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Science Writing Award

UKRI Medical Research Council

In partnership with The Observer

THE SHORTLIST 2021

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SHORTLIST AND SELECTIONS

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Cranberry juice won't cut it anymore

I'm a biomedical research scientist. My laboratory essentials are a white coat, bubbling liquid, and the occasional explosion. I make ground breaking discoveries every day. Crowds gather to marvel at my experiments and their life saving implications.

WINNER
VICKY BENNETT
GW4 BioMed
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This is at least my mum's impression of my PhD so far.

The reality of my current situation seems somewhat different. My shiny white lab coat was at first a wonderful addition to my wardrobe, but the many tanks of infected urine on my work bench are far from glamorous. (In fact, shiny white lab coat + infected urine = smelly yellow lab coat). Instead of crowds of admirers, 'the wee area' of our shared lab space is actively avoided. The consequences of any kind of explosion are not worth contemplating.

Welcome to the world of urinary tract infection research.

Urinary tract infections (UTIs) are not particularly pleasant. They occur when bacteria from poo come into contact with and enter the external opening of the urethra, the tube that allows urine to flow from the bladder to the outside of the body. If bacteria colonise the urethra, they then have direct access to the bladder. This is the ideal environment for them to multiply and spread upwards to infect the kidneys, or even enter the bloodstream.

For those lucky enough not to have experienced a UTI, the frequent urge to urinate and a painful stinging or burning sensation when passing urine are characteristic symptoms. UTIs are common for all ages, but obvious anatomical differences mean that women are more frequent sufferers, as a shorter urethra reduces the distance bacteria must travel to reach the bladder. With up to 60% of adult women suffering at least one UTI in their lifetime (compared to 12% of men) many see them as an awkward but inevitable part of life. Data on transgender experience of UTIs is limited but advice sites report they can be issue for "genital tuckers" and trans men taking testosterone. Some have even gone so far as to describe their experiences in song form. See 'Love song for my UTI' by YouTuber Lex Croucher for one of my favourite examples.

A short course of antibiotics will clear most infections. But the number of bacteria resistant to antibiotics is increasing. Someone with an infection which was once curable in a few days may now try several different antibiotics before finding one which works. And even if your symptoms do clear up, it may

be that the bacteria have not been fully eradicated, with around 30% of infections returning within six months. Many people must accept a life of chronic recurring UTIs and near permanent symptoms.

Every UTI also has the risk of developing into a life-threatening kidney or bloodstream infection. This risk increases with age, and for those with underlying health conditions. The ever-growing threat of antibiotic resistance means that chronic and severe infections are becoming more common. Even that well known mythical cure that is cranberry juice will not have any effect against multidrug resistant bacteria.

So, the solution is to find some new, better antibiotics, right? Something that kills bacteria quickly and is hard for bacteria to become resistant to. This essentially is the aim of my PhD project. I am trying to identify specific parts of bacteria that would make good targets for new antibiotics to attack. I will then use a computer modelling system to identify existing drugs which could be used in a new way to hit these targets and kill the bacteria. These come from huge databases of millions of drugs used for any purpose in medicine, not necessarily existing antibiotics. This is a process called 'drug repurposing'. If successful it will reduce the time and cost associated with new antibiotic development.

This leads us back to my urine tanks. In my research group we work with a bacteria called 'Proteus mirabilis', a common cause of catheter associated urinary tract infections (CAUTIs). Urinary catheters are the most commonly used medical devices. The catheter is a long flexible tube inserted through the urethra into the bottom of the bladder and is connected to a urine collection bag outside the body. They are used in people of all genders with medical conditions that make it hard for the bladder to empty naturally, as well as before or after some types of surgery. Depending on the situation, the catheter could be temporary or permanent.

But the presence of a catheter makes it easier for UTIs to develop. Bacteria grow much more easily on the catheter surface, and the tube provides a direct pathway for them to enter the urethra and the bladder. As the bacteria build up, they will eventually block the tube and prevent urine leaving the bladder. This causes urine to collect in the bladder, where it can flow backwards towards the kidneys, increasing the likelihood of life-threatening kidney and bloodstream infections, as well as causing a huge amount of pain from the urinary retention itself.

We recreate this situation in the lab by using real catheters inserted into replica glass bladders. A pump system pushes urine through the bladder and into the catheter at a body temperature so that we can monitor the effects of our experiments in as realistic a way as possible. We infect the glass bladder and leave the bacteria to grow on the catheter surface, where the build up of bacteria will eventually block the tube and stop urine entering the collection bag.

A key aspect of these experiments is reproducibility and reliability of results. Real urine is very variable depending on what someone has been eating or drinking, therefore I spend a day each week making up five litre tanks of artificial urine to use in my experiments to ensure consistency. This involves mixing water with urea and various salts such as potassium and sodium chloride. It even smells like the real thing.

The time taken for the catheter to block determines the success of different drugs. These could be tested in several ways, either by being flushed into the bladder through the catheter, dissolved in the urine, or applied as a coating to the catheter before it is inserted. The longer the time to catheter blockage, the more promising the treatment. And you would not believe the anticipation and excitement caused by watching urine slowly drip through a bacteria encrusted catheter.

Of course, I am not yet 12 months into my 3.5-year project, and there is a long long way to go before handing a patient a drug which will cure their infection. However, I really hope that my research will support the development of new antibiotic treatments to help patients with CAUTIs, chronic UTIs not treatable with existing drugs, and anyone that is fed up with that burning sensation when they pee.

Exploring psychosis using hypnosis

RUNNER-UP

ELISA BRANN

MRC Doctoral Training Partnership
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I sit in a dark room alone with a young woman called Jess. It's completely silent except for our steady breathing and the faint buzz of the computer that records the electrical activity of her brain. But then, Jess hears a voice. It's the voice of a man, she tells me. She feels him whispering into her right ear. It's as if he were standing just behind her. But he isn't. There is no one there. What Jess is experiencing is an auditory verbal hallucination, a phenomenon that is often associated with severe mental illness. Except, Jess is not unwell. In fact, she has no history of ever having had a mental health condition. Instead, I've hypnotised her to 'hear voices'.

