54| Non-Invasive Brain Stimulation – With Dr. Adam Woods

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NAVIGATING NEUROPSYCHOLOGY

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Speakers: Adam Woods, Ryan Van Patten, John Bellone

Intro Music 00:00

Ryan Van Patten 00:17
Welcome, everyone, to Navigating Neuropsychology: A voyage into the depths of the brain and behavior, brought to you by INS. I'm Ryan Van Patten…

John Bellone 00:25
…and I'm John Bellone. Today we're bringing you our conversation with Dr. Adam Woods on noninvasive brain stimulation. Dr. Woods is an Associate Professor in the Department of Clinical and Health Psychology at the University of Florida. His training is in cognitive neuroscience with a strong influence from neuropsychology.

Ryan Van Patten 00:45
Right. So today we get into noninvasive brain stimulation with Adam. But before that, I wanted to point out that it is September 1, which is our two year anniversary from the first NavNeuro episode ever released. Congratulations, John.

John Bellone 01:00
Did you buy me a present, Ryan?

Ryan Van Patten 01:01
[laughs] Never.

John Bellone 01:04
[laughs] Of course. Of course you wouldn't.

Ryan Van Patten 01:07
It's only been headaches. [laughs]

John Bellone 01:09
Yeah, we're really glad that listeners still find it useful. We get lots of comments and reviews that listeners are enjoying this so we could not be happier for that.

Ryan Van Patten 01:19
Yeah, it's been great.

John Bellone 01:20
We will keep doing this for many more years hopefully.

Ryan Van Patten 01:25
Okay, so to shift back to today's topic. As John mentioned, we talked about noninvasive brain stimulation with Adam. Specifically, we talk about transcranial direct current stimulation, or tDCS and transcranial magnetic stimulation, or TMS -

two of the more popular types of noninvasive brain stimulation, in particular in clinical psychology, neuropsychology for those neuropsychiatric conditions. These are complex techniques from a physics and engineering perspective and we do ask Adam to go into some of the technical aspects of each technique just to give us a baseline understanding. That's about the first 30, 35 minutes of our conversation with him. So just be aware of that. After that, we get into a lot of clinical applications, which are just fascinating. So I know I, for one, am thoroughly appreciative of Adam's knowledge in this area, which is a niche. It's a world in and of itself. But it's great for us to learn more about it. So without further ado, we give you our conversation with Adam.

Transition Music 02:34

John Bellone 02:43
Adam, thanks for joining us on NavNeuro. We're excited to have you on.

Adam Woods 02:46
Thank you for the opportunity to join both of you today.

John Bellone 02:49
We'll assume that our listeners don't have a background in noninvasive brain stimulation. We'll cover the basics, if you don't mind, and we hope to get into the weeds with you as well. But we want to be respectful of your time, obviously. After we address the big picture, we can go as granular as we can. We also want to emphasize the high degree of technical complexity in this area of study. We'll focus on what we do know as much as possible in order to provide our listeners with take-home points. But, just to start, could you tell us about transcranial direct current stimulation, tDCS, and how it works?

Adam Woods 03:26
Sure. So transcranial direct current stimulation is a technique that really in its current iteration came about in 2000. Investigators in Germany, Michel Nietzsche and Walter Palace, did some early experiments that have been inspired by work that had actually been done in the ‘50s and ‘60s, where that work had demonstrated that the application of a direct electrical current, a weak direct electrical current, could alter how neurons behaved in controlled studies in rats and in mice approaches and a variety of others. And these clever scientists then

decided to attempt to evaluate whether or not direct electrical currents, when applied to the human, can actually have an effect as well on neurons. And from that time, in 2000, we see an exponential number of papers that have used this technology. At its base, this technology, what we know today, which is not all encompassing by any means, is that the application of a weak direct electrical current to the scalp can penetrate the skull, the skin, the meninges, and stimulate the underlying gray and white matter tissue in the brain. That stimulation can subtly alter the resting membrane potential of neurons. In many ways you can think of the resting membrane potentials in terms of our readiness for that neuron to fire. If you nudge it up or down slightly, those neurons can be a little more likely or a little less likely to fire. At its base, tDCS is a technique. It's attempting to alter those resting membrane potentials to alter the probability that neurons that are stimulated are going to fire. And with that, it's an important distinction with other forms of noninvasive brain stimulation where you may actually cause the neurons to directly fire. You apply stimulation, neurons fire. In this case, we're not causing the neurons to fire, we're actually leading to these neurons being a little more likely, or a little less likely to fire. So tDCS is a technique that we call noninvasive because we're applying a weak electrical current that has actually been shown over the years to be quite safe and also quite tolerable when delivered in the typical range of current intensities, which we typically think of as one to two milliamps of direct current applied to the scalp. In a paper we did, I guess it was 2016, we show that in over 30,000 stimulation sessions, there had been zero serious adverse events. That means no one went to the hospital, no one developed disease, no one died as a result of the stimulation sessions that occurred in over 3000 people. So in many ways, that is a safety profile that is very exciting, where you can potentially impact the brain directly, and do so in a way that really plays into this concept of neuroplasticity. So before I just go on into a long monolog on all this, why don't you guys keep going with your questions?

John Bellone 06:32
That was great. You can keep going.

Ryan Van Patten 06:34
Great intro.

John Bellone 06:35

Yeah. It was a good summary. We'll obviously dive deeper, but I know your expertise lies more in tDCS than transcranial magnetic stimulation, TMS. But can you give us a broad overview of TMS and how it might differ from tDCS?

Adam Woods 06:52

Sure, absolutely. So TMS, or transcranial magnetic stimulation, the iteration that we all know today in the field really came about in 1985, with work by Anthony Barker. But the knowledge that underlies TMS, transcranial magnetic stimulation, actually was found by Michael Faraday in 1881. The principle that underlies the effects of TMS is electrical induction. So tightly wound copper around a coil and applying electrical current through that, you can generate an electromagnetic pulse. So TMS attempts to deliver an electromagnetic pulse through a coil that's applied on the surface of the head. And that electromagnetic pulse creates electrical induction within the tissue. So it's actually creating electrical current in the tissue, usually between 1.5 to 3 centimeters from the surface of the scalp. So really the surface of the cortex. To give a direct comparison, tDCS is also attempting to stimulate the cortex and the underlying tissues. The TMS generally generates about a 0.1 amp per meter square level of stimulation at the cortex, whereas TMS generates usually somewhere between 1.5 to 4.5 amps per meter square. So TMS is definitely a much more powerful electrical current delivered, it is also safe. Now, in terms of its safety profile, there has been, with certain TMS techniques, a number of cases where someone has had a seizure as a result of receiving certain types of TMS. That's not the same in tDCS. But even still, it is a very, very safe technique.

Now with TMS a critical difference between tDCS and TMS is that TMS is powerful enough to directly generate an action potential. So, for example, if I put that TMS coil over the motor cortex on the right side of my head, and it's a powerful enough TMS pulse to be above motor threshold, you'll actually see a twitch of the fingers or a motor evoked potential. That's actually a sign of the fact that you have generated action potentials in those motor neurons in the hand area of the cortex. As a result, you get movements in that limb in that stimulated region. So, again, a much more powerful electrical current. It is the older of these two techniques by almost 15 years, and it has a very robust and expanding literature, just like tDCS. tDCS, in many ways, is falling that pathway that was really forged by TMS in many ways.

Ryan Van Patten 09:39

This is a great intro and overview of the two different techniques. Before we get into literature and clinical disorders, let's touch on the technical side of both. So we'll

start with tDCS. Tell us about the parameters to consider when implementing the technique - current intensity, electrode placement, duration of stimulation, etc.

