WEBVTT

NOTE duration:"01:04:49.2180000"

NOTE language:en-us

NOTE Confidence: 0.930850923061371

00:00:00.890 --> 00:00:03.960 Hi everybody, good morning, we're going to begin.

NOTE Confidence: 0.94004762172699

00:00:04.490 --> 00:00:29.930 Today I'm proud to introduce our Grand Round Speaker Doctor Flavio Froelich Doctor Froehlich completed his International Diploma in electrical and electronic engineering at Imperial College, a diploma with distinction in information technology. An electrical engineering at the Swiss Federal Institute of Technology, a PhD in computational neurology at UCSD and actually did a postdoc here at Yale.

NOTE Confidence: 0.960734724998474

00:00:30.560 --> 00:00:42.640 He is currently an assistant I'm sorry an associate professor of Psychiatry Electrical and computer engineering neurology and cell biology and Physiology at the University of North Carolina Chapel Hill.

NOTE Confidence: 0.920203149318695

00:00:43.400 --> 00:00:50.730 He is the director of the Carolina Center for neuro stimulation and the founder and Chief Scientific Officer of Pullman Arnero LLC.

NOTE Confidence: 0.92415189743042

00:00:51.440 --> 00:01:15.560 Doctor Froehlich's work in animal models human subjects and bio electrical modeling focuses on noninvasive neuromodulator. E techniques and the network dynamics of the brain in psychiatric illness from modulating individual neuronal activity to global oscillatory changes to targeted treatments for neuro psychiatric disorders. Doctor Froehlich's work is transforming the field of neuromodulation and our understanding of the brain.

NOTE Confidence: 0.943784952163696

00:01:16.100 --> 00:01:24.070 In addition, he has an unwavering commitment to teaching and presents scientifically complex concepts is comprehendible clinically relevant and exciting.

NOTE Confidence: 0.887080729007721

00:01:24.670 --> 00:01:27.550 Thank you doctor for like for joining us today.

NOTE Confidence: 0.916689693927765

00:01:37.090 --> 00:02:05.700 Can turn on the microphone. Thank you very much for the wonderful introduction and thank you. All of you for being here today and not a microphone works and for having me so I understand I got a 5 hour slot so if you need a break in between just walk out, but I'll make sure

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you come back. So let's get started to see if we can do this in 4, 1/2 instead of 5, here my conflicts.

NOTE Confidence: 0.917273163795471

00:02:06.530 --> 00:02:15.570 So you know if you if you feel like there's a concern. Maybe that would be the moment to take your tinfoil hat out of your pocket.

NOTE Confidence: 0.877294182777405

00:02:16.600 --> 00:02:18.180 Before I start.

NOTE Confidence: 0.924822568893433

00:02:18.700 --> 00:02:43.800 Most importantly, perhaps I have the honor and privilege to be back at what was my home. Few years ago talk about what we're doing in my group would really let's just be clear, I'm the person answering emails and filling out conflict of interest forms all day long and there's the next generation. My second family. So to speak that has done all the work that I'll be showing today.

NOTE Confidence: 0.938453018665314

00:02:45.260 --> 00:02:57.130 So I'd like to start with a question to you and hopefully we can loosen this up and encourage you to also ask questions as we go along so I have a question for you, who has heard of this person before.

NOTE Confidence: 0.905008435249329

00:02:58.180 --> 00:03:23.190 And you would raise your hand if you did, great, so Lucia Kelly at C is in many ways that a founder of everything I'll be talking to you about today and you can guess all the obvious reasons why you haven't heard of her and why she isn't in the textbooks. But Lucia Kelly outs. It was in the lab and make this really fundamental discovery that a life.

NOTE Confidence: 0.956995368003845

00:03:23.770 --> 00:03:30.210 And that movement and nervous system activity has something to do with electricity.

NOTE Confidence: 0.91107964515686

00:03:31.230 --> 00:04:01.330 Does that sound a little bit familiar because you've probably learned and heard that Luigi Galvani made all his breakthrough discoveries using the frog preparation. But in reality, the key insights that that big step conceptual step. Forward was actually his wife, Lucia, so that was a really interesting time. Back then because the physics of electricity weren't very clear and how the nervous system works also.

NOTE Confidence: 0.917890608310699

00:04:01.330 --> 00:04:23.100 Wasn't very clear so in some ways, it was a period? Where we didn't have today's hyper specialization and if you wanted to understand life, which I think ultimately, we all in one or the other way would

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like to do you would be living in an environment and working in a way that brings together many disciplines that today often live in very different places.

NOTE Confidence: 0.926972389221191

00:04:23.800 --> 00:04:55.970 Now just one generation after the original discovery of electricity being generated in the nervous system and creating that force that generates movement at the interface with muscles. There is the nephew of galvanic. Giovanni LD name and he took this idea of that. The nervous system is an electric system and developed perhaps one of the first electric brain stimulation devices. So here you see a farmer treated with what you would call today major depressive disorder probably.

NOTE Confidence: 0.893703460693359

00:04:55.970 --> 00:05:20.780 And the contraption here is a vote Alec pile. So does this end, she wanted the first batteries, which was developed by Volt dump. The competitor of Galvani to any attempt to this proof. Galvani discovered and developed the battery and then in the next generation. When that conflict away. It was a combination of these ideas, leading to the first apparently successful attempts of noninvasive brain stimulation.

NOTE Confidence: 0.917523562908173

00:05:21.460 --> 00:05:54.710 And I tell you that story for many reasons one because I believe with Chia Galiots. He deserves more attention. Then she has received so far, too because I think that's a general pattern in science and medicine that I would like to help to change and the other thing is I'm standing here and I will be showing you lots of results from my group and we have this tendency to feel like we've made all this great discover is but ultimately and signs were going in cycles and hopefully every cycle were approving the ideas, but clearly we're standing on the shoulders of many Giants so 300 years later.

NOTE Confidence: 0.906340062618256

00:05:54.710 --> 00:05:59.730 It looks roughly like this so all that is really changes the purple light in the background.

NOTE Confidence: 0.918681859970093

00:06:01.800 --> 00:06:33.170 What you see here is just a slightly stage that picture of what I'll be talking about today so you have here my very talented postdoc who also is our photo model with lots of electrodes on the scalp, so these are EG electrodes to measure noninvasively measure macroscale brain activity and we'll get to that and barely visible underneath. There's a second set of electrodes that we use to apply very low amount of electricity.

NOTE Confidence: 0.915522336959839

00:06:33.170 --> 00:06:41.250 Low amplitude current in the hope to not do change and scope the brain activity patterns that we can record with EG.

NOTE Confidence: 0.919978022575378

00:06:41.810 --> 00:07:11.860 So, in many ways, the story today will be about how all the listening to the brain that we've done now for almost 100 years in terms of neurophysiology and using eug how we can leverage all these insights and start to learn how to also speak to the brain and use ascentia brains own mechanism of electric signaling to sculp enhance restore activity patterns in the hope that ultimately these approaches become safe and ultimately affective treatments.

NOTE Confidence: 0.935121774673462

00:07:11.860 --> 00:07:14.390 For serious mental health problems.

NOTE Confidence: 0.936284601688385

00:07:15.110 --> 00:07:47.800 So here is my electrical engineering slide. Just very briefly. I've already shown anybody looks like. In reality, so the fact. There's no hair here doesn't mean we need to shave the patients that just means. I don't know how to draw hair in Adobe illustrator that technique is very simple. It's called Trans cranial current stimulation and it's really embarrassing with simple because all we do is we apply a predefined amount of electric current that passes through the through the participant.

