Nature Podcast

Introduction

This is a transcript of the 1st March 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: Shamini Bundell
Hello and welcome to the *Nature Podcast*. This week, brain waves are making a splash, and mapping the landscape of childhood cancers.

Interviewer: Adam Levy
Plus, physicists find a fingerprint from the early Universe. This is the *Nature Podcast* for the 1st of March 2018. I'm Adam Levy.

Interviewer: Shamini Bundell
And I'm Shamini Bundell.

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Interviewer: Shamini Bundell
First up, astronomers have found evidence of the Universe's first stars from a period known as the Cosmic Dawn. The signal isn't quite what they expected. Here's Lizzie Gibney with more.

Interviewer: Lizzie Gibney
For the first few hundred million years of its existence, the Universe was a dark place. Only once electrons and protons had formed atoms of hydrogen, and hydrogen had clumped together, could the first stars begin to shine. So how can we study this long ago era? Using a telescope to detect the very faint light from those stars is extremely challenging. But physicists realise they might be able to detect early stars in a different way: through the impact that their light had on the hydrogen gas that still flooded interstellar space. That's what Judd Bowman and his colleagues set out to find.

Interviewee: Judd Bowman
Astronomers had been looking for evidence from this time for probably over a decade or two decades. This particular signal that we're trying to study is very hard to see because it's very faint. We're actually using radio waves to identify the fingerprints of the first stars, so we're making an indirect observation where we're seeing the effect that stars had on primordial gas around them.

Interviewer: Lizzie Gibney

The team looked for a slight dip in the intensity of radiation, known as the cosmic microwave background, an afterglow of the big bang itself. Energetic light from the first stars would have slightly changed the behaviour of the gas in the early universe, allowing it to absorb this radiation. That would create a tiny dip in the intensity of the radiation that should still be visible today. The trouble is that the frequency of this dip sits in the radio wave part of the electromagnetic spectrum and so the faint signal would be easily drowned out by waves made much closer to home by stars in their own galaxy, radio stations and even digital television. Judd's team had to minimise and account for these sources and when they did, remarkably they saw a signal emerge. It was almost too good to be true. So the team then spent the next two years checking it was real.

Interviewee: Judd Bowman
Our first reaction when we started to see the signal in our data was a cautious sort of scepticism and so after two years we passed all of these tests and couldn't find any alternative explanation for the feature we were seeing in our data and at that point we actually started to feel a little excitement.

Interviewer: Lizzie Gibney
The U shaped dip in radiation is tiny but packs a wealth of information. The longer the light has been travelling across the Universe, the more it is stretched, so the wavelength at which we first see the signal – the start of the dip – tells us when the first stars lived. That was at least 180 million years after the big bang. More than that, the end of the dip gives the point in time when the stars and galaxies had heated up the gas so much that the absorption signal stopped.

Interviewee: Judd Bowman
So we see that happening less than a hundred million years later, so by roughly 250 million years after the big bang. So that gives us two very important milestones in the history of the universe that we now have much more information on than we have had in the past.

Interviewer: Lizzie Gibney
Getting the first signal from these primordial stars is essential for understanding how later generations of stars formed, eventually culminating in planets and people. But the discovery also held a surprise.

Interviewee: Judd Bowman
So we've seen this feature and it looked very much like we'd thought except for one really big glaring exception. It occurs in the right part of the radio spectrum but the size of the feature, the amplitude of it is twice as big as we expected. And so that's very difficult to explain and requires possibly some new physics or some improvement in our understanding of the universe to account for that larger than expected amplitude.

Interviewer: Lizzie Gibney
This inconsistency with the predicted results has got other physicists excited. Here's cosmologist Rennan Barkana on how he felt when Judd showed him the signal.

Interviewee: Rennan Barkana

I was actually quite amazed. Initially I was sceptical. I wasn't sure. Judd was still making final checks but I decided to take it seriously and treat it as an interesting puzzle. The timing of the signal fell within the right ballpark but the amplitude was very, very surprising. The signal was way bigger than all of the range really. It was outside the range of possibility, so that seemed very exciting.