Adam Woods 09:59
Sure. So with tDCS, there are a number of parameters to consider. One of those, of course, is how strong of a current are you going to apply to that, so the intensity of stimulation. Typically speaking, most paradigms that have been used in literature today use between one and two milliamps, although we are seeing a number of studies coming up and are now using three and even four milliamps with the field pushing beyond that. In addition to intensity of stimulation, it's also a matter of where you're going to place the electrodes themselves for tDCS. In general, you have to have at least two electrodes, one an anode and the other a cathode. The anode is where current is injected into the scalp and the cathode is where current is pulled back out. So you're creating an electrical circuit and where you place these electrodes on the head is going to dictate the pathway current is going to go from the anode to the cathode, meaning it's going to dictate where in the brain you stimulate.

Now tDCS has a couple of different variations. One as we typically talk of is conventional tDCS, which uses, typically, sponge encased biocarbon electrodes. Biocarbon being rubber electrodes are embedded with carbon, so they conduct electricity. Those are encased in sponges that are saturated, typically saline, and they can be rather large - 25 centimeter square, 35 centimeter squared, so forth. And these large sponges are placed on the scalp, the resulting stimulation you receive from that as a very broad array of stimulated tissue. Alternatively, you can use an array of electrodes, a small, say, one centimeter diameter, silver-silver chloride electrode. They can be configured either in a 4x1 approach, kind of an X shape, or in any number of arrays of electrodes. In this 4x1 or X shaped electrode pattern, you would typically have, say, the anode in the center and in the surrounds of that X, you would have the cathodes. And, with that, you can deliver much more focal stimulation from tDCS. Some people refer to this as high definition tDCS or multi-electrode tDCS. But as a result of getting a more focal stimulation pattern, you also get a weaker level of stimulation of the cortical tissue and not as much depth of stimulation.

So determining where and how many electrodes you're going to place are a critical feature of dosing parameters that have to be considered. If you're targeting the frontal lobes, you may use something like what we think of as an F3-F4, that's a 10-20 EEG nomenclature. It's a grid based system that electroencephalography has used for many decades to determine common locations on scalps and heads

because all heads are different sizes. It involves a series of measurements that you take from known landmarks like the bridge of the nose, the bump on the back of your head, on the periauricular notches, and creating a grid that allows you to identify on these heads of different shapes and sizes, very specific locations, F3-F4 would be near the very front of the head, typically over roughly the dorsolateral prefrontal cortexes. So that might be a target location for a conventional tDCS montage to stimulate the frontal lobes. But if I were going to target parietal lobes, I might use something that's like P3-P4 or CP3-CP4. These are locations towards the back of the head, but over the parietal cortices.

In addition to that, there's also the duration of stimulation in a session. Very often, we see people using 10 or 20 minutes of stimulation. To a lesser degree, people have used 30 minutes of stimulation. The convention of duration of stimulation in many ways in the literature is based on what's been done previously and what was shown in those previous studies. There's nothing saying that a longer duration of stimulation could not be used. But with each of these parameters, they have an impact on the underlying tissue. And the ultimate results you receive in terms of excitability of tissue can actually be modified by these different parameters. There's some studies showing that, in stimulation up to 30 minutes, in the last five to seven minutes of stimulation excitatory effects may actually become inhibitory due to calcium channel involvements. Whereas also there's studies showing with 1 milliamp versus 2 milliamp, there could be very big differences in terms of how the tissue responds in terms of excitability onto those electrodes, which I can definitely dig further down into.

But in the parameter space, beyond that, you also have to think about how often am I going to stimulate people? It's an experimental design, I might do a single session of stimulation compared to a sham version of stimulation. If it's a treatment study, am I stimulating five days a week, three days a week? A lot of literature, even going back to the early 1950s and ‘60s had shown that additional stimulation, additive effect of stimulation, that stimulation on subsequent time points had greater effects than a single stimulation alone. So that's yet another parameter that's important. And then the more nuanced parameters become the timing of stimulation, especially in the context of clinical or cognitive applications. Am I applying the stimulation as a standalone intervention? Or am I applying this as an adjunctive intervention where I might be pairing this with some kind of cognitive behavioral therapy or cognitive training or something of that type? And there's actually been a growing body of literature from a group led by Colleen Loo and Donel Martin in Australia, as well as our group, the University of Florida, showing both from functional imaging studies, as well as from behavioral studies, the timing

of application actually has a significant impact on the outcomes from tDCS. Specifically, that stimulation during the actual training that you're attempting to facilitate tends to create much larger effects and potentially more clinically meaningful effects than stimulating either as a standalone intervention or stimulating before you were doing the specific task of interest.

So those are the major parameters. There are a variety of nuance parameters we can go into all day long, regarding electric shapes, size, so forth, and so on. But in terms of the major parameters for consideration, those are the top of that list.

John Bellone 16:20

You really have so many factors to keep in mind. You have a lot of control over it as well, it sounds like. Each of these can be modified to some degree. Just to solidify the differentiation further between tDCS and TMS for our listeners, would you think it's fair to simplify it down to tDCS is an electrical current, TMS is a magnetic field. Those are the two main differences, right? I know the electromagnetic force is paired together, so seems a little bit like a false dichotomy.

Adam Woods 16:53

I would say that both are actually electrical stimulation techniques. You're using an electromagnetic pulse to create electrical induction, but ultimately, the effective TMS is still based on the electrical current that is induced within the tissues. So I would think of both of them as electrical stimulation techniques. One is simply applying direct electrical current to the scalp. The other is using a very careful and clever application of this Faraday principle of electrical induction to deliver the same but more powerful current in the head by inducing electric current through this use of an electromagnetic field.

John Bellone 17:33

That really helps. Yeah, that really clarifies things. Can you give us a sense of the parameters of the TMS application, including single pulse versus paired pulse, repetitive TMS? Because similar to tDCS, this is often repeated many times. There's not just one application, right?

Adam Woods 17:52

That's right. That's right. So the same added principles appear to apply with TMS and apply to tDCS. The parameter space for TMS is similar and different. So, of course, you have the strength of the electromagnetic pulse that you're going to generate and that's going to dictate the strength of electrical induction that occurs in

the head. So the strength of the pulse is one. Pulse amplitude is often what is referred to in TMS but we're still talking generally about intensity. You have, of course, as you were mentioning, you have a single pulse, which is a single pulse of TMS delivered with a period of time given between that before another single pulse is delivered. This is a technique that's often used when you're attempting to determine motor thresholds. So this paradigm where you place the TMS coil over the hand knob of the motor region and then measure the motor evoked potential typically using muscle electrophysiology techniques. That would be a case for you to probe and adjust the amplitude of stimulations and the intensity to determine the motor threshold of that person for stimulation. That's a technique that's very often used to ultimately titrate how strong the pulse you're going to give an individual. That's often used in the context of setup for a repetitive TMS approach. A repetitive TMS is giving you a train of pulses at a certain frequency. So instead of one pulse, you might be getting 20 pulses in a second or one pulse in a second. And so, we often talk about this parameter in terms of hertz, 1 hertz stimulation versus 20 hertz stimulation.

Just like the intensity of tDCS, the frequency of TMS can have different impacts on the excitability of tissue. For example, by and large, the field thinks of 1 hertz repetitive TMS as diminishing excitability or inhibiting excitability, whereas 20 hertz stimulation is thought to facilitate the excitability of tissue after the stimulation session is done. There's also a method called theta burst stimulation, which gives you a very rapid train. And it can either be continuous theta burst stimulation or intermittent theta burst stimulation, where you can have varying bursts of stimulation with very rapid pulses that are delivered. This is definitely one of the newest methods in TMS.

And, as you mentioned as well, there's another paired pulse approach where you might actually pair the delivery of pulses relative to an external stimulus that is delivered, where you may attempt to inhibit or excite, for example, the tissue in relation to an actual event in a paradigm an experimental paradigm you're doing. But the depth of parameters in TMS is just as broad as the depth of parameters in tDCS. The shape of the pulse whether it's a square pulse or a sawtooth pulse or a variety of other features of the shape of that pulse is one that could also be modified. Typically, the user does not have access to modify that particular parameter, the pulse, it would be a manufacturer specific selection for the shape of the pulse. But it is a parameter that has and can be modified and used although less so, especially in clinical applications, where specific devices and specific parameters are being applied for treating a specific condition.

