CORTICAL NETWORK CHANGES
ASSOCIATED WITH APHASIA TREATMENT
JULIUS FRIDRIKSSON, PHD
UNIVERSITY OF SOUTH CAROLINA

SWATHI: Okay. Um, while I can't thank you again for… for sticking with us. But thank you, um, for, for spending your day here. I promise it did get sunny and cloudy and sunny again a couple of times since you've been here. But by time you leave I can guarantee it'll be pitch dark. Um, (Some people laugh) so, for, thank you for being here. Um, our last speaker, and then remember we have the panel session after that. Uh, and last but not the least is Julius Fridriksson from University of Southern ca—South Carolina. Julius is a Smart State Endowed Professor at the University of South Carolina where he also co-directs the McCausland Center for Brain Imaging. His work focuses on understanding the many facets of aphasia, including its neurophysiology and recovery. Fridriksson is the, Dr. Fridriksson is a principal investigator on the Center for the Study of Aphasia Recovery, which is also called C-STAR, which is also a multi, another multisite, uh, research program that's funded by NIDCD. And so he'll be talking about some of that work today. Please join me in welcoming Dr. Fridriksson, our last speaker for the day. (Applause)

JULIUS FRIDRIKSSON: Good afternoon. Um… I'm glad to see how many of you are still here. When I realized that I was gonna be giving one a the last talks, it was, I was reminded of many, many years ago, and you would have to be pretty old to remember this, ASHA used to have half a day on Sunday. So ASHA actually ended I think at noon on Sunday. And the first talk that I ever gave was on form and frequencies, differences in older and younger adults, (Some people laugh) and it was at 11:00 on Sunday. (Several people laugh) And I will never forget; I came into the convention center; there was nobody here. (Some people laugh) So I gave my first talk at ASHA in front of 3 people, including my Master's Thesis mentor, my girlfriend at the time, and one other person from the lab. (Everyone laughs) So I have the whole guide. But anyway, thank you, uh, than, you for being here. (A few people laugh)

So, you will notice that my title has changed, and I apologize. So, the data that I wanted to present here, I was a little bit too optimistic that when I wrote the abstract, back in I can't remember what, May, April, somethin' like that, that we wrote these abstracts, I thought we would have, uh, more of our analyses completed. So I had to change a little bit what I'm gonna talk about today I; but I still hope that you will find this interesting.

So I'm gonna be talkin' about predicting and enhancing aphasia treatment outcome. So I'm gonna focus first on the predicting part, and then get into the enhancing part. And then there, there I'm talkin' about brain stimulation, so electrical brain stimulation. So a little bit on the background. And you'll see in a little bit why this matters. Um, if you're new to this field, if you're a student, I think this is one of the most important papers in, in many years on aphasia treatment to be published. This is from the Briitenstein et al study. This is a clinical trial that was published last year in Lancet, and it showed that in chronic participants, treatment for 5 days a week for 3 weeks was superior to node treatment. You might say well, haven't we established that aphasia treatment works? Well I would say that this is by far the most comprehensive study, and it provides ca—provides class one evidence, that indeed that what we do with aphasia

actually works. I also wanna point out the two effect sizes that they got. One was a medium effect size. Uh, it's kinda weird doin' this on an angle, but I think I got this here. So a medium effect size for the speech production on the ANELT, and a small effect size, effect size for improvement in quality of life. If you haven't looked at this paper yet, and you're a student, I will strongly re—recommend you do so.

The other thing that I'm gonna touch on very briefly is the differences across aphasia treatment studies, which has made it difficult to compare outcomes from one study to the next. And, my colleagues talked about this earlier. When you look at neuroimaging studies in aphasia, there's a lot of variability across studies. And when you're looking at, and Cindy made this point very eloquently, when you're looking at naming versus sentence processing, there's no reason that you're gonna see the same patterns. And when you look at recovery, there's no reason why you would see the same patterns in brain activation. The same thing comes with aphasia treatment studies. We need for our studies to be more consistent with, with regards to things like treatment type, dosage, inclusion/exclusion criteria, and outcome measures. If you look at the literature for aphasia treatment, you will see lots a variability. So, on that note, I wanted to point out a recent paper that I came out, that came out that I think is very important. It was published in the *International Journal of Stroke*. The first author is Sarah Wallace, but it includes many other experts in aphasia, include a couple that are in here. I saw Steve Small here. Maybe he's, he probably left knowing that I was gonna talk. Oh he's still there. (A few people react) The other, I saw Leora Cherney and Swathi Kiran. I think that this group did an enormous task. And what they did was that they recommended different tests as outcome measures for aphasia treatment trials. And they simply, well, I shouldn't say simply, because it seems to me that this was an endeavor that took over 4 years. But in the end they, they… they basically voted on what they thought should be the primary outcome measures for language, communication, emotional wellbeing, and quality of life. For language they recommended the Western Aphasia, uh, Battery revised, but also for these other aspects. So, this will relate to what I'm gonna talk about ler—later, with, uh, regards to our overall outcome, but I wanted to point this out.

Another paper that I think is very important, that's from Swathi Kiran and colleagues, uh, Gillman, Gilmore, Dwyer, and Kiran, where they simply looked at what is the average increase on different aphasia tests in aphasia treatment studies. Also if you're a student, I think this is another paper that it's very important to look at, because it shows us what is the medi—what is sort of like the average effect size that we can expect. And they looked at this for example with the WAB AQ. And what they found is both within, uh, group design, and across groups, that the average improvement was about 5 AQ points. So those, uh, two papers that I think is very important. And this will relate to my talk here.

