BIOMARKERS OF LANGUAGE RECOVERY IN CHRONIC APHASIA
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SWATHI: Thanks for coming back, and we're on to our next talk for the session. It is my distinct honor and pleasure to introduce our next speaker in the symposium. Professor Cynthia Thompson is at Northwestern University. She is the Ralph and Jean Sundin Professor of Communication Sciences and Disorders at Northwestern. Dr. Thompson's research focuses on normal and disordered language and how language recovers in persons with brain damage. She has received several notable, notable honors, including the highest honors of the American Speech-Language and Hearing Association, and as you can see, has been continuously funded by several NIH grants. She's also the PI of the Center for Neurobiology of Language Recovery, an NIDCD funded P50 grant, which I think she'll be talking about today. Please help me welcome Cindy Thompson to give the next talk for the day. Thank you. (Applause)

CYNTHIA THOMPSON: Okay, THANK YOU VERY MUCH Swathi, and thank you everyone for coming. Um… and thank you the first 2 speakers for setting up some things for me to say as well. Anyway, today I was, my, the title of my talk in the program is the, is Biomarkers of Recovery. Well, that's not the title. (Several people laugh) I'm going to talk about biomarkers of recovery as part of this, but I'm going to cast my talk in a sort of larger framework, um, um, and emphasize the work that we've been doing as part of the Center for the Neurobiology of Language Recovery. Um… so… just in starting out with some comments talking about recovery of stroke, and this, these are things that have already been mentioned, especially by Peter just a moment ago, that it's a nonlin, linear process, and there are many different stages of recovery. And Peter really highlighted all the things that happen in early stages, or at least some of those. So we have neural repair processes that are going on, um, and that help spontaneous recovery period, which we're all very familiar with. But the focus of the work in our center, and my work for many years has been looking at, or charting recovery in chronic aphasia, both behavioral recovery as well as brain recovery.

So what we do know is the brain is an organ of plasticity, and you know, up until maybe 10 to 15 years ago, we didn't really think there was a lot of hope for people with aphasia, but of course we know this now, the experience is, um, drives the brain, and it's, uh, requires some, uh, stimulation and activity in order to change brain function.

So as we know well, there are 2 primary candidates for recovery in terms of the neural mechanisms that become recruited into the language network. One is, um… contralesional, that is opposite side right hemisphere, um, tissue, and the other is same side, ipsilesional, in the left hemisphere, and also we've been talk— people are talking a lot about perilesional activation. So these are all candidates for recovery. Which is optimal is still an emper—empirical question, and there are many factors that relate to what parts of the brain get recruited. So, just a general sort of idea in terms of the literature, about a year ago, we reviewed the literature from… too, and I can't see the slides over there, so I have to try to see them here—from 2016, to, or from 1996 to 2016. And at that time, there were 41 studies. I, there's a, there's more now. I think there's close to 60 now, because we're just undertaking the meta-analysis of treatment results,

and identified more just since 2016. But at that time there were 439 patients who had been studied in the literature, and of those, 99 showed right hemisphere recruitment. And this is an example of one; this is Julius Fridriksson's work, and this is a lesion in the left hemisphere, and this red part shows activation that resulted from, from treatment, and it clearly is left hemisphere. Another 90 studies, including one of our papers that we published in 2014, show la—right hemisphere recruitment, which Stephen might not be too excited to hear about, (Laugh) but it's true. In any case. But most of the studies in the literature sorry, have reported, uh, or 200 studies at the time, um, showed bilateral recruitment. So, um, and our st—studies have shown that as well. But the problem in the literature is, and this is been alluded to already today, is that there are many variables that are, um, involved in language recovery. Um, and, uh, I like to refer to them as these two opposite pieces, and one is organism intrinsic. We've talked – Peter talked a lot about those; and we have organism extrinsic factors, um, brain variables, which I'll be talking a little bit about today, and a lot of people are working on. Just what is the impact of the lesion on recovery? Um, things like perfusion, diffusion, resting state, bold signal. What about other variables such as cognitive variables? And, and we talk a lot about aphasia ser—severity, and somewhat about language impairment, but there are other things like depression, motivation, all those things that will likely be important and impact how the brain recovers. And then, on the other side, when things we have maybe more control over, is, are these organism extrinsic variables, and these are things having to do with the treatment that's provided, the type, the frequency, all these different things, dosage I'm sure all those things matter in terms of what happens in the brain. Um, and environmental variables, which are very difficult to study when we're looking at controlled recovery trials. So things like family, social context. Um, communication opportunities, all these things, need, will, ha—need to be considered. Although we're, you know, right now studying the things that we know how to study and can do well.

Another point I'll make in terms of the literature, um, review, e—then and now, is that most of the studies have looked at naming. Um, and, you can see that these are the number of studies, this purple is here, the naming studies; these are sentences processing studies, and these are Other. Um, and, Other is a wide range of, of, uh, behaviors, language behaviors. And this is just a pie chart showing the same thing. So, when we look and see whether or not the left hemisphere or the right hemisphere are recruited to… process language is highly dependent on what, I think, on what's being trained. And this has been discussed already, um, in, in the talks previously, that there are networks for language. For example semantic networks, naming networks are more bilateral, um, and I'll talk more about sentence processing and what's like a far word.