NOTE Confidence: 0.927235305309296

00:07:47.800 --> 00:08:18.640 Most of it through the scalp, some of it through this call some of it through the brain and that's it. There is no sophisticated spatial targeting there is no quantum computing. There is no machine learning. There is no cryptocurrency. It's really incredibly basic in some sense and perhaps just perhaps this is really going to be a great advantage. As we're thinking about disseminating potential new treatments in the communities Veri currently.

NOTE Confidence: 0.923049032688141

00:08:18.640 --> 00:08:49.240 You know are not really able to provide the kind of care and we would like to provide a little bit of terminology and I haven't made up these abbreviations. There are terrible, but essentially there's T DCS or transcranial. Direct current stimulation, which is a constant current and then there's TA CS and it stands for transcranial. Alternating current stimulation, but all it is, is a sine wave rhythmic signal and we'll get to why we would choose these waveforms, but that's all there is there's nothing fancy here.

NOTE Confidence: 0.939541101455688

00:08:49.240 --> 00:08:55.380 I think what we want to do is see how far we can get with this and that's going to be one of the themes today.

NOTE Confidence: 0.916161775588989

00:08:56.550 --> 00:09:27.600 So TV CS the use of constant current you know has been rediscovered. If you will about that 20 years ago. This is the paper

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by the way that everyone knows and just as a historic reference 2 years ago, the same thing was already published and no one sides that paper. You can also imagine with the reasons could be for this. But what I'm showing here is essentially convincing seemingly convincing demonstration that are very weak amount of electric current applied to the scalp can change cortical excitability.

NOTE Confidence: 0.917502701282501

00:09:27.600 --> 00:10:01.230 And the way cortical excitability sproc terrorist by using transcranial magnetic stimulation or TMS that you might be more familiar with which delivers a targeted spatially localized super threshold stimulation to activate motor cortex and we can measure the resulting electric activity in the muscle and what we see as a function of the direction of the TDCS of that week electric current at least in a time window. A few minutes. We can bidirectionally modulate excitability such at ATMs polls dipping the brain generates either an enhanced.

NOTE Confidence: 0.91980767250061

00:10:01.260 --> 00:10:29.010 Or, a reduced responds in the targeted muscle group, so just to be very clear. So we're combining 2 types of brain stimulation here. One is a weak electric current applied to the scalp, which seems to modulate excitability in the range of 20 to 40% and we're using another brain simulation modality TMS to probe the neuro physiological effect by Pinging Motor Cortex and measuring the resulting MVP.

NOTE Confidence: 0.910793423652649

00:10:30.090 --> 00:11:00.560 So that is great, but you know, enhancing muscle twitches is not over. Anyone wanted to stop so building on that there was a rapid escalation and growth of a new field and the field is essentially let's use T DCS for everything under the sun and more and there are thousands of TCS papers published and many of them seem to suggest that you can use TCS.

NOTE Confidence: 0.926020622253418

00:11:00.560 --> 00:11:31.650 To do really specific sophisticated things such as enhancing higher order cognitive function as a result of that there isn't a do-it-yourself brain stimulation community brain hacking community out there and there's lots of controversy. Around this and I want to highlight some of these aspects because if you're a clinician. You can be quite sure that some of your patients either will ask you about this, or probably have already tried this at home without telling you so.

NOTE Confidence: 0.915066957473755

00:11:31.650 --> 00:12:02.840 At that point we were curious to see whether this seeming ability to change excitability weather that could be used to model the cognitive function and I think we're probably one of the first ones to do a double blind placebo controlled study. Verda placebo is everything is the same. We apply a little bit of electric current just at the beginning of the simulation session

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and people can tell the difference. So the real stimulation and we use essentially changing IQ scale as the outcome and indeed with it find a significant.

NOTE Confidence: 0.839091062545776

00:12:02.840 --> 00:12:12.450 Difference in performance enhancement between sham or placebo stimulation thevaram simulation is starting right performed left prefrontal bilateral.

NOTE Confidence: 0.920616388320923

00:12:13.060 --> 00:12:43.790 Now the thing that got so many people on Reddit upset about me was that the effect goes in the opposite direction of that. Everyone thought it would so here is the gain in performance by doing the test again for sham and as a reduction of that gain or statistically significant 40 DCS right. So then the next thing is well. TCS doesn't works. He's just shown this and it's so we can't work, and brew, dismissing all of it, but I think we shouldn't do that because then we're doing exactly the same thing.

NOTE Confidence: 0.840138971805573

00:12:43.790 --> 00:12:53.780 As the people go like well, we strengthen motor court excitability. Now we can enhance calling their function. We should not swing to extremes. I forgot to render us I'm sorry.

NOTE Confidence: 0.915063560009003

00:12:54.860 --> 00:13:27.000 We will we should try not to swing to extremes and be really irrational understand that any scientific study. Even the ones that I believe are well done don't provide final answers and there's lots of sophistication right because if we say. TCS does work. It does not work. It's the same, like taking any kind of taking any kind of medication doesn't work or does not work right that is a very broad and seemingly stupid statements so we really want to be more detailed about this now, just to demonstrate the potential of TDC S so.

NOTE Confidence: 0.89961439371109

00:13:27.520 --> 00:13:50.940 Yeah, now 7 years ago, there was really beautiful well controlled study of TCS for the treatment of medication. Refractory auditory hallucinations in patients with schizophrenia and what you authors have shown is that after a five day paradigm of TCS trying to enhance activity and left prefrontal and decrees activity and temper parietal auditory areas.

NOTE Confidence: 0.913791596889496

00:13:51.630 --> 00:14:15.650 There was a statistically significant clinically meaningful improvement in auditory hallucinations, and even more shocking. Perhaps a month and even 3 months after that one week off stimulation. The clinical gains were maintained here in Reds, you see Dick reason symptoms for the app versus the blue the placebo order sham stimulation.

NOTE Confidence: 0.912247240543365

00:14:16.180 --> 00:14:38.660 Now, as a sum of you know much better than I do this is an incredibly hard and difficult to treat patient population and that was very exciting, So what I've done is I found that doctor your skin doctor, Gilmore in our Department say. Let's try. This too because if it's if it's that simple, then we should really aggressively pursue this and demonstrate and replicate the results.

NOTE Confidence: 0.905656397342682

00:14:39.170 --> 00:15:08.560 So we didn't quite exactly set up the study to replicate there were some you know fine details, which I'm happy to discuss but in a sense. Those are the result of our study and we also found a significant reduction in order hallucination scale. Here you see the role score on the X axis of that rating scale and some of the changes persisted a month later. But you see your 2 lines. The red and the blocks or the red is the TCS and the block is a placebo or the sham stimulation and obviously there's no difference here.

NOTE Confidence: 0.915430009365082

00:15:09.200 --> 00:15:40.430 Right so, so then so then when you compare these 2 results. I don't know which one is you know, there's no generalized truth. You can derive from this except that it's complicated and in some way it's also not surprising that something so clinically so challenging is more difficult than a simple study of using constant current and getting a reliable response across studies. One thing, which I want to point out when you compare it to results just kind of waving your hands.

NOTE Confidence: 0.885877013206482

00:15:40.430 --> 00:16:05.170 The difference here was actually in terms of possible effect right so there should be more precise. The placebo group where there was no decrease in symptoms here where there was a decrease in symptom here and that raises further questions of how careful our study designs are they double blind every really check that we were able to maintain the plant and some labor back on the ground of reality of how hard it is to do good clinical trials.

NOTE Confidence: 0.922165751457214

00:16:06.650 --> 00:16:22.210 As part of all this that pendulum started to swing back and perhaps the most dramatic one was this news article published think this is science at a really kind of nerve rattling 3:00 o'clock in the morning and.