I'm gonna, in the first part a my talk, I'm gonna talk about predictors of aphasia recovery. There are many different studies that have looked at what biographical or different factors relate to a, uh, aphasia recovery. Mainly looking at the natural history of aphasia. That paper by Holland et al, is a famous one. Other people have looked at, um, age is Terry Wertz and Nina Dronkers, suggesting that older age works against you. The older the, the person is when they had the stroke, the worst their long term outcome. Same thing with education. More education is thought to have positive effects on, on recovery. Sex; women, uh, are thought to recover better. Also, this is not definitive evidence by any means. And then time post stroke. This is by Cathy

Price, et al, suggesting that the further out from the stroke you are, the less recovery you will experience.

Perhaps the most effect on outcome is aphasia severity. And this has been shown in other studies besides the 3 that I reference right here. But suggesting that participants with more severe aphasia tend to show worse out, long term outcome. Both with regards to natural history of aphasia, and treated aphasia recovery. And I'll get back to this in, in, with our data.

So like Swathi said in her intro, uh, what I'm, I'm part of the C-STAR project for the Center for the Study of Aphasia Recovery. This is a multisite project. I'm only gonna talk about data from our first project. It's called "Predicting Outcome of Language Rehabilitation in Aphasia,' we typically refer to it as POLAR. My main collaborator there is my colleague and friend Dirk den Ouden. And our aims are two. The first aim is to identify biographical and cognitive linguist fa—linguistic factors that predict aphasia treatment outcome. And then we wanted to constrict the pr—construct the predictive model, of apha—aphasia treatment success, and made that mod—make that model available to, online to clinicians. So basically what we wanna do is to provide a therapy to a lot of different patients, come out with a model of treatment outcome, and then we would provide that to clinicians, so that the clinicians could then see, using our model, who was likely to respond to, to conventional language treatment, and who wasn't. Aim 2 extended that to look at where, whether lesion location could actually improve, uh, outcome prediction. And there we focused on the dual stream model. Both David and, and, uh, I mean both, uh, Stephen and, and Peter actually showed the dual stream model earlier. That's from Hickok and Poeppel, and we wanted to know whether damage to the speech and language areas included in that model, would actually improve the prediction beyond what we would get with the biographical and, and cognitive linguistic factors. And then we compared that to the old Wernicke Lichtheim Geschwind Model, which you are all familiar with.

So this was basically the, the… our thinking here. We would take biographical and cognitive linguistic factors, the default model would be going straight across here, do, using these factors to predict who responds to aphasia treatment. And then wanted, we wanted to see if we know how much damage there is to these language areas right here in the dual stream model, does that actually improve the prediction beyond the default model. And just for comparison, we, we looked also at the Wernicke Lichtheim Geschwind Model. And I'll get more into that later.

So, here's the study design, and enrollment timeline. So we have 2 groups. This is a crossover study. Here we go. So in Row 1 here, so Group 1, they start with baseline testing that includes a pretty comprehensive cognitive linguistic test, and MRI scanning. Then they go through 3 weeks of phonologically focused treatment, and I'll talk about what those treatment tasks are that we use. They, then they take 4 weeks off, and then they do, do 3 more weeks of semantically focused treatment. So that we have 2 treatment phases; phonological and semantic. We test them before and, and after each one of these treatment phases, then they undergo, uh, testing again at 4 weeks, and finally at 6 months. I'm gonna focus my prediction today only on the 6 months prediction. So given how, how, uh, somebody who comes in with aphasia today, given how they do with regards to their cognitive linguistic, uh, testing, and their bage—and their baseline biographical, uh, factors, can we know where they're gonna be at 6 months. Mkay. So… hard to find the cur—here we go. And then Group 2, does the same thing, except for they

don't start with the phonological treatment, they do the semantic treatment first, and then they cross over to do the phonological. This is a randomized trial in that we are only randomizing towards the treatment, uh, uh, timeline. So whether you get phonological first or semantic first. We do MRI baseline after the first treatment phase, after the second treatment phase, and then finally at 6 months post. So we do 4 different, uh… MRI sessions. Can you guys hear me okay? (Yes) Excellent. So, when we were coming out with the treatments themselves, we did not design any of these treatment tasks. These, and maybe some of the authors of these treatment tasks are here in the audience, I'm not sure. But, we went with, uh, semantic feature analysis, and the semantic barrier task, as well as VNeST as our semantically based treatment approaches. Every one of the participants in their, um, everyone of their treatment sessions, if they're doing the semantic, uh, uh, approach, they would spend 15 to 20 minutes doing each one a these, uh, treatments.

Then, for the phonological… phonological component, and analysis, phonological production task, and phonological judgment task, these were tasks that we thought we could say that focus more on phonology rather than semantics. But of course there's no way that you can isolate from the other. We were simply saying here's a treatment phase that primarily focuses on phonology, as opposed to a different treatment phase that focuses more on semantics. We never claim that we're somehow isolating these semantics versus phonology in those treatments.

The outcome measures. Um… for this course, we have 3 tasks. These are from Brian MacWhinney's AphasiaBank tasks. So we do the Cinderella task, the peanut butter and jelly; so basically ask the pa—uh, participant how you make a peanut butter and jelly sandwich, and then the, finally the broken window tasks. So the person gets a, a series of pictures, and they're asked to describe what they think is happening in those pictures, in a sort of a short story.

