#344: Brain ever changing: Neuroplasticity and its role in mental health

VOICEOVER:

This is Up Close, the research talk show from the University of Melbourne, Australia.

ANDI HORVATH:

I'm Dr Andi Horvath. Thanks for joining us. Today we bring you up close to emerging research into the therapeutic implications of brain neuroplasticity, the capacity for the brain to rewire itself in response to experience. Neurological and psychiatric conditions like schizophrenia, autism, anxiety and depression all exhibit a spectrum of severity but the burden is not just on the individuals but on their carers and larger communities. The need for an arsenal of effective therapeutic approaches to allow for healthier brain function is the challenge. One approach is getting increasing attention by researchers and that is the leveraging of the brain's own ability to change in response to our environments. Key to research into the complexities of brains and behaviours is the use of the experimental mouse model. What can we learn from mice that applies to humans when it comes to mental and psychiatric disorders and how could the mouse model provide insights into new therapeutic directions? Behavioural neuroscientist Professor Anthony Hannan is our guest today on Up Close. He heads the Neural Plasticity lab at the Florey Institute of Neuroscience and Mental Health. He and his team study the impact of genes and environment on our brains with a view to examining the capacity for the brain to rewire itself to get around neurological dysfunctions. Welcome to Up Close, Tony.

ANTHONY HANNAN:

Hello, Andi. Nice to be here.

ANDI HORVATH:
Before we get into neuroplasticity can you give us some background into the variety of neurological and psychiatric disorders? How pervasive are these in human populations? Maybe given us some examples.

ANTHONY HANNAN:

Brain and mind disorders including all of these neurological and psychiatric disorders are the greatest burden. When you add up the burden of disease, not just mortality or death but you add up the total burden across the lifespan and the way in which this impacts on people's lives then all of these brain and mind disorders together are a greater burden than, for example, heart disease or cancer or diabetes which are great problems in themselves but these brain and mind disorders are an even greater burden and they seem to be growing. The example is Alzheimer's disease and dementia. As our population ages and people survive heart disease and hopefully increasingly survive cancer then some of these diseases of ageing like Parkinson's disease, Alzheimer's disease, other forms of dementia are going to increase. They are increasing and this is going to be one of the great burdens of the 21st century.

ANDI HORVATH:

Not all of these diseases have adequate therapy, do they?

ANTHONY HANNAN:

Almost none of them have adequate therapy in the sense of prevention or full treatment or cure at all and that's really what we're trying to work on.

ANDI HORVATH:

Tony, can you comment on the pathology of spectrum disorders? How do genetics and the environment interplay with these? There must be a huge amount of individual variability. These things are complex.

ANTHONY HANNAN:

They're incredibly complex and I like to use the analogy that we're all dealt a genetic deck of cards at conception that we can do nothing about and some of us because of
our genomes start to move down a path towards brain dysfunction. The other side of the coin is the environment which impinges from conception onwards and we're doing some work with colleagues that shows even the environment of your parents and grandparents may impinge on brain development and brain function and brain disease which is a whole other area. What we're talking about with these brain and mind disorders is a very complex mix of genes and environment and obviously you can change your environment so that is a modifiable factor in the way that the genome is not a modifiable factor. Everything's a combination of genes and environment and we can look at identical twins for example and for a given disorder we look at that brain disorder and say if one identical twin has it and their genetically identical twin pair does or doesn't have it, as a percentage that gives us an estimate of how genetic a particular disorder is.

ANDI HORVATH:

I can blame my parents for some things but it looks like I can blame my grandparents for other things. How does that manifest across the generations? Because it's not cultural it's got to be structural, doesn't it?