NOTE Confidence: 0.87617963552475

00:16:23.810 --> 00:16:54.160 And that you know if you ever if you ever have trouble getting your papers published. It's about how you phrase your title right so learn from Emily Underwood because cadaver study. So here we have death right next comes either sex of religion. Let's see cadaver study cast doubts and how zapping brain might boost mood relief pain early this month. Your besakih

a great scientist greatest respect from showed a slide. I sent a murmur through an audience in the Grand Ballroom.

NOTE Confidence: 0.908921957015991

00:16:54.160 --> 00:17:08.700 Here it sounds like we're living this high life as scientists, which all of you know is not true right. It wasn't just the grizzly image of a human cadaver with more than 200 electrodes inserted into its brain that set people with spring.

NOTE Confidence: 0.900300443172455

00:17:09.470 --> 00:17:13.440 It was at those electrodes detected a rather what they failed to detect.

NOTE Confidence: 0.868550300598145

00:17:14.450 --> 00:17:26.050 And that just if you think text is not enough, and images of Earth Thousand Verts. So we have a dead body with lots of electrodes here, which for your own comfort and well being at truncated so.

NOTE Confidence: 0.930732548236847

00:17:26.600 --> 00:17:47.150 What happened here well what happened here is that people started asking really reasonable questions which is if you apply a very weak. Electric current to the scalp, most of it gets shunted, meaning it just flows through the scalp and goes back to the other electrode very little of it goes through this call into the brain? How can it be that a really weak electric current?

NOTE Confidence: 0.919815719127655

00:17:47.680 --> 00:18:17.940 Has any meaningful effect on the brain and I'd say it's a justified question because the literature has been doing T DCS and clinical slash behavior outcomes often in non double blind non placebo controlled studies and it looks magical and you have publication bias and file drawer effects and all these problems. It is it is a great question and it was an important study to really go and look in a human brain in a human body? What the resulting electric field strength.

NOTE Confidence: 0.905319809913635

00:18:17.940 --> 00:18:50.870 Delivered to the brain would be and the result was shocking the way it's presented here, but really not shocking did a few people have been thinking about this at this slightly more mechanistic level, which is the electric current is very weak, so the question is can a week electric current do anything? And here's the misunderstanding right because what that study shows is that the electric current is not strong enough to make neurons fired will right. This is not EMS where you make body parts. Twitch it's much weaker than that some people call it sub threshold.

NOTE Confidence: 0.915612697601318

00:18:50.870 --> 00:19:17.730 Despite them at that terminology has its own problem and I'm happy to get into that. So here we stand potentially world changing in terms of treatments potentially all the placebo effect potentially all hype potentially nothing there in terms of Physiology and that's when science starts would be fun because in contrast to politics. We still mostly use reason and have an agreed upon framework how to resolve this.

NOTE Confidence: 0.858687222003937

00:19:18.450 --> 00:19:21.980 And I think among videos. I'm not going to make more political jokes.

NOTE Confidence: 0.830869257450104

00:19:23.600 --> 00:19:27.330 Though I understand this is a favorable audience. Thank you.

NOTE Confidence: 0.897699058055878

00:19:29.230 --> 00:20:02.940 Here is my post Docs Antheum and what I'm going to show you is US going back to this basic T DCS effect because if T DCS really changes motor cortex excitability. We should also see something in the brain using eug and when I ask him to go back to the CDC S results. I was convinced we would fail to find something because and this again is my own biases. I've done few TCS. Studies have shown some of you. I've never found. Anything that confirmed the TCS could do anything.

NOTE Confidence: 0.924666702747345

00:20:02.940 --> 00:20:27.680 So, in my own biases. I thought TCS is not target enough we wouldn't find anything and let's just kind of close that chapter by going back to the original study approach of money playing motor. Cortex excitability and there was me being very, very naive and very biased. The only thing that I can say is I'm so glad that these 5 my own biases, we decide to go back and look at ourselves.

NOTE Confidence: 0.906347751617432

00:20:28.900 --> 00:20:57.420 And here is what we find so this was a very carefully done study with individual. Mr scans and newer navigation digitization of Electro positions. Lots of lots of really careful procedures going in there, but ultimately, we're doing TMS and we're looking at the evoked response by the TMS at the level of the brain and we find this nice sequence of evoked potential so there's a signature of the TMS that we can detect on the scalp.

NOTE Confidence: 0.918708622455597

00:20:58.060 --> 00:21:28.370 Now we can then source localize. These signals because EG signals as you might know a really spread out and smeared out server using math and the individual scans and individual digitised electoral positions to solve the problem going back and try to understand where the signals come from and the signals come from exactly where. You want them

to so here is here is the motor cortex activation. Then there's a some model sensory feedback loop and then this by noise masking and everything you see later on.

NOTE Confidence: 0.902575194835663

00:21:28.370 --> 00:21:58.560 Already's auditor responses to the TMS which by the way is a big controversy right now in the field. How much of that. EMS is actually neural and then I'm not sure if you have been following this controversy, but these results quite clearly demonstrate that in a very meaningful way. The brain area that we target does get activated. But you have to be careful because the later responses are indeed responses that that are not a direct consequence of the Energie delivered to the brain, but more of some of the sensor slash auditory nature.

NOTE Confidence: 0.925110816955566

00:21:59.310 --> 00:22:32.380 And here is the result that I've never seen like that before and probably I think you get one perk. A rear and these are the results of using now in a double blind placebo controlled study. T DCS to manipulate again. The response to TMS. This was double blind and the way we do this. The code is set up everything is ready for analysis and we get together around the table and someone comes in who has the code to Unblind. The study and the results come up in real time and this is the result that we got so these are 18 participants within participants study.

NOTE Confidence: 0.838921725749969

00:22:32.380 --> 00:22:39.410 Changing evoked potential for Sham Stimulation for a nodal and Cathodal TCS.

NOTE Confidence: 0.913139879703522

00:22:39.950 --> 00:23:11.760 This is the one time in my life, where I don't need to use statistics. I still do because we're idolizing the P value to our own detriment. But one or the other way. All my biases against something, as simple as a constant current could change cortical excitability very many ways resolve with this again. It's just one more study. But the nature of the study and the clarity of the results have had a profound effect and me, realizing how should overcome my own biases and how we need we can through your Physiology.

NOTE Confidence: 0.924399435520172

00:23:11.760 --> 00:23:43.340 Really understand how this works so we can then go and see whether the brain response is changed by by T DCS and that's what you're seeing here for the 2 in the two directions, so indeed not only for changing motor output, but also in cortical activity and in fact when we project them into cortex that really tight. Correlations between the change in brain activity and the output so at that point, hopefully if you've walked in here, saying.

NOTE Confidence: 0.903946995735168

00:23:43.380 --> 00:24:17.830 TCS is just this 9 Volt battery doesn't do anything we need to do ECT yes. We still need to do ECT. But maybe TCS there's something there and we can build on that by me, having demonstrated to you. There's a clear link between the TCS and an objective measure of output of the brain and ongoing activity and we're related that back your brain rhythms and I think the preprint is upon by archive so you can read about this because yes, I want to talk about brain rhythms right. So so far. We've talked about this kind of input output relationship and we often teach our students is how the brain works right sensory input comes in and.

NOTE Confidence: 0.90427827835083

00:24:17.830 --> 00:24:44.930 Motor or other action output comes out, but ultimately of course, the beauty of the brain is all its intrinsic built-in often the symphonic type orchestrate activity also known as the brain rhythms. And here's the Alpha oscillation, probably most of you have seen before which is kind of this default. Operational State of the posterior half of your brain if you don't actively engage with the visual world.

