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## **#380: Recovery from stroke: Harnessing the brain's capacity to overcome disability**

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 the latest research into maximising people's recovery from stroke, harnessing the capacity of the brain and body to overcome or bypass the disabilities caused by this major health calamity. A stroke is when the blood supply, and therefore the essential oxygen supply to brain cells, are suddenly cut off, compromising or damaging that particular area of the brain. The results can be debilitating, both physically and mentally, and accounts for one in 20 deaths in developed countries. Just how impaired people's motor activity or speech are, after a stroke, depends on the stroke's type and severity.

But on the recovery side, there's a growing body of evidence that proper, exercise-based intervention, delivered at the right time, goes a long way to getting stroke survivors back into near normal lives. Our guest on Up Close today has been working with stroke survivors for three decades. Professor Julie Bernhardt, who originally trained as a physiotherapist, now heads a global and multidisciplinary team of researchers looking into maximising recovery from stroke, and reducing the burden of stroke-related disability. She's based at the Florey Institute of Neuroscience and Mental Health in Melbourne. Welcome to Up Close, Julie.

JULIE BERNHARDT

Thanks very much.

ANDI HORVATH

Julie, what's actually happening when someone has a stroke?

JULIE BERNHARDT

I think you described it really well before, Andi, and that is that it's a very sudden onset condition, typically, in 80 per cent of cases, caused by a clot that gets lodged into the tiny vessels in your brain. That's enough to disrupt the blood flow, and it creates a cascade of damage in the brain that results, ultimately, in areas of the brain dying.

ANDI HORVATH

There are different types of stroke, right?

JULIE BERNHARDT

Absolutely. The other 20 per cent of cases are due to a bleed, where the vessel itself in the brain becomes thin or damaged, and then allows blood to seep out into the brain, and that can be quite a rapid event. It also disrupts blood flow, disrupts oxygen and nutrients to the cells, and creates damage.

ANDI HORVATH

Tell me about mini-strokes, what are they?

JULIE BERNHARDT

This is a really great question. So mini-strokes are often called transient ischaemic attack, TIA. So the definition of a TIA is that you get transient neurological symptoms. But they are gone by 24 hours after stroke. They used to be considered something that you were just really lucky if you had one, and they would go away. But now we know that they're often something that we have to be very conscious of following up properly, because they can, in many cases, lead on to a more severe stroke.

ANDI HORVATH

So it was like a temporary block, but it's a warning sign that this could happen again.

JULIE BERNHARDT

Absolutely, and typically it's caused by the clot type of mechanism.

ANDI HORVATH

So what are the consequences of stroke? What are the variety of symptoms that we see in stroke patients?

JULIE BERNHARDT

How long is a piece of string? The brain is so incredibly complex, and obviously with stroke, they are occurring in certain parts of the brain where the blood vessels are. However, that means they could be anywhere. So they could be in your speech and language centre, they could be at the front part of your brain and affecting your ability to plan and think. They could be in the back part of your brain and affecting your vision. They could be in the motor and sensory cortex, and affecting your ability to generate movement. So it is a myriad of problems that people face, and some people have said to me that it's the kinds of stroke that are less visible, where someone might have, for example, pain or sensory disturbance down a whole side of their body. But other people can't notice it. They have just as much trouble in coping as people who have quite profound effects with physical disability, because you just don't have recognition that this is still a really significant problem.

ANDI HORVATH

Is it also in the realm of emotion and behaviour and memory and thinking that gets impaired?

JULIE BERNHARDT

Absolutely. Again, some of those can be very subtle. It is challenging, I think, for people in the recovery phase where they get to a point where they look okay. But they are still really struggling with memory problems, with mood problems, and even with, perhaps, the ability to detect what someone - even a loved one around them - is thinking. They lose that ability to read faces. This can be really problematic, especially if you're trying to go back to work. It leads to quite subtle, but devastating, challenges.

ANDI HORVATH

So Julie, tell me about the incidence of stroke internationally. What are the figures?

JULIE BERNHARDT

So the World Stroke Organization quotes one in six of us having a stroke. Every two seconds, someone in the world will suffer a stroke. Every six seconds, someone dies of a stroke. Every six seconds, someone's quality of life will forever be changed, and they'll have permanent physical disability, or some other kind of disability. I think importantly, as well, there are a lot of people who have a stroke who would rate their quality of life as being worse than death. So there are lots of concerns about stroke as a burden of disease.

ANDI HORVATH

Do we know anything about developing nations and stroke?