ANTHONY HANNAN:

The implication of this is that it is what we call epigenetic. If you think of the genome this is three billion base pairs of DNA that's within every cell of your body. Admittedly a few cells like red blood cells don't have DNA in them but every other cell in your body has this DNA, three billion base pairs that is your genome so that's a starting point. One of the revolutions at the moment is genomics, the ability to understand for every individual what these three billion base pairs are and soon that will come down in price where it could be done for a few hundred dollars per individual and you'll be able to carry that around perhaps on a credit card device that could be taken to a general practitioner, another clinician, a health professional. At the moment we don't really know what to do with that very complex information but that's the revolution of genomics which will lead to personalised medicine and also precision medicine where we target therapies according to an individual's genome. The second revolution is that of epigenetics. Epigenetics really refer to above the genome. Those three billion base pairs rather than just being fixed as a computer code they can be modified. Think of these three billion base pairs as a very large encyclopaedia of the human genome and think of words and phrases and particular words being like genes, some of these words can be highlighted in italics or bold or underlined or with a highlighter pen. Those modifications dictate how strongly or weakly an individual gene being the analogy of a word is expressed and therefore these chemical modifications that make up epigenetics decide how each cell in the human body during development and adulthood expresses certain genes and then even across generations how environmental factors may alter phenotypes.
ANDI HORVATH:

My grandparents’ environment can actually change what genes and how they’re expressed in my body?

ANTHONY HANNAN:

This is a very, very new area of research and what I’m talking about is very new data from mice and in some cases from laboratory rats as well. We’re at the point in which we’re trying to work out whether these discoveries made in mice and rats can translate to humans but so many things that have been discovered in laboratory mice and laboratory rats have translated to humans that the likelihood is that this does translate. There are human examples, the Dutch famine where in the Netherlands due to war this whole population was exposed to famine in a particular period and down the track, as much as over 60 years down the track, they’ve been able to show effects on the next generation and are looking at grandchildren as well showing these effects of famine and starvation having metabolic effects on the offspring that are part of what we call transgenerational inheritance but epigenetics, not just inheriting the DNA, half the genome from each parent but you may be inheriting some of these epigenetic modifications. Very new area, we need to do a lot more research but it has enormous public health implications.

ANDI HORVATH:

Tony, I’ve heard you say the three revolutions in science are genomics, epigenetics and neuroplasticity and that these have paved the way for understanding and treating brain disorders. You’ve given us a good rundown on genomics and epigenetics. Let’s get into neuroplasticity.

ANTHONY HANNAN:

Yes so it is a revolution of neuroplasticity and the thing about the nervous system including the brain of course is that it's uniquely plastic, it can change in response to experience and this makes it quite unique from other organs in the body. The idea that some of these forms of neuroplasticity in the adult brain are actually a form of micro-development so the idea that the brain being the only organ in the body that never really stops developing and the idea even with things like learning and memory, if you remember something say of this broadcast then the idea being that in order to have a long term memory of that you've actually changed connections between a subset of neurons in your brain and we're talking about 100 billion
neurons connected by trillions of synapses, these connections between neurons so
incredible complexity. One form of neuroplasticity is involved in learning and
memory, a fundamental form of human cognition but then there are lots of other
forms of neuroplasticity and we're interested in how they act in health and disease.
We're particularly interested in how environmental factors like cognitive stimulation,
physical activity and stress can induce neural plasticity in the healthy brain but also
in the brain of people with particular neurological and psychiatric disorders.

ANDI HORVATH:
I'm Andi Horvath and you're listening to Up Close. In this episode we're talking about
neuroplasticity and how it can offer clues about mental disorders, with behavioural
neuroscientist Tony Hannan. Tony, I want to move to your work in the lab where you
use animal models to get insights into managing neurological diseases. Now how
can something like a mouse be used for a model for human behaviour?