Whenever I tell someone about my work I am almost always met with disbelief and the inevitable question "is hypnosis even real?". I don't blame them, after all, as a scientist I'm basically a trained sceptic. My research has enabled me, however, to reply with confidence that hypnosis is a very real phenomenon that can result in very powerful experiences. The problem is that there are a lot of misconceptions about what it is. Simply, hypnosis describes a scenario in which an individual enters a state of highly focused attention. During this state their perception (what they can experience with their senses) can be altered based on verbal instructions, known as suggestions. To respond to these suggestions under hypnosis requires cooperation and willingness from the individual being hypnotised, and how well you can do this varies from person to person. The technique has been used in medicine for over a century. It is regularly used by practitioners to help individuals change their behaviour, for instance helping smokers kick their habit. And remarkably, it can even be used in some instances as an alternative to traditional anaesthetics, including during brain surgery.

In my work, I use hypnosis as a tool to explore a mental health condition that can be very difficult to study, psychosis. This devastating condition involves perceiving things that are not really there (hallucinations) or believing things that are not really true (delusions). We most frequently see it in individuals diagnosed with schizophrenia, but it also occurs in other conditions such as bipolar disorder or depression. Approximately 5% of people who experience psychosis go on to commit suicide, making it one of the deadliest psychiatric conditions

you can have. Whilst it is usually treated using antipsychotic medication, sadly, one in four people do not see improvements. Consequently, developing new ways of treating the condition are essential and understanding what is happening in the brain is one important way of doing that.

But conducting brain imaging on someone while they are having a psychotic episode is no simple task. The individual is usually far too unwell to take part in research. Even for those who might be well enough, the use of medication or other drugs to manage their condition and 'quieten' the distressing voices can make any brain imaging data obtained difficult to interpret. We cannot tell what effects are because of the drugs or because of the psychosis.

This is where hypnosis comes in handy. By carefully crafting suggestions it is possible to create experiences in healthy individuals that sound a lot like what patients describe. Just like you can distil salt from seawater, it is also possible to separate out psychotic experiences away from the disease and the effects of drugs. Jess's experience of hearing a voice is just one of the kinds of psychotic symptoms myself and my colleagues have been able to create using hypnotic suggestions. We have also been able to mimic other symptoms such as 'delusions of control' (when you believe someone else is controlling your body) and 'thought insertion' (when you believe someone else is putting thoughts in your mind).

For patients these symptoms can be very distressing as they usually involve negative emotional content. For example, an individual might hear a voice saying cruel things about them like "nobody likes you".

But for our healthy volunteers we have been careful to create experiences that are emotionally neutral; they only ever hear a voice say a simple sentence like "the dog ran down the road". We have received ethical approval to create these experiences for our research and in contrast to what patients go through, many of our participants describe them as interesting and even enjoyable.

Now that we have been able to mimic these psychotic symptoms reliably and safely in healthy individuals, we have begun using different brain imaging techniques to peek inside our participants' heads and see what's going on. My research uses a technique called electroencephalography (EEG), which involves placing small sensors over the scalp that can record the electrical activity of the brain as brainwaves. One of the best things about using this technique is that it directly measures what the brain is doing and is great at telling us when in time the psychotic events occur. The process of 'capturing' the psychotic event using EEG is therefore relatively straight forward. It is similar to how kids in the 1990s used to record their favourite songs off the radio with their tape players.

We are still in the early stages of analysing the brain imaging data, but the approaches we are using have a lot of potential. Having an initial idea of what is happening in the brains of healthy individuals experiencing psychotic symptoms helps us make better predictions about what could be happening in patients. This information can then be used to design patient experiments more accurately, and ensure the time and effort spent collecting data on this vulnerable population can be effective. In the future, the work we do using EEG may also contribute to developing our understanding of how psychosis works and help us come up with new ways of treating it.

But when I think about what Jess described to me, I am also struck by what my research can say more generally about the human experience. All too often people with psychosis are alienated from society and mistreated by others who see their experiences as being far away from what we think of as reality. It is easy to think that the unusual experiences of psychosis are what make someone unwell. But exploring psychosis using hypnosis tells us a different story. The experiences of psychosis are not necessarily symptomatic of being unwell, in fact they are much closer to us than we might think. They're only a few suggestions away.

Teatime at Grandma's

I had just learnt how to make a decent cup of tea; taking orders from this lot was a challenge. Alice was constantly laughing about something and could barely take breath to give her order. Doris would sit sulking and stare at her tea until it turned cold. Peter would silently accept his cup with a smile and then, when you weren't looking, would scurry over to the sugar pot and heap in extra teaspoons.

RUNNER-UP
CATHERINE HEFFNER

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These were the characters of my grandma's new nursing home. Although they all had dementia, I was struck by how differently each individual was affected, with members of the group displaying a range of memory, speech and behavioural changes. As the months and years passed, I also noticed how time affected each of them differently. While most remained more or less the same, some would go through sudden and rapid declines in their mental functioning. Perhaps most jarringly of all, others even experienced dramatic personality changes, morphing from their bright and bubbly selves into silent and brooding figures.

The variety of change I saw amongst these patients reflected a small part of a much larger reality. Dementia is an umbrella term for a multitude of different disorders, together affecting 50 million people around the world. There is currently no cure for any of these disorders. Part of the reason for this is because we don't yet fully understand the processes going on in the brain that lead to dementia.

Whilst spending time at my grandma's nursing home as a teenager, my curiosity grew. What accounted for the differences in these behaviours? Why did the health of some patients decline so rapidly whilst others lived stably for many years? Feeling strongly indifferent towards science at that time, I was surprised to find my burgeoning questions were addressed in biology class.

Here we learnt that stretches of DNA called genes act as the instructions for the cell to make different proteins. These proteins form the toolkit for the cell to use in all sorts of functions. Changes in the genetic instructions are known as mutations and can affect the proteins produced so they can't properly perform their functions. Sometimes these proteins have such important functions that their mutation can affect the health of cells in the body, and consequently the health of the body as a whole.

I was immediately intrigued. These genetic mutations seemed like clues. If we could study the

mutations that were found in people with dementia and determine how they affect brain cell function, we might be able to understand the processes in the brain that go awry in dementia. If we understood these processes, maybe someday we could use them as targets for medicines!