So the talk, what I'm gonna talk about today is some of the findings from our multisite aphasia treatment study that we… we are now in, have finished year 5. We're in year 6 and hoping for 5 more years, but we just don't know. Is anybo—body from the NIH here? (Laughs) Just a little plug. In any case, um, what I'm gonna talk about the most though is this work that I've been doing in sentence processing. Um… both behavioral and neuroimaging recovery. And then I will talk about biomarkers of recovery at the end of the talk. And the reason my talk isn't totally focusing on that is because this is not easy work. And when I proposed this title, I thought we would be much further along in analyzing the data. We have so much data now, and it's not easy to do things like trying to plow through these things. We're making lots of progress. And also

too it, we've collected data for 5 years. And so we just now have our total cohort of people to actually start doing some of these things.

Okay. So, a little bit about the center. There are 3 goals of our center, and it is to study recovery of language and cognitive processes in chronic stroke aphasia. There are 3 treatments that are going on at 3 different sites, one is Anomia, and that's under the leadership of Swathi Kiran and David Caplan in the Boston area. Dysgraphia, which is under the leadership of Brenda Rapp at Johns Hopkins University and agrammatism which I'm in the leader of that at Northwestern. And a second goal is, or the main goal really in ta—in undertaking this whole center was to study the neural mechanisms of recovery in chronic patients, and also to identify biomarkers of recovery. So what we really want to be able to do at the end of the day is be able to predict, based on behavioral as well as neural data, you know, what the prognosis might be for a patient. We're, you know, barely scratching the surface with that right now, but that's the overall goal is to understand mechanisms of recovery.

So, and these are the sites, uh, just the different semantic representation of how the center's set up, and I also just, we just added our, um, uh, center in, in China. Um, Beijing Language and Culture University where we're doing the, replicating the sentence processing work in a tonal language, studying Chinese speaking people with aphasia all over the country. I've been I can't tell you how many cities in china. (Laugh) They're all, have loads of people, that's for sure. (Laughs) And lots of people with stroke; it's unbelievable. But any case, so, so far in America, we have run 103 patients. Um, they're all left hemisphere brain damage with one stroke. Um… all right handed with exception of 3m and in some of our analyses we leave that person out, those persons out. They're monolingual English speaking, so they're, the generalization or general al—generality of these data are limited to people who are monolingual English, English speaking, which is becoming fewer and fewer. Um… and so on. so these are all the kinds of, of, um, um, of the criteria that we use for including in all of our studies. And they, what we, ha- have done at each site is randomly, um, put participants in an experimental training group, and also in what we're call a natural history group, just trying to chart changes in language processing over time in chronic aphasia. They're controlled for age, education, and all those things that are typically done as well as AQ.

Across all sites, um, these are the lesions. Um, the axials and the laterals on the end, and then also this is a, um, lesion only picture showing lesions, and this is with FLAIR. And I won't go into details about that, but when we talk about the relationship between lesion and recovery, we don't know for sure how people are actually drawing their lesion maps, whether or not they're using this, um, the FLAIR data, or just, um, the lesion data which is cerebral spinal fluid as well as the dead tissue itself. So that's a whole nother story. Um, but in any case, these are our patients. Um, and we have… found that for all sites, that the natural history group, and the sites are color coded here from pre to post treatment, and this is pre and 3 months later just post testing. They received no treatment. There's no change in the healthy participants. Or not the health—sorry, the untrained, uh, people with aphasia. But for all 3 sites, we see that there is, this is baseline performance for each site, and we see improvements in all domains, across all domains. And, um, there's some decline at, this is another follow-up at 3 months after this second posttreatment, um, test, and they show some decline in behavior, but still better than baseline.

Okay. So I'm gonna dig into the results about the agrammatic patient, because that's what I love and care about the very most. (Laughs) Um, I think naming is fine too, but I, um, really am interested in sentence processing and I have been for my entire life. I was one of those people in high school who really loved diagramming sentence, it was my favorite thing to do anyway, so rather geeky. But in any case, people with agrammatic aphasia, one of the cardinal or a characteristic, um, ca—characteristic behaviors that they present is impaired ability to comprehend and produce noncanonical versus canonical sentences. Mkay. And just as an example, the kinds of stu—sentences that I study are, se—uh, sentences like these. Maybe I can move my pointer now. It doesn't work. Um, noncanonical sentences like, um, passives; "the cat was chased by the dog," or, um, object class, "it was the cat who the dog chased." Um, and these are the theories of studies where we've shown for fluent and non-fluent people with stroke aphasia, that they had difficulty with the noncanonical sentences in both comprehension and product, but less difficulty with canonical forms. Mkay.

And just getting into a little linguistics, for those who you who just can't stand linguistics, you could maybe take a little nap now if you wanted to. (Laughs) But in any case, these are the kinds of stu—sentences of our study. And I'm not so interested in, in any of the linguistic nuances about them except both are noncanonical, and we have mapped the neural mechanisms associated with both of these, with overlap, in, this for passive sentences, and this is for object class sentences. And then recently Eddie, Eduardo, sorry, just finished his PhD and is a postdoc at UCSF, San Francisco, ran a cohort of, these are all healthy people, looking at NP versus WH movement, those two sentence types, and found that there is a difference, and there's greater activation for, for, um, WH movement than for NP movement. You're glossing over; I can see you in the audience doing that. (Laughs) In any case, um, the reason I'm putting this out is because we care about what normal people do in order to understand what's happening with the, with the people with brain damage. So this is only just really for sort of the visual perspective of what we expect to see in people with no brain damage.