ANTHONY HANNAN:
Well this is where the revolution of genomics comes into it because now and in fact
for quite a while we've been able to directly compare genomes of many, many
animals including mammals like the laboratory mouse and humans so at every level
now we can say how similar they are. If we want to model humans and human
disorders we ideally want to start with another mammal in terms of evolution.
However, we also need to be able to have an experimental subject, laboratory
species, where we can actually do experiments that have enough control over genes
and environment that we can actually do those studies, find for example a
mechanism of disease, identify a new treatment, trial that in that animal model and
then take that into a clinical trial. That's really what our medical research is about.
The beauty of this technology now, we can say the genome level, that the mouse
genome is very similar to the human genome, well over 90 per cent similarity, we can
say where it's similar and we can even start to map how humans evolved. In terms
of evolution it's not an evolutionary tree. If you can imagine a spherical bush floating
in space evolution's really a spherical bush. The first living things on this planet sit in
the middle of that spherical bush and evolution has expanded outwards and humans
are sitting on one part of the bush and mice, laboratory mice are sitting nearby on
this sphere but we're not above them, we're just in a different part of the spherical
evolutionary bush. We can say how similar they are and it's quite strikingly similar in
terms the genome and what we also call the transcriptome. Genes are expressed as
nucleic acids, another form of nucleic acid, DNA gets transcribed into RNA, another
form of nucleic acid and then that RNA directs the formation of proteins, these
building blocks of cells and organisms. We can compare those transcriptomes and
proteomes as well to see how similar they are. Then at the next level we can
compare these neurons, these cells in the mouse brain with the human brain and
fortunately when you look at neuroanatomy, when you look at the structure of the
mouse brain all of the main structures that we can map onto the human brain are there in the mouse. Obviously our cerebral cortex has got much bigger, our brains have got much bigger but bigger is not necessarily related in a linear way to brain power. Elephants have very, very large brains, blue whales have very large brains but that doesn't make them smarter than humans so it's not just about the size of the brain, it's about the structure and function of the brain. Therefore in a laboratory species like a mouse we can actually be confident that we're close enough that when we test a new treatment in a valid mouse model of a disease we can then take that into a clinical trial.

ANDI HORVATH:

Tony, one of the diseases you were looking at is Huntington's disease and its equivalent in mice. Firstly, tell us about Huntington's disease and what do you observe in these mice?

ANTHONY HANNAN:

Huntington's disease is an extraordinary disorder. It's caused by a genetic stutter. The genetic stutter is a sequence of three bases of DNA; these are the letters of DNA, repeated. The only thing between an individual who will die quite horribly of Huntington's disease and someone who doesn't have Huntington's disease is just a handful of extra repeats of DNA that may only be say a dozen or two dozen repeats.

ANDI HORVATH:

So it's really genetic. What are the symptoms of Huntington's disease?

ANTHONY HANNAN:

Huntington's is extraordinary also in the fact that it's a triad of symptoms. It's a combination really of neurological and psychiatric disorder where you get cognitive problems which culminate in dementia in Huntington's disease, you can also get psychiatric problems like depression but the classic symptoms that people recognise are a movement disorder including chorea, these writhing dance-like movements that were first described by George Huntington in 1872.
What do you observe in the mice? Do the mice have these particular movement problems and how do you test a mouse’s psychiatric condition?

ANTHONY HANNAN:

These are good questions. Getting back to my earlier point we're really trying to improve what we call the validity of our animal models with the aim being that they will help us better understand these diseases and then better translate tests of new therapies in the animal model to clinical trials to help people and families with these diseases. The beauty of having a model based on a single gene disorder like Huntington's - this is a so-called Mendelian disorder - if one of your parents has it and they have the faulty Huntington's disease gene that has the genetic stutter expanded then 50 per cent of the children on average are likely to get that gene mutation, the other 50 won't and they won't get Huntington's disease. Just like a Huntington's family we start with a Huntington's mouse in which the human gene mutation has been inserted into the mouse genome and this has been a very powerful way in which you can actually create new disease models. In fact another evolution in recent years associated with genomics, it's really part of the genomic revolution but what is called gene editing, there's been a new discovery in the past few years. It's called CRISPR (clustered regularly interspaced short palindromic repeats). It stands for a technique that's actually based on taking the immune system bacteria. They've taken this as a new tool and what it really allows you to do is create any gene mutation, for example modelling a human disease, and insert that into the genome not just of a mouse but in other laboratory species like a rat. People are talking about using this technology eventually for gene therapy to try and correct disorders that involve specific gene mutations. You start with a mouse that has that gene mutation and then you can have 50 per cent of the offspring have the Huntington's mutation and then you have the control mice that are like siblings in a Huntington's family and they don't have the Huntington's mutation but they're matched for the rest of their genome, the rest of their genetics and then in an animal model you can control all the environmental factors which obviously you can't in a human population.

ANDI HORVATH:

Tony, using the mouse model what sort of environments were these mice subjected to?

