Airing Pain programme 68: The Brain and the genes

The science behind pain and its treatment, and why understanding it matters.

If someone steps on your toe, your toe hurts – simple as that, right? Wrong! Professor Rolf-Detlef Treede explains how the brain and nervous system make pain and why we can feel pain in a part of the body that hasn't been harmed. It's not just a question of good science, Treede argues – better understanding will decrease discrimination against people in pain.

Genes also have a role to play in the story of pain, says Professor Ana Valdes. Her research is helping to explain why some people develop conditions such as fibromyalgia, migraine or rheumatoid arthritis and others do not based on differences in our makeup at the molecular level. Even our psychological responses to pain are affected by differences in the nervous system. Valdes believes these more sophisticated approaches to pain offer hope of effective treatment in the future.

Paul Evans: Hello, I'm Paul Evans, welcome to ***Airing Pain,*** the programme brought to you by Pain Concern the UK charity providing information and support for those of us with pain and healthcare professionals. This edition has been funded by a grant from the Scottish Government.

Pain by definition is subjective. To try to measure pain objectively is really a little bit of a stupid question.

Paul Evans: [Laughs] Well, even the most stupid questions have good answers. Now, are we pre-disposed to developing chronic pain, does it run in families? Ana Valdes is Reader and Associate Professor at the University of Nottingham. Her research is focused on finding the epidemiological (that's the study of how often and why diseases occur in different groups of people) and genetic risk factors that contribute to a disease. So, is there a genetic factor to chronic pain?

Ana Valdes: We think there is and there are some published studies which show for example that for chronic widespread pain, there is a contribution from genes and there is a contribution also to things like migraine to severe migraine. Some of it is familial, some of it is not familial but it doesn't mean if you have this one gene you're going to get chronic pain. What happens with all these complex traits, as is chronic pain, which is very complex clinically – it's complex in terms of treatment – and the causes are complex. But if we…

more than trying to understand if it runs in families, which is important – I guess it's important if it runs in families – but more than that, we're trying to understand by using genetics as a way of investigating the molecular causes of pain, hoping that by understanding what are the molecular causes of pain, we might be able to treat it better or to diagnose it earlier or to diagnose it better.

So it's not just about finding the gene for pain, but finding which molecular pattern is it, what it changes. Is it in your nerves? Is it in your muscles? Is it in the brain and in which part of the brain? Is it something that's really inherited? Is it…? You know, so that's the kind of questions that we are trying to address.

Evans: If those are the questions, then what are the answers?

A. Valdes: The answer is that it's early days. Though we do know, for example, that people with arthritis pain, say from their knee, you can have a very unhealthy knee when we look at your x-ray but you have no pain. Someone else has a knee as unhealthy, or even less unhealthy, than yours and they have very severe pain. And what we're finding is that some of these genetic variants involved in peripheral pain, so in the pain that comes from your body, how you feel it can actually influence the risk of you having painful osteoarthritis or not having painful osteoarthritis, given the same amount of joint damage.

But also we are finding people who have had a surgery and are having this nerve damage type of pain, we find that some of the molecules associated with that, some of the genes associated with that, are brain genes that are related to synaptic plasticity. One of these genes we find seems to go also in association with fibromyalgia, a weaker correlation with fibromyalgia. So maybe we are finding some of the molecules that are implicated in chronic pain.

Evans: I have fibromyalgia and I can remember twenty-five or so years ago, being asked questions like 'is there depression in the family? Is there alcoholism in the family?' because there may be a link, not through alcoholism, but through the mechanisms that involve that and depression.

Valdes: Well we do find, I mean I'm not looking directly at depression, as I say – I'm only looking at fibromyalgia. Do the results we find for this type of specific pain from patients after surgery… is it similar to some of the things we see in fibromyalgia? But in our case we are looking at something called 'catastrophizing', which is how an individual copes with pain. We ask a person questions like 'how often do you feel that you cannot go on with pain?' Or 'do you feel your pain is really terrible?'

And the more they have these catastrophizing traits, the worse their pain. It is very related to depression and anxiety. Their pain is worse, their quality of life is worse and their sleep quality is worse. So, that is a kind of psychological trait, if you want, but what we find is that the same genes that are associated with the pain, first the catastrophizing trait is actually – if you look in the brains of these people – correlates with features in the limbic cortex in specific parts of the brain. So that already tells us, yes, it's in your brain, but that doesn't mean if I give you a slap on the face, you can get over it. There is something physiologically going on.

