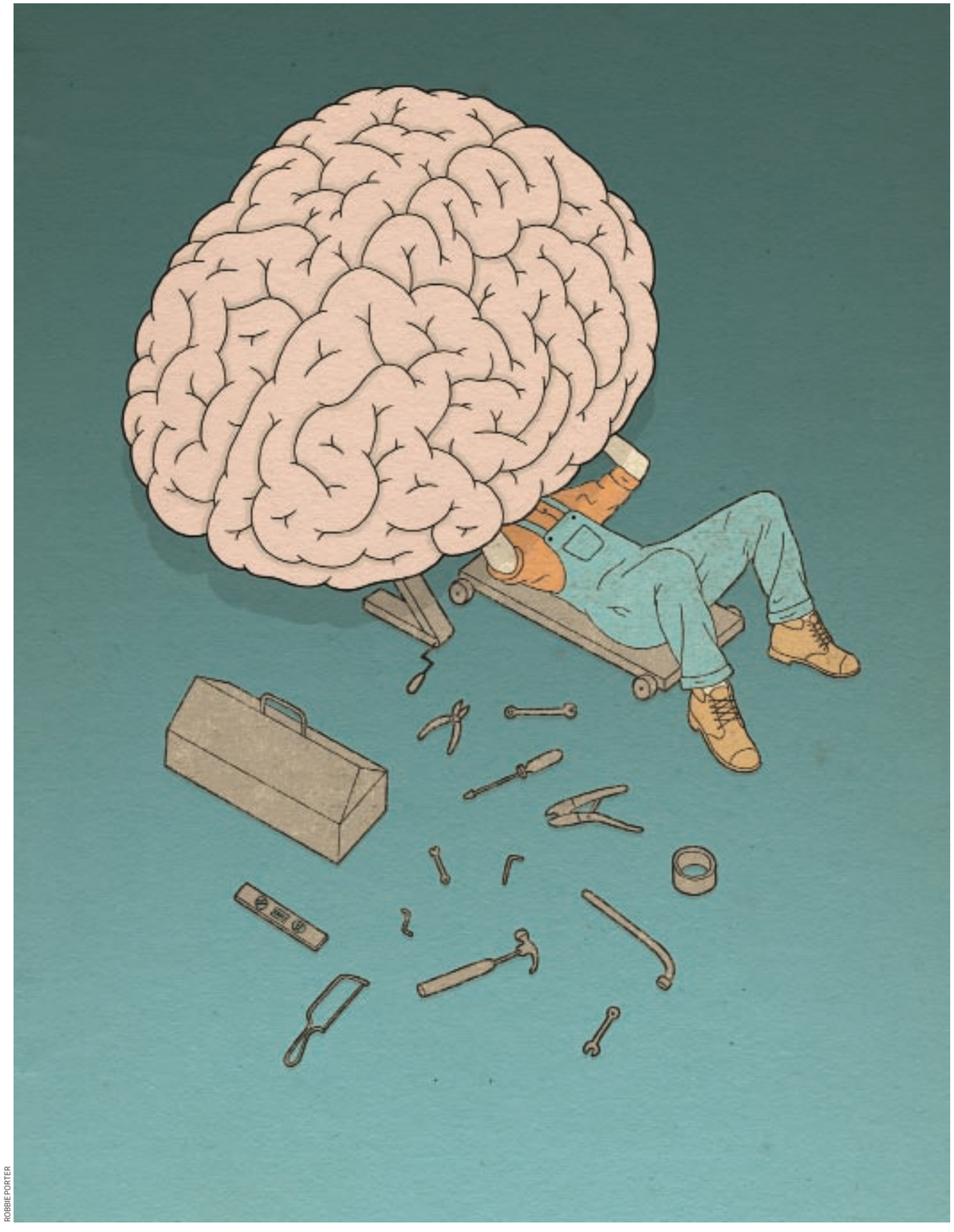


ROBBIE PORTER

Fantasy fix

Regrowing our brain cells is one of the great hopes of modern medicine. But could this idea be based on wishful thinking, asks Moheb Costandi

I AM sitting at a lab bench peering down the microscope at the brain of a chicken embryo. Dense networks of delicate young nerve fibres surround patches of newborn cells with their DNA stained dark brown.

