BRAIN-BASED UNDERSTANDING OF INDIVIDUAL LANGUAGE DIFFERENCE AFTER STROKE
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HELEN: As my next speaker walks up, it's my pleasure to introduce Dr. Peter Turkeltaub, and he's gonna talk about Brain-Based Understanding of Individual Language Differences after a Stroke. Dr. Turkeltaub is an Associate Professor of Neurology and Rehabilitation Medicine at Georgetown University Medical Center, and the Director of the Aphasia Center at MedStar National Rehab Hospital. His research addresses the brain bases of language, resilience, and recovery after a stroke, and neurological approaches to aphasia treatment. Please welcome me in, uh, please join me; I'm gonna get this right eventually when I introduce myself. (Laughs) Please join me in welcoming Dr. Peter Turkeltaub for the presentation today. (Applause:

PETER TURKELTAUB: Alright. Well, thank you for being here early in the morning. Thanks to Swathi and for ASHA for having me. Thanks to my brand new colleague Stephen for (Some people laugh) giving me a nice lead in. You'll see I think a lot of overlap in some of the ideas, and some areas where we, where we differ a little bit. I'll say, I think the first interesting difference between Stephen's work and mine is that I think we both saw the same problem within the literature, that there's a lack of reliability and this, these complication of using FMRI to study aphasia. And it might say something about our personalities that Stephen's approach to this problem was to solve these problems, and my approach to the problem was just to avoid them, (Several people laugh) by, by focusing on, non FMRI measures. So anyway. So, um, so thanks again. I'm gonna talk about this brain basis of individual with language differences after stroke.

This is sort of an odd talk. So I'm not actually going to tell you what I think are the brain bases of individual language differences after stroke, because I think like Stephen said, we don't really know right now. And so I'd rather not give you take home points, that are gonna change in a few years. So instead, what I'm gonna talk about is sort of my framework for how I go about understanding this, or how I think we as a community should be thinking about this, this problem. Here are my disclosures. And I'm gonna put my take up, take home points first, because I've crammed a lot into this talk, and I'm not 100% sure I'm gonna get through it all. So… the first point is that I think it's important to understand the brain basis of, of language outcomes after stroke. And I think there are 2 main components that we need to think about as Stephen alluded to. The first is how attributes of the stroke itself relate to outcomes. And the second is how the spared parts of the brain contribute. And they can contribute in 2 main ways. So resilience to the stroke, and then to recovery after the stroke.

And I'm gonna talk about different ways that the brain might change after a stroke, and I, I categorize these into 2 main categories; ones that are driven by intrinsic biology and ones that are driven by the environment, behavior mostly. And I think that we can get a better mechanistic understanding of how brains change after stroke, and how these changes relate to outcome, by looking for patterns in our in our findings that suggest specific types of change after stroke. So this has to do with things like the timing and the location of the, uh, of the changes.

So I wanna start with just a couple of very broad introductory slides to orient this. So I use the, the term "individual differences" maybe slightly differently from other people. So I wanted to clarify what I mean here. So the main point is that language and cognitive outcomes from stroke vary between individuals. We, we all know that. Every individual is different after their stroke. And the question here is why do people end up the way they do after stroke? Now some people when they refer to individual differences, are really talking about the individuals. And when I talk about individual differences, what I'm looking for are common features across a population that predict on an individual basis who's going to recover well or, or not. And when I talk about outcomes, I'm using this word to mean abilities in the chronic period after stroke. And it could be at any point. It's whenever we're seeing them that's their outcome, as we're, as, as we're talking about it, and it could be any ability that we're, that we're looking at.

Why are we interested in the brain? Well, behavior derives from the bran. So the brain is the organ of thought and cognition, and no matter what the cause of the change in the brain, the brain is what drives behavior. So I think if we're gonna understand why people end up the way they do after stroke, we're gonna understand this by looking at their, their brain. So the brain must explain these individual differences. We can't measure every aspect of the brain, so I don't expect that we'll do a perfect job of understanding why each person is unique after their stroke, but we can now measure a lot of different things about the brain. And so I think this can take us a long, a long way. And so our goal is to find features of brains that explain why people have the outcomes that they do.

And why is this important? Well from a clinical perspective, this will help us predict outcomes maybe early on after stroke, or predict response to treatment that I think we'll hear about this afternoon. It'll, it may help us develop new treatment. So if we look at people and we see features that are common to those who do well after their stroke, maybe we can take the people whose brains look like they're not gonna do well and turn them into the people who will do well. And from a basic science perspective, by understanding these problems, we can go a long way to understanding the brain organization for language and cognition, and the brain's capacity for plasticity at different points in life.