And then, finally, the same genes that are associated with these nerve damage types of pains are also associated with catastrophizing, or this feature of pain, where people feel that they cannot go on with the pain and this is terrible. So pain is an extremely complex trait to study with many components to it. We're not saying genetics is going to be the cure for chronic pain, but we feel we can contribute a little bit to understand it better.

Evans: That was Ana Valdes of Nottingham University. So what *is* going on in the brain to make us experience pain? Professor Rolf-Detlef Treede of Heidelberg University, Germany is a neurologist, that's to do with the nervous system, the brain, the spinal cord and the nerves. So to take a very simple example, if someone steps on my toe, why do I feel pain?

Rolf-Detlef Treede: You give a very good example. It seems to be very simple that when someone steps on your toe, your toe hurts. This actually is very complicated neurobiology. You have sensors in your toe that detect there's damage and they generate signals that are sent up to the brain along certain pathways. Then the brain recognises this activity and the brain has to have some concept of having a body. So the brain then projects this feeling into that part of the body where the brain thinks the information is coming from.

In the case of someone stepping on your toe, the information is coming from the toe, the brain thinks it's coming from your toe, so your toe hurts and this is where the damage is. However, you can also have the brain thinks it's coming from the toe when the damage is compression of a nerve from a bulging disc in your lower spine. The signal will end up going to the brain, on the same pathway or it could be generated by the toe itself or somewhere along the pathway, in this case close to the lower spine or it could be generated in the brain itself. In all these cases it's very difficult for the brain to tell where the information is coming from. There's a term which is called ‘projection’, so pain is projected to some part of the body, this is where we *feel it* and very often this part is exactly where we have the injury, then everything is easy.

Evans: And that makes sense doesn't it because if somebody *has* stepped on my toe, the brain identifies that the toe has been stepped on and sends the pain down there, which makes me move my foot.

Treede: Yes, yep. It's figurative to say ‘send the pain down there’. Actually, I have slides on that which looks like the pain is sent down there, of course although in reality, this is entirely happening within the brain. But I think it's a nice concept of saying the brain has a little puppet of ourselves and sends the pain down there, where it thinks it's coming from. There are many ways of having a mislocation. And I think pretty soon there will be an anniversary of Henry Head, describing head zones of pain referral of infections of internal organs. So there's a certain regularity, so when your colon has been damaged, this is misprojected but it's misprojected according to a certain rule and these rules are known to medical specialists.

So when a patient reports a certain type of back pain, the medical specialist should have the idea that this may be from the colon. Many people know pain in the left arm could be related to the heart or the gall bladder to the left shoulder and things like that. It's very important to acknowledge that, in a simple situation where you have an injury and it hurts where the injury is, it's the same complex mechanism. And the reason it's important to acknowledge that *is* because many patients feel pain in parts of the body where there's no injury at all.

Now some people may think those patients are crazy because we think the brain always localises the pain to an injured body part but that's actually not the case. Therefore it's important to know this, so you do not discriminate against people who report pain in the body part where there is no injury. It only means that the mechanism of that pain is not coming from an injury to that body part.

This takes me to neuropathic and nerve pain because in neuropathic pain it's always the case that the part of the body where the patient reports the pain has no injury, because neuropathic pain is generated by the alarm system itself. We call it ‘the nociceptive system’, the system that normally responds to injury and the system can also just generate activity on its own. If you have a car alarm system you know what I'm talking about – alarm systems can go off without an external cause and the alarm is real and you have to do something to switch it off and the same is true of nerve pain.

Evans: Well, the explanation sounds easy [chuckles]. How does one turn it off?

Treede: Ah ok, that's the more difficult part. Maybe I should give an historical perspective of neuropathic pain and its treatment. There was the term ‘intractable pain’ in the past century and you can look at the situations that are called ‘intractable pain’, they're basically

neuropathic pain conditions. Phantom limb pain was sometimes counted as such. In the context of back pain when there had been surgery, that [was] likely to cause additional damage to nerves, failed back surgery syndrome and many other conditions, pain from diabetic neuropathy…

So, there was this term intractable pain. In the 1990's some literature came out – or somewhat earlier – called 'how to treat intractable pain'. Which sounds like a contradiction in terms, but it turned out that people had discovered some ways of actually helping those patients that do not respond to the ordinary analgesics.