Also, of course, just like with tDCS, we have, how often are you going to simulate? A single session is great for experimental studies, but in treatment conditions, this is where multiple sessions, 20 or 30 sessions might occur over a period of time.

Ryan Van Patten 18:02

So, in terms of TMS, repetitive TMS is what we would see used in neuropsychiatric populations. Before one begins our TMS sessions, they would be given a single post TMS in the motor regions to titrate the level because I might need more stimulation than John or somewhere else, so it's individually tailored to the person. Then once they find the threshold to create an action potential for me, then I can transition to repetitive TMS for my treatment. Is that accurate?

Adam Woods 22:09

That's a great summary. That's exactly right. And you can think about the features of this to where skull thickness, CSF space, a variety of other features are going to be different for every single head. And so this is a clever technique for trying to titrate and personalize the application. This is actually an area where TMS has far exceeded tDCS. tDCS is still stuck in this fixed dosing era, where typically tDCS is applied, let's say, at 2 milliamps to every single participant. However, we know that every single participant's brain is slightly different. If you're testing a 20 year old versus an 80 year old, you could expect atrophy to come into play. People naturally have thicker or thinner skulls, differences in CSF space. And each of these impacts the behavior of electrical current for both TMS and tDCS. There's a lot of work ongoing in tDCS to move towards a more precision dosing application. Our group and a number of others are working on this at present. But TMS has used this technique for a very long time to try to titrate. And, as it's demonstrated, you can apply just a single intensity and get the same level of efficacy across all participants because there's a necessary titration of the strength of that pulse because of these different physical differences that will impact the strength of electric current delivered.

Ryan Van Patten 23:27

Yeah, that same principle applies to pharmacotherapy and psychotherapy, right? Like my pharmacokinetics and dynamics are different than someone else. So I need the right dose of medication. Yeah. It sounds like there's a lot of progress being made.

Adam Woods 23:42

That's exactly right. You don't talk to your physician about hypertension medicine [and] they give you that one dose that works for everyone. No, it's titrated based on height, weight, a variety of factors that are going to be necessary to both consider the metabolics situation as well as other factors. And so that titration is a critical feature.

Ryan Van Patten 24:01

Yep. So you had mentioned some research on safety in both tDCS and TMS where tDCS has, there has been, as far as I understand, zero safety concerns. TMS is close, but it has induced a few seizures. What about tolerability? So not so much worrying about mortality or morbidity but comfort during the procedure? What would someone expect?

Adam Woods 24:28

Well a quick side note on safety with tDCS. It is safe when done correctly. If you do not apply tDCS carefully and correctly, you can actually burn the participant's scalp. And so there are considerations to keep the techniques safe. And so we've spent a lot of time, we and a number of other groups, both in publications as well as teaching workshops and a variety of other things, because if not done correctly, a) it's not going to be safe, you may burn someone which is entirely avoidable if done carefully. But, b) you may not also have a reproducible approach that can be applied to each individual person consistently. And so outside of doing the method incorrectly and burning someone it is incredibly safe when done appropriately.

In terms of tolerability, tDCS has been very well tolerated. Typically what you experience is a tickling, prickling, maybe a mild burning sensation. But one of the participants reports, if you give them a scale of 1to 10, usually in the 1 maybe 2 range. At higher intensities, you get more skin sensations. One of the beauties of the skin sensation is that typically participants will habituate to the skin sensation within around 60 seconds and at most usually around 2 minutes. Now that's not to say that everyone habituates. They do, to some degree, habituate to the sensation so it becomes more tolerable after a short period of time. But many people will actually cease to feel the sensation of stimulation because it is very mild. When I first started tDCS, and I work with older adults primarily, I was really concerned that participants would be very, very worried and afraid of the technique. And I've been pleasantly surprised. I was like, “That sounds very cool. That sounds like an interesting idea. I want to try that.” But inevitably they come in and then we start their first session and they're getting ready, and they're a little worried. And then they feel the sensation. They go, "Wait, that's it? Oh. Okay."

Ryan Van Patten 26:27
[laughs]

Adam Woods 26:27
So it's very mild and it's very tolerable. Now as we move into the 4 and 5 milliamp range, that's going to change quite a bit. So what I'm saying is specific to the range, and it's been well studied to date, between 1 and 2 milliamps and now moving a little closer to 3 milliamps, it's very well tolerated.

In TMS, in many ways, the tolerability is dependent on where you're stimulating. tDCS will feel roughly the same no matter where you place it on the head. But because of the fact that TMS can generate action potentials, and we have these wonderful cranial nerves located across different parts that we can access from the scalp. If I'm stimulating over the parietal lobes where there's really kind of an absence of access to these, I don't really feel anything, what I do have is an experience of hearing a really loud click because I'm generating something relative to about 2 Tesla have a electromagnetic field and there's a loud pop from the coil. And so this is why with TMS, you are required to wear earplugs or hearing protection, because it can actually cause hearing loss because it's incredibly loud. It's like standing next to a jet engine that turns on and off in a matter of

milliseconds, or a couple milliseconds. And so that can be uncomfortable, with hearing protection that's very well tolerated.

However, if I move from parietal lobes to frontal lobes, well, there's all these cranial nerves that I have access to in the frontal lobes. And sometimes it can be relatively uncomfortable. When you stimulate, you may get contractions of the facial muscles and various other components. Now with that, with a little bit of experience of that sensation and knowing what that sensation feels like, that too becomes quite tolerable. You might sit with your eyes closed, the contraction of the eye muscles isn't so severe. And with the proper titration of TMS, that sensation is not going to be overwhelming. So it turns out TMS is also very well tolerated. But of course, it needs to be done correctly and appropriately, as well. But you can get some differences in sensation experience. The loud clicking noise is a constant you're going to hear, and those hearing protectors are really necessary. But participants who have a TMS and tDCS, both in clinical applications and research applications, have typically tolerated this very well. The one thing you can't account for is general anxiety. “You know what? I'm not sure about this. This is really scaring me. I'm not going to do this.” That's fine. And that does happen in both techniques, but the actual experience of it in and of itself is very well tolerated and very safe.

John Bellone 28:58
Gotcha.

Ryan Van Patten 28:58
Yeah. Overall, the side effect profiles that you're describing of both techniques, if we compare those to any medications, they compare very well. Right? A little tingling, very slight discomfort, a pop. If I could get that for most of these medications that are prescribed to people for neuropsychiatric conditions, they would love it.

Adam Woods 29:20
Yeah. Well, you took the words right out of my mouth, because that's exactly right. And that's the example I use. I'll put this against any medication on the market, but I'll take it because some of the side effect profiles we see in some of our mainstay medications aren't so pretty. And so, with that, what we're doing are techniques that are stimulating the brain and can have potential. They're not cure alls by any means, they don't treat everything, but there have been some very, very exciting effects of both TMS and tDCS out there. And now we see actually, in the past number of years, that TMS or rTMS is now FDA approved for actual clinical applications, which is a very exciting time for noninvasive brain stimulation, in general.

John Bellone 30:01
Yeah. I want to get to the clinical application in just a minute. You mentioned that you work primarily with older adults, can this also be applied in children and other populations?