Fast forward a few years, and my current work towards my PhD has led me to study one of these rare genetic clues. As almost always in science, this lead was established from many years of work from researchers before me. In the 1990s, scientists analyzed the genetic code from a large family with a peculiarly high prevalence of dementia. They identified a particular genetic mutation that was seen only in the family members with dementia and not in the unaffected members. The clue was found.

The next step for me is to figure out how this genetic mutation affects the protein it relates to. We know that this protein has the crucial task of repairing holes in the fatty membrane layer that coats cells. In the body, cells are under constant attack from different materials which can puncture tiny holes in this membrane. This is bad news for cells. Even tiny holes can allow the contents of the cell to flood out and material outside the cells to flood in, which can be enough to kill them. We think that brain cells might be particularly vulnerable to this kind of attack. Whilst cells in the body come in all shapes and sizes, brain cells tend to be long and spindly, forming a large surface area with a lot of potential for damage to the membrane. Thankfully, our cells come equipped with proteins that can quickly repair punctures, such as our protein in question.

In my PhD I am investigating whether the dementia-associated mutation prevents this protein from properly repairing membranes. To test this, I have been using a high-powered laser to zap very small holes in cell membranes. I do this under a microscope and watch the protein as it repairs the hole I zapped. At this point in my PhD, I have spent many happy hours zapping and filming cells with either normal repair proteins or mutated ones. I have noticed that the mutated proteins take much longer to respond to the lasered hole and may not repair membranes as effectively. While this is a subtle difference to the cells that I zap, one can easily imagine the implications it might have when scaled to thousands of cells in a person's brain, encountering damage every day across the decades.

Since we know that the genetic mutation I am studying is directly linked to dementia, we know this is a powerful clue. Most other kinds of dementias seem to be more complicated, as they are influenced by a combination of genetic and lifestyle factors that vary between patients, making it difficult to pinpoint the cause of the disease. However, as technological advances are increasing the ease at which genetic information can be gathered and analyzed we are continually identifying more clues, making this is such an exciting time to be in dementia research.

My hope is that by studying these clues and how they affect cell functions, we can build an understanding of the processes that occur in brains with dementia. From here, we could create medicines that directly target these processes and prevent them from ever taking hold of a person's mind. Perhaps then we would be in a better position to focus on the important things in life, like enjoying teatime at grandma's.

Shining a light on childhood adversity

"What's wrong with you?" An exasperated prison officer stands before Taylor[1] as the 15-year-old girl curls up on the ground. Unspoken, but even louder, is the officer's implicit answer to her own question: You are messed up.

The scene is a familiar one from my years of volunteering in a juvenile prison, where meltdowns, fights, and refusals marked the passing hours. Within those walls, authorities regularly echoed the question of the officer, and specialists answered them with a laundry list of difficulties and diagnoses.

But merely naming her difficulties does not explain why Taylor was in a crisis that afternoon. To go to the heart of the matter we must adopt what is called a "developmental perspective," a gaze that considers the life history of a person. In Taylor's case, this history includes repeated experiences of violence within her family, whose income fell well below the poverty line.

Why is her history of adversity relevant? Because who we are today is a function of what we have experienced in the past. Each of our lives is a unique tapestry, painstakingly woven together over time with the colourful threads of our genetic makeup and our life history.

Nowhere in the body is this more evident than in the brain. The first steps of brain development unfold according to a genetic blueprint while a baby is still in the womb. Then, as the child grows older, a new artist begins to guide her brain development: experience. The stimulation a child receives from her environment, the words she hears, the faces she sees, the loving care she receives, shape strong and efficient brain networks.

What happens, then, in the brains of children who do not grow up in contexts of loving safety and abundance? We need not look far to find such children, because over half of the adults in the UK experienced at least one adverse event during childhood (like abuse or neglect) while one in five grew up in poverty. And a history of adversity increases the likelihood a person will suffer from mental and physical illness, as well as challenges like addiction, poor educational attainment, and incarceration. Given the science of child development, it seems likely that changes in the mind and brain serve as steppingstones on the path from early adversity to these later difficulties.

Yet scientists disagree over the details of this pathway. Which aspect of adversity has the

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[1] Name changed for confidentiality.

power to change cognitive and socioemotional development? And how exactly does it get under the skin? A clear account would offer invaluable guidance to those who are striving to achieve justice and healing for children. The purpose of my PhD is to meet this need.

One reason for the disagreement is that a variety of experiences fit under the umbrella of "adversity." So, for my first project, I set out to simplify this picture by identifying dimensions of adversity, or categories of adverse experiences that share important features. In other words, do the threads of adversity take common colours in the tapestry of life? If so, we could better recognise and reweave them into opportunities for resilience.

To answer my question, I first obtained data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a large cohort study at the University of Bristol that includes rich measures of exposure to adverse experiences, such as abuse, neglect, domestic violence, and disruptions in caregiving. By choosing ALSPAC, I gained two advantages over previous work on early adversity. First, my statistical analysis would rest on a much larger sample size, strengthening the stability and credibility of my findings. And second, I could use reports of adversity gathered while my participants were growing up, rather than asking them to recall their past experiences after they had already reached adulthood, a common method of assessing adversity that is vulnerable to biases in memory.

Once the data was safely in my hands, I analysed it with a complex model called a network. One well-known example is the social network, which captures patterns of relationships among people. I chose to use a network so that I could accommodate complex interconnections between adverse experiences, rather than yielding to the temptation to reduce the whole tapestry to a simple cross-stitch. And critically, I could look for evidence of dimensions of adversity by testing whether the network contained any densely interconnected groups of variables.

As I had expected, I found two dimensions of adversity in the data. The first included measures of abuse and domestic violence, while the second included forms of inconsistent caregiving and financial difficulties. Adversity therefore seems to take two dominant colours in the tapestry of life: the warm threads of violence and the cool threads of deprivation.

Do these dimensions predict unique life outcomes? I thought they would: previous research found specific links between violence and emotional problems and deprivation and cognitive problems. But when I added measures of mental health and cognitive ability into my network, all of them grouped with childhood experiences of deprivation. And this pattern held up across the stages of childhood. So it appears that a broad path leads the way from early deprivation to a wide range of later difficulties.

