NEUROPLASTICITY AND
LANGUAGE RECOVERY IN APHASIA
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MA RGARET: Welcome back for the latter part of the research symposium this afternoon. Um, and, uh, we're very pleased that so many of you are still here. This is really just a wonderful unfolding story. I'm Margaret Rogers, I serve as ASHA's Chief Staff Officer for Science and Research, and before we begin, I want to do 2 things. One, first, again, thank the National Center for, the National Institutes of Health, the National Center for ever—oh, sorry, (Laughs) Nation—National Institutes for Deafness and Other Communication Disorders. We wanna thank them for the funding for this symposium. Um, it's wonderful; we're so appreciative. And I also want to, um, introduce again, for those of you who may not of been here this morning, uh, the person that is organized our, uh, symposium this year, which is Dr. Swathi Kiran. Dr. Kiran is a professor in the Department of Speech and Hearing Sciences at Boston University, and Associate Dean for Research at Sargent College, the College of Health and Rehabilitation Sciences. And she has brought together all of these speakers, and worked hard to make this work, so please welcome her warmly. (Applause)

SWATHI KIRAN: Thank you. As you probably notice, I got pretty bad at introducing everybody so I asked Margaret to help me do the introductions. (A few people laugh) Um, so, uh, alright. Thank you again for coming back after lunch. This is the time of the day where the blood is not in the brain, it's gone to other parts of your body. So I'll do my best to sort of bring it back up, um, and keep your level of interest. I do have to disclose that I have a significant financial interest in, in Constant Therapy with is now the Learning Corp., um, and that I've also been funded, um, through many grants, but most of the work I'll talk about today is part of the P50 that, um, that Cindy mentioned. She is the PI of the Center for Neurobiology of Language Recovery. Um, and also that Erin Meier, um, was funded by an F31, um, by NIDCD as well, and I'll be talking about her work as well.

Okay. So I'm gonna sort of almost pick up where people left in, in the morning. Um, and what we think we know so far about neural recovery in aphasia is, um, sort of encapsulated in this, in this figure. Uh, on the le—on the X axis you see time; hours, days that go onto a year, and on the Y axis you see brain activation. And, um, what we've tried to do here actually, what Erin tried to do here, was summarize data that we know about from acute lan—uh, aphasia recovery, as well as what might be happening in the chronic stage. And what we know from work from Argye Hillis's lab is that in the initial hours and days right after the stroke, what matters the most in terms of recovery is whether there will be tissue reperfusion in the damaged parts of the brain. And as long as that happens, there's better chance of recovery. In the weeks and months following that, what really seems to matter is the reorganization of structure and function relationships, and I'll get back to that in a second. Um, and in the chronic stage, which is months and years after a stroke, even though we know there's recovery, um, there's really a sort of like a, a black box, um, situation where we think it has to do with establishing new pathways and compensatory mechanisms, but we don't exactly know, know what 's going on. What we think is happening, at least in the subacute phase is, is informed by work done by Dorothee Saur which was already talked about this morning. Uh, and the idea here is that, um, what ultimately matters

in terms of recovery, is the reengagement of the left hemisphere brain regions. And this is shown in the slide, in this part of the lines here, where the left hemis—the, left hemisphere activation is marked by the small dotted lines, and the right hemisphere activation is marked by the larger dotted lines. And we're comparing those to what is normal activation which really doesn't change. And what Dorothee found was that reme—immediately after a slo—uh, a stroke, what you see is this depressed function in the left hemisphere, during that initial, uh, acute and subacute phase. But by the end of the year, improved language recovery was associated with left hemisphere regions coming back to normal. What she also found was that the right hemisphere also is not active as much initially, but there's an upregulation of the right hemisphere function, and ultimately that comes back down, and what matters is this balance, in terms of better recovery. So that seems to be the story of what's going on here. But we don't really know what's happening in the chronic phase. And as you've heard this morning, there's several reasons for that.

So I'm gonna try to take a different, uh, a stab at the data, and try to present to you a story. Uh, I'll just tell you that this is a hypothesis for what we think might be going on in naming recovery, 'cause that's the data of mind a little bit. And, uh, by the end of today I'm gonna try to help you think about these things with me in this sort of context.

What we think is happening is that there's a hierarchy of recovery. In this chronic phase, there's a hierarchy of recovery, with increased damage to the left hemisphere. And this is not our idea, this is a, an idea proposed by Heiss & Thiel back in tw—2006. But the, the main point here is that it's a network of regions that are activated in the service of language recovery. And, and this is really, um… points that both Stephen and, and Peter were making is that there's a cer—it, you cannot attribute language recovery to one part, one region in the brain. And what might be happening actually is sort of systematic shifts to the opposite side of the hemisphere, um, as well as to other parts of the brain. So this is a figure that I'll come back to often in the talk. Um, but the idea is that with increased damage, and depre—decreased language function, there are some systematic ways in which language reorganization, in this case, in the context of naming, might occur.

The other thing that I'd like to propose, or we're, that we're thinking about right now, is that to the extent that left hemisphere regions are spared, they're really important, and engaged in language recovery. And this is a point that Stephen made this morning, and I'm gonna show you data, uh, uh, with naming, with naming tasks that, that sort of makes that point as well.

And then, um, as, as; as damage increases in the left hemisphere, uh, it may be that activation shifts to the right hemisphere. And I think that's something that we've all sort of seen. But also, into multiple dimen—or domain general regions, such as the MFG. And I'm gonna sort of focus on MFG because it's been something that shows up a lot in our lec—our semantic processing and naming tasks.

And then finally, this last part of this sort of, this… pr—if—this framework is that… the degree to which this network typology instantiates, determines the extent of recovery that you will see in patients. So this will really come from treatment data that we've been looking at recently. And

the idea here is that the extent to which better efficient network typology exists will, the patients will show better improvement than those that don't have those efficient typology.

So my job really is to try to convince you that, or convince all of us, and we could be completely wrong about this in 3 years, um, and that would be fine (Laugh) as well; is that, um, there's, that it's not; that, that there's no one size fits all in terms of ran—language recovery, but it's not also the wild west. Um, there's, um, the i—that as damage increases in the left hemisphere, there's ways in which other regions get involved in, in terms of recovery. And somehow when, uh, based on how all that reorganization happens, will sort of determine how patients will improve. And so some patients who have better organization or better network organization will improve more in treatment, and out, have better outcomes than others who don't show the same kinds of improvements. Okay.

Um… so let me sort of step back a little bit, um, and tell you what we do know about imaging studies in aphasia. And again, remember that these studies are mostly naming and semantic processing.

