[MUSIC PLAYING]

STEVEN FORMAN: So you're going to be going along on a journey with me too of learning about TMS in schizophrenia, which I will get to at the very end. Before that, though, I'm going to basically-- let's see if I can do this. Oh, good. So I have to do this first. As Roy said, I work at the VA. Your tax dollars funds my mortgage and everything else. So this entire talk is all for me. It is not official government views. And so any problems with it, it's on me.

So the other piece to it is I come to you basically I have done a fair amount of research IN TMS, but not in schizophrenia. And what I'm particularly proud of right now is that over the last year, we've actually implemented clinical TMS at VA Pittsburgh. So we have an operating clinic. If you are a veteran or if your loved ones or friends should happen to be veterans and they have treatment-resistant depression, please send them my way. I promised Dr. Vishwajit Nimgaonkar that I would plug our clinic. So I've now done that piece.

But I come to you slightly differently than Dr. Kane and Dr. Kelly, who did fantastic-- I loved their talks this morning. But their talks were from the point of view of principal investigators describing their body of work. And I come to you basically as a clinical provider trying to communicate what TMS is. So I hope at the end of this, you'll have a better understanding of transcranial magnetic stimulation, which I will after this hopefully just say TMS, how it works, what the basic mechanisms are from the principles of electromagnetism, how the physics of that translate into changes in brain activity and behavioral and symptomatic manifestations, how people tolerate it, what it's like to actually do the treatment as a provider and what the experience is as a patient. And then finally, I will get to a little bit of the background and the work that's been done in symptom management in schizophrenia and psychotic disorders.

So with that introduction, we'll go into the what. So I already said, TMS is repetitive transcranial magnetic stimulation. And what you do in TMS is to generate these very intense, brief pulses of magnetic field energy. And the scalp and the skull are transparent to magnetism. So it goes through those non-invasively and can then alter brain activity underneath it.

And it turns out, to foreshadow, that by use of this in a particular way, that I'll get into detail later, we develop treatments for major depressive disorder that had failed to respond to pharmacologic treatment. So the current indication for someone who will come in for TMS treatment is someone who has a current MDD, probably moderate to severe, who has been placed on, for example, sertraline at a dose of, for example, 100 milligrams, for example, four solid weeks and has not responded to the medication. You could also-- it doesn't have to be one, it could have been two trials, four trials, 10 trials, but at least one. And that's that with respect to major depressive disorder.

That was first cleared by the FDA. The first device clearance was in 2008. So it's almost it's 10 years now since the approval. OCD was approved in 2018. And those are the only current indications.

Schizophrenia psychotic disorder, auditory hallucinations, they're active research topics. But they have not been FDA cleared. And there are very important manifestations and consequences of the fact that they're not FDA cleared at this moment.

I love this slide. And I must also give credit, our clinic opened slightly over a year ago. It is part of a nationwide VA rollout of TMS. And some of the groups that are intimately involved in this, the VA in South Carolina under Dr. Mark George, and the VA in Palo Alto with Dr. Michelle Madore are not as graphically challenged as I am, so I've used a number of their slides in this presentation. This is one of them from Mark George.

So I love this picture because the right side slide shows Dr. Barker doing a very early TMS demonstration in 1985. So Barker and Jalinous their group, sort of invented this, or maybe I should say reinvented it in 1985 and began to use the technology, initially to do peripheral nerve stimulation. But then they got the idea very rapidly that, well, let's try doing it centrally and see what the effects of these magnetic pulses are.

But what was interesting is Sylvanus Thompson in the photograph on the left, that's 1910. They were doing things like that in 1910. And so this immediately makes you think, well, what the heck happened? Why is there 75 year gap between Thompson-- because he was he was producing effects-- and 1985?

Well, there are a couple of reasons for this, of why nothing seemed to happen for 75 years, because there were perhaps three or four papers published right around there, proceedings of the Royal Society of London, et cetera, and then it disappeared. Well, part of it is technological. In 1910-- well, let me take a step back.

In order to generate magnetic fields of sufficient intensity to actually affect brain activity, you have to use an enormous quantity of electricity. And you have to be able to switch the electricity on and off very rapidly. And back in 1910, the only switches that they actually had were mechanical switches, throw switches, where you broke the actual circuit and connected them again.

