Airing Pain Programme 31: Brain imaging-looking into your pain

How pain can be seen in the brain, and the research showing pain to be a condition in its own right.

In this programme we feature two areas of research which are helping in the understanding of pain.

Professor Karen Davis, a neuroscientist at the University of Toronto, Canada, explains how brain-imaging technology has revealed the overlap between experiences of pain and other sensations such as fear.

Dr Yves De Koninck, Director of the Quebec Pain Research Network, discusses how the latest research on chronic pain supports the position that pain is a condition in its own right caused by abnormalities in the nervous system.

Paul Evans: Hello, I'm Paul Evans and welcome to ***Airing Pain***, a programme brought to you by Pain Concern; the UK charity that provides information and support for those of us who live with pain. This edition is made possible by Pain Concern's supporters and friends. More information on fundraising efforts is available on our Just Giving page at painconcern.org.uk.

Now, all too often a media headline will grab our attention by announcing a major scientific breakthrough in the understanding and management of chronic pain. Sometimes its bad science, but then again, it may have significance. So how do we differentiate between the two? Well, in today's programme I want to feature two areas of research which really are helping in the understanding of pain. Professor Karen Davis is a neuroscientist at the University of Toronto in Canada. She's a leading figure in the field of brain imaging.

Professor Karen Davis: That's an umbrella term to describe a number of different technologies that we have now available to us to look at how the brain is both functioning and how it looks structurally. The most popular techniques that people know about and have heard about now is using MRI, or Magnetic Resonance Imagining, to peer into the workings of the brain.

Evans: Are you telling me you can take a picture of my brain and tell me how I'm feeling?

Davis: That's actually a good question and that's where we have to be very careful with what we mean by being able to know how somebody is feeling or thinking. We can't exactly do that. What we can do is we can look at how the brain is reacting or responding or is put together in terms of structure related to some sort of feeling or action. And we can make a correlation in the relationship between these indirect measures that we see reflected in the brain and what you're thinking and feeling.

So we can't exactly do in reverse what people would like us to do, which is look at a picture of the brain, as you say, and be able to say with great certainty, 'Ah, I know how you're thinking and feeling.' What we can do is – the measures that we take from the brain, which are kind of indirect measures of brain function, they're not direct measures – we could say, well, *when* you're thinking or feeling this, sometimes, many times, we see a reflection of that in the brain.

Evans: In what way? How?

Davis: There are two basic types of imaging that we do using an MRI, one that you just mentioned, which is looking at what the brain looks like. We have more sophisticated ways of taking that picture of the brain now and actually measuring and seeing how the various elements in the brain look – so, the cells of the brain, which comprise what's called 'the grey matter of the brain' and the connections between the cells in the brain, which is called the 'white matter'. So I like to think of [the white matter and grey matter respectively] that as the kind of highways and cities of the brain. And so we can look at what that organisation is like and try to see if there are signs of abnormalities in organisation. So that's called structural imaging.

The development of these kinds of very high-end structural imaging approaches is relatively new on the scene. Perhaps in the last five years have we gotten really good at that kind of assessment. What people are more familiar with and have seen in magazines and journals are those pretty coloured pictures of the brain with kind of different coloured blobs, if you will, lighting up, so to say, in the brain. And that's a technique called functional MRI. And what functional MRI really is, is a way of looking at an indirect measure of the activity of the neurons. And it's indirect because it's really a measure of the hemodynamic response, so the blood-flow and the vascular response in need when neurons are active.

Evans: Basically when an area of the brain is working, is doing something, blood flows to that?

Davis: And you can pick it up. So the pretty pictures that we see now published in magazines, what those really are are colour coded statistical maps. So they're actually colour coded based on the statistical difference between what's happening when somebody is thinking or doing something or when you apply some sort of stimulus, like a pain stimulus, and the difference between what's happening in that state and what's happening in some control or baseline states. Those are all statistical maps.

Evans: If I experience pain, if you stick a pin on me now and I'm in your MRI scanner, you stick a pin in my hand; will a part of my brain light up?

