Nature Podcast

Introduction

This is a transcript of the 26th April 2018 edition of the weekly *Nature Podcast*. Audio files for the current show and archive episodes can be accessed from the *Nature Podcast* index page (http://www.nature.com/nature/podcast), which also contains details on how to subscribe to the *Nature Podcast* for FREE, and has troubleshooting top-tips. Send us your feedback to podcast@nature.com.

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Interviewer: Adam Levy
Welcome back to the *Nature Podcast*. This week on the show, we'll be looking at the ethical questions raised by model minds, and finding out about an updated structure for an important enzyme.

Interviewer: Benjamin Thompson
Plus, we'll have the search for methane on Mars. This is the *Nature Podcast* for the 26th April 2018. I'm Benjamin Thompson.

Interviewer: Adam Levy
And I'm Adam Levy.

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Interviewer: Adam Levy
Over the centuries animal models have been used for all sorts of biological research, and have enabled some major discoveries. But when it comes to studying something as complicated as human brain conditions, we really need human brain tissue to study. This week a diverse group of researchers, ethicists, and philosophers have collectively published a Comment piece, in which they speak out about their concerns for the future of brain research. Here's reporter Ellie Mackay to tell us more.

Interviewer: Ellie Mackay
The pages of *Nature* this week contain an image of something called a 'brain organoid'. It's novel, it has astonishingly futuristic applications, and it raises some interesting ethical questions. I spoke to Nita Farahany, lead author of the Comment piece about these organoids, and started by asking her about the current, standard way of studying human brain tissue – growing human pluripotent stem cells in a dish.

Interviewee: Nita Farahany
So, you could, for example, just create a 2-dimensional, like a flat sheet of cells. So, you might pick one kind of brain cell type and grow that in a dish, but it's limited in how useful it is, because it doesn't show you the interconnections between different brain regions or different cell types.

Interviewer: Ellie Mackay
So, what is the solution, what would be the ideal model?

Interviewee: Nita Farahany
What's ideal, is to be able to study brain tissue that's either still functioning, or to be able to grow something like a brain organoid that would mimic some of the functions of the human brain.

Interviewer: Ellie Mackay
So, mini brain organoids, it sounds very sci-fi…

Interviewee: Nita Farahany
Right.

Interviewer: Ellie Mackay
What are these organoids, and how are they different from these pluripotent stem cell sheets?

Interviewee: Nita Farahany
So, brain organoids are really terrific. They are three-dimensional pluripotent stem cells that can differentiate and even self-organise into different cell types that are all organised together.

Interviewer: Ellie Mackay
And, so, we're talking about separate brain regions, like the cortex or the basal ganglia, and you can combine those so there's communication between them?

Interviewee: Nita Farahany
That's exactly right. You can actually assemble different regions together that have been grown independently, and these brain assembloids can then have interconnections between the regions, so that you can actually have electrical activity that occurs across the different regions.

Interviewer: Ellie Mackay
And what sort of size are these organoids or assembloids?

Interviewee: Nita Farahany
Right now, the largest organoids are about 4mm in diameter, they have about two to three million cells, I mean, you know, this is tiny in many ways compared to an adult human brain. That being said, at least functionally, and even cellularly, they give us a much better proxy already than many of the animal models.

Interviewer: Ellie Mackay
And these organoids have already had applications so far, in studying things like the Zika virus, autism spectrum disorders and schizophrenia.

Interviewee: Nita Farahany

That's right, which is exciting, especially if you think about some of the ethical limitations of being able to do some of that research in humans. To be able to do it with human brain tissue creates quite an exciting opportunity and advance.

Interviewer: Ellie Mackay
And, you mention in the article that it's not just the organoids on their own that need to be considered, there's also the idea of putting human tissues in pigs or mice, for example, and creating what's referred to as a chimera.

Interviewee: Nita Farahany
Right. So, we already have started to create chimeras, so, taking an organoid and putting the whole organoid inside of an animal model, that would enable it to develop blood vessels that could allow it to grow. These are steps that we've already taken.