The measures that the, we derive are content words per minute, verbs per utterance, propositional density, semantic errors and phonological errors. If you're familiar with AphasiaBank, you realize that this is only scratching the surface with regards to the measures that you can get from AphasiaBank. But those are the ones that we focused on for this course.

We also do at every one of the testing time points, the Philadelphia naming test, so that's Myrna Schwartz's test, and there we derive, uh, uh, phonological and semantic errors, as well as correct naming.

The enrollment so far, uh… we're bout 2 ½ years into the… this 5 year project. We've enrolled 65 participants, 3 are control, so these are participants who, the controls have left hemisphere damage, but don't test aphasic. One person got tired of us and withdrew., (Some people laugh) and one per—so, and 38 people at this time have completed the 6 months follow-up testing, and we're done with the, discourse analyses and all the naming tests. So, the difference there with 27 people, or, so some proportion of those participants are either in treatment right now, or are waiting to do their final assessment session at 6 moths.

So I'm gonna talk about predicting long term outcome, using a sample of 38 participants.

Here's the enrollment so far. As you can see, most of our participants have been in the, in the 60 to 70 ye—uh, year age, age group. We even have persons of, as young as 20, let me see it, that person was 27, the youngest person there. And we tend to have more men than women.

Just a little shout out to our speech-language pathologists. We have 4 speech pathologists that work across the different sites. Uh, Michelle Martin, Allison Croxton, Anna Doyle and Sara Sayers. They're really the people that deserve most of the credit for the data collection. They do all the treatment and outcome measures. And Alexandra Basilakos who is a postdoc with me also did her PhD at South Carolina, and she was responsible for getting the preprocessing of all the data done for me.

What I'm gonna talk about here is that here are all the different outcome measures that we've focused on. But instead of looking at each one of these individually, that would probably take me till 7:00 tonight, so what I decided to do, was that I was gonna combine these into a single outcome measure, so an overall outcome. Um, what we did was that we simply calculated T scores for each one of these outcome measures, and then we added them together in a single overall outcome. Now I realize there's a lot a granularity that we're losing here, and this is not gonna be the end of all be all, of our analyses, we'll do a lot more analyses than this. But for our purpose today and looking at whether we can predict overall outcome, I think it's important, especially for clinicians who are working in the field.

So I wanted to show you, and this goes back to Swathi's paper, and the ROMA group, that you can look at our overall performance, which is the average of the, the different 9, the 8 measures that I showed you on the previous slide, and how that correlates with WAB AQ. And it's actually highly correlated. So that folks with, um… with high WAB AQ also tend to score very highly at baseline on the outcome measures. And that's what you would expect. But generally, fairly good correlation between WAB AQ and overall performance at baseline on the, the discourse and naming measures.

Um, here is the actual overall outcome. So improvement is what you see on the Y axis. And WAB AQ on the X axis. And not surprisingly, outcome does correlate with severity. The participants with less severe aphasia tended to do better with regards to this overall measure. It's not a particularly strong correlation, but it's there. So in the analyses that I'm gonna show you from now on, the prediction analyses, in every one of those, we controlled for WAB AQ just because of this initial severity. So, when you're looking at the measures that I'm go- the, the analyses that I'm gonna show you next, the WAB AQ is taken into account.

(Inaudible comment about the Y axis.

The Y axis?

(Yes)

The T score, so the improve—so, yeah. That was improvement with a mean of 50. In T scores. Yup.

So the statistical analysis that we used, this is actually a module in SPSS. We used what is called automated linear modeling. The nice thing about auto, automatic linear modeling is that it has a really nice way of doing data preparation. It deals with major outliers, and also what it does, is that it tries to group together different levels of nominal and ordinal scales. And you'll see that when we start looking at the outcome measures. It tries to really come up with the best prediction of outcomes, and it manipulates the, the factors that might be on a nominal, nominal or ordinal scale.

We use what is called the over fit prevention criterion. So instead of just running a straightforward linear regression, we train the model on 70% of the data, and we test it on 30%. So we're doing, that's our best way of doing out of sample prediction.

So, how well can we predict overall outcome use in biographical factors? I realize there's a lot of factors that go in there. With only 38 subjects, this is a lot. But what automatic linear modeling does, is that it actually penalizes you if you put too many factors in. And we played around with this a little bit. This seemed to be an, um, sort of like a, I wouldn't say a sweet spot, but this wasn't too much of a penalty for all these factors that we put in. So the first there is the NIH Stroke Scale, just an overall measure of, uh, stroke severity. And then sex, months post stroke, stroke age, test age, depression, whether people were taking anti-depressions, race, handedness, education, how much they exercise based on their self-reports, and then the presence of diabetes.

So here are the results for that. For that model we were able to predict 17.6% of the variance, which is not great, but it's highly statistically significant. And what we found, this is a bad looking scatter plot right there, looking at the actual measures, at the X axis, and the predicted measures on the Y axis. And you'll see why this is so dichotomous like this. The best predictor was how much people were estimating that they exercise. So folks that did better were the ones that were exercising more.

So there's something a little bit weird if you look down here though. If you see that, you have one or two days a week, and then that, as opposed to 3, 4, 5, 6 and 0. So what the, what automatic linear modeling does, is that it comes out with the best combination of these different levels, and it comes out with the prediction. So, although I think exercise is probably great for everybody, based on these data, I'll be a little bit hesitant because that 0 is there, suggesting that those who didn't exercise at all, did, (Laugh) did actually better than those who exercised 1 or 2 days a week. I would take that with a grain of salt.