Adam Woods 30:11
It can. So there are a large number of groups and a growing number of groups applying tDCS and TMS In children. There are special considerations that are required for applications in children. In fact, we published a paper - I think it was in 2012. Before a lot of work in tDCS in children had really come online, you'd see maybe one or two studies that time. And what we were seeing in those studies, they were applying the same 2 milliamps that are being applied to 18 to 95 year olds. And to us that seemed a little odd in that we know that, in children, their skull thickness is thinner, the CSF space is less, and there's a variety of other features. It's a smaller head, meaning it's a smaller medium to pass this amount of current through. And so we actually tested - me, Marom Bikson, and a few others and Sudha Kessler, tested computational models. So we did finite element computational models derived from magnetic resonance images that basically give

us predictive models of where the current is likely to go and how much current is likely to be there. And so we spent a great deal of time working on two MRIs from a child that was 8 and a child who was 11. And what we ended up finding was that 2 milliamps of tDCS in these children was basically delivering four times the current that would have been delivered in the average adult. And so what has happened since that time is the groups like Bernadette Gillick and others are doing phenomenal work in children with this work, very careful work have actually titrated their dosing, to reduce down to say, 0.75 milliamps, which would be comparable to certain parameters or even less using that early work to attempt to deliver a comparable level. Now, that said, if you look at the theoretically damaging tissue levels of stimulation meaning, at what point am I actually physically damaging the tissue, we are far below the levels that are thought to be damaging. And so it's not that those studies of children were potentially damaging, it's just they were in a different parameter space far removed from what we had tested so thoroughly in adults at that point. And so in TMS as well, there's careful consideration of titration. But again, using that motor evoked potential paradigm, you're already working to titrate that to an appropriate level of stimulation in that specific brain. And so with those careful considerations and considerations for applications, yes, both techniques are being used in child populations, but it takes a little more thought, just like in any special population, to make sure you're maximizing the safety of those participants or patients.

Ryan Van Patten 32:45

Yeah, that's really helpful. In research on both techniques, an important issue to consider is the control condition. Tell us about current methods for implementing sham tDCS and sham TMS.

Adam Woods 32:57

Sure, yeah. So the habituation principle I talked about where over about 30 to 60 seconds, maybe two minutes, you tend to stop feeling a majority, if not all of the stimulation effects from tDCS within this 1 to 2 milliamp range of intensity. The sham principles currently used is based off this concept of habituation where participants in all paradigms with tDCS, whether it's active or sham, we have a ramping period, where we typically ramp up over about 15 to 30 seconds from 0 milliamps up to let's say, 2 milliamps. The point of that ramp is for tolerability. It basically allows the skin to actively start habituating to that sensation. If I were to go from 0 to 2 milliamps immediately, there's a decent chance that I would get a retinal phosphine, which means a flash of light because I've stimulated the retinal nerve. And it also would hurt a bit more. But if I just take 15 to 30 seconds to ramp that

current up, the sensation starts very mild and gradually goes to the full sensation. But then usually within another 30 to 60 seconds, that sensation starts to peter off and go away. So for sham, we ramp up for 15 to 30 seconds, just like the active paradigm, hold the stimulation at full intensity constant for 30 seconds and then ramp that down to give you the sensation of stimulation without the full duration of stimulation. And so that's been the predominant sham method. Now that's not perfect as sham placebo goes because you are still getting some stimulation. The argument being that this is a much smaller dose of stimulation that is less likely to have longitudinal impacts on the tissue in the system. And so there's not currently what I would call an ideal sham. The ideal sham would be I feel nothing during active stimulation and I feel nothing during sham stimulation, requiring no stimulation at all. There's a number of groups working on better shamming approaches, they don't exist at present. So what we call a brief sham approach is what you will see in a majority of the studies within literature.

In terms of TMS, the shamming procedures there can vary quite a bit. Everything from having a sham coil that makes the same loud pops as you hear in the active coil that creates an auditory sensation that is very similar, but the physical sensation itself, you don't have the same experience. For example, if you're over the frontal lobes stimulating and you're getting those contractions of eye muscles and other features and experience in the cranial nerve stimulation, you wouldn't get that with only a sham coil. So instead, one of the techniques has become in both the active and sham conditions to apply a series of electrodes on the scalp. And in the active condition those electrodes are turned on, but you deliver the TMS stimulation giving you all these skin sensations. In contrast, though, during the sham condition, your sham coil is popping and making all the same noises, but these electrodes are actually giving a very quick pulse current. So like a square wave rapid - let's say you're doing 20 hertz TMS stimulation, it's giving a 20 hertz, rapid pulse electrical current stimulation to the scalp. And now that mimics the sensation perfectly. You get the same twitches, the same sensations, it's going to be roughly up at 8, 10 milliamps or so because with pulse current you can get much higher levels of stimulation. And so that is a perfect match of the active profile. However, though, there is the question of whether or not that pulse current is actually having some kind of active impact on the tissue. Presumably the TMS, which is still far more powerful at the cortical level, we'd be having a greater impact. But that's not to say that that is a perfectly inert sham approach. And so in both methodologies, there still needs to be improvement for having the perfect placebo. It's not like in drug trials where it's like I gave you a sugar pill. Done. It looks the same, the taste profile is the same, what have you. Done. So it's not there. But these sham techniques are fairly rigorous and they've been used and tested fairly

extensively over the last 10 to 15 years. So at present, those are the most common, I would say, rigorous sham principles. But I'll be the first to point out that they're not perfect.

John Bellone 37:14

Yeah, those are pretty clever though. So let's talk about the clinical literature. Can you tell us about the evidence for tDCS and TMS in neuropsychiatric conditions and also the potential mechanisms of improvement in those conditions?

Adam Woods 37:30

Yeah, so I would say a large body of work in both domains is in treatment resistant depression, unipolar and bipolar depression. And so, again, TMS had a 15 year lead on tDCS. By all means, it's much more advanced in this domain. At present, there are no FDA approved treatments using tDCS. But for TMS there are FDA approved treatments or applications for treatment resistant depression, as well as obsessive compulsive disorder. And so those two domains have received perhaps the most clear evidence in the context of pre-approved FDA trials in TMS. And it's now a mainline treatment that is being used all over the country for treatment resistant depression. If people had failed on two medications, at that point, they become potentially eligible for you doing TMS which usually is something like a 6-week 30 session, 40 to 60 minutes per session, series of treatments with repetitive TMS and tDCS. There has been a lot of work done in depression. And I would say probably more work done in depression than in other neuropsychiatric domains, although there's been a smattering of work across a wide variety.

So the evidence in tDCS today is not as convincing as TMS and that's part of the reason there's no FDA approved application for tDCS yet. But there has been a wide variety, there were a large number of small studies testing primarily unipolar depression and showing significant benefits, or at least benefits equal to a compared medication. And the medication on the top of my head, I can't recall, but André Brunoni, his work out of Brazil, he's been a leader in this domain. But there's also been mixed results. For example, Colleen Loo led a multinational trial for treatment of depression with tDCS. And ultimately, that trial failed. Now there were some selections of parameters that were perhaps not the best choices for the final trial where they stimulated 2.5 milliamps, which we don't know a lot about and then stimulated 30 minutes. In hindsight, it's unfortunate for them after that trial had already started [and] they were locked into the paradigm, data came out showing that the effects of stimulating beyond 20 minutes can actually reverse the polarity of impact on the tissue. And also demonstrating that 1 and 2 and 2.5 and 3, don't

deliver the same types of excitability to the tissue. An example being that at 1 milliamp a lot of what we know about tDCS is that under the anode electrode, it tends to increase excitability, but under the cathode electrode, it tends to decrease excitability. Then Michael Nietzsche and others did a series of beautiful experiments, the most recent coming out last year, that demonstrated that 2 milliamps, it actually turns out that you get a net increase in excitability under both electrodes. And then at 3, we find that it flips yet again. So the differences in parameters can cause different impacts. But if you step back before that trial and look at all the other individuals, smaller trials with 50 and 60 people and so forth, a 2 milliamp 20 minute application over a 6-week period, actually, it shows very promising effect sizes and overall effects for unipolar depression. Bipolar depression has been less studied. The trials that have come out on that have actually shown potentially even larger effects than unipolar but the actual sample size that have been tested with that are quite a bit smaller.