The important point for this, um, talk, and for the work that I've been doing is looking at whether or not these behaviors change when we treat them. And so this is, these are data from a series of studies that for the first public, the first study in 1996. But these are NP movement. Let's just say passive sentences. "It was the boy. The, the boy was chased by the girl." Or maybe those are WH . Does that say WH? (WH) Those are WH, okay. They're WH questions, like "It was the boy who the girl chased." Okay. And these re NP movement structures, "The boy was chased by the girl." Okay, so we don't care about that. But what we do care about is that this is acquisition. So all, this is, almost all patients, um, learn those structures, mkay. These are people with Broca's aphasia and agrammatism. What's also important to point out is that we test generalization form complex; these things like "It was the boy who the girl chased," to simple syntactic sentences, and we find generalization from complex to simple structures that are related. But if we train simple structures like who questioned, who did the boy chase, we get no generalization to "It was the boy who the girl chased." I mean it's intuitively, you think about that now, but, we didn't really expect to see this generalization form one form to the other, and it only happens if you train complex sentences first. And the same thing happened for NP or WH movement structures. So almost all the participants who have participated in our studies, show

the ability to learn these structures, to produce and comprehend, and they show generalization to structures that are less complex, that are linguistically related. So I just said all that.

Anyway, so just to give you an idea about what we do in NP movement training, this is for, um, in this set of studies, I wanna just say that we trained NP movement structures paths of sentences. And essentially what it involves is thematic role training using an active sentence form and building a noncanonical sentence from the active sentence form. And in this study, or in this series, that for 5 years, we've been training, um, sentences like this; "The boy was chased by the dog at the fairgrounds." And looking at generalization to truncated passes, like "the boy was chased at the station," and also to unaccusative verbs, such as "The boy fell at the factory."

Okay, this is the last linguistic side, but I just love it so much you have to look at it, okay. (Laughs) These are linguistic trees. This is for unaccusative verbs like "fall." Okay on linguistic theory, the, um, the moved object, moves the subject position. So "The man fell." Okay. "The man" is a theme, it's not somebody who's do—who initiated the following, he did the following; falling. Anyway, so in linguistic theory, the subject initiates in a post relative position, and moves to the subject position. The same thing is true in passive sentences, okay. So if you say something like, um, "The boy was chased by the girl," the "boy" originates here, okay, and moves to the sentence subject position. So those two are linguistically related. And the prior to this, there hadn't been any studies to my knowledge, that had looked at the relationship between those two structures. Now this matters in terms of the brain. Just in case you're feeling like oh, napping. (Laugh)

Okay, so. So those are the structures we train and tested for generalization. And here are the results. Um, and on the left hand side, the far left we can see that these are the trained structures. This is for production, and this is for comprehension. These are the trained forms. These are the long passes with adjunct clauses. And then next door to those, oh, and here are the acquisition curves for those. This is for co—production, and this is for comprehension. Um… and these are the generalization data to the easier passes and to unaccusative, which is pretty amazing. So they're linguistically related, they generalize from one to the other, and also as a check, we have object clefts here, and they show no change, and they're not related, okay.

So we kinda think about the brain here, alright. So if you're training a structure, and someone learns the, to compute that structure in comprehension and also to produce it, then there must be some neural pathway that's being used for that, okay. And so you could say that if a, if a simpler structure comes along, then they're probably, or likely, or theoretically, hypothetically (Laugh) using the same pathway, okay. So, that's one of the questions we wanted to know. We see these behaviorally; we've seen it on many, many studies since the early '90s, okay, but we don't know why. We don't know the mechanisms.

So one of the ways that we have undertaken an analysis of the mechanisms engaged in this improvement is looking at eye tracking, okay. And so we did pre and post treatment eye tracking studies. These are online studies. Those of you might not be familiar with it, but the… um, participant is sitting here viewing the set of pictures. This is the eye tracker, which is picking up, and I don't know if you can see it in that slide, but here is the eye right here. And this is wonderful people in my lab who over the years have done this eye tracking work. And the

question is, does sentence processing become more normal like, as a result of language treatment? Okay. So we had a couple of tasks to we used to test that question or answer that question. One is a syntactic priming task. Just briefly, participants listen to and repeat a sentence like "The Gorilla was lifted by the chimp." Then they see an action picture. Here it is a man lifting a woman. And they have to produce a sentence that goes with the picture. And what we do is we track their eyes as they're producing the con—sentence constituents for both passive and active forms. So "The man was lifting the woman,", or "The woman was lifted by the man," okay. And these are the different sentence regions where we're tracking their eyes.

So what do healthy people do? Um, in sentence production it's well known. Kay Bach and other people, um, Zenzi Griffin, have shown that normal people when they produce sentences, they do what's called incremental processing, okay. It's the processing strategy that's used mostly, okay. And what that means is that when they're listening to, or producing a sentence like "The boy was chasing the girl," they're gonna first look to the boy before they say it. These are the speech times. They say, they look to the boy, and then they look away from, after they've said it, they look to the girl. 'Kay, so that's incremental processing.

Okay so what do people with aphasia do? and these are data from pretreatment, these are, these are correct trials at posttreatment. At pretreatment you can see that there's no incremental processing. For either active or passive sentences okay, in their production. But at posttreatment you can see that there's, look at this; when I saw this I thought I was gonna cry. (Laughs) I was so happy. And I really did not expect it. And, you know, in a, and, part a me did, but yet there was a part a me that was really quite, um, skeptical as to whether or not we'd actually be able to see online changes. And then also too, you can see that downstream there's incremental processing at both sites, and, there is a correlation which you can't, probably can't see very well, or I can't from this angle, but there's a correlation between accuracy or response to treatment, and, the normalcy of eye movement patterns. 'Kay, so that's for production.