I am witnessing the end products of neurogenesis, the birth of new brain cells. It is one of the hottest topics in neuroscience, and the idea that we can boost the growth of new brain cells with various kinds of physical or mental exercise seems to have equally taken hold of the public imagination. On top of this is the exciting prospect that we could one day use new neurons to repair the brain after injury or disease.

But does it really happen? While there is good evidence that adult neurogenesis takes place in animals, there is reason to believe that does not necessarily apply to our own species. "Everyone wants to believe that functional neurogenesis happens in adult humans, everyone wants to believe that we can repair damaged brains," says Andrew Lumsden, head of the MRC Centre for Developmental Neurobiology at King's College London, where I saw the chicken brain. "But there's precious little evidence for it."

The current faith in our brains' regenerative abilities is in fact something of a reversal. For most of the last century, it was thought that neurogenesis was restricted to our time in the womb. "Once development was ended the founts of growth dried up irrevocably," wrote Santiago Ramón y Cajal, the 19th-century Spanish anatomist seen as the founder of modern neuroscience. "In the adult, the nerve paths are immutable."

One basis of this belief was our limited capacity to recover after a stroke or a blow to the head. Such injuries can have long-lasting effects on abilities like speech and movement. Plus the brain is so much more complex than organs with proven regenerative powers, such as the skin and liver. "How would new neurons usefully integrate into complex neural networks after the connectional plan of the brain is complete?" asks Lumsden. "One side effect of having a large and complex brain is that you wouldn't want naive newcomers barging in."

The first widely accepted evidence that adult animals could regrow their brain cells came in the 1980s. The work was done in male canaries, which learn new songs every year to serenade potential mates. Fernando Nottebohm of the Rockefeller University in New York showed that at the end of the breeding season, the canary's song-producing brain regions shrink, only to regrow the following spring. "Our results showed beyond reasonable doubt that neurons are born in adulthood and incorporated into existing circuits," says Nottebohm.

So adult neurogenesis can happen in birds, but what about mammals? In 1992, Samuel Weiss and Brent Reynolds at the University of Calgary in Alberta, Canada, isolated cells from the brains of mice that seemed to have the characteristics of stem cells. These cells are a prerequisite for regeneration in other parts of the body: they divide repeatedly and, under the right conditions, develop into mature functioning cells. When grown in the lab, the mouse brain stem cells gave rise to neurons, as well as other types of brain cell.

Did they also function as neural stem cells in nature? Fred Gage of the Salk Institute in La Jolla, California, and colleagues confirmed that they do, using the same technique that enabled me to see neurogenesis in the chicken brain. It involves injecting a chemical called BrdU into the blood. This compound is close enough to one of the building blocks of DNA that it is seamlessly incorporated into the genetic material of new cells, yet it is just different enough that antibodies will bind to BrdU and not to normal DNA. In other words, it can be used as a marker for the birth of new cells in the mouse brain. Gage's team also used antibodies that show the presence of certain proteins thought to be made only by newborn neurons.

Thanks to work such as this we now know that in adult mice, neurogenesis takes place in two areas in the walls of the brain's ventricles – central cavities filled with cerebrospinal fluid. This makes sense, because the nervous system starts out as a hollow tube running along the back of the embryo; neurogenesis occurs in the walls of the tube, and the newly born neurons migrate outwards to form the brain and spinal cord. In an adult, the ventricles correspond to the space inside the tube.

The two regions produce neurons with different roles: those born in one migrate a ›

"How would new neurons integrate into complex networks after the connectional plan of the brain is complete?"

long distance to the front of the brain, to a spot called the olfactory bulb, which deals with smell (see diagram, opposite). The other source of new cells lies in the hippocampus, a curled-up structure towards the base of the brain that lets us form memories. The new neurons seem to play a role in learning and memory, including learning new smells.

The story moved on in the late 1990s, when adult macaques were also found to grow new brain cells in their hippocampus. Monkeys are obviously a lot closer to people than mice are. What we really needed to do next was to look inside a human brain – but how?

The breakthrough came when Gage and his colleagues got hold of the brains of five people who had had cancer; crucially, while they were still alive they had been injected with BrdU so their tumours could be visualised. After death, the telltale BrdU showed up in the hippocampi of all five (*Nature Medicine*, vol 4, p 1313).

