LANGUAGE MAPPING IN APHASIA
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SWATHI: So it is indeed my, my great pleasure to introduce our first speaker of the day. This is my honor to introduce Stephen Wilson. He's an Associate Professor in the Department of Hearing and Speech Sciences at Vanderbilt University Medical Center. He's a competent neuroscientist whose research focuses on the neural organization of language processing; how brain damage impacts language organization in people with aphasia, and mechanisms of functional plasticity that underlie recovery from aphasia. He has been carrying out neuro imaging studies of individuals with aphasia for 16 years, and has served as a PI of 3 NIDCD funded projects investigating the neural correlates of language processing and functional reorganization in post stroke aphasia, and primary progressive aphasia. Please join me in giving Stephen Wilson a really warm welcome to this meeting. Thank you. (Applause)

STEPHEN WILSON: Good morning. Thank you all for coming. Thank you Swathi; Margaret. Um… so disclosures. Essentially I'm a professor which means, if you believe what I say it helps me in many ways. Um… I'd like to start by acknowledging all the people that have worked on the studies that I'm gonna present today, especially 4 of them who've really taken the lead on this research. Dana Erikson who I think is in the audience. Melody Yen, a PhD student at Vanderbilt. Sarah Schneck, I think I saw her back there, PhD student in my lab. And Julian McCaney, who is a speech-language pathologist in my lab. So thank all of them and all the other people who worked with me on these projects.

So I wanna start by defining what I Mean by language mapping and why I called; I taught language mapping in Australia. So in, not in Australia, in aphasia. (Everyone laughs) But you know. (Laughs) Okay. I was brought water, but I wasn't brought coffee. (Some people laugh)

Um… okay, so the, the, what language mapping is, is it, language mapping is identifying brain areas that are involved in language processing. We do this using functional MRI. And most of; this is actually the main clinical application of functional MRI in the real world, and it's used in pre surgical context. So if somebody's gonna have a surgery for tumor or epilepsy, we use language mapping to find which parts of the brain are critical for language processing, so that we can avoid resecting them and causing an aphasia. So language mapping is a, you know, a widely used clinical application of FMRI. And the way, and the way that it's done, is to compare two conditions statistically; a condition that involves language processing, and a, and a condition that does not. So I'm gonna go into a little bit of detail on these basics, just so that we can all be on the same page for, for my talk and also for the other talks today.

So FMRI. I know that most of you know all of this, but please bear with me for just a, a minute or two. So the, the patient or participant lies in the scanner on their back. We can present them stimuli, and we can have them make responses while we scan their brain. And with FMRI, we don't actually measure neural activity directly; we measure its neural vascular correlates. So this is a hemoglobin molecule, and it is an oxygenated hemoglobin molecule, and that's what those red things are. Those are oxygen, um… molecules that are gonna be, um… delivered to the neural tissue to support neural activity. So when neural activity takes place, the, the normal, um… the, the, um… metabolic requirements of that tissue go up, and, and the, the neurovascular systems responds by increasing the flow of oxygenated hemoglobin, which essentially washes out deoxygenated hemoglobin. Now this is very useful. The, um, I guess it's useful 'cause it's the way our brain works, but it's also useful because we can measure this. And in fact, it was in 1982, that (sounds like Fillborn) reported that T2 star weighted MRI signal is directly proportional to the ratio between oxygenated and deoxygenated hemoglobin. It wasn't till 10 years later that this was actually used to do functional imaging. But back then, that, you know, we had the, the sort of biophysical principles in place, to, to measure this difference in concentration between oxygenated and deoxygenated hemoglobin. So what we do, um, and again, I know that most people know this, but I don't think everybody knows this, so that's why I'm talking about it before we get into the details. The way that we do functional MRI is, we take a series of scans, approximately every 2 seconds, these days even every 1 second. We take, because we're acquiring a brain image every second or two, it has to be low resolution and has to be done quickly. And then while we're requiring this series of images, we essentially control the cognitive state of the participant. And in the case of language mapping, we control their cognitive state by either making them process language or making them not process language. And we can then do a statistical comparison between the scans that are acquired under the condition of processing language, and the scans that are acquired under the condition of not processing language. And so in a part of the brain or a voxel, a three dimensional pixel that is involved in language, we should see high signal when the person's processing language, and low signal when it's not. We do a statistical comparison, and from that, we can make a map of language areas in the brain.

The first person to do this in a really systematic and thorough way was Jeff Binder and his team in Milwaukee in the '90s. And this is a seminal paper from their group, and this is a series of sagittal slices running form the left hemisphere, through the left hemisphere, and into the right hemisphere. And the contrast here that's being shown, so the, the language condition was, you hear a sequence of animal names and you have to press a button if the animal is found in the United States and used by humans. That's a language task. And the control task was you hear a series of tone sequences, and you have to press the button if exactly 2 of the tones are higher, rather than low. So that's a non-language task. And so, the, the contrast between brain activity under those two conditions is what makes the language map. And as you can see here, this is actually a, actually a very good language mapping task, and it's widely used in surgical context for that reason, because it's extremely left lateralizing. The only right hemisphere area that you see is the cerebellum, which is right lateralized for language. And you see frontal language areas, temporal language areas, and parietal language areas, all activated by this task. So that's a, a really great language task that can be used in people who don't have aphasia, for reasons that are probably obvious to most a you guys. But I'll get into it.