These exciting results reveal that the cool threads of neglect and poverty are closely stitched into the fabric of child development. My study does, however, have a key limitation: I did not randomly subject my participants to experiences of deprivation. This, of course, would have been unethical. But with mere observation, we can only detect an association between deprivation and poorer mental health and cognition, not a causal relationship. I plan to overcome this obstacle in my second project by designing a computational model of brain development and testing the causal effects of early adversity.

But my initial findings already show us that we can help Taylor, and every child who grows up in situations like hers, by mitigating deprivation. This is an especially urgent task during the era of COVID-19, when an economic downturn has exacerbated financial difficulties and stay-at-home orders have restricted social interactions. If we want to achieve justice and healing for all children, we must work to end the silent pandemic of deprivation. From advocating for political change to simply lending a neighbour a hand, each one of us can choose to contribute to re-weaving the threads of deprivation into new designs of resilience and flourishing for every child.

Schizophrenia: the gene 'keeping it in the family'

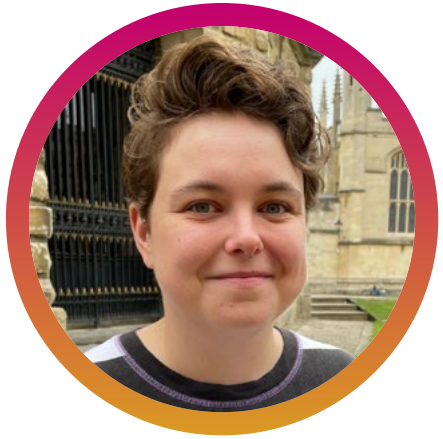
At the end of the day, you retreat into the safe sanctuary of home. Suddenly, you hear knocking at the door. You answer, but you can't see anyone outside. You grumble about neighbourhood youths, and go back indoors. Soon you hear it again, louder than before. The doorway is still empty when you yank open the door, the pranksters nowhere to be found.

You ignore the further knocking, but then you start to feel their eyes watching you through the curtains, and see threatening shadows moving outside. You've been seeing and hearing these tormenters for years, following you wherever you go. Your mum sees these monsters, and so did her dad. There is a chance your children will be haunted, too.

Schizophrenia is a psychiatric illness affecting one in 100 people in the UK. A schizophrenic person experiences a host of debilitating symptoms, including hallucinations, delusions, and paranoia. These symptoms can be disabling, and can exclude schizophrenic people from engaging with society. Only 10% of schizophrenic people are in employment, and it reduces life expectancy by 20 years.

The cause of schizophrenia is still a mystery. It's difficult to treat an illness that you don't understand, and many patients find the available medications give severe side effects, or that they barely help at all. To create better treatments, we need to understand how schizophrenia works.

To help us, there is one lead we can follow. It has been observed time and again that schizophrenia runs in families. This suggests that there is a genetic component to the illness, since we share genes with our family, and pass them to our children. Genes are codes in your DNA, which create all biological machinery within our body. Every gene has multiple variants, the same gene, but with slightly different coding. For example, different variants of the same gene code for either blue, or brown eyes. Some variants can be 'defective', and can contribute to a person developing certain diseases. Since schizophrenia runs in families, it is possible that they are all inheriting the same defective gene.



COMMENDED

PAIGE STREET

MRC Harwell,
University of Oxford

Recently in the United States, large numbers of these families were found. They live in Pennsylvania, and are part of the Amish people.

The Amish are a traditionalist sect of Christianity, with communities living in isolation. In closed societies, couples are more likely to have shared ancestry, since few outside people ever enter these circles. If there is a defective gene in the family, over time the number of offspring with this variant can increase. In the case of the Amish, this created large families with schizophrenia running down the generations.

Studying these Amish schizophrenics, researchers found defective variants of a particular gene in many of these people, zfhx3.

This gene has recently risen to prominence, and is being increasingly implicated in a range of disorders. It is part of a family of genes whose only function is controlling other genes. Like a puppet master, it pulls strings across your DNA, controlling the activity of a wide range of other genes.

My group has been researching this gene for years, we call it ZF. We study the defective genes behind psychiatric diseases, using mice. This is because mice and humans are 99% genetically alike, making mice perfect subjects for studying genes behind human disease.

The news about defective ZF variants found in the Amish gave us an idea. Perhaps ZF is controlling genes that are active in the brain, and if we find which genes, maybe we can discover more about schizophrenia. This is where my project began, and my first task was to see exactly where in the brain ZF is working.

I looked at mouse brains under the microscope, using a marker that illuminates areas of ZF activity. I saw that ZF was active in specific areas of the brain that are rich in dopamine, a signalling molecule that has important roles in learning and pleasure. This was big news, as it is widely thought that dopamine malfunction plays a role in schizophrenia.

I had found a link: ZF could be controlling the genes in these dopamine-rich regions, and its dysfunction could lead to schizophrenia.

To test this, we created a colony of altered mice. Using cutting edge techniques, we deleted the ZF gene out of their DNA. More precisely, we deleted the gene only in these dopamine-rich regions of the brain. This means we can look at the raw influence of ZF in these regions, and figure out exactly why it's needed there. Without ZF working in these dopamine-rich regions, would we make schizophrenic mice?

Truthfully, a mouse cannot have schizophrenia. Their brains are smaller and simpler, and mice do not have the cognitive power to experience the symptoms we see in humans. However, we can break down psychiatric illnesses into simpler behaviours, and test the mice on these. I do this by introducing them to environments that are designed to elicit a response, and measuring their reactions.

I have been studying these mice for two years, and their behaviour is truly puzzling. They are apathetic both to their own safety, and to new experiences. They sleep more often, but for less time. They over-react to sound, but under-react to light. They are highly aggressive with each other, with some mice having to live separately, however they are docile with humans.

I have also studied the brain structures of these mice, to try and gain insight into what could be causing these behaviours. Remember that ZF controls other genes. In these brains, I found significant defects in the signalling system of the dopamine-rich regions. This suggests that ZF controls the activity of the genes that compose this signalling system. With this system broken, brain cells are unable to communicate as they should, which may explain the erratic behaviour of these mice.