Davis: The short answer is yes, but not just one area. It's important to realise that unlike many types of senses – vision for instance, where there's a very specialised area of the brain, the visual cortex, that's involved in vision and critical for vision – for pain, you can't really point to any one particular area that's absolutely critical. If we could, that would be the magic bullet that surgeons could target and drug companies could target to get rid of chronic pain. But the pain experience is really involving a network of brain areas all over the brain.

So that's important to realise, that these things work together to not only give you the pain per say, the "ouch" experience, but also the nuances of that pain – so whether it feels burning or prickling or stabbing or shooting. All those pain experiences are encoded in this network and overlying all that is all the emotional and cognitive experiences that accompany pain, which also light up in the brain. So that may change depending on the mood that you're in; depending on your individual personality; depending on the context: whether you're being distracted; whether you're multi-tasking or something else.

So the actual picture you get in the brain can vary tremendously from person to person depending on a variety of factors. So absence of some areas of the brain lighting up doesn't mean the person is not in pain. It's just one of the variabilities based on that individual experience.

Evans: So when you come and poke a pin in my hand, the first thing I see is that you have a pin and you're coming towards me, so I have the fear because I know it's going to hurt and various other things, and everything is sort of interacting with this pain centre.

Davis: Exactly, exactly. So one of the issues that have made it very difficult for us to say, 'this is a *pain* network and nothing else in the brain' is exactly the situation you've just mentioned. There are dozens and dozens of experiments looking at non-pain experiences: fear, emotion… perhaps me looking at a spider, since I can't stand spiders, would activate a very similar, if not almost identical network in the brain, without the actual experience of pain.

And so this overlap of areas that play multiple roles has really been one of the obstacles for us to be able to move forward and say this is the network that we should be targeting for treatment, because if we target that network we may end up actually having a great number of side effects because we've also affected many other functions that we might not want to mess around with.

Evans: So in real terms of how it will affect pain management in the future, where are you going with this?

Davis: Because of this overlap of function – and this overlap of function isn't necessarily at the individual nerve cell level or the individual receptor on the nerve cell level – it's a problem with using brain imaging which shows you these blobs in the brain, that those blobs in the brain contain thousands and thousands of neurons that may serve different functions. So I think we need to couple the current brain imaging with some other techniques that will enable us to say that within that blob of activity, some of that is due to fear and some of it really is the actual "ouch" experience. And so we need to able to look more at a neurotransmitter level or single cell level to see at a much finer scale spatially, but also perhaps temporally, in time. So other techniques like MEG [Magnetoencephalography] or EEG [Electroencephalography] are now being married with MRI to get more detail as to what's going on within those blobs.

Evans: Professor Karen Davis from the University of Toronto. Now, Canada has a very strong history in pain research, it dates back to the collaboration between Professors Ronald Melzack in Canada and Patrick Wall in the UK. They established the first modern theory of pain back in the 1960s. Dr Yves De Koninck is the Director of the Quebec Pain Research Network in Canada.

Dr Yves De Koninck: They essentially first proposed what is now called in medical school 'the gate control theory' of pain. And essentially what they proposed is that there is a filtering of your sensory signal in your spinal cord before they're relayed to the brain. And they were trying to reconcile this – essentially, the psychological experience, or everyday life experience about pain – with a neurobiological substrate. How is the wiring? How is the neurochemistry in your spinal cord explaining this psychological experience?

Evans: So tell me if I'm wrong: when you say 'filtering', if I tell you you've won the lottery and I stamp on your foot, at the same time somebody tells me I've just lost my job and stamps on my foot, I would feel different pain to you? So something is happening between my foot and my brain to change how we perceive our feet being stamped on?

De Koninck: Absolutely. The example you give is often the one I give to students. If I stamp on your foot, it's not in your foot that you feel pain, it's in your brain. It's always in your brain that you feel pain. But between your foot and the brain it has to go through the nerves, the spinal cord, the lower part of the brain, up to the surface of your brain where pain is perceived. So, if the signal is altered anywhere along that path, it may lead to an aberrant perception: the same way that the same person doesn't feel pain the same way in two different conditions; the same way that two persons don't feel pain necessarily the same, and so on. Part of it has to do with our bodies' own ability to control pain sensation. If you're hurt then you need to save your child who's in danger, you'll just go ahead and you won't feel it.