Um… I looked specifically at aging. So aging did not come out as a best predictor. But because it had been shown to be a strong factor in other studies, we looked at whether aging actually predicted outcome in our sample, and it did. This is just the, the F test right there. And it is statistically significant. So folks, the older the folks get, the less response they show to treatment. So this is the improvement in T scores right here, this is the average overall improvement, and then the older you are, the less, uh, the response there is to treatment. It's not a great predictor, but still, the effect is still the—is definitely there.

So I looked at other studies that we've done, and this is from our TDCS trial which I will talk about next. The P value here for predicting treatment outcome based on age, is not statistically significant, but there's certainly a trend there, so that the older participants tend to not respond as well as younger participants. And then finally, I think Cindy showed one of our, my images from this 2010 paper. This was looking at aphasia treatment outcome, actually looking at anomia, and there we saw that there was a trend certainly that the older participants tended to respond worse to treatment than younger participants. Again, this is not statistically significant but I would think that across different studies, age is certainly an outcome factor that we wanna keep an eye on.

So what about the baseline cognitive linguistic testing, and, um, yeah, the, the different tests that we did at baseline. We looked at a, uh, apraxia severity, apraxia speech severity, using the ASRS, that's, uh, um, mainly Duffy that is associated with that. This dysarthria severity also on ASRS, and the WAIS, uh, matrix to reasoning to look at, uh, um, executive functioning. We looked at semantic processing using the pyramids and palm trees, and kissing and dancing tests. Those were highly correlated, so we put them together into a single factor. We used Cindy's, uh, Northwestern, uh, uh, assessment of verbs and sentences test to look at verb naming and verb comprehension, and then we averaged across several different subtests, from the PALPA for phonological processing.

Now, we actually did a little bit better with the baseline testing in predicting outcome. Again, this was highly statistically significant, and we explained 18 per-- .6% of the variance. The scatter plot here certainly looks a lot more respectable than the scatter plot that I showed you previously. These are the actual scores, and these are the predictive scores. And then we're trying to see can you predict out of sample. That is, for the next patient that comes in, using the data that we have, can you predict how well that one person is gonna do? So they, again, X axis is actual scores improvement, and Y axis is predicted improvement. And the best predictor here, was the verb naming test. So better people did on the verb naming test at baseline, the better they responded overall to treatment.

The final, uh, group of predictors that we looked at was the baseline measures that we use to look at outcome. So I described these earlier. Um, again, the discourse measures from, uh, AphasiaBank, and the 3 different measures, um, of naming. So correct naming, phonological errors, and semantic errors. We simply put the baseline levels of those factors in as predictors and then we looked at outcome. And here we actually did far better. So remember, this is predicting 6 months outcome. We were able to explain almost 42% of the variance, using those baseline factors. And again, here's the scatter plot showin' the relationship between actual and predicted scores, and there were 2 different factors that, uh, best predicted outcome. The better people could name a baseline, the better they responded to treatment. And what seems paradoxical, is that the more phonological errors they had at baseline, the better they responded at treatment.

So, I would not say these are the 2 tests that anybody should be using to predict outcome. I suspect that as we add more data, these predictions will become stronger, and we'll be able to disentangle some a these baseline measures. Because, keep in mind, some of them are certainly

highly correlated. And therefore, if it's highly correlated, if you're doin' linear modeling, if it doesn't add any explanation to the prediction, that factor ca-- is gonna be left out.

So goin' back to our prediction here, we do really well with the; well I would say fairly well with the default model, explaining at least just using the baseline factors, uh, over 40% of the variance in who responds and who doesn't with regards to overall outcome. And I, I have to preface that we are gonna look at, again, we're gonna look at, the, uh, the individual factors. Now, looking at whether damage to the different regions of the brain actually improved outcome prediction, and they did not. There was no improvement in our, R squareds by using the lesion data. Everything that we were able to predict was based on the baseline behavior.

So I'm gonna now next talk about something that Cindy talked about a little bit earlier, at, uh, you, she certainly mentioned it on the flair scans with regards to the lesion. And that is Leukoaraiosis, or white matter hyper intensities. We've been looking at this factor a lot, working with Argye Hillis for example. Leukoaraiosis is what you typically see here on a flair scan, or also you, we usually look at this on a T2 scan. These are these white matter hyper intensities that you typically see in white matter. This is thought to be associated with ischemic damage, micro bleeds, but the exact pathology is not known, but it's very well established that the more you have of these, the more likely it is that the person's gonna have dementia. So this is typically associated with aging. I would be careful to call this lesion da—uh, areas, because what we have found is that if you do deterministic tractography, you actually track quite a bit of fibers through these hyper intensities. So, even though there's change in the tissue, perhaps gliosis here, it's not like there aren't neural fibers there anymore. But, there are different ways to rate leukoaraiosis, or white matter hyper intensity. Neural radiologists typically rate these on, um, scales. We use a scale called the Fazekas Scale, there we have 3 different patients, and they have different levels of leukoaraiosis. This person here at the bottom, what we've highlighted there in blue, and we only did this for the right hemisphere, this person has the most severe level of white matter hyper intensity, and then these two people have quite a bit less. This person is probably the, the least severe person, and the most severe person. The Fazekas Scale is comprised of 2 subscales, but overall it gives you an idea of how much of these white matter hyper intensities are in, uh, are in an individual's brain. This is just, there's a lot a different studies that have focused on leukoaraiosis. White matter—so leukoaraiosis has been associated with like I said, older age, dementia, hypertension, diabetes, reduced renal function, other cerebral and cardiovascular risk factors, and worse outcome at the stroke. Um, Argye Hillis published this paper earlier this year showing that in acute patients, beyond what is predicted by the lesion, that the more severe leukoaraiosis there is at baseline, the worse the overall outcome is gonna be for that patient. So more leukoaraiosis, worse of recovery from post stroke aphasia.