What we do know is that there's a lot of brain regions that are active when people are, uh, being scanned, patients are being scanned doing function imaging tasks. Um, there's quite a bit of consistency across studies. Uh, again, something you heard this morning, that the left IFG's, uh, region that shows up in a lot of these studies is being consistently active. But, as you can see, there's a lot of other regions that show up as being active as well. So, probably recovery is, recovery is likely bilateral, and recovery likely involves the network of region, and there's no one star region in the brain, it's really a whole bunch of supporting casts that are, that are helping on here.

And then moving on to studies of functional recovery, functional connectivity after a stroke. There's fewer studies that have looked at this. But just to summarize this, this, the take home message, if you can read that there, is that function, functional connectivity and measures of network typology are abnormal in patients after a stroke. And they're often weaker, or lower than in healthy controls. And this data has been shown in acute stroke patients, um in resting state fMRI, that are, uh, across motor and other networks, as well as in acute aphasic patients, um, using resting state fMRI data. This has also been shown in chronic stroke, and in chronic aphasia there's a couple of studies, including Chaleece Sandberg's study.

There are fewer studies that have looked at functional connectivity and treatment in aphasia. And I, and, you know, Jeff's, this is Jeff's work, and he and I decided to bucket them this way. They're studies that show increased connectivity, as a function of treatment. So after treatment you see upregulator, or increased connectivity in specific parts of the brain, and these are the studies that show that. But there are also studies that say maybe it's not about increased connectivity, it's about normalization of that connectivity in the brain. So there's a couple of studies that say that what you see after treatment is really a, a normalization of the network. And then there are more recent studies like Susan Duncan's paper and, and Chaleece's paper that say well, it's a little bit more nuanced than that; you need to start looking at nodes in these networks.

And this is the right place to be. Because back in 2011, as Peter and Stephen brought this up, I also have to bring up this slide, but I won't go through it in detail, other than say that in addition to the left re—hemisphere regions, there are right hemisphere regions that are also involved in language func—recovery. But I wanna point out that even in that study, MFG was something that showed up in the patients. So, so thinking about a network of regions is a, is a, is a okay place to be.

This is just two quick slides about why we've been thinking about this. But I think Stephen already made this point, that when you're doing a, a semantic feature task, as Rajani Sebastian did in this study. When patients were doing a semantic judgment task, they showed a left hemisphere activation. But when the same patient was doing a picture naming task, we started to see bilateral activation. And we were surprised about it then, but we didn't know what we know now, and we should have probably expected this anyway.

But what was interesting is that in a different, totally different study, we scanned 3 patients with bilingual aphasia, and they all had, uh, they were asked to do ta—fMRI tasks in their weaker language, which was Spanish, and their stronger language, English, and we found very similar patterns; which was when they were, when they're processing words in their stronger language, English, we found mostly left hemisphere activation. That's the red dots there. And when they were doing the same tasks in Spanish, which was their harder language, we started to see bilateral activation. The point is that the same person can engage different regions of the brain including a de—a slightly expanded network, depending on what they need to accom—uh, account for that task. And that was a point that Cindy made before as well.

Okay. So, so moving on to this, the story about, uh, a network. Uh, Jordan Sims did a Master's thesis, uh, a couple of years ago, now, and here she was interested in looking at to what extent damage in the left hemisphere regions correlated with the amount of activation you saw in the rest of the brain. So we carefully identified which parts of the brain were damaged. Um, and then she, she correlated percent spared tissue, how much was spared, with, with percent signal correlation in these regions in the brain. And the, they were all doing a semantic judgment task. And what she found was that the more the damage to the left hemisphere IFG, left MTG, angular gyrus and supramarginal gyrus, the higher the percent signal change in this bilateral anterior frontal network, as well as other regions in the brain. 'Kay. So this was a bit surprising because we didn't expect to see this much, um, uh, change in these, these bilateral frontal regions that are not traditionally considered language regions. Uh, so the conclusion we drew in that paper was that, uh, uh, depending on the, how much of damage you have, and the kind of recovery you, the kind of high level performance you see, the bi—uh, that you, you might need a bilateral network that can serve an assisti—as an assistive network. She also looked at how these regions co-activated, uh, um, in the brain. So this are, these are, this is not a functional connectivity analysis, this is just looking at correlations in percent signal change. And what you see in the controls is the left hemisphere, uh, lateralized, act—high correlation between regions. But in the patients, that activation sort of shifts forward, as well as to the right hemisphere. And again, I think this point has been made across the talks today, that when you see this bilateral activation, that's probably not that surprising, and there are many reasons for that to happen.

But I do want to pause and say, so it seems at least, that a network of regions are involved in the, in the service of language recovery, and it, there's not any one region there. Okay. So on to the next point.

In the next dataset, I will be talking about data from the Center for Neurobiology of Language Recovery project. And this data really has been spearheaded by Jeff Johnson and Erin Meier, and I'll be sort of talking about their work back and forth. And, uh, in this study, as Cindy already talked about, we have, uh, a number of patients who are getting therapy. Uh, in our case it's 30 patients. 26 of them are getting the—treatment, and we have at least 10 who are not receiving treatment. But, uh, just a reminder that some of these patients go on to getting treatment in the… in the next phase. So they serve as deferred controls, and they come back and get treatment. Um, but the main point here is that these two groups are not different in their age, their months post onset, or their, their gender. And these are the lesion sites.

So the first question we wanted to ask was how important is left hemisphere, uh, uh, integrity, and to what extent are left hemisphere regions and right hemisphere regions involved in, um, contributing to, to performance and, and recovery? So this, in this project, Erin, um, essentially quantified regions in the brain like these, and, as regions of interest, um, and drew carefully, you know, we draw lesion maps, that we then, um, calculate percent signal, percent spared tissue in each of these regions, and we end up with a, with a map that tells us how much region is spared. And then she did the same thing for, for 4 white matter tracts; the arcuate fasciculus; the IFOF, frontal occipital fasciculus, ILF, and the uncinate fasciculus. And here we're actually drawing these tracts on, um, a template and, and calculating how much of these tracts are spared. And we do the exact same computation for both of these. So we get a measure of, uh, integrity in the gray matter regions, as well as integrity in white matter regions. Okay.

Uh, and this is just to give you a sense of how much damage we see across these, uh, these regions of interest. Of course the right hemisphere regions are mostly spared, um, and the left hemisphere regions that are damaged are the following.

