



# #197: Predicting and preventing epileptic seizures with neural implants

SHANE HUNTINGTON

I'm Shane Huntington. Thanks for joining us.

Epilepsy is a common and debilitating condition experienced by some 50 million people worldwide in which a constellation of neurological disorders can lead to seizures in the brain. Sufferers usually live with an ever present fear that their brain could betray them with a seizure at any moment. Although drugs can control epilepsy in some people, the side effects of medication can be worse than the disease. For others, even the best medications fail to keep their seizures under control and leading a normal life becomes near impossible.

Today on Up Close we are joined by two scientists trying to better predict and treat epileptic seizures using the field of science known as bionics. Professor Mark Cook is a Clinical Neurologist. He is Director of Neurosciences and Head of the University of Melbourne's Department of Medicine at St Vincent's Hospital. His collaborator, Associate Professor David Grayden, is a bionics researcher. David is Head of the Bionics Laboratory at the Centre for Neural Engineering at the University of Melbourne.

Welcome to Up Close, Mark and David.

MARK COOK

Thanks for having us along, Shane.

DAVID GRAYDEN

It's good to be here.

SHANE HUNTINGTON

Mark, I'd like to start with you. What are some of the causes of epilepsy and is there such a thing as a typical epilepsy sufferer?

MARK COOK

Well, there are many causes of epilepsy and, unfortunately, anything that interferes with or damages the surface of your brain can cause epilepsy so, understandably, there's a very wide range of possibilities, so people will be familiar with seizures occurring after trauma or association with tumours. In fact, many of the causes, even in adult life, are developmental abnormalities affecting the surface of the brain which are typically very small and subtle and which might not result in any other discernible change in a person's

abilities. So, epilepsy might be the only manifestation of quite a complex abnormality, but one which is quite small.

Nowadays with the aging population, causes like stroke and tumours which are often more commonly found in the older age range are becoming a more important cause, but it should be remembered that most epilepsies occur in children overall. And a lot of these are epilepsy which are thought to have an inherited basis of some sort although the number of patients who have an identified genetic abnormality is still very small.

SHANE HUNTINGTON

When a person is having a seizure, are they always aware of this fact?

MARK COOK

They're not always aware of this fact and, you're quite right, seizures are very different for different people. They're very individual and although they fall into a few big categories which we define as being either partial seizures developing in one area of the brain and often related to some structural problem, seizures might start in deep parts of the brain and synchronise very quickly and rapidly which produce primarily generalised seizures, as they're called, so they don't have a structural pathology, but the manifestations of them then are very difficult and, of course, how they affect the individual is incredibly complex and depends on their personality and their job and the responses of those around them to the seizures as well. So there are many ingredients there. You'd have to say everyone is very individual when it comes to their seizures.

SHANE HUNTINGTON

So would you necessarily know if you were standing in front of someone and they were having one of these seizures?

MARK COOK

Well you might not because the seizure might be very subtle and consist only of the experience of disturbed sense of memory, smell, taste, feeling, something like that, or they often are emotional or visual and obviously they're not discernible to those around. People might lose contact though and typically this lasts, depending on the kind of seizure, from a few seconds to a few minutes and in that period they might be obviously confused or they might have unusual movements, chewing and swallowing are very common, sometimes more complex, repetitive and purposeless movements, but usually it's just standing and staring.

SHANE HUNTINGTON

In terms of the triggers for these sorts of seizures, are there particular things that people with this problem avoid?

MARK COOK

The most reliable trigger is sleep deprivation by a long way, so sleep deprivation, stress, circumstances like that, intercurrent illness, obviously forgetting medications and so on, over imbibing with alcohol, all of these sorts of triggers are very well recognised, but there are some more unusual triggers, too. Some seizures have complex reflex triggers such as game playing epilepsies, decision making epilepsies, and not such a rare one is reading epilepsy and these manifestations of seizures are perhaps a little more common than we appreciate. A lot of people don't bring them up unless they're asked specifically because they are unusual and it's not always apparent to the observer that the link's a direct one.

