stints of 3–5 years from academia or industry, have broad latitude in what they fund, and actively engage with their teams, enforcing aggressive deadlines and monitoring progress along the way. By comparison, projects funded by agencies such as the US National Institutes of Health (NIH) typically see little engagement between programme managers and the researchers they fund, apart from annual progress reports. Projects funded by these agencies also tend to be those that are likely to succeed — and thus typically represent more incremental advances, says William Bonvillian, a policy researcher at the Massachusetts Institute of Technology in Cambridge who has studied DARPA.

Following the recipe

The DARPA model doesn't work if programme managers aren't given the space to fail, says Bonvillian. When the US government applied the model to developing national-defence technologies through the Homeland Security ARPA in 2002, he adds, this was the problem. The effort eventually collapsed. "If you don't get the culture right on day one, you have got a problem," says Bonvillian.

Researchers also point out that a successful ARPA needs a customer for the technologies it develops. In the case of DARPA, the US military was ready to purchase many promising inventions. ARPA-Energy (ARPA-E), which was launched in 2009 under former president Barack Obama to advance low-carbon energy technologies, addressed this challenge by helping grant recipients to develop plans for commercialization from the outset.

ARPA-E had the independence it needed to function well, researchers say. Still running today, the agency, housed within the US Department of Energy (DoE), has invested $2.8 billion in nearly 1,200 projects, which have attracted another $5.4 billion in private-sector investments and led to the creation of 92 companies.

Because it can take decades for new technologies to have commercial and societal impact, whether ARPA-E will transform the energy industry remains to be seen. But scientists have documented preliminary signs of its success[2,3], as measured by patenting, publishing and, in some cases, attracting venture capital for technologies originally funded by the agency.

"The answer is yes, the [ARPA] model works, or at least it did in this case," says Anna Goldstein, an energy researcher at the University of Massachusetts Amherst who has analysed ARPA-E's effectiveness. But that does not mean the model will solve all problems, she warns.

Researchers have responded to Biden's latest ARPA proposals with trepidation. Some scientists have questioned the need to create ARPA-C, rather than expanding ARPA-E. They point out that the two have similar missions, even though DoE secretary Jennifer Granholm has said they will not overlap. As planned, ARPA-C would seek to foster "game-changing" energy and climate solutions, including technologies such as small, modular nuclear reactors and low-energy buildings — innovations that also fall under ARPA-E's purview.

Questions also abound about ARPA-H. The Biden administration proposed that it should be housed within the NIH, which critics worry could stifle innovation.

In a guest editorial published in *Science* last month[1], NIH director Francis Collins and other administration officials acknowledged that the NIH tends to fund incremental research rather than bold new technologies that could transform the marketplace, and agreed that ARPA-H's organization must have a culture that values "bold goals with big potential impact".

The Biden administration is saying all the right things, says Bonvillian, although he still worries about whether ARPA-H will have the independence and the authority that it needs to operate within the biomedical-research behemoth. He also says the NIH will need to embrace the kind of interdisciplinary research that has been fundamental to technology development at agencies such as DARPA and ARPA-E. "If they set up an ARPA that is all biology all of the time, like NIH is, then they are going to radically limit its effectiveness," he says.

Others worry that the scope of ARPA-H's mission is too broad. Health care is a huge field. Given that there is already plenty of private investment in new drugs and medical therapies for prevalent diseases, Goldstein says, ARPA-H might be better placed to have an impact on neglected diseases that affect people living in impoverished and underprivileged communities. This area receives much less funding from other sources.

"The trick is setting the scope broad enough so that programme managers can wander intellectually and follow their noses, but not so broad that you try to boil the ocean," says Eric Toone, a chemist who helped to set up ARPA-E and now works for Breakthrough Energy Ventures, a venture-capital firm based in Kirkland, Washington. This is also a potential concern with the United Kingdom's ARIA, whose scope has yet to be defined, Toone adds.

Toone also recommends starting out small and letting new agencies grow over time. "The challenge you have with too much money is people's expectations wind up in funny places."

1. Collins, F. S., Schwetz, T. A., Tabak, L. A. & Lander, E. S. *Science* https://doi.org/10.1126/science.abj8547 (2021).
2. Goldstein, A. P. & Narayanamurti, V. *Res. Policy* **47**, 1505–1512 (2018).
3. Goldstein, A., Doblinger, C., Baker, E. & Díaz Anadón, L. *Nature Energy* **5**, 803–810 (2020).