Why was it called intractable pain? Because normal non-steroidal anti-inflammatory drugs didn't help much and also opiods at that point were considered not to be helpful. So the standard treatments that were also given out for post-operative pain and cancer pain, didn't really work. Now treating intractable pain had, I think, two historical backgrounds, one was coming from this cognitive behavioural therapy background, which we would interpret as utilising learning mechanisms for the benefit of the patient, which is logical because some intrinsic learning mechanisms actually also cause the pain. The other part is pharmacological treatment that was coming from two areas that seemed to be not very much related to pain. So the observation was that antidepressants were sometimes helpful and anticonvulsants, drugs designed to treat epilepsy, were sometimes helpful.

With respect to the antiepilepsy drugs, the mechanism at first glance is relatively straight forward. Epilepsy is too much electrical activity, speaking very simply, and chronic pain means electrical activity in the brain, so if you can somehow interfere with the electrical activity, it's not totally implausible that it might work.

Evans: Your turning down that electrical activity.

Treede: Turning down that electrical activity, dampening down that electrical activity. Of course not everything that turns down electrical activity works against epilepsy and not everything works against pain. Clearly, you have to have the clinical trial data to see what works. Some of the anticonvulsants work and some don't. So these two parts, epilepsy and neuropathic pain have some things in common but some are also different.

And the other part, antidepressants, has two components: people who are depressed often have pain as a part of clinical picture of depression and, in turn, if you have chronic pain, this really deteriorates your mood. So anybody with chronic pain fulfils some of the criteria of depression and therefore, one of the concepts was that maybe we're treating the depression and this helps the patients. This probably contributes but it's not the entire story as these

drugs can be beneficial to people who aren't depressed. The antidepressants can interfere with certain neurotransmitters systems…

Evans: So the neurotransmitter systems are the neurotransmitters, the systems where messages pass from one cell to another in the brain.

Treede: Yes, that's right. We have talked about electric activities, so the electrical signal stays within one neuron within a nerve cell that can travel a long distance, almost along the entire body from your toe to your brain stem, in the extreme case. But if you want to get a signal from one cell to another, you need some chemical signal and there are some neurotransmitters – actually, there is relatively a long list of neurotransmitters – there are some that basically transmit excitary signals, and that's glutamate. And that's involved in pretty much involved in everything, so it's very difficult to treat any specific disease based on glutamate.

There are some other neurotransmitters that have more restricted rules, two of these transmitter systems are involved in signals that are sent up from the brain stem to the spinal cord and modulate the signal transmission in the spinal cord. And the traditional labeling has been a descending inhibition, so that the body can inhibit the pain signal by the brain stem controlling how much input the brain gets. Here we have two transmitters, serotonin and noradrenalin, which are also important in the context of depression. So, the antidepressant drugs modulate the actions of serotonin and noradrenalin and when you modulate those actions, this can also be beneficial for pain.

Evans: Those drugs are the SSRIs, the serotonin selective re-uptake inhibitors?

Treede: It's a very good point for you to bring this up because they are the ones where the two fields again have separated. It's like with epilepsy, there's some overlap, neuropathic pain and epilepsy, but also some differences. The same is true with respect to antidepressants and neuropathic pain treatment.

The very classical antidepressants, the tricyclic antidepressants, like amitriptyline – off-patent for many years – is very non-specific, it does many things. Now for the treatment of depression, people have noticed that to really focus on the serotonin part, this is very helpful, because then you have fewer side effects, but you can still get the benefit. So these serotonin selective re-uptake inhibitors are more modern and better antidepressants and they don't help against pain, because for pain the noradrenalin side is more important. So, that seems to be the common denominator –those anti-depressants that also influence the noradrenalin side, they are also good against pain.

Evans: Many people are prescribed antidepressants for their neuropathic pain, so does that mean that depression is the illness?

Treede*:* *No,* because we know that in neuropathic pain patients, anti-depressants can help the pain even when they're not depressed. Having said that, we have this concept which is called ‘comorbidity’, so a certain person can have more than one disease and it's very frequent that a person who has a chronic pain could also have a depression. In that case maybe as a secondary consequence of the chronic pain, because depression is a mood disorder and clearly chronic pain deteriorates the mood. Then what clinicians often do, when they have the choice of different pharmacological treatments and each treatment addresses more than one thing, they have to tailor this to the individual patient. So if a patient has a chronic pain that has deteriorated the mood of that patient, then you would go for a medication, an antidepressant that helps the depression and the pain.