I am far from finished from studying ZF's role in schizophrenia. I will be continuing to study the behaviour and brain structures of these mice, until we have a more complete picture of everything ZF does in these dopamine-rich brain regions.

This powerful gene has yet to give up its secrets, and schizophrenia may be one of them. If we conclude that that ZF dysfunction is causing schizophrenic symptoms, this could make ZF a target for future drug development. A precision drug, which could repair the damage caused by ZF dysfunction. While this won't stop inheritance of schizophrenia, it could allow patients to be free of their symptoms, and hear no more phantoms knocking at the door.

Toward reward: how dopamine calls us to action

SHORTLISTED
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It's noon on a Sunday, and you're still in bed. You stare at the ceiling. You know you should get up, have a shower, get dressed; you're supposed to meet some friends today. But somehow, you can't bring yourself to move.

All animals need to be able to pursue their goals, whether that goal is food, water, shelter, or sex. But in mental disorders, this ability is often undermined. In depression, people can struggle to initiate behaviours that will get them to their goal, even something simple like getting out of bed or preparing food.

The mental health crisis has been growing in recent decades, yet the field of psychiatry has been dogged by failure. If you or someone you know has a mental disorder, you may share the frustration that not everyone is helped by prescribed therapies, and doctors cannot predict who will or won't be helped. The treatments currently on offer are not well understood. The most commonly prescribed antidepressants are based on the outdated hypothesis of serotonin deficiency, even though there is little to no evidence that people with depression have reduced serotonin signalling in their brains.

This lack of understanding means that mental disorders have been classified based on lists of behavioural symptoms rather than the biological mechanisms that cause them. This is like saying that a stroke and a migraine are the same disorder because they can produce similar symptoms. To tackle this, a new approach has arisen: instead of trying to understand individual disorders, we can try to understand the processes that might result in the altered behaviours we see in mental disorders. If we understand these biological mechanisms, we can design more effective treatments.

In my PhD, I study how brains allow us to pursue our goals. I started by looking for a part of the brain that might be necessary for goal pursuit. A promising candidate is a collection of neurons deep in the brain, which produce a neurochemical called dopamine. Recent decades of research have shown that dopamine neurons play a powerful role in motivation and learning; increasing the activity of these neurons can cause animals to

learn associations faster and choose particular actions. Studies have shown that a burst of activity in dopamine neurons represents a 'prediction error': the mismatch between the reward we think we'll get, and the reward we actually get. This burst of activity is used to reinforce choices that help us maximise our reward, that is, choices that will result in bigger and better rewards for the least cost. For example, if we try a new coffee shop that has tastier coffee at a cheaper price compared to our usual, we will learn to choose that new shop instead.

Could dopamine neurons guide the pursuit of our goals? To study how these neurons behave in real time while in pursuit of a goal, I devised an experiment where I trained mice to navigate a virtual reality environment and find a hidden reward, in this case, a drop of cherry-flavoured Kool-Aid. As they performed this task, I used a miniature microscope to observe the activity of their dopamine neurons.

I found that dopamine neurons had two types of activity patterns: bursting and ramping. I expected to see the bursting activity, as previous research has well-documented its role in representing 'prediction error'. I saw this bursting activity when the Kool-Aid was delivered, and once the mice had learned to find this reward, I also saw it when they knew the reward was coming soon. This happened when they passed a particular pattern on the wall that was always seen on the way to the reward. When you see a sign for your favourite coffee shop, your dopamine neurons will do the same thing, burst in activity, as you know that you can expect your reward soon.

However, what was far more interesting to me was the gradual increase ('ramping') in dopamine activity as the mouse approached the reward; I had never seen that before. I also saw that this ramp was steeper when the mice were well-practiced in finding the reward, as well as when they were paying more attention to the pursuit of the goal.

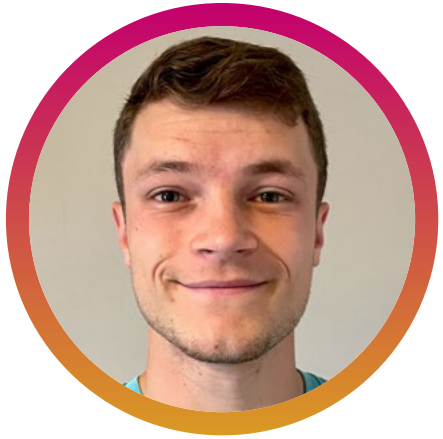
The burning question was: what is this ramp for? My analysis showed that ramping activity was followed by the mice becoming better at finding the reward the next time they tried. This suggests that this ramp might help us to improve our pursuit of our goals, allowing us to choose the best actions in the right places to help us get to that goal efficiently. If we go to our favourite coffee shop, we know where the shop is located, what obstacles are in the way, and where the door is. We can optimise our route and our actions to get that coffee as quickly as possible.

The bursting and ramping patterns of activity in dopamine neurons could reflect two different kinds of learning. Whether we're a mouse trying to find a sugary reward, or a person trying to get their daily coffee fix, there's two things we need to learn to get to our goal: when the goal is coming up, and what actions we need to perform to get us there. Dopamine neurons could cater to both these features: the bursting activity tells us that the goal is coming up, but the ramping activity keeps us doing the right actions along the way.

Perhaps you're still lying in bed. You get a text message with the address where your friends are meeting. Your dopamine neurons burst in their activity, but there's no ramping, no initiation of the sequence of actions that would take you to that address. Could a better understanding of dopamine neurons tell us why some people have difficulties pursuing their goals?

Our brains are the most advanced operating systems in the world, yet our understanding of them is in the Stone Age. Neuroscientists are trying to understand cause and effect: how do neurons act to produce behaviour? Emerging technologies provide researchers like me with the opportunities to delve deeper into these mechanisms, to tease out the different functions produced by the same machinery. While the journey is long and progress is incremental, every step brings us closer to understanding how brains work, and how neural circuitry might be altered in mental health disorders. Perhaps in ten or twenty years, we may be able to definitively tell a person the neurobiological reasons why they may struggle with some behaviours, and more importantly, have the targeted treatments available to help them.