JULIE BERNHARDT

Yes, what we know is that chronic diseases like stroke are overtaking communicable diseases as a burden in developing countries, low and middle-income countries, and of course in those countries they have fewer established facilities and resources to be able to manage stroke. So it is a huge burden.

ANDI HORVATH

Now it's not just old people that get strokes. There's a whole range of people who get strokes, young and old.

JULIE BERNHARDT

That's right, it even happens in children. It's less common in children. But childhood stroke is a reality. About 20 to 30 per cent of people with stroke are under the age of 55. This is very disruptive and very challenging, and of course once you have stroke in that young age, you're likely to have to live with it for the rest of your life.

ANDI HORVATH

So Julie, do we know what causes stroke, or even what the risk factors are? Like for instance is there a genetic predisposition?

JULIE BERNHARDT

There are in some cases. There are some kinds of stroke which have a genetic predisposition. They are familial, and we know a bit about them. CADASIL is one, and Fabry disease is another. But in fact we don't really have a good picture of stroke in the vast majority of people. Some of that is because we don't have enough data yet from large genetic samples of people with stroke. But also it's because stroke, probably, is going to be a multifactorial genetic challenge where you will have a number of factors that sit and come together to make you more predisposed to stroke.

ANDI HORVATH

Sure, and that includes diet and exercise.

JULIE BERNHARDT

Absolutely, so what we do know a lot more about than the genetic predisposition to stroke is the relationship between factors like high blood pressure, smoking, being overweight, not exercising, having high cholesterol, diabetes. These are not uncommon risk factors for cardiovascular disease. They are really important for stroke. They're also preventable in many cases.

ANDI HORVATH

Now are there differences in the population as well, say, between males and females?

JULIE BERNHARDT

Yes, there are some differences between men and women, but not as much as you would expect. Women are very similar in incidence to men. I think where we see some differences is in what care they receive, and I think that's something that's really worth looking at further. We are seeing differences in the kinds of treatments that men and women receive in hospital. We're seeing differences in who's eligible for certain treatments. I think this is an area where we really need to keep our eye on it, because there looks to be some inequities here. That's important that that's followed up.

ANDI HORVATH

I'm Andi Horvath, and you're listening to Up Close. In this episode, we're talking

about the state of science around stroke recovery with clinical researcher Julie Bernhardt. So Julie, tell me about how we currently manage stroke patients? Tell us about the public education campaign called FAST.

JULIE BERNHARDT

Yes, this is something that is worldwide, and they've deliberately tried to make it similar across the world. So FAST is a simple message that is trying to educate the public about the importance of time in stroke management. So Face, Arm, Speech and Time is what FAST stands for. These are facial droop, problem lifting your arm, speech, either inability to understand speech, or to express yourself. Then if these things occur all at once - so this is a sudden onset disease - then time is critical.

ANDI HORVATH

You mentioned time as a critical factor. Are we talking hours?

JULIE BERNHARDT

It is hours, but minutes is really important as well. So the new treatments that we have available for people with stroke, which are largely focused on the most common type, which is the clot type, are able to minimise the clot, or potentially completely remove the clot. Now if that can happen quickly, then this cascade effect that happens with the blockage can be reversed. You can end up really recovering, remarkably well. But this is time critical, absolutely time critical, and at the moment, we're looking at only being able to deliver these treatments within four and a half hours of stroke onset, so you don't have a lot of time. The other thing that's important to note is that in that four and a half hours, the faster you get to hospital, the better recovery you'll have, because of the fact that we have billions of cells in our brains. We need to try and lose as few as possible.

ANDI HORVATH

Sure, and all those very important connections to other areas.

JULIE BERNHARDT

Absolutely. We are trying here in Australia, and across the world, to find ways of making that more likely, and that's happening through telemedicine, and systems where we're trying to make sure that even in regional hospitals in different parts of the world, and in this country, we can still deliver those treatments, the clot-busting drug, or even extraction of the clot, which is the most recent advance in early stroke

medicine. These are really exciting treatments, but they are time critical. At the moment, only about 10 per cent of people, maybe in some countries up to 20 per cent of people, can have that treatment. So then, of course, there are a lot of people who cannot, and that's where recovery comes into play.

ANDI HORVATH

Julie, let's go back to some of the laboratory studies. How do animal studies shed light on the details about the process of effective recovery for humans?