And, in fact, there's a number of recent discoveries and some of my own research is highlighting that perhaps what happens in chronic pain conditions is that the body's own ability to repress pain in certain conditions is what's failing. What is emerging, I think, is the realisation that indeed chronic pain has to do with an abnormal function of your nervous system, of your nerve cells in the spinal cord and in the brain, therefore, meaning that chronic pain is a disease in itself. One of the long standing problems that we have in the clinic is that people often consider pain as just a phenomenon secondary to another problem – you know, you have cancer, therefore you have pain; you have diabetes, you've been hurt somewhere, you had an operation and you feel pain – the pain is just an alarm system that's telling you that there's something wrong.

Evans: It has a purpose.

De Koninck: It has a purpose, but more than that. People say if it's just secondary to another problem, let's solve the first problem and then the pain will go away. And in many many situations, it's the *pain* itself that is the really debilitating component of a disease. So there's a recognition that we need to target the pain itself, not just say, let's just solve the problem of the source and the pain will go away.

And in addition to that, the realisation that the pain in itself may be due to a malfunction of your nervous system and therefore has to be considered as a disease and therefore has to be treated as such. Research has actually highlighted that there are changes that occur in your spinal cord, in the lower part of your brain, inside of certain brain areas that are involved in the perception of pain, where information coming from your body, the sensory information, is processed abnormally, like epilepsy, for example.

You know, it's interesting, I often give the example that a hundred years ago epileptic patients were put in mental health hospitals because they were considered possessed and

people had no idea what to do. Over the years we've discovered that epilepsy is just a neurological disease that we can treat very well. Pain is sort of behind in that respect. It's only in the recent years that we're starting to de-stigmatise regarding chronic pain and realising that chronic pain may just be a neurological disease like others, we just have to find the sources and the way to treat it and then people can go on with their normal lives.

Evans: So we just have to find the source. You're a researcher, what have you found?

De Koninck: [Laughs] So, I mentioned earlier Patrick Wall and Ron Melzack and their original theory was essentially saying that there's a filter at the level of your spinal cord where the sensory nerves coming from your skin, from your body, everywhere, converge: information is processed there, before it's relayed to the brain, where pain is going to be perceived. So how that processing occurs will determine, essentially, your sensory experience. And many of your body's own abilities to repress pain take place there.

Evans: This surprises me, really. You're saying that it gets processed – or some of it gets processed – *before* it gets to the brain?

De Koninck: Yes exactly! And in a sense it's actually interesting that it gets processed where it enters, right away into your… what we call the central nervous system, the spinal cord in the brain, rather than being processed higher up in the brain. You could say, 'well, let's just gather everything at the level of the brain and the brain cells will decide what information is meaningful or not' and you could say, 'well that maybe it's actually an economic way for our body to function is to actually filter signals right away at the entry point so that you don't spend exaggerated energy to process it higher up.'

Evans: I'm going to keep with this – this processor in the spine, *is it actually filtering it or signalling it in different directions*? Is it like a railway control, if you like, we have all the railway lines and one is sending a train that way and the other is sending a train that way – is that what's happening?

De Koninck : That's very interesting that you put it that way, because for the longest time, there's been this debate in the field as to whether you have essentially one relay – one track, to take your analogy – where all the information converges and somehow the signal gets encoded in there and it's going to be interpreted higher up, versus, the idea that there may be a whole bunch of different parallel rails, that each have to do with certain sensory signals, like touch, stroking touch, temperature, itching, pain and so on. And then people have been saying well – one of the problems with the idea that you have separate tracks is that the doctor can just go in and cut the wrong track, the one that signals pain, and you will be fine.

And when you do that sometimes you can relieve pain, but for only a certain time and then it comes back.

Knowledge now is converging to say that, indeed there are all these parallel tracks and information is essentially channelled in these different tracks. But there is room for cross talk between these tracks and this cross talk is controlled by these control neurons I was telling you about, what you call the local inhibitory neurons. So you have a bunch of pathways – you have all these inhibitor neurons that are repressing the cross talk between these tracks. But in certain conditions, that control can be lifted a little bit and allow some cross talk so that normally when I just touch your skin, gently, it is just perceived as a normal touch signal. But if some of the cross talk between that channel and the pain channel is lifted a little bit, some of the information will be going up the pain channel and that same touch will be interpreted as pain.