The problem when you're trying to break circuits with that much electricity is they tend to arc. And so the technical, pragmatic difficulty with promulgating this technology back then is that patients are sort of uncomfortable sitting next to what is, in essence, an open arc welder. So that's one piece as to why it did not catch on.

The second piece is also historically we're sort of-- I think of us as being in the third phase of neuropsychiatric interventional modulation. The first phase was around the 1880s, '90s, 1910s, and lasted until perhaps the '40s. And that was the era of psychodynamics, Freud, Jung, et cetera. And science progresses-- Dr. Kelly mentioned it this morning. She had to go to NIH and sort of beg them for money, because if they weren't really thinking of the biome, people weren't thinking about funding it. Well, when Thompson was doing this electromagnetic stuff everyone was thinking about id, super ego, and other stuff like that. So he didn't get any follow through.

So the second phase was sort of the 1950s to, its still where we are now, the era of psychopharmacology-- Thorazine, SSRIs, second generation antipsychotics. And we are just from '85 on, but I would argue, OK, call it 2008 as the set-off date when they finally gotten approval clinically, we're now at the age of neuroelectrical modulation.

It's true ECT has been in existence since the '40s. And it is electrical. And I will describe some of the differences between ECT. But as everyone probably in this room already knows, there are some obvious problems with ECT or at least stigma and other issues. So this is the first relatively more easily promulgated neuroelectric modulation technology.

So anyway, that's the reason why somewhere out there in the multiverse I like to think of an alternate universe where there was a Steampunk TMS that really took off in 1910. And we'd be doing the work back around-- my equivalent in 1919, would be doing what I do now. But anyway, we won't know it. In this universe, we do it with these devices.

And what allowed Barker and Jalinous to do what they did was the development of electronic devices. Solid state switches, transistors, et cetera, made it possible to make machines that were this size and coils that size.

TMS works through the principle of electromagnetic induction. So bear with me if your physics is old. But Michael Faraday in the 1830 discovered electromagnetic induction. And to describe basically what's going on, there's a relationship between electricity and magnetism. When you push an electric current through a coil, that coil generates a magnetic field. The magnetic field is perpendicular to the direction of the current flow.

Now, just as time varying or time changing current flowing through this coil produces a magnetic field, a time changing, time varying magnetic field applied to a conducting element, be that a wire or a brain, induces a current flow in the conducting medium. Now, as I said, the scalp and skull are transparent to magnetic fields and, in fact, are electrical insulators. So magnetism can get through the head. Electricity, if you wanted to directly apply it, because the scalp and the skull are insulators, it's hard to get electricity directly through the scalp and the skull.

And that's why when you do ECT, you have to use high voltages and generally decent level currents. And it's painful. That's the reason why nowadays ECT is done under general anesthesia. And it's a very good treatment, fairly benign under these conditions, but it requires anesthesia, because it's painful.

And anyway, you use time during magnetic fields to induce the current in the underlying brain tissue with TMS. And that can then affect neural firing. And the neural firing can be shaped to modulate how the brain is working.

So this is a picture, a schematic of what a magnetic coil looks like. So TMS coils come in various configurations for various reasons. The simplest one is this sort of donut-shaped coil. And you can see-- actually, I'm going to take my pointer out if I can find it.

So there's a lot of current flow, 8,000 amps. And the pulse is generally about 20 microseconds. So you have 8,000 amps running through this thing. And as it runs through, it generates a very high, 1.5 Tesla magnetic field strength, which is on the order of the strength of your standard MRI machine. Some MRI machines now are three Teslas, but it's sort of ballpark for the same, which are very big magnetic fields.

To give you a rough idea, lower level magnetic fields are not really thought to do very much. We all have these ubiquitous phones. So the phone magnetic field is maybe 1/10,000 of that strength. So it probably doesn't do very much. And the Earth's magnetic field is on the order of 1/20,000. So these are very big fields, and you need that kind of current to generate it.