COVID AND THE BRAIN: RESEARCHERS ZERO IN ON HOW DAMAGE OCCURS

Growing evidence suggests that neurological symptoms arise through multiple mechanisms.

By Michael Marshall

How COVID-19 damages the brain is becoming clearer. New evidence suggests that the coronavirus's assault on the brain could be multipronged: it might attack certain brain cells directly, reduce blood flow to brain tissue or trigger production of immune molecules that can harm brain cells.

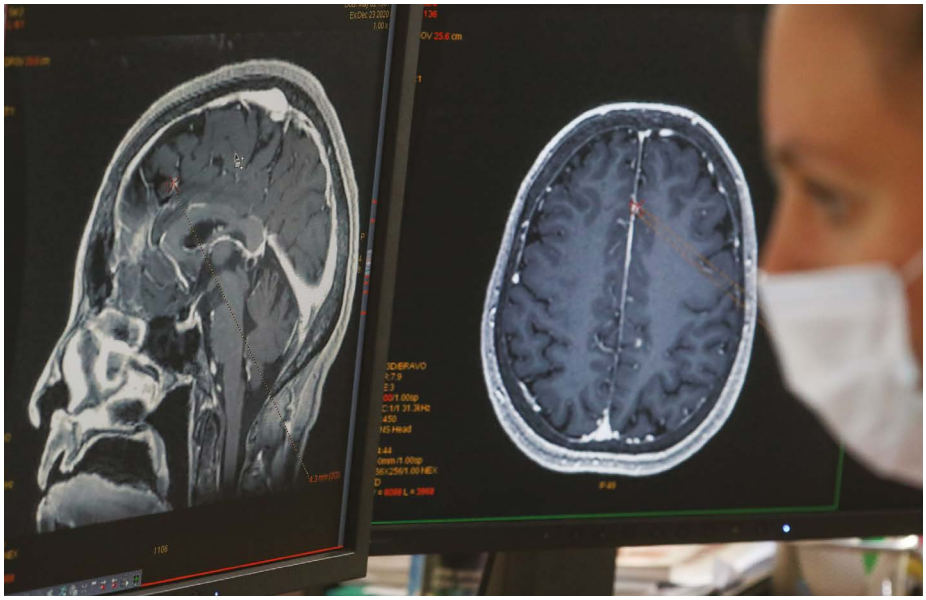
Infection with the coronavirus SARS-CoV-2 can cause memory loss, strokes and other effects on the brain. The question, says Serena Spudich, a neurologist at Yale University in New Haven, Connecticut, is: "Can we intervene early to address these abnormalities so that people don't have long-term problems?"

With so many people affected — neurological symptoms appeared in 80% of the people hospitalized with COVID-19 who were surveyed in one study[1] — researchers hope that the growing evidence base will point the way to better treatments.

Early in the pandemic, researchers speculated that the virus might cause damage by somehow entering the brain and infecting neurons, the cells responsible for transmitting and processing information. But studies have since indicated[2] that the virus has difficulty getting past the brain's defence system — the blood–brain barrier — and that it doesn't necessarily attack neurons in any significant way.

One route by which SARS-CoV-2 might be accessing the brain, experts say, is by passing through the olfactory mucosa, the lining of the nasal cavity, which borders the brain. The virus is often found in the nasal cavity — one reason that health-care workers test for COVID-19 by swabbing the nose.

Even so, "there's not a tonne of virus in the



STANISLAV KRASILNIKOV/TASS/GETTY

Researchers are trying to understand how the coronavirus SARS-CoV-2 affects the brain.

brain", says Spudich.

But that doesn't mean it is not infecting any brain cells at all.

Studies now suggest that SARS-CoV-2 can infect astrocytes, a type of cell that's abundant in the brain and has many functions. "Astrocytes do quite a lot that supports normal brain function," including providing nutrients for neurons to keep them working, says Arnold Kriegstein, a neurologist at the University of California, San Francisco.

In a preprint posted in January, Kriegstein and his colleagues reported[3] that SARS-CoV-2 preferentially infects astrocytes over other brain cells. The researchers exposed brain organoids – miniature brain-like structures grown from stem cells in the laboratory – to the virus. Among all the cells present, SARS-CoV-2 almost exclusively infected astrocytes.

Bolstering these lab studies, a group including Daniel Martins-de-Souza, head of proteomics at the University of Campinas in Brazil, reported[4] in a February preprint that it had analysed brain samples from 26 people who had died with COVID-19. In the five whose brain cells showed evidence of SARS-CoV-2 infection, 66% of the affected cells were astrocytes.