What people have to see is that this cross talk can happen at several places from your foot to your brain, so that maybe you can cut it at the spinal cord level, a specific pain pathway, and therefore the pain signal should not go up anymore. So if there was cross talk before you cut – then you know you've cut the pain pathway, so nothing should go through and you should not feel pain anymore .But then that cross talk can occur higher up, and then you'll cut again at that level, but it can happen again higher up.

You know, the amazing thing about the brain is its enormous, what we call in scientific terms, 'plasticity', its enormous ability to reshape, reorganise itself constantly. We all know about the cases of people who become blind and the areas of their brain that normally processes vision is now processing other sensations. It's just amazing how the brain reshapes itself. And it's the same thing with the pain system, you know, you go in and try to cut different places or the simplistic neurosurgical approach would be to say, 'oh let's just go in and cut' and then it will reorganise itself higher up in this form of this cross talk that I've been telling you about, to sort of *defeat* the doctor.

So what we've actually discovered in our research is that this control mechanism that's separating the signal between these tracks is failing in certain chronic pain conditions, in what we call neuropathic pain, and that pain that's due to damage to the nervous system – either damage to the sensory nerve or damage to the spinal cord after a spinal cord injury and other conditions, for example, the painful neuropathy that develops after diabetes. So at the level of the spinal cord, those control neurons, or the control mechanisms – so the nerve cells that are responsible for the control are actually not the ones that are in trouble. It's the neurochemical mechanism – so nerve cells communicate between them through chemicals. Nerve cells are characterised by electrical activity in your brain and it's like an incredible

entanglement of wires where signals go through and it's processed that way. But in between nerve cells communication is through chemicals, and there are chemicals that are inhibitory and others that are excitatory. So your local control neurons are releasing an inhibitory transmitter that acts on the nerve cells that will repress their activity. So if you have a whole network you just repress the activity of some of these interconnecting nerve cells and you prevent the conversation between your tracks going up to the brain.

To go into the details of our finding – we actually found that the nerve chemical that inhibitory control neurons are using is called gamma-aminobutyric acid and glycine. They're two small molecules that these cells secrete and that act on neurons to open certain channels – ion channels – that are permeable to chloride ions. The technical… but in the end, what is important to understand is that those chloride ions, when they flow into the cells, they actually inhibit the cell. For them to be able to flow into the cells, the cell has to maintain always these chloride irons low in concentration, so that there is a gradient, so that they will want to flow in, not flow out.

Evans: They are valves, in other words.

De Koninck: Yes exactly. That's a very good analogy. For them to flow in, you have to have something that will maintain the chloride concentration very low in the cells and, for that, nerve cells have pumps; they have little pumps on their surface, pumping chloride irons out all the time. And it turns out that we found that what happens after injury, to a nerve for example, that the cells in the spinal cord, the neurons in the spinal cord lose that pump; chloride irons accumulate inside the cells and then that little inhibitory signal – that neurotransmitter, neurochemical – that inhibitory neurons secrete and bind to that valve to open it; now instead of causing inhibition to these cells, cause excitation, because now there's been chloride accumulation and not enough chloride irons flow out.

So you've inverted your filter into an amplifier, if you want. So you can imagine now that all these cells that were there to repress all the cross talk between these rails, railways, going up your spinal cord is failing now and, in fact, not only failing, it's actually perhaps even amplifying it. And that can explain why touch, which should go along its dedicated rail, actually now crosses to the pain pathways and now signals pain.

So we found that originally – we actually found that the loss of this pump was actually secondary to a local inflammatory response inside your spinal cord. Your spinal cord and your brain are very separate from the rest of the body and your body has its own immune system and immune cells, some of them are called microphages. They are these little cells in your skin and your body that go survey all the time your body and whenever there is

something foreign, an entity or whatnot, they go in and then they chew it up, and they are the first barrier against any invading entity. Your brain and spinal cord have to be protected from some of your immune system, so it has its own internal immune system. So the microphages of the brain are called the microglia, tiny little cells that also circulate and travel through your brain and spinal cord all the time and they scan everything and they look for any damage and any degeneration or whatnot, to clean it up, to let the system regenerate.