Alright, so here's my second disclosure slide, which is that I'm not a very well organized person. So Stephen pointed this out to me at a recent meeting, and my students chide me for this whenever I accidentally show my Gmail, on, on a, on a screen. This is the total of unread messages in my inbox as of Thursday. I think it's probably about 200 higher now than, than it was. And this is my desk at home. As I was working on this talk also on Thursday, that pile of papers I think, uh, I think this is like W2's and stuff from last year when I was doing my taxes. (Several people laugh) I just want, I wanna point out a couple of other things that I think are amusing on this desk. There's 2 computer mouses, uh, here, (some people laugh) And, the reason that happened is because one runs out of batteries, and then, rather than like going to get another set a batteries (Laugh) I just find another computer mouse. But now it's been like that for 6 months, and it's really confusing, because, only one of them actually batteries in them. (Laughs) The last thing is this red pen that's precariously perched on top of this stapler. I don't know what that's doing there. (Some people laugh) And there's, there's one more thing about my organization which is that, uh… 6 months ago I accidentally bought this shirt that requires cufflinks, and I don't own cufflinks. (Several people laugh) But I persist in wearing it anyway because I just keep forgetting. (Laughs) So okay.

So anyway, so… so I am not an organized person. But when I approach a problem like understanding individual differences after stroke I, I find it very helpful then to keep my… my ideas organized. So I've developed this taxonomy of how I think about the brain basis of, of stroke outcome. And, and, what I'm gonna do in this talk is sort of take you through this, uh, this and explain what I mean by each thing. Maybe give some examples of, of things that I think fit into each category. This is not perfect, so just like you know when we try to categorize people with aphasia into syndromes that has a lot of problems as, as we all know. This is the same way. Whenever you try to categorize things binarily like this, you're gonna have some things that don't fit in, some things that are a little squeegee in, in one category or another. But I still think it's useful as a way to organize our thinking. And to,. And to interrogate our ideas to see where we think they fit into this sort of scheme.

Alright, so I'm gonna start by talking about what the stroke itself contributes to outcomes from stroke. And the first thing I wanna say here is a point that Stephen made, using some of the same figures that Stephen used to make it, which is that language is not one thing. We've known this for a long time, that there are multiple different brain regions, and multiple processes that are involved in language, that we require a large scale brain network in order to perform language function, that there's individual, there's specialization of individual areas of the brain to some degree, but that networks of these regions are required to perform complex functions. And regardless of how we look at it, we find the, the same… we find the same thing. And so… the important thing to say about that is then it's logical to expect that different strokes are gonna cause different problems, and that when we look at outcome, and when we try to understand the brain basis of language outcomes after stroke, we can't look at language as one thing. So I think it's not that useful to talk about for instance, overall aphasia severity, when we're trying to investigate brain basis of outcomes. We need to be looking at, at least one level of specificity higher than that. So this is an example of our attempt to do that. We were doing a clinical trial of TDCS, and we were using this clinical battery which is, you know, mostly the same kinds of tests that we all use to assess our patients clinically. And we didn't do anything fancy with error analyses or anything, we just threw all these scores into a, into a principal compo—uh, principal component factor analysis, and found that these basic scores measure about 4 different, um, dissociable things, which we labeled using the labels you can see here. And when we used a technique called Lesion Symptom Mapping; and in case you're not familiar with this, I'm gonna show a couple of examples of this throughout the talk. This is a technique where we take a large group of people with a stroke, we put all their brains in the same geometric space, and we march through the brain, and at each little location in the brain, we separate the group into people who have a stroke at that spot, and people who don't have a stroke at that spot, and then we compare their behavior. And that tells us to some degree whether that region of the brain is important for the given function. That make sense? Okay. So when we apply that to these, to these measures, we find that these separable processes, likewise map onto different regions of the brain. And so that's why I think it's important to at least interrogate outcome at this level of specificity if not a higher level of specificity.

Okay, so now I'm gonna talk about a couple a features of lesions that are important for outcome. The first is lesion size, just how big a person's stroke is. And there are two reasons that I think this is important to think about. The first is that the, the larger the lesion. The more likely that any given important structure is damaged. And that's just a mathematical truth. And so when

we look at any variety of different scores of different processes, many, many of them are related to lesion size, for this reason alone. And so that's shown here in a paper with Andrew DeMarco who's getting a lot of recognition in this, in this session, which is awesome. He's a postdoc in my lab who came from Pagie Beeson and Stephen Wilson before.

So the second reason that the lesion size is important is that we know that these different regions interact with each other in, in networks. And the larger a lesion, the more profound disruption of information flow through the network. And we're understanding more about this through network neuroscience approaches which have, which people have been using for the past couple of years in aphasia. There's more to learn about this, but I think this is another reason that lesion size will tend to be important, especially for functions that rely on integration of processing across different brain regions.

