Recovering Movement with Professor Charlotte Stagg

Summary

In this episode with Professor Charlotte Stagg, we talk about non-invasive brain stimulation techniques used to understand how the brain adapts to new challenges in the recovery of motor function after stroke.

Keywords

Brain stimulation, learning, stroke, people, recovery

Transcript

Hello! It's Ritika, Katy and Neddy and you're listening to the CortexCast.

Neddy

Hi there! My name is Neddy and in this episode, Ritika and I interviewed Dr. Charlotte Stagg, who is a Professor of Human Physiology at Oxford University, and head of the physiological neuroimaging group. Charlotte's research primarily focuses on understanding how the brain adapts to new challenges, specifically in the recovery of motor function after stroke, using multimodal approaches and treatment to help develop new adjunctive therapies. So Charlotte, thank you so much for making time to see us. Would you mind giving a brief overview of your background and how that led to the career path you're on now?

Charlie

Yes, of course, it's a real pleasure! Thank you for having me on. So I'm Charlie, and I did medicine as an undergraduate subject. So I thought, age 16, I wanted to be a doctor. And I went to medical school, and realized very early on actually that I wasn't very good with the blood and needles and ill people parts of medicine, but I really loved the science. And I really loved physiology in particular. So I did a physiology degree halfway through and then went back to medical school, finished that, and worked as a doctor for a couple years, and really became very, very sure that I liked the science and I didn't particularly like being a clinical doctor. I then decided that I wanted to do a PhD - I probably wanted to see if I wanted to be a scientist - and at that time, I had been living down in Bristol, in the West Country in the UK, and my then boyfriend, now husband, was in London. And after four years of driving up and down the motorway, we got a bit fed up with it. And so this is not how you should choose your PhD - we got the map out and I looked at places that were about halfway between Bristol and London that might do some decent science, and found Oxford and thought it looked much nicer than any of the other places along that line. So I applied here, and came to do my PhD – DPhil – and then stayed. And it was a lot of fun. I loved my research, I still work with patients with a lot of clinical research. But I really enjoy the day to day work.

Neddy

That's really interesting. Ritika and I were talking earlier about how the majority of people we speak to, once upon a time wanted to become doctors, but eventually led to discovering that research is

something that they want to do. And this leads me to my next question of - what is stroke? And more specifically, what is it that you do?

Charlie

Yeah, yeah, of course. So we work with people who've had a stroke. Stroke is when you get a loss of blood flow to one part of the brain - so it can either be a little clot or a little bleed in the brain. And if it's big enough, it will cause the death of some of the brain tissue. And that leads to people very suddenly having symptoms and it depends which bit of the brain it's in as to what symptoms they have but you might find that people suddenly can't see in one part of their vision or they can't speak or they can't move their hands or their legs. And we are quite good at treating that very early on. People make really good recoveries early now. But we know that a lot of people are still left with problems after they've had a stroke and we know that people get better gradually over time, over months to years. But we don't really understand what's happening in the brain that means that people who really couldn't move their hands slowly learn to be able to. So what my group - my research - is particularly interested in is understanding how we learn to do specific movements with our hands and how do people do that - how we learn to play the piano, how we learn to play sport, how we can learn motor movements - and then how that is disrupted after a stroke and how we might be able to help with drugs or with brain stimulation or with something else to try and help people to recover that function.

Neddy

You mentioned brain stimulation, would you mind giving an overview of what brain stimulation is and how you use it in your research?

Charlie

So the idea of non invasive brain stimulation, which is what we do, is that we absolutely are not surgeons, so we don't cut into people's heads - we stick very much outside the scalp. The idea is that we put very small electric current into the brain: the brain is an electric organ, it's how it functions. It's how the cells communicate with each other and it's how we can move and talk and do all the other things. So what we try and do is just gradually change - modulate very slightly - it's like slightly nudging the activity of the brain to just help it to do it a bit better. The best analogy we've come up with really is if you've got a small child on a swing, and if we think the healthy brain is swinging quite a lot, because you've got a child who's worked out of swing itself. My children are still quite young so I sort of saw this in action over the last year. And there comes a point when you're growing up and you work out how to swing yourself right and then you can start going really high but before that you're kind of just wiggling around, nothing's really happening. What we're trying to do with the electrical stimulation is push at the right points - we can help the child swing to get higher and higher. And then we think it's analogy that the higher you swing, the better that is for the function that you want. So we put in electrical current, or we put in tiny magnetic fields that change quite a lot, that induce electric currents, to just try and push that swing to try to help the brain's natural rhythms and boost the rhythms we think are important for learning.

