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Title	*Understanding human pain, suffering and relief through brain imaging*
Description	Using examples from her research, Professor Tracey illustrates some of the exciting developments in brain imaging -seeing exactly how the brain is affected by its environment-and discusses how this research impacts on modern medicine, law and society
Presenter(s)	Irene Tracey
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Tracey Well good morning ladies and gentlemen. Thank you all very much for giving up your Saturday morning to come and hear a little bit about pain and suffering. I think you've self selected yourselves. You're obviously my type of people if this is a topic that you're interested in and I want to do little test on you before we actually get going.

I am going to spend about 45-50 minutes exciting you I hope about how we can use brain imaging tools, not only to understand how the human brain works and what we're actually developing here in Oxford and what our future plans are. But to bring you up to date on sort of current views about how we look at pain, particularly chronic pain and how imaging has contributed to really forcing us to re-think about that problem as a major medical problem now in society.

So it's going to be pitched for people who aren't necessarily from a scientific background, but I have put in some real data for those who might be from a more biological and medical background. So there's hopefully a little bit everybody and mostly it's quite good fun and then we'll end and have some questions. I'm sure we'll generate quite a few.

So this is where I work. It's up on the John Radcliffe Hospital site in Headington. It's a purpose built imaging facility. We're very fortunate. And at the end of my talk I am going to tell you a little bit more about that imaging facility and a little bit more about what our current plans are and future plans are for taking imaging into the 21st Century in the decade. This is a far picture as you can see, a beautiful weekend in Oxford. Not very often we get such lovely blue skies, you're very lucky. It seems to be case, every Alumni weekend, it's always a beautiful weekend isn't it?

Right, here's a little test then. You've all signed up to get up early on a Saturday morning and come and hear about pain and suffering. So there's something wrong with you right from the start clearly. So if one saw that lever, hands up, if you would, not knowing what the lever did, pull it? Very good. I'm very interested in those who wouldn't pull it. Okay, so you're going to pull the lever and that happens to you. Okay. (Laughter) So you get zapped. Now, hands up again, those who said they would pull it, would decide, "I really probably shouldn't pull that again?" Pretty much most of you. So you're normal. That's the normal reaction. (Laughter)

I'm actually just going to dim the lights here, hold on because the brain images. Let me just dim those a little bit. Now, if I am going to select the next people to come into my laboratory in the way I use this as a screening process for those who are like minded, this is what a pain scientist would do. You would ask the question "I wonder if that would happen if I did it again?" And

you'd keep on pulling it. So that's the sort of people we are in the lab. We inflict pain on people, we try to relieve it as best we can, but mostly we basically have a torture chamber up there. And all of you will be very welcome to come and participate in any of our experiments. I've left all my contact details and just don't tell the ethics committee I've advertised that today.

Right, so let's think about pain, because pain is a really interesting topic. It has use relevance for philosophers. It's obviously got enormous relevance in medicine, but it is an experience that we all have at many points throughout our lives. Hopefully for most of you in just an acute, good warning way. Because that really is what pain is. It is a sensory emotional experience that allows you to be aware that something has happened to you that is probably going to cause you further damage, so you'd better avoid it. Okay, so it's got a good warning role.

But going along with that and we'll talk a little bit more about how that's sort of acute good warning role transmutes itself and becomes then redundant. It's lost its warning signal and now this is just a permanent state and is no longer serving a warning role. Going along with that, if you look historically and even currently in society, we have tremendous biases about pain and we have a lot of expressions in everyday language that includes the concept of pain in these sort of biases we have. And I've just picked a few there, so we have common expression like, "No pain you don't get any gain," So somehow it's good to suffer, it's good to go through some agony, it's good to have some pain.

And this really does permeate and it's a problem actually in trying to change philosophically and in a sort of paradigm shift in the medical profession these biases and these attitudes to pain. But for some reason it's a good thing to suffer. So women in child birth for instances, would be another classic one. Somehow that's good for the baby, it's good for the mother not to relieve the pain. Many, many other instances where we have prejudices about giving people analgesics, you must be a junkie, there must be something wrong with you, you're a wimp. All these sorts of things.

And I think what I am hoping to get you to think about today a little bit, is how really the evidence, particularly in the context of chronic pain is forcing us to rethink about that and it's time we actually thought differently about pain in the 21st Century and it is unacceptable to have people, particularly in the developing world not have access to Gold standard and current medications for pain relief. And we've got to get rid biases and these prejudices about pain, it is no longer necessary for people to be living and suffering in chronic pain. So that's the sort of scene I want to set.

And these are just numbers. Chronic pain now is one of the biggest medical health problems in the developed world. We haven't got the numbers in the undeveloped world, but in the western world approximately 20% of the adult population are defined as having a chronic pain disorder. And the definition of chronic pain is, once you've had that acute pain symptom, you've hurt yourself or you've had some disease that has a pain like symptom that goes with it, that tells you something is wrong with you. That's good.

Normally though, within normal tissue healing time, two, three, four months, that pain should go away. But sometimes the disease process or the injury process has indeed fixed itself and gone away. But the person is left in permanent pain and it's taken on almost a life form of its own. In effect, I want you to think about chronic pain as a disease in its own right when it's made that transition into chronicity.

And so defining chronic pain is pain that outlives normal tissue healing time, 20%, one in five of the adult population have chronic pain disorder. Far more prevalent in the elderly population, so as we have an increasing population that is obviously living longer and more elderly this is going to become a higher number. It is more prevalent in women for reasons that we're not really sure of yet. And the cost is astronomical. And so if you take the cost of actually treating people, coming in for pain problems, pain related problems, the cost of people not turning up to work because

they've got a migraine, they got backache etc. The cost in Europe in the last audit last year was 200 billion Euros per annum and in the US $150 billion.

So it's a huge economic cost. It's a huge loss in terms of contribution to society and the workforce. And obviously it's an enormous burden for the families and obviously the individuals who are suffering those chronic pain disorders. So those are the statistics and I am afraid to say that the management and treatment of that group, that one in five is actually very poor. And it is a huge unmet need.

And so for the majority of those people who have chronic pain, the current drugs we have available at best will be efficacious in about 40% of that group and the amount of pain reduction that 40% gets if the drugs work for them is really just taking the edge off if you like. You're getting a 30% reduction in their pain. So you can do the math and realise you've got 60% of 20% of the world's population in chronic pain. That's an awful lot of people out there just suffering and managing and not finding any current medications working. And really the reason we failed so badly in treating that is that we've just been looking at it all wrong.

We've constantly been looking at the problem by thinking, "If we fix the thing that caused the pain and the warning symptom in the first place, then of course the rest will go away." Failing to recognise that that constant pain and barrage for certain individuals will set up and trigger off a whole set of new mechanisms and new things going wrong in the body which do indeed take on a life force of their own. And that's where we should be looking, that's what we should be understanding because those are the places and the targets we should be developing new therapies for. And that's the new knowledge that we've got really in this last decade.

So it's hopeful because I think in the next 10 to 20 years, we've got all this new science and this new understanding and now we've got in the pipeline new things coming forward that are targeting that new understanding. And so we do hope that there will be better medications. So we need different ways of thinking about the problem. We need new techniques. It's a subjective experience that is pain. We will come onto that in a moment. We need ways to objectify it. We need ways to be able to quantify it in the human body without just always relying on the verbal subjective description from the individual which can be subject to all sorts of biases and sort of errors. Not errors in terms of what they are experiencing, but errors in how it's translated verbally to the doctor, so unravelling what's actually going on behind the scenes.

What I have done is I've called a few pictures from various pain suffers, who happen to be, some of whom are very famous artists like Freda Carlo and then others who are less famous artists, who actually tried to capture what their pain was. What the suffering element of this thing that they're living with and has tortured their lives and disabled them from really participating and has in effect become their identity. And I think it's very good to look at because it really just gives you the sense of extreme suffering and torture that these individuals are experiencing. So they tried to capture again the multi-dimensional aspect that is pain. It's not just a sensory experience.

The thing that really is most disturbing is the way it just consumes your whole mind. All your attentional resources, all your emotional resources are just being consumed by this pain that dominates every aspect and every minute of your day.