We've done some work in collaboration with a group out of the University of Istanbul on gambling disorder. And so we published, I guess a year or two ago, a paper where in the gambling disorder clinic that they have there we ran a small two week trial attempting to increase excitability in frontal cortices with tDCS. And Serkan Özakbaş was one of the lead authors on this paper. And we actually found some very positive effects on the Turkish version of the Iowa Gambling Task and a variety of other gambling related executive function measures, after a 2-week intervention versus sham intervention in a group of about 20 gambling disorder patients. So a lot of the work clinically done in tDCS is really at the pilot study level, or what I think of as a pilot study - 20, 30, 40 participants. Those studies are small, and so they're not representative of the population. What those studies do is tell us is, “Hey, look, there's really potential promise in these domains that deserve larger trials for larger study in a population level size.” For TMS they've had those studies in depression and they were actually very successful. One of the estimates for TMS was something like 36% reduction in symptoms in treatment resistant participants, which is incredibly exciting and one of the reasons it's FDA approved. And so the evidence for tDCS in the clinical application side is not as far along as TMS, but there is a lot of promise within the field, not just in neuropsychiatry, but also within Alzheimer's disease, remediation of cognitive aging, prevention of MCI in a variety of domains.

John Bellone 42:40
Earlier you mentioned neuroplasticity as one of the potential mechanisms. Is that what we think is being modified here?

Adam Woods 42:47

Right. So the concept is, for tDCS in particular, as well as TMS for that matter, is the idea that we're impacting how these neural systems fire with one another. The concept of Hebbian plasticity and, in a nutshell, Hebbian plasticity is those things that fire together wire together. And so the concept underlying both of these in a very general sense is this is an artificial method for potentially impacting the neuroplastic response of tissue, either increasing the neuroplastic response of that tissue in sync with other regions or decreasing. So if you have aberrant connectivity and firing in these regions attempting to suppress that or in the idea of trying to facilitate gains in cognition or other domains, you might be trying to excite or increase connectivity on these systems that may be either from disease state or otherwise depressed in some fashion. But ultimately attempting to have lasting impact through the alteration of neuroplasticity. And a lot of this principle of neuroplasticity is based on the fact that when both of these techniques, the period during stimulation, sure you see an effect on these different markers, but you stop stimulation of either tDCS and TMS, and those effects last beyond the period of stimulation. The fact that we can have these lasting impacts is a critical feature of the arguments that were impacting or altering the neuroplastic response in this tissue and some type of meaningful and lasting way.

Ryan Van Patten 44:11

Yeah, that's great. You had mentioned that you do a lot of work with older adults and you also mentioned cognition. So I'd like to transition to that domain. In particular a really exciting application of tDCS for cognition in older adults, as the NIA funded Augmenting Cognitive Training, or ACT, in older adults study where you're pairing tDCS with cognitive training. Tell us about ACT.

Adam Woods 44:36

Yeah, I'd be happy to. So the ACT study is the first ever phase three clinical trial. So that means a clinical trial, the size of population level, that's attempting to demonstrate definitive clinically meaningful impact in a population. Whereas phase two trials are really going to be for the efficacy generally demonstrating promise of these techniques. Phase three is that next step that leads us to where we could say this is a technique we need to put into play in clinical application. So ACT had the fortunate experience of being the very first phase three trial and was funded, as you said, by the National Institute on Aging. And the focus of this trial is to attempt to remediate cognitive decline that's associated with getting older, so age related cognitive decline. As we get older, as many of you probably know, there's a variety of elements of cognition that decline like executive function, attention, speed of

processing, working memory, but not all domains of cognition to clients. And, in fact, our linguistic skills, like vocabulary and other language elements, tend to be very stable with age, and in fact, might get a little better as we get older. But these other domains like executive function and attention, working memory decline, and those declines have an impact on our ability to remain independent in our environment. And so this trial was really focused or is really focused on attempting to remediate that decline that we see so commonly with aging. And in so doing attempt to change the trajectory of decline in these older adults with the hopes that that change in trajectory could alter their transition state to something like mild cognitive impairment or Alzheimer's disease. In the first phase of this trial, the first five years of this trial, our goal is to evaluate that remediation effect. And hopefully with continued funding, we'll be able to follow these participants over 5 to 10 years to actually directly evaluate our ability to change their trajectory of decline, their potential conversion rates to mild cognitive impairment, or Alzheimer's disease.

The trial itself, as you said, is about pairing cognitive training with transcranial direct current stimulation. The principle of this entire study is in fact neuroplasticity. Cognitive training, often called brain training, or, in many ways, this is a computer game that specifically focuses on training different elements of cognition. In this case, we're attacking working memory and speed of processing. Two of the features of cognition change drastically as we get older, and also underlying a wide variety of our abilities to help us maintain independence in the environment and our quality of life. And so not all cognitive trainings are created equal. In fact, there's a lot of cognitive trainings out there that have shown nothing more than you get better at the game you're trained on with zero transfer to anything meaningful. But a few trainings that have been studied over the last 20 to 30 years like the Useful Field of View training from the large ACTIVE trial, which had almost 3000 participants in it and was led by Karlene Ball at University of Alabama, Birmingham. It actually showed not only that it can transfer to activities of daily living, but it also has lasting effects from giving cognitive training 10 years prior. They're still showing benefits of this in 10 year follow up.

Ryan Van Patten 47:59
In cognitive functioning?

Adam Woods 48:02

Yeah, in cognitive functioning, as well as in driving performance. So participants in ACTIVE actually showed that they had less motor vehicular accidents, other citations and so forth, at both the 5 and 10 year follow up as compared to control

conditions and other training types. And recently, a paper led by Jerry Edwards out of the University of South Florida, showed that those that received the Useful Field of View training actually had a significantly decreased conversion rate to mild cognitive impairment and Alzheimer's disease.

So what we did in ACT was take the best of the best in terms of cognitive training. Took those that had the most research showing potential transfer and efficacy. And then the concept was, can we make them better? If we take a technique, cognitive training, which is based in neuroplasticity, training these cognitive systems to talk with one another and communicate efficiently to improve performance. Can we take a technique that can artificially increase neuroplastic response of tissue and facilitate the overall outcomes from cognitive training? So an adjunctive intervention strategy. Participants in the trial undergo three months of cognitive training, both working memory and speed of processing domains. At the center the speed of processing is that Useful Field of View task which has been renamed Double Decision by the company that owns it. And then at the center of our working memory are N-Back versions of training, which has also shown a variety of effects and transfer and lasting impacts on cognition. During that time, for the first two weeks of intervention, participants come into the lab or the clinic and they receive five days a week of tDCS applied to the frontal lobes at F3-F4. So stimulating the entirety of frontal lobes, at 2 milliamps for 20 minutes. The training itself is 40 minutes. So for the first 20 minutes, they receive stimulation, and then they continue their training for the next 20 minutes, both leveraging the acute and after effects of stimulation. So five days a week for two weeks. Then after that they take home a 4g LTE enabled laptop that we give them, that then allows them to do their training at home four days a week. And on that fifth day of the week, they're coming in for another stimulation session. So they get stimulation once a week for the remainder of that three months. So over that three month intervention, we, of course, measure them with multimodal neuroimaging, neurocognitive assessments, as well as functional abilities assessment, acquisition of blood and a variety of other markers at baseline before intervention, at the end of the three month intervention, and then again at one year. And so, we've currently randomized 307 participants in this trial, and so we're working on randomizing the last 53 participants. This is a collaborative effort between the University of Florida and the University of Arizona. And we hope to have the final participants randomized in the next six to eight months, which then puts us one year from completion of the total trial.

John Bellone 50:56
Awesome. We look forward to hearing the results. We'll wait on bated breath.

Adam Woods 51:00
Me too. [laughs]

John Bellone 51:00
[laughs]

Ryan Van Patten 51:00
Yeah, hopefully positive results might lead to FDA approval for tDCS for this application.

