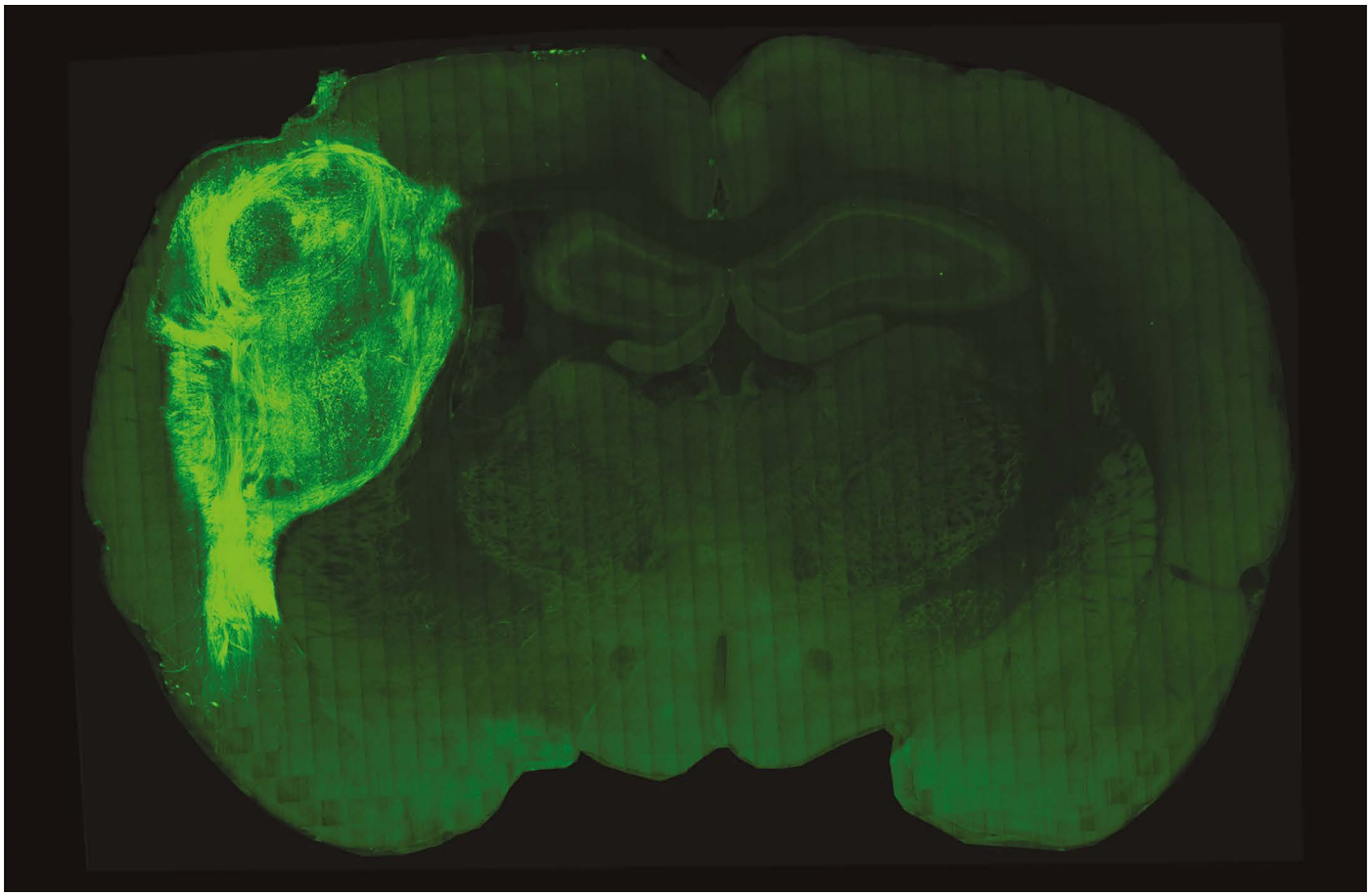
News in focus



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Researchers have transplanted a human brain organoid (bright green) into the brain of a newborn rat pup.

HUMAN BRAIN CELLS IMPLANTED IN RATS PROMPT EXCITEMENT — AND CONCERN

Rat–human hybrid brains offer new ways to study human neurological disorders, but also raise ethical questions.

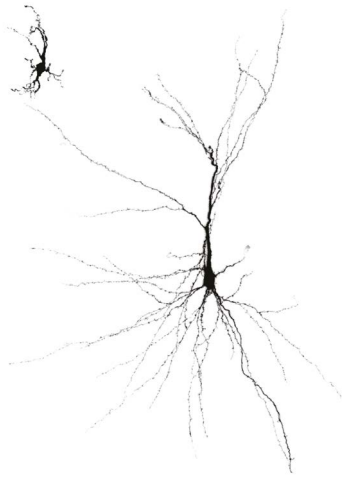
By Sara Reardon

Miniature human-brain-like structures transplanted into rats can send signals and respond to environmental cues picked up by the rats' whiskers, according to a study. This demonstration that neurons grown from human stem cells can interface with nerve cells in live rodents could lead to a way to test therapies for human brain disorders.

Scientists would like to use brain organoids – tiny brain-like structures grown from human stem cells – to study neurodegenerative and neuropsychiatric disorders that humans develop. But the organoids mimic human brains only so far. They don't develop blood vessels and so can't receive nutrients, meaning that they don't thrive for long. And they don't get the stimulation they need to grow fully: in a human infant's brain, neurons' growth and how they develop connections with other neurons are based, in part, on input from the senses.