How does that actually implement in the brain? Many folks here probably have seen similar diagrams as this, which is here is the incoming nerve. Here's the outgoing nerve. Up here, there is the nerve gets a signal. And the signal in this nerve propagates by having a voltage go across the nerve membrane, until it gets to the bottom where that voltage affects these vesicles. Vesicles are like little bubbles of oil. And inside the little bubble of oil are the neurotransmitters.

And what the voltage does when it gets to the end here, the vesicles merges with the outside membrane of the nerve cell and releases the neurotransmitter into the space, which is called the synaptic cleft. It diffuses across. These molecules then bind to things called receptors, which are proteins on this end. And when they bind, the shape change actually makes a voltage change across here. And then that voltage goes down through the next.

So the brain actually operates as a combination of pure electrical transmission of a signal. And then right at the synaptic cleft it turns into a chemical transmission of the signal. And then it turns back into an electrical transmission of the signal. So that tells you that there are two opportunities that we have to influence signaling through the brain.

There are the chemical side. And that's the medication part. And then there's the electrical side. And for stimulation we have the technologies of our TMS. We have ECT. And there are some others as well. There are deep brain stimulators. There are now transcranial direct current, alternating current, random current stimulators. But I'm talking about TMS today because it the most well-established, the only-- and basically it's FDA cleared. I'm not talking too much about ECT.

So this slide describes a little bit about the differences between ECT and TMS. So I already described this a little bit, which in ECT you're directly pushing a current all the way through the brain. And when it works activates all the neurons, all in parallel. They are all firing off simultaneously. And by definition, you get a seizure.

If you don't get a seizure with an ECT stimulation, your ECT is not going to work. ECT without seizure is failure. So every ECT session must result in a seizure, or you're not having an effective ECT treatment.

Now, those seizures, way back when, you know, *The One Flew Over the Cuckoo's Nest* depiction of ECT is sort of draconian and horrible. We don't do that anymore. People are under anesthesia, that we've come up with better techniques to minimize sequelae. But they're still associated with cognitive deficits.

One thing ECT does do it can reach deep structures. Now, TMS, because magnetic field strength drops off precipitously with distance from the magnet coil, you only can hit the sort of surface layer of the brain. And because of that directionality, you remember, we had the coil and the magnetism was sort of spinning around at 90 degrees to it. So the current flow that gets induced by those magnetic field gradients is actually tangential to the cortical surface. And it doesn't get in very far. So that's a difference.

So we can't really reach deep structures directly with most TMS coils. We don't need any anesthesia. When I have my patients come in, they're sitting in a really comfy chair. They can walk, talk-- well, they can't walk because they have to sit in the chair with the coil against their head. But they can walk into the office, sit down, have the treatment, and then walk home or drive home. They don't need an accompanying person like you do for ECT. And except if we have a very rare, unhoped for adverse event, seizure is not occurring for TMS to work.

What they found when they initially began to investigate-- huh, yes, OK-- so when they began to investigate TMS, initially in the motor areas of the brain, they found that you could do repetitive sequences of pulses. And depending on the frequency of the repetition, you would get different results.

If you did a low frequency sequence of pulses and continued it for a period of time and then measured the excitability of the brain after you finished, the excitability would decrease with numbers of pulses. Conversely, if you did a higher frequency repetition sequence of pulses-- I say here greater than 1 hertz or 1 cycle per second, but in reality it usually is greater than 5 or 10 hertz-- you instead increase the excitability.

So this immediately offered the possibility to people who are doing this work, hey, we can modulate brain activity. We can do it in a directional fashion. If things need to be low, we can drop them down. If things need to be increased, we can raise them up.

And because TMS is also targetable, we can direct it to particular regions. And this coil, I showed you the picture before of the sort of donut coil. Imagine you had two donuts next to each other. And right at the center point where they touch, the magnetic fields add together. So right there at the center point-- they call this a figure 8 coil-- the magnetic field doubles in strength. So that's what allows you to target, because that center point of the coil is the place where it's the highest magnetic field.

And you have a region of about-- call it a 1/2 square centimeter where it's the highest level. Yes, it drops off from there. So theoretically, you are stimulating at a lesser and lesser degree as you move away from that center point. But right there at the center point is where you can place your coil. And if you know where you want to put it, that's where you put the center point of the coil.