ANTHONY HANNAN:

The first key study we published in 2000 was an experiment based on the idea I had
which was to actually modify the environment of the mice to see how that changed the disease. Now at the time Huntington's was considered the epitome of genetic determinism. It was written up in text books as 100 per cent genetic so it was going against the dogma but we wanted to see whether this actually had an effect on Huntington’s disease. What we found with a graduate student at the time in Oxford, Anton van Dellen, was that those mice given a more stimulating environment, it’s what we call environmental enrichment, it enhances levels of cognitive stimulation and physical activity compared to standard housing conditions which were a lot more boring. The environmentally rich mice showed a dramatic delay in onset of Huntington’s disease. That was our starting point. One of the revelations of this was that if a supposedly 100 per cent genetic disorder like Huntington's could be modified by these environmental factors then essentially every brain disorder is modifiable by these kinds of environmental factors which gets back to the concept of neuroplasticity.

ANDI HORVATH:

This made a real impact in the scientific world because it was the first time the influence of the environment was shown to have such an impact on these animals. What happened next?

ANTHONY HANNAN:

Next as in most scientific projects it was a question of how this might be happening. In the Huntington's model we've followed it up where we've been able to show that we can model the cognitive deficits culminating in dementia in Huntington's disease. We made another discovery that we can model depression-like signs that are a major problem in Huntington's disease as well and we're able to show that environmental enrichment could delay both the dementia and depression-like symptoms in this mouse model. Then we've been looking right down at the level of cells and molecules focusing on particular brain regions but also looking in other parts of the body to work out how cognitive stimulation and physical activity might be beneficial in this mouse model.

ANDI HORVATH:

Give us a picture of your laboratory. What do you make these mice do? Do they do mazes or what sort of tests do you run on these mice that show that they're depressed or show that there's some dementia or learning problems?

ANTHONY HANNAN:
There's a whole range of tests and just like a neurologist or a psychiatrist might have a large battery of tests in order to establish a) that a subject has the disorder but b) at what stage they are in the disorder then we do that for mice. If you like we're neurologists or psychiatrists for these mice and we have a range of different tests. We have cognitive tests that are essentially mazes. An exciting area we've moved into in recent areas is where we give mice essentially - in a little chamber we give them iPads or tablet devices and they learn to poke their nose up against particular objects on the tablet screen in this chamber and if they get the answer right they go to the back of the chamber and they get a little bit of strawberry milkshake, which they love. They'll work quite hard to get more strawberry milkshake. Essentially the importance of this again is about translation. These tests that are done are directly analogous to human neuropsychological testing, batteries of human cognitive tests.

ANDI HORVATH:

If I'm a depressed mouse do I not like strawberry milkshake or what happens there?

ANTHONY HANNAN:

In a mouse model of depression and as I mentioned before we were the first to discover that we could model depression in an animal model of Huntington's disease and essentially up to 50 per cent of people with Huntington's get depression and some might argue it's because you know you're from this family but the mice don't know they have the Huntington's mutation and across a range of different tests they show these behaviours. Importantly when you give them a clinically effective anti-depressant drug, for example something like Prozac or a similar drug, then it corrects these behaviours so we know they're clinically relevant behaviours. Now one of these behaviours is a test of what we call Anhedonia. A core feature of human depression is Anhedonia, a loss of pleasure seeking. Hedonic responses are pleasure seeking responses in humans and we can model those in mice. In mice we can give them a choice between a tube of normal water or sweet water containing sucrose or saccharine. A control healthy mouse will choose to drink over 90 per cent of its fluid from the sweet water. However, in this model when we get other measures of depression, what we call depression-like behaviours, at that stage the mice drink less and less of the sweet water moving towards 50 per cent where they cease to appear to get this hedonic pleasure seeking response. Again we can correct that by administration of a clinically effective anti-depressant drug.

ANDI HORVATH:

I'm Andi Horvath and our guest today is behavioural neuroscientist Professor Tony
Hannan. We're talking about insights into neuroplasticity and its relation to neurological disorders like Huntington's disease right here on Up Close. Tony, are there differences between male and female mice in the lab, because we see some differences in society between males and females, humans when it comes to depression or certain disorders?

