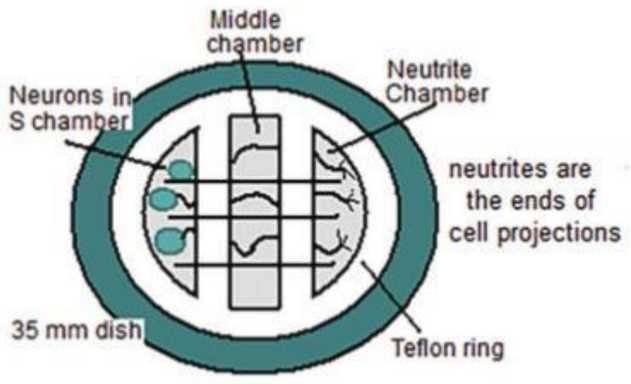
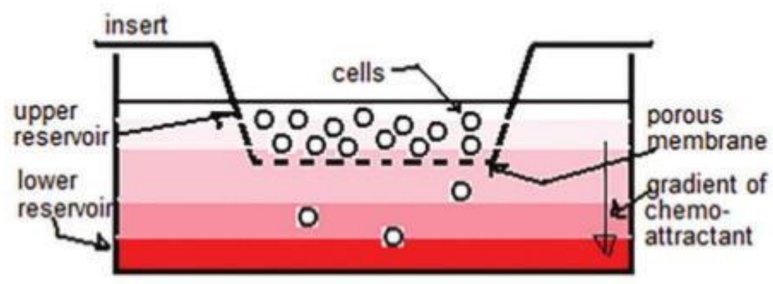
Display model of brain tissue

The human brain is perhaps the most complex organic structure there is

S ANANTHANARAYANAN



Campenot culturing chamber



Transwell culturing insert or Boyden chamber

The human brain has a hundred billion neurons, or nerve cells, and a trillion supporting cells. The brains cells train themselves to carry out tasks of cognition, reasoning, automation and memory, in ways that baffle computer scientists. But, the complexity of its functions apart, the living brain is a delicate organ, and a study of its physical structure is not within easy reach.

Hsih-Yin Tan, Hansang Cho and Luke P Le, from the National University of Singapore, the University of North Carolina at Charlotte, Sungkyunkwan University, South Korea, University of California at Berkeley, Harvard Medical School and Brigham Women's Hospital, Boston, in a review article in the journal, *Nature Biomedical Engineering*, recapitulate current laboratory methods to get a glimpse of the brain's working. With the help of a scaffold that holds human nerve cells, the methods seek to create a model of a bit of brain, that allows conditions that lead to different brain diseases to be simulated and studied, the paper says.

The brain, being, quite literally, the nerve centre of the body, needs both protection and nourishment. In respect of nourishment, the brain receives blood supply – three quarters of a litre, which is 15 per cent of the blood circulating in the body, every minute. The supply comes through two main sets of arteries, the carotid arteries to the front of the brain and the vertebral arteries that supply the rear parts of the brain. While the arteries are "autoregulated", to keep up the supply of blood, the two artery systems are interconnected, so that supply continues even if one stream is blocked.

As for protection, the brain is kept separated or quarantined, one may say, from physical contact, even contact with the bloodstream. A system of tissue, known as the blood brain barrier, only permits what the brain needs, which is oxygen, glucose and nutrients, like amino acids, to pass from the blood to the brain, and not any infection, things dissolved in the blood, or some large molecules. Antibodies and immune cells are kept out, even therapeutic agents are not admitted. Within the brain, however, there is a system to receive, by diffusion, what the brain cells need, and to evacuate waste.

The paper explains that this system, which separates brain tissue from the bloodstream, while keeping the environment within the brain steady, is a key component of brain function. Damage to the system, mechanical or biological, results in the entry of harmful substances and disturbing the internal balance, leading to damage and loss of brain cells. Conditions like formation of plaque in the blood vessels in the brain could increase the pressure and lead to rupture of blood vessels, which could also come about if there is physical injury, like a blow to the head.

These, and other brain conditions that arise from genetic or pathological causes, need invasive study to understand and analyse. As it is not practical to carry out such studies in a living brain, the recourse has been to animal studies. Animal studies are not effective, the paper says. For instance, studies on the brains of mice have shown that a gene that promotes a particular protein leads to conditions like Alzheimer's disease. However, as the ratios of neurons and other cells in animals are different from the ratio in humans, and there are different immunological responses, the results of the gene and Alzheimer's disease in mice cannot be carried over to draw conclusions about the human brain, the paper says.

There is hence a need, the paper says, for a functional model of the human brain, which can more realistically represent the characteristics and capture the way the brain responds to different kinds of stress. It is with such a "working model", the paper says, that we can understand brain mechanisms and the reasons for many brain diseases. This would bring brain research on par with other fields, like analysis of civil structures, or aircraft design, where parameters are varied and measured on models, as a means of discovering the behaviour of the real objects.