So this focality of TMS offers an opportunity. And the directionality adds to the focality as an opportunity for potential neural modulation. So as I was kind of alluding to, it's important. You have to figure out where you want to aim your TMS.

So in the mid to late '90s, a number of investigators began to look at mood disorders with the new technique of functional neuroimaging. Helen Mayberg's group and a couple of others basically demonstrated that along with major depressive symptoms, you got hypo frontality. And although there was some dispute about this-- some papers showed it yes, some paper showed no-- there was a general consensus that the frontality was a little bit more left-sided than right-sided.

So here you add two pieces of knowledge-- major depression, low, left-sided, prefrontal activity, and a technological device that if you can target, place it over a region, and depending on how you set up the frequency, you could boost activity. So the idea was that you would aim an excitatory TMS sequence right to that spot.

This is the frontal lobe, temporal lobe. This becomes late important later. And this thing called the motor strip, I'm going to highlight it here because we use that now clinically. If you aim your TMS coil right about here, this is the region of the brain that has motor control for the hand and fingers. And you can actually move the coil around and by carefully adjusting the position produce a thumb twitch on the opposite thumb. So this is the left side of the brain. And if you TMS pulse the motor strip right around here, I can make your right thumb twitch or your right index finger twitch or you're right wrist twitch depending on moving the TMS coil.

If I adjust the strength of the TMS stimulator up and down, as I go up, the region of stimulus broadens. So you'll go from a thumb to multiple fingers to the whole wrist. On the other hand, if I turn it down, eventually you'll no longer be able to visually discern any kind of twitching. By convention, the stimulator strength that produces a barely visible twitch of the thumb half the time-- so you have to do this repeatedly-- is called the motor threshold. And it's different from every person to every person.

We use the motor threshold conventionally to define how much strength to stimulate each patient who comes in for treatment. And, in fact, the FDA-approved protocol requires that you do the treatment at 120% of the motor threshold. So that's why I have the motor strip up here.

So this is just to remind me to say that, yes, we want to do an excitatory, sort of higher frequency stimulation for treatment of depression.

So lo and behold, after a number of initial small trials, open label, then they went to small randomized, control trials, and then they did meta analysis, and then finally, they had industry sponsored what I think of as huge phase III randomized control trials for hundreds of millions of dollars, and after two of them were successful, in 2008, FDA finally gave approval of the neuronetics machine for treatment of treatment-resistant major depression. And you can read the description. And TMS took off.

Since that approval probably about seven manufacturers have subsequently gotten approvals-- well, I shouldn't say approvals. They're called clearances for devices. And clearances go in two phases.

The first company that has to go through-- this is a lot like pharmaceutical approvals-- the first company that has to go through has to do these big major trials, hundreds of millions of dollars, show safety and effectiveness. Subsequent device manufacturers only have to show substantial equivalence to the other guys in order to get approval. It's very similar to the initial drug company and then subsequently the generic guys.

And this is the standard protocol. So someone will come, a veteran will come to me with treatment-resistant major depression. I will evaluate she or he and find out that, yes, diagnostically they're appropriate. There are no contraindications. But the protocol is a high frequency sequence, which means 10 hertz or 10 pulses per second for 4 seconds. You repeat that every 30 seconds for 75 cycles. And that's basically a 30-minute session while you're being stimulated. And if you do that on the left dorsolateral prefrontal cortex over repeated sessions, you boost the activity of the hyperactive cortex back towards normal. And you hopefully see improvement of the depressive symptoms.

A lot of advantages to TMS. One, it's an outpatient procedure. No anesthesia. You can drive home afterwards. Because the patient's awake, alert, can talk, you can monitor very closely. Has a low side effect profile. It's not a med. Pretty well tolerated, even in patients who are fairly sick. It's a treatment option for folks who other modalities didn't work. My patients have-- and not just mine, but across the country-- pretty well accepted. Because it is new technology, a lot of people come in and say, oh, this is pretty cool. And there's a lot less stigma than ECT.

And this is the number one most significant feature of TMS versus ECT. There is zero-- zero-- evidence of any negative cognitive consequences. They've studied it very carefully. And so far, no amnesia, no anything, which is a very big winner for TMS in my opinion.