Okay. So why would we need to map language in aphasia? Well, it's to address the kind of questions that Swathi outlined in the introduction. If we're interested in studying recovery of language, after, after stroke or in any other kind of aphasia, we are potentially interested in functional reorganization, and so we wanna see how language is changing. So what, so we do know, as Swathi said, that language recovers, and it recovers variably, and it has a, a time course that is somewhat decelerating, with the earliest gains being most rapid. Um, I, I'll just put up a couple of slides from some of our recent papers and presentations. So this is just showing the first 15 days after stroke, and we see recovery taking place in that time very rapidly. This is the first 3 months after stroke in one patient, showing recovery in a range of different language domains. This has a, logarithmic scale actually, so even though it looks linear, it's kind of a decelerating time course. And, this is a poster by Mary Goodman who is here today, at, from Pagie Beeson's lab, showing that recovery persists many, many years after stroke, well into the chronic phase. So now we've got our time courses in years, and we're still seeing improvements, even years after a stroke.

So, language is unquestionably recovering. And, I, I'll give you a very salient example. This is a gentleman that we studied in my lab, um, Sarah studied, Sarah Schneck. Um, and as you can see has a very large frontal lesion extending into parietal, and taking out all the underlying white matter. And this is the kind of ri—lesion which you, you'll all understand causes Broca's Aphasia. And, in fact, this gentleman did have Broca's aphasia for many years, but now he's 8 ½ years after his stroke, and he described to us a, a slow gradual process of recovery, and this is a sample from his connected speech sample at our recent evaluation. "I'm very enthusiastically working on a novel. That's the second novel. I'm, really wanna have it done this year, in the, in the mid/late fall, so I, it's taking up lots a my time. I'm, uh, trying to, uh, I'm adjusting my schedule t, to be earlier in the da, day. Actually at times starting before the sun is up." That is the speech of somebody with that lesion.

So how is that possible? This is just kind of astonishing if you think about it, and really makes clear like that there must be some kind of functional reorganization going on. We just don't really understand what it is yet.

What we do understand is that there is an organization to the language network in the neurologically normal brain, and this is 3 different models. Our model, Hickok and Poeppel's model, and Cathy Price's model. And I'm, and there's as many models as there are researchers. But my point is not the details of the model, um, but the fact that we do have a stance that certain regions do certain things, and that there is a structure to all this, which implies that, you know, if it gets damaged, then something has to change. We also know that in principle, it is possible for language to reorganize dramatically. And this from Alissa Newport, and Peter Turkeltaub, who's one of my co-speaker's today, in kids, if there's a perinatal left hemisphere stroke, language will happily reorganize to the right hemisphere, and look very much like it would normally, except that it's a mirror image. So in principle, the, this sort of intricate organization of the language networks is capable of being laid out in different brain areas. But does, does that happen in post stroke aphasia? I think it's actually much less clear. So, um… my… grad student Sarah Schneck and I have been working on a systematic review of all of the studies of functional reorganization of language in post stroke aphasia, and we have found 72 of them up to 2017 that have at least 6 participants. And this is a bunch more that have less than 6 participants, but I'm not gonna say anything about those, 'cause my mom always told me that if you don't have anything nice to say, then don't say anything at all. (Some people laugh) We need, we need to have sample sizes, that, that's my point. So this is a, kind of a plot of the, the… the studies that have come out. The first one's in '95, and there's a lot, even 2017, and we're gonna add even more in 2018. Using different tasks to map language. And from this literature, um… we have identified 4 main themes as to what the mechanisms are of, of neuroplasticity in recoveries in post stroke aphasia. And the first one is by far the most strongly supported by evidence, and that is reactivation of core left hemisphere language regions. So this is… paper from Dorothee Saur and colleagues, very, very famous paper; I think it's the most highly cited paper in the field, showing that early after stroke, language regions were damaged and did not activate. Subacutely, there was some potential right hemisphere compensation. I don't wanna get into that; that's not really my point. My point is that in the chronic phase, language in aphasia went back to looking pretty much like it would in healthy controls. So those language areas in the left hemisphere that were temporarily dysfunctional as the result of a stroke, actually regained a lot of their function. And that is the most robust, replicated, and trustworthy finding from the field, as the only one that I truly believe.

Another mechanism, which I think happens sometimes, is recruitment of right hemisphere of homotopic regions. And this is my colleague, um, I guess, hey my colleague, my friend Peter Turkeltaub, um… (Several people laugh) I guess you—when do you become a colleague? If, if you're a, you know, we, we haven't written any papers together, but we, you know, talk science and…

(Inaudible comment)

Okay, we're colleagues. As of, as of like 10 minutes ago, my colleague Peter Turkeltaub, (Some people laugh) his very nice meta-analysis of, um, a subset of this literature. It has much tighter inclusion criteria than our study. So it it's, it's a, uh, 12 studies I think. And, and it does seem to suggest that language reorganizes to the right hemisphere in recoveries from aphasia, and some of Peter's own work suggests that too, and I'll let him make that case.