Ritika

Do you think that brain stimulation techniques, apart from the direct effects they are supposed to have, also have any indirect effects?

Charlie

I think that's a very, very good question. And they undoubtedly have other effects, right? I mean, humans come as a sort of complete package. And we have massive psychological buy-in to these things. The placebo effect is something we deal with all the time - it's amazing how if you put something on someone's head and say 'This is going to make you better', it makes you better. So it is really, really important to consider that - we are very careful to control the things we know about. The best way we think of controlling for most of this stuff in all kinds of brain stimulation is to do it to the bit of the brain you think's going to do the thing that you want, but then also to do it as an active control - so do exactly the same thing to the neighboring bit, right, that shouldn't have those effects with the idea that if it is sensation, or sound, or vascular changes, or all kinds of things that have been suggested (and are entirely reasonable, we may well do all those things) then you should sort of control out for that. And you should be left with, really, hopefully, the sort of main effect that you're interested in. Research is always pushing what we can record, right. So we do work mostly in humans - and there are really good reasons for that - but we can't get the detailed recordings we can get from our animals, which is why we use them: we can't put electrodes in people's brains. Because they don't like it, we don't get ethical (approval). And that's fine, too, we have to do everything non invasively. And that means we can't get quite the precise measurements that we can get in other in other ways. And so we have to be really careful that the measurements we are getting - we understand what they are telling us and what they're not telling us. And we really push the boundaries of what we can measure. And what the MRI scanners can do and what the other scanning approaches can do.

Neddy

It's really amazing, actually!

Charlie

It's good fun - one of the delights of my job is that we work not only with a great group of brilliant neuroscientists and clinicians; but we work with the physicists and the analysis people – we've got mathematicians, we've got engineers, we've got software engineers, we've got people who take MRIs apart – really, it needs this kind of multidisciplinary approach to get this stuff to work. And that's really exciting. Because you learn all kinds of stuff that you never thought you would as a neuroscientist and it's great.

Neddy

Do you think (*therapeutic*) outcome can be accurately predicted early on for an individual (*stroke*) patient?

Charlie

That is the key question. And it's really strange talking to academics who don't think that's an important question because you speak to one patient who's had a stroke and that is the first question they will ask - right? And, of course it is what everyone wants to know. No, we can't. There are some algorithms now that are reasonably predictive, though. About 85% of people we can sort of give an approximate answer to, but that means that 15% of people we can't, and we don't know who that 15% are. For science, that's pretty good, right? 85% prediction, we'd all be quite happy with that! But for clinical work, that's

not good enough. Because with that, you need to be able to do it for every single patient, because the patient doesn't care that you can do it for everybody else, they care that you can do them. I think there are two great myths of stroke recovery that are not helpful for people who have had a stroke and their carers and are not helpful for research. One is that if you have a bad stroke to start with, that's it forever. And it isn't – you know, people can really recover - it depends on all kinds of factors. And the second is that people only recover for the first six months, and then there's no recovery after that. And that isn't true, either. People can recover for years and years.

Neddy

So there's hope!

Charlie

Definitely, definitely hope! And there really is - people do recover. But it gets harder - it's hard work. You know, it's much easier to learn stuff as a kid than it is as a grown up. And what we're trying to do is out why - right - so we can try and help.

Ritika

How do you think that this kind of non invasive brain stimulation therapy, for example, can be taken to places like developing countries that are low in resources?