NOTE Confidence: 0.90156751871109

00:24:45.640 --> 00:25:16.250 Why do we care about brain rhythms? Here's a historic answer and this is really interesting because this is less than 10 years after Hunsberger publish his work on EUG and he got. I'm not sure if you know the story. But he got a lot of pushback for his claim that you could not invasive record is rhythmic activity patterns, but less than 10 years later. There was this paper in this paper, essentially redefined an illness named epilepsy that of course, has been around since we have any.

NOTE Confidence: 0.896672427654266

00:25:16.250 --> 00:25:29.170 Type of written or other record of humankind and it redefines. The seemingly very mysterious illness as a paroxysm of cerebral dysrhythmia as a disease defined by its disorganized rhythmic states.

NOTE Confidence: 0.916882932186127

00:25:29.900 --> 00:26:04.110 And here's an example from an animal experiment. So here we have a physiological slow wave like oscillation. And here we have the same network am exhibiting electrographic seizure you so you see the same network can exhibit very different types of rhythmic activity patterns and if your neurologist Ornette Politologist. You understand what this means and you can do meaningful diagnosis. Based on that and you can understand how to treat the patient and obviously this is a case where you can see this right and I think some of the themes that I'll be developing with you today is that for other illnesses ultimately as.

NOTE Confidence: 0.91376143693924

00:26:04.110 --> 00:26:22.200 Electric activity of really defines who we are, and how we feel having interact with the room, there might be other changes or

dysrhythmias or pathological alterations to this brain rhythms that might not be that obvious but still really meaningful in terms of understanding the illness and potentially developing new treatments.

NOTE Confidence: 0.92241632938385

00:26:23.090 --> 00:26:54.100 So here is the framework how I would like to go about this and obviously I stole the terminology from Pharma industry and tweaked it for my own good so the idea of rational design and the way how I want to talk to you today about is essentially 1st. We need a target and that target now is not a receptor. Ori biochemical signaling pathway or anything like that. The target is now an electric activity pattern off the brain so we're really at the much more metal scale macroscale level.

NOTE Confidence: 0.923397243022919

00:26:54.100 --> 00:27:21.340 Thinking about the brain and a target would be something of course, that correlates with some behavior output very interested in whether correlator symptom severity. Rather, its correlates with cognitive performance one or the other way we want to go after a brain activity pattern that we know at the level of correlation is related to what we want to change in our patients or in our research participant population.

NOTE Confidence: 0.91552072763443

00:27:22.140 --> 00:27:53.690 The question then is how to engage these targets and you know week electricity based on what I've just shown you will be. You know the star of the show, but not only and ultimately what we want to be able to show is that the patients get better or the cognitive function improves right? That's what I call the target validation and you know the icing on the cake is to be able to demonstrate that there's a relationship between how you change, these brain rhythms.

NOTE Confidence: 0.89753270149231

00:27:53.690 --> 00:28:24.760 And how to behave route put there to symptoms have changed if you do that in a study where you control. You know stimulation versus Sam Placebo intervention. You're actually the point where we can start with speculate about the actual causal role of rhythms and changes to rhythms in terms of behavioral output so that's the framework will be following by the way target engagement and this is just a little sigh com site. Note here target engagement means one thing to me, it means other things for other people I found this on Twitter.

NOTE Confidence: 0.898560047149658

00:28:24.760 --> 00:28:35.640 Hashtag target engagement, it took me a few seconds to understand based on your laughters I realized it also took you a few seconds because that means engaged at the store target.

NOTE Confidence: 0.886738359928131

12

00:28:36.610 --> 00:28:40.100 Very very happy for this couple.

00:28:42.280 --> 00:29:04.600 Beautiful but just a reminder for all of us right because ultimately for us to change the world and I think that's why we're here to change the world. We need to be able to communicate and that's just a little sample of how I failed because I was looking for something unscientific. Twitter, thinking, I would find lots of stuff related to my work, but all I found was this now.

00:29:05.120 --> 00:29:16.860 There might be a deeper connection and I was unaware of because few days later. I found this paper using TA CS to improve romantic relationships can be a promising approach.

00:29:18.050 --> 00:29:30.470 And this paper is no data. It's very confusing. I don't understand what it is. It made me very much less excited about publishing frontiers. If I can say that.

00:29:32.780 --> 00:29:58.160 But here's again the hype problem right one or the other way, so let me show you how this plays out in a basic healthy human control study how we really approach. This question of Target in rhythms to change behavior and this is work by a postback research and lab going to grad school next year. Trevor McPherson and one of my post Docs in scientific director virus enter Justin Riddle.

00:29:59.280 --> 00:30:29.390 We're using here a rector cube working memory task and I'm going to glance over a lot of details because I brought about 400 slides, but the idea is this you have information to encode that you need to keep in mind, and I'm sorry for oversimplifying it for those of you who are experts in working memory. But the basic idea is you have visual input and then it goes away and then afterwards. You could ask about it, so somehow. I need to activate it and maintain in prefrontal cortex and of course, Israel said. You know everything about working memory in prefrontal cortex because?

00:30:29.390 --> 00:31:02.020 A lot of the pioneering work has been done that this institution was very adding here is extra information, which is when the input disappears. We're going to tell you on which side which part of the visual input of the visual field is actually relevant for the question that you will have to answer afterwards. So we're giving you an extra hint how you can direct your internal processing resources to be more successful at the task and then if we compare behavioral performance between where we've given you this hint.

NOTE Confidence: 0.888948321342468

00:31:02.020 --> 00:31:22.290 Versus at there was a neutral Q So now you know error, pointing essentially both ways. You know you do better with that additional information. Not meaning somehow this is meaningful and while you're trying to keep the location and colors of these squares in your mind given this extra information water that actually matters is behaviorally relevant to you.

NOTE Confidence: 0.90928453207016

00:31:23.440 --> 00:31:54.450 If we then go and look and what that means for the brain. We can do EG and measure brain activity and brain rhythms and understand what the presence of that helpful. Q outdoors in your brain and what it does is it increases. Theta oscillations midline. Theta Theta oscillations that have been routinely found this cognitive tasks and also by the way more recent evidence seems to suggest your ability to recruit from the Theta Oscillations predict outcome of depression treatments for various different treatments.

NOTE Confidence: 0.905016243457794

00:31:54.450 --> 00:32:27.050 So essentially the addition of that queue that kind of internal spotlight. Vertigo is reflected and this is just a correlation enhancer recruitment of frontal. Theta oscillations and then a little bit later. If we compare how the brain is different. When we're told to pay attention left versus to the right. We see we see a lateral ization of the Alpha oscillations and the Alpha rhythm as some of you may know is really an active way how we engage and disengage with visual input so in essence. We have these structured sequence of activation were 1st.

NOTE Confidence: 0.918036282062531

00:32:27.090 --> 00:32:39.830 Frontal cortex signals that there's something additional information as meaningful, namely that. Q followed by a targeted allocation recruitment of the relevant hemisphere mediated by Alpha oscillations.

NOTE Confidence: 0.906108558177948

00:32:40.530 --> 00:33:11.400 So this is so far more or less your standard EG cognitive neuroscience study. There's one more thing that I want to show you so the question then is does that recruitment office. Alpha oscillation by hemisphere really have something do with behavioral performance. And yes, it does if you look at the difference. The strength by which I can dynamically resource resource allocate left versus right by recruitment Alpha oscillation that correlate with the behavioral benefit I get from using the queue.

NOTE Confidence: 0.913426280021667

00:33:11.400 --> 00:33:29.000 Again, that's still a correlation, but really suggesting that the regulation and engagement of hemisphere by Alpha oscillation posterior brain areas really have a direct relationship to how much this directional cue is a behavioral importance to us.