Interviewer: Ellie Mackay
And when researchers transplanted human brain cells into mice brains, they created human-mice chimeras that showed improved learning.

Interviewee: Nita Farahany
Yeah.

Interviewer: Ellie Mackay
So, at what point does one of these chimeras become human?

Interviewee: Nita Farahany
So, putting human glial cells into mice enabled them to perform better in certain learning tasks, does that make them more humanlike? Potentially, but I think that they're still, you know, a very far distance from being human.

Interviewer: Ellie Mackay
And, what about the organoids themselves, could they be defined as human?

Interviewee: Nita Farahany
That's a very tough question. So, how do we define human, is a question I think, that gets to the very heart of what do we think of as personhood, and what do we think of as alive versus dead. Those are some of the questions that we think will be posed by the exciting advances in this field.

Interviewer: Ellie Mackay
And, it's been shown with some of these organoids, that they have the ability to respond to external stimuli like light, so they're responsive, are there then questions of whether they could become conscious, even?

Interviewee: Nita Farahany
I think right now, we think the possibility of any consciousness in these organoids is extremely remote, but the mere fact that it is remote, rather than impossible, creates a

need for us to have the conversation now about greater research that unpacks consciousness, whether or not we can detect it, and if so, how we might address that.

Interviewer: Ellie Mackay
And, why not stop the research altogether if there are these concerns?

Interviewee: Nita Farahany
So, we believe that it would be unethical to stop the research at this point. This is our best hope for being able to alleviate a tremendous amount of human suffering, that's caused by neurological and psychiatric disorders. And while every technological advance brings some risk with it, we believe that these are risks that can be addressed with ethical guidelines, rather than calling for some kind of halting of the research.

Interviewer: Ellie Mackay
And so, you've published a long list of guidelines including some methodological considerations, such as how to handle and dispose of these organoids, as well as what consent would be needed from donors, for example.

Interviewee: Nita Farahany
That's right.

Interviewer: Ellie Mackay
But other issues like welfare may even need addressing if these organoids, perhaps in the future, are developed further and are considered more humanlike. Are you worried as a group that this is a reality that's fast approaching?

Interviewee: Nita Farahany
I think if you look at the people who made this call together, these are the scientists who are really at the cutting edge of a lot of this research. We recognise that it is a remote possibility today, so one of the things that I think is really powerful about this Comment is that it brings together scientists, ethicists and philosophers working in this space, to put guidelines and frameworks into place before we're right up against that reality.

Interviewer: Ellie Mackay
So, what do you hope the next steps will be?

Interviewee: Nita Farahany
We hope that it is a call to action, that it starts to spur a great deal of conversation that could enable and help guide the kind of deep ethical quandaries of this terrific and exciting field of scientific progress.

Interviewer: Adam Levy
That was Ellie Mackay talking to Nita Farahany from Duke University in the United States. You can read the Comment piece at nature.com/news.

Interviewer: Benjamin Thompson

Right listeners, for this next section of the podcast, I want to jump straight to the end. No, not of the show, but of your chromosomes. You see, the ends of chromosomes are capped by short sequences of DNA that are repeated many, many times. Together, these repeats are called telomeres, and they're made by the enzyme telomerase. Now, telomeres protect chromosomes from damage, but also act as a kind of built-in countdown timer. Each time a cell divides, its telomeres get a bit shorter, and when they're down to a certain level, the cell stops dividing or dies. In humans at least, most cells don't produce the telomerase enzyme, but a lot of cancer cells do. In fact, some estimates suggest that as many as 90% of tumours produce the enzyme, which helps them to keep dividing indefinitely. And it's not just cancer, telomerase malfunction is involved in a number of genetic diseases as well. Telomerases role in disease makes it an attractive target in therapies, however, efforts to produce drugs aimed at telomerase have been hampered, because researchers don't have a detailed structure of what the human enzyme looks like. Things have taken a step in the right direction this week though, with a paper published in *Nature* that gives a more detailed insight into the makeup of the human telomerase enzyme. The papers first author is Thi Hoang Duong Nguyen, who also goes by the name Kelly, from the University of California, Berkeley.