In–DNA Jones: readers of the lost mark



SHORTLISTED
ROSS HANNAH
MRC Human Genetics Unit
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"I live in a big, green house". As a reader, how would you now describe my house? You can recognise two important adjectives in the sentence, but one has been marked by the author to tell you to ignore this information. It is not a foreign language, you can still recognise the word "green". But importantly, you understand that you are not meant to acknowledge this part of the sentence because it has been marked out. Authors have a tool chest of markings: ~~strikethroughs~~, underscores, punctuation! Which convey how a sentence is intended to be read. In fact, marks hold just as much power over the fate of a sentence as the letters themselves.

This concept has very powerful and exciting implications in the treatment of cancer, one of our greatest antagonists. Cancer cells frequently misread the cell's "handbook" due to messy markings. What if we could understand these marks better? What if cancer has been hiding secrets in how it mistakenly scribbles across these instructions? Shall I start at the beginning though?

In every cell in your body, you carry a manual entitled "How to Build You". Like any book, this Human Holy Grail is coded with strings of letters which make up your DNA. In the same way we recognise sets of letters collectively as words, strings of DNA can be recognised meaningfully as genes.

A gene may work individually or collaboratively, like words in a sentence, to instruct individual aspects of your body's cells. And like a snowflake, we all carry variations of our genes. Your genes may describe your hair as curly or not curly, or as one of many colours. With approximately 20,000 such genes in your DNA, your cells have all the necessary information to build a human.

So how do your cells read this manual? Cells are experts in understanding how to interpret DNA. They diligently decide which genes are required for the task at hand and which are marked as being immediately unimportant, such as a brain-specific gene in your heart cells. Importantly, cells understand that two people do not necessarily require different variations of a gene to infer different instructions. For example, if a cell were to read "curly, brown hair" and "curly, brown hair", a different physical outcome would occur even though the letters are the same. Marks and modifications to the letters themselves allow for identical DNA to

be interpreted differently. This makes up an entire subfield of genetics, called epigenetics.

One such mark is prominently found across your DNA with a significant function. A gene with this mark is still present, but functionally "inactive" and ignored by the cell. This marking is called DNA methylation (ugh, chemistry jargon! Don't worry. When I say "methylation", just think "~~strikethrough~~"). In a healthy cell, methylation marks are spaciously spread across your DNA with little effects on genes. However, intense DNA methylation in a single gene can render it "unreadable". This happens naturally for genes with no immediate role in the cell.

However, when cells become ill or diseased, we see that the highly regulated pattern of gene inactivation starts to become more erratic and harmful to the cell. Imagine the well-oiled machine of 20,000 genes working together, what would happen if the wrong genes became inactivated or activated at the wrong time? This causes chaos in the workplace.

So how might I use these markings to treat cancer? Cancer occurs when the fundamental rules that all cells are to abide by are broken. These instructions include an expiration date, a speed limit for making new cells and "stay at home" orders to not infiltrate other organs. Like a game of Jenga, cells can usually adapt when one of these hallmark rules is threatened, but a cell will become unstable if too many rules are broken.

In cancer cells, the pattern of DNA methylation is dramatically changed. Overall, methylation marks are lost across DNA, but interestingly, a few genes actually gain intense methylation instead. In other words, "my green house" in normal cells becomes "my ~~green~~ house" in cancer. This is concerning as some of these heavily marked genes have crucial roles in preventing tumour growth. Amongst the chaos, important genes become inactivated, and this is where I come in. If I knew how methylation marks were changed in cancer cells, could I leverage this understanding to better predict tumour severity and develop more efficient cancer therapies? It turns out I could.

My research aims to evaluate two important aspects of a patient's cancer: the gene variants present and the pattern of methylation in those genes. I intend to look for peculiar patterns. For example, what if almost all the patients sharing one, specific gene/methylation combination also showed particularly aggressive cancer? And in contrast, what if almost all the patients with alternative combinations showed relatively less aggressive cancer? In other words, what if the gene or methylation profile allowed me to predict the aggression of the patient's tumour cells? Game-changer!

Therefore, if a patient is diagnosed with a new tumour, I could potentially analyse their genetic and methylation information as a marker to predict rapidly and accurately how aggressive their cancer may be. And that is just the tip of the iceberg. Predictive "biomarkers" have the potential to reveal all sorts of crucial kinks in a tumour's armour before any surgical or chemotherapeutic treatment is required. Given how complex and variable tumour severity can be, this is an important arrow in the patient's quiver when battling cancer.

So how might this shape cancer treatment? Currently, a cocktail of chemotherapeutics is used to simultaneously target a range of common tumour profiles in the hope that one will be sufficiently effective, and any unwanted side effects will be minimised. In a revolutionary healthcare system defined by personalised medical techniques, biomarkers could be used to profile a patient's tumour like profiling a suspect from a crime scene. The better the profile, the more specific the treatment can be. This biomarker approach could dramatically improve our ability to treat specific cancer subtypes with the best overall benefit to the patient's health.

So, tell me, how can you tell the difference between a normal cell and a cancer cell using only DNA methylation data? Simple: a cancer cell would not know that my house is green. While the mismanagement of markings is one of many defining features enabling this devastating disease, there is at least one redeeming quality. We can commandeer this information to discover which cards cancer cells are holding before they can play their hand.

It's in the blood: the race to treat frontotemporal dementia

"The look he gave me, I can only describe it as a look like there was no one home"

This striking moment is the first memory Hannah has of her father's dementia. She recalls how he started to go missing, making obscure financial decisions or laughing when his grandchildren were upset. In 2017, at the age of 60, he was diagnosed with frontotemporal dementia (FTD).

Few people have heard of FTD. Unlike Alzheimer's disease, this form of dementia mainly affects your personality, behaviour and language. It is the second most common form of young-onset dementia, usually affecting people in their 50s but symptoms can start from any age. Patients often lose empathy for their loved ones, lose their ability to speak and lose their sense of self. Currently there is no cure.

For Hannah's family, the news got worse still. Around a third of people with FTD have a genetic component, meaning it can be passed down from generation to generation. Hannah had suspected this as she recalls similarities between the look in her father's eyes and that of her grandfather years before. Her grandfather had passed away, aged 57, with what was recorded as complications of Alzheimer's disease. At the time, little was known about FTD.