Another mechanism, my, my colleague Julius Fridriksson, um… has shown that new left hemisphere regions might be recruited outside of the typical language areas. And finally, more recently, there's been a focus on the recruitment of the main general networks like attentional networks and frontal parietal control networks for instance. These are often bilateral. And I'll demonstrate that with a study from Andrew DeMarco who, um, I worked with, along with his mentor Pagie Beeson, showing that as a function of treated recovery this gentleman recruited bilateral parietal regions to support his treated recovery.

So those are the, the mechanisms. But as I said, only the first one is really replicated strongly, and the other ones are very sporadic, and, the, they differ from study to study, and we really don't know what the, you know, how often they happen, when they happen, why they only happen in some patients, under what circumstances, you know, to, how important are they really; we just don't know. And the reasons why we don't know, I think, um, I would summarize in this next slide.

There's major challenges to understanding neuroplasticity in post stroke aphasia. First, how do you study language processing when it is impaired? So you guys heard me describe Jeff Binder's excellent task, which is really good at identifying language regions in people who don't have aphasia. Imagine tryin' to explain that task in apha—person with aphasia, let alone having to perform it. How do you study something when the function that you wanna study is damaged? How do you get a person to do language processing when that is their very problem that you're interested in? Secondly, even if you can, we have compounds of difficulty, success, failure. So you try and compare people with aphasia to neurologically normal people, and you know, one group is doing the task and the other group is failing the task. That's gonna have very different neural correlates. What about if the people recover over time? Now you're comparing, if you wanna like do it within subject's design, you're looking at somebody that was unable to do something, and now they're able to do it; that's gonna have different, that's gonna have neural correlates, that may not be language per say. It may just be like success or failure, you know, error monitoring, frustration. Thirdly, um, the validity. The psychometric properties of language mapping paradigms are questionable. The validity, which means can they identify language regions and test, retest for liability? I.e., do they give the same answer if you ask the same question twice, have not really been quantified systematically for most, um, most of the time. Fourth, and it's hard to do group studies. And we need, in FMRI we usually need group studies to get enough power. That that's hard in aphasia, because everybody's different, every lesion is different, every patient is different. We have possible hemodynamic abnormalities that Cindy Thompson has stressed, and, uh, uh, Dorothee Saur's group Altamura, et al. And that makes it tricky, 'cause we're studying, as I mentioned, we're using a neurovascular correlate of neural activity, um, so that's kind of, you know, using that in a disease where neurovascular coupling is potentially altered; that's kind of an issue. (Laugh) And finally there are practical challenges to this kind of research. It's recruitment, you know, very challenging, and other people have other medical problems. Um, they, many of them have had issues with MRI compatibility, especially these days with all the implants and all the stents and everything. Mobility is a problem, getting people into the scanner.

So I'm not gonna try and solve all the problems of the world today, only half of them. And, I'm go—gonna specifically address the first 3 of these issues which are essentially to do with the language mapping process in aphasia, or how do we go about identifying language areas in people with aphasia, so that we can understand how they may, or may not be reorganizing.

And to do that, I wanna think about what it, what a language mapping paradigm needs to, needs to be. And I think there are 3 things that it really needs to be. It needs to be feasible, i.e., people with aphasia need to be able to do it. It needs to be reliable, which means that if you test somebody that's not changing, like let's say somebody that's in the chronic phase, and you test them a couple a weeks apart, it should give the same result. And we're gonna quantify that with the Dice Coefficient which I'm gonna explain, 'cause un, unless you do psychometric FMRI research, you probably haven't heard of the Dice Coefficient before. But it's a measure of the extent which two areas or volumes overlap;. So if there's no overlap at all, that would be a Dice Coefficient of zero. If it's a perfect overlap, a Dice Coefficient of one. 50% overlap would be Dice Coefficient of 0.5. So again, if we have 2 activation maps, on different occasions, we can quantify how similar they are to one another. And then thirdly, validity. So does it actually identify language regions? And, we can, as I said, as many—there's as many of where language regions are as there are researchers. But, one thing that we do know, is that language regions are in the left hemisphere in most people. And, I know that that, according to some reviewers, (Laugh) that's a controversial opinion (Laughs) I've been told. But, you know, you don't get aphasia from right hemisphere strokes. So that, I'm just gonna leave it at that. Left hemisphere regions usually. Left fem—left hemisphere regions, I, I was like heads shake, and heads nod. Su you know, in 90% of people, 90, 90, 95% of people with aphasia have left hemisphere stroke. And so there's a very big difference between the left hemisphere and right hemisphere language.

So we want our language mapping paradigms to identify healthy hemisphere areas. At least that's my contention.

Okay, so let's talk about some of the language mapping paradigms that are widely used. And whether they meet this criteria. So narrative comprehension is a great paradigm that I've used a lot myself and it's been used in many excellent studies. It involves comparing, listening to narratives, to listening to backwards narrative, or, or some kind of acoustic modification that renders it unintelligible. And… it's really feasible, because everybody can listen to stories, right, and you can like make the stories be simple, and like, you know people with aphasia can certainly lie in the scanner and listen to stories. And so it has that, it meets that basic bar of being… feasible.