ANTHONY HANNAN:

This is an excellent point and our approach with these mouse models has always been on first principal what can we do to most closely model these human brain disorders? On first principal for a disorder like Huntington's and essentially all of the brain disorders that we study we know that they occur in men and women and therefore we've studied this in males and females. Admittedly some scientists have chosen for various reasons to focus more on male mice or male rats, including for the argument that oestrous cycles, these sex hormone cycles occur in the female animals and they may confound or confuse some of these experiments. That's a whole issue that the medical research community is now grappling with and increasingly we're seeing that the community is saying no, if the disease occurs in men and women then you need to be modelling it in male and female animals. An example of the importance of this, that's how we made this discovery of the depression-like behaviours. Essentially with these behaviours we see them more strongly at a certain age, because this is a progressive disorder, in the female Huntington's mice than the male Huntington's mice.

ANDI HORVATH:

Is that because they're wired differently?

ANTHONY HANNAN:

Potentially. We don't entirely know why but it fits with clinical depression in the human population where the ratio of women to men is two to one so the, if you like, sexual dimorphism is what we call it in this mouse model of depression fits with clinical depression. Now in terms of the wiring there are a number of potential reasons. The simplest is potentially sex hormones and that's something we've been looking into, in that men and women have different sex hormones, but also at the genetic level, that women have two X chromosomes, men have an X and a Y and just that difference can mean during development that male and female brains can wire a little differently. Obviously on average human men and women are far more similar than they are different but the biology and the neuroscience says that some of these differences between men and women are genetically ingrained, they are innate, they are partly nature and some of the differences that develop in men and
women there is an element of nurture as well.

ANDI HORVATH:

Tell us about the phrase neurons that fire together wire together. What does this mean to a neurobiologist?

ANTHONY HANNAN:

This key phrase is the essence of neuroplasticity really. The idea as I was saying before that the brain never really stops developing and therefore some of what happens in the adult brain I think of as a form of micro-development. Therefore, think of learning and memory, the idea we think when you learn something new and are able to remember it later on the way in which you've encoded what is often very complex information in your brain, this kilogram-and-a-half of grey and white tissue inside your skull, the way in which you can encode this is by neurons that fire together wire together. That is, amongst the hundred billion neurons in your brain there's a subset and they're activity during that experience has led to a strengthening or weakening of different connections or synapses between subsets of neurons. That is the way in which this engram or this information is stored in the brain. A great example is I give in lectures to undergraduates is my grandmother who lived to 101 and sadly my grandmother up until about 95 she was really as sharp as a tack, a wonderful woman and then she had some mini strokes, what they call transient ischaemic events and it caused a form of dementia in her final years, which by the time you get over 90 a very, very large percentage of people will have dementia sadly. At that stage she couldn't always remember what she'd had for breakfast and yet at times she was recalling events that had happened when she was five or six years of age. This is quite extraordinary that essentially she'd carried around his very complex information, these memories in her brains for over 95 years in a kilogram-and-a-half of soft tissue within her skull. I tell these students who are often sitting in the audience with their smartphones and their tablets and their laptops that those devices in front of them, they'll be lucky to get anything sensible out of them in five years' time let alone 95 years let alone the complexity of recalled memories which can have sensory components like smells and sights and sounds and the sense of touch. That level of complexity and storage in the human brain is just extraordinary.

ANDI HORVATH:

Your work in this area of environmental enrichment regardless of the genetic odds has really meant that neuroplasticity is the key to wellbeing. Does this mean I have to really watch my diet and exercise? Does this mean if I don't use it I'll lose it?
ANTHONY HANNAN:

Well sadly the public health researchers are telling us that physical activity and diet are two really key features. There are other aspects like cognitive stimulation particularly for brain disorders like Alzheimer's dementia, staying mentally active seems to be particularly important. Then the other major environmental factor, stress, being able to manage chronic stress and deal with stress and not be overwhelmed by stress is another factor, together with sleep which relates a little bit to stress as well. Getting back to physical activity and diet some public health people are now saying that sitting is the new smoking. The people who choose to or because of their occupations have to remain seated for 12 hours or more a day, that this is not ideal in terms of health and that we need to deal with that. Sitting's just one particular activity. The broad idea is physical activity. The way I like to think about all of these things is in the lens of evolution. I think there's two great lenses to look at the brain, the lens of development, how the brain develops and functions and the other major lens is how evolution has sculpted the brain, including the human brain. Effectively we all have genomes that evolve over thousands of years so effectively we have genomes that are very similar to our caveman hunter-gatherer ancestors and they haven't changed much. If some of these disorders are changing that tells you that it's what I call the "environome", environome being the whole range of environmental factors that impinge on you from conception to old age. In fact the suggestion is that it could be your parents and grandparents as we've discussed as well. We can change our environments and humans are adapted, our genomes and our brains and our bodies are adapted to caveman hunter-gatherer ancestral lifestyles which had a lot of physical activity, which had an enforced healthy diet with limited food sources so you had to go and hunt your food, gather your food, fruits and vegetables. We are evolved to be very physically active and to eat natural healthy foods. Therefore, all of these factors, inactivity, being sedentary, having a poor diet is not only bad for brain disorders - we know a range of brain disorders it impacts on - it's bad for other disorders like cardiovascular heart disease, cancer, diabetes. Conversely things that are good for your body are good for your brain.