Interviewee: Kelly Nguyen
So we're interested in telomerase because we want to understand the basic mechanism, how it works, right. So, as in simple terms, you know proteins, enzymes, usually they fold into this three-dimensional shape, and knowing the shape is very important. It helps with manipulating it, it helps with drug design, and doing further studies on it, so it opens up a lot of doors to many possibilities.

Interviewer: Benjamin Thompson
Telomerase has been studied in a lot of eukaryotic organisms, from protozoa to humans. And while the specific makeup of the enzyme may differ from species to species, a couple of things are similar.

Interviewee: Kelly Nguyen
So, telomerase has two main components across all eukaryotes: telomerase reverse transcriptase, this is a catalytic subunit, and telomerase RNA which carries the template for this copying reaction.

Interviewer: Benjamin Thompson
So the telomerase reverse transcriptase known as TERT, and the telomerase RNA, are what enables the enzyme to produce repeating DNA sequences. In 2013, a group of researchers produced a low-resolution structure of human telomerase, which looks a bit like the letter 'C'. The team suggested that the enzyme was made up of two lobes, each containing TERT and the telomerase RNA, connected by a linker in between. Now, Kelly and her colleagues propose an update to this structure. They used a technique called cryo-electron microscopy to help them build up a picture of what telomerase looks like down to its DNA substrate. This work, again, shows a structure with two lobes, but the details are different to what was suggested before.

Interviewee: Kelly Nguyen

When we were able to get to high enough resolution, to see what's in each lobe, we found that one lobe has that catalytic subunit surrounded by telomerase RNA, and the other lobe had something that we call the H/ACA ribonucleoprotein. And this is actually the very interesting part, because this is where there's been debate in the field, whether there is two lobes and two copies of TERT and the telomerase RNA, or just one and then the rest of them are other factors.

Interviewer: Benjamin Thompson
Kelly's work suggests that the latter is more likely, with the human telomerase enzyme comprising of two distinct sections tethered together. One of these sections contains the TERT and telomerase RNA we talked about before, while the other is this H/ACA ribonucleoprotein complex, which Kelly thinks could help the enzyme with things like localisation within the nucleus. The human telomerase structure presented in this new work is the highest resolution yet, but there's still work to be done.

Interviewee: Kelly Nguyen
So currently we're at 7 to 8 angstrom, where we can see the architecture, we can fit models into it, but we're not at the resolution we can see side chains of amino acids, so therefore we still have a long way to go. For example, for drug design, whether we want to correct or right something binding to telomerase, we need to see these atoms of the drug binding to atoms of telomerase, so we will need 3 to 4 angstrom resolution, so high resolution, so currently we're at medium.

Interviewer: Benjamin Thompson
While a higher level of detail is needed before drugs can be developed to target telomerase, its role in so many cancers and genetic diseases means that this work, medium resolution or not, will offer researchers new insight into its structure. To read Kelly's paper, and an associated News & Views article, head over to nature.com/news.

Interviewer: Adam Levy
Still to come we've got the News Chat, but before then I just wanted to thank our listener Fowzan for getting in touch. Fowzan tells us his two sons Ibrahim and Imen enjoy listening to the show in the car with their dad. We're thrilled to hear that the podcast nourishes your curiosity and inquisitiveness.

Interviewer: Benjamin Thompson
Well, if you'd like to get in touch and let us know where you're listening to the show, you can do so on email: podcast@nature.com.

Interviewer: Adam Levy
Or, if you'd like to leave us a nice review on iTunes, that would be amazing as well, and it would help us get the podcast out to even more listeners. Right now though, let's get back to the show. It's time for the Research Highlights, bought to you this week by Shamini Bundell.