To give brain organoids this stimulation and support, neuroscientist Sergiu Pasca at Stanford University in California and his colleagues grew the structures from human stem cells and then injected them into the brains of newborn rat pups, with the expectation that the human cells would grow along with the rats' own cells. The team placed the organoids in a brain region called the somatosensory cortex, which receives signals from the rats' whiskers and other sensory organs, then passes them along to other brain regions that interpret the signals.

Human brain cells mature much more slowly than rat cells, so the researchers had to wait for more than six months for the organoids to



Human neurons created from stem cells and transplanted into a rat brain (right) grow more fully than those cultivated in a dish (left).

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become fully integrated into the rats' brains. But when they examined the animals' brains at the end of that time, they saw that the integration had been so successful that it was almost like adding "another transistor to a circuit", Pasca said at a 10 October press conference.

Paola Arlotta, a molecular biologist at Harvard University in Cambridge, Massachusetts, is excited about the results. "It's an important step in allowing organoids to tell us more complex properties of the brain," she says, although she thinks that the transplantation procedure is probably still too expensive and complex to become a standard research tool. The next step, Arlotta adds, will be to work out how individual human neurons — not just fully developed organoids — are integrated into the rat brain.

Behavioural trigger

In their report, published in *Nature*, the researchers describe how they genetically engineered the neurons in the organoids to fire when stimulated with light from a fibre-optic cable embedded in the rats' brains (O. Revah *et al. Nature* **610**, 319–326; 2022). The team trained the rats to lick a spout to receive water while the light was switched on. Afterwards, when the researchers shone the light on the hybrid brains, the rats were prompted to lick the spout, meaning that the human cells had become integrated well enough to help drive the animals' behaviour. Furthermore, when the researchers prodded the rats' whiskers, the human cells in the sensory cortex fired in response, meaning the cells could pick up sensory information.

To demonstrate the promise of their work for studying brain disorders, Pasca and his colleagues also created brain organoids from the stem cells of three people with a genetic condition called Timothy syndrome, which can cause symptoms similar to some seen in autism. The tiny structures looked the same as any other brain organoids grown in a dish, but when the researchers transplanted them into rats, they did not grow as large as others and their neurons didn't fire in the same way.

Rusty Gage, a neuroscientist at the Salk Institute for Biological Studies in La Jolla, California, is glad to see these results. In 2018, he and a team of researchers reported that transplanted human brain organoids could be integrated into the brains of adult mice (A. A. Mansour *et al. Nature Biotechnol.* **36**, 432–441; 2018). Mice don't live as long as rats, and Pasca and his colleagues hoped that because newborn rat pups' brains are more plastic than those of adult animals, they would be better able to receive the new cells.

"We've got challenges out there for us," Gage says. "But I do believe the transplantation procedure will be a valuable tool."

Some of the challenges are ethical. People are concerned that creating rodent–human hybrids could harm the animals, or create animals with human-like brains. Last year, a panel organized by the US National Academies of Sciences, Engineering, and Medicine released a report concluding that human brain organoids are still too primitive to become conscious, attain human-like intelligence or acquire other abilities that might require legal regulation. Pasca says that his team's organoid transplants didn't cause problems such as seizures or memory deficits in the rats, and didn't seem to change the animals' behaviour significantly.

But Arlotta, a member of the National Academies panel, says that problems could arise as science advances. "We can't just discuss it once and let it be," she says. She adds that concerns about human organoids need to be weighed against the needs of people with neurological and psychiatric disorders. Brain organoids and human–animal hybrid brains could reveal the mechanisms underlying these illnesses, and allow researchers to test therapies. "I think we have a responsibility as a society to do everything we can," Arlotta says.

LABS THAT HANDLE DANGEROUS PATHOGENS SURGE IN WAKE OF COVID

India, Singapore and the Philippines are among those building new laboratories at biosafety level 3 or above.

By Smriti Mallapaty

In the wake of the COVID-19 pandemic, plans are afoot to build more than 40 high-level biosafety laboratories around the world, in places including India, the Philippines and Singapore. Investments in biosafety labs often follow epidemics, but many researchers are concerned about the growing number of facilities that will handle some of the world's most dangerous pathogens.

Some scientists worry about the huge cost of maintaining biosafety-level-3 (BSL-3) and BSL-4 facilities, whereas others fear the risks posed by these labs, such as the possibility of making pathogens more dangerous or of microorganisms escaping.

But researchers in the countries that plan to build these laboratories say the facilities are needed. The lack of high-security labs in some regions became particularly apparent during the pandemic, because work on the live virus that causes COVID-19, SARS-CoV-2, must be done at a BSL-3 or BSL-4 facility.

"The pandemic exposed the weakness of health systems worldwide in recognizing and responding to emerging threats in public health," said Bharati Pawar, India's minister for health and family welfare, at a ceremony to mark the start of construction for one of the nation's new BSL-3 labs in Bengaluru last month. "In this light, the critical element of any preparedness programme is lab preparedness," she said.

Around the world

India's plans are among the most ambitious. The country is in the process of building five BSL-3 facilities and is planning at least another nine. Four institutions have also said they will construct BSL-4 labs with the highest level of containment. India currently has only one such facility that is operational. And the government has committed to building four new national institutes of virology, two of which will eventually handle BSL-4 pathogens.

BSL-3 laboratories are designed so that scientists can safely work with potentially lethal and inhalable pathogens in a contained environment. Experiments are done in sealed workspaces in which the air is filtered and not recirculated, and the entrance to the facility is typically secured by self-closing doors. BSL-4 facilities, in which researchers work with fatal