NOTE Confidence: 0.897498190402985

00:33:29.760 --> 00:34:00.810 So the next question, then is you know is any of that causal and what we've done here is a study with multiple study visits where we applied TMS so this is non magnetic stimulation super threshold different frequencies because we've seen the relevance of Theta up from the relevance of Alpha and parietal areas server doing Alpha Theta stimulation frontal and Alpha Beta stimulation parietal relative to in a rhythmic control stimulation and what we see is there is this dissociation.

NOTE Confidence: 0.847169160842896

00:34:00.810 --> 00:34:32.880 That essentially for for the Alpha stimulation if we simulate Alpha in front enhance Alpha slash upfront weather should be Theta. We're impairing behavior, but not when we apply Alpha stimulation posterior now when we apply Theta stimulation. We impair performance. If we stimulate order should be Alpha, but we don't worry stimulate stimulate it from so bunch of important thing and this is all preliminary but not that probably my people said I think about 30 people in here.

NOTE Confidence: 0.918233931064606

00:34:33.440 --> 00:34:46.950 The bottom line is this There's no actual significant handsome of cognitive function right. But there is a frequency and site specific detriment. If we misalign the frequency of the stimulation to the indulgence brain activity patterns.

NOTE Confidence: 0.89320033788681

00:34:48.250 --> 00:35:18.700 We can the problem with these studies is we don't really know in detail. What's going on inside the brain and that's why the animal experiments. I'm going to show you a few slides from very talented graduates endangered wrong in the lab and here we're switching to other brain that also exhibits Alpha oscillations and that is not the mouse and not there at that does not have Alpha oscillations in the way humans have. But the ferret which is a carnivore and my relationship with fair. It is actually started here at Yale University, many years ago.

NOTE Confidence: 0.884440422058105

00:35:18.700 --> 00:35:52.370 But here we're using the first in a very different way from one way back. When I was a postdoc because here we're training favourites innate cognitive control task, which is a sustained attention task where you see already animal and it's working for reward. And there's a touch screen, and this delay period were nothing happens. But the animal knows as an infrequent but behavior relevant stimulus come up on one of these 5 squares and his mask and when the stimulus comes up the animal goes and touched it with the nose and gets a reward for it. So we trained the animals in his task is sustained attention. So it's not selective attention is much more of A.

NOTE Confidence: 0.910291433334351

00:35:52.370 --> 00:35:54.090 Cognitive control process.

NOTE Confidence: 0.875930964946747

00:35:54.720 --> 00:36:26.270 And the beauty of doubt this now can leverage all the modern systems neuroscience techniques of Multisided Recordings and optogenetics to go after the same questions to understand how it is cognitive control task how the different rhythms matter for behavior performance. So the first thing again is we can go and correlate we can go and look at the rhythmic activity powder and see how it correlates with reaction time and recording here on the three nodes higher order visual thalamus, which is part of the film, according network. It generates the Alpha Oscillation Bestir parietal cortex kind of the more posterior part of it.

NOTE Confidence: 0.907337486743927

00:36:26.270 --> 00:36:57.510 Which is the visual Association part and primary visual cortex and I don't have time to go into the details but what you see when you see as a function of frequency of rhythms present in these 3 structures simultaneously recorded that around the Alpha bound for all these brain areas behavior performance is decreased, which corresponds it out. This engagement attentional disengagement mediated by Alpha Oscillations and for the slower Theta frequency based on these correlations there is a gain.

NOTE Confidence: 0.860746502876282

00:36:57.510 --> 00:36:58.500 In performance.

NOTE Confidence: 0.90680456161499

00:36:59.210 --> 00:37:24.800 So what we can do now is optogenetics in thalamus and stimulate the different frequencies. We use very strongly drive neural activity in thalamus, but now we can simultaneously recording cortex and understand how changes in thalamus, which has been hypothesize to really bring back together and help integrate the activity and different cortical areas in cognitive tasks that is impacted by this activation.

NOTE Confidence: 0.881883502006531

00:37:25.350 --> 00:37:57.620 And here is looking at the functional connectivity at the strength of interaction between thalamus and Cortex. So optogenetic stimulation is frequency specific here with stimulating Alpha of the bit fast and ferrets for those of you have noticed. Here we stimulating Theta and you see a strengthening of that. Follow more cortical interaction here during the task and there's also a strength of the interaction to the primary Visual Cortex and very intriguingly. At least for the Alpha frequency this problem are data. We have more than still cooking but essentially.

NOTE Confidence: 0.878828525543213

00:37:57.620 --> 00:38:07.650 There's a hint of an of evidence that simulation of thalamus really actually strengthens the interaction of the two cortical nodes

that are both connected 2000.

NOTE Confidence: 0.89936226606369

00:38:08.400 --> 00:38:37.070 The question then is do any of these changes in this oscillator network architecture reflected in behavioral output because that's what we want to demonstrate that when we manipulate the specific rhythm or ripping interaction behavior performance changed accordingly and again. This is early data. I'm showing you but indeed it looks like that as we've seen from just the Correlations. If we strengthen Alpha the animal is slower to response, which would correspond that is kind of.

NOTE Confidence: 0.903332054615021

00:38:37.640 --> 00:39:07.750 This engagement and when we look at the number of trials. Verde animal just misses completely data stimulus came up right? That's you driving missing the pedestrian that suddenly steps onto the street. There's really there seems to be this Association where with Alpha again. This engaging is posterior network. There is an increase in the number of trials or assemble Smith versus a Theta engagement, we reduce the number of.

NOTE Confidence: 0.885233044624329

00:39:07.750 --> 00:39:26.840 Isle of Mister of emissions so that just shows you the framework how in animals and especially mild species that do have the same brain rhythms functionally. Find as in humans. We can now go in with electrophysiology down to level of action potential cause away understand the interaction.

NOTE Confidence: 0.891631782054901

00:39:27.610 --> 00:39:58.240 Now none of this is something to do with that weak electric fields right because so far. Reviews TMS wrong. Super threshold simulation. We've used off the genetics where we strongly drive action potential firing but let me go back to that week electric current and this is a historic figure made right here. Not quite in this room. But in one building over and that what this figure shows you is a brain network isolate in a dish that likes to now and 10 exhibit is bursts of action potentials in a more or less rhythmic way.

NOTE Confidence: 0.908215761184692

00:39:58.240 --> 00:40:32.810 And what I've done here when I was a postdoc here is I use the waveform of the overall network activity of recorded from an intact animal and apply that week electric field to the network and what you see here is there was a very clear and strong and trainment or alignment of timing of action potentials through that very weak perturbation, suggesting and it's still not reduce model system of an in vitro preparation of a cortical network that networks that have the mechanisms to exhibit negativity pattern really do respond very strongly in terms of adjustment of timing at least.

NOTE Confidence: 0.900908708572388

00:40:32.810 --> 00:40:34.140 So this week electric fields.

NOTE Confidence: 0.911826014518738

00:40:35.770 --> 00:41:06.820 And when I when I moved to North Carolina. What what I thought if this is a way how the brain generates an electric field and structures activity. Maybe we can use this to shape neural activity and ultimately a developers into treatments. So the first step was to understand you know under what circumstances is weak. Rhythmic electric fields can really modulate network activity patterns and these are results from computer simulations were sense. You've tried a bunch of different stimulation frequencies.

NOTE Confidence: 0.899718105792999

00:41:06.820 --> 00:41:16.340 Which would be the plots here a column by column and a bunch of different stimulation amplitudes and every little plot shows the overall rhythmic network activity pattern.

NOTE Confidence: 0.902014136314392

00:41:17.100 --> 00:41:41.840 And what you see here color code. It is that there is a part of this parameter space. Murder is a strong and tramuntana, handsome of the rhythmic activity and it's centered on the indulgence frequency of that computer simulation. So the network is also doing a 3 Hertz and if you tune your stimulation frequency to the endogenous built in frequency if the network you can train the activity.

