Andrew Jackson Interview

00:08 B Why do you use macaques in your research?

00:12 AJ We are interested in the brain, the spinal cord, the nervous system and things that we can do to help when those structures goes wrong. We are very similar to other primates, we are very similar to monkeys like macaques. We are less similar to rodents, rats and mice that are often used for other studies in science. One of the real advantages of monkeys, non-human primates is the similarity in their brain structures to humans.

00:44 For example, my research is interested in ways to treat the arm and hand after paralysis. Primates including humans and monkeys have developed a unique pathway by which signals get from the brain to the muscles controlling the arm and the hand. That's not shared with mice and rats, who walk on all fours and use the fore limbs for locomotion rather than the types of movements that we do with our hands like reaching for objects, grasping them, manipulating them.

01:24 To study the pathways that control these behaviours and ultimately to work out ways to restore these behaviours in humans, we need to use a species that has a similar arm and hand function to humans.

01:38 B How do you use macaques in your research?

01:42 AJ What we are interested in is ways to restore arm and hand function. Firstly, we need to understand how the brain controls the arm and hand.

02:38 B How do you use macaques in your research?

02:41 AJ What we are interested is understanding is how the brain controls movements of the upper limb and then see if we can build devises to restore and replace that function in people who are paralysed. The first question we are interested in is how is information represented in the brain before it is sent down to the limbs to produce a movement. In order to do this we use very fine metal electrodes, they are fine metal wires that are inserted into the brain, to listen to the activity within the brain.

03:15 Within your brain there are a large number of brain cells and neurons. They communicate with each other by sending little pulses of electricity and we can listen to these pulses of electricity using these fine wires inserted into the brain. If we can understand how those pulses of electricity actually relay information about movements, then in a paralysed person we can take that information out of the brain and use it to control an assistive device, for instance, a wheel chair, a prosthetic arm or possibly even use it to restore movement to the paralysed limb itself.

03:50 A lot of our work involves training animals to perform particular movements and then listening to the activity in the brain at the same time as the monkeys are performing these movements.

04:12 Once we understand how those movements are encoded by the electrical pulses in the brain, we can listen to those signals and we can use those signals to control other devices, like cursers on a computer screen. Then we see whether the monkeys can learn to use these brain signals in a new way in order to move a curser around the screen to targets. These are very complicated tasks but we found that the monkeys are very good at learning these new ways of using their brain cells to control computer curses.

05:16 B When do you think that you might be able to apply this to humans?

05:19 AJ There has already actually been a small number of trials in humans where they have put very similar wires inside the brain of paralysed patients and have taken those signals and used them to control computers and robotic arms.

05:55 AJ What is very exciting is that we are just starting to see some humans trials of this technology. There have been a small number of patients implanted with similar electrodes to what have been developed in experiments using monkeys. These patients were paralysed and were able to use these signals to control computer cursers and robotic arms.

06:14 The next step is to see whether we can use these signals to actually help them move their own paralysed limbs again. The way that we are investigating this in monkeys is to see whether we can use similar type of electrodes, similar fine wires now positioned in the spinal cord. If we deliver electrical stimulation to the spinal cord we can produce movements of the paralysed limb. By connecting these two sets of electrodes, recording signals from the cortex and then using those signals to deliver stimulation to the spinal cord, we can effectively bridge the injury and therefore restore the pathway from the brain to the muscles. This will allow patients to move their own limbs again and that's the real dream I think.

06:59 RS Do you have to injure the Monkeys to assimilate this or can you do it …?

07:07 AJ At the moment what we are doing because we don't want to produce permanent injuries in the animals, is using a drug which we can inject into a part of the brain and cause a reversible paralysis that last for several hours. This allows us to test our ideas and see whether we can restore function to this paralysed arm and hand without having to do a permanent injury to the animals. A couple of hours afterwards this drug will wear off and the monkeys are back to normal and using their arms normally again.

07:39 B That's one way that you have tried to make this research less distressing for the macaques, are there other ways?