But there are some things that come with it. So like an MRI machine, when you fire off a high-intensity magnetic pulse in a device that basically has a plastic cowl around it, the magnet flexes. And the magnet flexes the plastic. And a vibration of a plastic produces a sound. In essence, you have a very high cost speaker.

So you make these loud rat a tat noises. And the stimulation itself, you can feel. There's an odd sensation. It's almost like getting a static electric sensation in the winter here where you're wearing wool socks and you touch the doorknob. It feels a lot like that. Not painful, but not something that you say, oh, yeah, I love that.

So if you're doing that 3,000 times while you're sitting in a chair and having this loud rat a tat right on your forehead, a lot of people have headache, particularly in the first few sessions. I usually in treatment actually ramp up treatments to the 120 of motor threshold over the course of the first one to five sessions. And that helps my patients tolerate it. By session 5, a lot of times most patients are actually tending to fall asleep in the chair. So the headache stuff tends to go away.

Mild discomfort at the sight of the stimulation, partly due to the same reasons that I just described, but also partly due to the fact that-- remember, I told you about the fall off with distance. So you basically have to really press the coil against the person's forehead, because you don't want any gap. And so you push this thing against and person's head is holding in place. So there's a little bit of discomfort there.

The stimulation sounds are very loud. Patients don't actually know this because-- or notice it or perceive it that way because they're 20 microseconds sounds. And the human ear is not particularly good at appreciating sound intensity as you get very, very short stimulations. So they think, ah, it's not that loud. But it's really it's about 110 dB.

So there is risk of hearing loss if you don't do something to protect it. So it is a requirement that any patient who comes in-- we have these high-end earplugs that we put in, 32 dB protective earplugs. You have to wear it for every treatment. And as a treater, I also wear them because I'm doing this all the time, even though if I'm stepping further away, a few feet away, the intensity goes down. But if you're there occupationally exposed, treaters who do this wear ear protection and so did the patients.

Now, we get now to the rare side effects. Just like with antidepressants, for which every once in a while you flip from depression to mania with antidepressant treatment, particularly if you've not managed to recognize an underlying bipolar diathesis as opposed to a pure unipolar depression, it happens. Same thing with TMS.

And then finally, the really rare side effect, which nonetheless is the thing that's the major concern clinically, is the possibility of inducing a seizure. It's an excitatory stimulation protocol. Therefore, yes, it happens. But it's really rare. Basically, current estimates are in the order of 1 in 30,000 treatments.

And I try to explain to my patients who come in, a seizure is scary, particularly if you haven't had one. But it is not from the standpoint of clinical medicine a really worrisome event. They're handled. They're self-limited, last a minute. They don't have any long-term sequelae. Unless the patient should happen to fall out of the chair and hit their head, they don't have any real problems. And we have a very nice char and can put it flat and with sides that go up very quickly.

And so seizure itself is not a problem. There's no evidence that TMS induces epilepsy or seizures that occur post stimulation. So there is no requirement to report this to the Department of Transportation. It won't affect your driving privileges. Just like ECT, which has a seizure every session, just because you go to ECT doesn't affect your driving privileges, as would be affected if you actually had a spontaneous seizure in your general life and it turned out that you ended up with a diagnosis of epilepsy.

So anyway, those are the major side effects. Now, there are some disadvantages. Number one, it requires daily treatment. This means Monday through Friday for 30 plus treatments. So that's 4 to 6 weeks minimum. And that's a lot of commitment, basically, an hour a day at least repetitively. And this is a real barrier, clinically patients have turned me down probably 50% of the time for consults. They say, I just can't do that.

On the other hand, human beings are actually pretty good, if they really want to do even some difficult tasks daily. Look at Peloton. So I think of it, it is a barrier, but you have a discussion with the patient as to how much they want to try this new modality.

I've already described the time. It is true that since the initial clearance for the 38-minute protocol, there have been approvals for small shortenings of it. Some of the shortenings are dependent actually on the machine duty cycle. Depending on what your motor threshold is, you can't shorten it below a certain amount.