The paper carries out a review of the methods developed so far, to build a bit of the brain, using brain cell cultures, coaxed to form into desired structures with the help of mechanical scaffolds. Building on early methods of growing neuron cells on Petri dishes, were the *Campenot Chambers*, of specially shaped Petri dishes to guide the cell growth. An improvement was the *Transwell culturing insert* or the *Boyden chamber*, which separated cells by a porous membrane, the two sides to represent the "blood side" and the "brain side", which helped assess migration of cells across thin barriers.

More effective simulation of the 3-D structure of brain cells has been by growing cells in a 3-D microenvironment of a gel – to act as the extracellular matrix for cell growth. These structures have enabled recording spontaneous activity of neural and other cells and key mechanisms and pathways. However, there are limitations, the paper says, in simulating how brain cells relate to surrounding tissue – and these are better modelled in the *brain organoid culture*.

Organoids form when cells, derived from stem cells, organise themselves into 3-D structures. These cultures can be shaped to replicate a great part of the complexity of an organ, or specific aspects, such as the kind of cells that grow in the culture. "A simplified version of an organ produced in vitro in three dimensions that shows realistic micro-anatomy," is one way it has been described. The advances in biomaterials engineering and genome editing techniques, to enable neural cells to be grown, have enabled such mini-brain models to be formed, the paper says. The techniques have become sophisticated and we are able to create personalised brain models, using the patient's own body cells and re-enacting the path of disease progression.

Progress in organoids, with advances in 3-D printing techniques to build matrices to guide cell growth, has promoted brain modelling as a prime candidate for study of major neurological diseases. The development of Amyloid plaque, implicated in Alzheimer's disease, is one. Parkinson's disease, the second most common neurodegenerative disease, is another. Then, there is brain cancer. And next, what happens when there is traumatic injury to the brain. Mini brain modelling has the potential to develop precision and personalised therapy for diseases of the brain or the nervous system, the paper says.

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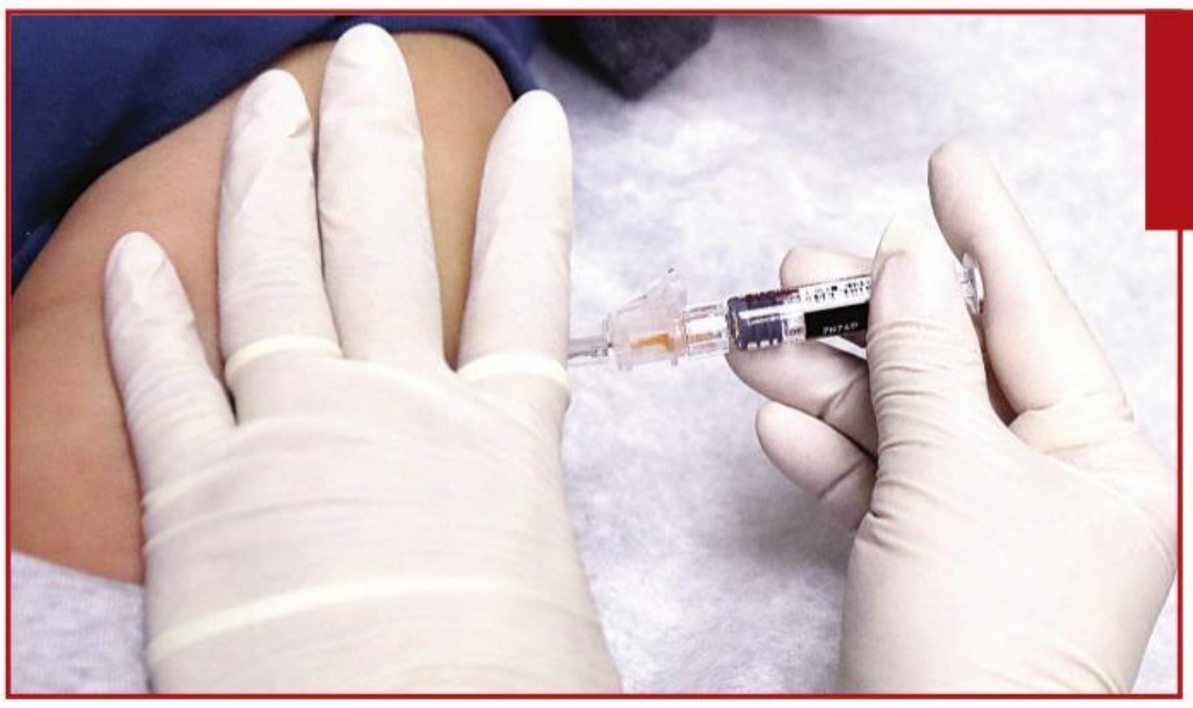


