Transcript of Cerebrum Podcast – Rewiring the Brain: Zapping With Precision

Guest: Maheen Mausoof Adamson, Ph.D., is the senior scientific research director for Defense and Veterans Brain Injury Center (DVBIC) at the VA Palo Alto Health Care System. She is also the clinical associate professor of Neurosurgery at Stanford School of Medicine. Adamson's expertise and interests span employing translational neuroscience methodologies for diagnostic and neuromodulation treatments for frequent health problems in patients with Traumatic Brain Injury (TBI). She also employs advanced structural and functional imaging modalities and biomarker assessments in veteran and civilian populations with brain injury. She has been a leader in identifying sex/gender differences in brain injury, particularly in the veteran population. She currently serves as principal investigator and Site-PI on numerous neuromodulation clinical trials funded through the Department of Veterans Affairs and Department of Defense.

Host: Bill Glovin serves as editor of *Cerebrum* and as executive editor of the Dana Foundation. He was formerly senior editor of *Rutgers Magazine*, managing editor of *New Jersey Success*, editor of *New Jersey Business Magazine*, and a staff writer at *The Record* newspaper in Hackensack, NJ. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: Did you know that there are more than 10,000 patent filings for brain-based devices that claim to help people develop muscle memory faster, lose weight, sleep better, overcome depression, anxiety, addiction, you name it? Many of the websites featuring these devices cite science as backing up their claims. How many of these claims are scientifically valid? As consumers, how can we separate hype from science?

Welcome to the *Cerebrum* podcast. To help us answer those questions is Maheen Mausoof Adamson, who is on the phone with us from Palo Alto, California, where she's Senior Scientific Research Director for the Defense and Veterans Brain Injury Center. She is also a Clinical Associate Professor of Neurosurgery at the Stanford School of Medicine. Maheen works with patients who have suffered traumatic brain injury and has worked on numerous neuromodulation clinical trials funded through the Department of Veterans Affairs and Department of Defense. Maheen is the author of our latest *Cerebrum* article, "Rewiring the Brain: Zapping With Precision," which is available at dana.org. So with that said, welcome to the *Cerebrum* pod. Thanks for being on the phone with us.

Dr. Adamson: Thank you very much for having me.

Bill Glovin: In your article, you talk about constructing your own device as a middle school student growing up in Pakistan. Is that where your interest in the field first started?

Dr. Adamson: In Pakistan, when you enter high school in ninth grade, you were asked to choose whether you wanted to be in the science division or whether you wanted to be in the humanities area, and I chose to be in the science division, and we did have these science fairs, and in one of those science fairs, although they were not as elaborate as they are here now, I did construct a device with my brother's help, and I remember some of my friends were creating the water maze and other devices, but I ended up making this electromagnetic device with my brother, and it was fascinating for me to see that you could move all these metals, and that is where my interest actually began.

Bill Glovin: So when and why did you come to the US?

Dr. Adamson: I actually came to the U.S. when I was 19 because I was interested in learning about different disciplines other than law and medicine. I wanted to explore anthropology. I wanted to look at archeology, and I thought that in the U.S. you could explore more disciplines. When I came to the U.S. I started taking all these different classes about world history and archeology, but because I was inherently a biologist, I ended up studying biology, neurobiology in particular and it's been nonstop since then.

Bill Glovin: Maybe you can explain to folks who are not that well acquainted with this topic very basically the difference between neuromodulation and brain stimulation, or is there even a difference?

Dr. Adamson: In the article we actually say that they are the same, so brain stimulation and neuromodulation are used in the literature sometimes as one and the same. However, brain stimulation is actually the act of stimulating the brain, and neuromodulation is what happens when you stimulate the brain, and what is the result of the brain stimulation. That's how I would like to think of it.

Bill Glovin: Neuromodulation was first used in the fifties and sixties and is now rapidly growing. Why is that?

