabilities and benign tumours in nerve tissue, that he inadvertently created his first smart mouse. The disorder is caused by a mutation in a single gene, and Silva thought that models of the disease might allow him to investigate the molecular mechanisms underlying learning and memory.

In one model, Silva and his colleagues found that Ras, a family of growth-promoting signalling proteins, had enhanced activity in a subset of neurons that inhibit the firing rate of connected neurons. Steven Kushner, a postdoc in Silva's lab, engineered a mouse that had a constantly active form of one of the Ras proteins, Hras, but only in excitatory neurons, which increase the firing rate of connected neurons. The team was

surprised to find that these animals learned and remembered things much faster than normal mice in certain memory tests[1]. After just a single trial, the engineered mice learned to link a minor electrical shock with specific surroundings, causing the animals to freeze in fear when placed back in the cage where it first received the shock. Normal animals don't learn this association with such a mild shock.

The team was able to identify how this enhanced learning came about at the molecular level. Long-term memory is believed to be based on the strength of the link between two nerve cells. What Silva's team saw was an increase in the amount of the neurotransmitter glutamine being released at the synapse — the junction between two neurons — in the Hras mutants, which strengthened the connection at that junction through a process called long-term potentiation (LTP).

"The thrilling part is being able to connect these seemingly slight differences at the molecular level to dramatic differences in observed behaviour," Silva says. "That's a sign that we're really starting to understand the core processes of learning and memory in the brain."

Unlike Silva, Tsien had set out to create a smart mouse when he developed Doogie. He focused on brain-cell receptors for the chemical NMDA (*N*-methyl-D-aspartate). First linked to long-term memory in the late 1980s, the NMDA receptor is often referred to as the brain's 'coincidence detector' as it is activated only when two connected cells fire simultaneously. The receptor enhances LTP, with the end result that the brain can detect the connections between seemingly separate events, such as seeing fire and feeling pain.

Tsien created Doogie by overexpressing a subunit of the NMDA receptor called NR2B. This kept the receptors open for longer, strengthening the synaptic link and making it easier for disparate events to be linked together. "They all thought I was crazy," recalls Tsien. "They said the brain has been optimized by evolution. You won't be able to improve it."

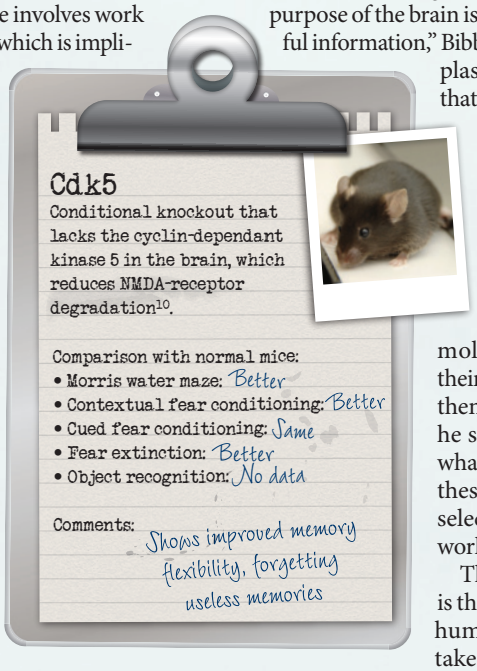
When Tsien published his results[2] in 1999, the media reacted with excitement and hyperbole. *Time* magazine put the research on its cover, asking whether researchers had finally found the "IQ gene".

Doogie and the enhanced mutants that have followed in its wake share more than just the accolade of being smart. "What's most striking about these different animals is the convergence," Silva says. Nearly all of the mouse strains show enhanced LTP. "There are so many different ways to tinker with learning and memory, and yet almost all of these improvements work through the same mechanism," he says. According to Silva and others, this is evidence that LTP is a fundamental feature of learning and memory, and that by increasing plasticity it is possible to increase cognitive capacity.

The damage undone

Being able to genetically engineer an animal with enhanced brain power is exciting, but can a brain that has already developed abnormally be fixed? In some instances, the answer may be yes.

One promising example involves work on a protein called CREB, which is implicated in memory formation. In 1995, Tim Tully, a neuroscientist then at Cold Spring Harbor Laboratory in New York, managed to improve memory and learning in a mutant fruitfly[3] by overexpressing a form of CREB. He and others built on this work in mice to try to tackle a rare genetic condition called Rubinstein–Taybi syndrome.