The second task was for comprehension. And this was a simple sentence picture matching task, and one we do clinically. They're presented with 2 pictures with reverible ac—uh, action, and they are asked to point to the ac—active form, or point to the passive form. So point to "The boy was kissed by the girl", or point to "The girl kissed the boy.' I don't think that's "kissing", it's "lifting" I think, or "hugging" or something. In any case (Laugh) what we do there then is we track their eyes, in these time bins, where they're looking. So when they hear the sentence "The man was lifting the woman", we track their eyes in each of these spins. And what it turns out, in healthy people, um… a lot a this work is by Jenny Mack and also started by, um, um, Mike Dicky when he was in my lab as a postdoc, um, and so on. And so, it's really exciting to start seeing more and more work coming out. But in any case, this is what healthy people do. They do what's called prediction, 'kay. So when they hear a sentence and they hear "the man", they look to the picture where the man is the agent. Mkay, this is what healthy people do. So Grodzinsky was really wrong, that's not; that's an agent first strategy, which is not compensatory, which he suggested was what people with aphasia do. It's, it's not compensatory, it's normal. So you can see here that when there— these are for passive sentences. So this is prediction. So they're hearing "the man" and they're looking to the wrong picture because they're predicting an active sentence, okay. And then at the end of the sentence, the once they hear the verb, "the man was lifted," they pick the right sentence. So the sentence integration is

called seman—we call it semantic integration. So those are the normal processes. But what's important is that, um… what the patients do. Now at the top are the treated group, and this includes both correct and incorrect responses, and you can see that pre, prior to treatment they're showing no production and no integration. But after treatment this is not whopping, but it is a trend towards prediction, and for the correct responses it's bigger. But the more important thing is we see integration. And comparing that to the untrained patient, they show no change in eye movement, okay. So, we see all, offline and online changes in passive sentence production and comprehension.

Okay, so what about the brain? What happens? So we also measure, um… functional activity, neural activity during passive and, and active sentence processing. And here are, um, this is our co, cohort at Northwestern, where we have the lesion; it's overlapping in the left hemisphere. Um, and, the, on the bottom are the controls. These are the trained participants. And, what we found by you know, really analyzing the lesions is that they have overlap in the frontal operculum, the IFG, all left hemisphere. And in posterior regions as well. So there was a lot of, over 50% overlap in these regions of the brain, and no difference, um, in the lesion volume between the two groups in anterior or posterior brain.

So the task we did is a simple sentence verification task, where they're lying in the scanner, and they hear a sentence such as "The boy was pushed by the girl," and they see a picture of either the boy pushing the girl, a girl pushing a boy. And all they have to do is say does this sentence match this picture, mkay. And these are the post, um, treatment, up regulation. So this, these are regions, and they're all in the right hemisphere. This is just a, a lateral. I don't know how well you can see that. Can you see it Maggie? Okay, I can't see it from here. But any case, there's a right hemisphere activation, up regulation in the right hemisphere anteriorly and posteriorly. And there's no change in, at all, in any activation for the untrained patient. Mkay, that's what's on the bottom.

Alright, so, and then just as a, a little aside, I wanna share with you some recent da ta that we just finished in primary progressive aphasia; a patient with agrammatic PPA. Um, uh, we trained him on passive, just exactly like what we did with the stroke patient, and then when he was finished with that, we trained him on WH movement structures object clefts, okay. and, what we found which was surprising, is, is completely experimental, we didn't now, but these are the data. This is… um, production I think. Can't see. Yeah, this is production. And essentially it's a multiple baseline or multiple probe technique where we first trained passives, and you can see there's acquisition, no change in object clefts. We train object clefts and it, they improve. And this, these are the comprehension data that are happening. Yeah, I think my pointer just went out. Oh no. In any case, so, he showed acquisition, the same level of act, activation that, or, or, or recovery that we see in our stroke patients. And when I was in China in August, this patient sent me an email. At that time he was in week 8 of treatment, and he said "Thank you good science, and my treatment team. I think my brain is working the words." (Some people laugh) And he was right, okay. so we did 3 polis neuroimaging with him. Isn't that cute. Um, and it, uh, this is posttreatment for passive, okay. This is upregulation, and you can see it's bilateral. But if we look at his atrophy pattern, you can see that it, it's all left. Right/ And it's left, um, primarily anterior, that's, that's gaping in to the posterior brain as well. But so these, this is what he did posttreatment, active, posttreatment for passive sentences, that was not active at

pretreatment. Then we trained, um, the objective relative clauses, and you can see that he showed, is losing this left hemisphere activation,. And I don't have another atrophy map. I just got these data like 3 days before I came, and we haven't looked at the, the posttreatment atrophy scan, but I'm guessing that it's gonna be larger, um, and encompass more of the left hemisphere. But you can see again, that there's right hemisphere activation, posttreatment. Okay, so, um… what's really striking is to look at the healthy patient doing the same task. The stroke, healthy people, the people with stroke aphasia, doing the same task, and… this pointer is not very happy. And the PPA patient that I just showed you is on the right hand side. And what we found is that there's right hemisphere recruitment of homologs of the left hemisphere that are activated by healthy listeners. And I've highlighted those in yellow if you can see them there. So, when healthy people active the left hemisphere, some of those regions are activated in the right hemisphere, so they're homologous. Alright. And also, we found that the healthy people also recruit right hemisphere regions for normal sentence processing, and those are recruited by the patients, both stroke patients, and the pe—person with primary progressive aphasia. So, um, those are the patterns that we found in this dataset.