Charlie

I think that's a really key question. So, the classic brain stimulation technique - the sort of the clinical application of this really - is deep brain stimulation for Parkinson's disease. So people who have Parkinson's sometimes have DBS, where they have an electrode implanted into their brain and it is - for the right people - it can be revolutionary. It's not for everybody. But that is neurosurgery. It's incredibly expensive. And there's a map of where it's done. And basically, the map was North America and Europe, a bit in China. But that was it. And the rest of the world was just gray. And you're like, yeah, that's not quite, you know, it's not really where we want to be, is it? So absolutely, the kind of experiments we're doing at the moment, trying to understand this stuff is very technical, it's very expensive. It needs a lot of people, you know, it's not going to be around the world. It really isn't. We're one of a handful of centers around the world that are doing this stuff. But the actual brain stimulation, especially the electrical stimulation, actually, and one of the reasons we're particularly interested in it, is that it is basically just a battery and two pads, right? So you can build one, if you Google the right thing on the internet, you can find the instruction – DON'T build it, do not use it on yourself, it's not a good idea. But you can get it for $50. Right. So if we can work out what we should be doing with it, it's really scalable. You can sort of you know, that's the kind of technology that you can really imagine going out around the world, right? Despite the fact that it's not as effective as the surgery. And you don't get as beautiful recordings, as you do if you put an electrode in someone's head, and all the rest of it. That's why we're keeping pursuing it because it has - if we are going to make any difference, we have to be able to do it in a way that is, you know, at least applicable to most of the global population if not everyone.

Neddy

Can the mechanisms underpinning recovery be clarified to optimize recovery?

Charlie

That's what we're trying to do - is trying to work out what on earth the brain is doing with the idea that if we can work out how either healthy people learn new things, or how people can naturally recover after stroke, we can try and intervene and boost those mechanisms, make them stronger with the idea that that will help people recover. We think it's a useful thing to do, because they're sort of beginning to be little tiny hints that that's true. So there are small studies that need to be proven in bigger clinical trials, that brain stimulation - so you mentioned direct current stimulation - after stroke when you do it at the same time as physiotherapy. So we get people in, we give them the brain stimulation, we get them to move their stroke affected hand. People who did that who had brain stimulation at the same time got much better compared with people who did that but had a placebo sham stimulation - and stayed better for at least sort of, well, we measured them for three months and we kept in touch them because we knew them quite well. But for at least three months. There's a real idea that we can (*already*) understand a little bit about what that brain stimulation is doing and sort of in its basic form that seems to help. What we're now trying to do is understand the next step so that we can make that brain stimulation better, and then intervene a bit better, and then hopefully make those effects even bigger.

Neddy

And with the brain stimulation that you just mentioned, how often was it induced within the period of three months?

Charlie

So they came in Monday to Friday of week one and Monday to Thursday of week two - because we didn't want to come in at the weekends! And they didn't want to come in at the weekends. Nobody does! Do you want to come to the John Radcliffe on a Saturday afternoon? No. Right? So, they were really tired - it was a massive thing for them. And they were amazing to do it. Yeah, our researchers were quite busy for those weeks. And they came in and they had to have an hour session every day, and the first 20 minutes of that they had stimulation, then the therapy for the rest of the hour and then they went home, they came back the next day.

Neddy

Okay - I actually read your most recent paper on the dynamics of cortical GABA in human motor learning. I thought this would be an amazing opportunity to kind of expand a little bit on the interesting results from that paper.

Charlie

Thank you. I'm always very daunted when people have read these things! So as I say, we're very interested in what is happening in the brain as we learn stuff. And we can look at that in people who've had a stroke, but they've had a stroke, they tend not to be very well. And as it can be a little bit difficult to do really long, intense studies with them. It's very difficult to stay in the scanner for two hours. So as a sort of model, we take undergraduates - who tend to be quite happy lying in the scanner for two hours in return for some cash - pop them in an MRI scanner, and look at what happens in their brain as they