Dr. Adamson: I think with every field you start with a certain hesitance, and I think common folk or people who are the consumers were much more hesitant to use the technique. I think people were scared, because from the beginning, neuromodulation was based from a very invasive technique in those days. It was called the electroconvulsive therapy, and it got a very bad name, I think, not just because of the fact that it was invasive, but also because of the media and some of the movies that were made. I think as time has gone on, the techniques have become, they're becoming very, very well known, and there's a lot of scientific evidence behind these techniques, and people are much more appreciative of them and are able to use them and utilize them for their health benefits.

Bill Glovin: Your article discusses two types of devices, invasive and noninvasive. Can you describe the differences?

Dr. Adamson: So invasive is basically what the word actually means. So invasive to me, the way we wrote it in the article is it's used for most severe cases, and it usually involves surgery, which means you would have to cut open the skull and actually go inside the brain to install or to put the electrodes in. So that means it's an invasive surgery. An example of that would be deep brain stimulation, and usually it's done in more severe cases.

Noninvasive is something that you do not have to do any surgery, and you usually don't have to do anything other than just sit there in a chair and use an electromagnet or direct current to actually move over your head in a certain spot so you can modulate the activity inside the brain by passing the current or the electromagnetism through the skull. I am not at all saying that there are no safety concerns with noninvasive. There are some safety concerns, and the inclusion, exclusion criteria of the patients is one of the biggest things that we have to keep in mind. Who is eligible for such a noninvasive technique? And there are certain FDA rules that you have to follow, but otherwise there is no surgery involved in noninvasive.

Bill Glovin: So let's take invasive for a second. What is that used for, in terms of treating disorders?

Dr. Adamson: So the example that I would give for invasive surgery that leads to is deep brain stimulation, and that has been a very strong area of research and has shown incredible benefits in Parkinson's disease, for example. I do not do deep brain stimulation myself, but the circuitry of deep brain stimulation has been worked out very well by Helen Mayberg as well as DeLong and Helen Mayberg's work actually used functional MRI circuits and validated that treatment for depression. And by putting the deep brain stimulation in subcallosal cingulate areas. And I think it is very important that these patients that suffer so much from severe diseases like depression and also Parkinson's, they can really benefit from these invasive surgeries that use deep brain stimulation.

Bill Glovin: So how exactly would it work for somebody who has Parkinson's, for example? Can you describe exactly how it would help them?

Dr. Adamson: It is actually one of the things that, again, I don't do deep brain stimulation work, but what they have shown is they particularly put electrodes in an area called the substantia nigra, and they can actually modulate the release of the neurotransmitter dopamine by stimulating that area. It is done in a way now, and there are some articles and some literature out there that actually they can do this also remotely and monitor the stimulation of these neurons in the release of this neurotransmitter remotely, and in severe cases of Parkinson's this can actually help with the movement disorders, and it is released throughout the day and in a manner that actually helps them with their function.

Bill Glovin: Can the same treatment, using a device that affects patients in different ways, in other words, might it work on one patient and not the other, and does that have anything to do with something called the brain fingerprints?

Dr. Adamson: So that is a very interesting question, and it's a very challenging question, because we are all, as neuromodulation scientists, thinking about this and using different ways to characterize a patient using not just their response to the treatment but actually their genetic makeup as well. So what I mean by that, we're not there yet, but the idea is that when you treat a person, some people respond to a treatment, their response to treatment is much nicer. The outcome is they have a lot of benefit from it, and some patients are what's called non-responders. They don't respond, or they don't respond as well as another patient.

The reason we think, as neuromodulation scientists, is that there are certain things that can be at play here. One is that it depends on the severity of their symptoms of the disease that we're addressing. Another thing is if you look at the mechanism of something called repetitive transcranial magnetic stimulation, which is RTMS, which is what I study, the mechanism of that is based on trying to change the concentration of neurotransmitters within the synaptic cleft, which is the main area between two neurons through which they communicate. If you're changing the concentration of that neurotransmitter, there are certain predispositions in each individual on how much that neurotransmitter can be made by their genetic makeup. So based on a person's genetic makeup, they either make a lot of kinds already or they make less of the neurotransmitter. So when I stimulate that area, you are already predisposed to make more or less. So in a way, my response to that treatment is going to be modulated by what my genetic makeup is in order to make that product.