ANDI HORVATH:

Not that I'm trying to get out of exercise but is there a drug I could take that could perhaps mimic the effects of physical exercise and cognitive stimulation?

ANTHONY HANNAN:

One of the ideas that have come out of our research is the concept of enviromimetics. I would suggest that these are therapeutics, not necessarily drugs
but they could be drugs, which mimic or enhance the beneficial effects of cognitive stimulation and physical activity.

ANDI HORVATH:

You've made up that word, haven't you?

ANTHONY HANNAN:

Yes.

ANDI HORVATH:

Enviromimetics.

ANTHONY HANNAN:

Yes.

ANDI HORVATH:

Okay.

ANTHONY HANNAN:

What I'm suggesting is, using these mouse models if we can work out right down to the level of molecules and cells how cognitive stimulation and physical activity benefits the brain and the body then any new therapeutic like an enviromimetic would be on the background of staying physically active, having a healthy diet, et cetera, and the idea that someone who actually is physically active and has a healthy diet might actually get more benefit from a particular drug or other therapeutic. This is not either/or so no one is suggesting that you lie on the couch and take pills.

ANDI HORVATH:

Tony, finally, taking the knowledge from the laboratory to publication to the realm of
actual public healthcare, it's extremely important. What do you see in the future happening?

ANTHONY HANNAN:

Well I take the model from the Florey Institute where I'm based and one of the attractions for me, I was actually brought up in New South Wales, trained in Sydney and then Oxford and I've come to Melbourne because of this unique neuroscience and medical research environment where you have neuroscientists like myself who are interacting on a weekly basis with active neurologists, psychiatrists, clinical researchers and trying to actually do translation. There's a lot of talk about clinical translation but the question is how you actually do it. From our perspective the starting point is to have these valid high quality animal models that we keep working on and we keep improving because obviously there are brain disorders like schizophrenia, autism spectrum disorders and various other disorders that are genetically very complex and environmentally very complex and we still have a long way to go to develop better models for those disorders. We're working on that but once you develop the model, the idea being that you systematically and rigorously test it in these valid animal models and then you interact and pass this on to the clinicians and the clinician researchers who actually take this information and take it into clinical trials. They have to prioritise because often there's potentially a large number of therapies they could test in patients and they have to use this basic science to say which ones do we try first, how do we test them and how do we go back and forth? It's not unidirectional. They then feed information back to us so the human genetics is being fed back to the people to make for example new mouse models and the brain imaging in humans is being fed back into these animal models and then we feed forward potential new therapies. It's a loop. It's a bidirectional loop. It's not a unidirectional process.

ANDI HORVATH:

Tony, thanks for being our guest on Up Close and thanks for stimulating our brains.

ANTHONY HANNAN:

Thank you, Andi. It's been a pleasure.

ANDI HORVATH:

We've been speaking about neurobiology, neuroplasticity and their relation to human mental health management with behavioural neuroscientist Professor Anthony
Hannan. He's head of the Neural Plasticity lab at the Florey Institute of Neuroscience and Mental Health. You'll find a full transcript and more info on this and all of our episodes on the Up Close website. Up Close is a production of the University of Melbourne, Australia. This episode was recorded on 4 June 2015. Producer was Eric van Bemmel, audio engineering by Gavin Nebauer. Up Close was created by Eric van Bemmel and Kelvin Param. I'm Dr Andi Horvath. Cheers.

VOICEOVER

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