Interviewer: Lizzie Gibney
According to Rennan, the dip being much bigger than predicted suggests that the gas in the early universe may have been colder than expected.

Interviewee: Rennan Barkana
The question is what could be even colder and actually cool it down? And then I realised that the only candidate is dark matter.

Interviewer: Lizzie Gibney
Dark matter is one of the biggest mysteries in physics. We think it exists because of its gravitational pull on visible matter, but it's never been seen. Rennan says that because dark matter interacts with other matter only very rarely, this would have allowed it to stay cold and particles of dark matter could have then acted like ice cubes to cool the hydrogen gas. If this is what we're seeing, it has huge implications for the hunt for dark matter.

Interviewee: Rennan Barkana
If it's proven to be correct, it's a clue about what the dark matter is and how it interacts. So it would mean that the dark matter has an interaction, does collide with ordinary matter, and that by itself was very interesting and particle physicists will explore that.

Interviewer: Lizzie Gibney
If Rennan is correct, this would be the first time we detected dark matter through anything except its gravitational effects. It would also make dark matter much lighter than physicists expect. That could explain why no dark matter has been seen in experiments so far. For now this is all speculation. But thankfully, physicists won't have to wait too long to corroborate the findings. Experiments in Europe and the United States, some involving much larger arrays of instruments, will soon study the radio signal in greater detail. Judd is eager for other teams to confirm their findings, but also to explore other exotic explanations for this very surprising result.

Interviewee: Judd Bowman
I think Rennan's idea is incredibly exciting and would be fantastic if it's borne out as future observations continue to probe this feature. I'm sure additional ideas will be proposed by our colleagues as the results are published and they read more about it and have time to think.

Interviewer: Adam Levy
That was Judd Bowman of Arizona State University talking to Lizzie Gibney. You also heard from Rennan Barkana of Tel Aviv University. Their papers are both available now on nature.com/nature and Lizzie's news piece is up at nature.com/news.

Interviewer: Shamini Bundell
Still to come: watching DNA wind, and examining butterflies' double-sided wings – that's in the Research Highlights. But first, Adam is finding out about the symphony in our heads.

Interviewer: Adam Levy
Eagle eared listeners of the *Nature Podcast* may remember a study that made waves in 2016, literally. People with Alzheimer's disease have reduced gamma waves in their brain signals. So, neuroscientist Li-Huei Tsai, attempted to nudge the waves back into their normal rhythm. To do this she placed mice with an Alzheimer's like condition in a box with a rapidly flashing light, like a mini disco, when she measured the signals of a key signifier of Alzheimer's, amyloid, back in 2016.

Interviewee: Li-Huei Tsai
We found that with just one hour of light flicker treatment in the visual cortex of these mice, they show about 50% reduction of the amyloid load. That was the moment it was just, I think it's a once in a lifetime kind of experience.

Interviewer: Adam Levy
Fifteen months on from the publication of her paper, *Nature* are publishing a feature looking at the potential that brainwaves offer for a whole host of conditions. I got back in touch with Li-Huei to find out how things were going with her research on Alzheimer's. She told me she wasn't the only person to be taken aback by her findings.

Interviewee: Li-Huei Tsai
Yeah, the reaction was overwhelming. Since our paper was published, I received numerous messages from people all over the world.

Interviewer: Adam Levy
Some of this response came from fellow neuroscientists. Neuroscientists like Robert Knight at the University of California, Berkeley, who hadn't expected brainwaves could have a physical, measurable effect on amyloid plaques in the brain.

Interviewee: Robert Knight
To me it was very surprising. I really hadn't thought that some driving at some specific frequency would actually lead to removal of plaque burden.

Interviewer: Adam Levy
Still, there's a long way to go before we know whether this approach could treat Alzheimer's. There have been many promising efforts to treat Alzheimer's in mice that have failed to work out in humans. So how can we know if this approach stands a chance?

Interviewee: Li-Huei Tsai
We've been burnt hundreds of times so I think this question is completely fair. It's better that it works in mouse models than it doesn't work in mouse models.

Interviewer: Adam Levy

For Robert there are two important next steps to build on our understanding: one theoretical, one practical.