08:03 AJ We are developing a number of approaches to try to minimise the amount of disruption to the animals' normal behaviour by making these recordings. We use electrodes that are permanently implanted within the brain and that allows us to make recordings without having to restrain the animals too much. We are also developing wearable electronics which the animals can carry, which allows us to take recordings while they are behaving naturally within the home cage

environment. This allows us to be able to do experiments without being too disruptive to the animals' normal behaviour.

09:01 Now we are also interested in seeing whether we can refine these techniques that we use to train these animals to perform these behaviours. What we are interested in is can we develop automated systems that can sit inside the cage where the animals normally live and the animals can interact with these devices and learn the tasks as part of their natural behaviours within the home cage. So we have developed an automated feeding system which I can actually show you a video of.

09:37 We are also developing techniques to refine the way that we train animals to perform these complicated tasks. We want to see how much of the training we can actually do within the animals' natural environment, so within the home cage where the monkeys live. We have developed as system that we can attach to the front of the cage, and the animals are free to come into this system and perform a simple task. The task involves buttons which are queued with lights. As the animals come into the cage, the buttons light up and if they press the correct button they receive some Ribena juice, which they like. They are very inquisitive and they come into this device of their own free will. You can hear the tones, indicating every time they press the correct button.

10:28 We also have a tunnel which they come through, this allows to identify which animal has come into the reader by using RFIV tag which they have under the skin, very similar to what you might use with a pet dog or pet cat. This allows us to see which of the animals are interested in performing these tasks and how many button presses they are doing each day.

10:58 We are finding that these monkeys can learning these tasks very quickly within their natural environment, it's sort of like enrichment it's an interesting, fun game for them to play. What we next want to do is to move this device down to the breeding centre, so we can put this device in front of all the animals at the breeding centre, at the centre for macaques, and see which of the animals that most like to play these games, which of the animals that are most inquisitive, and we think that those might be very good animals to use for this experiments. In this way we hope to be able to select animals that are bright and inquisitive and that are well suited to a laboratory environment, therefore to improve the welfare of the animals and also improve the science and use fewer animals to do these experiments.

12.17 The other advantage of these training techniques is that by training the animals to volitionally, of their own free will engage with these tasks we can also improve the husbandry of the animals. Using similar techniques of rewarding the animals, here we are showing that we can persuade the animals to move around the cage environment of their own free will, so the animal has learnt to associate this carabiner with getting a reward. You can hear that every time the animal touches the carabiner, she hears the same tone and gets a reward. Now by placing the carabiner in the second cage the animal knows that what she has to do is come into the second cage to get the reward. This allows us to move animals around and get them out into the lab in a way that much less stressful for the animal because then they are in control and they know what they are supposed to do, they are happy to do it because they are getting tasty food for it.

13:20 RS Can you take us through a typical experimental sequence of what happens to the animals from home cage out to experimental place and back again? Timescales,… so that we get an overview of the kind of things done to the animals.

13:36 AJ A typical experiment would run like this; the animal would come out of the cage of their own free will and they would be taken to the lab. We use a very small amount of restraint, we restrain the arm and perhaps have a collar around the neck but aside from that the animal is ……

14:07 I'm actually quite proud of the minimal restraint that we use for our experiments, but then you start talking about restraint and people don't realise that a lot of other people that do these experiments, sort of fix the head and what we are doing is better than that but maybe don't need to ……

14:30 In a typical experiment, the animal would come out of the cage of their own free will and be taken to the lab and sit in a chair and start performing some of these movement tasks. At the same time we then start listening to recording these signals from the brain. We listen to what the individual neurons in the brain are doing. This process to set up the experiment takes maybe half an hour. The animal will work, typically do 300-500 successful trials over a period of about 2 hours. The monkey is getting rewards, tasty foods, fruit and nuts for doing this task. It is something they enjoy and find quite interesting.

15:15 At some point during that experiment we may change the experiment, to such that now in order to successfully complete the task rather than making movements with their hand, the task is controlled directly by these signals from the brain. This allows us to look at different ways of extracting information from the brain, different ways that we can read the brain signals out. At the end of this process the animal is then returned back to the home cage, the whole experiment takes maybe 3 hours.