But, is it reliable and is it valid? We invest—started investigating this a couple of years ago, because, I, I was planning to use this paradigm. And so what we did is we got 4 older adults without aphasia, um, and studied them a couple a weeks apart. And so essentially they're, they, they're unchanging, right. And we looked at this contrastive narrative as it's backwards. So let's just look at Participant One, for example. So Time 1 looks, looks pretty good actually. We, we see a left frontal language area, and a left temporal language area, and we don't see much in the right hemi sphere, so that's all good. Time 2, it's mysteriously disappeared. Time 3, it's back, and this time with some help from the right anterior temporal lobe. And Time 4, the, that's sticking around still, but now the left frontal lobe's disappeared. Okay, this is an example of what it looks like to be lacking in test, retest, reproducibility. So, it's just not very reliable. And like if you, if you're interested in studying reorganization over time, then of course, if you're looking at somebody who's static, it ought to be static, and if it's not static, then how on, how on earth are we gonna study change over time if we can't, you know, even document stability. So it's somewhat limited in reliability, and it's also sort of limited in validity, like in the sense that the right temporal lobe is frequently active, like in this stroke for instance.; Um, and I don't wanna say that like the right hemisphere plays a neural role in language, um, it certainly does, absolutely, but we do want a paradigm that focuses on the left, because if we're gonna see reorganization, we need to know what's happening to those left regions that are really critical, rather than what's happening to those right lesions that are playing a role, but make, are not in the, in and of themselves crucial.

So, it's only moderately reliable and only moderately valid. Picture naming's another widely used paradigm, such as in this excellent study. Smile. (A few people react.) But even though it, even though it can be put to good use, and it is put to good use in that study that I put up there, if you read all the details. It's about comparing correct and incorrect naming trials. It's very cool. Um, but as a language mapping paradigm, it has limitations. So first it's also limited in reliability. You'll see differences between these maps on the 4 occasions. But maybe even more problematically, it's, it's very limited in, in validity. The picture naming is very bilateral in most people. Actually most are normal in people with aphasia, and I think the reason for that makes sense. It's be; the reason it's so bilateral is because it's so easy. And because it's so easy, instead of identifying language areas, it tends to just get sensory motor areas that are involved in doing pictures, processing the objects, speech production. Um, in people with aphasia, it's like somewhat more lateralized because picture naming is more challenging and more linguistically challenging for them, but still it's not a highly lateralizing paradigm. So I'd say it's not a, it's not a great paradigm to use, studying language reorganization.

What about semantic decision, the, the wonderful Binder task? Well, it's very reliable and valid, and we know this because it's bein' investigated extensively in the pre-surgical literature. And I won't go into the details, but it, is very reputable. The problem is it can't be done by people with aphasia. And so Szaflarski et al use this task, and this is left MCA stroke not recovered, so in other words aphasia post MCA stroke. Semantic decision accuracy, 47.6. That's a total tone of (inaudible words) tasks. So they're, they're below chance. They're actually also below chance on the tone decision task. So it's not surprising at the, in instructions, in, are extremely complicated. So, you know it's very difficult. Even though this, this actually ends up being a really great line of work from the Szaflarski Lab using this task, but I, I think we have to take it with a grain of salt, because I think it's hard to, to read too much into results when patients have been failing at the task systematically. So it's not feasible, as is, people with aphasia, even though it's very reliable and valid. So what are we gonna do? I, I, we thought that semantic ma—semantic decision was gonna provide the best basis to move forward with. Um, but we needed to make it doable by people with aphasia. And so what we wanted to do was make it adaptive. So we wanted to have a very simple task, um, where the, the instructions would be easy and would not change, and would match across the two conditions, and then we would be able to manipulate difficulty using the stimuli rather than the task, and that way we can make it different levels for different people. So the task is really simple. The task is you see two items and you press a button if they match. That's the only thing we need to communicate to the patient. And in my experience, we can, we can communicate that to almost everybody that has aphasia.

So, what are the two things; what does it mean to match? In the, in the language condition it's two words, and a match is any kind of semantic relationship. So calendar date, that's semantically related. If they go together, you press the button, if they don't go together, you do nothing. It's actually a lot easier to do a go, no go, than to, to choose between 2 buttons, people with aphasia, for reasons that I'm sure are to do with frontal lobe functions.

And in the control condition, if you see two symbol strings, and you press the button if they're identical. So, you don't have to task switch, because the task is always the same. Like you're always looking for a match and pressing a button to a match. The only thing that changes is the nature of the match, which that's kind of like, but, it just comes. Like you know you're not, there's not, there's nothing else you can do with those stimuli, right? It's not like you're confused about like what to do with them. Um… and then we can also manipulate the level of difficulty. So calendar date is like moderately difficult, but we can do cat/dog if somebody has severe aphasia, or we can do, um… I don't know, soliloquy eloquent, if somebody's doing really well. And so what we do is we do an adaptive staircase procedure. And this is showing the trials, as, throughout the experiments. Every time you get 2 right, you go to a harder level. And then if you make a mistake, you drop back. And so that allows us to tie trade it exactly to each individual's, um, level of performance, where they're getting about 80% correct ideally.