So that is a very molecular way of explaining that each person's response to treatment may be different. Now, I don't know how that would be related to what's called brain fingerprinting. It could be. Brain fingerprinting in my mind is something that has to do with EEG, which is looking at overall evoked potentials over the cortical activity, and of course that is a higher order from looking at molecules. So if we could capture how the cortical EEG is, it may be related, but I think it's at this point I'm more interested in how we can characterize the treatment based on a person's genetic makeup.

Bill Glovin: I was very intrigued about the idea that you could conduct a clinical trial for a device that is planted in someone's brain. That seems kind of risky. Are clinical trials particularly difficult in this field?

Dr. Adamson: I think they are particularly difficult, yes. And I will say, since we're talking about two different devices, one device is invasive and the other is noninvasive. In invasive devices, of course they're difficult because you are looking for patients that are severe, and you have to recruit them, and you have to specifically go through some of the risks that could happen with surgery. Usually these trials have a good recruitment mechanism for a clinic and for a hospital, and that's

one of the things about clinical trials that I find very difficult, is finding the right type of patients and also recruiting them into the trial.

For the noninvasive category, the ones that I do, clinical trials are also quite challenging. And the reason why is not only do we have to recruit the type of patient that is specific for that trial, with inclusion-exclusion criteria based on all the safety and all the MRI safety and the FDA rules, we also have to retain them in the study, because the protocols we use are not a one day protocol. The FDA approved protocol for major depressive disorder is 20 sessions, which means they have to come in almost every day for a consecutive two and two and a half weeks. Maybe you could do two treatments a day. Which means you have to bring these patients in, you have to retain them, and we cannot really tell what's going on unless we do really good follow up. So follow up is hard. Retaining the patients is hard, and finding the right patient in the first place is hard. So those are logistics that are very, very difficult, but I think we're doing great because we are just working very hard at it and I think the scientific community realizes that.

Bill Glovin: A few minutes ago you, you talked about that invasive deep brain stimulation is very helpful in Parkinson's and depression. How about noninvasive, or is that also what we call transcranial direct current stimulation?

Dr. Adamson: Yes. So in the article I had divided these into two categories, invasive and noninvasive, and I actually do the work in noninvasive, which is RTMS, repetitive transcranial magnetic stimulation. So this type of treatment has been approved by FDA for major depressive disorder as well as obsessive compulsive disorder. There is a lot of evidence for this, and there's some incredibly wonderful people doing a lot of work in this. It is being clinically rolled out within the VA as well for treatment of major depressive disorder. It is being used to treat overall pain, TBI associated headaches, anxiety, post-traumatic stress disorder and other symptoms of traumatic brain injury.

It is noninvasive in the sense that it is an electromagnet that is positioned on a particular area of your brain and that area of the brain is stimulated according to a certain protocol, and we look at the effects of the stimulation by looking at standardized tests of neuropsychological performance, self-reports on depression scales and other scales. We also look at biomarkers. We look at changes in the blood in terms of the proteins that are changing. We also look at functional brain connectivity and other kinds of structural changes in the brain. Because we're able to look at these objective markers, we're able to see the changes that it is actually helping the patient with the problem.

Bill Glovin: So what would be required in terms of treatment visits? How long would a session go on for? But is there an average that you can tell us about, or does it just fluctuate according to the patient?

Dr. Adamson: It's a pretty big range depending on the type of disorder you are looking for and what is approved, and whether you're doing it off label or whether you're

following a specific FDA approved protocol. In my studies and in the studies that I'm involved with my collaborators, we're doing several things. I'm following a 20 session protocol, which means I can do three sessions in a day, each session is 20 minutes long and then you can actually miss a day or two and then make sure that they come back, so you can complete 20 treatments in about two and a half weeks or something. And the most important thing in this is that you either use the treatments that I'm using, the protocol that I'm using, it's a excitatory protocol, which means that you stimulate at 10 hertz.