learn a new motor task. So what we actually do is do a motor sequence. It's like a very simple piano piece. And it's a sequence of buttons that you press, and that repeats and repeats and repeats, and you get better at it over time. It's not a fascinating task, but people get better at it. And what we're then doing is looking at what's happening in their brains whilst they're getting better with the idea that that's probably also what's happening when people who've had a stroke are recovering. So this study we used MRI scanner to look at the concentrations - so the amounts - of various chemicals in the brain. We were very interested in two chemicals in particular, which are the neurotransmitters - so the way that the cells communicate with each other, to allow us to do stuff. There are lots of them around but the two sort of major ones are glutamate, which is an excitatory neurotransmitter - which means if the first cell signals to the second cell using glutamate, then the second cell becomes more active - and we're also interested in looking at GABA, which is the inhibitory neurotransmitter - which means if the first cell signals to the second cell using GABA, then the second cell becomes less active and stops doing stuff. So the way we work – and our brains work - is that we're in this delicate seesaw between these two things, because we need to be able to do stuff but we don't want activity absolutely everywhere, because then we'll have seizures and bad things will happen there. So there's a sort of balancing act. But one of the things we have discovered through this study and through other things is that in order for humans to learn, what we need to do is just reduce that inhibition. So reduce the break a little bit to allow the cells all to just become a bit more active, because that allows them to produce - we think - allows them to sort of produce stronger, new pathways that allows them to learn the thing that we're trying to learn. So that decreasing inhibition is really, really important. So I think that was the key takeaway of that paper, we are very interested in hand function. And the primary motor cortex, as the name suggests, is the sort of major motor area of the brain. That's the area that mainly controls our hands. So when we learn something with our hands, we can see a decrease in this inhibition there, we see a decrease in the break, we get more activity there and that seems to be a mechanism by which we learn. But we see similar things in different brain areas as well. So if we look at how we learn a visual task, then we see that change in inhibition in the visual system. If we learn a space navigation task, we see that in the temporal lobe. We see it in the bits of the brain doing the learning, and not everywhere else. So it's not a general thing. It only happens in the bit of the brain that is trying to learn that particular thing.

Neddy

So did you come across any challenges when conducting this study?

Charlie

Yes, I think research is always challenging. Whatever kind of research you do. So my work - up until very recently - has been entirely in people. We've started working a little bit in mice just recently, because they're very unique, we can learn some really important things from that work. But most of our work is in people because we care very much about complicated behaviors. And mice do not learn to play Chopin nocturnes, however much we try and teach them! So we're very interested in doing it in people. I like working with people, it's fun - you get to know our participants, it's great. We do work with 18 year olds quite a lot - don't always turn up at 8 am -no - they're always pretty good actually. They're pretty reliable, and they're pretty good fun. So sometimes they don't learn. I'm terrible at learning motor tasks. It's completely ironic – my group refuse to let me take part in any of our studies, they're like 'You're terrible, you don't learn anything, you can't do it!'. Some people are good at this and some people are bad at this. And it is traditional that about halfway through a scan someone will need to go to the loo or will need a drink of water or will fall asleep. That's the commonest one. So there's lots of challenges that you learn with working with the scanners, and the scanners are big bits of kit. And we have a research

scanner that there are really not very many of in the world. It's a very high field. And like it's a very delicate piece of kit and it breaks. And we have researchers here, we're trying to make it work better, which they do, and they are brilliant. But every so often in the process of making it work better, it breaks. So it's not always - not always - plain sailing!

Neddy

So would you say of your planning stages of the experiments? Just like pretty much smooth sailing?

Charlie

That study probably was. So it was building on work that we've done before. And we had a really clear hypothesis and a really clear question. And it's probably unique of all my papers, actually, we had a really clear question. We knew what it was. It was fairly easy to work out how to collect the data, we collected the data, we analyzed it, it did what we thought it would do - we were right in our hypothesis and we wrote it up, that basically never happens. But that is the one example where it did.

Neddy

So like you mentioned a lot of fancy equipment, so would you mind just giving like a brief overview of a common equipment that you use on a regular?

Charlie

Yeah, no, absolutely. So I work at the WIN, which is the university brain imaging center. And we are very lucky in that we've got a lot of cool kit! So most importantly, and most expensively certainly, we have a big MRI machine. Most people will be familiar with the idea of MRI - they're in most hospitals - and it's a magnetic imaging. And what you do is you put people into the scanner, there's a magnetic field, and we can just slightly excite the protons in the brain and as they relax back, they release that energy and we can look at that energy coming back and form images. And so if you go into the hospital for an MRI scan of your brain or your knee or whatever it is, you'll get these beautiful images. What we do is (A) we've got a stronger magnet. So the seven Tesla magnet is strong enough to pick up a double decker bus. We're very, very careful about metal anywhere near it because it just gets sucked in. So it's really useful because it's so much stronger, it allows us to really look in detail - to get much more detailed images than we would with a standard scanner that you'd find in a hospital. That's quite cool. But as I say, there aren't very many of them in the world. And we do and they - we are pushing it all the time to do new stuff, so does tend to break reasonably regularly. So that's the MRI scanner we've got so we've got a seven Tesla, which is our fancy one, we've got two, three Tesla, which are much more normal ones that we do brain research on. And we've got all our brain stimulation kit, which we've sort of talked about. So we've got our electrical stimulation, we've got our magnetic stimulation - so we deliver a very short magnetic pulse of about a Tesla - smaller, that will just pick up a car - and that will cause an action potential in the brain. So it will cause the cells to fire. And so if you put it over the primary motor cortex – we talked about that already, the bit of the brain that controls the hand - you get a twitch. So we can use that to see how easy it is to get information from the brain to the hands - that can give us an idea of how active the brain is and what it's up to – which can be very useful. And the other bit of kit we haven't talked about, but we should talk about, because it's cool and it's new and we think it's really exciting, is ultrasound. So again, people will be probably familiar with ultrasound from scanning babies, right - the thing you put on the mother's tummy with the gel, and you get a nice picture of the baby. Great. So this