Then we also, um, performed a meta-analysis of healthy people. um, reports in the literature for sentence comprehension and production. We separated it out. There were some differences in comprehension versus production. But these data here are the meta-analysis for both. This is for 60 published studies, excuse me, with 966 participants, and 784 foci. Um, and this is was done by Matt Walensky and Eddie Eduardo who's in the audience, and also David Caplan and myself. Um, and so those are, that's the network.

And so what we did then with the patient data is we, um… looked at upregulation in the sentence processing network that we identified, um, and also, we looked at upregulation in a domain general network, um, the dorsal attention network, as described by Corbetta and Colleagues. And what we found, this is for offline improvement. So for, this is associated, upregulation in these brain areas, associated with improvement on the behavioral task following treatment. And, you can see that there is, um, significant; this is right hemisphere, this is left hemisphere. There is a significant correlation between treatment, responsiveness, and upregulation in these regions in the sentence processing network, and there's also a correlation with, with increased, uh, performance in the dorsal attention network. Okay, so that's for offline processing.

We also did the same thing for online processing, um, and here is the online figure. Um, and what we found, or what we did with this, this remember is prediction. So when you hear "the man" you look to the picture of the man doing the action, right? Resulting in incorrect passive responses. So what we did is we, we, um… uh, calculated a prediction score. And, essentially just reflected whether they're predicting or not during that time window. And we correlated the prediction score with… um, upregulation in the sentence processing network and the domain general network. And what we found is for prediction there is a strong correlation. It goes down because it's pa—that means prediction. Okay, um, so there's a strong correlation, significant cor—correlation between um, prediction, emerging prediction, and, um, sentence, the sentence processing network areas. But, it doesn't correlate with the domain general network. Conversely, we also conduct, um, calculated a score for thematic integration. So, sort of a, a, uh, numeric representation of this part of the sentence processing, and correlated those scores with upregulation in both the sentence processing and the domain general network. And here we do

not see a correlation between integration and sentence processing network, but we see a correlation between integration and the dorsal attention network. And thinking about it makes perfect sense that we're really, uh, when we're parsing a sentence originally in the beginning, and this you have to sorta care about syntax about this, when we parse it, parse sentences, our brains are actively engaging syntactic processes. Okay, but, downstream we're really relying more on things like working memory and attention than the actual syntactic process itself. So, this is just a guess of what this means, but we were surprised to see it.

Okay, so, those are the sorta the core data that I wanted to present today. And now I'll talk a little bit more about you know what, what this means. So, I wanna just talk a little bit about promoting plasticity. So what have we learned over the years about how we can promote changes in the brain, and changes in behavior? Um, and I, I think it might have been Peter, or maybe it was Stephen who already mentioned Kleim & Jones who have worked with animals. It was Peter who talked about the, some of their work, um, in, um… animal models. And in 2008, uh, sort of a seminal paper by, um, a, a lot of us, but, um, Stacy Ramer was the first author on this paper in 2008, and these are the… there were 10 principles that Kleim & Jones came up with. Um, and I won't go through all of them, but I'll go through the ones that are the most salient for, um, the work that I've done. And I will say that, um, Swathi Karin and I just finished, um, it's a, a paper under review, where we've recast these 10 principles based on the extant literature. Not on ours, but everything that's in the literature. Okay, so, we boiled it down to 6 principles, where the first one for us is, um, use, improve, or lose it, okay. and Kleim & Jones had said, made those into two; use it, use it or lose it, and use it and improve it, okay. So to us those are sort of saying the same thing, so we compiled those into one. Um, and the second one that's relevant to the work that I've done, is "specificity rebuilds targeted networks." And this was just called Specificity by Kleim & Jones. Saying that if you train a specific task, it's going to recruit the brain mechanisms for that task. Okay, right? Yeah? You agree with me? No? in any way? (Laugh) Um, you know, some of these games that are done for, to improve cognitive functioning, you know, I have people ask me, "Well if I do crossword puzzles, is my brain gonna get better?" And I said, "Well the networks are gonna get better for crossword puzzles," you know, and that's it. So it, when we're pushing the brain behaviorally, we're pushing a network I think.

And then I won't go through these all, but this is salience, which has to do with sort of the environment, some of those variables that I talked about early on that have not been studied extensively at all, if at all, um, and the effect that they have on brain recovery. Another one is repetition in intensity. We know that repetition also builds um, neural networks. And so these are going to be very, very important variables to study in terms of how do they pair with different treatment approaches. Um, this has to do with generalization. And the one that we added is "Complexity promotes learning and generalization." So we now have 6 principles of neuroplasticity where there were 10.