Now sadly the way we assess and try to capture that in the lab is by doing that. And say, put a little dash on this line as to how much – we're not doing a good job. Now obviously, it's done a bit better than that, but that's the problem. Is that we try to capture a very three-dimensional multi-factorial experience into these one-dimensional measures of how intense is it, how much is it distracting you etc. And they're just not really meeting the measure. So we need other ways to try and unravel it, untangle it.

Now pain is a perception. And this is what leads us to brain imaging. Ultimately you don't have pain unless you have a brain and unless you have a conscious brain and you're actually awake. Because pain only comes about by virtue of those signals coming in from where you've damaged

yourself, up the spinal cord to the brain, the brain processes them and you have the conscious experience of pain. It is a perception. Just like this is a visual perception, but like all perceptions in all of neuroscience in the sensory domain, perceptions can be terribly misleading.

So hands up if you think the yellow line at the back of the railway track is wider than the yellow line at the front of the railway track. And be honest now. Well done Diana, you're the only brave one. There's something wrong with you if you don't. So do you all see that the yellow line is wider? Yes? But visually that's what you see yes? Do we all agree? That's your perception, okay. There's nothing wrong with your eyeballs, you might be a bit short sighted, I see a few people with glasses. But fundamentally, you don't have visual problems.

Truthfully, those visual inputs are going into your brain, and the appropriate area of the brain to process it, but the result of the perception that you see is not linked to actually the reality of what is there. Because when I do that, it's pretty obvious that those two lines are exactly the same. And that's the problem. What comes in doesn't relate to what you experience and what you perceive. And there's many visual tricks like that, that I could show you, but that's just one. And that is the problem of pain.

And this is beautifully illustrated in these two real life examples here, where that input which in pain, we refer to as the nociceptive input, that's a fancy term coined by Sherrington here, a former Wainfleet professor in physiology. When he first observed that under the skin there were specialised receptors whose job it was to detect things that are basically going to damage your tissue and those he called nocieceptors. So those are the things that immediately transmit the heat, they're sort of pin pricking all the chemical burns and they'll send the signals in. So those are the nocieceptors and that's if you like, the nociceptive drive. So that's coming in and that's producing when it's processed by the brain your pain experience.

But what I call linearity between those two things is not always equal. Normally it is. If I burn you more, it's going to hurt more. And the pain experience will go up with the nociceptive input. But very often those things are highly non-linear.

So real life example. These people are very strange. They meet at weekends and they have body piercings all over them and they hang themselves from their body piercings. Now I don't know about you, but I look at that and I think that looks really painful. Big nociceptive input, but you ask them, they don't feel any pain to that. So here we have a high nociceptive put, very little pain perception. They actually wanted to come to the lab and for a television documentary, do a documentary to prove that they really did have super high pain thresholds.

The trouble is they have all these metal body piercings all over their body and I worked in a very powered magnet (Laughter) and those two things they don't go very well together at all. And they had some body piercings in some most unusual places, which we were not willing to spend the necessary time and effort to get out. So we did some psychophysics on them which basically is a fancy term for assessing on the bench if you like, their pain threshold. And indeed they do have very high pain threshold. They are somehow are able to block that nociceptive input. So they really don't have a high pain experience.

So that's one example. Here's another real life example of builder in London who was rushed into, I think it was University College Hospital in London. You can see there's this 12 inch nail driven straight through his boot there. And he is writhing in agony. And they're trying to calm him down so that they can carefully open the laces of the boot and open the boot and as they do this they suddenly get the boot off and they realise that the nail has gone between the two toes and it hasn't cut anything whatsoever. (Laughter) And of course, he feels a fool at that point. And I'm sure the story has been embellished over the years, but that in effect is a true story. The moment he saw that there was no damage of course the pain went away. (Laughter) But in essence he had no nociceptive damage, but he was having a very big pain experience.

So that's the problem, you've got this lack of coupling if you like, between the two. And what really we've been doing over the years in many labs around the world using brain imaging tools, which gives you a wonderful capacity to look into the human brain and see what's going on, is we've been trying to understand what are all the different things that contribute to those signals coming in from the periphery, that come in on these two fibre type systems here. So they're coming into the spinal cord and then they go up to the brain and that's when you have a pain experience.

And what we've been trying to understand is, how is it, that if I change for instance your mood and make you little bit sad or make you really anxious about the pain or I distract you and get you to do a very complicated mathematical sum whilst I'm burning you and so I distract you. Or I try and convince you that this medication is absolutely fantastic, you're going to have a wonderful effect, so really build up your expectations. I can completely manipulate these different factors. And if I do that, these are all factors controlled by your brain. And so if I change the nature of your brain, before he signal's even come in. When they now come in, they're entering a place that's very different now because you're distracted, or you're a bit more anxious or you're a bit more depressed.

And by doing that, I change the way those signals are processed and if I do that, I change your experience. And so we can start to understand why is then that if you've got heightened anxiety, you're very depressed, you're very hyper vigilant to your pain, it makes it worse. How can we understand where that process is going on within the brain so we've got targets to try and block it. Yes? So that's the type of thing we're trying to do. Is unravel all these different things that we know are really important for changing the pain experience and get a neuroanatomical marker if you like for that.

So what I'm going to do is tell you a little bit about brain imaging first of all and the evolution of brain imaging particularly in the context of Oxford's contributions to that. And then give you a taster of the types of experiments we do. So you get a real sense of how we design these experiments in order to do just that. And at the end, I'll sort of alert you to some of the more worrying data that's just very recently coming out now of brain imaging work. That's saying, if we really do leave these patients, about 60%, untreated, unmet and they're just living with their pain day in and day out. Unmet, untreated, the consequence of having that constant barrage going in all day, is that you basically cause permanent potentially irreversible neurodegenerative and chemical changes in the brain.

Okay, and that's very alarming and that really then starts to put, sort of in the definition of a disease, pain in a new category, particularly chronic pain.

Okay, so can we actually do that? Well we have a range of different methods now. If I gave this talk 15 years ago, I would have one or two techniques I could tell you. We could look at the human brain now. We've got a wonder repertoire; very simply, they give you two ways of looking at the brain. You can either look at the brain as the neurons are actually talking to each other and that's in the sort of chemical electrical way, very fast. So those techniques we have again here in Oxford. These are techniques that we call electro `[[cephalography 0:17:36]]` or magneto cephalography. We've got centres that do that that give you a direct window on the electrical activity of the brain.

But of course once the electrical activities happened and the brain has sort of communicated to different regions, you've got to feed those neurons. And so you have a concomitant increase in blood flow to give oxygen and glucose to feed the cells so they can keep firing. And that is a process that takes about six seconds to occur. And we have other techniques that looks at the blood flow to those different brain regions. And those techniques give you great spatial, what we call 'spatial resolution'. We can see down to a few millimetres, exactly where that process is going on. That's very powerful.

And those techniques are the ones that I predominantly use which is a functional magnetic resonance imaging, which is basically an MRI machine with extra bells and whistles that allows you take this type of data. And there are other techniques called positron emission tomography. And together basically increasingly we're using these methods in what we call a multi-model imaging way. We're combining them all so that we can look at everything. Of course, we always want more as scientists, so we don't just want the blood flow, we want the electrical and the blood flow and the chemistry, because I want to look at every physiological aspect of how the brain works in that one individual and relate it to their symptoms and what they say and their genetics. And that's basically the new frontier now, is we're combining all these methods together.

So that's what we've been doing and that's the problem. So let me just go back a bit then and take you on a little detour about the brain. And how long and surprisingly long it took us to actually, first of all put the brain as the seat of where reason is. And the organ that actually processes sensory experiences like taste, sight, touch, sound etc and how Oxford has contributed to that.

So the very early attempts, well first of all they thought it was in the heart and initially – because that sort of made sense, you know it's pumping all this blood around and the blood is communicating to different sorts of the body. So there's a sort of logic to that if you're back there in early antiquity. Then they thought, well there's these big sort of holes in the brain full of fluid, these ventricles, maybe that's what is important. So you can just see here these early sketches of these divisions here in the brain, of these different ventricles. And people thought that this was where the different aspects of your awareness of experiences occurred.

So here's a more clear illustration of that where basically obviously the eyes, you can mostly – again the face and the head is where most of your sensory experiences come from. You think about all the things you experience, they are mostly around your head. You've got your hearing; you've got your smell, taste, sight. Touch is really the only one that extends beyond in the rest of the body. But everything else is all around your head. So it made sense. It comes into the front, all these sort of senses. Then it get passed to the middle ventricle where it's sort of reason and rational thought occurs. And then you lay it down into your memory system at the back.