This discovery got worldwide press coverage, and from then on research on adult neurogenesis skyrocketed. The idea chimed with the growing belief that after injury the brain is more adaptable, or "plastic", than we had thought.

Gage's study has not yet been repeated as human brains that have been pretreated with BrdU are thin on the ground, but there is other supporting evidence. A similar kind of study was done using 15 different antibodies for proteins produced by immature neurons; they were used to stain the brains of 54 people who were up to 100 years old when they died. There were similar patterns of cell birth in the human hippocampus as in that of mice (*PLoS One*, vol 5, p e8809). The number of new cells fell as people got older, "but we saw the process up to very old age", says Gerd Kempermann of the Center for Regenerative Therapies in Dresden, Germany, who did the research.

There is also evidence for stem cells in the human brain, thanks to people who have had surgery for epilepsy. A last-resort treatment is to remove the part of the brain where the seizures originate, which is often in or around the hippocampus. Various groups have managed to isolate what look like stem cells from these scraps of tissue. They have limited capacity for growth in the Petri dish, but can generate neurons. "This is of the greatest importance," says Nottebohm. "It shows that this reservoir might be exploited for purposes of brain repair."

The cells could potentially be used to treat conditions like stroke, Alzheimer's and Parkinson's disease. Researchers such as Gage have been inundated with phone calls from people with all manner of neurological conditions desperate for help.

Reduced neurogenesis has been implicated in depression and Alzheimer's disease, partly because people with those conditions have smaller hippocampi than normal; perhaps the problem is their neurons are not being replenished as they should be. Also, drugs such as Prozac have been found to stimulate hippocampal neurogenesis in mice, and there is now a school of thought that says this is probably how they work. The pharmaceutical industry seems to be convinced, as various firms are trying to develop antidepressants that work by boosting neurogenesis.

The notion that exercise and "brain training" can encourage our brains to generate new cells comes from the finding that mice produce more new brain cells if they take exercise and have a more interesting environment to live in. It is now a widespread belief, and one that firms selling brain-training products are happy to encourage.

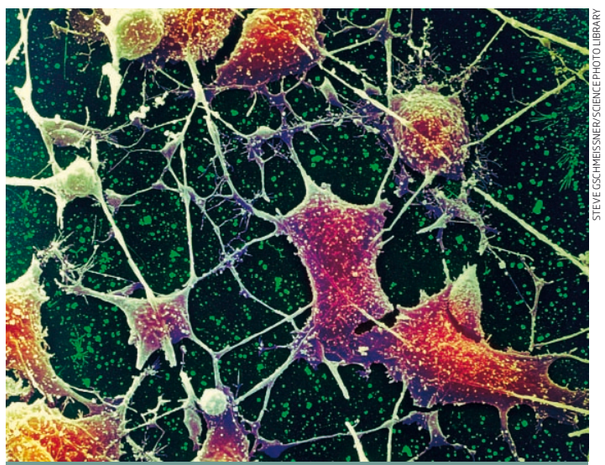
Yet despite the hype, the case for adult neurogenesis in humans is far from proven. Perhaps the biggest sceptic is Pasko Rakic, famous in his field for painstaking work in the 1970s showing how newborn neurons in the embryo migrate to the developing cortex. Indeed, his hand-drawn diagrams appear in textbooks to this day.

Now head of Yale University's neurobiology department, Rakic has investigated neurogenesis extensively in monkeys. Although he has not worked on human brains, Rakic is sceptical of the work done on his own species and is not shy about saying so (*Nature*, vol 478, p 333). "The data from mice cannot be applied to humans," he says.

Sceptical enquirer

For starters, Rakic says experiments involving BrdU are unreliable, as the compound itself can induce cell division. Another source of error is that it may also label dying cells. To overcome this problem most studies now also stain with antibodies that bind to proteins made by immature neurons, but there is still debate about which proteins identify new neurons reliably. And some of the macaque studies that so convinced us that neurogenesis happened in primates used only BrdU staining.

Rakic also points out that antidepressants start working within about six weeks, but he estimates that any neurons born in the adult human hippocampus would take about a year to fully mature. "It's just not possible that antidepressants work by producing new neurons," he says.