Interviewee: Robert Knight
First thing is we need to know more about the physiology of the brain waves, so basic science on what they represent and what information transfer they're involved with needs to be determined. So that's the basic science and then the other side is how do we know it works? There's only one way to know it works, whether it works, you have to do clinical trials.

Interviewer: Adam Levy
For clinical trials, this approach has an advantage because a flashing light is both simple and safe, this method can be tested in humans quicker than a new drug, for example. Le-Huei has cofounded a new drug company – Cognito Therapeutics –which has already begun investigating the potential for people with Alzheimer's.

Interviewee: Li-Huei Tsai
They have initiated human studies in a small cohort of people to evaluate the safety and visibility of this approach in humans.

Interviewer: Adam Levy
This work illustrates the importance of brain waves for healthy brain function but there are still some pretty fundamental questions about what these fluctuating patterns of electrical activities even are.

Interviewee: Li-Huei Tsai
To be honest with you I think there are still a lot of question marks in terms of, you know, how the brain waves are initiated, what's the precise cellular mechanism and how is it maintained.

Interviewer: Adam Levy
Li-Huei's work is part of a growing body of research calling attention to these electrical oscillations. That's according to Walter Koroshetz, director of the National Institute of Neurological Disorders and Stroke at the NIH.

Interviewee: Walter Koroshetz
Over the last ten years, the oscillatory activity has drawn a lot of scientists to understand its function. The oscillations are kind of a marker that cells oscillating together are involved in a certain function together, whether they be in one brain region or spread across multiple brain regions. But still I think we're at the very beginning of understanding the oscillations as a marker of activity.

Interviewer: Adam Levy
Brainwaves appear to be reducing amyloid plaques in the brain by triggering immune cells called microglia and this, Walter says, could have implications way beyond Alzheimer's.

Interviewee: Walter Koroshetz

The basic finding here is that there's a frequency dependence between neuronal firing, particularly in these interneurons and microglial activation, so that basic finding, I think, has implications all over the nervous system. So, for instance in epilepsy, the activation of microglial epilepsy, where you have very rapid firing, is an area of intense investigation and so I think that this interaction between circuit activity and the microglia is I think incredibly important and I think is going to be incredibly important for many conditions, both normal development and response to injury or pathologic conditions.

Interviewer: Adam Levy
And Robert Knight agrees that researchers are increasingly attempting to harmonise brainwaves for all sorts of different issues.

Interviewee: Robert Knight
There's been an explosion in brain wave research so in a way if you think about it a lot of the method are trying to get the orchestra to play in tune so I think that's been a huge focus in neurological disorders, for instance in stroke, psychiatric disorders, ageing. Pick your area and different people are trying to apply predominantly extra-cranial stimulation to improve behaviour. But I think it has tremendous potential applications.

Interviewer: Adam Levy
That was Robert Knight, who's based at the University of California Berkeley. You also heard from Li-Huei Tsai who's at MIT, and Walter Koroshetz, director of the National Institute of Neurological Disorders and Stroke at the NIH. There's a feature all about brain waves in this week's *Nature*. Find it at nature.com/news. And to hear our original podcast piece on Li-Huei's research, check out the episode from the 8th of December 2016.

Interviewer: Shamini Bundell
Stay tuned for the news, where we'll be filling you in on the UK universities strike and the tool that can spot duplicated images across papers. Now, though, it's time for the Research Highlights, read this week by Noah Baker.

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Interviewer: Noah Baker
Have you ever dreamt of making lassos from DNA? Well, it turns out that the protein, condensin, has already mastered that. Condensin helps squeeze DNA into cells but researchers have quibbled over how. To end the cycle of speculation, a team nailed down a strand of DNA at each end. They tagged it with a fluorescent dye and set condensin on it. The orange dye enabled the first live footage of condensin in action to be recorded. The molecule latched itself onto the DNA and started reeling the strand in from one side, threading it rapidly into a large loop. Cast an eye over the full paper in *Science*.