TRAINING YOUR IMMUNE SYSTEM

Vaccines against Sars-CoV-2 will have side effects – and that's a good thing

MATTHEW WOODRUFF

In 2021, hundreds of millions of people will be vaccinated against Sars-CoV-2. The success of that Covid-19 vaccination campaign will heavily depend on public trust that the vaccines are not only effective, but also safe. To build that trust, the medical and scientific communities have a responsibility to engage in difficult discussions with the public about the significant fraction of people who will experience temporary side effects from these vaccines. I am an immunologist who studies the fundamentals of immune responses to vaccination, so part of that responsibility falls on me.

Simply put, receiving these vaccines will likely make a whole lot of people feel bad for a few days. That's probably a good thing, and it's a far better prospect than long-term illness or death.

Immunology's 'dirty little secret'

In 1989, immunologist Charles Janeway published an article summarising the state of the field of immunology. Until that point, immunologists had accepted that immune responses were initiated when encountering something foreign – bacteria, viruses, and parasites – that was "non-self."

Janeway suspected that there was more to the story, and famously laid out what he referred to as "the immunologist's dirty little secret": Your immune system doesn't just respond to foreign things. It responds to foreign things that it perceives to be dangerous.

Now, 30 years later, immunologists know that your immune system uses a complex set of sensors to understand not only whether or not something is foreign, but also what kind of threat, if any, a microbe might pose. It can tell the difference between viruses – like Sars-CoV-2 – and parasites, like tapeworms, and activate specialised arms of your immune system to deal with those specific threats accordingly. It can even monitor the level of tissue damage caused by an invader and ramp up your immune response to match.

Sensing the type of threat posed by a microbe, and the level of intensity of that threat, allows your immune system to select the right set of responses, wield them precisely, and avoid the very real danger of immune overreaction.

Vaccine adjuvants bring the danger we need

Vaccines work by introducing a safe version of a pathogen to a patient's immune system. Your immune system remembers its past encounters and responds more efficiently if it sees the same pathogen again. However, it generates memory only if the vaccine packs enough danger signals to kick off a solid immune response._As a result, your immune system's need to sense danger before responding is at once extremely important (imagine if it started attacking the thousands of species of friendly bacteria in your gut!) and highly problematic. The requirement for danger means that your immune system is programmed not to respond unless a clear threat is identified. It also means that if I'm developing a vaccine, I have to convince your immune system that the vaccine itself is a threat worth taking seriously.

This can be accomplished in a number of ways. One is to inject a weakened – what immunologists call attenuated – or even killed version of a pathogen. This approach has the benefit of looking almost identical to the "real" pathogen, triggering many of the same danger signals and often resulting in strong, long-term immunity, as is seen in polio vaccination. It can also be risky – if you haven't weakened the pathogen enough and roll out the vaccine too fast, there is a possibility of unintentionally infecting a large number of vaccine recipients. In addition to this unacceptable human cost, the resulting loss of trust in vaccines could lead to additional suffering as fewer people take other, safer vaccines.

A safer approach is to use individual components of the pathogen, harmless by themselves but capable of training your immune system to recognise the real thing. However, these pieces of the pathogen don't often contain the danger signals necessary to stimulate a strong memory response. As a result, they need to be supplemented with synthetic danger signals, which immunologists refer to as "adjuvants."

Adjuvants are safe but designed to inflame

To make vaccines more effective, whole labs have been dedicated to the testing and development of new adjuvants. All are designed with the same basic purpose – to kick the immune system into action in a way that maximises the effectiveness and longevity of the response. In doing so, we maximise the number of people that will benefit from the vaccine and the length of time those people are protected.

To do this, we take advantage of the same sensors that your immune system uses to sense damage in an active infection. That means that while they will stimulate an effective immune response, they will do so by producing temporary inflammatory effects. At a cellular level, the vaccine triggers inflammation at the injection site. Blood vessels in the area become a little more "leaky" to help recruit immune cells into the muscle tissue, causing the area to become red and swell. All of this kicks off a full-blown immune response in a lymph node somewhere nearby that will play out over the course of weeks.

In terms of symptoms, this can result in redness and swelling at the injection site, stiffness and soreness in the muscle, tenderness and swelling of the local lymph nodes and, if the vaccine is potent enough, even fever (and that associated generally crappy feeling). This is the balance of vaccine design – maximising protection and benefits while minimising their uncomfortable, but necessary, side effects. That's not to say that serious side effects don't occur – they do – but they are exceedingly rare. Two of the most discussed serious side effects, anaphylaxis (a severe allergic reaction) and Guillain-Barré Syndrome (nerve damage due to inflammation), occur at a frequency of less than one in 500,000 doses.