We do the same thing with the perceptual matching task, 'cause that also gets easier and harder, depending on how the person does. And… and ba—and, and, here's how we manipulate difficulty. So I, I kinda told you about the, the language one. Like we basically, we manipulate frequency, concreteness, length, age of acquisition, and the closeness of the semantic relationship, and the speed of presentation. So we manipulate 6 different variables simultaneously to make it go from being a very easy task to being a very hard task, but it's always the same task. In the perceptual condition, we manipulate the similarity of the mismatched strings, and we also manipulate presentation rate. So both, basically both of these tasks end up being performed with about 80% accuracy by most people.

This is our validation study a this paradigm, which was mostly carried out by Dana. There she is. Um, it was really just, uh, a tour de force. It, this, we did this study like while the University of Arizona MRI scanner was in the process of, like, while, while a new hospital was being built around the scanner. So like the main challenge for this study was to like, figure out each day what the route through the construction site would be, and communicate that to the individuals with aphasia, and their caregivers. (Laugh) After, apart from that, everything else was very straightforward. What we did is we scanned 16 people with aphasia twice each, um, and 14 neurologically normal people, and we wanted to look at, can, can people do the task, how reliable is it, how valid is it in the sense of, it, doe sit share left hemisphere regions in people who do not have brain damage, and is it sensitive to frontal and temporal language; can we reveal frontal and temporal language areas in people who don't have brain damage. So, we, on each occasion we assessed language function with our quick aphasia battery, which I am not gonna talk about today, but you can read it in Plus One if you like, it's open access and freely available to anybody that wants to use it, and it's highly correlated with the web, although it takes only 15 minutes to administer, that's the web correlation for the overall score. And then we also had like high correlations in the subdomains. So we used that to quantify our individuals with aphasia. And what we find is that we had a very diverse sample. So they, they were recruited from a community aphasia group. We had, um, more or less a third Broca's, a third conduction and a third anomic, with some, some sort of caveat, I mean you know these labels are just labels and there's only so far that they'll take you. But, this shows their, the, each individual's performance in different language domains and, and you can see that they had different profiles of strengths and weaknesses, um, into wide, and a wide range of severity.

Okay, so our first question; feasibility Um, we found that all patients were able to learn and perform in the cha—the task above chance. So this is the, you know, ideally they should be at about 80%, and the, for most of them we thought that was the case. We had one person that was really, uh, he really struggled, but he was just above chance. Um, and one who was essentially normal. I mean her WAB IQ was above 98, so she wasn't technically you know, in that sense, she was, didn't have aphasia, but she did. Um… but you know, she, that's a ceiling effect. So la—later on, we ac—actually, and in now controlled, she actually got some ceiling effects too, like people were doing just too well. So in the end, we ended up later modifying the stimuli so that we got most of the, this is in healthy controls, we got most of them off the ceiling. So basically we got people, everybody right around 80%, except people that, um, uh, very, um, had very severe aphasia.

Okay, second question; so, so it's feasible. Um, now as to, this is what the activation pattern looks like in the neurologically normal controls. It's, see it's like you get a nice left frontal activation, you get a nice left temporal, you get right cerebellum; you don't get anything else much in the right. And this is what it looks like in the people with aphasia. And this is kind of the most important two slides of my presentation probably. Um, I'm gonna, I'm gonna do all, I'm gonna put all 16 people up. So I've got 8 on this slide, I'll do the other 8 on the next slide. And for each patient, I'm showing time one and time two. So remember, these are chronic aphasia people. So, then nothing is changing, right. We're doing this like a, a week or two apart. So, um, really there shouldn't be any change. Um, and what you see is, uh, and then the, the lesion is shown here in, in blue. Hopefully you can see that. Um… so you can see, um, that we get really good test, retest reliability. Like all the patterns get, the patterns get duplicated, like quite precisely from one time point to the next. And you'll see that, just glancing at this, you can certainly see that these are abnormal language maps, right. This is a person that has some damage. Can see the damage there. And you see they're completely lacking in a posterior temporal language activation. They do have an, a small anterior temporal one. So, we're able to characterize an individual aberrant language network in a way that's reproducible.

I don't know if anybody notices anything about the laterality of all these activation maps. Not that we're gonna say anything about that.

Here's some more. This is, this one is difference, right. This is; so I guess I will say something about it. (Some people laugh) Uh, only one of our 16 individuals has clear right hemisphere language. And we don't know how he started out obviously. Um, but he did become aphasic after a left hemisphere stroke. So, he probably started out left lateralized. He was right handed, yeah.

Okay, so you can see, um, yeah, so the two main takeaways from this, that it's very reproducible, and that it's mostly left lateralized, but definitely not normal. Um… in contrast, the we looked at 2 other para—we looked at those two other paradigms, to compare. So narrative comprehension and picture naming. And see in normals, this is what I took, said about narrative comprehension. We see that the group level very clearly is quite bilateral, and, and it's not very strongly, it's not very sensitive to the frontal region. It's very good for the temporal. And our test retest is not as good. I'll, I'll kind of show you some summary data on that later, rather than going through the gruesome details. Picture naming is very bilateral in, in normal.