[Jingle]

Interviewer: Shamini Bundell
Have you ever wanted to sober up speedily? Researchers in Los Angeles have been raising the bar in their field with some anti-alcohol pills. The treatment takes the form of two ingestible nanocapsules. One contains enzymes that turn alcohol into acetaldehyde, while the enzyme in the other pill turns the toxic acetaldehyde into acetate. This process is similar to what the liver does naturally, and the pills were shown to quickly reduce blood alcohol levels in mice. In humans this could be useful for preventing liver damage. Raise a glass to that research over at *Advanced Materials.*

[Jingle]

Interviewer: Shamini Bundell
And from the bar to the bedroom, what's so great about sex? Well, researchers have turned to stick insects to find out. Certain species of stick insect in the genus *Timema* have been reproducing only asexually for a million years. The researchers compared five asexual species with five sexually reproducing species, and looked for differences in their RNA. They concluded that the asexual insects had more harmful mutations in their genomes than the sexual ones. This supports the idea that harmful mutations are one of the big disadvantages to reproducing asexually, although sexual reproduction isn't without its disadvantages either. Get some more insect sex education over at *Molecular Biology and Evolution*.

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Interviewer: Benjamin Thompson
Right then everyone, it's time for the News Chat, and I'm joined here in the studio by Nisha Gaind, one of the News Editors here at *Nature*. Nisha, how are you doing today?

Interviewee: Nisha Gaind
I'm well, thanks Ben.

Interviewer: Benjamin Thompson
Excellent, well thanks for joining us. Well Nisha, last week on the News Chat I chatted to Richard Van Noorden about a future satellite that's going to be sent up to look for methane above oil wells on Earth. This next story is also about satellites and methane, but a little but further away. What have you got for us?

Interviewee: Nisha Gaind
That's right Ben, we've got a satellite that's circling the planet Mars, that's just reached its scientific orbit, and it is poised to solve one of the most controversial mysteries in Martian science, and that's why methane is found on the red planet.

Interviewer: Benjamin Thompson
So, who's put this satellite in space then, Nisha?

Interviewee: Nisha Gaind
So, this is a joint mission of the European Space Agency and Russia's space agency Roscosmos, and it's part of a broader mission called ExoMars. The orbiter that we're

interested in and talking about today is called the Trace Gas Orbiter. It launched in March 2016, and it reached the planet in October 2016, but since then it's been doing a special kind of manoeuvre, where it circles the planet in a series of quite erratic orbits in order to get to the correct position.

Interviewer: Benjamin Thompson
It can't be the first time that people have looked for methane on Mars though, surely?

Interviewee: Nisha Gaind
No, and other crafts have found methane on Mars, NASA's Curiosity sees it, and so does another Mars orbiter calls Mars Express. But this is the first time a spacecraft has been specifically designed to look for methane. Methane is what they call a trace gas, it's present in very small amounts, along with other gases like water vapour and ozone, but methane is of particular interest to researchers because it could be a signature for life, and that has everyone excited.

Interviewer: Benjamin Thompson
And why then is methane you know a signature for potential life?

Interviewee: Nisha Gaind
If we think about methane on Earth, 95% originated from current and past biological activities, such as cows and livestock and so on. So, it's quite natural to ask whether the same is true on Mars. But it could also have a geologic origin, that means that it could come from chemical reactions between water and rocks, or it might be stored in crystal cages below the surface.

Interviewer: Benjamin Thompson
So, if methane has been discovered by other rovers then, what extra sort of information is this satellite going to give us, and how much is kind of already there?

Interviewee: Nisha Gaind
Researchers have been looking for methane on Mars for 50 years or more, but they have only been detecting hints of it for about 15 years. And many of those findings have been quite controversial, and met with both immense interest and criticism. Curiosity now detects a background level of methane of about .5 parts per billion. By contrast on Earth, the concentration is about 1,900 parts per billion, so, it's a very, very low level of methane. But what's really interesting is that researchers have also seen huge spikes in this concentration. Sometimes they detect what might be big plumes of methane, or just slightly smaller burps, and there are many hypotheses about why these spikes might occur, but there's no real consensus. This orbiter is going to look for methane like no probe has before, by circling the planet continuously it's going to be able to build a global map of methane and these other trace gases, and it will be able to see where it varies by location and also how it varies over time.