In the first question, she asked, which of these struct—which of these measures; we have a whole range of gray matter measures, and we whole, we have these, um, white matter tracts that are bilateral. Which of these actually predict baseline naming performance, as well as therapy response? So when we don't control for lesion volume, and we just say which of these predict naming performance, pretty much everything does. And that's a waste. Um, so, uh, we find significant correlations between baseline naming, of that, on a BNT, and treatment response, something that I'm going to come back and explain later on, called the Proportional Maximal Gain. And a majority of the left hemisphere gray and white matter tracts. 'Kay. But when we control for lesion volume, everything goes away, and the only thing that remains here, um, are significant relationships between the BNT and the left ILF, inferior longitudinal fasciculus, and the left IFOF. And this is actually fairly consistent with recent findings from Leo's lab, but the point here is that these are actually left hemisphere tracts that predict, uh, BNT performance, and when we look at response to in, treatment improvements, proportional gain, in, in the treatment outcome, uh, it's exactly the same two regions. Um, so I know that, uh, I, I think it was you Peter, that said white matter matters, and that's exactly the same conclusion line we had here, is that these are important, because what they're doing, is they're actually connecting parts of the

brain that need to be functioning, especially in terms of treatment outcomes. So, so the, the point here that we came away with was, okay, wait; maybe to the extent that left hemisphere regions are spared, they're really, really important in language recovery, and maybe important parts of this network.

So then, uh, we went on to doing a couple of other studies. So now I need to explain the methods a little bit, because it involves dynamic causal modeling, and I'm not sure all of you know how that works. But it's essentially based on task based fMRI data, but you're doing hy—hypothetical connections between regions, with the idea that you actually think there's a directionality to the data. So the way this works in this really quick animation, and we stole this from Mohammad Seghier's, um, paper, is that you define a hypothesis, um, and something like patients with patients with aphasia rely on inter in—in, interhemispheric connections, but those specifics depend on the site of damage. Then you identify effects of interest, um, that you wanna look at, uh, and then you build a DCM model that inc—includes inputs and connections. And the key thing here is that you have to build these models, thinking about how these regions will talk to each other, where the input is, and, and where the direction is. Once you do that, you have to then define a whole bunch of other plausible models, and it doesn't have to be an exhaustive connection to connection kind of a thing, but things you think that are somewhat plausible in the brain. But they end up being quite a few of these models. Uh, and then you extract volumes of interest in each of these regions, um, in each of those sort of, uh, uh… um, nodes in this model, an then you estimate these models for all subjects. And in our case, we're gonna do this for healthy controls, as well as for patients. And then we determine how well the actual data in, that we've collected fits these models. So we estimate model fits, um, by doing these basion— these, uh, basing model selections. And, uh, because of the number of models we have, we sort of col—clumped them into families of models that we think are like, are similar to each other, uh, and then we can also ex, uh, extrapolate, um, inference on parameters, or connections. Mkay. So that's sort of the process here, is a quick, um, overview, but, but you'll notice that I, when I talk about the data, I'm really talking about model fit, as well as parameter inferences, which is actually what's going on in the connections here. Just skip through all this part, but I'm happy to come back if people have questions.

So the first study was the first, first study looking at this in patients. We said let's keep it simple, let's just look at 3 nodes in the left hemisphere, middle frontal gy—middle temporal gyrus in the blue, left inferior frontal gyrus, and left middle frontal gyrus, 'kay. Um, and they're doing a, um, and here we are building, uh, all the possible combinations of this model that we think would be, um, would, you know, would play out, uh, and we're doing this in the context of a picture naming task. Just to appease Stephen right now, we sort of do those back and forth between picture naming and semantic fea—uh, feature judgment for the very reason that you brought up, is that I don't think we feel comfortable with any given task. But you'll see that in the data. And so this is with, uh, 10 controls and 13 patients with aphasia. And, what we found here was that once, you know, we had to divide these into buckets of, into families, and what we found was that the best—the data that best explained the healthy control data was family that, that ex—essentially had all the models where the input was to be LIFG. So LIFG was sort of the modulator of the connections between these 3 regions. And that makes perfect sense because it's left IFG, uh, is picture naming, and that's what we were expecting to see. But for the patients it's actually not left IFG, that's the winning the model, it's this, this other family of sa—of

models, which is really input to the MFG. So at the end of the study we thought, oh, okay, left hemisphere is critical in the recovery of naming net, in the, in the left hemisphere naming network because that's what modulating, um, the, the 3 connections, and I, I don't show you here, but it's also associated with the, the actual data in the task. So in a, in a, in a follow-up replication study, we took the exact same design but now applied it to semantic feature judgment tasks. It's the exact same 3 regions, MFG, IFG, and MTG. And we're building the same kinds of models now. Um, and the task here is a semantic feature judgment task. So they're looking at a feature, uh, an, an object, and they have to decide whether that's made of, uh, if it's made of wood, or they have to decide if it's black or white, and so forth.

Now we have 25 patients with aphasia, and healthy, um, 18 healthy controls, and there's some very subtle differences in the methods of the way we did this analysis that I can come back to. But what we found here was now that in the controls itself, uh, LIFG was not the strongest node in that 3 node network. It was actually MFG. Even for semantic feature judgment task. And of course for us that made sense, because in the semantic feature judgment task, you have to make these decisions about, about, um, choices of features and, and that's what we thought, uh, would be reasonable for the MFG to be doing. It's sort of following work by Sharon Thompson Shultz.

But in the patients, actually there's a much stronger fit with MFG. And, um, the, the, and, and tryin' to explain the data, 'kay. So the, the, here the MFG was a clear winner in terms of modulating the other 3 nodes. And when we started to look at the connections strengths, so these are the, this is what I was saying is the inference, um, part of the connections, you can see that both the controls, and the patients show high values of connections between MFG and IFG, but the patients actually show a slightly, slightly higher, um, connection strength between MFG and IFG. Um, and again, I, I, I'll just tell you the big, the high level story here, 'cause we went back and looked at how each of these things correlated with activation. But there was indeed greater modulation of left MFG on LIFG in the patients relative to healthy controls. So there, this connection is stronger for patients than it is for controls. And then the actual FMRI task accuracy in semantic performance was related to how strongly connected the MTG and IFG were. So again, the point is that, there's no one region. Yes, um, these 3 regions talk to each other, um, and there's a, it's, what I wanna call a nuance dance between these sets of regions.

But of course the main thing here was that we only looked at 3 regions. We only looked at the left hemisphere, um, and there's really this other part of the brain that we have not looked at yet. So that was sort of the next part of her dissertation was to say okay, if, as and when damage increases in the left hemisphere, does activation actually shift to the right hemisphere, 'cause we're only looking at left hemisphere so far, and does this play out in terms of other regions in the brain.