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Interviewer: Noah Baker
The kaleidoscope patterns on many butterfly wings differ from one side to the other. Biologists have found that a gene called *apterous A* known for its work on beetle wings is

also the evolutionary artist behind the double sided design. The team mutated the gene in caterpillars of the African squinting bush brown butterfly. When the fully fledged flutterers emerged from their cocoons, they displayed similar patterns on the top and bottom of their wings. Cue rapturous applause for *apterous A*. mutations in the gene may also be behind some of butterflies' splendid diversity. Flutter over to the *Proceedings of the Royal Society B* for more.

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Interviewer: Shamini Bundell
Next up, reporter Anand Jagatia takes a look at new research into the genome sequences of childhood cancers.

Interviewer: Anand Jagatia
In the developed world, the leading cause of death by disease in children over the age of one, is cancer. Fortunately, childhood, or paediatric, cancers are rare and cure rates have increased to about 80% which is fairly high. But that's a number that hasn't really changed much in recent years.

Interviewee: Stefan Pfister
Honestly in the time that I have been involved in paediatric oncology which is the last 15 years, there was not too much progress. We basically are stuck at 80%.

Interviewer: Anand Jagatia
This is Stefan Pfister from the German Cancer Research Centre.

Interviewee: Stefan Pfister
We will probably not get much further by doing more of the same which was largely optimising chemotherapy and radiotherapy protocols and combining them in a meaningful way.

Interviewer: Anand Jagatia
To try and get over this upper ceiling of 80% his group has taken an alternative approach: to look at the genomes of the tumours themselves in the hope that sequencing their DNA could tell us more about the mutations that may be driving cancer and provide targets for treatment. This week *Nature* is publishing two papers which analyse the genomes across multiple cancer types in children. The papers represent the first ever analyses of this type and Stefan Pfister is one of the authors. His study looked at almost one thousand tumours across 24 cancer types.

Interviewee: Stefan Pfister
Research is usually deceased focus, right, so everyone is doing a genome study in a particular type of cancer but usually we don't really make the comparison with other cancers and because paediatric cancers are really fundamentally different from adult cancers, we cannot really extrapolate so much from the adult world and what we felt now was timely was to take all of this data together and to really assess what is specific about one cancer type or a set of cancer types in comparison to the others.

Interviewer: Anand Jagatia
The study highlights several key ways in which the genomic landscape of childhood cancers differs from adult cancers.

Interviewee: Stefan Pfister
On average, in paediatric cancers in comparison to the typical adult cancers, the number of mutations across the whole cancer genome is about 15 fold lower and what we conclude from this is really that also when trying to specifically use some of these mutations potentially to attack the tumour we probably have a higher likelihood of finding something to fight.

Interviewer: Anand Jagatia
The analysis also looked at mutations that the children were born with as opposed to those that accumulated in their lifetime.

Interviewee: Stefan Pfister
We think there is probably about 10% of paediatric tumours that are caused by inherited factors. There are any of these that basically also come along with either resistance to certain types of therapy but also with a higher sensitivity of secondary malignancy so these are the patients that we want to really filter put to make sure that even when curing the first tumour, to not induce the second tumour based on our therapy a few years down the line.

Interviewer: Anand Jagatia
The studies also found that the mutated genes in childhood cancers are generally different to those found in adult cancers. In adults, while multiple cancer types – brain, pancreatic, liver – often share the same mutations, in children, different cancer types tend to have their own specific set of mutations, all of which confirms what paediatricians have long known: that we have to think of childhood cancers as separate from adult cancers. This is Mimi Bandophaday from Harvard University who wrote a News & Views article on the studies.

Interviewee: Mimi Bandophaday
So you can imagine that an adult who develops a tumour, they've been around for many years and themselves have had more exposure to environmental things that can cause mutations which can cause cancers, for example: UV light in the sun for melanoma or cigarette exposure for lung cancer for example. Whereas children we see cancers sometimes even before babies are born. That gives us a clue that unlike adult cancers where you can get an accumulation of mutations that might then force a cell to become a tumour, in paediatrics often it just takes one and then that can actually trigger a tumour to form.

Interviewer: Anand Jagatia
So what might all this mean for cancer treatment? Stefan and his colleagues searched for mutations that could potentially be targeted by existing drugs, or drugs in development and in 50% of the tumours, they found one.