Interviewer: Benjamin Thompson
And so, if it's all systems go then, when can we expect the first results back to Earth?

Interviewee: Nisha Gaind
The project scientists are now in a phase where they're trying to figure out what the probe sensitivity is, whether it's going to be as good as they hope it will be, and that can be affected by things like Martian dust. So, the next month or so will be aimed at finding the sensitivity, and then within the next few months they expect to start receiving data, the data that everybody has really been craving about methane on Mars.

Interviewer: Benjamin Thompson
Alright, well let's move on to our second story then Nisha, and this couldn't be more different, and in this case, we're going to be looking at postdoctoral funding and the state of funding for early career researchers in the Netherlands.

Interviewee: Nisha Gaind
Yeah, so this is a really interesting study, and it's looking at how the fate, that's a bit of a loaded word, of junior researchers, or early career scientists could be decided by whether they get a certain grant early in their career.

Interviewer: Benjamin Thompson
So, who's undertaken this study then, and maybe, what have they found?

Interviewee: Nisha Gaind
So, this has been done by a group of researchers based in the Netherlands, and what they've done is look at a particular early career grant that is given out by the Dutch National Science Funding Agency. Now, when scientists apply for grant funding, they're often ranked, and what the researchers did here was look at the applicants who just qualified for the grant, and then look at the applicants who just missed out on the grant, and they compared how their career paths continued.

Interviewer: Benjamin Thompson
Hm, so a fine line then between, I guess, in inverted commas, success and failure, and what happened to these two groups?

Interviewee: Nisha Gaind
What the researchers found is that the successful group, so those that just qualified for the grant, went on to secure more than twice as much research funding in the subsequent 8 years. And, they also found that the winners were 50% more likely to become a professor than the ones who just missed out on the grant.

Interviewer: Benjamin Thompson
And do they offer any suggestions as to why this might be?

Interviewee: Nisha Gaind
Yeah, well, one of the reasons is just that researchers who lost out on the grant were much less likely to apply for future funding. In fact, the researcher who led the study said there is a group of very young, talented scholars who have bad luck, and they don't get the same resources to bring their ideas to life.

Interviewer: Benjamin Thompson
And this seems like a, you know, fairly important result then, to at least give an idea of how one's career could go depending on whether you're just over or just under. Has anybody else been looking into this at all?

Interviewee: Nisha Gaind
Yeah, this isn't necessarily a new finding, it's just that the researchers were able to compare the fate of the young academics in a slightly different way in giving more detail, but previous studies have made very similar findings. For example, the same was found for a particular early career fellowship from the US National Institutes of Health.

Interviewer: Benjamin Thompson
Alright, well I guess the most important question Nisha is then, what can we do about it?

Interviewee: Nisha Gaind
Well, funders say that they're aware of this problem, that early success can influence their future careers, and what other researchers say is that this really emphasises the need for thoughtful, informed mentoring of young academics about applying for funding and persevering with these sorts of applications.

Interviewer: Benjamin Thompson
That does seem like a fairly important story then, that could affect a lot of people's careers. Listeners, for more on the latest science news, head over to nature.com/news, and in case you didn't catch it, Nisha made her debut on the latest edition of our roundtable show Back Chat, hosted by none other than Adam Levy.

Interviewer: Adam Levy
Yeah, so this month we were talking about sexual harassment in academia, the cult of celebrity in science, and a social media sandal, no prizes for guessing what social medium that was about. Listeners, you can find that wherever you get the *Nature Podcast.* I'm Adam Levy.

Interviewer: Benjamin Thompson
And I'm Benjamin Thompson, thanks for listening.