So now I wanna spend some time on, uh, a little more time explaining you, to you what we're, we're showing here, okay. So this black line is telling you the amount of damage. Um, when there's no damage, and the person is per, performing perfectly normally, you get to see, you see this, this network, but it's pretty left lateralized. Um, and the idea is that MFG, IFG, an MPG and angular gyrus are all part of this language network, in our case semantic lexical semantic network. Um, there's a less contribution of the right hemisphere. When you have posterior damage, now you're knocking out the posterior nodes, and there's still, um, activation in the left

hemisphere, but there might be some slight shifts to the right hemisphere. The key point here is that we've now included MFG in this model. When you get anterior network, uh, when you get anterior damage, um, the, you're, we're knocking out this node here, and we're tryin' to see what happens, and now you get the picture. When you get down to the, the more severe, uh, case, you, uh, essentially don't have any left hemisphere activation left, and all of the activation is happening in the right hemisphere, and, and these are patients who are highly impaired, in the dataset.

So, so the way we tested this was again to build these dynamic causal models, but now we're doing it across a series of these, these families. So I feel like I have to explain this to you a little bit in more detail. So in this case, Family One would be a left lateralized connectivity, but we have 4 different options of what's happening here, and there's subtle differences between these models in terms of where the input is and where the connections are, but they're all saying that if you, if, if the data fit any of these models, then we're really talking about a left lateralized connectivity.

If patients had posterior damage, now, um, the connectivity would sort of shift forward. Um, but, and there's subtle differences again, but the idea is now this is a frontal anterior weighted connectivity. If the patients had anterior damage, sparing MFG, so in the previous one also, MFG is spared, because it's not part of the original MCA distribution network. In this case, if the patients had anterior damage, sparing MFG, we would start to see a shift towards posterior regions, and to now right hemisphere regions. And then in this data we ended up combining both models 3 and 4, because the more damage you had, more extensive damage you had, or if there was complete damage to the left hemisphere now, essentially, uh, the connectivity was all going to be in the right hemisphere, and we call that Family B, with the right lateralized connectivity.

Okay, so what we found, first, again, in terms of whether the, which model best fit the data, we found that in controls, as you would of expected, uh, Family One, which is the lest, left lateralized connectivity best fit the data, 'kay. So this is a, this is essentially saying the best fit is Family One for healthy controls, but it's also explaining a lot of the data for our patients. So there's a split between the two models. There's no winning model here. There's a split between these two models, one of which is left lateralized connectivity, uh, and the other one happens to be Family C, which is a bilateral posterior weighted connectivity. Um, and that means that you have anterior dam—you may have, if you have anterior damage, the posterior bilateral network is sort of helping out. And when we looked at the con—the connections, um, we saw essentially the same kinds of results. So in healthy controls you start to see connections in the left hemisphere that are fairly strong with some connections, um, in, in MTG here. Um, and in the patients, um, there is this strong connection with MFG and IFG, but the, you, but you can see right away that there's a lot of, uh, there are also connections in the right hemisphere and posterior, so that's what this data is trying to explain there.

Um… and then we had to decide. We had to also look at whether this model that best explains the FMRI data also lines up with the kinds of lesions we're seein in the patient, as well as their behavioral data outside the scanner. So now we're starting to, we, we have to decide how much of the, how many of these patients fit into these lesion groups, and to what, did we actually get

an interaction between where the lesion was and how best the data fit, um, each of these models. And indeed there's a significant interaction of lesion group 2 which is, um, uh, anterior damage sparing left MFG, and this Family C, which is exactly what we would be expecting if we were to put, um, um, if we were to go back to this framework, and that fits with this model, which is patients who have anterior damage, um, with, uh, patients who have anterior damage will show this shift towards the right hemisphere and bilateral posterior, uh, connectivity. Um, but I have to say that, that this is the representation of the average of the growth. Um, and this is not captured the individual differences. And if you, if you saw my previous slide, there was already another set of patients who don't fit into this model, the, the Family One also explains the da ta. Um, but the, for the most patients in this study, this is the, the data that best fits the, the results.

Okay, so, so all we, um… wanted to show here, or at least what, what we came away thinking here was as damage increases in the left hemisphere, and now we're systematically looking at how that's happening, activation shifts, shifts to the right hemisphere, as well as multiple demand regions, such as MFG. And I have to say we, we chose to look at MF, MFG, and it's definitely part of that network. Uh, but my suspicion would be that if we went further forward, we'd probably end up with other regions, um, domain general regions as well.

Okay, so we're at the halfway point now. Um, and so far we're, only been looking at patients without the treatment data. We've been looking at patients who, uh, are, uh, are all sort of, uh, analyzed at that pretreatment scan, and we're looking at which measures of this actually explain their performance at that time point. So next I wanted to, um, spend a little bit of time telling you about what we've done in treatment. And Cindy already talked about, uh, some of this before, but let me just recap it in the context of the naming treatment here. Um, so, um, as in the broader center for, uh, center design, as well as in our specific design, patients come in, and we do a very extensive baseline language and cognitive assessment. And this is all, this is all 3 of, all 3 sites do all of these assessments. We get a really rich dataset of pretreatment baseline measures, um, and then we select treatment stimuli, as well as stimuli for fMRI scans. And then patients receive an fMRI scan, um, uh, before the start treatment. And then they go on to getting, um, treatment for, for 12 weeks for, for 4 hours each week. Then when they finish that, they, they get a second fMRI scan, and then again we do all these posttreatment assessments that we did at the beginning, again at the end of treatment again. And here we're also collecting data from the healthy controls, but this is really all the data I was showing you until now. This subset.

The treatment itself as you, as you all know is, uh, our semantic feature based naming treatment. We have patients come in, they're getting treatment for typical or atypical examples within the category, we're looking for the complexity effect that Cindy mentioned. But for the purposes of this analysis, it's really just trained items. We're not getting into the complexity discussion here. Um, but they come in, and they are, um, go through a category sorting task, then they name pictures, then they review or analyze a bunch of semantic features for that specific target; is it worn on the head, is it made of wood. Then they name the picture again, and then the, the last step in treatment is to put this word in context. So they're asked to generate kinds of items within that category that may or may not include the tr—the target set. And what we're calculating here are two things. Uh, we're calculating effect size, which, uh, I think many of you are comfortable and know about. This is just capturing the amount of gain by the stem on a standard deviation and the baseline data, but we're also calculating proportion maximal gain.

And this is essentially posttreatment minus pretreatment, divided by discounting the na—items they already get in treatment. So it's the number of items correct, minus by the pre—minus the pretreatment score. So it essentially does not take into account, um, the true baseline, the, all the, the basic baseline, it get, it sort of gets to a, a nuanced baseline. So how much gain can they make. And I'm telling you this because it does matter in terms of how we dis, we, we look at the rest of our data. For most part, when we look at our treatment results, as Cindy already pointed out, we see that our patients are improving as a function of treatment. So these are pa—these are the treated group, they improve in the, for the train items, um, that they're being, they're being, um, exposed to, and they do not improve on the control items. Um, at, and, they're probed exactly the same frequency. The untrained group, uh, which I said was 10 patients, uh, do not change on any of these measures, and that's good. So there's a specificity to this treatment that we're targeting. And the fMRI data look very similar. Uh, uh, the healthy controls can of course do the task fairly effectively, uh, but the trained patient, uh, the patients, the trained patients show an improvement in their naming accuracy, and the untrained patients don't show any change.