Okay, so… when we look at test retest for reliability in terms of that dice coefficient, you can see that it's more, that this adaptive semantic paradigm is more reliable than the other two paradigms, and that's highly statistically significant. And, it, they're told that finding is impervious to all the things that you can tweak to make your analyses come out the way you want them to. And anybody in the room that does neural imaging that, will know what I mean. I'm talking about thresholding, I'm talking about closer sizes, regions of interest. We try it many different ways. Red means good, left, right, less red means bad. Um, it's the opposite in politics. Um… and… (Several people laugh) as you can see the adaptive semantic paradigm … Oh actually I, I read in the ASHA guidelines that I wasn't s'posed to say things like that. (Several people laugh. It's just an opinion. (Laugh) Um… you can see that the adaptive semantic paradigm outperforms the others in, in almost all circumstance—in, in all circumstances actually. Um… and… in terms of validity, we see that it, it yields left lateralized activation in most neurologically normal people. Weirdly, we had one person in our sample of 14 who has clear right hemisphere language. And I, and I was just certain that this person was gonna be some kind of freak of nature. Um, first of all, she must be left handed; no. She must have left handed family members; nope. Now I, I'm like okay, we may, maybe; did we make a mistake preprocessing? No. Um, I'm gonna watch her video, she's gonna be like some weirdo who should have been excluded. Noe. (Several people laugh) Perfectly normal person just goin' around like anybody else with language in her right hemisphere. Really makes it hard to write a paper when one of your normals has the, what's really like found in like less than 1% of the population. But anyway. So, here, here she is, messin' up my graph. (Everyone laughs) Um… but, if we, if you interpret laterality a s… deviants, you know, kind of going in either way, you can see it's, it's very lateralizing. And interestingly, even though, you know, the narrative paradigm does an okay job at, at laterality, um, and shows that this person is indeed the most right lateralized. Although notice how like whereas the semantic paradigm shows the other 13 healthy controls clearly left lateralized, narrative actually shows 4 out of 14 with more right than left. And that, that's just, those, those are, honestly, that's just not right. And, you know this is the picture, the picture naming, very, very bilateral. And, and, um, doesn't show anything special about the lady who is special. And in people with aphasia, we, you know, we don't really have any (inaudible word) expectations about what laterality should look like. But, like I said, and actually found that everybody is pretty much left lateralized apart from this one. Um… and narrative does not show that as clearly by any means. Picture naming kind of does, surprisingly. Though not clearly, but at least it shows it. And again, this doesn't matter how you, how you tweak your analyses. We can detect frontal areas, with adaptive semantic paradigm, but not with the other two. We can detect temporal areas with semantic or with narrative, but not with picture naming. So… we get to color it all green. Um, so it's, I think it's a gr—it's a viable paradigm for looking at language reorganization after stroke.

Okay, so why does it work? Well, I think it works because, um, both of the tasks are adaptive, so you kind of put people into this, you, you control very tightly the processing that's going on. That's, that's the really critical thing. Like in all of these other paradigms, you don't really have tight control over what's happening. Like in narrative, people can do what they want with those backwards speech. Some people get really interested in it; some people ignore it, and then you get, and, and the same person might do a different thing on two different days. Whereas, when you're doing this task, I can tell you, it's really hard. Like it, you're guaranteed to, to make errors, because it's gonna adapt to a point where you're gonna make errors. So you're forced to be like you know, really pushing it. You're pushing your language system, or you're pushing your sort of perceptual system, and you don't have time to be doing any mind wandering or anything else other than what we want you to do. So it's highly constrained. Single button press helps. We have a sort of structured training that helps, and it's, and it's and it's an active task, not just a passive task. It still has many limitations, things that I'd like to, um, address in the future. Um, so it, you know, and it identifies these core la—frontal and temporal regions, but it certainly doesn't identify every language region. Like it doesn't get at speech production regions, and like I, and it doesn't really get at the right hemisphere, which even though I scoff at sometimes, I don't deny is actually important for language at some level. Not all patients can perform the task, although most can. Even though we try to control perform and match it exactly, we still get some ceiling effects in some of the healthy controls. And even though we have the best test, retest reproducibility of the paradigms that we looked at, it's still not perfect. And you know, you always wanna strive to be, to be better.

So kinda like in terms of what, addressing one of those limitations, the one that we don't map all language areas, but we're now working a phonological version of this task, where instead of the, the judgment being meaning related, it's a rhyme judgement on pseudo words. So you read two pseudo words like hyperbol— (sounds like hypermilical and cyperprilical), stuff like that, and you have to press the button if they rhyme. And this paper was writ—is first authored by Melody Yen, and middle author Andrew DeMarco from, who's, uh, in Peter's lab now. And what we found, and this is just in neurologically normal people, is that we can reliably activate the left super marginal gyrus with this paradigm. You can see they're circled. This is the rhy—the rhyming paradigm. We also did a syllable counting one, but I'm not gonna talk more about that. Like, so we don't get that super marginal with our semantic paradigm, but we do with the rhyming paradigm. And you can sorta see there how rhyme activates that in almost every subject, whereas semantic essentially never does.

So this is kind of giving us a way of starting to look at not just language areas as a general kind of unitary monolithic thing, but like different language areas that are involved in different aspects of language. So, you know, going forward, it, what we do in my lab now is we run both tasks on, on all the people with aphasia that we work with Um, and in that way we hope to… um… you know kind of identify differentiated language regions and how they're reorganizing.