So, we wanted to see whether leukoaraiosis in our 38 participants actually predicted outcome. And it does. Uh, the prediction there again is not perfect, but it was statistically significant with a P value of .013, showing that more severe leukoaraiosis, which is what you see in the, the… X axis, the, the more severe, uh, rating of leukoaraiosis, the worse those participants did in treatment. So essentially if you're a, if this is closer to normal here, those participants tended to do far better, or somewhat better.

So what does leukoaraiosis do to the brain? We have a study that is in review right now, by Leo (last name) and Janina Wilmskoetter who is a post doc with us, looking at the relationship between the fiber length and the severity of leukoaraiosis. And what we did there was that we simply looked at—let me go just back here. We looked at the different regions of interest, and tracked all the fibers between those different regions of interest using, uh, in Euclidean space. We divided the length of the fibers into 3 different categories. So short range fiber, medium range fibers, and long range fibers. And then we looked at changes in fibers. Let me see. There we go. So these are the folks who get a severity rating of 0 at baseline. These are essentially folks that had no or very little leukoaraiosis. This is what we would expect hopefully in all of us in here, with regards to the distribution of long range fiber, midrange fibers, and short range fibers. But as you go to the more severe leukoaraiosis, that what you see is a proportion of loss of long range fibers. Now for the sake of time, I'm not gonna talk about there's another analysis that they did was that they showed that although leukoaraiosis is not directly related to aphasia severity, if you look at how it's mediated by the number of long range fibers, you actually get a very strong prediction, suggesting that folks with higher levels of leukoaraiosis and greater loss of at long range fibers, tend to be the participants with the more severe aphasia, when you factor out lesion size.

So discussion so far. So with regards to our Aim One, biographical factors provide moderate predictive power based on neuropsych and speech language tests provide improved prediction. And baseline scores on the outcome tests provide, at least in our sample, provided the long—best long term prediction. We did not improve by including lesions. Um, like I said, with only 38 participants, I think these data are promising, but we, we're hoping to get, uh, a sample size in the 3 digits. At that point I hope that our tests, our models are gonna be what, a lot more potent. Um, what we're tryin' to do here in the end is to come up with a model that can be used to guide treatment, so the folks that have a very high likelihood of responding to impairment based treatment, that they can then be stratified into language specific treatment, and those folks who have less, or far less recovery potential, perhaps we could focus more of our attention then, on compensatory strategies.

We haven't gotten into the treatment type yet. We started looking at that, but with only 38 participants, there's only so much power that you have. But at least based on those preliminary data that we have, it seems to be that the order of treatment matters for some patients. So whether you got the phonological treatment first, or the semantic treatment first. White matter disease, it does seem to influence treatment outcome, and that is related to the loss of long, long range white matter fibers.

Okay, so that ends the first half of my talk. Actually doin' pretty well on time here. So I'm gonna talk about a study that we published this summer that is on transcranial direct current stimulation. I talked a little bit about this at last year's ASHA, but I have a much more comprehensive dataset to share with you now. So if you're not familiar with TDCS, um, it's a very simple setup. It uses two pad electrodes placed on the head, and they're connected to a direct current stimulator. And the current is passed between an anode elect rode, and a cathode electrode. The decent current flow then hypo—hypothetically goes across the cortex. The current flow is inward under the anode, and outward under the cathode. Um… why would you use TDCS to treat aphasia? Well, there are many, including studies that we've shown here

today, some studies suggest that changes in cortical activation support improved language processing in aphasia. TDCS can be used to modulate, either excite, or inhibit, inhibit cortical activity. We typically see excitation under the anodal electrode, and inhibition under the cathodal electrodes. And therefore perhaps, TDCS can be used to enhance, boost or change cortical activation during aphasia rehabilitation or therapy to improve outcome. That's the basic premise behind this.

So, there are many different, there are many preliminary studies on this topic. Specifically on targeting the left hemisphere to, with TDCS to, to improve aphasia treatment outcome. I apologize if I left anybody out there that really should be included as far as the, the preliminary studies, but it's a large number. Several others have looked at the effect of TDCS, for example on the right hemisphere, and, uh, for, and the cerebellum as well. The limitations so far have been small sample sizes. Not all the studies have been randomized, and not all of them have used blinded outcome testing which is probably a, a major problem.

So that brings me to our randomized control trial that was published earlier this year. The study question was for individuals with chronic post stroke aphasia undergoin' aphasia therapy, does anodal TDCS enhance outcome. I'm not gonna talk about what is called the Futility Hypothesis. If you read our paper in *JAMA Neurology*, that's what the, the… that's something that is fairly typical in the clinical trials realm. But we actually wrote a supplementary paper that came out in the journal *Brain Stimulation* fairly recently that shows the superiority analyses, and that's what we're used to. So does anodal TDCS improve outcome better than placebo or sham if you will.

All participants received aphasia treatment. It was using a task that I'll explain here fairly quickly. The treatment itself lasted for 3 weeks, 5 days a week. They were randomized to either receive anodal TDCS, or sham. Or that's the placebo or the control condition. And we controlled for aphasia tribe across the, the, the treatment arms. It was double blinded, so the participants were, were blinded to what condition they were getting, and the clinicians who administered the TDCS and scored the outcome measures were also blinded to whether the participants were getting real, or anodal TDCS or sham TDCS. The study design was pretty simple and straightforward. We had a pool of participants. At the beginning they were randomized to either get anodal TDCS or sham. We tested their naming ability before and after this 3 week treatment phase, and we tested them again at 4 weeks, and at 6 months.