But what's sort of interesting and, um, was really sort of confusing initially, is that there's quite a bit of variability in our treatment dataset. Not everybody in our, in our, in our group improved. Uh, and there's sort of this range of how much patients improved, um, in their treatment. Um, so when we set the effect size cutoff, at, um, at a 4 here, we got 2 clear groups, a group that improved in treatment, and a group that, that did not make this cutoff. Um, and I'm going to call these people, we're calling them responders, and we're calling these people non-responders, because no matter what category they were exposed to, they didn't seem to benefit from the treatment.

Okay. So, now on to the imaging part. Um, for this analysis we're not talking about DCM, which is an effective connectivity measure, we're talking about functional connectivity, which looks at time correlation but does not have that directionality piece to it. But we sort of do the same process. If you preprocess the functional time series, you de-noise the data, You then identify regions of interest that you wanna be looking at, and of, and of course I this case we selected about 38 regions of interest, um, that we had identified to be active in healthy controls, much like Jeff Binder's paper that Stephen mentioned. So those are, uh, are potential regions of interest. Then you look for de-noise time course, um, correla—ea, uh, in each of these regions. Then you calculate, uh, correlation matrix for each of these regions, um, and you're looking for pairwise correlations in these regions. Um, an then ultimately that feeds into a weighted graph, undirected graph network. And weighted just means that you start binarizing these correlation values. It's not, there's no directionality here, and everything that I'm gonna tell you is controlled for multiple comparisons.

Okay. So when we look at this, uh, this particular analysis, we decided to compare our patients to healthy controls. Um, so when we look at our treated patients, relative to healthy controls, we're, you're looking at a pretreatment graph, um, on the top, and you end up seeing posttreatment at the bottom. When we compared treated patients to healthy controls at the pre time point, there are already quite a few differences between healthy controls and patients. And when you see these red knobs with lines, it essentially means that, um, that these are all connections and, uh, nodes that are higher for healthy controls relative to patients. And if you

see anything in blue, it means that it's higher for patients relative to controls. So right now, all of these connections are stronger in healthy controls than for, than for patients. But after treatment, a lot of these connections go, these red connections go away, and what that means is that after treatment, there's some sense of normalization in the patient, such that there's lesser difference between healthy controls and patients after treatment. And there's at least one connection, uh, node connection here that's higher for the patients which seems to be higher than for healthy controls.

We also had our, our untreated patients, so we did exactly the same comparison, and there are fewer differences to begin with in this population relative to healthy controls. But because they did not get treatment, they're not doing anything in that 12 week, um, and they're, they're not getting intensive language therapy in that 12 week period. We don't expect to see change in the second time point, and we don't see change in the second time point, 'kay. So these look pretty similar.

When we look at, um… as I said we looked, we, we've got this group here now that's pretty heterogeneous, so we decided to divide them up between into responders, which is 17, and non-responders, uh, with is the, the rest of them. Um, we found that, uh, the subgroup all, you know, has quite a few differences with healthy controls. So there are some regions that are stronger for healthy controls, but there are others that are actually stronger for patients relative to healthy controls at pretreatment. But after treatment, uh, all those differences go away, and there's no significant connections or nodes that are stronger for healthy controls relative to patients at this point.

Finally we have the non-responders here. These are the people who did not show that gain in treatment. There's again quite a few connections and nodes that are stronger for healthy controls versus this group. Um, and sadly, none of these change after treatment.

Okay, um, so, so next we're gonna, we're, we try to look at it slightly differently by looking at graph theoretical metrics. So I need, I feel like I need to explain this also a little bit. A short course on graph theory. Um, and what we're trying to do here really is, um, to look at, um, two measures, two broad measures. One is a measure of integration, and another is a measure of segregation. Um, and if you were at the talk on Wednesday, I'm sorry I went through this pretty quickly. I'll try to explain it a bit more in detail now. But the idea in integration is to, to, the, it's the capability to transmit and combine information from regions throughout the network. So if you're looking at something like network strength, it's the average strength off every node in the network. So nodes with, with high strengths, um, are highly connected. And so you take the average network str—the node strength and compute the network strength for them.

Um… we also calculate, um, another measure called Network Global Efficiency. And here you're calculating node, when you calculate node global efficiency, it's now well connected each node is to other nodes based on the shortest path. So obviously this, um, is stronger than, um, than from, than here. And you compute the average for the, of this for every node, and you end up with the measure of network global efficiency. And these are just measures of network integration, how well connected, or how well integrated the brain is. Then we have measures of network segregation which is really the propensity of the network to support specialized

processing, so this is really how clustered is your network and how, how well connected are these clusters and how efficient are they. So the first measure we're calculating is something called na—Node Clustering Coefficient, and the idea here is that you have a higher, um… let me just get to that point. Um, so the idea here is that node clustering coefficient is higher for a node that has more connections than one that's less connected.

And finally, we also calculate something called Network Local Efficiency, which is exactly the same as, uh, network, uh, global efficiency, but now we're doing it at the node level. And so the idea is that a node with, a network with high local efficiency is more segregated, um, into efficient local clusters, um, at that local level.

So there's no right way to look at this, but we chose to look at 4 measures. There's many, many options to choose from. Uh, but we chose these 4 measures because network strength and network glo—global efficiency, the higher the network strength and the higher the global efficiency are indicators of a more highly connected, highly integrated network, and then measures of segregation tell us how clustered and efficient these clusters are, so measures of, of, uh, segregation such as higher clustering coefficient and higher local efficiency, are indicators of a network that's composed of many specialized clusters that communicate easily amongst themselves. But the key point here is that in the healthy brain, you can't have either one of these, you have to have both of these working together, and this balance between integration and segregation is really what's optimal for the, for, for the efficient brain organization. So there's no one thing that needs to work here that's gonna be magical.

So we went back and looked at this data that I just showed you in terms of functional connectivity maps in terms, in terms of these network measures, and now you're looking at numbers here, because it's actually the difference between healthy controls in patients, corrected for multiple comparisons in terms of what we find. Uh, and the, but the data is exactly the same, the story's the same. Before treatment there's actually significantly higher network strengths, network global efficiencies, so higher, significantly higher measures of segregation before treatment and after treatment, even though these values reduce in the value, uh, reduce slightly. In the untreated patients the story's exactly the same. There's higher network integration. Before and after treatment, the measures of segregation are not significant, and they don't change, um, over time.