16:00 This shows the kind of information that we get from the brain during these experiments.

16:20 This shows the kind of information that we get during these experiments. What we have here is the signal from all of these different pieces of wire

16:31 What we have here is the signal from all of the electrodes in the brain. The clicks that you are hearing are actually the electrical signals that they neurons are sending to each other to communicate, it is what we call action potentials. You can see that we can records action potential from a large number of different neurons inside the brain. The reason that we record all these neurons is that the way your brain works…

17:25 RS You told us the outline story in the beginning, so what we are doing now is developing the story of the research root. So we are listening to the neurons, watching these neurons and so we are finding out the sorts of patterns typically associated with a particular movement or whatever. So then, it's the next stage after that, what do you do with the information.

18:00 AJ These experiments allows us to listen to the signals that are coming from many different neurons inside the brain. The reason we are doing this is because the brain is a very democratic organ and the movements you make are determined by the activity of a large population of neurons. It's almost as if every neuron gets one vote in the election about how a movement is made. If we can understand what these neurons are voting for, we can see whether we can artificially create the same movement in a robotic arm or a computer curser.

18:40 Where we are going with this is, if we can really understand how the brain is encoding these intentions to move, then in a paralysed person we can send these signals back into the nervous system at a sight lower than the injury. We will be able to restore activity below the injury and then send these signals out to the muscles and be able to get a paralysed limb to move again.

19:12 B Would your research be possible if you couldn't use macaques?

19:17 AJ This wouldn't be possible without macaques. The types of techniques that we are using are at a very experimental early stage. It wouldn't be safe at this stage to be doing this in humans. Particularly for instance, putting electrodes into the spinal cord in order to stimulate and create movements of a paralysed limb. Someone with spinal cord injury may still have some residual function, it wouldn't be ethical at this stage to be proposing a dangerous invasive surgery, which might remove the small amount of function that they have left in their spinal cord.

20:00 At this stage being able to use monkeys is essential for us to develop the techniques. Once we have them to a stage where it's working well and we have demonstrated that the techniques are safe, then we can start thinking of using these techniques in patients to be able to restore movements to them.

20:19 RS Can you tell us about the collaboration with medics and how that works? Do you have medical people in your research panel?

20:34 AJ We do have some. We are in conversations all of the time with surgeons at Newcastle who are starting to use some of these techniques in human patients. We are beginning to see a translation of techniques that were developed in animal experiments, predominately in monkey experiments that are starting now to be used in human patients. It's a long process to get something from a successful demonstration in an animal all the way through to showing that it's safe and effective to use in humans.

21.08 One of the exciting things is that this is just starting to happen with the brain implants. The first few human trials are starting with these patients. We are very interested in pushing to the next level of being able to use these signals and to send them back into the spinal cord but this is still several years away from being safe to be done in a human.

21:40 B If trails are starting in people, why do you still need the monkeys?

21:46 AJ That's a good question.

21:51 The work I was explaining to you about the spinal cord implant, this is something that isn't being done in humans at the moment. This is something that we need to test in monkeys.

22:11 At the moment there is only one type of electrode which is used for human recordings and which has been approved to be safe. What we are interested in is, if we can understand how better to read signals out of the brain, there may be other types of electrodes that may be better for that. We can't do that in patients because we can't try out lots of different types of electrodes or lots of different types of technology. It's really encouraging that we are starting to use some of these designs in people but there is still lots of improvements that can be made. Understanding how to better read signals out requires the whole system to be there, it requires the whole brain to be functioning and..

23:02 B I asked you that partly because I think that's what people might think and also because I think the issue is around accuracy. The one about people isn't so great, maybe, but you started that with the improvements. Maybe cut if off at the point where you say the ones that are being used in people need to be improved and that's why we use macaques.

23:34 AJ The work that I was telling you about, spinal cord implants, we can't currently do that in humans. We haven't shown that it's safe yet, we need these experiments in monkeys to show that it's safe and that it works. Also, the electrodes implants that are now being used in humans still need some improvements, still need some refinements. One of the problems is that the signals aren't very stable from day to day. We need to see whether we can develop better electrodes, better techniques for using those electrodes and better ways of putting the whole system together. These are experiments that can only be done in monkeys at the moment.