JULIE BERNHARDT

We've been using animal models for research for a long time. The limitations of human research, of course, is that we don't necessarily follow people for long enough to see these really ongoing changes that happen in people with stroke further down the track. In the animals, we are able to look at what's actually happening at the molecular level in the brain. This is an important area to try and help us understand when the window might be for best opportunity to deliver our treatments, and get the best outcome for our - in this case, animals. But for us, of course, with humans. The only other way that we can start to do this is by looking at brain imaging as well. But it's not yet sophisticated enough for us to understand the window.

So a lot of our research before with animals has been looking at giving them a stroke, either by creating a temporary blockage in the brain, or a permanent blockage in a vessel in the brain, and creating a large stroke. We typically use rodents, rats, because they're a larger animal, or even non-human primates. However, that's becoming less common these days. When we do research with the animals, we're trying to study both the immediate effect of the stroke, and then the impact of certain treatments on brain repair. Those treatments are coming in a number of different guises. We have groups who are working in exercise, groups who are working in more broadly environmental enrichment, which incorporates exercise as well as socialisation and novelty. We have people working on specific training regimens with animals to see if they can improve recovery, and we have, of course, people working in stem cells and also working in pharmacological treatments.

ANDI HORVATH

Alright, so you've been giving your rats some exercise-based interventions. Is it as simple as that? Are they running round in wheels?

JULIE BERNHARDT

So I don't do that research directly, but we've been looking at doing systematic reviews of animal literature in a number of key areas. In enrichment, in constraint-induced movement therapy, which is where the rodents have one of their four limbs constrained, and are forced to use the one that is paralysed to see if that will help them. There's actually a parallel of that in humans called constraint-induced movement therapy. Then also in exercise. So in the exercise literature, what we see is that if you pre-exercise an animal, then their recovery is much better. This speaks to the fact that we do know that if we exercise, we are likely to have better recovery from a raft of diseases.

Then there's models where we're looking at putting rodents in environments where they must exercise for certain schedules of exercise, and at certain times. When we look at that literature, what we see is significant benefit in behavioural outcomes. So the animals improve on their behavioural testing if they've had a stroke, and if they've been exercising. What is yet to be understood in that literature is because we've got different groups who are doing different paradigms within their research, we still don't have a clear picture of when is the right time for doing the exercise, how much is needed to actually get the benefit, and also what schedule is needed. Exercise is just that simple little word. But it's actually very complex in how we deliver it. That's what we're trying to understand in the human condition.

ANDI HORVATH

Sure. So what do we know from these rodent studies about the windows of effective recovery using exercise-based intervention?

JULIE BERNHARDT

The literature looks like that there is an early time window. What we don't know is how early is too early. It looks like the window could be between five days and 30 days, and it could be earlier than five days. It's just that some of the studies don't actually start earlier than that. But there are some acute inflammatory responses that happen really early on, and there's some concern that we need to let those adapt and change before we start delivering intensive treatments. We've certainly found that in our human studies. So we looked at this literature with animals. We also looked at what we knew about acute care in humans, and determined that at that point in time, nine years ago, when we started this project, that the early time window looked important.

We had to try and come in early and see if we could deliver a more intensive exercise-based approach, or physical activity based approach. When we put that into a clinical trial - and that was a huge study, we piloted it, and it was looking incredibly promising - we actually found that this very early time window was not the right window. That, in fact, starting that early could be detrimental to recovery. So somehow, it's interfering with the recovery process, and that's really put us onto a

new path of trying to understand what is that window. But leaving it to later than a month is not likely to be the right approach. So my concern in our current models of how we deliver care is that there are a lot of people with stroke who actually don't even get any rehab in that first month. It could be that we are missing a really really important window for them to get the best recovery possible.

ANDI HORVATH

Julie, what is the overall effect, or value, of exercise in stroke recovery?

JULIE BERNHARDT

So exercise is when we apply a specific intervention that's repeated that is aiming for cardiovascular fitness. That's the definition of exercise. If we think of that, we've got a couple of ways that we're applying it right now, and testing it. One, we're looking at if we can do a short burst of intensive exercise, prior to someone learning, does it improve their learning ability? We do know that exercise has this wonderful global effect on the brain. This is a really interesting target that we're working on now, because it could be incredibly valuable. If we could exercise someone briefly, either on a bike, or some other mechanism, and then try and do the learning task. If it showed benefit, that would be eminently translatable.

So that's one of our targets. The second target is just looking at fitness in general, cardiovascular fitness. Now the reason for fitness being important is because people after stroke have profound loss of fitness, and really significant changes in muscle physiology. So they have increased fat in their muscle, they lose lean muscle. Of course, that in itself can mean that it's much harder to move and get around. So fitness can work at the level of muscle. It can also work at the level, we think, of bone, and help prevent fracture. But also we know it has, again, a global effect on mood, and depression is really common after stroke, as is fatigue. So fatigue, and depression, very common sequelae, both of them we feel can be changed by exercise. So there's another target.