SHANE HUNTINGTON

If we consider the time shortly after when the seizure occurs, what sort of results are there for the patient both physically and mentally? What sort of things happen shortly after the seizure is complete?

MARK COOK

After people have a major seizure they're often very confused and it's a bit like turning the computer off when it's midway through a process and starting it up again; it takes a while to get things back into order. This has sometimes profound effects on memory and recall for some time afterwards. Some people feel that they're never quite the same after they've had a prolonged major seizure, perhaps because their oxygen levels might drop very low during it. Most people though are having complex partial seizures where they go blank and behave in a confused manner for a minute or two. After them, they're usually not with it and are often a little bit aggressive and combative in the recovery phase, this often causes trouble when people try and restrain them, but that usually lasts 10, 15 minutes, that sort of period. Sometimes the area of brain in which the seizure started doesn't work properly for a while after the seizure and this is called a Todd's paresis and might lead to weakness down one side, disturbance of speech or vision which provides a valuable clue as to the origin of the seizure so clinically it's very helpful if that occurs, but that can sometimes cause very specific disabilities in the older patient that's often confused with a stroke.

SHANE HUNTINGTON

David, I'd like to now talk a little bit about the sort of measurement of some of these things in the brain. If we want to look at the activity within the brain that's causing some of these things, how do we go about this? How do we measure the type of electrical and other activity in the brain that would cause this?

DAVID GRAYDEN

Well it's normally done using what's called the electroencephalogram which literally means the recording of electrical activity in the brain. It can be done in several different ways. The most common is just to put electrodes on the outside of the head and probably most people will have seen somebody who's had these EEG electrodes on. The signal is very weak so we try to record in good clean conditions, but we're recording in the vicinity of microvolts there and then there's a lot of noise that can be in that signal because it's on the outside of the head it can pick up muscle activations and things like that. But we can put many, many electrodes, up to maybe 256 electrodes now on the outside of the head. Other possibilities thought are to get the electrodes closer to the brain and that's to actually place them

under the skull and that can be done in two ways. One is to take a portion of the skull off and put a grid of electrodes down onto the surface of the brain. Another is to push a length of electrodes, so electrodes that are along a stylus, down into the deep structures of the brain. Obviously we don't want to do that very often because it's quite an invasive procedure, major neurosurgery to do that. That's only done for people who really need that sort of recording.

SHANE HUNTINGTON

When you look at brain activity, how do you distinguish between what would be considered normal activity and the type of activity that's either associated or leading to these seizures?

DAVID GRAYDEN

Mainly in terms of what rhythms you see in the brain. So normal brain activity, there's particular rhythms that are obvious. Mainly the activity looks random, but if you analyse it and look at what's called the spectrum of the signal, you can see that, for instance, when a person's eyes are closed there's a dominant alpha activity which is around about 10 to 14 hertz. There can also be beta range of activity which is higher frequency, associated with muscle control there's some very high frequency activity. Whereas seizures, in a full blown seizure you can see across the brain a very low frequency activity, sort of around about three hertz or so, and that sort of represents the neurons of the brain have got themselves into a state where they're just slavishly following that rhythm and they're not able to do other sort of more complex processing.

SHANE HUNTINGTON

When we consider this abnormal brain activity, do we have an idea of why this isn't there all the time, why it's only odd intervals maybe due to particular circumstances?

DAVID GRAYDEN

I think that's still a very open question and part of our research is actually looking at that, but we do need to try to understand why, in particular for these focal seizures, there's a small region of the brain that might be causing the epilepsy, why doesn't it happen all the time and why doesn't it spread to the rest of the brain all the time. Sometimes it just will remain localised into that region.

At the moment, there's not really a good explanation. The main approach that we're using is to try to model the brain and to understand how the neurons are behaving and what we're finding is that there's a sort of chaotic response and that the neurons can behave in a certain regime but then sort of a confluence of events that come together and maybe a change in the overall excitability of the brain as well can lead to the unusual activity being manifested.