NOTE Confidence: 0.883234620094299

00:41:42.590 --> 00:42:14.840 And it has his inverse triangle shape is actually well known from physics and dynamical systems. It's called the Arnold tongue people have studied it for much simper systems like metronomes and clocks. Hundreds of years ago, just one other feature. I want to point out is if you're mistuning your stimulation frequency relative to what the network does indulgently. We actually found at least in this computer simulations, the opposite effect, namely suppression of the oscillation, so to me. That's a note of caution that if we do TCS and we think we simulated the frequency in the hands that productivity pattern.

NOTE Confidence: 0.907001972198486

00:42:14.840 --> 00:42:26.850 And we don't actually doing your Physiology, we might actually have the opposite effect right so these simulations suggest that this specific tuning of the stimulation to the network activity pattern is crucial for this.

NOTE Confidence: 0.909988105297089

00:42:27.480 --> 00:42:57.710 This was just Thierry until about a year ago when we had the chance thanks in the brain initiative to do this in ferrets and I

don't have time to go into details but you see again this inverted triangle here, suggesting that the same mechanism. The same theoretical mechanism of how you have to tune your week rhythmic perturbation to enhance neural rhythms can also be found in the entire brain. Importantly, the bottom plots here showed changing firing rate, and there's nothing there.

NOTE Confidence: 0.89567756652832

00:42:57.800 --> 00:43:13.950 So we're really talking about a perturbation at adjust timing by not overall firing rate details for the aficionados and it's on the preprint server. We actually found that there's one type of neurons, which more selective responses simulation. That's another talk. I don't have time to give today.

NOTE Confidence: 0.892401576042175

00:43:15.080 --> 00:43:46.130 Alright so I've given you all this basic science preclinical stuff and you know your pages are beeping and you need to go and treat your patients, but so is the reward for making food at first I guess 40 minutes or something of this 5 hour lectures were going to shift to the clinical trials and I hope that this is of interest. So this is in collaboration with Doctor Rubino. Another yield product. Some of you might know and this is a first clinical trial of TCS.

NOTE Confidence: 0.924572467803955

00:43:46.130 --> 00:43:55.000 For the treatment of major depressive disorder. It was a double blind placebo controlled study peril group randomizing patients and do one of 3 arms.

NOTE Confidence: 0.915125608444214

00:43:55.510 --> 00:44:26.180 The first one was 10 Hertz, TA CS target. Alpha oscillations because there's a slightly controversial yet quite substantial literature on the role of differential engagement of left and right hemisphere, corresponding to an ask symmetry in Alpha oscillations. The second one was at the control frequency at 40 Hertz because we want to make sure that we do, find an effect is not just because we applied electricity. But it's really specific to the stimulation frequency and the 3rd one was inactive perceiver sham stimulation.

NOTE Confidence: 0.912712872028351

00:44:26.810 --> 00:44:47.370 We chose this simulation montage in a way that the two frontal sites left and right received the same polarity. Rhythmic stimulation and hope that if there's really something there about the relative balance of activation left and right that is shared synchronization would strengthen the interaction and restore that balance and.

NOTE Confidence: 0.864802539348602

00:44:48.020 --> 00:45:04.220 Here to clinical results so this was a small study, but double blind procedure controls. I'm showing the results from a patient

stop matters bottom. BDI and I don't think we need to introduce this with this audience. So clich administer scale self report depression symptoms normalized to one.

NOTE Confidence: 0.874240636825562

00:45:04.790 --> 00:45:06.360 Here is the 10 Hertz Group.

NOTE Confidence: 0.883322596549988

00:45:07.310 --> 00:45:15.120 Baseline after 5 days of stimulation 2 weeks 4 weeks here is to 40. Hertz group and here's the placebo group.

NOTE Confidence: 0.884993970394135

00:45:15.740 --> 00:45:42.370 So first, the 40 Hertz group we can interpret that goes when we queried for blinding. We were not successful and blinding to 40. Hertz group from the participants because the 40 Hertz simulation activated the optic nerve, too much and create the flickering perception that enabled presumably the participants who guess stimulation condition better than than better than random so we have to ignore the middle. One and now we're discussing left versus right.

NOTE Confidence: 0.896012008190155

00:45:43.170 --> 00:46:15.460 Primary outcome of this study was negative because primary out Kim Norman is done. TCS before very optimistically. We chose 4 weeks. There was nothing there. There's something on exploratory analysis. Clearly, there in terms of responders at 2 weeks. If you compare this to this right so tantalizing but definitely no no final answer, but promising enough that we felt there would be worked to build on in fact when you look at the G. We're looking at changes in Alpha Oscillations, the black dots or the statistically significant.

NOTE Confidence: 0.885359883308411

00:46:15.460 --> 00:46:46.810 Electrodes that have significant change in Alpha oscillation sever comparing gender 3 groups here and what we find is that in that Emirates group. There is a significant suppression of left front laugh oscillations, which is very intriguing because if you believe the Alpha symmetry literature, which I know has question marks. Nevertheless, there's there's a good reason why we're doing TMS on the left. Hemisphere right and lack of hyper activation will correspond to too much Alpha.

NOTE Confidence: 0.913005948066711

00:46:46.810 --> 00:47:03.240 It is quite intriguing to see that by stimulating both sides in synchrony were able to selectively reduce the presumed or hypothesize pathological increase in left front laugh oscillations. None of it in the other two groups.

NOTE Confidence: 0.900853455066681

00:47:04.020 --> 00:47:34.550 And nothing statistically significant maybe this was friend level here, persisting effects later on for weeks later, not sure about that, so this is intriguing because it seems to suggest that indeed the target. Brainerd and router and there's a very simple story about Alpha symmetry and re storing symmetry that you can tell based on this. But while this is very exciting. There also lots of open questions because the standard way, have most of us probably like to think about TSCS is.

NOTE Confidence: 0.874087035655975

00:47:34.550 --> 00:47:53.250 If you stimulate at a given rhythm you in hell style activity, but seemingly here over a week of Simulation. There is a perhaps homeostatic reorganization and we really don't know what's going on server about to start a follow-up study where we're doing EG serially everyday to really understand overtime? How do you out false elation changes?

NOTE Confidence: 0.871585607528687

00:47:54.090 --> 00:47:55.170 How am I doing on time?

NOTE Confidence: 0.848651945590973

00:47:57.050 --> 00:47:58.580 Great awesome perfect lips.

NOTE Confidence: 0.903707981109619

00:47:59.430 --> 00:48:31.540 So more recently, we, we went back to his hypothesis that if you stimulate their three and a 4 to 2 front sights left and right in synchrony that we should really strengthen the functional interaction. In a frequency specific way or the functional connectivity between these 2 places, so we've used Loblaw see an approach to kind of localize active little bit better and measure the functional interaction from F3 to everywhere else and we indeed found specifically for Alpha TCS and this is data across multiple trials.

NOTE Confidence: 0.898109257221222

00:48:31.540 --> 00:49:04.070 A significant strengthening specifically that frequency and this is measured using phase log index between the two sites, suggesting indeed that if you have an is at least is free. Electro montage or 2 electrodes receiving face stimulation. You can strengthen the function interaction, which we did not find that this is a control for the procedure. TS yes, so more work to be done. But it does appear not only that the functional organization of rhythms and interaction of large scale brain networks matters for how we do cognitive and how we feel, and experience, the rule, but also.

NOTE Confidence: 0.892291128635406

00:49:04.070 --> 00:49:18.760 That perhaps very weak electric Karen at least applied repeatedly can outdo these interactions and perhaps and a sillen open question because those were the first. The first clinical trial of TACS in the precious I've shown you perhaps ultimately be of clinical value.