Another typical comorbidity – when you have chronic pain you don't sleep very well and actually you sleep much worse than patients with a sleep disorder. Some of the medications that are used against neuropathic pain improve sleep. So, if you have a patient that has a major sleep problem and chronic neuropathic pain, you would go to that drug class that also improves also the sleep condition. Again, if you have a patient that has their comorbidity of depression, you go for the antidepressant, if you go for the comorbidity of sleep disturbance, then you go for the medication that helps sleep.

The same logic applies to all the other drugs, because the older drugs also have multiple mechanisms and this is really the task of the prescribing doctor, to take into account the entire situation of the patient. The patient doesn't just have one diagnosis, usually they have more than one thing and even if the deteriorated mood does not yet fulfil the clinical diagnosis of depression, it might be helpful to improve the mood, one way or another.

I shouldn't end this without saying that medications aren't everything. The treatment is always multi-modal and that means there has to be some behavioural, psychological component to it, usually some element of exercise or physical therapy.

Evans: Yes, the term comorbidity, no person is one illness, in fact, a person is not an illness, a person is a person.

Treede: Absolutely

Evans: And chronic pain is a biopsychosocial condition, which means that it's life, it's mind and it's *living.*

Treede: Yep.

Evans: We are all those things.

Treede*:* This maybe brings us to the point of quality of life. When we talk about quality of life in the context of chronic pain, we think of aspects of everyday life, such as activities, family life and so on. However, when you talk about the quality of life in general terms, then the absence of pain is one of *the* major constituents of quality of life. So if you talk, let's say, about endocrinology, peripheral neuropathies, the absence of pain is a major issue for quality of life and actually, it's even a predictor of mortality. The same can probably be said about cardiovascular disease, definitely for cancers, so if the cancer is controlled and there is no pain, the quality of life is better, than if the cancer is controlled and there *is* pain.

So clearly pain or absence of pain is a major factor of quality of life, but it's not the only one and this is in the psycho and social domain of the biopsychosocial model. It sounds very complicated but day-to-day living activities play a major role, the wellbeing from the patient's perspective – not some biological parameter, blood count or imaging finding – but really the wellbeing of the patient plays a role. And here pain is defined as a subjective feeling, so pain is when it hurts.

The one thing we haven't approached is the plasticitiy of the system and we tend to think that the sensory system has a certain setting and that it stays like the setting of your microphone, set to a certain sensitivity. Now this is not true for the nociceptive system, this really becomes much more sensitive, whenever something important happens it immediately becomes much more sensitive. And then it becomes boring then it becomes less sensitive again and so it's highly plastic and this is not really appreciated very much.

The sensitivity of the nociceptive system is different between people, but in the same person, it is also very different over time. The simplest thing, is if you consider you have an injury, it could be a minor injury, so you don't even see a doctor. You have a cut, or a burn, or some kind of injury doing gardening work this time of the year, or what-have-not, then the injured body part becomes more sensitive to potentially damaging stimuli.

So many things that wouldn't normally hurt, relatively mild touch or sharp objects are more painful. And you may also notice that you are more sensitive to heating, so that heating is actually painful. And that's a protective mechanism. So, the warning system of the body enhances its sensitivity, its gain, whenever there has been an injury. It does it at all levels, even at the very peripheral nerve endings. Here we know some of the mechanisms plus certain channels and so on, but also in the processing of the signals of the central nervous

system. We know most detailed information about the spinal cord, so when the spinal cord has received a strong warning signal, then it becomes more sensitive to the next signals, as if it were listening to see if there were more to come and that would be the central sensitization and the other would be the peripheral sensitization.

Evans: So it's *learnt,* for want of a better word, what happened last time and works to avoid that same thing happening again?

Treede: It is a learning mechanism, absolutely. Many people use the word pain memory and it's not quite clear what they mean. If you look at memory research, there are lots of different memory and the simplest type of memory is basically non-associative, just by repeating stimuli. There are two things that could happen, one thing is, the response could becomes less, that's called ‘habituation’, when the stimulus is boring or unimportant, usually when it's weak, or sensitization could happen when the stimulus is strong or important or threatening.