SHANE HUNTINGTON

Mark, according to our sort of knowledge of the human genome and that of other closely related primates like the gorilla, they're our closest sort of genetic cousin in that sense, do we have an idea of just how widespread these conditions are? Do they just affect humans? Do they affect primates, other animals?

Where do we see this?

MARK COOK

Certainly primates are affected by epilepsies and certainly other higher species are so everyone with a cortex really can generate seizures, you just need to be able to recruit enough neurons into the activity. So they're very well known in dogs and cats, but certainly there are genetic causes as well recognised in both those groups, but as with humans a lot of them have a structural cause, so cerebral tumours in dogs particularly. Some breeds are especially prone to a kind of tumour called a meningioma and these are very well recognised as the cause of epileptic seizures.

SHANE HUNTINGTON

Mark, with people that actually have epilepsy, what are currently the sorts of treatment options for them?

MARK COOK

So you'd have to say they're still relatively limited. We have a range of medications to treat epilepsy, there are other interventions such as surgery and, as well, there are some novel interventions which involve stimulation of peripheral nerves, but I'll come back to that. Medical therapies were first recognised the century before last with bromides as a therapy for seizures, and these were effective but had a lot of side effects, and then in the early 1900s the barbiturates were recognised. The recognition of these led to the first systematic search for effective drugs. Later, this resulted in the development of Dilantin but that wasn't until the 1930s. Before, there'd been a lot of interesting dietary therapies for epilepsy, though for various reasons they sort of waxed and waned in popularity. There again, a diet called the ketogenic diet is effective in some kinds of epilepsy, most especially some peculiar metabolic causes of epilepsy, but in children particularly, ketogenic diet is recognised to bring about control in a significant proportion of people. If the epilepsy is caused by structural pathology of some sort, a scar or small tumour let's say, and that's in an area which is accessible and which is in an area which is safe to operate on, so for instance areas controlling speech and movement are less safe to operate on, then it might be possible to remove it. This has really surged forward with MRI imaging and the ability to very accurately locate and also to stereotactically locate for the surgeon during the procedure. So that's a very important therapy, too. Some interesting treatments have been therapies like vagal nerve stimulation where it was discovered that stimulating the vagal nerve, which is a nerve in the neck that's travelling between the brain and the chest, can be stimulated regularly and that this stimulation seems to modulate cortical activity, presumably through projection from the deep structures that it's connected to. And that's an interesting treatment which has recently led to some similar developments, trigeminal nerve stimulation for instance, and other nerves that travel between the brain and the chest directly have been stimulated in an effort to control seizures with similar sounding results so far.

Only one device is commercially available at the moment. That's the vagal nerve stimulator. There are serious issues around the funding of it because it's very expensive. The drugs though, there's lots of drugs and over the last 20 years the number of drugs has increased very dramatically, but, regrettably, it would have to be said that this hasn't actually resulted in a terrific improvement in the number of people successfully controlled, which would still run, say, 60, 70 per cent of people on medication. The drugs have their own problems. They cause sedation, they might have other peculiar side effects such as rashes or

liver dysfunction and mood and cognitive side effects are quite a significant problem still.

SHANE HUNTINGTON

This is Up Close, coming to you from the University of Melbourne, Australia. I'm Shane Huntington and in this episode we're talking about epilepsy and seizure control with Clinical Neurologist, Professional Mark Cook and bionics researcher, Associate Professor David Grayden.

Mark, you're working with a company from the United States called NeuroVista that's producing devices that will help, hopefully, predict seizures. Can you tell us how these work and what sort of information you're getting?

MARK COOK

David and I first became involved around a project where we tried to predict seizures because a lot of patients and their carers believe that they can accurately predict seizures and sometimes it seems they can with hours or perhaps even longer warning. Our endeavours weren't too fruitful but we did come to interact through that with a group of people, some of whom included those from this company, NeuroVista, based in Seattle who engaged us in a clinical trial which we ran between the other University of Melbourne teaching hospitals.