24:09 B Is it difficult to get research with macaques approved?

24:14 AJ The UK has one of the strictest rules in the world for authorising, licensing and monitoring the use of animals and monkeys in research. In order to be able to do this work we have to write a project license which then is approved by the home office. In that approval process there are a lot of questions asked; how the animals are being looked after? What safeguards are in place to ensure that the animals don't suffer unduly during these experiments? That whole process can take anything up to a year before a license is granted. It's really important because it means then that the animals are well looked after.

25:38 The UK has some of the strictest rules in place governing the use of animals in research including monkeys. In order to get this work approved we have to write a project license which gets reviewed both within the university, the ethics panel within the university, the home office and also by external reviewers. As part of that process we ensure that the safeguards are in place, that animals are going to be well looked after and that they are not going to suffer unduly. Also, part of that review ensures that this work requires animals to be used and that the benefits of the work outweigh any costs in terms of animal use.

26:28 Each animal stays within the experimental program for a maybe several years. They are initially trained on these complicated tasks which can take anything up to a year.

We record from them over an extended period, maybe a year or more and at the end of these experiments the animals are put to sleep. We may do further experiments during a terminal procedure where we are able to collect even more data form these animals. At the end, they are killed while they are in their sleep. After they are killed we take various parts of the tissue and send that off to other researchers around the UK. A number of different scientific questions can be asked with this tissue. We really try and get the most amount of data possible out of each animal because they are very valuable animals.

27:31 B Did you have anything else? When we were taking about the training and the home cage you said that you are going to start using it at CFM, I thought you had already used it at CFM?

27:46 AJ We have used it at CFM.

27:50 B One thing that it would be quite good to get across because this is a film mainly about CFM, is how relationship with them has been good.

28:09 RS Perhaps making a general point about the science cooperative effort and one aspect of cooperation. It's not competitive is it?
Something along the lines of …, connect to the point about things being externally checked to get your license. It's one aspect of how scientists are connected with people all over, seeing each other's work.

29:07 B One thing that we do have to make clear is that is where your macaques came from. That is the legal situation. The monkeys that we use all come from the centre for macaques. I don't know how much you want to say about the training.

29:52 AJ The monkeys that we use come from the centre of macaques. That's great because we then know that they have been brought up in a good environment and ..

30:13 The monkeys that we use come from the centre for macaques. That's great because we know that they have been brought up in a good environment and that these are going to be happy and healthy animals. What's really exciting is that we are now able to use this automated training at the centre with the cooperation of the staff. This is in order to start some of the early training stages down at the breeding facility. What that means is that when the animals come up to Newcastle, they have already learnt certain associations and they already have something that is familiar to them. They know that when the lights come on, they press the button and they get the juice. I think these kinds of things may ease the stress of relocation from the breeding centre to Newcastle. It means that right from the start we can get the animals into a routine and start performing these tasks. They come to us knowing what they are supposed to do.

31:40 RS A personal question; how you fell into this research and what is it about this work?

31:58 AJ The brain to me has always been fascinating. I actually started out life in Physics, the problem with Physics is that we understand so much about it. To find things in Physics that we don't understand you have to build a particle accelerator under Geneva and smash particles together at really high energies. Or you have to go back

to the first few milliseconds after the big bang to find something that physics doesn't understand.

32:30 The brain is not tiny, it's not way out in space, it's about a kilogram, we all have got one and yet we really understand very little about how it works. That to me was always fascinating. The other great thing about studying the brain is that it gives us an opportunity to develop technologies that may help people. There are so many devastating conditions such as spinal cord injury, other forms of paralysis due to things that have gone wrong with the brain or things that have gone wrong with the nervous system. As we understand more about how the brain works we can develop technologies that can help people.

33:25 B Where there any points that you…

33:40 AJ Do you want to film this or is it a bit gruesome.

33:49 RS So we just need to put it into context, the animal is under anaesthetic.