Interviewee: Stefan Pfister

By having a certain genetic mutation this of course does not mean that the tumour will be responsive to a drug that is targeting this gene or this mutation but then we also have the 50% of cases where we don't have a very clear drug target and there we really have to learn a lot more about vulnerabilities.

Interviewer: Anand Jagatia
Mimi says that these findings are cause for optimism but she also told me that cataloguing the mutations is only the first step.

Interviewee: Mimi Bandophaday
The next key step is we need to understand how the mutations are actually causing the tumour cells to grow. So if you have a mutation in gene X, what does that do to the cell to make it more oncogenic, is the word that we use, or to behave more like a tumour. And then we've learnt from, this is where the adult cancers will guide us, we've learnt from our adult colleagues that cancers are – they're stubborn things in that we may treat a cancer with a medication; they will adapt or evolve to become resistant. So in addition to identifying targets, working out how the targets are causing cancers and how to inhibit it, we also need to work out how the tumours are expected to become resistant so that we can go in with combination treatments to try and stop these tumours from becoming resistant to single agents.

Interviewer: Anand Jagatia
Nevertheless, childhood cancer analyses like these could be important for future research. Mimi hopes the approach could help create more tailored and less damaging treatments for children.

Interviewee: Mimi Bandophaday
I'm a researcher but I also see children in clinic. I actually went back to school and did my PhD after training to become an oncologist because I couldn't bear to see children come to clinic and for us to have no treatments to offer. I believe that these sorts of studies and other studies that are going around the world at the moment collaboratively will move the bar and I really hope that by the time I retire, things are going to be different. When kids come to clinic with what are currently incurable brain tumours and we're going to have treatments that will target their tumours and a way to give these kids and their families hope and a chance.

Interviewer: Shamini Bundell
Mimi Bandophaday and Stefan Pfister talking to Anand Jagatia. You can read both the analyses and the News and Views article at Nature.com/nature.

Interviewer: Adam Levy
Finally this week, it's time for our News Chat and Richard van Noorden, *Nature*'s Features Editor joins us in the studio. Hi Richard.

Interviewee: Richard van Noorden
Hi Adam.

Interviewer: Adam Levy
Now, in the UK, universities are dealing with a strike. Who's actually on the picket lines?

Interviewee: Richard van Noorden
There are around 42,000 academics on strike. It is a big strike and around 25,000 of them or so are researchers. This is 14 days of strikes planned over four weeks. The first five days, as we're talking, were due to end on the 28th of February and more than 60 universities are involved and this is a strike about pensions, about academic pay. It's one of the largest strikes in Britain's recent history.

Interviewer: Adam Levy
You mentioned that it's about pensions. What's the dispute actually referring to?

Interviewee: Richard van Noorden
Well, the problem is a 2017 valuation of the main pension fund for many employees at Britain's universities and according to that valuation it has a deficit of more than 12 billion pounds. And, Universities UK, a body that represent British universities propose changing the way the pension income comes in from having a guaranteed element to being entirely dependent on return from investments from stock markets and according to some models that would cut pension income by several thousand pounds a year depending on your salary. Now, that's going to affect the pensions of at least 190,000 faculty members and staff in the UK. They are very angry about it. This is all up for negotiation right now. As a result of the days of strikes that we've seen so far, talks are being resumed between Universities UK, but they're not yet changing their view of the deficit of this fund.

Interviewer: Adam Levy
And how unprecedented is this kind of industrial action by academics?

Interviewee: Richard van Noorden
Well for the UCU, this particular union, it's essentially unprecedented. In recent history, a decade ago, there was a one day walkout strike but here we're talking about two weeks overall of strikes and not just lectures to students but a strike on all work including scientific experiments and some conferences have already been cancelled.

Interviewer: Adam Levy
Fourteen days of not doing experiments seems like it would really quite disrupt a lot of work.