Then finally, there's another area that we think is important in stroke, and that is changing sedentary behaviour. So this is the opposite end to exercise, but on the continuum. What we know from a lot of large studies now is that the more couch sitting that we do in long bouts, the worse our health. This is independent from whether we exercise an hour a day. So if you spend a lot of time lying or not changing your position and being sedentary, even if you do exercise, you still are having these serious health problems. So our other target in stroke is to change sedentary behaviour, because it's a great target for people who have some disability. If we can just reduce the length of time that they spend in these long periods of sedentary behaviour, it can improve their cardiovascular condition. It can change their glucose metabolism, it can change their cholesterol levels, and it can have a

good health benefit.

ANDI HORVATH

So what are the differences in exercises that you give patients for motor recovery or, say, speech recovery?

JULIE BERNHARDT

What we do know, with many models, both in non-human primates, and in rodents, is that task-specific training, where you actually get them to do the task that you're trying to help them recover with, is critical to recovery. It looks like it's in the rodents important to have that as well as an enriched environment that is trying to keep them stimulated.

ANDI HORVATH

So mentally stimulated as well as physically stimulated?

JULIE BERNHARDT

Absolutely. So cognitively, socially, and physically stimulated. So what we have in the humans is we need to look at how often we deliver the task-specific exercises. So for example we looked at standing, walking, sitting practice to recover your balance. These are the tasks that you're trying to train. In speech and language, you're trying to train language. So there are different models that are being used right now, and there's an international study running called VERS. This study is looking at starting within a week of stroke onset, and getting people with language disturbance aphasia to have treatments that are appropriate for their disturbance, and to see if continuing this treatment for that first month is going to make a difference. So that's happening right now. It's very exciting.

ANDI HORVATH

So is recovery about brain plasticity and about making new connections, or is it about repairing old ones?

JULIE BERNHARDT

That's a great question. In our field, in rehabilitation, a lot of what we've been doing in the past has been focused on teaching people to compensate for their loss. Now

compensation is natural. We as humans will adapt very quickly to injury. You've probably had one yourself where you might have a sore ankle, and you start to adapt how you move. Well, if you keep doing that, then you'll always walk that way. In stroke, it's very important to try and be clear. Are we trying to help with compensation, or are we directing our treatment to recovery? I think that what we really are trying to do now is develop treatments that are targeting recovery, which is about brain repair and change, not just about compensation. That's a real shift in our thinking.

ANDI HORVATH

I'm Andi Horvath, and our guest today is clinical researcher Professor Julie Bernhardt. We're talking about new insights into the recovery process for stroke patients, here on Up Close. Julie, can you share some anecdotes of patient recovery and surviving a stroke?

JULIE BERNHARDT

Yes. They won't necessarily speak to how fabulous our care is at the moment, but I'll give you an example of someone that I think took on their own recovery and did a fantastic job. This is a man who had his stroke and had said, in the early phase, that all he wanted to do was go back to riding his bike. He was told that that would never happen, he wouldn't be able to go back and ride his bike because he had problems with his balance. He had problems with his ability to generate movement, with his leg. He had problems with his arm, so he couldn't grip the handlebars of his bike. He went through rehabilitation with not, I think, a lot of encouragement that this is something that he could achieve. Then he went home and he set about just saying well, I don't really care what you think, I'm going to make this happen.

He positioned his bike in his corridor in his house. Every day he would sit on his bike and he was close enough to the walls that if he overbalanced, he would be able to stop himself from falling over and he just practiced over and over and over again, until he achieved his goal, which was to get back riding his bike. Now I think this is a good example, because it speaks to both hope, which is a theme that I like to speak about in stroke recovery. But also talks to the importance of really listening to the goals of the patients that we are working with, and trying to work with them to come up with ways of delivering treatments that are going to help them achieve those goals. Now what he was doing was repetitive task practice, which we know works, and he just had worked out how to do it for himself. So that's a perfect example.

There's another person who was a narrator, an author, a medical practitioner who lost all of their speech and language. Now this person had a really devastating stroke that completely changed their identity and their ability to work. Now what's important about this individual is that I got to see them speak seven years later. At a conference, they were asked to talk. Two things were abundantly clear. One, they

had recovered a lot of their speech and language, and still had that beautiful craft of being able to make a fantastic presentation. Two, that they were still incredibly angry at the fact that someone had said, you will never be able to do this again. I think what's important in speech and language is that the time frame for that can be much longer for recovery, and that needs to be recognised. It can be years before you get complete recovery of speech. It's just a different temporal relationship, and we don't really understand that.