There are labs and other places that are also using inhibitory protocols for different disorders, so one hertz, and of course there are other protocols that are now being developed that are shorter in duration and have received a lot of wonderful feedback from the consumers as well as patients. One is called a theta burst, which is much shorter, and I think that's where the field is going. It's because 20 treatments, it's quite long and retaining patients is quite long. But patients are willing to come and do it. Theta burst is a shorter protocol. There's another protocol that I'm following with another collaborator at UPCSD, and it is particularly for improvement of pain symptoms, and that's only for five days, and it's one session of stimulation that takes about five to 10 minutes, and it's for five days. So depending on the patient needs, depending on what you're treating, the protocols can vary, and we were seeing effects in all different ways.

Bill Glovin: Now all of these methods, are they all FDA approved?

Dr. Adamson: So the method that I'm using for treatment of, I'm particularly looking at traumatic brain injury patients, and they have chronic problems. So their traumatic brain injury happened five to 10 years ago. I am using an FDA approved protocol for major depressive disorder, but I'm using it in TBI patients, and one of the most important things to understand from this is that that protocol was approved for major depressive disorder, not for traumatic brain injury patients. So for a researcher to actually borrow a set protocol and use it in different population, you have to go through what's called an FDA IDE, which is investigational device exemption, and people are very scared of going through any of this, but I actually have two of those now, and FDA has been incredibly helpful in developing this protocol with me and making sure that I am following all the safety protocols and doing it correctly in a population that has not been studied before.

Bill Glovin: Interesting. And we hear all the time about people who are sort of doing this on their own, buying devices over the internet, not having sort of medical supervision. Do you find that as well, that there's a population out there that is putting themselves at risk by using noninvasive stimulation?

Dr. Adamson: So I have actually two answers for that, and I'm going to go ahead and explain both of them. I'm very fortunate to live in a very self-aware, very educated environment in the Bay Area. People are always full of questions and always reaching out to providers and to researchers, asking them opinions about what

they can buy on the internet, and I'm hoping that they're very, very careful about what they read and not just Google it and buy it. I've had a lot of inquiries, so I think there's a lot of smart people out there who ask the right questions, but I also think that there's a lot of people who are very desperate, and I'm worried for those people because they do buy these things online.

Now, the kind of research that we do, obviously those machines cannot be bought online. They're obviously very big machines. They cost a lot of money. There's a lot of regulatory stuff that you have to go through. There are certain devices that are available online that are FDA approved, and they are what I call at-home version of doing something like this at a much smaller scale, and they are FDA approved, and I think that there's a lot of evidence for some of them to improve at home, say, migraine, but at the same time it is a much smaller effect and it is something that you can do at home, but it does have evidence that it does provide some relief.

Bill Glovin: Interesting. Are there enough regulations or oversight when it comes to wearable brain devices?

Dr. Adamson: I think we are at the beginning of this. We don't have enough data that integrates what is happening in the brain when we stimulate it with what's happening with a wearable. I think FDA needs to really watch this space very carefully, and as more data comes out, as we provide more pilot data, more grants are funded, I think depending on patients' needs and their specific symptoms, we have to be very careful and provide more guidance in this, because right now people are just discovering how a wearable can be connected to how you stimulate certain areas in the brain, in your own brain, and that is what I wrote in the article, that that really would be precision medicine, is I know how to start it and I know how to stop it, and I know my dose, and I know exactly what I'm targeting it. And I think those are questions that still need to be answered, and we have to be very careful, and FDA will have to create rules around it, but it's a fascinating field and I know we'll do that.

Bill Glovin: In your work as a clinical researcher, take us through some of the kinds of patients you'll be treating this week and what you hope to accomplish.