What several groups are finding more and more, is that these microglial cells, after an injury, a spinal cord injury, or peripheral damage or what not, they will transform themselves, they will inflate, they will migrate toward the area where the sensory nerves are coming into the spinal cord and they will start doing things. And one of them is to secrete a factor which we found is actually responsible for causing the neurons to lose that chloride pump that I was telling you about.

So it seems that in the end it's actually your immune system, the inflammation inside the spinal cord that is repressing, if you want, your control mechanism to prevent the pain signal to flow through. Anyway, all these things are interesting findings – you might say, 'well that's all very nice, but what's it doing to my grandmother who is in pain?' What's very promising for us as researches is that this research is actually unveiling a number of new molecular mechanisms that maybe underlying the development of pain hypersensitivity or aberrant pain. New mechanisms automatically mean new targets and new targets mean new promises for the pharmaceutical industry to try to develop new drugs that may be helpful to alleviate pain. We are not trying to develop necessary drugs that will come and repress neural activity, nerve cell activity – we're trying to give back to the body its own ability to produce its own analgesia.

Evans: So you are trying to mend the body, rather than reduce the pain.

De Koninck: If you want, yes, let the body just handle the pain for itself. Each of our bodies, if they are functioning very well, has tremendous abilities to actually repress pain. The advantage of a strategy that's trying just to restore the body's own ability to repress pain is that you may envisage that it may have less side effects. Because if you come with a drug that inhibits nerve cells like many of these drugs – and many of them are working great at it, they are great tools to treat pain like morphine, for example – the disadvantage is that with morphine is that it acts in many, many places and it comes with a lot of side effects. What we call benzodiazepines, valium or derivatives of that are also drugs that try to enhance your body's own ability to produce inhibition. These drugs actually don't act by themselves. What they do is they help your body's own chemicals to produce inhibition.

Evans: Dr Yves De Koninck, Director of the Quebec Pain Research Network in Canada.

Now let me just remind you of Pain Concerns usual words of caution, that whilst we believe the information and opinions on Airing Pain are accurate and sound and they are based on the best judgements available, you should always consult your health professional on any matter relating to your health and well-being. He or she is the only person who knows *you* and your circumstances and therefore the appropriate action to take on your behalf. Now don't forget that you can put a question to our panel of experts or just make a comment about these programs via our blog, message board, email, Facebook, Twitter and of course pen and paper. All the contact details are at the Pain Concern website – which is painconcern.org.uk. And you can download all the editions of ***Airing Pain*** from there, too.

We'll end this program by picking up an earlier point that was raised by Dr Yves De Koninck. And I guess that if we asked 100 people with chronic pain whether they would rather have their pain suppressed or have their body restored to the point where it was before the pain began, then 100 people would say, 'Please put me back to where I was.'

De Koninck: Yeah, sure and of course this is a long and daunting task to get there, but it's definitely the objective. If you start with the idea that chronic pain is to do with a malfunction of the system secondary to something that happened, being able to work that back to restore it, is the ideal because if you do that then you fix the problem once and for all. Unfortunately for many, many, many diseases, like neurodegenerative diseases, all that we have as an arsenal is tools to palliate. But the more research we do and the more we understand what are the sequence of steps that are driving the nervous system, your spinal cord and your brain, the more hope I think we can have of actually going down that route of fixing it back for good, if you want.

Evans: This year, next year, next century?

De Koninck: Oh boy! These discoveries are very exciting for us researchers, but we know what to target. But then the first step is to actually find drugs that will do what we want it to do. That in itself is actually a pretty complicated path and once you've found it, then you have to go through the sequence of testing to make sure it's not toxic and that it does not have side effects and so on and so on. So unfortunately it takes a long time to get there.

Evans: But finding the root of the problem – the target as you call it – is the first step to the Holy Grail.

De Koninck: Absolutely, absolutely – yes.

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