NOTE Confidence: 0.886670589447021

00:49:19.580 --> 00:49:49.590 I want to shift gears go back to uh some theorem. You've met before is now collaboration with doctor yards cooks. So here we're looking at auditory hallucinations, going back to that study have shown you the beginning, where we did not find an effect for constant current so here we have the we had the opportunity to do it. Another perceiver controlled study where we enroll patients medication refractor auditory hallucinations, and we randomized them in 3 groups. We have the TVCS is before we have to proceed was before.

NOTE Confidence: 0.907841682434082

00:49:49.590 --> 00:50:18.370 But we have now a third arm where we're using 10. Hertz TICS and the idea is that we strengthen the functional interaction. Between these 2 sites that were target with TDCS name. The left frontal areas and temporal parietal auditory areas. So we came up with again. A3 Electro Montage. Worthy ideas for stimulating these 2 sites together so TCS attempts to change activity levels. TCS tries to change the functional frequency specific interaction between these 2 sites.

NOTE Confidence: 0.900212705135345

00:50:19.210 --> 00:50:49.410 First clinical trial of TCS full stop and also schizophrenia. So I want to show you some of the results that I'm going to focus on the neurophysiology. So here you see Topa graphic Maps of changing this rhythm and Alpha oscillations as a function of the treatment group an as a function of time. So here is in a fifth day of 5 days of Simulation. Here's follow up one week. Afterwards, one month. Afterwards, what you see. And this was statistically significant what you see that selectively in the 10 Hertz group.

NOTE Confidence: 0.890233218669891

00:50:49.410 --> 00:50:51.590 There's an enhancement of the Alpha oscillation.

NOTE Confidence: 0.897011458873749

00:50:52.210 --> 00:51:21.120 That persists here a trend level that that persists and none of that in the TCS and Sham Group. So to me. This is very promising demonstration that repeat application of TCS as some people call offline or out, lasting effects that if you do this multiple times through whatever plasticity mechanism. You want to invoke because I don't know which one we should which one it is, we can in a persistent way strengthen these network activity patterns.

NOTE Confidence: 0.896272540092468

00:51:22.450 --> 00:51:51.340 If you look at the frequency of the Alpha oscillation, specifically of the functional interactions of function frequency. Uregi textbook tells you that the Alpha frequency is a marker overall for the integrity of the white matter bundles between thalamus and Cortex and it's kind of this

broad marker of system health. If you will and the textbook tells it is what it is what we found here and these are all the patients against click by group and we're looking at the frequency of the interaction. We found that in the tenor it's group.

NOTE Confidence: 0.908278822898865

00:51:53.130 --> 00:51:57.650 Every single participants, which change your Alpha frequency to 10 Hertz.

NOTE Confidence: 0.887517154216766

00:51:58.600 --> 00:52:23.510 And this is 24 hours after the last stimulation, so there's no contamination. No immediate artifact. So we're able to change the Alpha frequency in these patients. None of this effect in TCS or placebo. Some of it still persists a week later, a month later. They've returned toward ever before which inspired us in a follow-up study now overall so we randomizing then in a maintenance period with weekly simulations for 8 weeks.

NOTE Confidence: 0.900263667106628

00:52:24.330 --> 00:52:55.200 Now, what else can I tell you about my TCS did to the brains of these patients? Well, one of them and that there's also work from Yale and in many ways, is looking at the auditory. Steady state response, which we know at 40. Hertz the audio response is impaired in patients with schizophrenia. So we looked at whether that auditory kind of more local sensory processing response could alter by TCS and you see this here split up again by treatment group. This is changing. The steady state response again a marker for if you will a brain of someone?

NOTE Confidence: 0.890132546424866

00:52:55.200 --> 00:53:02.510 With schizophrenia and we found the TCS specific increase in the auditory response of 40 Hertz.

NOTE Confidence: 0.90899920463562

00:53:03.600 --> 00:53:36.700 None of it in T DCS and perceive A and some of it still persisted a week and a month later that trend level, so by strengthening increasing the frequency and strength and the strength of these Top down functional network in the Alpha frequency, seemingly as an extra benefit. We're getting here improvement, or restoration of more basic auditory processing network features. In fact, if we then look at what the relationship is between that restoration of the auditory steady state.

NOTE Confidence: 0.907284259796143

00:53:36.700 --> 00:53:58.790 Response that I've written big input and the clinical improvement, measured by the auditory hallucination rating scale. We actually found significant correlations for a 5 and week. One again further demonstrating that indeed re storing these basic perceptual network mechanisms correlate and if you will predict clinical clinical outcome in this study.

NOTE Confidence: 0.916771650314331

00:54:00.480 --> 00:54:17.340 Finally, I want to show you one more study, which was just a single session of stimulation, which is I think a huge irrelevant, but also very controversial topic. At least when you talked in urologist because I'm shifting gears. Now I want to talk to you briefly about chronic pain.

NOTE Confidence: 0.870950996875763

00:54:18.300 --> 00:54:48.530 Is work by Sunday on again and the very talented graduates unilab and what we've done is we've enrolled patient with chronic low back pain, the only study where we never had any worries about enrollment right within 24 hours. The study was fool. If you ever get frustrated but then recruitment rate for your studies to start studying chronic low back pain and it was a single session. So it's really just about the more instantaneous effects where we use 10. Hertz TCS versus perceived was a crossover study.

NOTE Confidence: 0.917277991771698

00:54:48.530 --> 00:55:10.260 Now why would we want to stimulate the brain if it's about pain in the back. Well, some of you might know this emerging literature demonstrating that chronic pain has very little to do with mechanical injury or constants, medic canickel injury, but that the brain of patient with chronic pain in many ways looks very much like the patient of a depressed person and we don't understand this yet, but the idea was this.

NOTE Confidence: 0.916378855705261

00:55:11.030 --> 00:55:41.520 Now the idea is very simple. Maybe the persistent perception of pay or pain experience has something to do with hyper excitability of some other sensory motor circuits. It's the same idea like with the auditory hallucinations, where we think that the pathological unstructured activity in auditory areas generates perceptions of hallucinations well. Maybe we can just translate this and move to some other sensor circuits. If that's true. Then we would expect their patients with pain have less Alpha oscillations because remember Alpha oscillations the mechanism.

NOTE Confidence: 0.890653192996979

00:55:41.520 --> 00:56:02.870 Which cortex goes offline and indeed when we looked at the standard at you know zero to 10 pain rating scale and also the disability index, and correlate with the strength of the Alpha oscillation. We start to see the central located. Some other sensory motor deficits so the more your Alpha oscillation is impaired. The more severe your chronic low back pain.

NOTE Confidence: 0.892288148403168

00:56:03.900 --> 00:56:35.070 So that's essentially the first step that would be the target identification. The next question is can, we use THC. Escena montage should target. These areas and restore Alpha oscillations. And yes, we can. And this is again. It's just a single simulation sessions overlooking immediate before

24

and after, so I don't know yet about multiple treatment days as we've done in the studies. I've just shown you. But here's the change in Alpha oscillation with TCS versus sebo. So it was a crossover study right because just a single session and that we found. Indeed, a significant strengthening of the Alpha oscillation.

NOTE Confidence: 0.895778477191925

00:56:35.070 --> 00:56:43.830 In the areas that we know based on the previous slide. I just showing you that reduced Alpha oscillations means more chronic pain.

NOTE Confidence: 0.864132165908813

00:56:44.780 --> 00:56:55.130 Then finally the question is did re storing galpha oscillations improve ping. So we're looking now for a correlation specific to stimulation and that's indeed what we find.