Interviewee: Richard van Noorden
Yeah, it will be difficult to make up missed lab time. We talked to one chemist who said he was crossing the picket line because he had very sensitive equipment that just did need to be switched off. One computer scientist told us his team might not be able to bid to host a five million pound training centre in Artificial Intelligence because of the strike, because the opportunity was announced just two weeks ago and has a very short deadline for applications. So he said I'm potentially hurting my university's finances by endangering this bid but I think that my own and other universities are jeopardising the future well-being of their staff, so this has to be stood up against.

Interviewer: Adam Levy
So when can we actually expect this to be resolved to some extent?

Interviewee: Richard van Noorden
Well the board that runs the pension scheme has to submit its final decision on the changes by the end of June to the country's pensions regulator so I suppose at that point we will be seeing a decision on whether those pension schemes are going to be changed. But perhaps the strike action will lead to some change before then.

Interviewer: Adam Levy
We'll have to keep an eye on that story but for now let's move onto our second story of the week which is a new tool to spot duplicate images in papers. Why is having a tool like this important?

Interviewee: Richard van Noorden
Well, journal editors are very concerned about the proportion of duplicated images that we see in research papers. Some studies of large numbers of research papers in the biomedical sciences have suggested that a good small percentage, perhaps as many as 4% of these papers, contain suspicious images. So now computer scientists say we can do this with software and we can look over thousands or hundreds of thousands of papers to spot images that are duplicated between them so that could be an extremely valuable tool.

Interviewer: Adam Levy
What have these researchers actually shown this tool doing so far?

Interviewee: Richard van Noorden
Well this is a paper on the BioRxiv pre-print server so it hasn't been peer reviewed but its researchers at Syracuse University in New York and they say that they've got an algorithm that crunched through hundreds of thousands of papers in the PubMed database. They specifically chose the open access papers in this database because you can extract images from them without any legal implications. And they picked out more than two million images and then the algorithm makes a kind of characteristic digital fingerprint of each image and then essentially compares images to find duplicates. Now this is computationally extremely intensive and in fact they only compared images across papers from the same first and corresponding authors. So then after they'd done that, the algorithm had flagged up these potential duplicates. They then manually examined about 3,700 of these flagged up results and they said well, we think on the basis of that about 1.5% of the papers in this open access database would have suspicious images in them.

Interviewer: Adam Levy
This seems like a really useful proof of concept. But in order for it to be useful it needs to be adopted by publishers for example.

Interviewee: Richard van Noorden
So the algorithm isn't public, apparently, says researcher Daniel Acuna because of the risk it could trigger false allegations but he plans to licence it to journals and research integrity

officers and they say they are interested and Elsevier, the publishing giant, says that it would support some kind of publisher wide initiative whereby publishers would create a shared a database, a private shared database of all published images against which you could quickly compare new papers. This has already been done in the field of text plagiarism so why not for images too?

Interviewer: Adam Levy
So what's done at the moment? Are images just not checked in papers at all?

Interviewee: Richard van Noorden
Well, very few journals actually employ people to manually look at the papers that come in, such as the EMBO Journal and they pick up quite a lot of problems before peer review. But that's just a few journals. Most journals do not employ someone to screen images and manuscripts and even *Nature* just runs random spot checks on images in manuscripts.

Interviewer: Adam Levy
So, say you've found two duplicate images, what does that actually tell us about the research practices that went into those papers in which they were found?

Interviewee: Richard van Noorden
Well, it depends on the context. It could be an appropriate use of the image from earlier work and they've reused it correctly and cited it as such or it could be outright fraud. So this algorithm is going to be a kind of automated pre-screen that someone is always going to have to look at to determine whether the use of an image is potentially fraudulent or suspicious enough that one would need to go back to the authors to ask them to address the issue.

Interviewer: Adam Levy
Richard van Noorden, thank you for joining us. For all the latest science news head over to nature.com/news.

Interviewer: Shamini Bundell
And for a look behind the news, make sure to give backchat a listen. February's roundtable discussion features a look at scientific disputes, as well as scientific flukes. Find it on the *Nature Podcast* feed.

Interviewer: Adam Levy
Stay tuned for next week's show, where we'll be bringing you a look at a science fiction classic. Until then, I'm Adam Levy.

Interviewer: Shamini Bundell
And I'm Shamini Bundell. Thanks for listening.

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