Here are the participants. We, we screened 89 participants. 34 were al—were randomized to the anodal TDCS condition, and 40 were randomized to the sham condition. So the primary analysis which is one week post treatment, compared 34 participants, to 40 participants.

The treatment task itself, I was explaining this to Cindy earlier. This is not a treatment task that I would ag—expect anybody to be using in clinical care. The reason why I like it, it's computerized, and when we were coming out with this trial way back when, it was a nice way to control for the treatment type across the treatment arms. So the treatment task itself is very simple. The person sits in front of a computer, they have headphones, and they have these green and red response buttons right here. They see a picture on the screen, and then they hear a word and see the mouth of the speaker, and they have to decide by pressing a green button if what they saw and what they heard and saw the speaker say, matches or not. So if they, they think it

matches, they press the green button, if they don't think it matches, they press the red button. We, in this task we had correct matches, semantically related matches, I mean semantic rela— related foils, phonological foils and unrelated foils. And then they got immediate feedback. So they got the smiley face, yay, you got it, or the frowny face if they did an incorrect response. So the task itself is really simple. They did this for 45 minutes a day for 3 weeks, for 5 days a week. Um, the inclusion and exclusion criteria, the main inclusion criterion was that they could only have had a single event ischemic stroke. And you know if you treat people with aphasia, this excludes quite a bit. They also had to be greater than 6 months post stroke. Most of the participants in this trial were at least one year post stroke. The exclusion criteria included history of brain surgery, seizures during the past, previous 12 months, and greater than 80% naming accuracy on the Philadelphia Naming Test. We wanted to make sure that we would not enroll participants who were so mild that they were close to the ceiling. We wanted to make sure that we would have some room for improvement. The TDCS itself, we used a very simple, uh, stimulating device. It outputs one milliamps of stimulation. If, if you're familiar with TRDCS you realize that's very low stimulation. The anode electrode was placed on the left scalp over targeted posterior cortical region. So we did fMRI on everybody at baseline, and we targeted this posterior region in our participants that had the greatest cortical activation. No surprisingly, we saw bilateral activation in all of our subjects. I know this is Stephen's favorite task, 'cause he spent every waking hour for the past 2 years bashing it. I still like it. (Several people augh) But it worked for us. It worked for us. The cathode electrode was placed on the contralateral super orbital frontal scalp region, so it's really just above the eyebrow. So three's one electrode back here, and one electrode on, above the right front, uh, right eyebrow. So all participants completed these two fMRI sessions at baseline. The anodal TDCS stimulation was started at the beginning of the behavioral treatment session, and it remained active for the first 20 minutes of the 45 minute treatment session. The sham however, was started for 30 seconds, and it was gradually turned off within 45 seconds. That's because TDCS when you first turn it on, and some people would say longer, you get tingling effects that make you think that, um, you, so that you know what the condition is. The electrode placement here for all the participants if I remember correctly, the blue, are the coordinates for where we, uh, did stimulation for the people in the active group, or the anodal TDCS group, and the red is where the electrode was placed for the, placed for the ones in the sham group. The mean, uh, cortical location here in Euclidian space, was almost exactly the same for both groups. It was within one millimeter. And it was in the posterior, uh, STS for both groups. You see Stephen it's a great localization task.

Alright. So outcome factors. The primary endpoint was changing correct naming at one week post treatment. We looked at both trained items and untrained items. Um, the post, we calculated the post, uh, pre to post treatment change. Uh, that was the difference between the average of the two pretreatment, uh, sessions, and average of two posttreatment sessions. So at one week. We also looked at 4 weeks and 6 months. Naming accuracy was scored on the PD, PNT scoring guidelines, and last on this slide, which I think is very important, is that we asked the clinicians, the SLP's and the participants at the end of each week to guess what treatment condition they thought they were in. did they think they were in the anodal condition, or did they think they were getting sham, or essentially no stimulation.

Here are the results. What we see here for the blue, for the… come on. Here's the blue line. This is the improvement on the Y axis in the naming outcomes. So at one week post, there was

an improvement of 13.9 words with the anodal, uh, TDCS group, and 8.2 words with the sham. The difference was 5.7 words, or 70% increase in the anodal over sham. A one tailed T test, uh, showed that that was, this was statistically significant, and these different, this test was adjusted for aphasia severity. The same pattern was apparent at 4 weeks. For the anodal group, we got an improvement of 16.8 words, for the sham, it was 9.4, or 79% increase in anodal over sham. This was again statistically significant. And then finally at 24 weeks or 6 months post, it was an improvement of 14.9 words, for the anodal group and 7.1 words for the sham, or an increase of 109%. And again, that was statistically significant.

So do I have like 15 minutes, is that right? Excellent. So . . .

Inaudible comment)

I'm sorry?