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Mature neurons like these can't regenerate, but is there a reserve of stem cells in our brain?

Gage counters that immature neurons could in fact be more useful than older ones because they might form connections more readily. "The other way to look at it is that newborn cells have an extended period of plasticity," he says.

While Rakic is possibly the most prominent sceptic, there are others, including those who work on human brains. They include Arturo Alvarez-Buylla, a developmental biologist at the University of California, San Francisco, who demonstrated the migration of newborn mouse neurons to the olfactory bulb.

Alvarez-Buylla identified the path they took through the brain, now called the rostral migratory stream (RMS). Migrating neurons look distinctly different to old, established cells: they have finger-like projections that feel their way and detect chemical signals. This unique appearance means migrating cells can be spotted under the microscope.

Alvarez-Buylla's team has examined about 100 human brains and a similar number of tissue samples removed surgically. In their latest study, published last year, they saw the RMS, as well as a new stream of migrating cells that branches off the RMS and leads to the cortex at the front of the brain, responsible for higher thought processes. But both streams tailed away by 18 months of age and almost completely disappeared by early adulthood (*Nature*, vol 478, p 382). "We concluded that if migration occurs, then it is very scarce," says Alvarez-Buylla.

They are not the only group to try this approach. In 2007 another team saw a strong RMS in adults (*Science*, vol 315, p 1243). But last year this was contradicted by a similar study that found tiny numbers of migrating neurons in the RMS, but no new cells in the olfactory bulb itself (*Cell Research*, vol 21, p 1534).

Another kind of study found no evidence of neurogenesis in the cortex in later life. Jonas Frisén of the Karolinska Institute in Stockholm, Sweden, and his colleagues tried to exploit the fact that there were higher levels of radioactive carbon in the atmosphere in the 1950s and 1960s, thanks to fallout from nuclear bomb tests. Any cells that were born in those decades should still have more such carbon in their DNA. They examined the cortex from the brains of seven elderly people, but the neurons' radioactive carbon levels were uniform (*Proceedings of the National Academy of Sciences*, vol 103, p 12564).

So while reams of data on neurogenesis in mice continues to accumulate, the evidence for it occurring in humans is patchy, to say the least. In all, there have only been about a dozen studies in people. They have provided zero evidence for neurogenesis in the cortex, contradictory evidence for the olfactory bulb, and limited evidence for the hippocampus. Even there, the number of new cells seems to dwindle to a mere trickle by old age. Can there really be enough to do anything useful?

Maybe the old dogma was right and the brain does favour stability over plasticity. Maybe the neural stem cells that persist into adulthood are an evolutionary relic, like the appendix. In humans and other primates smell is no longer such an important sense as it is for rodents; for us, that role has been taken over by vision. If neural stem cells are indeed just a leftover from the past, they come at a high cost, as they seem to be the origin of brain tumours.

"Maybe the neural stem cells that persist into adulthood are an evolutionary relic, like the appendix"

The debate will no doubt continue, but some are unhappy with how forcefully Rakic makes his case, in print and at conferences. "Rakic was reasonable in demanding higher levels of proof," says Nottebohm. "But he railed against adult neurogenesis so aggressively. I found him too negative." Nottebohm and others fear that Rakic's combative approach is holding back the field.

Gage, on the other hand, thinks Rakic has helped to make it more rigorous: "He challenges the weaknesses in their work and it's up to researchers to address them."

What are the implications if the sceptics are right? It doesn't necessarily eliminate hope for using neural stem cells to heal. Even if these cells do not normally function past childhood, it may still be possible to coax them into action with the right mix of chemical signals. Another approach being investigated is to transplant lab-grown neurons directly into the brain. But both those ideas are a long way from reaching the clinic.

So while such uncertainty remains about the field's central premise, that we can routinely regrow our brain cells, it would perhaps be wise to interpret the findings of animal studies with more caution. "How much neurogenesis occurs in older people, and how much it contributes to plasticity, are still open questions," says Alvarez-Buylla. ■

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Brain boosting

In infants, new brain cells are generated in two areas. Whether this also happens in adults, and whether the new cells can merge with into existing brain circuits, is hotly contested