Characterized in humans by severe learning difficulties, as well as short stature and an increased risk of developing tumours, Rubinstein–Taybi syndrome is caused by mutations in the gene for the CREB-binding protein. Neuroscientists had assumed that the cognitive defects caused by the syndrome were irreversible — especially as the condition can be diagnosed before birth. But in 2003, Tully and several others showed that administering drugs that increase CREB activity in mouse models of the disease dramatically improves the animals' ability to learn[4–6].

"We get complete recovery in adult mice," says Mark Mayford, a neuroscientist at the Scripps Research Institute in La Jolla, California, who was an author on one of the studies. "I was pretty amazed."

The success stretches beyond Rubinstein–Taybi syndrome — the cognitive defects in other developmental diseases such as neurofibromatosis, Down's syndrome and fragile X, a genetic disorder that causes a wide range of behavioural and intellectual deficits, have all proved to be reversible in mice[7]. Although it remains unclear if the same approach can be applied to humans, Tully and others are bullish. "This work is a shot across the bow of the future," says Tully, now chief science officer at Dart NeuroScience in San Diego, California, which has been investigating compounds that manipulate the CREB pathway. "It shows us just how important increasing plasticity can be, and how we can put plasticity to work."

James Bibb at the University of Texas Southwestern Medical Center in Dallas says that drugs developed as a result of this work could be used to treat conditions such as post-traumatic stress disorder and drug addiction, which require people to unlearn negative associations. "The purpose of the brain is to help us learn useful information," Bibb says. "By increasing plasticity, you can push that process along."

Silva imagines a near future in which people with learning and memory disorders will be slotted into a number of categories, based on the molecular specifics of their disorder. "We could then target the therapy," he says. "We could use what we've learned from these enhanced mice to selectively fix what isn't working."

The concern for some is that otherwise healthy humans would want to take such drugs in a bid to make themselves smarter or stave off age-related cognitive decline. "I think these drugs are going to lead to some real slippery-slope issues," says Martha Farah, who heads the Center for Neuroscience and Society at the

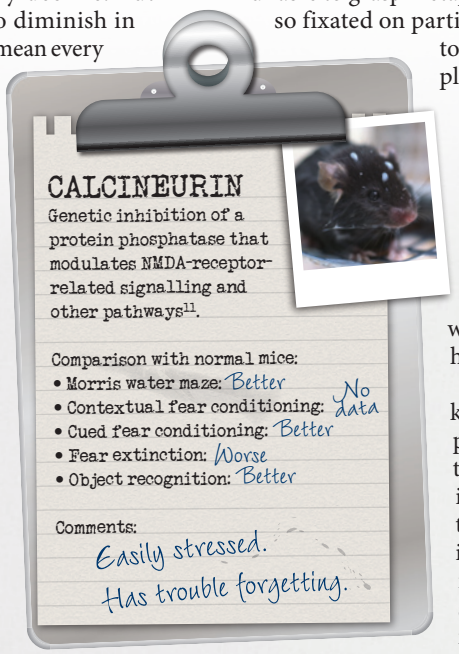
T. SILVA

UNIV. TEXAS SOUTHWESTERN MED. CENTER

University of Pennsylvania in Philadelphia. "There is no clear or objective line between a normal brain and one that needs treatment. For instance, we can say that we're only going to use these memory drugs for people with demonstrated memory decline. But your memory starts to diminish in your thirties. Does that mean every 40-year-old is going to be taking these pills?"

Farah notes that this is already starting to happen with drugs used to treat attention deficit or sleep disorders, as these act as mental stimulants. For instance, one in five respondents to a web poll run by *Nature* in 2008 admitted to using some of these drugs, such as Ritalin (methylphenidate) or Provigil (modafinil), to enhance their focus and productivity[8]. "You get more and more people taking them for less and less severe conditions," she says.

I. MANSUY/ UNIV. ZURICH



Risky business

Little is known about the side effects and trade-offs of both the current usage or the drugs in development, but initial clues offered by smart mice raise concerns. The Hras strain developed in Silva's lab might be good at learning, but its fear response for a relatively benign stimulus would be counterproductive for a wild mouse. Its enhanced memory is both a blessing and a burden. Silva cites other strains of smart mice that excel at solving complex exercises, such as the Morris water maze, but that struggle with simpler mazes. "It's as if they remember too much," he says — possibly taking in irrelevant information such as the position of windows or lights but missing the big clues.