is the same thing at slightly different frequencies, but we put it on head. We can again use it to just change how the brain cells are firing. So use that to try and push that swing. And the exciting thing about that is we think we can go quite deep in the brain. So you can get all the bits in the middle of the brain that are really, really important that none of our other techniques will allow us to interact with.

Neddy

It's really amazing.

Charlie

We're very excited about it. Now talking of things that don't work - that has been years getting that to actually function, but it is now working, we're beginning to do some experiments. So that's (*Neddy:* really cool!). Yeah, we're quite, we are quite excited about it. We'll see. We'll see how much of it works! But it's been a real engineering challenge.

Ritika

What are the biggest challenges you had doing this throughout these years? And what does a day in your life look like?

Yes, I was shocked that one of my DPhil students is organizing a 10 year anniversary of our research group - I don't know where that decade went! I've been incredibly lucky with my students and my staff, they have been brilliant. I run a research group very much as a collective. We're not very hierarchical, partly because I think we get better science and partly because I do not have the time to micromanage people. And so they're given quite a lot of freedom. And they do brilliant things with it. I think, you know - I should have looked it up - somebody said 'You hire brilliant people, you let them get on with it - right - and I think that's what you do'. And I want them to have the ideas that I don't have. Because I can have the ideas I have, I want them to have the ideas they have. And I want them to argue with me. So that has been fantastic. And mostly I've just been really, really lucky. Increasingly, I have realized that actually, I'm just going to work with people who are nice human beings, because it just makes the world a better place. And once you've made that decision, actually, the lab becomes really nice place. What does the day look like? It's a giant juggling act! So I got two children and two dogs -actually the dogs take more energy than the children sometimes – the mornings are getting the kids to school, get the dogs fed and walked and that's all done by about nine. And then I'm like, surely I've done a day's work and it turns out, I haven't. So I get to work for half past nine. And then it's meetings with the group - they don't let me near actual experiments very much anymore. So occasionally, I get to go and play with a kit - but less than - less than I used to. Helping them with papers and grants and all kinds of stuff that makes machinery go around. I mean my job primarily is to get money for this to carry on. And to help people progress in their careers - be that get their PhD or you know, get those papers, get that grant, get that next postdoctoral position. And that's the nice bit actually – I mean I love the science. I love the science. That's why I do it. But actually seeing people progress and get their PhDs and then go onto postdocs, and then go onto being a PI is just really lovely. No, it sounds very corny, but no two days are the same. So I do a bit of teaching, a bit of lecturing, collaborations from all around the world. I'm just finishing up revisions on a paper from a group that we collaborated with in Taiwan who are brilliant. Had a visitor from Australia today. It's a really global game, and it's really good fun.

Ritika

I had no idea you people had – so much work!

Neddy

Do you have any advice to your younger self and what would be the best way to get into science?