And that persisted all the way; even Leonardo Di Vince made beautiful wax casts of these ventricles and labelling them in terms of again, these different divisions. But they were also questioning at the time the sense of that because they thought that well maybe all that sort of fluffy stuff around the ventricles, the grey matter, that they thought was just the sponge, shock absorbing, protecting the ventricles. Chances are that's got something interesting to do with all this and maybe we're missing the point there. And of course, there were classic things like Phineas gauge and accidents that sort of suddenly made people realise, actually it's that fluffy stuff that is the important part and nothing to do with these ventricles anymore.

Well now we come to Oxford and Thomas Willis who was the Sedleian Professor of Natural Philosophy, he really started to want to understand anatomically more about the human brain and also anatomically most parts of the body. So he very carefully chartered and if you're in St John's and the library, they've got beautiful original additions of some of his works and his anatomical drawings. And so really he was the first sort of guy – well many people did, but he was the first Oxford person to really put it on the map.

And it's a very interesting story because what they used to do, was they'd take bodies who had basically be hung because they'd been stealing bread or up to mischief. And do you know 'Dead Man's Walk' behind Merton College? Which was where I was an undergraduate. So that's where the bodies were brought along having been hung somewhere further down the Abbingdon Road. And what young Thomas Willis would do, is he would be ready there to capture the body because that was a wonderful organ to start doing his dissections on. And he would bring it down and he had a laboratory in a little alleyway. He was one of the tutors at Christchurch.

I was there for seven years as a tutor of meds myself there. And he was there – don't forget Christchurch was where the original anatomical library was in the University for Human Anatomy. So he would be capturing these bodies. He would bring them along and would dissect them and he was the first one really to start to show us about the blood flow into these different parts of the brain and to start really label up the anatomy.

It's very interesting; the place where he actually did his dissections was this little alleyway here in this building, so the story goes. And he would take them and very carefully annotate. This is now more commonly known as the Chiang Mai Restaurant. I don't know if you've gone to it. It is a very nice Thai restaurant. It might put you off your next pad thai, I don't know. But anyway, that's where, supposedly, he would go and do that, so he was a very important first initial person.

And then unfortunately we went through an era of madness. I just call it the era of folly. Where a Viennese physician called Franz Joseph Gall decided that anecdotally he would observe at dinner parties that people who had sort of very protruding foreheads or unusual bumps, he sort of noted that that seemed to go with a particularly personality type. You know, they'd be either extrovert or they'd be very shy. So he created this potty idea that the sort of bumps and lumps in you skull, indicated something about what was inside and that indicated your personality and your character. So he started to carefully characterise and number and name the sort of pattern of lumps and bumps basically across your skull. And this is called phrenology.

And this persisted staggeringly all the way through the Victorian period, because the Victorians with their wonderful enthusiasm for engineering developed, never questioning the original idea, just went on and made better and better instruments to measure it. So they had all these fancy machines in your parlour that you could stand on and it would give you more accurate measurements of your lumps and bumps and relate that to your personality and character. And this went on and on and in fact, it went on until about 1920 something or other. The Phrenological Society of London was finally disbanded, which I think is quite staggering.

So that's sort of the era of folly and that persisted for a long, long time. And you've probably seen in shops. Do you see those little china heads, that's the phrenology map and that's where it comes from, this idea, the lumps and bumps.

Okay, well then we had Sir Charles Scott Sherrington another great Oxford man. He actually got around, this is actually him at his window at Quays College Cambridge. He was also in London and of course we all claim that it was in our institutions that he did his noble prize winning work. I don't think that will ever be resolved. But anyway, he was great and I particularly like him because he has two great contributions that fit exactly with the type of work that I do. And it also reflects how science was in those days where you basically were polymath and you had the luxury and the leisure to do lots of very different things and not be so focused as we have to be these days.

So he not only was the guy that – in those days again you could ethically just play with yourself, and cut yourself open and measure things. So he was recording from these pain fibres and burning himself and doing things and noted these specialise pain receptors. So he was very important for reflexes and the idea of nociceptive reflexes, you stand on a nail or a drawing pin on the floor and you reflex. He worked out all that, that's largely what he got his Nobel Prize for. But he also coined all these ideas about pain and really linking this idea that we've got these specialised receptors in the body.

But he also was critically important for the imaging and the bloody flow and the brain activity coming back to the brain. Because also, he was the first person in the most elegant of experiments using absolutely no equipment compared to what we have these days. He basically was the first person to describe and confirm with evidence that the amount of brain activity you have is in a one to one relationship related linearly to how much blood flow goes to that part of the brain. So this idea of coupling electrical neural activity to blood flow, Sherrington proved. I won't go into details as to how he did that.

So what this is here, just for those of you who haven't seen this. This is actually how profused your brain is. This is putting a cement mixture into your veins and capillaries, after you're dead, and then letting it set and then rotting away all the rest of your grey matter. And that's your three dimensional architecture of your blood effusion in the brain. It is a highly profused organ. You can see in the grey matter it is very much more dense here, than in the white matter.

But if you've never seen that before are you surprised at the amount of profusion, it is an extremely highly profused organ. So it doesn't take a rocket scientist to think, well if it's that profused, probably the blood flow is really important for doing something. And indeed it is, it is the one that's obviously going to be feeding that neural activity. So he showed that coupling between blood flow and metabolism.

And then of course then, subsequent to that, we still didn't have non-invasive ways of looking at that. We had the science, but we didn't have the techniques. So the most common way that people tried to map the brain and work out which bit did what, was to in surgical procedures, this is Wilder Penfield who is a Canadian Neurosurgeon, he would during operations, probably completely unethically, poke about. And so rather than getting on with the job of chopping out the bit that was causing the epileptic seizures. He would spend a little bit of extra time recording and seeing what the person experienced.

Because the thing that's very little lucky and serendipitous about the human brain is once you've gone through and opened it, actually inside the brain there's no pain receptors so you can poke and prod and it won't hurt the individual. So you can wake them up and then you can record or you can stimulate and you can then ask the person, well what did you experience? So a nice illustration of that for instance is, if you stimulate the position marked 11, the woman fully conscious described curious sensations. The recollection of a woman, the recollection of the woman calling her child is evoked by stimulating there. And at a circus `[[?? 0:28:03]]` slightly mad I think.

But anyway, mostly what he did was map which bits gave you different sets of experiences. So this think called the homunculus, a particular part of the cortex will be where I'll feel my face being touched. And then my trunk, my arm, my hand, my legs, my feet. So we map that very carefully. The same for the motor bits, stimulate that, I move my arms. Stimulate another bit, I move my leg. So mapping all these things. So obviously that was fine in the 60s up until then, but then you know that had to be dropped.

And we really had to wait until we had magnets and this is where Oxford comes back in again. So Sir Malcolm Wood was academic in the physics department here in Oxford and I believe he used to live in North Oxford, I think on Northmoor, I'm not quite sure. In his garden shed, he would be practicing with the development of super conducting magnets. The idea that you could keep the magnet at a high homogenous magnetic field strength without having to constantly be supplying electricity.

So we had electro magnets then, but we didn't have what we call super conducting magnets. And so he developed that and from that formed Oxford Instruments which is the main supplier for all then the clinical MRI machines around the world. And so the development of these magnets opened the path for what is modern imaging, both diagnostic structural imaging and obviously consequent to that, all the other ways we can use those techniques to look at the human body.

And it's just one of the serendipitous things again why magnets, why the body, well it's just again, one of those lucky things. Most of what we're made up of, the protons in our water, carbon, phosphorus etc, have this property of what we call magnetic spin. So if you think of it that we are able to interact with them inside a magnet, so they lend themselves to being seen if you like, once you're inside a very large magnetic field, so we can manipulate them and we can look at them. And it's just one of those very lucky things.

So again, from that we were able to develop in Oxford again, in biochemistry, George `[[Rada 0:30:05]]` and others were the first people to really start the invivo application of imaging and

the fact that we knew that we had these chemicals in our body that were susceptible to magnets. But it was again in the biochemistry department here that the first experiments were done to prove and show that yes indeed we can start to actually see non invasively in a living thing all those chemicals. And that was just fantastic. That's suddenly opened up non-invasive invivo work.