So in terms of use it, improve it, or; use, improve, or lose, um, the idea is the training that drives a specific brain function can lead to enhancement of that function. This is what Kleim & Jones said on 2008. And how we've translated it is that treatment of impaired language processes result in recovery of the neural mechanisms associated with that process. And they can be new ones, they could be recruitment of old parts, that were not available at the time, or regions close

to that. Um, and then on the corim—converse side, is that failure to drive a specific brain function can result in functional degradation. Now I don't know of any data that have shown that, but we do know that our control participants, or natural history participants didn't show any change in those networks. Whether or not there was any degradation going on for not doing that, I sort of doubt it specifically for that function. But, um, those go hand in hand. The second principle that I think that we can speak to with our data and our findings, is that specificity rebuilds targeted networks. Um, and Kleim & Jones said in 2008, "The nature of the training experience dictates the nature of the plasticity." So this was mostly based on animal studies. So if you train, you know, animals pick up pellets, mkay, some of, uh, Randy Nuttle's(?) early work; then these, I think they were adult squirrel monkeys, that you can't-- they did, um, uh, brain mapping, um, of the motor cortex in these monkeys, and they showed that there was change in the motor cortex adjacent to where the hand was; oblate the hand area, train them to do this pellet picking up, and there's change in those areas that are adjacent to it. So this is what it was based on. The nature of the training plasticity dictates, nature of the training experience dictates the plasticity. So they didn't get changes in the motor cortex of these monkeys in strange places, they got them in obvious places that could obviously take over the function. So this points to I think for language, um, the use of treatment that's focused on impairments that exploit what is known about normal language im—representation and processing. Okay. And there are several studies, or several treatment approaches that do this, that have been shown to facilitate acquisition as well as generalization to related structures, simpler structures, um, you know see (inaudible words) really well know, semantic feature analysis of phonomotor treatment by Diane Kendall and others, um, for network strengthening training, and treatment of underlying forms. So these are treatments that actually exploit a process, or they're based on psycholinguistic principles that we think activate the same processes as in healthy people, based on the eye data.

Okay, so then the last one is, um, Complexity Promotes Learning. Um, and, essentially this just means that top down training improves underlying neural cognitive processes required for both complex and simple, simple forms. Um, and this has been shown across a number of domains. It was first shown, um, by Fred Eckman in teaching English as a second language, teaching people to learn English who were Spanish speakers. They improved in language faster and more efficiently if you trained the complex structures first. He essentially said if the, you train the complex structures, the simpler ones that are related come along for free. So that's been shown first. There was also shown by David Plaut, which was really, really exciting to me, in 1996, using computer stimulation. So he had… um, and I won't go into the details for that. And I'm sure some of you probably know that work, but essentially what he did is he had complex and simple, simple items within a computer network, he oblated the network, and then he retrained the typical items, and sought, saw no generalization to atypical and so on. This is a, a basis of, um, Swathi's work, per naming, and we've seen it also in sentence processing. We've seen it in acquired, um, dyslexia, um, a paper by Ellen Riley. And also it's been shown in developmental phonol—phonology for children, um, learning language, that by training complex structures first, there's generalization that occurs better learning to simple ones.

Mkay, so those, that's, those are the principles of complexity. Or of plasticity.

So the last bit I wanted to, um, talk a little bit about, are some, some of the… end roads we've made into understanding some biomarkers of recovery. Um, there are two that we've, we've looked at. We have not examined the posttreatment data yet. We've only examined the pretreatment data. Um, but they're promising. And also we're looking at, our group is looking at white matter track int—um, integrity. That's being headed up by Swathi. Maybe she'll talk about that today. Um, in any case, the question here is, um, can these neural factors, together with behavioral measures, predict recovery? And so what we're moving towards, or, uh, attempting to do is move towards, but we're calling a precision medicine approach to aphasia rehabilitation. So I mentioned earlier in the day, I mean, we envision a day where we could do maybe some simple neuroimaging tasks that could be done clinically, and administer this bare bones set of behavioral measures, and be able to predict whether these people will be a responder or not, to one or another treatment. So in our case, we're attempting to see whether they'll be good responders to naming treatment, based on certain data of their brain, and how they do on a pretreatment probe. Will they respond to treatment for agrammatism based on that, or will they respond to spelling treatment? Those are the ones that we're studying right now. There could be many other treatments that could come into the mix later. So this is the whole pers—per—purpose of this.

In terms of perfusion, we're talking about cerebral blood flow. Um, and this just shows, um, a healthy brain on the right, um, and, a damaged chronic aphasic patient on the left. Uh, and perfusion values are known to be disruptive in people with aphasia, okay. And blood flow, blood carries oxygen, oxygen, and other nutrients to the brain, and so if there's a disruption in blood flow, it probably affects behavior. This is the, sort of the thinking about that. Um, in any case, we've studied, um, perfusion, and numbers of patients. Oh, and I wanted to just say one other thing. Is that, until just a few years ago, within I think this last at least 10, but maybe only 5 um, perfusion was thought to be a really important, um, post stroke factor in acute strokes, mkay, that, and but it would resolve other time. This is a lot of Argye Hillis's work and so on. But, we only started studying, and I think the first paper was, uh, the one reported by Tracy Love, that she and I and others studied one patient, and then there was a few other studies that it started showing in chronic patients that they have abnormal perfusion as well. So that was one of our goals in this, in this project is to study perfusion. And, um, we have the pretreatment data, uh, analyzed, and it was actually published, um, for, in 35 patients. There were 20, 21 from Boston, 9 from NU at the time, and 5 from Johns Hopkins at the time. Um, and what we found, and we looked at, um, bilateral ROI's, um, and just looked, the perfusion values can be, they're automatically extracted rom, um, the, um, image, and then we looked at the relation between, um, um, different ROI's and the perfusion values across regions. And what we found, and this is, um, we found differences in hemispheres. And this had been reported before, but what we found is a little bit different than what had been shown before, is that rather than hypo-perfusion, uh, it's, I think Julius's group and some other groups, and Jessica Richardson I think's paper said that there was, um, they found hypo-perfused tissue. So under-perfused tissue in the left hemisphere. But what we actually found is, and this is just with 35 patients; now we have 103. So we're redoing all of these analyses with the entire, um, group. But we can see that the perfusion is not statis—different across hemispheres, um, in the left and the right for the patients, okay. Um… these are, yeah. But, in the left; in the right hemisphere, it's hyper-perfused. So we found greater blood flow in the right hemisphere than in the left hemisphere in patients as compared to controls. Um, and so then we looked close, more closely at where those regions