Adam Woods 51:06
We also have a number of other applications with tDCS. In fact, there's a large chronic pain study that we just started. That's at the University of Florida and University of Alabama, Birmingham being led by Roger Fillingim. And that's another application area outside of neuropsychiatry and cognition that has shown a lot of promise. And that's the treatment of chronic pain with tDCS applied to the different montage location, still 2 milliamps for 20 minutes. But the intervention interval itself isn't necessarily three months. In fact, we've shown strong impacts of as little as five consecutive days of stimulation, over stimulating over the motor cortex and contralateral frontal regions that are cued relative to the side of unilateral chronic pain. Our paradigms have typically been in older adults with knee osteoarthritic pain. And what we've actually found is that in a pilot study we published a few years ago, and 40 participants, 20 in sham 20 in active, that we had both significant improvement starting at day one of intervention, lasting through five consecutive days. And then still there three weeks later, when we stopped following an initial cohort. Where they had a Cohen's d effect size improvement in clinical pain severity of 0.75, which is a large effect size, but more importantly, their mobility significantly increased. They weren't in as much pain, and so they were up and moving around. And that has a big impact on your maintenance of independence and your functional abilities and also ties into cognition. And so, at present, we just started a ProACT trial that is going to evaluate 360 older adults with knee pain, and evaluate the impact of tDCS on knee pain after this one week intervention with longer term follow up to evaluate its clinical efficacy.

Ryan Van Patten 52:56
You've touched on this Adam, but in general, how long do the benefits of tDCS persist? You can talk about TMS as well. What do we typically expect, say, for depression? You can also touch on cognition and other areas.

Adam Woods 53:13

Yeah, no, that's a great question. I think it's more of a known quantity in TMS, less of a known quantity in tDCS and in fact, we'll have some of the longest term follow up data at the completion of ACT that exists for tDCS. Now we've shown effects that last for two weeks after two weeks of intervention. Some people have shown the effects lasting four weeks or six weeks. There have very rarely been studies investigating effects lasting at three months and beyond following any type of tDCS intervention. So the duration of these effects is still a bit unknown. We've shown some benefits - actually, we're working on publication now from a two week cognitive training tDCS trial. We showed benefits after two weeks of intervention that lasted three months, but that is going to be pretty much the longest follow up that's currently going to be published. We'll know more as a lot of the trials that are ongoing now doing longer term follow up.

There's always this misconception that you do a stimulation intervention and then it has to last forever. That's not how medication works. You don't give someone diabetes medication once and they're done forever. It's something where, with both tDCS and TMS, this is something that may require return intervention or treatment visits. TMS is a great example of this. When going in for TMS treatment, there are very few people who go in, receive six weeks of TMS, and then never need TMS again for depression. It does occur but at a very rare rate. More commonly, it might be that someone goes in for six weeks and then six weeks later or a month later, their symptoms return or in a better case scenario, which they're really trying to get to, three or six months later, then you come back for these six weeks interventions. But there's a lot of variability in the duration of these results. And I believe that tDCS will probably follow this same pattern because for these techniques, the main difference in many ways is that intensity of current delivered, a pulsed approach versus a direct approach, they're both impacting neuroplasticity, they're both using electrical techniques. My guess as we get more and more long term data in tDCS is that we're going to see these effects that are going to vary in duration person to person. And then over time, there'll be a need for either booster sessions or another series of intervention sessions. But at present, we don't know the answer to that. I do not think, at least from my opinion, it's going to be a one and done. I go through this once and I'm great forever. However, if we look at things like cognitive training, where you see results lasting out to 10 years, those effects have actually decreased, they just haven't decreased as much as the control conditions. And so there may be applications where you could do this once, say later in life, and that's all you need to do. But depending on the application, there may need to be consideration for what would I think was remission and then recurrence, right? So we may push depression into remission with TMS. But then, as it recurs, we need

to apply the intervention again. And so definitely more knowledge in TMS there in the field at present, and tDCS is trying to make up for that 15 year head start that TMS has at this point.

Ryan Van Patten 56:29

I hear you. Booster sessions are not the worst thing in the world. In depression, in these psychiatric conditions, just getting someone out of an episode can be great behaviorally, can allow psychotherapy to take root. Then if they have booster sessions every so often after that, like we say, that's not bad. On the cognitive side, you have the cognitive training piece that's being tied to the tDCS, potentially. That can continue over time. I wanted to bring in a few other modalities here. EEG and event related potentials, or ERP, techniques can be used to monitor the physiological effects of tDCS, as I understand. So tell us how this works and what the ultimate objectives are.

Adam Woods 57:00

We published a paper, a methodology paper, not too long ago regarding inherent artifacts in electrophysiology data with tDCS application. There are some very special considerations that need to be done to actually apply electrophysiology methods with tDCS. You're injecting a very large current and trying to measure a very small current and that can have impacts that are unexpected at times. For example, in some of the early work integrating these techniques, we were noticing this variable, roughly 1 hertz increase in EEG activity. It was kind of amazing. At first, we were so excited. Then I put a pulse plethysmograph graph on, and it was my heartbeat.

Ryan Van Patten 58:02

[laughs]

John Bellone 58:02

Oh no...

Adam Woods 58:03

[laughs] Yeah, right. We had stimulated and we had caused local blood flow response from delivering electric current to the skin, that's a known factor. We had done so in such a way that anywhere around the stimulating electrodes, you had enough of that increase where I could actually pick up the heartbeat. So that has to be factored out because otherwise you may find an amazing effect in that 1 hertz

range that isn't, in fact, anything. EEG is a physiological artifact. The other thing is when you put electrical current through the skin, you artificially change impedance. In fact, you make impedance far better. One of the things that you're doing in tDCS if you're monitoring impedance so that how good the connection is between the electrodes, is that when you start putting current in, your impedance will drop down and look pretty amazing. It'll improve two fold very often. That's because you're opening up the pores, you're impacting the skin, and you're causing basically that contact medium to get further into the skin to give you better overall conductivity in that circuit that you've created. Well, in ERP, very often what we look at are the amplitude changes between these very specific, let's say p three hundreds or 200, or whatever, right? Well, if I'm at a recording site, that's right adjacent to a stimulation site and that stimulation is altered impedance, guess what? My ERPs are going to get real big around that site of stimulation. But that's not necessarily from tDCS. That's from actually stimulating the scan and changing impedance and your recording electrodes that are adjacent.

So, okay, as long as we know these things, there are things we can do about it. We can factor out heartbeat, we can measure these and actually put through a filter to factor that information out. In terms of the skin impedance, if we measure impedance throughout, I can actually measure how much impedance is altered artificially and I can covary that out. There's a lot of complexity to using these techniques. It's a nice idea, in the sense of I'm putting in electrical current, I'm trying to get out electrical currents. And assuming you don't overload your amplifier by putting in lots more current than I was expecting, which in most current iterations of EEG technology you won't. But assuming that's not happening, then you have this potential for really recording information from the electrical output of the head to try to look at kind of how the temporal dynamics in terms of ERP in terms of latencies, or in terms of amplitudes, are being impacted by the stimulation approach. So, in principle, it's a great idea. It's just not a simple idea because there are technological elements that have to be considered in order to acquire viable information.

The same is true in TMS. There's actually a lot more work, again, that's been done in TMS to actually integrate and create TMS compatible EEG caps, where you have passive electrodes, where you can deliver your pulse and very quickly record after that pulse is delivered and attempt to filter out the electrical noise that was generated by the actual TMS pulse doing electrical induction. So in both cases, EEG is a technique that is attempting to really look at the "when" of the brain. When something is firing in concert. So it's a great temporal dynamic tool for asking questions if you're improving. Of course, this idea of neuroplastic response to tissue and improving the overall function of these systems and they're firing, if you're

increasing the excitability of the tissue, you should, in theory, be able to measure some of these. It's not a great "where" tool. If you're looking for where in the brain that's going to be more in the MRI realm. But with careful consideration in the methodologies, it's a technique with specialized equipment that you can definitely apply and apply well to ask some very interesting questions.

John Bellone 1:01:51
Just to step back for a second, is there a primary advantage to TMS over tDCS in terms of clinical outcome?