So it's a great history and tradition here in Oxford both in terms of magnets and application of non invasive technology. And indeed the very early experiments that really brought together what Sherrington had done all those years ago. This idea that the blood flow was coupled to the neural activity and the change that you could produce on an image due to the change on the oxygenation of that blood was again done in biochemistry here back in the 70s.

And it took then a few more decades later, another labs like Harvard and obviously imaging itself was invented by Sir Peter Mansfield in Nottingham University in the physics department there. He won the Nobel Prize for that recently. So we've got a great tradition in the UK for this and Oxford has been a huge player in that evolution.

This is our scanner here and in essence what you're doing with functional imaging is you're putting somebody like yourself inside the scanner, we lie you on your back and we put you in. Your head goes on there. Inside you go, you can see it just looks like a standard clinical machine. As I say, it's got these extra bells and whistles and then we'll have you do something, like look at a visual stimulus or in my case, I'll burn you. (Laughter) And you will experience pain and your brain will activate and then there will be this coupling of flood flow, a change in the blood flow to that part of the brain and I can capture that and I can see where it is and I can label it up.

And so that's basically the technique. The advantages of it are that it is non evasive, I don't inject you with anything, it all relies on just these serendipitous endogenous things that happen anyway in your brain. As long as you've got no metal in you, I can put you in again and again and again, which means that we can do patients over time, we can put drug interventions in and we can monitor. It's very powerful and as I say non invasive. And it gives you this great spatial resolution. So it's a very powerful tool and since this invention that's really where we opened up that black box of the human brain and it's just taken off as a massive area of neuroscience.

We have again these other techniques, all available in Oxford, different ways to look at the human brain in action. They are just getting more and more plentiful and basically in my lifetime certainly, we're going to be imaging genetic expression all the way up to perception. So we can pretty much image everything non evasively and that's increasingly the way one wants to move things because you want to look at the person don't you and you want to relate to what you see to what the person actually is telling you. That's the Holy Grail. We don't always want to always be extrapolating, from taking tissues out onto the dish and putting it back in. If we can do it all non evasively, that's obviously the best.

Okay, well back to pain now then. This is what will happen to your brain. If I took you, put you in my scanner and burnt you on the back or your hand, you would activate all these brain regions. And very simply, don't worry about at all about these fancy neural anatomical names, that's not relevant here today. I just want you to get a sense of what type of brain regions you activate and why.

Because if you think about even just a paper cut. I am sure all of you when you've opened an envelope, you've cut yourself yes? So just think what you do when that happens. One, you are suddenly aware of where it is exactly. You're aware it is a cut type sensation and you're aware of how intense it is. And you associate the thing that caused it, with what it is, "I mustn't do that again, that was silly of me, I should use the letter opener." If it's particularly unpleasant for another ten minutes or so, it's sore when you touch, you'll avoid it, or you'll be a little bit careful to it.

You do all those things and of course they're all underpinned by different aspects of brain processing. Different bits of the brain are basically allowing you to do that. So you'll have

bits that are what we call the sensory discriminatory bits, the bits of the brain that tell you where it's coming from, it's on my finger, it's not on my toe. They have bits which tell you what type of pain it is. It's a cut, it's not heat. How intense is it?

Then you'll have the troublesome bits, which in an acute cut like that, aren't so problematic, but when you're in the chronic pain setting, become very problematic and that's the effective motivational cognitive. "It's taken all my attentional resources, it's just hurting. I'm not working anymore, I've lost my job, my family structure has broken down, etc, etc." And those bits again, all underpinned. So very crudely we have a core set of brain structures that underpin that multi-dimensional experience which gives you the sensory discriminatory arm and then the effective motivational arm.

And here's some real life examples now. I am going to give you a taste of some of some the experiments. So again, if you still don't believe me that this technique works, this is the first sort of proof. If we take again, yourselves and we put you in the scanner and we burn you with a higher and higher temperature, 35 degrees, 47 is about pain threshold generally, 47 degrees. So you're up to 50 degrees. Can you just see that on these slices – now all the data I am going to show you from now on, if it's more yellow, it means it is more active and so that's bad. Okay, the brain has got more and more excited about processing these signals.

So you can see can't you, as you take the temperature up, you become very much more excited in your brain? Yes, it becomes more active. So it definitely is recruiting more areas and alerting to you the fact it hurts. Okay, so that's nice, that's sort of objective evidence, that goes with the nociceptive input in a linear way that also goes with the verbal report, that it hurts more. But we all know don't we, that we've got different pain thresholds, yes? Who thinks they're a bit macho and they have a very high – you know they can take anything? Good for you. Right, anybody ginger in the audience? Ah-ha, yes, you have unusual pain experiences, genetically too, it's well understood. Okay, so the rest of you are wimps, is that correct? (Laughter)

Right, so this is this experiment. Take a room full of people like here and give everybody on the back of the leg the same temperature. Let's say 50 degrees. So it's definitely going to hurt you. But as you would expect, some of you will squeal and say, "Ah that is awful on a rating out of ten, I am going to give that nine. That's very, very painful." And some of you will be telling me, "That's absolutely fine, I'd say that's six." And the question is, is that true? It's again, going back to this subjective reporting of pain. Can I really believe that the people who said, "No I didn't feel anything." They're not just blokes and I'm a woman experimenter, they're trying to be macho – it has happened, many times. Is it true what they're telling me?

So the imaging can provide that objectivity because indeed, if you said it really hurt and you're in the high group, look what happens to your brain. Very, very active, yes? Here. And if you're in the low group, you don't activate it as much. Of course, the interesting question is why? Why is it that if you're in the high group, you set off all these brain regions? Presumably, a lot of it will just be genetic, it's just right at the get-go, at the point I am putting the temperature in, you've got an unusual, a different sort of threshold of your receptive, those nociceptors and they're just sending the signals in very dramatically.

But that won't be the whole story. Through childhood all the way through to adulthood, when you do this experiment, many things will change the way you've been wired up. Many things will influence that wiring up. Many things will change the tone of it. And so this nurture nature thing will start to contribute to what fundamentally makes you and your central nervous system the way it is as an adult. So the joke I always say to my children when they fall over in the playground, I just ignore them, tell them to get a grip, get over it. So I am wiring them up to be like this.

Which is not true, Paul's my neighbour and he knows that's not right at all and we don't do that. But that in theory is it. Over fussing and nurturing and all the rest of it – I am not suggesting that one shouldn't do that, I am just saying that those cultural influences that we do, of course it's

going to change things as the central nervous system is developing. And we're only just now in neuroscience starting to try to grapple with those very hard, more societal influences on how the nervous system works and how that fundamentally changes who you are. So that's something that again is an area of active research now. What's going in to making those two groups so different? I'll come back to that point.

Well other things that will influence the amount of activity is just your sort of emotional state. If you're a bit more of an anxious one and that's just your disposition or you tend to always approach things with a slightly pessimistic sort of approach, it's going to influence how you're going to experience things. So what we want to do in these sets of experiments was look at how emotions can impact and specifically how anxiety and anticipation will influence those nociceptive inputs to change the pain experience.

And I am going to spend a little bit of time describing this experiment because it will give you just a real taste of how we design experiments. So this is a sort of real life example. So again, take healthy people like yourselves, put you in the scanner and I am going to give you a visual cue and about ten seconds after that cue, you're going to experience a thermal sensation. And I want you to remember what you see to what you get. And tell me afterwards okay? That's all you're told.

So in you go and I give you a triangle to look at. And about ten seconds later, I give you a lovely warm low temperature. So you think, "Well that's very nice." I get a triangle, I get a lovely warm sensation. And then after a couple of those, I'll give you a square and actually I'll do the same. So you think "Okay I have to remember two symbols for this one warm sensation." And I do that a few times. Lull you into a sense of security. Then, do the square again, but this time I give you this one, a very high temperature.

So, on a ten point scale, when I've thresholded your strong pain to be about eight, I give you eleven. And we keep that quiet from our local committee okay? So we burn you very badly, okay? And I then do a few more of these. I do that another two occasions. That's it. And then I never do that one again. I just keep on giving you these. But do you know what happens?

What do you think, every time you see the square, you think "Oh no, what is she going to do?" (Laughter) "Is it going to be the nice one or is it going to be the bad one." And do you know what we do, we always do, particularly British people? We assume it's going to be bad. We prepare for the worst possible outcome, up goes our anxiety ratings. So it's a classic manipulation, it's a behavioural conflict design where you're in this conflict. You don't know which one it's going to be, better prepare it's going to be the bad one. And that's what we do.