But what's really the, the story's really here now. When you look at these responders, there's a higher measure of networks, uh, strengths for the healthy controls, but there's already no difference in this higher global efficiency, the network global efficiency for the responders. And there was no difference anyway in the measures of segregation. Oh, sorry. Uh, after treatment all those differences go away, so there's no differences now between healthy controls in patients.

When we look at the non-responders, not only is there a significant difference in the measures of integration between healthy controls in patients, there is also a significant difference in the measures of segregation. And those reduce a little bit after treatment, in fact they become nonsignificant after treatment. Um, so the main point again that I made before is that in, by the time we get to end of treatment, there's no difference between responders and controls and there's already pretreatment differences between non-responders and healthy controls in this

dataset. So, so we're really starting to scratch our heads literally here, because we also looked at changes before and after treatment, and we didn't find anything. And this is because we're, you know, of course controlling for multiple comparisons, nothing bubbles to the top. Um, and so we started to think that maybe the, um, the meas—uh, maybe the data wasn't, you know, we didn't have enough subjects to start looking at this. But there are also differences between responders and non-responders upfront. So we start to see that responders and non-responders are different in, on some major measures that have been coming up in the talks today, including lesion volume. So the responders had lower lesion volumes, higher WAB AQ's, higher BNT scores, and did better on the FMRI task both before treatment and after treat, treatment. So, they, they seem to be better, their networks seem to be better and they seem to be doing better in general even before they start treatment.

So just to sort of do a quick summary here, and then I'll try to wrap up, uh, uh, another quick study, and then I'll wrap up. Before treatment what we found was that patients had a normally low functional connectivity, um, and this is fairly consistent. But these responders had more control like connectivity and network integration and segregation than non-responders. After treatment, at least in this group, connectivity seemed to normalize, but it remained reduced in non-responders, and non-treated patients. Network strength normalized in the non, in the responders, um, uh, but segregation normalized in the non-responders, but integration did not. Um, so as I said before, non-responders had larger lesions, more severe aphasia, more limited changes in connectivity network properties, and res—and res, than responders. Uh, and so the first question that we also had, was oh God, you know our treatment doesn't work. This is really not something for, that works for a lot of patients, and we just wasted these people's time. So just to make sure that that wasn't really the case, that, you know, there was something here that everybody seemed to show some benefit from, we went back and looked at the data. And now we're not looking at picture naming which is what the previous analysis was about; we're looking at semantic feature judgment, so it's a different task. But we're still looking at pretreatment scans, and we're tryin' to predict posttreatment gain. So it's a slightly different analysis here. We're saying what does the brain look like here, that would predict the amount of gains they make in, in terms of, um, behavioral improvements, and now we're looking here at, uh, proportional maximal gain.

So I just said that, what aspect of treatment predict outcomes. And again, we're looking at exactly the same measures I just described to you before. We have 2 measures of network integration, 2 measures of network segregation. And when we look at measures of network integration, we find that higher network strength is related to higher proportional maximal gain. So the higher the network is already connected, the more they improve in treatment, the higher the global efficiency, the more they improve in treatment. And like everything else you've heard, the larger the lesion, the less they improve in treatment, and the older the patients, the less they improve in treatment. And these were all significant. What was not significant in the model was month post onset that got kicked out from the model.

When we look at measures of, um, when we look at measures of, uh, of segregation, the result, the model, overall model is significant, but these measures are trending significant, so higher average clustering coefficient is associated with higher gains, but this measure is not significant, not .05. And higher local efficiency, um, is also associated with hither proportional maximal

gain. But again, like in this analysis, lesion and age, the, the hi—larger lesion and the older age are associated with lower gains in treatment.

So what we found here at least, was that pretreatment measures of network integration, so the, the way the brain's connected, predicted naming treatment outcomes for these patients. Measures of network segregation didn't do as much of a good job. They're trending significance, but then they don't completely explain the data. But what I think was really important for us to understand, and I'd like to say that again here, is that this is after controlling for lesion, age, um, which are, what we think are the usual suspects that predict poor outcomes. Even after controlling for that, the way the network is organized, the, the integration in the brain, and with the, the efficiency in the brain, does actually predict treatment outcomes, or is associated with treatment outcomes.

Okay. So we can also, uh, because we calculate these network level measures, we can also drill down a little bit, and look at node level measures. So we look at the exact same things; network, uh, node, um, efficiency, node strength, and node local efficiency. But now we can look at it in specific regions of the brain. So, so what Jeff did was he divided the, the data into the responders and non-responders, 'cause we wanted to see what are, what is it a, which parts of the brain are actually different now. Um, so the analysis I'm going to show you now is just looking at the difference between responders and non-responders. 'Kay, we're just taking that group and trying to look at them separately, and we're tryin' to hone in on what parts of the brain might be slightly different.

So, so just to give you a quick summary of that, when we look at node strengths, there are quite a few—oh, actually I should tell you what you're looking at. Um, so in each of these cases, you're looking at a contrast between responders and non-responders, um, in terms of ne—node strength measures. And if you see anything in red, it means it survived, um, the, the significance test, and is significantly higher for the responder, ne—group than for the non-responder group. And if there's anything in blue, then it means that's the node that did not survive the significance test. And so you're looking at a, a shot, a snapshot of node strength, a snapshot of node global efficiency, and node local efficiency, and you're not looking at average cluster, clu—uh, you're not looking at the clustering coefficient because it's not significant in this analysis. But right away you can start, you see that there's quite a few regions that are actually stronger for the responders versus non-responders. So responders have higher node strength in the left anterior singulate, right IFG tri, and right IFG opercularis. 'Kay. So these regions are more sort of integrated with the rest of the network. They have higher global efficiency in several left hemisphere regions including left MFG, left LIFG opercularis, not surprising, but also right hemisphere regions such as right SFG—ooh, can't see that there. There. Right SFG, right MFG, right IFG op, right AG, um, and, uh, left precuneus. And then, the, the only region that has a higher local node efficiency, is right IFG, uh, in the, in the responders.

So, I just wanna point out that these are all pretreatment measures. These are all the measures in, uh, of network connect—uh, network strength before we even started treatment with these patients. Some of them go on to being responders, and some of them go on to not responding in treatment. But these, these are preexisting differences in these patients. So it seems at least that, that the relative preservation of, of these measures of global, and to a certain extent local

efficiency, may be a biomarker of treatment. So if you have these things preserved with these levels of efficiency, you end up, at least this data seems to suggest that you end up improving in this naming treatment outcome.

So these are very limited in terms of the scope, but, but the results are promising, because it tells us that even before patients start treatment, they're coming to us with a certain level of organization in the brain that may predispose them to getting something out of our treatment versus not.