Adam Woods 1:02:00
Well, one of them you've got FDA approval.

John Bellone 1:02:01
Sure. Right. Of course.

Adam Woods 1:02:06
[laughs] It's a jest.

John Bellone 1:02:07
What's your bias? Towards the tDCS, I'm sure.

Adam Woods 1:02:10
I am perfectly biased towards tDCS by all means. But, at present, though, with tDCS, it would be an out of pocket expense to participants. So there are a large number of clinicians out there that are applying tDCS to their patients, because of their clinical judgment in terms of, "All right, this is a safe approach that I feel confident may have a benefit and has a low risk portfolio for my participants." So every time I teach a workshop, at least a handful of clinicians are like, "Yeah, you know, we're in our health system and they're allowing us to do this. And here's the stipulations we were given, but it roughly is about $200 per session out of pocket for the participants." With TMS because of the FDA approval and then the resulting approval by insurances for coverage, it actually becomes something that is more accessible to participants at large. If your insurance covers it, this is something where your 6 weeks of intervention would not be out of pocket. That makes it more accessible. So in the present era, accessibility to insurance payments is a major feature that is important. I hope we'll see that tDCS will also reach that level because tDCS is a much less expensive technology. The cost per session for TMS

before FDA approval could sometimes be $800 to $1,000 per session. So only those with means could actually access it. tDCS is closer to accessible but still not fully accessible because $200 for, let's say, 6 weeks of intervention for five days a week is nowhere near affordable to general patients. So time will hopefully balance that equation. But the inexpensiveness of tDCS gear also has worked against tDCS because the companies that are invested in tDCS technology are not necessarily able to charge $70 and $80,000 per unit to have a large income on these units. The way that the FDA typically works, these would be industry sponsored trials. That's how TMS received its FDA approval where companies went out and sponsored multimillion dollar trials to test efficacy, found efficacy, submitted to the FDA after pre-approval for the trial design and received their FDA approval. For tDCS working in a market where this technology is actually on the shelf very often, or not actually on the shelf but accessible already to the public in different formats, and not an overall expensive technology. That lean market of sorts means that there weren't necessarily companies jumping out of the woodworks to sponsor a phase three efficacy trial. Hence, we've gone through the National Institute of Health to try to get those types of trials funded, which is very atypical for the device technology sector.

John Bellone 1:04:55

Along these lines, when should this be on our mind and in our recommendations as neuropsychologists in terms of recommending this or referring patients to consider this?

Adam Woods 1:05:07

Sure. I mean, at this stage, it's still true that anyone can do anything they want to their body technically. I very often get emails from people in the community saying, "Hey, I bought this stimulator online and I'm going to apply it to myself, my husband, my child, and so forth." My response to that is that we're not there yet.

John Bellone 1:05:27

Right. Don't try this at home. [laughs]

Adam Woods 1:05:29

Right. "Hi, kids, don't try this at home." It is a very safe technique. So there is a lot of ethical discussion in this realm of, "Well, if it's safe, then why not?" Right? People buy stuff that's probably less safe off the shelf in their supermarket or in their drugstore that have other nasty side effects. Why not allow them to? Again, people can do what they choose to their body, but if they're going to ask my opinion, especially when it comes to the case of children, I'm going to say, "You know, what?

We're not there yet. Let us get these trials with long term efficacy data, long term safety data completed. And then let's have this conversation." I'd like to see that one year data, I'd like to see those follow up data. Again, very safe. Some of my colleagues in the field will be like, "No, they should just do what they want." And that's an opinion. My opinion at this point is if you're in the context - and I've spoken to many clinicians in this context who say, "Look, I have a patient who has been resistant to six different medications. They tried TMS, but it wasn't effective. We're out of options here. They want to try this technique and I'm comfortable as a clinician prescribing this to them. We're going to do this out of pocket at their expense. So on and so on." That all comes to a very complex equation of malpractice insurance and various other things. In that unique scenario, the clinician makes that decision, in terms of options, this is one we have that could have promise and has a very good safety profile. That, again, is within clinician judgments because we do give our clinicians a lot of room in terms of their clinical judgments. I think looking at the literature for many of these successful, but smaller depression trials, that might be a case where I, the clinician in that circumstance, I might be willing to consider it. As a neuroscientist by training, who happens to find himself leading six different clinical trials, not where I expected to be as a PhD neuroscience student, but loving every minute of it, I of course want to see the data. I want to see the evidence because I always asked the question, "Would I do this to my mother? Would I do this to my wife? Would I do this to my child?" Give me the data I'm looking for, and the answer is absolutely yes. But I want to see that data first. I think we'll get there but it's just going to take us a little bit of time.

John Bellone 1:07:35

Is that your same opinion for TMS? As clinicians, should we be thinking about TMS the same way?

Adam Woods 1:07:42

I look at TMS differently because we have that data. We have that long term data where we follow people for years. People have now gone in with clinical treatment of depression, we see the remission and recurrence rates. We have a lot of long term data in that context. So when it comes to depression treatments, and now OCD treatment or off label treatment, I'm definitely far more comfortable. I think, of the two of these, tDCS is the safer of the two techniques. We have no seizures today with tDCS, which is great. But again, in the process of the approval of medical technology, TMS is already there. That application has been demonstrated and thousands of patients have been treated, far beyond thousands in fact. But in tDCS, I, as a scientist, but as a clinical translational scientist, want to see us

complete at least one of these trials showing at the very least that, after a year, having done intensive stimulation over period of time, that we do not have significant or serious adverse events that are unexpected and potentially related to the study. I can say at present in ACT, we don't have those. We've got a lot of data points so I think in short order we'll be there where we can at least say, safety profile wise, at these doses, over time, this is a great safety profile. But, again, those data are not published yet. I want to wait till that is completed. At that point, my opinion will shift.

John Bellone 1:08:27
I agree. Be cautious. Definitely. Do you know if TMS is widely available for patients if they want it?

Adam Woods 1:09:16
I'll give you an example in Gainesville, which Alachua County has 250,000 people and we have two TMS clinics, private TMS clinics in Gainesville alone. In every major city and even non-major cities, you will find that there are either in the university psychiatry departments or private clinics that are offering TMS treatment. It's becoming very widely available. Now in your more rural areas, you're less likely to find that but there is definitely a very quickly growing accessibility for TMS training.

Ryan Van Patten 1:09:49
Yeah. In addition to what we've talked about already, including the ACT trial, tell us about the future directions of research in tDCS and TMS. You know, 5years, 10, 20, 30.

Adam Woods 1:10:02
Sure, I mean, of course, we're trying to finish these trials we have currently going. We're also looking at new applications, different applications. There's a lot of desire in the field to run a definitive tDCS depression trial, potentially the combination of cognitive behavioral therapy. I hope that in the next 5 years, we see that trial well underway. The pathway over the next 5 to 10 years for tDCS, I think will be that pathway that was tread by TMS about 5, 10 years ago, which was finally getting the initial trials completed to get an initial FDA approval. Once that's in place, then it's really a matter of time before insurance coverage becomes an opportunity. So I think the movement of research into clinical application will be a big part of the next 10 years, hopefully, 5 years. I think that what we're seeing now more than ever is appropriately sized trials are being funded by NIH and other institutes around the

world. I can think back to 2010, not that long ago in the way of things, 10 years ago, you couldn't get tDCS funded by NIH unless it was a stroke application or some other obvious rehab application. Nowadays, there are special calls. There's a special program announcement at NIA alone regarding neurostimulation in ADRD with specific focus on noninvasive. We're seeing the availability of funding for appropriately sized research and clinical trials coming about. So that in the next 5 to 10 years, what I hope to see is a movement away from the 5 and 10 and 20 participant pilot studies that people tend to make far too much of and movement more into the 100, 200, and beyond appropriately powered samples that really start to tell us exactly what tDCS can do at a population level rather than in a nuance sample level.