Charlie

I think the most important thing is to do things that you really love. I think there's an awful lot of pressure on people to follow certain career paths. We talked a bit about people sort of feeling that they should do medicine. And I think partly because, you know, most of us - I think most scientists, you know, like science and want to help people right – I mean, who doesn't? And I think we sort of get cordoned into medicine, but people get sort of cordoned into other things as well. And I think having the courage to realize that it's not right was very stressful at the time. But I'm very, very pleased that I said, I don't want to do this anymore. I think I want to do research. I think that's what I really, really want to do. And it was a very difficult decision at the time, but it was the right one. So I think I would advise people to really think about what excites them. And that doesn't have to be what interests everybody else. But you've got to find your thing. And it doesn't really matter if all your friends go, that's really boring. Like, fine. I don't think it's boring. I'm going to do it. Have courage in that. And yeah, have courage in your ideas as well - pursue the ideas you think are worth it. I sort of laughed and said, our ultrasound has been giant engineering challenge. It's taken over 10 years. And it's working. And it's taken over 10 years, amazing groups of amazing people who are not me, you know, I sort of turned up occasionally and went 'Oh, is it working yet, oh no?'. You know, it's been, it's been a wonderful group of engineers, and physicists and all kinds of people making it work. And that really has been just doggedly going 'This is going to be cool. This is going to be important. This is going to allow us to answer questions we can't answer now. And those are important questions, and we're going to keep going.'. So I think having, yeah, the determination to keep going. So working out what it is you really, really want to do. And then having the sort of determination and the courage to think you know what, I'm just going to keep doing that.

Neddy

Yeah. And rejection is just redirection - as cheesy as that sounds?

Charlie

It is - it is true. It doesn't always feel like it at the time. But yes, I mean, being an academic, it is a career where you get told many ways in which we're not very good at something, a lot. And it is really important to learn that - they might not be right. And that actually, that's - they can have that opinion but you can have another go and do something slightly different. And these days, I sort of - when I get rejections, which we all do all the time, I sort of get cross about it. And I allow myself about a day to get really annoyed and just grumpy about it. And then I'm like, right, okay, I've done that now - how do I go on from here? And I think that's the important thing is, I think acknowledging that you are going to be upset by it and then yeah, thinking, okay, have they got any points? Should I listen to any of those things? Should I redirect myself slightly? Or am I just going to keep going with that.

Ritika

Oh, one more thing is you've been here a while now, how have you seen it change?

Charlie

I have been here. I've been here 18 years, which feels like quite a long time. I think one change that I've really seen, that I have noticed and appreciate is I think we are much more inclusive and much more diverse as a university than we were 18 years ago. I think we that has genuinely changed, and Oxford had, and certainly probably still has, to some extent, a reputation of being quite elitist. And I think that is becoming less. I think we are absolutely and unashamedly intellectual elite and we always will be. Like, you know, we take people who are incredibly bright, and that is what we do and I'm not going to pretend for a minute that isn't what we do. But I think that's the thing - I think that's the thing that should matter in the rest of it doesn't. And I think increasingly it's feeling that that's true. I think we've got more senior women around. I think, having Irene who I've known for many years as an early director of the center - who did my transfer report, terrifyingly - is now our Vice Chancellor. Having another woman is really important. I think the place is changing. I don't think it's changing fast enough. So I want - I want that to carry on. I'm at St Hilda's, which is what former female colleges: it's really lovely. It's really inclusive. It's really interesting. And it's a sort of model of what this place could be like. There are other places that are less like that. And I think I would like to bring them all - all with us. So I guess that's the most important thing, because I think, I think the science we do is brilliant. I think the only way we're going to carry on doing brilliant science is if we get all the brilliant people. Not all of them – some other people can have some of them, but the 'brilliantest' of the brilliant people, and that involves everybody. Oxford is not for everybody. But if you think it might be for you then apply, you know, and if you think neuroscience might be for you, then apply. Find out. Don't be too scared to try. Because the worst thing that can happen is that you fail, and that's okay. And we all do all the time. But if you don't try, you'll never know. And I think it's really important for Oxford that we encourage people who feel like they don't belong here. Because people do belong here. And it shouldn't matter. And it matters less and less what background people are from. If people feel like it's for them, if they feel like they want to do neuroscience then they should give it a good go and if it doesn't work, that's fine. Go and do something else. That's okay. But if you don't try you'll never know.

Ritika

In this podcast with Charlie, we dived into the many kinds of non invasive brain stimulation techniques used to study how humans learn new tasks. She explains her experience of being a physician-scientist and group leader at the University of Oxford, and details the nuances of arranging and managing interdisciplinary efforts to build, run and analyze data from large scale studies with human participants. She also shares her perspectives on how the scientific community of Oxford has evolved over the years and advises the next generation of scientists on how to deal with rejections and failure.

Katy

Thanks for listening in on our conversation today - we hope you enjoyed it as much as we did. Please keep an eye on our social media to find our next one.