Farah sees a parallel between these mice and one of the few case studies of an individual with profoundly enhanced memory. In the early 1920s, the Russian neurologist Alexander Luria began studying the learning skills of a newspaper reporter called Solomon Shereshevsky, who had been referred to the doctor by his editor. Shereshevsky had such a perfect memory that he often struggled to forget irrelevant details. He was able to recite in Italian several stanzas of Dante's *Divine Comedy* after one learning session, even though he was unfamiliar with the language. Although this flawless memory occasionally helped Shereshevsky at work — he never needed to take notes — Luria also documented the profound disadvantages of such a capacious memory. Shereshevsky, for instance, was almost entirely unable to grasp metaphors, as his mind was so fixated on particulars. When he tried to read poetry, for example, "the obstacles to his understanding were overwhelming", Luria wrote in his book *The Mind of a Mnemonist*. "Each expression gave rise to a remembered image; this, in turn, would conflict with another image that had been evoked."

For Luria, Shereshevsky's struggles were a powerful reminder that the ability to forget is as important as the ability to remember. Enhancing human memory in individuals without severe cognitive defects might prove counterproductive.

Many scientists are concerned that the animal models of enhanced cognition might obscure subtle side effects, which can't be studied in rodents or primates. Farah is currently looking at the trade-off between enhanced attention — she gives human subjects a mild amphetamine — and performance on creative tasks. Other researchers have used computer models to show that memory is actually optimized by slight imperfections, as they allow one to see connections between different but related events[9]. "The brain seems to have made a compromise in that having a more accurate memory interferes with the ability to generalize," Farah says. "You need a little noise in order to be able to think abstractly, to get beyond the concrete and literal."

And then there's the problem of non-cognitive side effects. Because many of these learning and memory enhancements involve molecules that regulate a wide variety of fundamental cellular pathways, such as CREB, it might be impossible to restrict their action to the brain. The Doogie mice, for example, seem to have an increased sensitivity to pain. And the *Hras* gene mutated in Silva's mice is commonly mutated in cancer.

"There's no such thing as an enhancement without side effects," says Nobel laureate Eric Kandel, a neuroscientist at Columbia University in New York and co-founder of Memory Pharmaceuticals, a biotechnology company in Montvale, New Jersey, that is trying to turn his research on LTP into novel drug therapies for memory disorders. "It often takes years to fully understand all the side effects. The mice will help us work out some of the bugs, but these will still be very risky treatments."

Although Silva recognizes the risks of enhancement, he remains hopeful that the performance of the normal human brain can be improved by neuroscience. "We're getting to a point where we almost need these enhancements," he says. "We don't have enough attention, we don't have enough memory, we don't have enough awake hours. There's clearly a demand to optimize the human brain given what it needs to do in the information age."

Like Kandel, Tully has spent much of the past decade trying to translate the biochemistry of memory into useful medical therapies. He remains enthusiastic, although he is also aware that the road ahead is littered with false leads, mistaken hypotheses and treatments that work in mice but fail in clinical trials. It's been ten years since Tsien, now at the Medical College of Georgia in Augusta, created Doogie, and although that's a short time in research years, Tully, for one, is getting impatient.

"When I began working on these learning and memory drugs, I had no grey hair and I thought I'd find a drug that might be able to help my parents," Tully says. "Now my hair is mostly white and my parents are dead. I'm just hoping that we can find a drug in time for me." ■

Jonah Lehrer is a freelance writer based in Los Angeles, California.

1. Kushner, S. A. *et al. J. Neurosci.* **25,** 9721–9734 (2005).
2. Tang, Y.-P. *et al. Nature* **401,** 63–69 (1999).
3. Yin, J. C. P., Del Vecchio, M., Zhou, H. & Tully, T. *Cell* **81,** 107–115 (1995).
4. Bourtchouladze, R. *et al. Proc. Natl Acad. Sci. USA* **100,** 10518–10522 (2003).
5. Alarcón, J. M. *et al. Neuron* **42,** 947–959 (2004).
6. Korzus, E., Rosenfeld, M. G. & Mayford, M. *Neuron* **42,** 961–972 (2004).
7. Ehninger, D., Li, W., Fox, K., Stryker, M. P., & Silva, A. J., *Neuron* **60,** 950–960 (2008).
8. Maher, B. *Nature* **452,** 674–675 (2008).
9. McClelland, J. L. in *Memory Distortion: How Minds, Brains, and Societies Reconstruct the Past* (ed. Schacter, D. L.) 69–90 (Harvard Univ. Press, 1995).
10. Hawasli, A. H. *et al. Nature Neurosci.* **10,** 880–886 (2007).
11. Malleret, G. *et al. Cell* **104,** 675–686 (2001).

P. MURPHY