(Inaudible comment)

Okay. So, at the time when we were putting in the grant to, um, fund this trial, there was a paper that came out in the journal *Neuron* that suggested that… response to direct current stimulation was dependent on BDNF genotype. And this was in a mouse model, suggesting that mice with, to make a very long story short, a mice with what we would call a typical BDNF gene, or brain derived neurotrophic factor, that those mice responded much better to TDCS, as opposed to mice with an atypical gene. Brain derived neurotrophic factor is, is crucial for brain plasticity, and is thought to effect many different levels of, uh, across neural pr—uh, in neuroplasticity. I'm not gonna go through this long slide here, but basically to say that in normal subjects, with people with typical and atypical BDNF genotype, there's approximately 18 to 30% difference in the secretion of activity be—dependent BDNF. It's not that folk, folks with atypical BDNF genotype don't secrete BDNF, it's just that it's a lower level. This has been shown both in animal models and in humans. It is, it is different in different racial groups, but, in majority of our participants, we should see this difference of 18 to 30% in secretion of BDNF.

So on that note, we collected a 2 milliliter whole blood sample from all of our participants, and we did genotyping on 66 of the participants. We completed the genotyping on this polymorphism, RS, RS 62 65, and there are 2 different genotypes that are of, uh, actually 3 that are of major interest here. The typical one which is present in 40, 30 to 40, I mean the typical one is, is present in about 60 to 70% of the population, and the atypical one, which is val/met or met/met, is in about 30 to 40% of the population. We actually had a little bit more than that in our sample. I think 40, it was 40+% that had the atypical genotype. These results that I'm about to show you were published earlier this year also in the journal *Brain Stimulation*. But based on that animal study; I'm gonna cruise over this one. Based on, on that animal study by Fritch et al, in neurons, we su—we hypothesized the participants would get anodal TDCS, that those with typical BDNF genotype would respond far better than those with atypical BDNF genotype. By the same token, there should be no difference within the sham group. So the treatment response should be the same. So you should see an interaction if we can replicate their findings. And we pretty much found that exactly. Um, we found no main effect of genotype on treatment outcome, however, there was a statistically significant interaction, so that in the group, like at

anodal TDCS, which is what you see right here, that across the board we saw much better improvement in the group with typical BDNF genotype compared to those with atypical BDNF. We did not find a statistically significant difference in the sham group, in fact, the folks with atypical BDNF, if anything, we redoing a little bit better. But this wasn't even close to being statistically significant in the sham group.

So, the overall results of the trial were positive. The superiority analyses are encouraging but these are not definitive. This was not meant to be a definitive randomized controlled trial. There's a lot more work that needs to be done. We need to replicate this finding. If this is ever gonna be ready for prime time in clinical practice, we need a study that is powered at baseline to be a definitive trial. And that's not what our study was meant to be. But again, I think the results are very encouraging. The BDNF genotype did predict the response to anodal TDCS. Very importantly also there was no, there were no ad—serious adverse effects associated with anodal TDCS in our study. So in our study, the total number of anodal TDCS session, it was somewhere north of 600 and nobody experienced serious adverse events. During the time we were doing the study, there was one person that had a, a seizure not in the treatment session, but the night of a treatment session, and luckily for us, that person was in the sham group. And then again, further research, I think we need to verify this.

So is TDCS, um, ready for clinical management of aphasia? Well I've said it twice so far; I don't think so. I think that we need to know a lot more about how robust these findings are. We need to know more about where to stimulate. Do we need MRI for electrode placement? If that is the case, yeah, I think that this is gonna be a major detriment for, for rehabilitation, but t, not everybody can get an MRI scan. But also should we look at genetic markers, when deciding who is gonna get this TDCS or, or not. And finally, as with everything in aphasia treatment research, we don't know what the best dosage is.

So there was one serendipitous finding that we came across that we did not expect, and I'm gonna share with you. That's also included in that brain stimulation paper that we published earlier this year. So, what we found is that if you look at BDNF genotype at baseline, before any treatment, the folks with atypical BDNF genotype actually scored far worse on language tests than the folks with typical BDNF genotype. And we did a, uh, an anova(?), on the 4 subtests from the WAB, and found the main effect but there was no interaction. But across the board they were doing worse on the WAB. We also looked at the other outcome test that we have. There was no difference on the pyramids and palm trees, no difference on the ways, but the same effect was there for the Boston naming test, the PNT, and we also looked at other factors, and goin' from top to bottom there, like education, the people with atypical BDNF genotype tended to be more depressed, but they also tend to have more severe aphasia. We tested everybody, we asked everybody whether they had diabetes or not. There was an effect of diabetes that may be spurious, I don't know, but it's not in the direction that you would think. The people with a typical BDNF genotype were far more likely to have diabetes.

Now and that kinda reminds me, and I've said this to my students time and again, there is no BDNF genotype in the brain. It's a gene that expresses many different things. One a the things that it influences is brain plasticity, but that's not its sole purpose. It influences many other things in the body. If you look at the literature, um, it's been looked at in relation to

cardiovascular factors and renal function. So we might replicate this, but it might just like I said be a spurious finding. There was no difference in lesion size. We were close with age. The people with atypical BDNF tended to be a little bit younger, and there was no overall difference in stroke severity.

There is one study that has actually looked at BDNF genotype in aphasia before ours. And what they found was that there was no difference in aphasia severity in acute patients, or early aphasia treatment success. Now our current data suggests that BDNF genotype based on the sample that we have, which is not large for a genetic study, is associated with aphasia severity. So why the discrepancy in findings? It could be that if you're looking at long term neuroplasticity that is needed for somebody to recover from aphasia, that if you test them in acute care, there hasn't been enough time for that brain plasticity to occur. In our study, the average time post stroke was 3 ½ years, so it could be the case that those participants, it was just enough time for those group differences to show up. And again, there's not a huge difference in BDNF, activity dependent BDNF secretion, it's only 18 to 30% across the two groups.