This is an implantable device where electrodes are put inside the skull over the surface of the brain, as David discussed earlier, to get really high quality EEG signal. This is connected by a wire to a pacemaker sized metal box implanted underneath the collar bone and it transmits signals to a handheld unit which provides an indication of the likelihood of a seizure in the hours ahead. This has proven very interesting. It has shown for the first time the natural history of seizures recorded through intracranial EEG. And of course, we've never done that before. The EEG has only recorded for periods of a week or so intracranially. So to have ambulant patients and record their EEG has really been startling. We've seen the number of seizures that people report is quite different from what they're experiencing. We've seen that there are other changes in the EEG which occur over time once surgery has been done on the brain. All very, very important findings in themselves, but as well, the device does predict seizures pretty well and really well for some patients, so there's still a lot to be learnt about that and it's still a really, really exciting area where the company involved are applying some very novel algorithms to searching through the data that's acquired and recognising new ways of predicting seizures and I'm talking about predicting many minutes or even hours beforehand.

This might have a lot of other implications for therapy because at the moment a strategy for therapy is to provide medications which work over very long periods and provide a very constant level of drug with the side effects that we mentioned, to avoid the unpredictable events, but if you know when they're going to happen, it might affect how you strategise your therapies, you might look at shorter acting therapies that are provided when you know a seizure is going to happen. But it has tremendous implications in terms of lifestyle. If it were accurate enough, for instance, someone might be able to drive and at the moment if your seizures aren't controlled, you can't. It might affect your employment, it might affect how you spend your leisure time. There are an enormous number of implications of the ability to predict them and it's entirely analogous to earthquake prediction.

SHANE HUNTINGTON

David, obviously there is a lot of data processing that's going on here. What level of data processing is required and in terms of the timeframe you're giving patients, how is that related to the particular type of seizure that they might be about to have?

DAVID GRAYDEN

At present, we're investigating a lot of different possibilities in terms of seizure prediction and it takes an awful lot of processing. So we make use of the Victorian Life Sciences Computing Initiative supercomputers to help us with that work, especially in terms of the neuromodelling and other sorts of modelling work where it can take on even a desktop computer, it can take hours to process minutes worth of data. The aim, of course, is to be able to process in real time, but once we know exactly what we're looking for, I think that we can do that with a device that's implanted. And in terms of predicting the seizures as the NeuroVista device does and then perhaps also determining what sort of intervention to make at that stage.

For the different types of epilepsies, some of them are a bit easier to predict than others and we find that for particular patients, the prediction rates are very good with low what's called false positive rates which are the false predictions. Others, it just seems nearly impossible and I think that's mainly because of the different types of epilepsies.

SHANE HUNTINGTON

Mark, you work with a few patients who have these devices implanted. What do they do when they get this prediction that a seizure is going to occur? Is there anything they can, at that point, what action they could take to actually prevent it?

MARK COOK

Well at the moment we're studying somewhere they take medication when their state changes, so their device recognises the state they're in and the likelihood of a seizure so if they go up a rung in the likelihood of a seizure, that they take some medication at that time to try and prevent it. So we're still studying whether that's working yet. Now it's different, of course, whether they think it works and whether we can prove it works, so we're still in the midst of that.

Probably most significantly for patients so far, it affects their daytime activities so one patient was having a lot of trouble at the workplace because of the seizures that were occurring there, now if his situation changes he can take himself home or perhaps take medication, but he can change his circumstances to make his day to day life a lot easier. This is really important to him. Another guy who used to have seizures playing cricket, for instance, is able to avoid being in the embarrassing situation of having a seizure in public or on public transport, for instance, through the use of his predictor.

So those sorts of effects have been the greatest so far, but I think, as I mentioned, we're just touching the edge of what the possibilities are with devices like this.

SHANE HUNTINGTON

David, when you talk about modelling here, I mean we're talking about modelling the human brain which is something that I guess has been a challenge for many decades and not done successfully, how do you go

about the type of modelling that you need to do in order to get the information required about these seizures?

DAVID GRAYDEN

One of the key things that we're looking for is how the brain is different in people with epilepsy and so there's less of a need to model every little piece of the brain to do that. So what we normally use is what's called a mean-field model where we assume that neurons within a small portion of the brain are sort of acting in concert with each other and we don't need to model each neuron but we can model a small section of the brain as a whole. And what we're interested in is then how these small parts of the brain, they're often called the cortical columns, interact with each other and what the connectivity strength is like between them and how active each one is.