ANDI HORVATH

Julie, your research program isn't just at the level of the patient, it's about the radical redesign of hospitals and clinical spaces, that is, the environment, an enriched environment, if you will. You now also work with architects and designers to fashion more effective clinical spaces. Now it was mice and rat studies, again, that led you to look at other factors that influence recovery, particularly the physical environment. Tell us about that.

JULIE BERNHARDT

So yes, we'd looked at environmental enrichment. That is an area that's very very well known in people who work in animal models of stroke, but also in other areas. It's what we have to do for our animals in the zoo so that they maintain their wellbeing. Now this is well known in the animal space. So when you talk to researchers in a range of diseases including diseases that are genetic in nature, you can see that putting animals in environments that are enriched, so they're larger cages with opportunities to exercise, novelty and socialisation, you can actually change the path, the temporal path of a disease, such as Huntington's disease. This is research that Tony Hannan here in Australia is very well known for.

Also when we look at stroke recovery, our review that we did years ago, pooling all of this information together, shows remarkable improvements in recovery in animals that have this enrichment compared to those that are housed in single cages or with one other animal. So this enrichment, you could create a parallel, if you think about how people are housed after they've had a brain injury in hospital. This set us on the path with a PhD student of mine, Heidi Janssen, to look at what could we put inside existing buildings to enrich the environment for someone who's had a stroke or a brain injury. So in Heidi's work, she looked at creating individual packages of enrichment, and communal packages of enrichment.

So what that means is that for the individual, we would go and talk to them and say, so what are the things that you like to do that you find make your life enjoyable, worthwhile. Those things, which might include audio books, or reading, or music listening, or doing puzzles, or accessing the internet, or whatever it is that people like to do - reading newspapers - these things we could deliver to them, to their bedside, and they could access them whenever they like. Then the communal enrichment was

creating a space within the hospital environment where people could go to again engage in social, cognitive, and physical activity. So creating this model within those hospital environments.

This pilot work looked quite promising. We changed, in the first study, the amount of time people slept, and people sleep a lot in hospital. So they were sleeping less. They were more cognitively active. More socially active. Not more physically active, and I think this is our big challenge, because people with stroke are often dependent on others to move. But having improvements in cognitive and social activity, and reduction in daytime sleepiness, is all really promising. So we've now moved that on to another study into four hospitals, and we're trying to implement the same kinds of approaches. But it also made me think back to all of the hospitals I've worked in, and the fact that what we're trying to do in enrichment studies like that, is we're trying to retrofit something into an existing building.

That really sparked my interest in challenging that notion, and saying, well, why don't we actually look at the whole building itself, and its role in creating a healing environment for people with stroke. That set me off on the path of looking at evidence-based architecture, and what do we know about what the environment can or cannot do to change healing. That has led to the project that you were describing before about trying to redesign hospitals.

ANDI HORVATH

The future's looking good. But should we put more efforts into prevention, or is recovery really the key?

JULIE BERNHARDT

We should be putting more effort into prevention. Prevention is obviously better than cure. The complex thing about prevention is that behaviour change just seems to be so complicated. We do not seem to be able to shift things like taking your blood pressure medication. Taking your medication, full stop, if you have high blood pressure, is really problematic. Exercise would be fantastic. We've been working in that space for a long time, trying to get people to exercise, change their diet. So I think with stroke, a lot of the challenge is that the main factors that come into play in causing stroke are things we've known about for a really long time. Unless we probably completely rethink that, change the models that we have in place for encouraging people to develop better habits and behaviours, I don't think we're going to make progress.

I do think it's a very very important place for us to be working. The other comment I'll make is that I don't think that there's a lot of government support for prevention. Where do we, as people trying to help develop better ways of prevention, where do we find the support and finances that we need for doing that research? It's a

challenge.

ANDI HORVATH

Julie, thanks for being our guest on Up Close.

JULIE BERNHARDT

Thanks very much Andi. It's been a pleasure.

ANDI HORVATH

We've been speaking about recovery from stroke and the many factors critical to maximising recovery with Professor Julie Bernhardt, head of the stroke division 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 12 October, 2016. Producer was Eric van Bommel, audio engineering by Gavin Nebauer. I'm Andi Horvath, cheers.

VOICEOVER

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