Hannah was told that she has a 50% chance of carrying the faulty gene and developing FTD. Over the next 10 months, whilst watching her father's condition deteriorate, she deliberated as to whether she wanted to find out if she is also a gene carrier. Eventually, she concluded that she could not live with the uncertainty and decided to get genetically tested. It was not good news. Hannah carries the same version of the gene as her father and will develop FTD. Each of her young daughters has a 50% chance of the same fate.

For Hannah, and many others in her position, the only solution is finding a treatment. In other words, finding something that will stop the disease from developing in the first place.

Yet hope is on the horizon. Clinical trials have started for this form of dementia.

Hannah carries the faulty version of a gene called progranulin. This gene is an instruction booklet for creating the progranulin protein, which in the world of brain cells, is a Jack of all trades. It fights viruses, heals wounds, recycles and repairs cell machinery

SHORTLISTED

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and grows the cell. However, in people like Hannah, the faulty gene means that only half the required amount of this protein is created.

This is where the clinical trials come in. They aim to increase the levels of the progranulin protein in the brain and stop the disease from developing in people like Hannah, who do not currently have symptoms, but carry the faulty gene. However, if these trials are in people without symptoms, how will we know if the treatment is working? For this, we need definitive measures to test the treatment's success. One way to do this is to look in body fluids, like blood and urine, or even better, the fluid your brain sits in: cerebrospinal fluid (CSF).

For my PhD, I am developing tests to measure different molecules in blood, urine and CSF and assessing whether there are differences in people who carry the faulty gene and those who do not. For this, it is important to first establish what we already know. We know that people with this gene have lower progranulin protein levels and we can actually measure this in their blood. We also know that this reduced level leads to the complex symptoms of FTD. However, we need to understand what happens in between.

One way to work this out is to think about what the progranulin protein does in the cell. In order to carry out its extensive responsibilities, we know it recruits other proteins, such as prosaposin. Together these two proteins move into cells and carry out key functions. In fact, according to research, progranulin cannot do many of its jobs without its trusted sidekick, prosaposin.

Therefore, in my PhD, I want to ask: are prosaposin levels different in people with the faulty gene? And can we measure this in their CSF?

The first step in developing this test is to find another type of protein, known as an antibody, that sticks specifically to the prosaposin protein. We could then use two of these specific antibodies to make a prosaposin sandwich (not as appetising as it sounds). By also attaching a label onto one of the antibodies (or "bread slices"), we can measure how much prosaposin is in the CSF (i.e. how many "sandwiches").

One of the biggest challenges when developing these tests, is that some proteins are not present in high enough levels in the blood or CSF. To overcome this, we use ultra-sensitive machinery to detect very low quantities. To give some scale to this, if you had 18 million Olympic swimming pools, our machines could detect the equivalent of a single golf ball.

So, at 8AM on a Tuesday morning I was in the lab starting my experiment. This was the fifth trial and I was hoping that the subtle changes I'd made to the method would yield positive findings. Over the next nine hours I would pipette, shake, wait, wash and repeat. I was hoping to show that we can detect the elusive prosaposin protein in CSF. By 5PM, I was anxiously waiting as the numbers start to show up on the screen. I looked in amazement as the results suggested the experiment had worked. I had developed a test in CSF for the prosaposin protein.

One week later, I ran the experiment again, this time testing our precious CSF samples from people who carry the faulty gene. With another anxious wait and some eager graph creation, I found that prosaposin was higher in these carriers. This exciting result could help explain why these people develop FTD, adding a crucial piece to the puzzle of our understanding of this form of dementia. It could also be a useful measure in clinical trials to help establish whether treatments are working.

However, this is only the first step in a long journey of discovery and there is much more to find. For Hannah and many other families like hers, life is a ticking time bomb, knowing that at some point this disease will take them from their loved ones. I am hopeful that we will beat FTD but it is vital that we find the right treatment to save lives before more generations are affected.

Collaboration is key: unlocking new clinical knowledge

SHORTLISTED

BINDU VEKARIA

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The University of Manchester

Mathematics, the very word is off-putting to so many people. I often hear people talk about maths and statistics like it is some enigma that they just can't crack and yet maths is all around us. Throughout the COVID-19 pandemic, we have seen many graphs in news conferences, and heard daily numbers, but how do maths and science actually feed into the government's response? With a range of people with different requirements, how do we know what to prioritise? Well, success can only be achieved by working together: the challenge is how to do this effectively.

My PhD focusses on interdisciplinary research, the idea of taking methods from one field and using them in others while working with people from different skill sets. I work in an area of mathematics that tries to answer questions such as: 'do patients offered a new treatment (like a vaccination) survive longer than those without?', 'how long do we expect someone to stay on an intensive care unit (ICU) in a hospital?', or 'how does a patient's demographics, like their age, gender and ethnicity, affect how long they will live for?'. All of these can be answered using a branch of maths and statistics called survival analysis. We use survival analysis when we are interested in analysing the time to some event of interest. This could be time to a heart attack, relapse of a cancer, or time to failure of an electrical component in a computer, to give just a few examples.

I take these survival analysis methods and try and apply them to areas of healthcare where they are not already used. The hope is that this will help clinical experts answer important questions in a new way and provide more information about our health.

For example, during the pandemic there has been a real concern that COVID-19 cases would overwhelm hospital capacity in the UK. In preparation for this, the Nightingale hospitals were established. However, whilst more beds were being made available for patients with COVID-19, less beds were available for patients with other healthcare conditions. Knowing how long patients will spend in different parts of the hospital is important when planning on how many beds will be available for other patients. Having an idea of this

time benefits both hospital and patient. For example, better bed planning can reduce cancellations of non-COVID related surgeries and procedures.

My research put me in a unique position to help out with this question. It was very challenging. I had to work with medical doctors and virologists at the Manchester University NHS Foundation Trust and learn their language and about the workings of a major hospital, to really focus in on what the relevant questions were. We concluded that not only is it important to look at overall length of stay in the hospital, but particularly in the ICU, where the demand was highest.

I also worked with data engineers, the heroes working thanklessly behind the scenes who take data entries from across different parts of the hospital and connect this data to tell the story of every patient's hospitalisation. Without them, there'd be no data for research, and improvements to hospitals and healthcare would be much more difficult to make.