Okay. So, in the last part a my talk, which I guess we'll go for another 10 minutes or so, 5, 10 minutes. 'Kay. Let's, let's kinda put this into practice. And I'll show you some interim data. So this is the gentleman who we talked about before who said, I'm, you know, who's got really excellent language despite this… you know complete destruction of Broca's area, and all the underlying white matter and anterior parietal. This is his, these are his language areas. So you can see, he's got, uh, he has a posterior temporal language area, Wernicke's area. It's definitely ventral to where it would normally be. And if you look at a lot a these like I do, I can tell you it's, I don't have statistics to back that up, but having looked at hundreds of these, say it's like definitely ventral to normal. There's this. Is, is that important that there's this? Like you know like I said, supramarginal is not used in our task for, um, neurologically normal people. But it is by him; angular too. Angular gyrus. And also of course, I'm sure nobody failed to notice that the right hemisphere region, hemotopic to Wernicke's area, is activated. And look, this is not just like excessively ventral, right, this is actually in the sphere temporal focus where it would normally be over here. So we; so the, so I guess my… my point is like we don't really know from this single patient like which of these atypical activations are responsible for his exceptional recovery. Is it all of them? The, I mean do you need all of that, or is it, or is one more important than another? Those are the kind of questions that we're really gonna only be able to answer when we have a very large number of patients. And then we're gonna be able to do some really cool analyses where can actually look at the relationship between recruiting different patterns of reorganization and outcomes. And it's, and in, in particular those analyses need to take into account individual patterns of structural damage, because we have to think about outcomes in relation to what would have been expected based on structural damage. And I know that some people are working on similar lines like Peter. Um … but, you know it kind of gives us like a, a starting point to start to think about like okay, we can look at a person who has a great recovery and say okay, these are the, uh, this is the way they've reorganized their language, and, ultimately we, we'll also look at people that have less good recovery and, and we'll start to understand the differences.

So first steps towards that. Which, what, which brain regions are actually involved in language processing in people with aphasia? Well, like I said, like we saw already, the first thing I can say is it's mostly the left hemisphere, um… but, we're looking at that, I mean that's just kind of anecdotal based on that, you know case series that I talked about before. Now let's look at a group study. And so this is, um… like I said, we're doing a longitudinal study of… recovery after stroke, but this is just a cross sectional analysis. This is an interim analysis. It's not really like a final dataset. It's the first 41 patients that we've recruited. And they, and they could be at many different times per stroke, this dataset. So it goes everywhere from 18 days up to 11 years. And it's people varying widely in severity. So from this is out of 10, our scale, so like if you multiply by 10 if you wanna think in terms of WAB IQ, from 9 to 97. You might say 97's not aphasic, but you know, it can be. And this study is really spearheaded by Sarah Schneck and Jillian Lucanie, SLP's who, um, recruit these pe—we recruit these patients at the bedside, we test them 2 to 3 days after stroke, and then we try to follow them from a year. And we drive, Sarah and Jillian drive all over middle Tennessee and southern Kentucky, and test people in their homes, and, we're getting a really cool dataset of, you know, how people recover after stroke and how that relates to neural correlates. We scan them if we can. We, we just do behavior, behavioral data if we can't.

So just our interim findings. So which brain regions of people with aphasia use to process language? Well, it's these ones. Do they look familiar? Hopefully they do. That's the norm, that looks very normal. If you told this was a map of normals, I'd be like, I'd be like okay. And in fact, here, here's the normals. This is 31 normals. So with extra power we do see a little bit in the right in normals, but like don't get you know a bit of right hemisphere stuff, but like let's not get too excited about that. Um… by and large you see those are very similar. And if we compare aphasia to normal, um… statistically, you see basically these are the areas that are less active in aphasia, and it, it makes total sense, of course. It's like left frontal, left temporal. I mean, yeah, I mean 'cause these regions are damaged in a lot a people. And also, right cerebellum, which is not damaged in anyone, right. So this is like clear diaschisis. Like when the, when the left language network is damaged by stroke, you, you see a functional, um, deficit in, in the right cerebellum. So, so this is, I mean the main, the; this is all like, this is like essentially replication of what I said is the finding that I trust in the literature, which is the left hemisphere, the language region's a, are good for processing language and damage in the mo—is na—is bad.