were, um, and we found that the ROI's with greater perfusion in patients ex, were in control, um, were hyper-perfused, um, are shown in red. So the hyper-perfusion was mostly in the right hemisphere, and in blue, this is hypo-perfusion. So we saw this varied pattern of, sorry; there's s'posed to be a slide there. Oh it's not there. maybe it is. Oh. I pushed the wrong button, sorry. Okay, so, we saw this varied pattern of hypo and hyper perfusion across the two hemispheres. Okay, so, and, but also, and importantly and surprisingly to me, is that there was no correlation between language ability and perfusion. Okay, so we don't know if that's gonna hold though. And also we sort of thought about this upregulation in the right hemisphere, that maybe it's just an effect of brain damage in the left hemisphere, this auto regulatory. So when you've got something going on that doesn't allow the blood to flow through the left hemisphere, i.e., a stroke, then it might shoot more blood to the right. We don't know the answer to that. But it could be partly that. But if it, that were the case, we wouldn't see this, uh, regional, um, hypo-perfusion. In any case, we're now undertaking another analysis that's going to look at, um, these same regions, um, in the whole cohort, and correlate it with their language behavior at baseline and changes in treatment. We also looked at perilesional, um, perfusion, and found what has been reported by others, um, that the regions closest to the brain are the ones that are, um, the most hypo-perfused. This was, um… I think 6 millimeters, 06, 6 to 12,or 15 and, 15 and out, for the rest of the right hemisphere. Um, but in any case, what the problem with this only is, is that, and we ran into it too, is that we are not sure you know what the effect of these FLAIR data are. I mean how were people actually calculating their lesions. Um, and we also, are create—just now created some mass. Uh, yeah, here are the questions. How should perilesional space be identified or defined, okay? Should it be rings around the lesion? Um… and, what we found, and this is a, um, one a the, a PhD student in biomedical engineering, at Northwestern, became interested in all of this stuff, and he developed some, um, perilesional masks, that separate hypo perfused tissue from perfused, normally perfused tissue in perilesional rings. And there are differences. And so now we're doing an analysis that's going to look at bold signal in those regions controlling for the perfusion value of those regions. So, you know, I don't know if it's gonna take us any further, but at least it will help us understand when we think about recovery of perilesional regions, it probably matters in terms of whether or not there's hypo-perfusion. But I've also thought about in terms of perfusion, that, um, it should improve. Okay, if we're, if it's true that when we're doing treatment we are stimulating a neural network, okay, that neural network by the virtue of it working is delivering oxygen and other nutrients to the brain. Okay, so it could be argued that if you do a task over and over and over and over again, you know, the brain is working, the blood is going there you know because it has to go there in order for it to work; it could potentially reverse perfusion. So that's where we're going with this next. So that is perfusion, um, recruited to support recovery, and what is the relation between perfusion and bold signal. Okay.

And then the last thing, um, that our group just finished, and Brenda Rapp is the person who's done most of this work. Um, Actually Nicole Dickerson who is a postdoc in her lab, but these are all based on our data. Um, uh, she's looking at resting state. So, at both pretreatment and posttreatment is the goal, but we've just finished this study looking at pretreatment. In resting state, what it does, is essentially provides a measure of the intrinsic brain activity. This is done, during the resting state, our scans are 7 minutes, where the patients are lying in the scanner, and we're just recording their activity. I won't go there into the details about this, um, but essentially what we're measuring is what is called fALFF. Uh, we call it alfalfa, but. (Some people laugh)