This is exactly what the nociceptive system does, so when there is a real injury, that is important, so by the real injury it becomes more sensitive in the periphery, in the central nervous system. But this is a memory process that doesn't last very long. It is long term memory but in the sense of about one day. I usually compare this with studying for an exam, where you memorize things for the next day and then you start forgetting. The same thing happens with our warning system, if the injury heals, then we forget about it, but if we have repetitive injuries, then we enforce the learning and maybe we can have a longer lasting memory. So, the term ‘memories’ is absolutely appropriate.

Evans: So what happens when you say normally that memory will go within a day what happens if it doesn't?

Treede: That's really the big question. An interesting thing about chronic pain is that many people can have had the same injury and don't develop chronic pain. So the idea is there must be individual differences to susceptibility to develop chronic pain for some kinds of injury. I mentioned after injury the pain goes away one or two days. It's also true for major surgeries and most people can be discharged very quickly and they don't have pain.

However, some 10 or 20 per cent still have pain and the big question is, is this due to a delay in the healing process? Maybe in some cases. But in some cases this may really reflect a different a priori setting of the warning system. In these patients, the warning system has a longer memory than in other people. The individual differences, we can actually measure those and the idea is that maybe an important contributor to chronic pain is

this individual susceptibility to having longer lasting pain memory than the average population.

Evans: That's Professor Rolf-Detlef Treede of Heidelberg University.

I'll just remind you of my usual words of caution, that whilst we believe the information and opinions on ***Airing Pain*** are accurate and sound, based on the best judgements available, you should *always* contact *your* professional on any matter connected with your health and wellbeing. He or she is the only person who knows you, your circumstances and therefore knows the appropriate action to take on your behalf.

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Now I'll end this edition of ***Airing Pain*** with what may or may not be that stupid question I referred to earlier, I'll let you be the judge. Can pain be measured?

Treede: Usually I say there are no stupid questions, this is my one exception. This is according to the definition - pain is what a person feels. It's defined as an unpleasant emotional and sensory perception that is related to injury but may also be unrelated to injury, it is just the subjective, first person experience that is pain.

There is a term for the other thing, the thing we can measure objectively, that's ‘nociception’. It goes back to a famous British reflex physiologist, Sheridan, who noticed that some reflexes are elicited by potentially damaging stimuli. No matter which modality they come from, they elicit defensive reflexes. This led neurobiologists to discover the nociceptive system that senses either damage or impending damage – it’s a warning system.

And activities of this warning system can be measured, of course. You can start in the periphery – even in people – you can measure the peripheral nerve activity. You can measure reflexes, also in people, spinal reflexes, you can measure cardiovascular reflexes and you can measure brain activity with electrophysiological means, like EEG [electroencephalogram] or you can do PET [positron emission tomography] imaging. But this is really looking at signal processing in the nociceptive system and whether or not this activity leads to pain, depends on the internal state of the brain and many things. So really, pain or not is the subjective report, that's the definition.

Evans: I mean, that is interesting, as we're conducting this information in a dark*, pit* of a room, with no light and with actually very, very unpleasantly loud air-conditioning. If we were outside in the sunshine, my pain score and perhaps your pain score would be completely different.

Treede: Well, *absolutely*, one of the most powerful way to modulate pain is attention, the effect size is pretty much the same as that of strong analgesic medications. You could say if you have a headache, so if you do mental arithmetic, you could say you get as much pain relief as a pain killer. Now when you have a headache, you probably don't want to do mental arithmetic, so it doesn't have a practical consequence. But the effect of attention control is extremely powerful.

Evans: This is where talking therapies cognitive behavioural therapy, visualisation, meditation all play their part in our pain.

Treede: Yes, absolutely, so the cognitive part of cognitive behavioural therapy is relatively explicit about these things and the behavioural part is less explicit, where we just use learning mechanisms of the nervous system to enhance some behaviours over other behaviours.

Contributors

- Ana Valdes, Associate Professor and Reader, Faculty of Medicine and Health Sciences, University of Nottingham
- Rolf-Detlef Treede, Professor of Neurophysiology, Heidelberg University, Germany

Contact

Pain Concern, Unit 1-3, 62-66 Newcraighall Road,
Edinburgh, EH15 3HS
Telephone: 0131 669 5951 Email: info@painconcern.org.uk

Helpline: 0300 123 0789
Open from 10am-4pm on weekdays.
Email: help@painconcern.org.uk

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