Very recently, some newer, much fancier machines have gotten approved for something called theta burst stimulation, which has an approval of a 3 and 1/2 minute protocol. At VA right now, we don't have one of those machines. But they are available. And I believe the TBS, the theta burst stimulation, will begin to penetrate more clinically as it becomes more economically viable for folks.

So because someone's in a chair for better part of an hour and the machine is occupied, it's somewhat resource limited. So that's another limitation with it. And most of the time, the general consensus is for safety reasons, we want patients to be on a stable medication course, stable medical conditions, no active substance use, particularly those medicines or substances that might make seizures more likely-- stimulants, alcohol withdrawal.

And so it's also probably not the most useful tool for an acute crisis, someone coming directly into the ER for suicide, for example. But I have treated several inpatients. These are generally people who've been inpatient for a week or two. And the inpatient unit is thinking, huh, we don't know what we're going to do this time. They've been here 10 times before. Why don't give Foreman a call. And I've had some success with those patients.

Generally recognized contraindications, I described some of them-- seizure disorders themselves, tumor, if you've had severe head trauma, the drugs I mentioned, medications, lack of sleep. Generally, if someone comes to me in the morning and says, hey, Doc, I've gotten less than an hour of sleep last night. I say, let's punt it for today and come back tomorrow.

Metal in the head for obvious reasons. If you have metal in the head, that can conduct electricity. The induced current will be even stronger in that metal. And that could heat up. And that's really not what you want to have happen. So anybody that has these kind of things in or near their head, that rules them out pretty much for TMS.

So now, having described what clinically TMS typically is done these days, which is for the cleared reasons-- major depression and a little bit OCD, let me go on to schizophrenia. So why would you want to even think about TMS in schizophrenia? So, number one, just like major depression, there's a lot of medication resistance in schizophrenia. So coming up with an alternative therapy, particularly one that's relatively well-tolerated, pretty benign, relatively easy to implement with the exception perhaps of having to come every day, that would be a nice thing if it worked.

Schizophrenia is somewhat different than major depression because, at least for me-- this is my personal sort of viewpoint-- depression is kind of a unitary construct. When you talk about depression, you can sort of summarize it as sad, down. You can use two words. You know, mood's down. Movement's down. Attitude's down. Appetite's down. Sleep is down. Everything's down. You don't have to use a lot of other descriptive stuff.

But schizophrenia actually has a very much more heterogeneous presentation. There are positive symptoms. There are hallucinations. There are negative symptoms. There are cognitive deficits.

So you think to yourself, OK, in schizophrenia, we're probably not going to find a spot. But maybe there'll be multiple different spots that we can aim at depending on the symptomatic heterogeneity. Once again, reminds us TMS is focal. So we look for those spots.

Negative symptoms have some overlap with depression. So the obvious extrapolation when people were beginning to think about this was to say, OK, we already have approval for doing work to move up the depression. Why do we aim it at exactly the same spot since we have an approval for that?

But before that, there's this other spot. And Roy actually sort of anticipated this a little bit. This is the temporal parietal lobe right here. And this is where most auditory processing goes on. And early neuro imaging, initially PET scan and SPECT scanning, then later FMRI work, seem to find associations between auditory hallucinations and high activity in this region of the brain. And as Roy mentioned-- I'll get to it in a minute-- Dr. Hoffman saw this and knew about TMS and said, hey, guess what? Why don't we take a look?

Both of these regions are, of course, on the surface. They're reachable by TMS. And this is high. This once thought to be low. So you're going to do inhibitory here and excitatory here. And there's my slide again to remind everyone low frequency is inhibitory. High frequency is excitatory.

So to get back to Dr. Hoffman, 1999, actually probably before that. But these are the first reported results. They recruited three patients with refractory auditory hallucinations, did an inhibitory TMS protocol with those folks right at the temporal lobe. And lo and behold, this is open label, their auditory hallucinations scores went down.

I'm just going to skip, rather than go through a bazillion little tiny studies, I'm just going to skip to the latest meta analysis that I could find for what's going on with schizophrenia symptoms. So Kennedy published in 2018 a meta-analysis. So a meta-analysis, the term has been used multiple times here. I'm not sure if everybody knows exactly what it is.