So some of the quite exciting work that we've been looking at is being able to take a signal that's been recorded from a person or perhaps an animal that is an EEG signal and use that to infer what the underlying structure is in terms of that coarse interconnectivity and excitability of the different columns.

SHANE HUNTINGTON

When we talk about some of this work where you're putting electrodes beneath the skull on the brain, I mean this sounds very invasive, I understand you're working on a less invasive version of the same sort of thing to help get this information.

DAVID GRAYDEN

Yeah, that's a project that's currently funded by the National Health and Medical Research Council which is try to help localise where seizures are occurring without the need to put the electrodes onto the surface of the brain. That procedure is only done for these people who are possible candidates for resection or to have the piece of the brain removed that is causing epilepsy. But if you wanted to know exactly which part of the brain to remove, you want to know exactly so you don't take too much or you don't take too little. So this project is trying to take the electrodes back onto the surface of the brain but again create a model now of the head, so a model of the skin, of the skull and of the brain tissue itself in terms of its electrical conductivity properties so that we can account for all of the different sorts of structures that exist for different people and allow the electrodes that are on the outside of the brain to be just as useful as the ones that are inside. So this again also takes enormous amounts of computation, but we feel that if we can develop this to a degree that will be acceptable in the medical community, that it's possible that there will be less need to have these long periods of time when people have electrodes placed so invasively in their heads and, instead, they can come in, they can have their MRI scan, they can still spend some time in the hospital being monitored, but hopefully that would be sufficient.

SHANE HUNTINGTON

I'm Shane Huntington and my guests today are Clinical Neurologist, Professor Mark Cook and bionics researcher, Associate Professor David Grayden. We're talking about epilepsy and seizure control here on Up Close, coming to you from the University of Melbourne, Australia.

David, once we have the knowledge of the brain in terms of where the seizure is occurring and that sort of

unusual electrical activity, is it possible to counteract that?

DAVID GRAYDEN

Yes, that is our ultimate goal. The first thing is that when we know where the seizure is coming from, it is possible to perhaps place electrodes in that region to first of all predict when the seizures will occur very reliably for a person that is outside of a hospital environment and then also to counteract that activity by directly stimulating the brain. In the first area, we're looking at using very low levels of electrical stimulation to stimulate the neurons in such a way that the person can't sense it themselves but using the EEG recordings, we can detect that and we look for how that changes over time. And that is giving us a very good measure of excitability of the brain and, as mentioned before, if the brain is in a more excitable state, it's more likely to have a seizure. That's true for most people it seems.

So we are developing algorithms that would be able to make use of that information to do the prediction and then since those electrodes are there doing the prediction, if we sense a seizure coming on we can then hit it with a higher level of stimulation. And this is a project specifically on that now funded by the Australian Research Council in conjunction with St Vincent's Hospital and the Bionics Institute to look at how we can most effectively stimulate the brain in order to stop a seizure from occurring.

That is quite a complex problem because electrical stimulation of the brain can cause seizures in even normal people and so the application of the stimulation, we need to make it occur at the right time and use the right sort of stimulation paradigm like when we deliver the stimuli, how often we deliver them, whether it's an even interval between stimulations or a random interval, all those sorts of things we're trying to address.

SHANE HUNTINGTON

Do you find that in a given patient the area of unusual activity is fixed or does it move around?

DAVID GRAYDEN

It moves around. For some, that region is very localised. What we are finding though is that this excitability measure that we're looking at seems to occur across the whole brain; it's not just in the region of the seizure generating tissue. So we're hoping that we may not necessarily need to know exactly where it's coming from in order to be able to do the prediction, and that seems to be coming true.

SHANE HUNTINGTON

Mark, when we talk about surgery here, and we are talking about removing sections of the brain, how do we know that the problem that has occurred is not simply going to be translated to another part of the brain and that that kind of removal of brain tissue will be successful?