Vaccination against Sars-CoV-2

Early data suggest that the mRNA vaccines in development against SARS-CoV-2 are highly effective – upwards of 90 per cent. That means they are capable of stimulating robust immune responses, complete with sufficient danger signalling, in greater than nine out of 10 patients. That's a high number under any circumstances and suggests that these vaccines are potent.

So let's be clear here. You should expect to feel sore at the injection site the day after you get vaccinated. You should expect some redness and swelling, and you might even expect to feel generally run down for a day or two post-vaccination. All of these things are normal, anticipated and even intended.

While the data aren't finalised, more than two per cent of the Moderna vaccine recipients experienced what they categorised as severe temporary side effects such as fatigue and headache. The percentage of people who experience any side effects will be higher. These are signs that the vaccine is doing what it was designed to do – train your immune system to respond against something it might otherwise ignore so that you'll be protected later. It does not mean that the vaccine gave you Covid-19.

It all comes down to this – some time in the coming months, you will be given a simple choice to protect yourself, your loved ones and your community from a highly transmissible and deadly disease that results in long-term health consequences for a significant number of otherwise healthy people. It may cost you a few days of feeling sick.

Please choose wisely.

The writer is instructor, Lowance Center for Human Immunology, Emory University, US. This article first appeared on www.theconversation.com

PLUS POINTS

New whale species?

Scientists searching for a little-known species of beaked whale, which has only ever been found dead, believe they have stumbled across another new species of whale off Mexico's western Pacific coast. If confirmed, the new species would be a significant new discovery, and one among some of the planet's largest mammals.

The research team spotted three of the whales while on the lookout for Perrin's beaked whale, specimens of which have only ever been seen when they've been washed up dead on the shore. The team, led by the non-profit Sea Shepherd Conservation Society, were near Mexico's remote San Benito Islands on 17 November, when they saw the whales. But they didn't initially realise they were looking at what could be a previously unrecognised species.

"These animals popped to the surface right next to the boat," Jay Barlow, a marine mammal biologist at the Scripps Institution of Oceanography in San Diego told *Reuters*. "It was just a phenomenal encounter. It's very rare to even see a beaked whale, and to find a friendly group of beaked whales, it's even rarer," he said.

It was only when they later studied the photographs they took of the animals that they realised they could be looking at a species which has never been described before. The whales' teeth were unusually placed, Barlow said, and underwater recordings of the whales' calls also suggested they were unique.

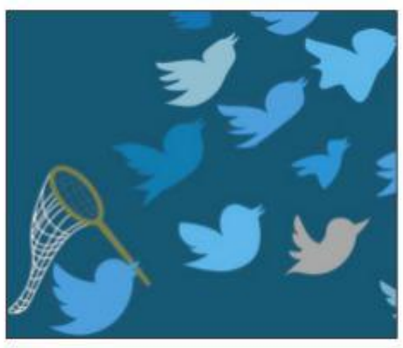
The research team took three water samples in the vicinity of the animals in hopes of getting an "environmental DNA sample from their sloughed skin cells," which will be submitted for laboratory analysis. This could help determine whether it is a new species.

Researchers hope to mount another trip next year to see if they can find both the new beaked whales and Perrin's beaked whale. Beaked whales are named for their pointy, beak-like snouts, which resemble those of dolphins. They are found mostly in remote waters, such as those off the San Benito Islands.

Despite their large size – growing up to five metres (16.4 feet) long, they can be difficult for humans to observe as they tend to swim and feed mostly at depths of over 900 metres (3,000 feet), surfacing only occasionally for air. At such depths, the animals have a better chance of avoiding their main predator, killer whales.

– THE INDEPENDENT/AGENCIES

Tackling disinformation



A team of researchers, led by Yida Mu and Nikos Aletras from the University of Sheffield's department of computer science, has developed a method for predicting whether a social media user is likely to share content from unreliable news sources. Their findings have been published in the journal *PeerJ*.

The researchers analysed over one million tweets from approximately 6,200 *Twitter* users by developing new natural language processing methods – ways to help computers process and understand huge amounts of language data. The tweets they studied were all publicly available for anyone to see on the social media platform.

Twitter users were grouped into two categories as part of the study – those who have shared unreliable news sources and those who only share stories from reliable news sources. The data was used to train a machine-learning algorithm that can accurately predict (79.7 per cent) whether a user will repost content from unreliable sources sometime in the future.

Results from the study found that the *Twitter* users who shared stories from unreliable sources are more likely to tweet about either politics or religion and use impolite language. In contrast, the study found that users who shared stories from reliable news sources often tweeted about their personal life, such as their emotions and interactions with friends.