Dr. Adamson: So I have been working within the VA Palo Alto system for about 15 years. I have worked with veterans, and I've also worked a little bit with the military and civilians with post-concussive symptoms. I think what's important to understand is that veterans who come to me for traumatic brain injury problems, they had their traumatic brain injury a long time ago and they still are suffering from symptoms. So a patient that is enrolled in my clinical trial is first of all either going to have mild or moderate traumatic brain injury. I have some severe patients that I've dealt with, but mostly they are mild and moderate. But the key thing to understand with these patients is that they have suffered a lot, and they have chronic problems that are not just one problem, but a lot of them. So they will have a traumatic brain injury associated headache. They may suffer

from post-traumatic stress disorder. They may also have depression. They may have anxiety, they may have overall fatigue, overall pain, sleep problems.

So when we see patients, for us, traumatic brain injury, it's a very big umbrella term, because under it we have all these comorbidities that we are dealing with. And these patients are incredible in terms of coming in and being in the clinical trials with us and helping us actually keep them in the clinical trial and come back to us for follow up. And it is a challenge to really tease out what's happening in the brain if you have more than one problem. We, as scientists, would love to have a pure sample of patients, but there is no such thing, and I think it makes my job very exciting and challenging because we can actually characterize a patient based on their most salient symptom, and try to treat that symptom. And that's what I've been trying to do, is to look at either cognition, improvement in cognition, improvement in pain, improvement in depression, but that doesn't mean they don't have other problems. So that in crux is what my patients look like. Veterans with a lot of comorbidities.

Bill Glovin: I mean, have you seen people kind of walk out of your clinic after being treated for a period of time completely okay? Or is that very rare?

Dr. Adamson: I actually am going to do very honest with you. My clinical trials are double blind trials, and I actually don't see the patient as much. I see them once or twice. I try not to see them. My research assistants see them, and my lab members see them, because what ends up happening is that we take our baseline testing, and then we treat them, and then on the last day of the treatment we take our full treatment outcome assessment. We all also get an MRI, and then we ask them to come back in six months. So we actually are able to keep in touch with them and see whether they've approved, and I only see what the improvement is in terms of numbers and in terms of grade scans. I actually don't, when I see them, they're all just wonderful people. I don't like to say that I've seen a change in them because of what we did. This is, again, a double blind clinical trial and I'm not a provider.

Now this is a completely different story when you talk to a clinician who's using RTMS in their clinic to treat depressive patients and they will tell you stories, although my colleagues have told me stories who are providers, that they have seen changes in their patients, but then again, it's treatment. It is not a double blind clinical trial.

Bill Glovin: Right. Does neuromodulation, as it relates to finding answers for depression and other disorders, get the necessary funding that it needs?

Dr. Adamson: I'm a scientist and I am always asking for funding, so my first answer would be no, but if I really do give you a much more of a guesstimate, if you compare developed countries where this is really happening a lot, it's happening a lot in Netherlands, U.K., Australia, the U.S., I think everybody is really doing well and providing us evidence to move this field forward. It is not the best amount of funding. I think there is still some hesitance from the grant agencies and from

the granting agencies, specifically in terms of certain disorders or areas where there's less data, so I think there needs to be a little bit more funding specifically for areas like Alzheimer's disease or traumatic brain injury, because these areas that are just starting to use neuromodulation. If you look at it in an international front, I think we need a lot more funding. There is a lot of brain injury and a lot of dementia happening in a lot of other countries where this technique is just about to start, and I think collaborative efforts are really necessary in order to provide this treatment to other countries as well, so funding has to start from global consortiums.

Bill Glovin: Well, this is a topic I think we could talk about for hours, but I think that's a good place to end. So I want to thank you again so much for your fascinating article, "Rewiring the Brain: Zapping With Precision," which is available at dana.org, and thanks for all your important research in an area that is vital to the health of our veterans. Here at the Dana Foundation, we wish you luck in all your research and in treating patients or doing your clinical research work.

Dr. Adamson: Thank you very much.

Bill Glovin: And I'd like to thank the listeners, and we hope you enjoyed our *Cerebrum* podcast with Maheen Mausoof Adamson. See you next time.