It's a standard trick and it works, because you can see. I have made your anxiety go up. Of course, the interesting question is, what happened to your pain? When you're more anxious, yes? High anxiety, but actually I've given you exactly the same warm sensation. Well of course, your rate it more, yes, significantly so. So I've given you the same temperature, it's coming in from the periphery at the spinal cord, but the brain is now in an anxious state. And the way it processes that signal is very different and that contributes to a heightened pain experience.

And then of course we're imaging all that, working out when you say it's more painful, is it just like turning the heat up, is it just activating all those brain regions or is there an exquisite place in the brain which is where anxiety turns the gain up. And that was indeed what we showed was that there was an exquisite place – don't worry about where it is, it is a little area actually around the hippocampal formation, which you think of often as memory, but actually it's exactly where this manifestation should be based on a lot of other work that had been going on in preclinical models, and that's what you do. Is you activate this structure that is again, part of this sort of anxiety amplification network.

We've now translated that into patients. We've taken patient's rheumatoid arthritis and we're squeezing their painful joints, and what we have shown is that those patients who actually have a very low disease activity but they complain of more pain and they seem to be more depressed

as well – we they are more depressed. The manifestation of that is through that structure. So ten years later, we've been translating that now into patients and understanding why is it they've got less disease activity, yet they've got more pain? It's because of these mechanisms in the brain that's gone wrong in that particular group.

So again, diagnostically, we can translate the basic science into hopeful new ways of looking and unravelling and diagnosing or helping to diagnose the pain behind complicated patient types.

Well another sort of major area of interest for us is this concept plasticity, so I've described the idea that that transition from acute pain which is good into chronic pain is because if you've got that constant barrage coming in all the time of nociceptive signals, something is going to change. The system is going to respond to that, that's a very standard concept in neuroscience. And it is reflected in that picture there that plasticity and sort of sensitisation or amplification is basically a change in the pattern. It could be a change in the spatial pattern or it could be change in the magnitude of activity. But either way it's a change. The system responds, it melts, it becomes plastic, yes?

And that's a very normal good and adaptive response in many things. So a classic example would be post-stroke, another part of the brain will take over the function to enable recovery for say a motor performance. And so you can use it in a good way. Unfortunately in chronic pain it's maladaptive, so the plasticity that's sets up is problematic. And there is this phenomenon called 'central sensitisation' which is a fancy term for just, if I have bashed your thumb a lot, constantly with a hammer, and I'm constantly sending in signals, this plasticity occurs. And it underpins these classic symptoms that we see in patients. Not only just spontaneous pain, but if you just put a brush on, just a normal brush, this is burning pain for them.

So this is a normal, what we call a 'beta input', this is the touch system, this is not the pain system, but now somehow the touch system is piggybacking onto the pain system and giving them an excruciating pain, so clothes and jackets and lying in bed at night is intolerable because it's causing, due to that mechanism, this problem. And this really, this physiological change of plasticity is what underpins all chronic pain states. And that's the new sort of knowledge and that's the bit that we all try and work on very dramatically.

If you don't believe me, this is patients taken from pain relief here in Oxford where again, we've just taken a little brush, like a paint brush and we just stroke their arm where they have this problem and look at their brain activity. This is not the touch system; this is the pain system active. So again, a normal touch just sets everything off on fire. And with that they have burning pain.

So it turns out that one of the most interesting and important areas in the brain for keeping that central sensitisation going, if you like, feeding it. And again this is the big thing that underpins all chronic pain so we can stop it, we've done it basically. Slight exaggeration, but you know, it's a very important role. It's this system that is one of the older systems we have in the human brain and it's really exquisite and it's unique for pain. In that in the brain stem, which is this part of the brain here, we have this beautiful and very old, because the brain stems are a very old structure, all the rest of it has sort of evolved later on in the human brain.

We have this system called the 'descending pain modulatory system'. It is a system that is unique to pain and it is there to modulate pain. Why? Because pain is really important. And when you're a caveman and you've been chased by a lion and you've had half your leg bitten off, you don't want to be distracted by the pain and stop. You need to block it to get away because the consequence is going to be much worse. So we have set up and we have a system in our bodies which can very powerfully modulate the pain experience.

And it does it through this brain stem and the way it does it, is it communicates all the way down, to that entry point in the spinal cord where those signals are coming in the periphery and it blocks it. So that's what we call the 'good' descending system, what we call the 'anti-nociceptive system'. That basically releases endogenous opioids, that's what it does. The enkephalins, the

endorphins that we have, that is the system that you tap into in these situations of arousal and you communicate down and you block the signals coming in. So if they're not allowed in, they don't come up. If they don't come up to the brain, you don't feel pain.

That is exactly the system you tap into when you are distracted. In sporting battle when you're blocked, in the placebo effect, which we'll come onto in a minute. Now unfortunately it has a very bad arm. It also can communicate down in a pro-nociceptive way and turn the volume up. Now you might think evolutionary, why on earth would be so stupid as to set up the system to do that? Well when you have hurt yourself, you want to be reminded that you've hurt yourself, so you that you alter gait, you protect it. So by amplifying it a little bit, it just keeps it fresh in your mind that something is wrong.

So again, unfortunately, through the same system, through a different cell type, there's 'on and off cells' we call them, it can communicate down and it can turn the volume up. And the very recent realisation is that it is that system that underpins this amplification process of central sensitisation. And so if we can block it, we're well on our way to stopping that major physiological phenomenon that underpins all chronic pain. So we've been doing the first applications of that in the human brain and imaging that in a way that we can mirror some of that and sort of do it. Obviously, there are ethical limitations on me as to how much I can inflict pain on people and fortunately, you'd be amazed at one we can do. (Laughter)

But one of the ways that we can mirror some of these symptoms without having to go to patients, which obviously it's troublesome for the patients – we do do patient studies but they come with extra confounds. That sometimes when you want to do a very specific question, you want to not have those confines, you just want to ask the one question. So in fact, interestingly, the way we can elicit this plasticity safely, that reverses, is to get chilli peppers, not like that obviously, I don't just get them and rub them on you. But basically, in a pharmacy, you can extract the active ingredient of chilli peppers, Capsaicin.

Because Capsaicin is a compound that binds to a particular nociceptor that's part of this family that we've now discovered recently in the genetic side of pain, that is a family that basically is what we call a 'polymodal' receptor both the chemical combined to it, but also it's what heat communicates to. That's why when you eat chillies it's hot, that's why you have a perception of heat, because it's the same receptor, that heat, when you burn yourself, thermodynamically talks to, the same receptor is what binds the active ingredient to chilli pepper and so the percept is heat and burning pain.

So what it does is it binds and it sends these signals in for an hour. And after an hour of leaving the cream on, burning away on you, we set up some of those changes in your spinal cord and your brain. Now, be relaxed, when we wipe it off, it all reversed in about an hour, so it's safe to use. So we can mirror that. So basically, what we showed is the first evidence in humans that indeed this little bit of the brain stem does become recruited. We validated that by taking one of the standard drugs that's used to treat neuropathic pain or pain of injury that sets up this phenomenon, a drug called 'Gabapentin'.

And we've shown that indeed that brain stem, if we bring the drug in, we've shown again, confirmed that the brain stem becomes very excited when you move into this centrally sensitised state, so this is confirming our first evidence. So it's always nice to do an experiment again and get the same answer. So that's nice. We go from no central sensitised state to central sensitised state and the brain stem becomes very lively, but the drug blocks it.

So that's all very exciting, it's all confirmatory evidence and we've just published another paper, which I won't go into, it would take a bit too long to describe, that causally really confirms that that brain stem is a bio marker now for central sensitisation. And we've again translated that into patients and in this study, in patients with osteoarthritis, hip pain, who are traditionally not thought to have a lot of central problems. Everybody just thinks, "Well take the hip out and they'll

be fine." But in a certain group they're not fine actually and the pain's still there. Why? Because they've lived with that pain for ten years and for a certain group, they've made that transition to chronicity.