So this is a point that I made at the beginning of the talk, that, um, that the degree to which this network typology instantiates, determines the extent of recovery in the context of our naming treatment, in the context of this naming dataset. And for sure, the patients who have better efficient typology show greater improvement than the ones that don't have these regions more efficient.

So I'm gonna wrap up with the, with the last slide, which I think is where we are at right now. And I will be the first person to say that we got it all wrong. But what we think we're, what we, what we're starting to think right now is that when somebody has a stroke, you, you see this huge decline in performance. And of course they're improve, and that's what the data suggests to us. But we, but in our dataset, we've got these differences in responders versus non-responders, or, high, you know better improvers versus not. And we think that this difference is really how the brain has tried to, to reorganize during this time. And for some people it, it, it's benefitting and helping them, and for others, it's probably not. What treatment does, is it sort of up, it, it enhances that, um, it just boosts that further up, because they're getting stimulation, uh, behavioral stimulation for a consistent time point. So for the people who seem to have this network going for them, and they seem to have certain parts of it well set up, they actually do benefit from treatment and start to look more and more like healthy controls. Whereas the folks who didn't have that instantiation before or during the course of recovery, don't get as much benefit from treatment, but they also, you know, were probably not going to because of the way their brain had, um, had reorganized. So we don't know what's actually happening here, what comes first, but the, this, this difference definitely ex, exists. And some of this has to do with the network integration, um, uh, domain level integration and segregation measures.

Um, so this is where we are at right now. We've got a long way to go from here, but at least we know what to prove, um, what to disprove, and what to confirm and, and throw away. I'll stop here because I really don't do this work alone. (Applause) And I have to give time for questions I can take few.

MARGARET: She does, and I'm just going to see if there's any of our research mentoring pair awardees, uh, from NIDCD that might start our discussion.

Q: Hi. Thank you so much for a very interesting talk. I wanted to go back to your point about how you've been finding these activation of these more domain general parts of the brain, activated for people with aphasia. Do you have any insight or thoughts about how that might inform clinical practice, or, or interventions, and do you think it supports one intervention approach over another?

SWATHI KIRAN: Okay, let me sure, make sure I understood that. So what does domain general regions have to do with clinical interventions?

Q: No, I mean, how do you think we should be targeting that in therapy? And do you think we should/

SWATHI KIRAN: Yeah. Um, no, that's a really great question. And, um, uh, it's actually something that we're tryin' to do in a different, in a different project. The idea is that if… so what we don't know is if these regions are actually engaged to assist in recovery, or they actually just upregulate for that time when we're doing the fMRI task, or whatever that particular small snapshot is. We don't know if they're actually always active um, in which case there would be huge, um, things for us to be thinking about in terms of treatment. So I think the real way to answer your question first will be to see what's happening over time, and see if they're always engaged. And if they are, then there's 2 things that can happen as possible treatment options. One is to, to use them as stimulation sites in TDCS, and see if you get a better boost in brain function when you stimulate MFG or not. Uh, and but the second is to then maybe focus behavioral therapy on not just language function and what these regions might also be involved in, which is other nonlinguistic cognitive function tasks as well. Um, I mean I am a believer that there is more to language in aphasia, and, and that includes these impaired cognitive, um, deficits that we, we see in these patients. And maybe we could spend some time targeting that as well. And the reason to do that will be because you're now boasting, you're boosting these re—the, a—the domain general regions.

Q: Thank you much for, thank you very much for the talk. So for both the responders and the non-responders, did, did they receive previous therapy before they received SFA? Did they have a history of getting speech therapy/

SWATHI KIRAN: Yes and, yes and no, but I can't tell you exactly who got what treatment . . .

Q: Okay, yeah . . . .

SWATHI KIRAN: Because they're all chronic. So they have to have had, um, treatment. . .

Q: They, they've had some therapy. So I just sorta wonder if, if there, you know, there could be this natural disposition toward, toward this functional efficiency. But it seems like also just the experiences people have had in the past could shape, **(Um-hm)** whether they're predisposed to benefit from ther, therapy, like having previous therapy experiences **(Yeah)** that they're boosting on. Or even therapy that was maladaptive, and, and caused them to form maladaptive networks.

SWATHI KIRAN: Yeah, no that's a really great point. And, and, um, um, you know that's exactly what Peter was saying in his talk. And we don't know exactly what's happening. But I can tell you that it was in the case that all our responders got previous therapy, and the non-responders didn't. That wasn't the case. Um, everybody had some form of treatment. And, um, we have, we have documented what that therapy was, but we have not gone back to see, uh, what that effect might be. Um, I, I'm a little ca—I'm a lit—little hesitant about calling something

maladaptive, ‘cause we don’t completely understand that yet. But clearly there’s something different about these people. Yes. Uh, Paul and then Brian.

PAUL: So, fascinating stuff, and I’m really glad that you’re looking at all the kinda network based measures of this. Um, I’m curious kind of interventional-wise, what you think we can do to modulate networks specifically, and if there’s kind of like a, you know, where you’re going with the, the network measures to kinda target treatment to hopefully make non-responders more like responders.

SWATHI KIRAN: That’s another grant proposal to write. But. (Several people laugh) And I can’t think about the question right now. Well I’ll tell you that, that, uh, I Mean it is definitely something that we’re thinking about in terms of what’s next. But if I didn’t know this, if I did not look at this data, if we didn’t look, in our lab, look at this data and really sit on it for so long and think what was going on, I would have never thought right hemisphere regions were that important. Um, and if somebody asked me where I would pick the best stimulation sites for something like TDCS, I would always say left hemisphere regions. So that’s making me rethink this a little bit. Um, so I don’t, I don’t know. I mean it, it, is it good to now stimulate right hemisphere IFG opercularis, ‘cause they’re clearly higher, there’s a higher node efficiency in the people who end up responding, so it seems to be something that works for them? I don’t know. But, that seems to be a worthy cause to follow up a little bit on and see. Brian has a question there.

Q: Uh, it’s (inaudible words) . . .

SWATHI KIRAN: Oh I’m sorry, okay. (A few people laugh)

Q: I can hand it to you next. Um, hi. Thank you so much. Um,. I had a quick question about, um, I, I saw that you had looked at the ACC and the prefrontal cortex, and I’m wondering if you, uh, thought about looking at other regions that were sort of, uh, known for this language control network like the basil ganglia, and I saw, at some point there was some connections that are going subcortically, or if that was thought about in maybe a, a way that you could look at it through dynamic causal modeling, or if, um… we were seeing sort of damage to these regions in these people with aphasia, that may have changed their outcome.