Ultimately, I, together with a small of group of mathematicians, created a planning tool that takes local hospital admission rates as inputs and outputs the expected future bed occupancy at different time points. During the pandemic, this model was used by all hospital trusts in the North West of England. Each trust has used it to help manage bed planning, tailoring the tool to their needs, without needing to share any sensitive data. It's safe to say, if any cog in this wheel of experts was missing, we wouldn't have been successful.

So, what does this mean when we're not in the middle of a global pandemic?

The potential of such collaborations is endless. In another part of my PhD, I am currently looking at data on the number of suicides in the UK. Experts in the field have a theory that the year in which you're born may be connected to your risk of committing suicide. However, there is not enough statistical evidence to support this theory yet. I hope to shed some light on this theory and inform clinicians and psychology experts. They can then use this information to make recommendations to policymakers to help reduce the risk of suicides.

And really, that's what interdisciplinary research is all about. It's about working together to provide better outcomes for individuals and society as a whole. In the immortal words of Helen Keller: "Alone we can do so little; together we can do so much."

Casting the net to understand an invisible virus

SHORTLISTED
SARAH WITHERS

MRC Doctoral Training Partnership,
The University of Manchester

Monday morning, 8:15AM. I trundle up to the aquarium, open the doors and immediately get the unmistakeable feeling that I'm being watched. Sure enough, tanks upon tanks of distinctive black and white striped fish stare back at me: Zebrafish, or Danio Rerio if I am being pernickety.

Of the vast number of fish in this large room, there are only two I am interested in. I make my way over to them and give them a pep talk. Well, more like a plea deal.

'Please breed for me today and I promise I will never ask again... at least not until next week,' I say under my breath, perfectly aware of how strange I must look and sound, but these fish drive a hard bargain.

The couple in question are a male and female fish, separated in their tank by a small divider.

'On your marks, get set, go,' I say in my head this time, whilst I remove the divider between them.

Fortunately for me, within minutes of being reunited, the male begins to chase the female in a playful fashion, and the female (clearly enjoying the attention) starts releasing her eggs, which fall to the bottom of the tank ready for fertilisation. I breathe a quiet sigh of relief. This is going to be a good week for my experiments.

Anyone picturing this scene may be forgiven for thinking I'm a marine biologist, but I'm not.

I am a neuroscientist, researching a rare genetic human disease called Aicardi-Goutières syndrome (AGS).

Never heard of AGS? Let's begin with something a little bit more familiar. When a virus called COVID-19 started ravaging the world in 2020, face masks became the new fashion accessory, and alcohol gel the new currency, in an attempt to try and stop the virus from spreading. Now, imagine if these measures were not effective and instead the body is tricked into thinking it is infected with a virus which isn't there. From the outside it would be difficult to tell the difference due to the body producing an almost identical response as it would if actually infected with a virus.

These circumstances are a very real issue for sufferers of AGS, a disease that affects around 500 families worldwide, and is most commonly identified from birth. The cause lies within the human body's own self-defence mechanism, which is usually efficient at getting rid of viruses and other nasty threats before they can cause any harm. However, one of the main reasons why viruses are still present is because they use our own body against us. They are the freeloaders of the microscopic world, using up all the natural resources within every cell, and taking exactly what they need to thrive and multiply within the body. This is where part of our body's defence mechanism comes in by making proteins that have the job of removing all of the excess resources we have in our cells so they can't be used up by these viruses. It is these extremely important proteins that stop working in AGS, with dire consequences. The build-up of these natural resources makes the body feel like it is under a viral attack, despite none being present. So, it fights back. Hard.

Small chemicals within the body called type I interferons are the first line of defence against viruses. They pack quite the punch, quickly immobilising the virus, and stopping it from wreaking havoc. This is extremely effective in cells that are plagued by lots of viruses, but in normal healthy cells, these little interferons are deadly, causing a whole host of terrible things to happen to the cells they come into contact with. Unfortunately, in AGS, the bulk of this attack occurs in the central nervous system, where the brain and spinal cord are found. The outcome is a lot of symptoms affecting these areas, such as brain dysfunction and damage, and also movement problems, presenting as muscle stiffness and weakness.

You may have already guessed my main tool for studying this devastating disease: zebrafish larvae. Yes, I am a fully-fledged member of the zebrafish fan club, and a big advocate for their use in scientific research as a way to reduce the use of larger mammalian animals, such as mice and rats, where possible.

Zebrafish are extremely versatile, and can do a lot more than swim around a tropical fish tank. They share over 70% of their genes with humans. Quite a high number for an animal that still lives in water and has gills and fins. I collect the eggs after adult fish breeding and change their genetic make-up so they develop AGS, thus generating a zebrafish model of the disease.

Despite my adoration for these fascinating creatures, it appears that the feeling is not reciprocated. As a third-year PhD student, a much larger proportion of my time than I would like to admit has been spent learning the hard way that there are many difficulties associated with animal models. At times, they seem to do everything in their power to disprove all of my theories and ideas.

With this model I have been looking to understand more comprehensively what causes the disease in humans and how that results in the specific symptoms. These symptoms in the AGS zebrafish have been identified using a variety of techniques. For example, the zebrafish have been stained with a particular chemical to count the number of dead cells in the brain, which translates to brain damage. I have also used software designed to track the movement of the zebrafish over a fixed time period, to determine any movement problems. Fortunately, the techniques were successful at highlighting similarities between the AGS fish and the patients, with the brain damage and movement problems, to name a few.

I now aim to try and cure the fish of their symptoms, using drugs which may be successful in human patients. This is extremely important, as, due to AGS being such a rare disease, there are not many human patients to perform clinical trials on. Therefore, by trying the drug on the fish first to see how useful it is at relieving the symptoms, it increases the confidence that the same drug will have beneficial effects on the patients.

So, the next time you are in a pet shop or an aquarium and spot 'Danio rerio' on the placard, just pause to contemplate how a tiny fish is making such a big splash in helping to fight the invisible virus that is AGS.

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DR ROGER HIGHFIELD
MRC Council Member
and Science Director of the
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Journalist, Author
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