They have set up some of these changes, and indeed we've just shown that if you pre-select the group that are likely to have that as problem, well surprise surprise, again that little marker, in that little brain stem, it's on, in that group, yes? So again, we're developing and parallel the sort of basic science understanding of the mechanisms and then taking it into the patient groups to understand what is going on. And this is a huge target for drug discovery. We do a lot of work with industry, trying to help them use imaging as a way to better get drugs that are most likely to work and not fail when they are taken out into large patient cohorts and pick the winner. And imaging has a very important role to play in that and we do a lot of work with industry doing just that.

Well now I want to finish with a few fun experiments of the more cognitively emotional stuff. And attention and distraction sort of the cognitive modulation of pain. You're all aware if you ever have suffered some pain disorder, maybe you've tried to distract yourselves by listening to some music or watching a good film. And to a certain extent it can work very effectively. Why? Well again, we come back to that beautiful endogenous system that we all have. If only we could all learn to tap into it better. Because that is the system now that we're looking at the good arm, the anti-nociceptive arm, the blocking.

And so again, this idea, you change the context, you change the pain, here's a very old illustration of somebody having a nasty surgical procedure pre-anaesthetics, you can see the writhing agony, bring the beautiful woman in and a big kiss and everything is fine. So you change the context of the situation, change the cognitive set and the distraction and the pain will be different.

And we did some very early work again showing that when we had people be distracted from their pain, not only did their pain rating come down, so now they're not attending to their pain – I won't go into how we did it. But you can see on their rating of pain, it was eight. We've managed to bring it down to about seven, why? Because we've got that little system again and the brain stem active.

Of course, the interesting question is, when I am distracted and thinking about something else, think of it as a driver in a car on pedal. What you're doing is you're either putting your foot on the accelerator or you're not. Or think of it as the brake maybe. So something has taken the foot off the brake. Allows that to activate, it talks down, swooshs out endogenous opioids, blocks the pain, less comes in, you feel less pain, it's as simple as that.

But what you can see across individuals, as some people are great at it. So this is what we do often in science, is we will plot a change in one parameter versus a change in another. So that's the change in the amount of activity in the structure, versus the change in the subjective rating. And you can see some subjects, if you're really good and you were excellent at distracting yourself, you managed to move yourself two points on a ten point scale, you went from eight strong pain down to six moderate. Because you were really able to take the foot off the pedal and activate that structure.

Some subjects were absolutely rubbish at that. Why? We don't know, but that's an area of work. Can we make these people become these people? Can we train them to access this system that we all have.? And I'm sure we can and that's the basis of cognitive behavioural therapy.

So here's the modern equivalent of it. You want to train and get used to psyching yourself and this is how now really you use your endogenous system in everyday life. This is taken from the recent World Cup. I was amazed when I was digging out these pictures that just the common methodologies used for inflicting a nociceptive input (Laughter) was not just once, but it seems to be (Laughter) a clear strategy used there. But no matter how much nociceptive input was there, those guys – the goal is the try, they're blocking their endogenous system. I feel we should use my

experiment as a pre-selection process for the England squad, going into the next one. (Laughter) That's all we need to do. Exactly, yes. Okay, well I'll skip over that for time.

The other topic under the sort of cognitive umbrella if you like is this idea of re-appraisal and this is the latest ways were thinking about things. And what I mean about that is that it's all about the meaning. So let's take an example. Any of you sporty and do long distant running or anything, or used to maybe? (Laughter) Maybe that's the more relevant question. Some of you are admitting it.

Okay, so if you can remember, that very pleasant feeling, you've done maybe a 10K run or you've played some rugby and the next day you're stiff and you're sore. It's physical hurt. But actually it's quite nice. It's not because you're sick and a sadomasochist, it's because it's associated with something good. Again, go back to child birth, yes it really does hurt, but it's associated with a positive outcome so somehow you don't mind it so much.

So again, whilst we're in this position where we've not got very good therapy to treat pain, ways that we're looking at it, is to say well maybe we can just change the meaning. Maybe we can have people re-appraise the pain and think of it in a different way. Change the hedonic value if you like from not being an unpleasant hurt, but into being something pleasant.

And one of the ways that we've been looking at that is to look at religion. I don't know if any of you came across this because the press went mad over it last year when we published this one, it was actually one our hardest studies to publish because of it being a bit controversial. It wasn't controversial in what we had found; it was just because it was obviously a study with religion which is a sensitive topic.

Basically, what we were looking at, is this idea that if you are a religious person and you've culturally been brought up in that way and you've used religion as a means in a positive way with a concept of a benign and comforting God etc. Then somehow you've developed different strategies of how to cope with different situations. So chances are, in a situation of pain and suffering, you will tap into that system. And that has to be driven by some neuroanatomical process, particularly if you've been a lifelong person cultured in that way. So it goes back to that nature nurture thing I was talking about.

So what we did in this design is, we took practicing Catholics, not just tick signed up Catholics, people who are very spiritual – not that Catholics aren't spiritual. (Laughter) I say that as a Catholic. So people who very much involved in that and clearly use religion a lot, daily prayer etc. And then people who were atheists. And in a very standard design called a 'mood induction' design, where we basically give them pictures that are meaningful in the context of their religion or not and matched. So both groups, the atheists and the practicing Catholics had 30 seconds to look at either the Virgin Mary or, this is the lady with the `[[Urman 0:56:41]]`. So we spent about six months trying to get the pictures just right and matched and going into which one and resourcing.

So basically, you're now in a state where if you're a practising Catholic that obviously has huge associations of meaning and you go into that sort of state, if you're an atheist it doesn't and then similar sort of reaction to that one. So after this mood induction phrase, we then electrocute you with some pain. In fact when Sandy `[[?? 0:57:06]]` was doing this on the news quiz, she said "I'm sure in Oxford they're just doing it as a cheap way to electrocute Catholics which seems like a good idea." (Laughter) But that was not the hypothesis or reason behind the experiment.

Anyway, we did that and then we took all the ratings, how much did the pain feel when you were say a Catholic, in that condition versus that condition, same for the atheist. All sorts of measures of effectiveness ratings. And basically, surprise surprise, we found that compared to the atheist group that the religious group did indeed get analgesia when they were looking at the Virgin Mary compared to looking at the lady with the Urman.

And it was specifically via activation of a particular structure in an area of the pre-frontal cortex which is an area that I have just skipped over the data for time, but a series of experiments both by us and by others. Outside the religious area but looking at what these particular pre-cortical regions are doing in the context of re-appraising. So when you can emotionally detach from something – and again, there's been a lot of work looking at emotional detachment and it's mediated by activating this tiny little structure called the 'ventrolateral prefrontal cortex', which basically sits about there. And if you can detach yourself from that, again when you have different situations of control over something and you perceive that you have more control over others, all mediated via the structure.

So these are the hypotheses that we set about that people who are religious tend to have, what we call, a lower internally [[?? 0:58:26]] control because they spent their whole lives offering it up so to speak. They can emotionally detach. They are used to the idea that somebody else is controlling, rather than being very much a control freak and other work had shown that this was an exquisite structure for mediating that and surprise surprise, that was exactly the structure that only the Catholics activated in the context of this experiment.

Moreover, and this is very powerful in science, not just to show the region, but to show that that region and the amount of activity in that region correlates with the behaviour. So the amount of activity and that tiny little structure correlated with the amount of analgesia that they got. And as I say, it was a real devil to publish this one. But in the end, we got it out because it just being so controversial.

It just contributes to that concept that these societal influences, these ways that you are brought up, they will change obviously the way you are wired up. They will change the way you approach certain situations and how you will utilise that. It's not unique to religion. I could have picked for a football fan, David Beckham. And I probably would have got similar sorts of results. We're not saying it's specific to religion, or anything about belief states. We're just saying that something that has been lifelong cultural influence in a positive way that you have used to benefit you, will change the way you are wired up. And sure enough you can't argue the fact, one group activated that and the other group didn't. That's the data.

So that's just a little taste of these new areas that we're going into which are slightly more complicated type of experiments to design because you're looking at some of the sort of more – well they're perceived as woolly, but they're not, they're just harder in terms of societal and nurturing influences.

Of course the placebo effect, again thinking about belief is again another classic belief type manipulation. You're changing the meaning. You're manipulating in a conditioning way that this drug is going to work. You condition a person to expect a positive outcome and then you give them a pretend sugar pill and because they've conditioned to expect it to work, what do they do? They kick in those structures. And it turns out some of these structures, like we've just shown, that ventrolateral prefrontal, these are the structures that become important. And what do they do? Where are they communicating to, to drive placebo analgesia? Guess where? It's the descending modulatory system; it's that brain stem again. We're back to that endogenous opioid system.