In terms of TMS, I think what you will see both in research and clinic is similar in that it will start to see more expansion of the clinical indications for TMS. We've already seen in 2018 that OCD, or obsessive compulsive disorder, is now FDA approved for usage. I think we'll see the number of those applications expanding. I think that in the technology space in general, we're seeing a lot of movements within the neurotech space towards noninvasive methods going for FDA approvals. In the research space, TMS is a wonderful tool, just like tDCS but in different ways for investigating the potentiation of activity in terms of the neurons, neuroplasticity. It's got a tool that is very focal in nature and allows you to pick apart and probe brain-behavior relationships and very nuanced ways. As these technologies become better integrated with multimodal neuroimaging and other methodologies, the amount of information you're going to learn both in patient populations as well as the brain in general is going to continue to expand because we have this artificial means to probe the brain, alter how it behaves, and evaluate its impact on behavior, cognition, and symptoms of interest in different disorders.

John Bellone 1:13:16

Awesome. Well, this has been super interesting. This is very cutting edge stuff. Really glad we got a chance to talk with you and cover this. We do have a couple of bonus questions before we let you go. I know you had mentioned that most of your training is in neuroscience proper. I believe you identify as a neuropsychologist as well. I know those lines are very blurred between those two fields.

Adam Woods 1:13:39

So I'm not a neuropsychologist by training. I'm a psychologist trained to study the brain, if you want to call that neuropsychology.

John Bellone 1:13:45
[laughs]

Adam Woods 1:13:44
In terms of clinical neuropsychology, no. I am in the Department of Clinical and Health Psychology at the University of Florida. My training was a PhD cognitive neuroscientist. I was trained as a neuroscientist, but I've worked with neuropsychologists and my early mentors were all neurologists and neuropsychologists. So they kind of bias me a little bit in terms of my clinical interest. My work has always been in science. Don't get me wrong, science for the sake of science is great, but not for me. Instead, my goal is to take my science and find a way to use it to actually impact and improve health and well being in one way or another. If we can do that in one person, we can do it in 10. If you can do it in 10, you can do it in 10,000, so forth, so on. So I came from a heavy methodology, experimental background with lots of influence from neuropsychology and neurology. That kind of led me down this clinical trial space, which I wasn't classically trained in but then trained in when I came to University of Florida as a junior faculty member in our Clinical Translational Science Institute. And now find myself as the lead PI of multiple clinical trials, which in the past had been MD territory, not PhD territory. It's kind of fun to see that shift. The scientists that are doing basic science and finding these new techniques and then taking those and translating them into a clinical application. So clinical translational science is center to what I do, but I won't say I'm a neuropsychologist. I just moonlight as one in my department, but I'm not clinician by any means. I'm looking to find ways to inform all of our wonderful clinicians on the next wave of treatments.

Ryan Van Patten 1:13:45
Yeah, neuropsychology has so much to learn and we can benefit so much from neuroscience, for sure, and psychology more broadly.

Adam Woods 1:15:34
Well, it goes the other way as well, right? The fact is, neuroscience very often ends up at the bench and never at the bedside. So neuroscience has a lot to learn from neuropsychology, because actually, this application, interventional neuroscience or clinical translational neuroscience, it's the marriage of neuropsychology and neuroscience that really has driven the work that we're doing at University of Florida. But I also think it is going to drive the next wave of novel techniques and technologies for patient intervention.

Ryan Van Patten 1:16:05

We ran into you at INS 2020 and that's just showing how neuropsychology, especially INS, I think, does really look to and benefit from neuroscience. I love to see that. To see talks and workshops at our conferences that include techniques such as noninvasive brain stimulation.

John Bellone 1:16:27

So feel free to take these bonus questions however you want. You can answer more generally speaking for the field of neuroscience, if you'd like. But the first one is just if you can improve one thing about the field, again, either neuropsychology or neuroscience, what would it be?

Adam Woods 1:16:41

I'll say six of my eight PhD students are neuropsychology students. And I work in the area of neuropsychology within the departments. So I think that very often across our neuropsychology training programs, we get wonderful clinical training sometimes to the exclusion of solid research, experimental and clinical trial design. That's not to say that's universal by any means. But what I would like to see in the field, we have to come out as competent clinicians that can make an impact. But we also, if we're going to pursue this academic research world, and try to make an impact with our science on our clinical populations, I'd like to see greater and greater focus and balancing the quality of that research training, that methodology. I think the UF program has done a great job of that in that we have very intensive clinical neuroscience courses that these students take. But as a science junkie, there's always room for more. But yeah, I think that the field too is, in many ways, staying at the forefront of technology, the bread and butter of neuropsychology. Things have changed so drastically over the years, to the common application of MRI, where in the past it was, "All right, I'm going to go in, I'm going to talk to you, I'm going to do some assessments, I'm going to tell you where that lesion is," which is always amazing. Now, it's like, "Well, I know where it's at. It's right there." So we've watched neuropsychology evolve as a result of the technologies that have now empowered neuropsychology, the field, to go even further than before. So I think moving forward, as long as we continue to evolve with the technologies that are at our fingertips to get us into the brain and impact the brain, then the field is going to continue to flourish.

Ryan Van Patten 1:18:25

Agreed. Last question, Adam, what is one bit of advice you wish someone told you in your training or someone did tell you that really made a difference? We're looking

for an actionable step trainees can take they might not have thought of that would improve their performance.

Adam Woods 1:18:41
Good question. Learn to say no. [laughs] I think some of the best advice I ever got that I totally ignored the first five years of my faculty career was to say no to things, to be selective at what I agree to do and what collaborations I agree to do. I've been fortunate to have lots of wonderful collaborators, but there's only so much science one can do in a day. It's too easy as a trainee to come in and be so excited about everything. I was that way. I didn't want to say no to anything, I still don't because it's all really cool and exciting. But, at a certain point, you have to be able to say no in order to both keep your sanity as well as give the amount of time necessary to do great work in a domain. That doesn't mean do only one thing. No, that wouldn't be a good diverse portfolio, if you will. But learning to be selective and saying no. That has a cascading ability to then help you balance life and work. As students we often work 80, 100 hours a week, and that is something that sets you up long term to really end up burning out horribly in short order. So being able to say no to specific things and then use that time you gain to focus on the things that are making the most impact on your career. You're not going to always know what that is, so asking advice often of those around you, those who have succeeded what have you. But then using time as well to really build in that balance of having both work and life. They're connected by all means. I guess it all plays into time management strategies in some ways. I got pieces of that advice throughout my career, it just took me a while to actually realize that I was being an idiot and not listening to good advice.

Ryan Van Patten 1:20:27
[laughs] I hear you. That is good advice. Learn to say no, unless it's one of your graduate students.

John Bellone 1:20:33
Unless it's Ryan, and I'm asking him to do me a favor.

Ryan Van Patten 1:20:38
[laughs]

Adam Woods 1:20:38

[laughs] I'm sure I will get complaints from faculty in my department for having given that class. My graduate students will hold it over my head and they have a right to do so.

John Bellone 1:20:45
[laughs]

Ryan Van Patten 1:20:46
Without a doubt. [laughs] Adam, this has been great. Thank you for taking so much time. This is such an interesting topic. Many people in neuropsychology know just a little bit or may have read in a textbook about TMS and tDCS, but the depth really helps. Thank you.

John Bellone 1:21:02
Yeah, thanks again.

Adam Woods 1:21:03
Well, thank you for the opportunity. This has been wonderful.

Transition Music 1:21:05

Ryan Van Patten 1:21:09
Well, that does it for our conversation with Adam. As always, thank you for listening. We want to remind everyone that select NavNeuro episodes are available for CE credits through INS. Just go to navneuro.com/ins. There's instructions on that webpage. Again, thanks so much and join us next time as we continue to navigate the brain and behavior.

Exit Music 1:21:34

John Bellone 1:21:58
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Ryan Van Patten 1:22:09

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