This is I think our last, last analysis in the pa—in the presentation. So now this is asking the question, are there any brain regions where activity is predictive of better language function. And we found 4. And again, I don't wanna like present, present this as like the end of the story, mainly because we haven't really taken structural damage into account. And what we really wanna do is a more sophisticated analysis that does take that into account. But I think it's still like a little bit interesting just to look at it in this kinda simple way. So there are 4 regions we found where activity was predicted as better language function. And I'll give you an example of what that looks like here in the left superior temporal sulcus. So here, this is showing on the, the Y axis is people's language function as measured by the quick aphasia battery. And on the X axis is the amount of signal change in this region. Like the, the extent to which this region is recruited for language processing. As you can see, the healthy controls here in gray, they all of course have know—you know, ceiling language function. And essentially every normal control uses this region to process language.. It makes sense that the most important language region of the brain. Um, there, as you see in the patients, we have a very robust correlation. So people that have more severe aphasia tend not to, in, uh, recruit this area. Now this, this is kind of trivial, because in many of them this area is destroyed. So that's actually not that exciting. But still kinda cool. But what's more interesting is these other areas in the right hemisphere, because of course these are never destroyed, right, these are all left hemisphere stroke patients. And so in the right hemisphere we see in healthy controls, there's variability. Like most people don't really recruit right STS very much, for language processing. They like have it like for just above zero. Some do, and some, you know kinda have below zero. So there's like a variability in the healthy population. And then in aphasia, you see that there's actually a correlation between recruitment of right posterior STS and outcome. So there's not like they're recruiting right STS above and beyond what the control group were. Like it's not like they've, you know gone beyond. It's like they've got the same distribution, but whereas in the healthy controls it doesn't matter whether you do it or not. In people with aphasia, it seems that it does matter. So the people that didn't have much right involvement, perhaps, perhaps this is all pre-molded. And the people that didn't, weren't using their right posterior STS, um, have worse aphasia outcomes than people that were. We don't know that for sure of course, 'cause we don't know how things looked before the stroke. But that's kinda why we're doing the longitudinal study. And this is just cross sectional here.

Superior temporal sulcus. I'm sorry. Yeah. Like, um, superior temporal sulcus is… really where Wernicke's area is. Right. Wernicke thought that it was in the superior temporal gyrus, which is really pretty close, considering the material that he had to work with. But in language mapping we see again and again and again and again, that the superior temporal sulcus is where the critical language regions are.

Okay, so… in conclusion, I've tried to explain why it's so difficult to map language regions in aphasia. And the real core of it is that we're tryin' to map a function that is impaired, and it's hard to get people to do something that they can't do when you wanna study that thing. I've shown how we designed and implemented adaptive language mapping paradigms, with semantic and phonological, and demonstrated their feasibility, reliability, and validity. And, and gave like a, just a sort of initial look at some of the results we're getting by using these paradigms to look at functional reorganization in recovery from post stroke aphasia. If you'd like to learn more about our work, or use any of our tools, please take a look at our website, aphasialab.org. Um, we have got the quick aphasia battery up there, we've got the tasks, uh, adaptive language mapping, all the stim, you know stimuli and scripts and everything, documentation and everything you need to implement that if you wanted to. Um, and all the papers that describe this. The main paper that I talked about is published in Human Brain Mapping earlier this year. And finally, just like to again, thank all the people that, that did these studies and NIDCD for funding our work, and thank you all very much. (Applause)

MARGARET: We have time for one or two questions.

Q: Inaudible.

MARGARET: Could you wait until we get a mic?

Q: Morning. I know there are a lot of connectivity studies on the human brain. Would you say that the… the paradigm for studying connectivity should be adapted to the language and to the language tasks that you have just mentioned? Or is, or is there a paradigm where we would be able to co—collect the information for different aspects of language? Because now it worries me that maybe, uh, naming versus construction of, of words and, and syntax, it would have different results. Is there a, a paradigm of testing that you would recommend that would cover many areas of connectivity studies?

STEPHEN WILSON: So are, are you thinking about wanting to identify seed regions for doing connectivity analyses? I think that these tasks could be used for doing that. And it's possible to look at connectivity with these tasks. That, I guess I didn't talk too much about the details of the, the, you know, the FMRI implementation, but this is a bl—it's like a 20 second block design. So you've got plenty of data to, to do connectivity if you wanted to. You, you know you could use, you could do connectivity analyses based on, on these tasks if you wanted to. If I can do only one task I'd do the semantic task, is the most robust and reliable.

MARGARET: 'Kay, is there a question from any of the research mentoring pair? Quick on, from anybody? Alright.

STEPHEN WILSON: Natalie.

MARGARET: That'll be.

NATALIE: Right thank you. So I was wondering in terms of the, the adaptive paradigm. Is that something that… for FMRI in general that we should be maybe thinking about using adaptive paradigms kind of across the board and, and what that gives us? And does it give us more… robust activation versus regular block designs that aren't adaptive?

STEPHEN WILSON: I think it probably, I think there are many cases when it would be a good idea to do things adaptive. Um… whenever like, you know, and I think ceiling performance in FMRI is always gonna like limit your signal power basically. I think it's, as soon as people are finding something easy, you're not gonna be getting as much out of the brain as you, as you wanna see. So I think there's like, yeah, there's very many contexts where making things adaptive could be helpful. And we kind of, we're kind of doing another study right now, and I, and I see Ian Quillan in the back of the audience there; he's leading this study in my lab where we're looking at the effect of difficulty just in, in healthy controls on, on you know like what's it like. What are the, what's the brain difference between doing a difficult language task, and easy language task, difficult central task, easy central task. So we're gonna try and get a better idea of like what is really make, what's, what it means to manipulate difficulty in that way. But in general, the answer's yes.

MARGARET: Well thank you Peter. Uh, and . . .

STEPHEN WILSON: Thank you very much.

MARGARET: thank you so such—or sorry, thank you Stephen. (Applause) And remember that Stephen will be part of the panel this afternoon, so if you have a question, write it down, so you remember it, and we'll return to those opportunities.