And many experiments have shown exactly that, that the pain and true opioid but placebo you're activating again these pre-frontal areas and they're doing it via that descending system. So if you don't believe in placebo or you thought it was just hand waving, I'm afraid there's about ten years of 50 odd experiments proving that not only just from functional imaging but now from chemical imaging, showing it is via that endogenous opioid system. It is a really powerful effect. Really powerful. It's the bug bear of drug discovery. Because you're placebo arm is just so good. You'll be amazed at how good it is compared to a lot of drugs, some of which many of you are on. (Laughter)

So that's there we are with placebo effect. And again, it's all part of this cognitive umbrella of changing the meaning, changing the association. And it opens up new targets. Now we know where these are being mediated, the interesting thing about them is that some of these frontal areas, actually we can we reach with some of what we call non invasive or interference methods. Again, ethical ways we're allowed to tinker with the human brain, in a way that we can zap you through your skull, through techniques like transcranial magnetic stimulation or direct cortical stimulation, we can just get it going a little bit. We can just start training it up.

And the beauty is, some of those areas that we're identifying is really important for changing the meaning of pain. So if you like, we're taking the hurt away without changing the signal, but it's a good therapy potentially. We can access with some of these new technologies we're got, so that's again a new and current line of work going on in the laboratory.

Okay I'm just going to skip to this one, pain without a nociceptive input. What about these people who are the malingerers, they are pretending they are in pain. Can we use imaging as a lie detector? Well indeed there is a whole neuroethical lecture I could give you on the use of imaging for things like that and we're doing a lot of work with the practical centre for neuroethics here in Oxford with Julie [[?? 1:03:37]] developing imaging for trying to answer questions about why do people make certain moral judgements as opposed to others? Why is it that we have certain biases and strong beliefs, how do you change a belief that taking some cognitive enhancement is a bad thing, why do we think that? What is it that would change somebody's belief states and think about something differently?

These are all things that are accessible now by imaging. But they have societal ethical implications of, do we want to have the techniques out there being used? And let me tell you, there are many, many venture capitalist firms funding labs in the USA that offer this type of imaging data as data you can go and use, to using your medical legal cases for lie detection, criminality, discrimination etc. My own view is that they've got enormous potential to do that, but we're not ready yet.

Because everything I've shown you has been done with group data. In order to be confident that the data is meaningful and that this is how any group of 12 people would behave if I took any 12 around the world. We have to use a group at this point. We are not ready yet to do it on the individual. That's the next era. Yet these companies offer that as a service. And I think they will probably unfortunately give us a bad name before we're ready. But they do have the potential to deliver and be used in these situations.

So pain without a nociceptive input is a classic medico-legal. They claim they've got whiplash injury, medical insurance cases etc. Can you put them in a scanner? I'll get a request pretty much once a month to do that. We don't do it, for those reasons I've just described. We will be able to soon.

Well some of the ways that people have fun tackling this, is to look at situations when you feel a pain like state but obviously you're not getting any sensory input and that would be – one of the first attempts to do that was to look at empathy. And it's a lovely experiment done by [[?? 1:04:21]] London, and what they did, is they took women. And they chose women specifically, sorry to the guys, but they thought that the women would be more empathic to start with. So they put the women in the scanner and they imaged their brains whilst they were receiving the thermal pain. And you get all those brain regions on.

Then they took the pain device off the women and they put it on their partner's hand. And the women are lying in the scanner watching their partner at the end of the scanner being burnt. And they imaged the women's brains watching the partner being burnt. And what did they find? Well they found that the overlap was pretty substantial. The green is real pain for the individual female; the red is where she activates when she's watching her partner being burnt. And the interesting thing is – don't worry about again where, where they overlap is all the sort of effective – remember I described that effective arm of pain? The effective emotional arm. That's where the overlap is.

Fun experiment. It would be lovely to have put the men in and shown maybe, I don't know, I won't say it. (Laughter) They did do another experiment with men which was the [[?? 1:05:26]] one and just as a digression I will tell you about that because again it was a great experiment. But let me just finish the women's one. What they also noted was that the more empathic the woman was towards seeing her partner being burnt, then the more active these emotional structures became.

And the repercussions of that, they're actually quite important. You know, if you are a carer looking after a patient with chronic pain in your loved one or an empathic physician. You're not just there as a blank non responsive participant, you are activating enormous sets of your brain every day. And if telling you the consequences of all that are true, then this is going to take a toll as well. So fun experiments, but they have important messages to say as well.

Now the [[?? 1:00:00]] one was great. What they did is, they got actors in and they had men and women as the participants and the actors came in and they were doing some sort of gambling type task. I might have the details a little wrong. But the story goes like this. And the actors were chosen deliberately, some of them to be cheaters. And then the men and the women in the group would work out who was cheating and who was a bad person to play with.

Then they would put the men and women in the scanner; image their brains whilst they watched these actors being burnt. Now when the people who were known as being the cheating actors were being burnt, the men activated all the pleasure centres. (Laughter) So the [[?? 1:06:51]] the [[encumbrance 1:06:52]] they had true [[?? 1:06:54]]. The women didn't interestingly. So again, fun experiments, repercussions. War, politics, who should be running these countries and making decisions with regard to that. That's the data. I'll let you make the decisions. We could talk about that over questions.

Okay, so this idea of social hurt, this idea that emotional hurt, abuse of your partner, etc, you know, what happens? If we can extrapolate there, again some experiments have been done to look at this and again you're activating some of the structures again that physically the pain will activate. So this idea that these more sort of woolly emotional social hurt, they really do. They tap into the central nervous system and they will activate certain structures. And if you remember this terrible when Beckham got sent off and we lost the ability to get into the final there against social emotional hurt. We've all experienced it in different situations. It will activate and it activates and overlaps with your pain centres.

Well the last few slides then, again a bit of fun about new directions we're going in. Relief. Relief is obviously what we want. And we've done a lot of work looking at gold standard drugs and how they're working in the mechanism of action. But again, I want to encourage you with trying to think about relief differently and encourage people to think about relief. For a drug to be approved, it has to go through a certain criterion by the FDA and European authorities and they're very obsessed with uni-dimensional intensity reductions on a certain scale. When a patient comes in and they say they have relief, they don't describe it as "I've got a 40% reduction on my pain intensity scale." That's not relief.

Relief is just like pain, it's a multi-factutorial experience. A small relief in intensity that buys you maybe the ability to go and play tennis again and the knock on consequence of how that makes you feel, very different. So again, it's not a simple thing. And what we're trying to do is understand the neuroscience of relief to open up the discussion, the debate to think about relief in a more intelligent way.

It's a bit like predicting the weather from the air temperature. You can't do that. It's just not that simple. So that's a new area we're going in and we've used a lot of drugs, opioids and things and again I'll just skip over this for time.

But one of the areas we're interested in, it goes back to new areas of targets. Is this interesting observation of just when you think about relief, and when you have release like state it's quite

pleasant. But the pain and pleasure system have a remarkable degree of overlap. This is a fun review that you might want to read that we wrote that summarises this. And Jerry Bentham had this idea. Nature has placed mankind under the governance of two Sovereign masters, pain and pleasure. It is true. On the hedonic value, we swing. Yes, we're an equilibrium and we seek pleasure and we avoid pain. So we're homeostatically at a hedonic equilibrium. That's how we live our lives.

Now what we've been trying to do is make the hedonic value of pain pleasurable and we've done a few experiments doing that because you're not expected to read this table, you're just meant to be impressed that there is a big list of brain structures here that activate at a systems level whether you are in a pleasurable rewarding state or you are in pain. And that probably really surprises you does it? The extensive overlap of the pain and pleasure system.

So if it's got such overlap and I'm not talking about unusual people who seek and find things – I'm talking about just that's the way it is. Maybe we've got a way to truly flip the hedonic value and indeed that is what we've been doing. Again, these pre-frontal areas and other areas have proven to very, very interesting. And we've been looking at how your disposition changes how you are capable of doing that. Who would admit to being a pessimist in the room? Come on, there's got to be more than one. One, two, three. The rest of you are all optimistic is that so? I'm a real optimist so it kills me to say this, but sometimes it is good to a pessimist.