33:55 AJ I don't necessarily want to talk about this stuff.

33:59 B My concern is that it looks like blood on those bandages.

35:58 AJ This shows some footage of an actual experiment. Here, the monkey is controlling this yellow curser and moving it to various red targets that appear on the screen. The monkey isn't controlling this using her hand, she is controlling this curser using signals from the brain. What you can hear in the background, these clicking sounds; these are the electrical signals from a single neuron in her brain which are driving the curser on the screen.

36:34 An important point to realise is that if you are paralysed by an injury to the spinal cord, all of the brain cells within your brain are still functioning. If you intend to make a movement, intend to move your arm, these neurons start firing off electrical signals. Now because of an injury those signals don't get to the arm and therefore the muscles aren't able to contract. There are signals still there in your brain and we can use these techniques to read those signals out and either send them to an external device, to a computer or to a wheel chair so that you can communicate with the world, and you can move around in the world.

37:14 Ideally what we would like to do is to send these signals back into the nervous system, below the level of the injury and therefore construct an artificial pathway by which these brain signals can get out to the muscles and allow you to move your own paralysed limb again. This is what patients ultimately really would like, to be able to move their own limbs again.

38:36 Work done in the United States has shown that it's possible to take these brain signals and used them to control a robotic arm. In the early experiments with monkeys, they were able to show that a monkey was able to use this brain controlled robotic arm to feed themselves. Recently that work has just been

replicated with human patients, for the first time paralysed humans patients are able to use brain signals to control a robotic arm, to for example, pick up a cup and drink from it.

40:00 What we are interested in is using these same signals from the brain to reanimate a paralysed limb. The way we have been testing that is to deliver electrical stimulation to the spinal cord to produce movement to the limb. In this case, the monkey is asleep and we are producing movements by delivering stimulation to different electrodes in the spinal cord. This monkey is anaesthetised as you would be for a surgery.

40:29 What we are starting to do now is to be able to deliver this stimulation in awake animals, where the animals are themselves controlling the stimulation from recordings from the brain. We use a pharmacological technique to reversibly disrupt function in the motor system, to be able to paralyse the monkey's hand in a reversible way. We are then able to treat this paralysis by delivering brain controlled stimulation of the spinal cord, effectively creating an artificial bridge to take signals from the motor areas of the brain and relay them to the spinal cord, bypassing the site of injury.

41:20 These are some of the electronics that we use to make these recordings. These are some of the data coming in.

41:36 These are the signals called action potentials which is how neurons communicate with each other. Here we have action potentials recorded from a range of different neurons inside the brain. We can also record signals like this; these are called local field potentials. They are a little bit like an EEG signal, which is recorded from the scalp. One of the things we are interested in is trying to understand the relationship between brain signals that we record with electrodes inside the brain and how those are related to the kind of recordings we can make in humans using electrodes placed on the surface of the scalp.

42:43 We have a variety of different tasks, this device here allows us to measure the forces that the animals produce with their wrist and we have other devices here where ……

43:12 This is a device that allows us to measure the forces being produced by the wrist. The animal places their hand over it and it can push down on the device. Inside here there is transducer that measures the amount of force that the monkey is producing in her wrist. The monkey is trained to use this device to control a curser on a computer screen and she moves the yellow curser to the red targets that appear.

44:06 I'm producing the forces in order to move this yellow curser to the targets. Our monkeys are rather better than me at this, they are trained to make accurate movements. At a certain stage in the experiment we might change it, so that the curser is now controlled by the various signals that we are recording from the brain. The monkeys don't mind this, in fact they quite enjoy controlling the curser with their brain and they carry on moving it around.

44:42 RS When they control the curser with their brain, are they doing something else with their hands?

44:49 AJ This is a very good question. One of the questions we are particularly interested in because often what we find is that the movements themselves will drop out. The monkeys are a little bit lazy, if they can get away with doing the task and getting the food without having to make movements, sometimes they will choose to do that. This isn't always the case, in other cases the movements continue. What we are quite interested in, is looking at how closely is the brain related to the movements and how easy is it for those to become decoupled.