So a meta-analysis , we've described randomized control trials in the previous study. They're the gold standard because the patients and the investigators don't know who gets the active treatment and who gets the placebo treatment. And that eliminates the bias that's present in an open label studies.

Well, as Dr. Kelly said, she had this relatively modest-sized, randomized control trial. 20 people or so got randomized. And it cost $1 million plus. So generally, particularly in the beginning of investigating anything, you're not getting very large randomized controlled trials.

And statistically, you get more and more what they call power, which is the ability to actually discern the true effect as you get bigger and bigger samples. And, yes, when they really want to, pharmaceutical companies can run 1,000-person studies, but they spend $200 million on it. And usually, you don't have that. But if 10, 20 small randomized controlled trials have been done and they have enough commonality-- in other words, they're measuring a measurement of outcome that is either the same or similar enough that you can combine the data-- the statistical analysis techniques of meta-analysis allow you to combine them and get some of the benefits of going from a single 20-person trial into a multiple 10, 20, 30 trial study that then has an n of 900, 1,000, 1,600.

It's not quite as good as if you actually designed and did a trial of 1,000 or 2000. But it's a lot cheaper. And it's a lot better than just saying, OK, we have 10 trials. 6 are positive. 4 are negative. So it's obviously positive. This gives you a much more quantitative description of the outcome.

This thing over here is called a forest plot. Or I kid you not, look it up in Wikipedia, they also call them blobbograms. And what you see is a depiction of the outcome of this trial. This is the mean outcome. And this is the sort of distribution of that trial.

And what you do is you can look at the picture and the sort of variation of where these sit in this horizontal graph go from this side, which favor the active treatment, to 0, which means no effect, to the other side, which means favoring the sham or placebo treatment. And they come up with this grand mean with a sort of diamond shape beyond it, which is the grand error bar of the meta-analysis. And if this is on this side, the full analysis favors the active TMS, as long as these diamond wings don't touch 0. If they touch 0, then it's non-significant.

So here's what happened when they analyzed. In the full meta-analysis they were able to identify 30 randomized control trials of TMS versus sham in patients with schizophrenia. 14 of them had the same symptom scale. So that's the auditory hallucination rating scale. So they can combine those and do an appropriate meta-analysis. And that gave them an n of 578.

And basically, if they combined it, the meta-analysis result was the TMS improved the auditory hallucinations at a fairly highly significant rate. And they were only moderately heterogeneous, which means that the differences amongst the trials were only moderate. They also found that a couple of covariates affected the positioning of this grand mean older folks and higher antipsychotics were associated with a small reduction or a movement to the right of the grand mean.

So this is the result. This is the latest data on auditory hallucinations. It does look like TMS to temporal lobe can have some benefit on auditory hallucinations.

So now, let's take a look at negative symptoms, for which there's really not a lot of good medication treatment as we've already been told. Well, if you look at this graph, it's a lot more scattered around the middle obviously. And even though the grand mean is almost at the same point you can see that the diamond is a lot more broadly distributed. So it's a lot closer to non-significant. But it's still-- since it didn't quite touch 0, it was significant only at the 01 level here.

So there is a suggestion that TMS to frontal lobes, an excitatory protocol, very similar to the one used for depression, might help negative symptoms a little bit. However, there is a caveat here. Along with the negative symptom improvement, they got positive symptom worsening, or a trend towards it. And that shows in the next slide-- that we're using the PANSS scale there, which is the positive and negative symptom scale, in those sets of studies.

So here's what happens. And you can see probably-- you can even tell what's going to happen before you got down to the bottom. There's a lot more stuff over here. And so this is the positive symptoms subscales within the PANSS. And it's now over here to the right, which means actually that the TMS made it a little bit worse.

In this case, the diamond is touching the zero. So it's non-significant. It's sort of trend. But it's worrisome. You don't want to just sort of jump in and do that if you think you might be making something worse.

TMS is pretty safe, generally regarded as and patients really tolerate it pretty well. But it's not FDA cleared. And this is the most important little piece to that. Since it's not FDA cleared, your insurance won't cover it.

And that's a big issue because TMS can be expensive. You're having these treatments every day for an hour. Ballpark cost for a TMS treatment is $100. So a course of TMS if you're paying it out of pocket could be anywhere between $5,000 and $10,000. If you're in the Bay Area, multiply that by 50%.