MARK COOK

That's a complicated question and there's a lot of argument over that still, so I think what we need to distinguish is, David's quite right, the changes we observe across the whole network are certain present

with seizures that might originate in one area. I guess the best example I can give is that if you've got a very, very small abnormality on the surface of the brain that you can accurately identify and prove that that's where seizures are starting, if you remove it you usually fix them permanently. Not always, whether that's because of the injury you've produced or because of the injury having had long term effects on the network otherwise, all of that's still a very contentious area within neurology currently.

SHANE HUNTINGTON

You mentioned earlier that epilepsy is often found in children. Do we have an understanding of the causes of epilepsy at this point or are we still a long way from that? You did mention certain injuries can cause epilepsy, but in children is this something that they just grow into?

MARK COOK

A lot of these injuries have presumably occurred as the brain's developing so these very subtle developmental abnormalities have occurred as neurons are often migrating to their final destination on the surface of the brain, because neurons actually begin their life within the centre of the brain or in the ventricles and actually migrate out to the surface. It's a very complex system and the opportunities for disruptions in the wiring and communication between them must be enormous. So a lot of seizures occur around those sorts of circumstances.

Now some of those migrational abnormalities have a vascular cause, so there's failure of blood flow locally or some other restricted injury, whereas others have a genetic failure, so the process which controls the migration is disrupted. Other genetic causes that have been recognised involve control of the ion channels which govern the electrical activity of the membranes of the neurons and these render the neurons, in some cases, to be more easily excited and it has been shown in some of the primarily generalised epilepsies to be the cause.

SHANE HUNTINGTON

With the surgeries we're talking about, do you extend these down to children or does the seizure problem have to be particularly severe to even consider surgery as an option?

MARK COOK

It certainly can be done in children, even infants have had surgery for epilepsy very successfully. It usually requires that there's a cause which isn't going to go away and that seizures have occurred with a certain frequency so that they're disabling and are not adequately treated with a trial of, conventionally we say, at least three medications.

SHANE HUNTINGTON

This is a very unusual project in that it brings together yourself with a medical and neurological background and a hospital and an engineering school here at the University. What is being done differently as a result of that collaboration that has, I guess, added to the way in which we're approaching epilepsy that hasn't

been done before?

MARK COOK

We're very fortunate in that we have such an innovative, exciting and dynamic engineering department who, from the outset, have been interested to participate in projects like this and that's obviously critical. As well I would say, and I'm sure David would agree, one big distinguishing feature is we take the engineers right into the clinical environment. Now the opportunities for engagement with people in the non-medical areas, such as engineering and chemistry and so on, are enormous and yet rarely exploited sufficiently. We often think of bringing them together after the fact and trying to get together around specific problems, which is great, but if we could look towards integrating the problems at a much earlier phase of education on both sides I think this would be enormously useful.

SHANE HUNTINGTON

Mark, just finally, you mentioned before that there is testing going on and many of the patients feel as though they're benefiting already, but in a literal scientific rigorous sense are we closer at this point to being able to detect and potentially prevent seizures?

MARK COOK

No question.

SHANE HUNTINGTON

Professor Mark Cook, Director of Neurosciences and Head of the University of Melbourne's Department of Medicine at St Vincent's Hospital and Associate Professor David Grayden, Head of the Bionics Laboratory at the Centre for Neural Engineering at the University of Melbourne, thank you for being our guests on Up Close today and talking about epilepsy and seizure control.

MARK COOK

Thanks, Shane.

DAVID GRAYDEN

Thank you.

SHANE HUNTINGTON

Relevant links, a full transcript and more info on this episode can be found at our website at [upclose.unimelb.edu.au](http://upclose.unimelb.edu.au). Up Close is a production of the University of Melbourne, Australia. This episode was recorded on 7 May 2012. Our producers for this episode were Kelvin Param and Eric van Bommel, audio engineering by Gavin Nebauer, background research by Dyani Lewis. Up Close is created by Eric van Bommel and Kelvin Param. I'm Shane Huntington. Until next time, goodbye.?

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