NOTE Confidence: 0.88761705160141

00:56:56.140 --> 00:57:25.290 Here in here there's also something frontal and that's another conversation. I don't have time for a bit. Maybe afterwards and we're done, but we don't find this for perceiver stimulation so In other words, If you come in the more real false eyes impaired. The more severe ear pain. That's the target identification. I showed you the target engage were able to strengthen these Alpha oscillations and the target validation is that when you receive in the day. You received simulation the more I managed to restore your Alpha oscillations the more your pain symptoms improve.

NOTE Confidence: 0.916353225708008

00:57:25.850 --> 00:57:57.580 There is also a significant improvement in just pain symptoms without correlation to brain activity, but you see so now. Remove we've done a very you know, I think we've been on a really exciting long journey moving from using constant current out looking inside the brain, hoping for miracles all the way to hopefully you agree would agree with me to a very targeted rational pipeline of going after brain activity signatures brain rhythms as potential treatment targets and in many ways. This should be the end of my presentation.

NOTE Confidence: 0.908084809780121

00:57:57.580 --> 00:57:58.490 But it's not.

NOTE Confidence: 0.89194518327713

00:57:59.470 --> 00:58:31.440 I'm going to show you some other thoughts. I have when most of them don't relate to brain stimulation directly, but I'm just taking the Liberty to share reveal a bit more. But other things are keeping keeping me engaged and excited. So here we're seeing Theta oscillations again your midline frontal Theta that we've started one of the earlier study. I showed you. We talked about this cognitive rhythm here and how it relates to the treatment of

treating response oppression. All this, but this is actually a correlation with progesterone levels.

NOTE Confidence: 0.909034848213196

00:58:31.440 --> 00:59:04.410 Measured in saliva in healthy controls across many participants and that's just a reminder for us that the reminder for myself. You know, we have our expertise. We focus on one thing and everything fits that lens, but I'm trying very actively to to encourage my trainees to collaborate and look and you approaches and here's essentially outcome of US measuring salver sex hormones and pretty much all our research participants and we found no correlation for estradiol if I know correlation for testosterone.

NOTE Confidence: 0.870753705501556

00:59:04.410 --> 00:59:31.160 But for progesterone there's a strong relationship to Midland frontal feet. All solutions where their nose means in terms of Neurosteroids and modulation with Gabaergic signals and we can speak a lot about and I don't quite have all the answers. But there's just one thing for the aficionados and this is again just since discovering which I want to briefly show it to you when you do F MRI in cognitive task. You see this bilateral activation right dorsolateral prefrontal cortex when you do EG you see it in the middle right.

NOTE Confidence: 0.820560157299042

00:59:32.450 --> 00:59:34.620 Is that as a puzzled anyone before?

NOTE Confidence: 0.886224746704102

00:59:35.130 --> 00:59:41.390 No maybe should but when we actually do source localization. We found the Theta right where we should.

NOTE Confidence: 0.884356915950775

00:59:42.320 --> 00:59:52.750 So, your midline, Franklin feeder might very well. This correlation with progesterone, but you see. It also in general. That's where it is might really be just a result of how the electric fields add up.

NOTE Confidence: 0.881204426288605

00:59:53.250 --> 01:00:02.400 And in reality activity comes here from the tool and the way you would find them in functional magnetic resonance. So just just hopefully something to discuss some think about.

NOTE Confidence: 0.906812131404877

01:00:03.180 --> 01:00:35.250 You know neuroscience kind of often stops here right there were looking at the brain. But in reality, especially if you want to understand the costs of psychiatric illness. I think we need to look much more broadly, and I think one of the most exciting new directions is to look at the interaction between the immune system and the brain and specifically at the

gut microbiome, so this is a ferret study and all I want to show you here is we've done probably first placebo controlled study of probiotics in ferrets right.

NOTE Confidence: 0.901602625846863

01:00:36.300 --> 01:01:09.610 And here to 3 species at group or general that we have administered relative to a control and based on the sequencing of stool samples. We were able to enhance the relative presence of these types of bacteria and I don't have time to go into this. But in essence. We used affair biggest charity social social species that they're interact with each other. A little bit like dogs. We found significant correlations between our ability restore and re modulate the gut microbiome.

NOTE Confidence: 0.891558289527893

01:01:09.610 --> 01:01:44.620 And behavioral outcomes in terms of you know, preferring novel animal versus familiar animal and this kind of social interaction tasks and that's just here is a reminder to us yes. Let's get excited. But I think one thing we specialize in but ultimately if we want to progress. I believe we need to be much more broader and bring together many different things. Ultimately, all goes back to this right so this is a ferret brain stain for my own, through development right all our brains could wired up prenatally postnatally whatever else will learn and all our experience shape us is not just electric brain stimulation shape sprain right.

NOTE Confidence: 0.894480109214783

01:01:44.620 --> 01:01:52.650 Is everything that we do that shapes? Who we are and ultimately will be reflected inverted wires go and how strong they are and.

NOTE Confidence: 0.911235213279724

01:01:53.240 --> 01:02:25.080 You know there are many ways. How do in beneficial ways out the brain connectivity and TCS might be one of them here is another one here's my oldest daughter, Sofia playing a cello ensemble here. My 3 younger kids in violent lesson. And if you think about rhythmic timing sensor input internal state output what the brain does and what we try to perturb with TSCS playing music together and learn how to play music probably taps into very similar mechanisms. So let's keep an open mind, and really think broadly about.

NOTE Confidence: 0.914351284503937

01:02:25.080 --> 01:02:32.470 How we can improve lives beyond the thing that you know I happened to study and published papers on in fact you can study this.

NOTE Confidence: 0.90123325586319

01:02:33.110 --> 01:03:05.820 To buy knowledge is ovro Premier it might be or not the music was pretty mainstream. You know, a client and off Music Mozart.

Stuff like that, but we celebrated to purchase it before EG system by inviting this classic or death and simultaneously recording brain activity for musicians with some people call hyper scanning and in many ways. I think ultimately to understand the psychiatric illness and the human condition, will need to understand how we interact with our relationships are believe it or not, that would suggest there is a physiological under pending.

NOTE Confidence: 0.871580362319946

01:03:05.860 --> 01:03:13.010 In terms of not with an individual brain. Dustbot weather network of brain does and how to synchronize which we can probe with approaches like this.

NOTE Confidence: 0.8937668800354

01:03:13.800 --> 01:03:48.230 Finally, let me just summarize with what we're I think we're going, so status quo future. We were taught to think us about us into paste individuals, but in reality of rule over all ecosystems of more foreign cells and own cells will learn about different organs and we focus on the brain. But in reality, many of the organs. We have or actually oscillating systems that are all connected in various ways. If everything were linear that week perturbation like TCS could never have such a profound effect. But the thing about biology and your Physiology in particular is highly nonlinear.

NOTE Confidence: 0.917176783084869

01:03:48.230 --> 01:04:18.850 It's very dynamic, not static. I've shown you some results that suggest that this really sophisticated machinery. We have is very sensitive to smartly time, but very weak perturbations, which kind of goes against this idea of how robust robust. We are as individuals. Everything I talk to you today is in some of the other way can go back to thinking about the brain and the body as an electric system and finally let's start to shift perspective and think about what networks of brains instead of individual brains mean?

NOTE Confidence: 0.914183676242828

01:04:18.850 --> 01:04:45.510 This is my very last slide my most important message, especially to the more junior members of the audience. Mentoring is my priority. If there's anything in here that you feel means that I or someone in my group can help you with what your passion? Is police please. Please don't hesitate to reach Adam. Please do reach out to me email. Direct message Twitter online. Whatever you'd like one or the other way. Thank you very much. It's been a pleasure. Thank you.