It's easier to think about. But fALFF is just a measure. Is, what it is, is a, a range of low frequency, or, or low frequency range within the bold signal that can be extracted from the bold signal when you're analyzing the data. Um, and then, um, what intrigued us is that there has been low levels of fALFF have been associated with schizophrenia. People with schizophrenia have these low, low frequency, um, fluctuation. It's also been shown in Parkinson's Disease, and there's been some study, a recent study suggesting an in fa-=- in aphasia. Shows as a resting state. So again, we're really thinking about can resting state possibly be a predictor of recovery. Okay, if there's no resting state, then does that mean anything in terms of whether or not they'll be able to recruit those, that tissue for recovery? Okay. Um, and on so—there's a stu—a couple of studies that have just now shown that, um, there's a positive relation between resting state and behavioral measures. So in this study, we had 64 of, um, patients in the cohort, um, and here are their lesions. They're, um, looking the same is, in a way. Um, they were from across sites. Um, and this is a paper by Nicole Dickerson that was presented Academy of Aphasia this year. Um, but so the results so far, uh, are that, these, what we found is that fALFF values are significantly lower in lesion versioned versus healthy controls. So we replicated this study that's just shown that if you have brain damage and it's from a stroke, or it's from some other problem such as Parkinson's Disease or schizophrenia, that it does affect those low frequency fluctuations. Also found that larger lesions are associated with lower fALFF. So that's kind of interesting too, sort of interesting. We don't know how that's gonna play out. But what we did find, which is pretty really interesting, (Laugh) pretty really, and relates to what Peter said, is that we found 5 regions. So it's, 5 plus 5 is 10, in contralesional areas, oaky. So if the right, um, um, superior temporal gyrus, was, had low fALFF, the left; if the left had it, the right had it. So there were 5 pairs, which was really, I mean we're puzzled over this; we don't know yet what this is gonna mean. But it does mean I think, that there is obviously communication as Peter talked about, between right and left hemisphere regions, we talk about homologous brain, um, activation which is what we've found in our studies, and so there might be something to this. But what we, um, did find too, is that, this is the last 2 findings, is that fALFF values in some regions were, um, correlated with, um, the severity of sentence processing or naming abilities. So there were two region—or, let's see 7 regions, and they're shown in yellow. Now we can't—we haven't even thought about tryin' to think about why these are, except I like that this superior temporal gurus, is, um, has, shows low fALFF in the left, but it extends from left to right, for, this is for people with sentence processing. So we've been able to correlate fALFF values in certain regions with sentence processing deficits, and similarly we have found, she found 5 regions that correlated with severity of naming. So, we think that there's some hope for this, um, in terms of its ability to predict recovery. And just this one last, um, study that was just completed by Michael Iorga, and he's a MD PhD student at Northwestern, and he took an interest in our data as well, and he studied a cohort of, of our participants, in trying to predict. Used behavioral measures, those are pretreatment behavioral scores, and resting state to try to predict recovery. Um, and we, we haven't had a chance to really tease out all these findings and see exactly what they mean yet, but what he really found, just an upshot of it, these are the Boston people at the top, these are the 3 di—we did, did 3 different models. So he tried to do prediction models based on, um, this behavioral data, he did prediction models based only on fALFF data, and prediction with mixed. And so there's behavioral fALFF mixed for Boston, I think this is Johns Hopkins, and for Northwestern. And the best model used both fALFF and pretreatment scores, which is not surprising, but really interesting in terms of. And these were predictions of their posttreatment

scores as well recorded them. So we think that there is potential for, um, building models that, that will predict recovery with hopefully as little data as possible.

So in summary, this is a figure that we put together to try to conceptualize where we've been and where we might, are going, um, in stroke induced aphasia. As I said, that there are both organism intrinsic and extrinsic factors, and we can't just say you know, that this treatment's going to work, or this part of the brain's gonna be recruited, or any of those things, because there's so many factors involved in it. Um, and we, we're making, taking steps, tiny steps right now in tryin' to understand the whole picture. But there's brain be—variables, which I've already, I've talked about, uh, here, and also, um, baseline behavioral measures. You know it makes a difference whether or not a person maybe has an anomic aphasia, or an agrammatic aphasia. Or I'd rather call them sentence processing deficits or, um, let's go semantic processing deficit. Um, then we hopefully will be able to build models based on these to predict outcomes. And then we have these organism extrinsic variables, which are sometime need to be built into the model as well. So the treatment, we're starting to understand some things about some treatments, but there's also this whole environment piece that we, we don't know. So those factors are going to take, come into the mix as well, and then when we have language and brain recovery eventually. (Laugh)

So just some take home points. We found that treatment does improve sentence processing abilities. We've shown that in numbers of studies. We've showed both offline and online changes. We've shown that for sentence processing, um, the right hemisphere is recruited more so than left hemisphere areas, and that they are homologous largely to left brain regions that are, are activated by healthy people, or they have the same regions activated by healthy people in the right hemisphere. Um, we also wee, and what I think is really important, is that we see changes in the sentence processing network. Now it would be interesting to take a naming network, which we probably can do since we've identified all these net, networks, and look to see whether or not the changes for sentences showed upregulation in naming. The prediction would be no, but maybe it does; I mean I don't know. So, um, it, this looks like a specific affect, but we won't know until we do all the work. Um…

(Someone makes an inaudible comment.)

Oh sorry. Thank you Loraine. (Laughs) Okay, good. So, um, the right hemisphere regions are recruited, um, there's correlations between offline and offline processing, um, and the last point is that, um, there are brain variables including perfusion, resting state, also white matter. Those are the 3 that we're mainly looking at, and will, they do now show us distinct patterns in people with brain damage and, and aphasia. And so we're hoping that that will be helpful for us in the future. And then the last thing I wanted to just highlight those 3 points neuroplasticity again, and sort of put them in the context of brain, that treating impaired processes, hances—enhances recovery of the neural network, networks associated with those processes, and, I wanted to just make the point that we haven't studied this in other domains, but I'm sure that they do differ. I mean Swathi gets different activation patterns than I get. Brenda gets different activation patterns than either of us get. So it depends on what you're treat, treating, um, drives neural processes. The second principle is that specific treatment will reflect, um, brain changes. And reflecting reorganization of those particular processes. Um, and finally, this whole idea of

complexity. You know, we reported in 2003 for the first time. Um, and people are just, haven't really picked up on it, some really have, and it hasn't really made it into mainstream speech and language pathology for people who treat people. Um, but what we, we keep seeing it; it's been shown across domains, and also it does suggest in terms of the neural mechanisms that we're driving a neural mechanism, and that that same, network can be used for, um, both simple and complex structures. Okay.

So that's all for today. I wanna thank the people in, currently in my lab, um, as well as the NIH for their funding. Um, and… also, um, thank all of my collaborators, um, over the years, uh, and PhD students and postdoctoral fellows that have been in my lab; I couldn't of done any of this work without all these people helping. So I wanna thank you for your attention. (Applause)