The evidence currently for this off label is for the 1 hertz temporal parietal TMS for auditory hallucinations. And as I just described, high frequency to the frontal lobe may do a little bit of something for negative symptoms, but you got to worry about potentially making the positive symptoms worse.

So take home message from this, because I'm very enthusiastic about TMS, as you can probably guess for the way I talk, we've barely started to explore the parameter space of electromagnetic stimulation. You can vary frequency. You can vary location. You can have multiple coils. You can link it to regions that may not even be the simple ones.

I'm going to go back for a second. Actually, Roy, how much time do I have?

5, 6 minutes.

OK, so I actually prepared a little something in case. I'm going to come over here. All this is basically, call it 1990s science in terms of how we think about neural activity and how it affects the brain. Single spots, front is down. Push it up, depression gets better.

But that's really not how the brain operates. I mean, we don't think that, oh, this is grandma. Oh, this is I've got to go to the cleaner after I finish this talk. Oh, why can't the Steelers ever have offense?

No, you think it's more like this-- pattern of activation across the brain.

Thank you. So more recently in the development of the science, we've gotten more sophisticated. I was involved in neural imaging in the very beginning of a functional MRI back in the mid '90s. But the last 10 years, instead of having these one spot kind of models, we've now gotten to something called the connectome.

And I just recently came on a paper, and I've been trying to get my head around it. Science improves through three basic mechanisms. One, technologies develop. Two, mathematical techniques and statistics develop. And three, old scientists die.

And so I've been trying to get my head around it. And I found this paper that I thought was fantastic. And I thought it was particularly fantastic. I talk about it because it had a Pittsburgh connection. And they did a study-- and I'll try to explain this without messing up.

And the Pittsburgh connection is actually Dr. Shaun Eack over here. And so I didn't even know he was going to be here. So that was surprising this morning. I'm watching him do the introduction. I said, wait a minute, I recognize that name. So I go onto my paper. And I said, oh, yeah, OK, cool. So if I get this wrong. He can fix it.

So what they did-- and it was a joint study between his group in Pittsburgh and Alvaro Pascual-Leone-- he's up in Beth Israel Boston-- who's one of the two or three best TMS groups in the country. So they took a group of patients with schizophrenia and negative symptoms. And instead of looking for just this one spot, they identified a network of regions that were connected together.

And they've now-- with statistical techniques that let you put a measurement to the connectivity, not the activity itself, but the connectivity across the network. And they and they were also able to link the actual level of connectivity to the intensity of negative symptoms expressed, and furthermore, find a link of that to a node in the cerebellum, which is kind of surprising because the cerebellum wasn't thought of being related to any of this stuff.

Why was that important? Because in earlier work, Pascual-Leone's group had shown that particular stimulation patterns to the cerebellum node could change connectivity in motor circuits. So what they decided to do, having found that in the initial group, they were then going to recruit a second group of patients with schizophrenia, have them go through the same neural imaging investigation, find the circuit, find the node, and then treat those patients with the new TMS protocol that had been found in the other study to effect the circuits in the motor study. And then they were going to bring them back, remeasure the neural connectivity, find out whether the TMS had influenced it in the same way it had in the motor study, and then see whether on an individual basis the change in connectivity affected the negative symptom manifestation.

I don't know, did everybody follow that? No? Well, like I said, I've been working on it for three weeks. I was trying my best.

The key point is this was-- to me, it's fantastic because it sort of foreshadows a sort of new era of how people do these kinds of investigations. It actually is a proactive, forward thinking interventional style, whereby one gets away from these associational studies and now basically can make causal inferences about affecting things. And you can find new ways of influencing brain activity on a much more sophisticated level, on the circuit level, which we think is a much more accurate description than the single blob descriptions that I showed here.

So anyway, the reason I said watch this space is this kind of analysis I think over the coming future is going to open up things and in time, although right now it's not cleared for treatment in schizophrenia, I have no doubt that there will be TMS or other kind of neuroelectrical stimulation protocols that will allow treatment in schizophrenia and various specific domains in the disorder. Thank you.