Infected astrocytes could explain some of the neurological symptoms associated with COVID-19, especially fatigue, depression and 'brain fog', which includes confusion and forgetfulness, argues Kriegstein. "Those kinds of symptoms may not be reflective of neuronal damage, but could be reflective of dysfunctions of some sort. That could be consistent with astrocyte vulnerability."

Given all these findings, researchers want to know how many brain cells need to be either infected or damaged to cause neurological symptoms, says Ricardo Costa, a physiologist at Louisiana State University Health in Shreveport whose team is studying SARS-CoV-2's effects on brain cells.

Unfortunately, there probably isn't a simple answer, says Kriegstein, pointing out that damage to cells, including neurons, in some regions of the brain will cause more dysfunction than will damage to cells in others.

Blocking blood flow

Evidence has also accumulated that SARS-CoV-2 can affect the brain by reducing blood flow to it – impairing neurons' function and ultimately killing them.

Pericytes are cells found on small blood vessels called capillaries throughout the body – including in the brain. A February preprint reported that SARS-CoV-2 could infect pericyte-like cells in brain organoids[5].

"Can we intervene early to address these abnormalities so that people don't have long-term problems?"

In April, David Attwell, a neuroscientist at University College London, and his colleagues published a preprint showing evidence that SARS-CoV-2 can affect pericytes' behaviour[6]. The researchers observed that, in slices of hamster brain, SARS-CoV-2 blocks the functioning of receptors on pericytes, causing capillaries in the tissue to constrict. "It turns out this is a big effect," says Attwell.

It's a "really cool" study, says Spudich. "It could be something that is determining some of the permanent injury we see – some of these small-vessel strokes."

Attwell suggests that drugs used to treat high blood pressure, which involves blood-vessel restriction, might be useful in some cases of COVID-19. Two clinical trials are currently investigating the effect of the blood-pressure drug losartan to treat the disease.

Immune malfunction

There is also growing evidence that some neurological symptoms and damage are the result of the body's own immune system overreacting or misfiring after encountering the coronavirus.

In the past 15 years, it has become clear that in response to infection, some people's immune systems inadvertently make 'autoantibodies' that attack their own tissue, says Harald Prüss, a neuroimmunologist at the German Center for Neurodegenerative Diseases in Berlin. This can cause long-term conditions such as neuromyelitis optica, in which people experience symptoms such as loss of vision, and weakness in their limbs. In a review published in May[7], Prüss summarized evidence that these autoantibodies can pass through the blood–brain barrier, and contribute to neurological disorders ranging from memory impairment to psychosis.

This pathway might also operate in COVID-19. In a study published last year[8], Prüss and his colleagues isolated antibodies against SARS-CoV-2 from people, and found one that was able to protect hamsters from infection and lung damage. The aim was to create new treatments. But the researchers also found that some of the antibodies could bind to brain tissue, suggesting that they might damage it. "We're currently trying to prove that clinically and experimentally," says Prüss.

In a second paper, published online last December, a team including Prüss studied the blood and cerebrospinal fluid of 11 people critically ill with COVID-19, all of whom had neurological symptoms[9]. All produced autoantibodies capable of binding to neurons. And there is evidence that giving patients intravenous immunoglobulin, another type of antibody, to suppress the harmful autoantibodies' action is "quite successful", says Prüss.

These pathways – astrocytes, pericytes and autoantibodies – are not mutually exclusive, and are probably not the only ones: it is likely that people with COVID-19 experience neurological symptoms for a range of reasons. Prüss says a key question is what proportion of cases is caused by each of the pathways. "That will determine treatment," he says.

1. Chou, S. H.-Y. *et al. JAMA Netw. Open* **4**, e2112131 (2021).
2. Serrano, G. E. *et al.* Preprint at medRxiv https://doi.org/10.1101/2021.02.15.21251511 (2021).
3. Andrews, M. G. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2021.01.17.427024 (2021).
4. Crunfli, F. *et al.* Preprint at medRxiv https://doi.org/10.1101/2020.10.09.20207464 (2021).
5. Wang, L. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2021.02.09.430349 (2021).
6. Hirunpattarasilp, C. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2021.04.01.438122 (2021).
7. Prüss, H. *Nature Rev. Immunol.* https://doi.org/10.1038/s41577-021-00543-w (2021).
8. Kreye, J. *et al. Cell* **183**, 1058–1069.e19 (2020).
9. Franke, C. *et al. Brain Behav. Immun.* **93**, 415–419 (2021).