SWATHI KIRAN: Yeah, that’s a great question again. So in this analysis, the regions we picked for analyses were based on what the normal studies and aphasia studies have shown us. So we went and looked at the literature, identified regions of interest, and then did our analyses. And if they included ACC and precuneus, then we found that. Um, so we didn’t include basil ganglia because it probably didn’t up as one of the region, the, the top regions to, to be looking at based on our search. But I’ll just say that, um, Shelisa Sandberg has, in her dissertation, she looked at abstract and concrete networks in a very similar approach, slightly, you know, almost similar approach, um, and she, she had many more regions, right Shelisa, um, that are non-language that show up. And so it, it’s definitely there, it’s a matter of whether you’re looking there or not.

MARGARET: 'Kay, we're gonna take one more question from our RMPTA folks, and then we'll open it up to the audience.

Q: Hi Swathi, great talk; thank you. Um, I was wondering if you looked at correct and incorrect responses separately, or, just 'cause there are probably very different performance levels on the picture naming task between the people with aphasia and the healthy controls. So for example in the dynamic causal modeling study, um, if there was a difference, or if, you know some of these differences might be related to making errors or aware ness of errors. Um…

SWATHI KIRAN: Oh… uh, I, I'm tryin' to remember the details. I, I think in the first study we definitely did not. But, uh, by the end, by, by Erin's dissertation, I think she started to look at that. I'm not sure if it made it in to any paper. But I think what I, um,… uh… we do look at differences between correct and incorrect responses in early level analyses. But what I'm showing you now I think is including all of them. Not that sh—or that we can't look at it that way, we just need enough trials, um, to be looking at, and to have got that part. Yeah.

BRIAN: So there, there's this other literature that's really interesting to sort of think about, comparing which is the, uh, uh… over the years, the study of children with early focal lesions, uh, who have; you know, when I first heard the first part of your talk, I said my gees, this looks almost exactly the same as what we find, given the right hemisphere involvement, particularly for frontal areas, but then the bilateral for, for the temporal areas. And then it, then it started to diverge when you got into some of the more details. So, you know, and 'course I didn't know how much was really the, the language activation or the attentional activation. But, um, it, it is an interesting, it, the kid with the focal lesion shows you the end state of this. But of course then you have another dimension which is you know, age at which the problem occurred. And you know, critical period effects and all that. And, and then you know you were saying well if, if you, you know if you have the, uh, complete right hemisphere involvement, then you have almost no language you were saying that. But then you have these cases of children who have, you know, left hemispherectomies, and then they totally recover. So (Laughs) it's just, you know, there's a lot of points of similarity, but then there may be many points of divergence, if you look at . . .

SWATHI KIRAN: So Brian, are you saying that this data seems consistent with the . . .?

BRIAN: It, yes. Well the basic finding, this was stuff we did back around 2000 or so. Um, and we did have FMRI, but now of course it's so much better you know. But, um, was that, yeah, that, that there was huge right hemisphere. And, and that was the two, there were two ga—two patterns. There, so, for, uh, for the frontal, you know, really for the IFG type of damage, uh, uh, you, you got, uh, right hemisphere. So it was contralateral. But you had ipsilateral for, for some of the temporal, uh, lesions.

SWATHI KIRAN: I mean I, I… I, I would lo—I think we need to think more about what, how this reorganization fits in with, with early stroke. I, I, that's definitely, uh, when I come to visit peter and Alissa in March, that's probably what I'll be asking you guys. But I don't know how it fits. I, I'll be the first person to say that this whole thing has so many holes in it you can, you know, punch it out of any place. It's, it's not air tight by any long shot, but at least, um, there are

parts of it where, um, it, that seem to make sense. And maybe they make sense in other populations like young kids as well. But they also have to start making sense across the language domain. So we have to, the next obvious question is are these similar to, (Yeah) what's happening in Brenda's writing, and Cindy's, uh . . .

BRAIN: No in, in general it's very consistent. But there are these, you know, all these wrinkles, yeah. (Laughs)

SWATHI KIRAN: Yeah, there's a lot of wrinkles, and I think those are the ones that need to be ironed down.

MARGARET: 'Kay, we probably have time for one more question if there is one. I thought I saw one up here.

Q: So, I might have missed this in your talk, and I'm sorry if I did. But you did talk a bit about how the responders and the non-responders differ at that neural level in terms of their brain organization before they start treatment. But I was wondering if there are any behavioral characteristics that also differed between the responders and non-responders that might have influenced their response to treatment.

SWATHI KIRAN: Yeah. Um, and there were. That's what I was showing, was that they were worse, the responders were higher, uh, showed higher accuracy on the fMRI task both before and after treatment. They had smaller lesion volumes, and, and higher WAB scores. So they're off the bat as a group, um, better. Um, but, um… that's not the only thing that explains their data. Uh… Sure, yeah.

Q: Okay. So, but I'm thinking about something like speech production or. So were there characteristic features in; I understand relative to the task. But if you look at their overall, you know underlying cognitive processes and speech production ability.

SWATHI KIRAN: So, um, yeah. So this is a; so, let me just make sure I remember this. So, all of the, the treatment data, the behavioral data actually came out in a different paper that Natalie Gilmore is the first author on. And what we found there was that the patients who ended up responding, also ended up generalizing to, from atypical to typical, or typical to atypical. So they showed that sort of generalization. And they also generalized to the rest of the aphasia battery, Palpa, and some other measures of, uh, that we've developed for our semantic phonological processing. And the non-responders don't show any change, on any of these behavioral measures, as a function. And so they don't generalize within the category, they don't generalize to naming, the, uh, BNT, and they don't generalize, um, to standardized assessments. Is that what you're asking?

Q: Well I guess I'm sorry, I, I was thinking more in terms of trying to understand why they didn't respond, going back and looking at the pretreatment performance data. Is there anything in terms of underlying cognitive processes, or… speech production characteristic features? So like if they had a lot of (inaudible word) aphasias, **(Um-hm)** you know, they're just not gonna be able to respond to the treatment for more of a peripheral reason than… yeah . . .

SWATHI KIRAN: Natalie's nodding at me, so I'm assuming that, that when we, we did look at our pretreatment cognitive measures and speech production measures, and, um, um, I think that there might have been differences there. No? I'm not. We've looked at that data, but, um, we can talk about it offline.

Q: Okay, yeah . . .

SWATHI KIRAN: Because we are looking at pretreatment language and cognitive measures, (Um-hm) and I don't wanna say now whether it means that the responders are totally different (Um-hm) from the non-responders. But for sure, pretreatment cognitive, uh, and linguistic measures, including verbal production skills predict outcomes. (Um-hm) I don't know which of those are the responders versus non-responders, that's the part I don't know.

MARGARET: Thank you Dr. Kiran. (Applause)