Here's our team that worked on the TDCS study. Um, a little bit of, uh, plugging here. I wanted, uh, if you're not familiar with the C-STAR lectures, we have a lecture every other week that is broadcast. If you're interested in seeing those lectures, email my colleague Dirk Den Ouden. He is in charge of them. If you wanna be on our list serve, they're free of charge. You can see them on GoToMeeting.com. We've had many excellent people come and give lectures. Many of the lectures have been given by our postdocs as well as principal investigators on the, the trial. I mean on the study. And then finally, if, if you would, we have a little survey that I was hoping you could help me out with. We're trying to look at if we do a phase 3 trial, and show that a TDCS is indeed a good way to improve aphasia treatment outcome, as a speech-language pathologist, what kind of a boost in treatment outcome would you have to see with TDCS to incorporate it into clinical practice. So if you don't mind writing down that, um, address right there, and g—and, this is like a 5 minute, uh, survey, it takes really no time. If you could fill it out, I would be much obliged. Oh, and between "aphasia" and "survey" that's an underscore. So that's it. Thank you. (Applause) Do we have time for questions?

SWATHI: Yes. We have time for questions. And then we'll take a quick (inaudible word) break and, we'll have a side presentation at the end.

Q: Thank you; that was a great talk. Um, just a quick clarification. Um, did I hear you right that you used a one tail T test, um, uh, for the results?

JULIUS FRIDRIKSSON: for the TDCS?

Q: Yes.

JULIUS FRIDRIKSSON: Yes.

Q: What, what was the rationale for that, because I don't . . .

JULIUS FRIDRIKSSON: Because you would never expect TDCS to make people worse.

Q: I would not have expected. I, I, 'cause I don't know, I'm just . . .

JULIUS FRIDRIKSSON: You've gotta base it on the previous literature.

Q: Okay. 'Kay . . .

JULIUS FRIDRIKSSON: That was it.

Q: Okay.

SWATHI: That would be something/

JIM K.: Yeah.

SWATHI: No. I thought you asked me a question.

JULIUS FRIDRIKSSON: Oh no, no.

SWATHI: Other questions? Yes.

Q: Could you please repeat how much, um, stimulation you were putting through the electrodes?

JULIUS FRIDRIKSSON: One milliamp.

Q: Thank you.

Q: Thank you, that was great. Just very quickly, um, considering older people exercise less, probably, uh, as a pattern than younger people, are you able to pull apart the age in the exercise finding?

JULIUS FRIDRIKSSON: No. Uh, so with 38 participants, probably not. But it would be nice to see if there was an interaction there. So maybe you can ameliorate the effects of aging by exercising more. That, that's what I hope we'll see. But, I think that looking at sort of interesting interactions, we probably need a lot more power than what we have. But that's a great question.

SWATHI: What, 1, 2?

(Inaudible comment)

Q: Thank you for your presentation of your research. I was wondering what was your rationale for choosing BDNF specifically as the genotype to look at, and if there are other ones that you think may also be predictive of outcome, aphasia outcome.

JULIUS FRIDRIKSSON: Yeah that's an excellent question. So I, I take no credit for actually having looked at the BDNF. I will say that this was actually pointed out by a reviewer of our grant when it first went in. So, I would like to know who that reviewer was. (Some people laugh) So if you are an NIH reviewer, if you have excellent ideas for people, make 'em. Because I had, I had not seen that paper. It did, I think it was in press when we submitted the grant, that's why we targeted the BDNF gene. We have been collecting genotype data now in the POLAR study that I talked about earlier. We've added probably 20 something folks to that sample, and we redid the analyses and we get the same results. We're also looking at just… uh, you know, out of curiosity, we're also looking at FOXP2. If, we haven't done anything with those results yet. We don't have that many participants that have done the POLAR genotyping. But I hope that maybe that will show us something interesting as well.

Q: Julius, thanks. It's Jamie. Thanks (Laugh) for a great talk.

JULIUS FRIDRIKSSON: Jamie.

Q: Um, I had a question. I think, um, a major strength of what you're doing is, is, and what everyone has done here is it's a very sort of model guided approach, and sort of testing dual stream models, and testing a, a set against alternative models like Wernicke Lichtheim. One thing I sort of I… I wondered, and I didn't see anyone doing was sort of adjusting these base models for what you would expect to see in aging. I didn't see anyone doing that, right. So what you expect to see are these herald, uh, effects, dedifferentiation. Basically you're, you're looking at an aging brain, applying a young person's model to it. **(Yeah)** Is there any way to adjust dynamically so that you would sorta like—You know basically the idea is like you're gonna expect anterior shifts, you're gonna expect more right sided stuff anyway, just because of aging. **(Yeah)** How do you incorporate that into your base model, or can you?

JULIUS FRIDRIKSSON: well, I mean the most straightforward way is just to run that as a covariant. Um, I don't have any brilliant ways to look at it beyond that. I know Bruce Crosson has been talkin' about this for a long time, that we should probably take this into account. But it makes sense. Most people with aphasia, at least half of them in South Carolina are ove—over the age of 60. So if you're seeing these major effects, not just the effect of aging on treatment outcomes, but also things like leukoaraiosis, I don't think we can ignore that. But I, I, I don't have a brilliant answer for you, sorry.

SWATHI: So we're gonna take a, there, oh yes. One more question then.

(Inaudible comment)

SWATHI: Yes, no? Wait for the panel discussion?

MARGARET: Yeah, we're just movin' into the panel, so we would like you guys to get up there.