So what we've been trying to do is again in the context of understanding new ways of thinking about how much relief people get or how much they think they get and how much they report and where we could maybe target new ways of changing the hedonic value of pain. How can we capture some of these more unusual personality traits? I don't mean just depression and anxiety, the more medical ones, I mean thinks like pessimism, not just the fundamental things about the way you approach everything in your life. Your whole disposition of framework will influence how you respond.

And we have been absolutely amazed at the data we've been getting. Looking at personality types and how they influence again how your brain activates, completely differently. So what we've been doing in this experiment is simulating a sort of thing that we call psychological relief, so not true pain relief, where will give you pain and then we will give you a drug. But relief when you think you're going to get something bad. So imagine you're walking out in the street and you're going to step off the curb and you see this bus, and you think "I'm going to get killed" and then you just miss it, "Phew, it didn't happen." So it's that 'phew' effect, yes?

So the way we do that again is a standard design, where will give you a cue to say, "We're going to burn you now, sorry, but it's coming." And sometimes we do. We give you bad heat, but sometimes we don't. We give you a safety cue and you think, "Oh phew, it didn't happen." Well surprise surprise, guess what you do in this period here, when you're looking at the cue and you're a pessimist. You're dreading it. Your ratings of dread go up. You think, "Oh I'm bound to get the burn, it's bound to happen" etc. Yes? That's exactly what you do and that's exactly the ratings we got.

Whereas the optimist, "Oh well, whatever" sort of attitude. I think I might have – yes I did show it. Okay, so higher dread ratings if you're a pessimist. But do you know what's really, really interesting? When you get the safety cue, if you're a pessimist, it goes back to this concept of hedonic equilibrium. You actually rate the pleasantness of that relief significantly higher than the optimist. You have a big rebound. So you end up at zero. You get more dread, but you get a bigger bang for your butt, so you come back.

But if you're an optimist, you didn't dread it so much, "Oh it didn't happen, so what." You don't get so much, yes? And what's very nice is that behavioural thing is mediated and reflected by brain area, which is called the 'mucus acubens' it's your addiction bit if you like, but it's where we know rewards is deeply seated, it is the reward sort of bit of brain, yes? And what was very

nice is indeed that was the bit that activated and this is rare to see in imaging, but let me show you what happens.

Forget the bottom line, just the top, this when you see the safety cue. There are your little mucus acubens going mad, it's exactly where it should be. But look what you do, if you're a pessimist, you have a huge swing up and look what happens if you're an optimist. Totally diametrically opposite behaviour. Absolutely remarkable to see such a divergence again in a structure like that biologically.

Just to show you, these subtle things, they really influence how you work and we're very interested in this idea of hedonic equilibrium and how again in translating that into patients and expectations about relief. And then when they do get relief, how they assess it and what perspective they take about that in their lives. You know, we have underestimated the relevance of that.

Okay well, if we don't cure it, this is what happens. So if we don't cure it and we now look at the brains of chronic pain patients who have just been living with pain for 10 to 15 years, where at best they've been taken the edge off the pain, I'm afraid the consequence of, you can again take an imaging sequence or you just look at the amount of grey matter you've got. And if you do that, this is in a patient with chronic lower back pain, but it's now been done in about 15 studies across all sorts of different pain conditions. If you quantify your grey matter, it is significantly reduced. And where predominantly is this occurring, back into those pre-frontal areas. So when you control for sex and age, it's about 27% loss of your pre-frontal grey matter is going.

Female 1 You mean you become stupid?

Tracey Well possibly. Or the consequence of that – it's going to be more subtle than that, but the consequence of that, having shown you how important that pre-frontal cortex is for perception and all sorts of things is that if that's an `[[acrose 1:14:51]]`, then the repercussions of some of these findings is very important. One is, is it irreversible? Is there then no comeback for that individual? And if this structure is so pivotally wound up to those descending systems, well this is going to make things much worse now because you're not able to talk to that system, that's the driver. How you're able to talk and boost those endogenous opioids, you're not getting the benefit of that, etc, etc, etc.

But more, it means you've got structural, and we know from other techniques, chemical changes. Which means technically if one looks at the definition of a disease, which is from the Oxford English dictionary here. This is something that we're politicising a lot at the moment in the UK because it will change everything in terms of access to different types of services. If it is classified as a disease it changes everything. And if you look at the definition as defined by the OED, we've just got an article published next month again discussing this, technically with a all the data I've shown you and now with the structural data, chronic pain fulfils those criteria. So that's the next era coming I think. I think there's a bit of a debate probably going to go on in societies whether we should be thinking of product pain as a disease. And then that changes access.

Okay, I said I would finish with FMRIB. This is FMRIB. Again, you would be very welcome any of you to come and visit us and have a look. You don't have to do our pain experiments obviously. It's a wonderful facility. We really are a world class imaging laboratory and that's been due to a lot of effort of a lot of people that's come through the lab when we set up ten years ago. And we've got a fantastic team about 90 people now are based there, scientists and clinicians, every type of scientist we need, every type of clinician pretty much. So it's a wonderful environment to be in, all very young. I'm the oldest one there in fact.

We've had a huge output in the ten years we've been operating, both in terms of papers which is our sort of money if you like, that's how we get grants and how we advertise and publish that what we're doing is of use to society. And obviously we have a great training element in terms of our PHD students with about sixty successful PHDs and MDs completed in that time.

What about the future developments? Well just over the past couple of years with enormous help from Diana [[Stent 1:16:53]] here in the Development Office and Nicola Pullman from the University Development Office and obviously all my scientific and clinical colleagues, we've managed to raise 8.4 million which is what we need to do if we want to upgrade and keep our facility in terms of the kit we use up to date, state of the art, world leading. And because we're a very multi-disciplinary lab with a great strength in methods development and acquisition we need to have good kit to get the best physicists and engineers and mathematicians wanting to come to the lab for the next 10 to 15 years.

And also the best neuroscientists wanting to use those tools to understand more and more about how the human brain works. So it's a very exciting time. As I said, we've been 10 years in operation, so we have to overhaul the system now. So largely what I've been doing, with my colleagues, raising this money and now I am happy to report the builders are in, and we are now installing a new 3-tesla scanner which is a beautiful small, very neat machine. It's almost desktop. It's a very open, a lot more friendly for patients, a lot more easy for us to do and inflict more pain type things on people. (Laughter)

And then a big beast of a machine, a 7-tesla, it's only going to be second one in the UK. We are going to be the MRC's flagship centre for that nationally as a national facility for ultra high field imaging. The quality of the data we get at 7-tesla is just extraordinary. So we suddenly see things in the human brain we've never been able to see before. It changes again everything. Not just structurally but obviously the amount of signal we get means that we can take functional imaging to the individual. We can look at the [[NF1 1:18:21]]. And then we can look at other things.

I mean obviously I'm a neuroscientist, so I am interested in the brain. But as a centre I want to expand and work with our colleagues at the [[?? 1:18:28]] orthopaedic centre, who we work with, in the context of joint pain, but we can look at the joints. And just look at what you can suddenly see. As you move from a standard clinical machine at 1.5, a finger joint, look at what you can see, it's remarkable. So coupled with our guys who are really clever at all the analysis and segmenting things and quantifying things, it's a whole new era where we can start to look at deep structures, almost with inevo histological type resolution.

So that is what's coming in the next year. We should have all those systems installed by about next May and then that will give us a lot of new things to exploit and develop. And hopefully you will see the fruits of that in the next 10 to 15 years.

So I'll just finish by saying, we've come a long way. [[Daycart 1:19:10]] proposed the idea that you put your foot in a fire, a bell goes off in your head and you experience pain. Obviously we've got Sherrington who contributed both the concept of nociceptors but also blood flow which opened up the capacity to develop inevo imaging tools to look at the human brain. And we've been in the lab very much putting that all together.

But I have stop by thanking obviously the group. This is my past group who I've shown some of the work and my current team. This is my own personal pain team which has been separate to obviously all the others there looking at other diseases. And I'd like to acknowledge obviously all the control subjects and all the patients that have participated in our experiments, very patiently. And obviously enormous contributions from our funding councils and from various collaborators.

So thank you very much for your time. We've overrun a little bit, but I will be very happy to take some questions. I think coffee is on until about half past eleven, is that right? Yes. So I think there's a roving mike. And so I will finish there and thank you for your time.