So lesion size is important, but of course size isn't everything. So here are two people who have roughly a, approximately the same size lesion, and, and of course none of us would expect these two people to have the same kinds of problems after their stroke. And that's obvious based on the figure that I just showed you a minute ago, that different regions, uh, damage in different regions cause different, different problems. So the second important thing to consider is location, of course. And, uh, location can be important for a lot of different things. So it's not just our, our, uh, our sort of classic language processes that we think about line phonology or semantics, or, or even executive processing here, or comprehension. They can be important for, for things that you don't ordinarily think about. That, or also important outcomes after stroke. So I'm just throwing up 3 examples of studies, lesion mapping studies that we've done, looking at things that are sort of non-canonical language skills. On the left is a lesion mapping study that we did of post stroke depression symptoms. So in this study we found that de, depression symptoms in the chronic period were related to self-perceived physical disability. Inversely to education,. Which might be a socioeconomic status issue, and then to damage in this region of the dorsolateral prefrontal cortex. And if you read the literature on major depression this, this finding makes a lot of sense. The second is a study on, uh, on detection of patient's own phonological errors during a naming task. And here we find a lot of frontal white matter that's important for this, for this function. And the last is this interesting dissociation between forward and backward digit span, where even though these tasks are very similar and require a lot of similar processes, there's some overlap in the lesions that relate to deficits in these, but they're actually quite dissociable. And this I think has to do with the, the kind of ways that we maintain the information for these two different tasks. So the point is that location really matters, and it matters in, in ways that you wouldn't always think.

The second part of location that really matters is the white matter damage. And this has been known for a long time, from work from Marnie Naeser and, and others. We've shown it, uh, a few times recently that in the context of picture naming, when we look at this network of, of picture naming areas, we find that overall lesion size matters. We don't find that damage to any specific gray matter region matters, beyond what lesion size tells us about picture naming. But we do find that the integrity of several white matter tracks in the left hemisphere and one inter hemisphere of tract matter. And this finding on the right is just a dissociation between white matter that's important for sentence comprehension, and word level comprehension. And for

word level comprehension, this succeeded what gray matter could tell us also. So white matter matters.

Okay, last thing to say about lesion contributions to outcome. So the lesion is why the person has aphasia. They wouldn't be seeing you if they didn't this, uh, stroke, um, or some other problem with their brain. And so I think this, what I've just talked about, the lesion contribution to outcomes, should explain most of the variability between patients. And so I think if you wanna understand why people end up the way they do after, after the stroke, the lesion has to be the first thing, uh, to consider. And then after, as Stephen said, after understanding the expected outcome from an individual person's lesion based on things like size and location, and white matter damage and, and maybe other measures that we could add to this as we learn more. Then we can understand what the rest of the brain contributes, um. As to why a person is doing better or worse than we might of expected, given, given their stroke.

Okay and that leads into the next part of the talk, which is about this spared brain. And when I say spared brain, I just mean the parts of the brain that aren't directly damaged by the, uh, by the stroke. And there's two… uh, there's two things that I think about with the spared brain. Factors that contribute to resilience to the stroke and, uh, changes that are related to recovery. So I'm briefly gonna talk ab out resilience, and then they rest of the talk will be about, uh, recovery.

So what do I mean by resilience? Well, the question here is why do some people who have big, bad strokes, have relatively mild deficits, even shortly after the stroke. And the answer is that their brains are organized in a way that makes the resilient to the stroke. And you could say the opposite for people who have surprisingly severe deficits that are, seem out of proportion to their stroke damage.

Now one thing that I forgot to put on this slide that I realized last night, is I think that resilience also has to do with a person's capacity for recovery. So, things about their brain that make them able to recover better, even if there are things that don't change over the course of recovery. And things that I think fit into this category are, ideas like brain health. So Argye Hillis's group, along with Julius has been publishing recently about… white matter disease uh, burden, also called leukoaraiosis, which is the chronic small vessel, the schemic disease that causes really junky looking white matter, and probably interrupts formation flow throughout, throughout the brain. So that really matters for, uh, for recovery. Likewise, if you have prior strokes, then, um, in the right hemisphere, we've known for a long time that that portends a poor outcome. Probably things like Alzheimer's pathology, and other factors that, um, that impact the brain function in general, will impact outcomes after stroke. There's this other concept called Cognitive Reserve, which I think is mostly a descriptive term for resilience that's associated with higher levels of education and regular mental activity. I think you, this is not usually very well specified in terms of what this means, but you can think of it as like if you have a richer semantic web, that web will be more resilient to damage in any di—individual location. And then there's factors about brain organization. So we talked about lateralization a little while ago. This is sort of the easiest one to point to. There are probably other examples where brains can be organized in ways that make them more or less resilient to strokes. Um… so, it's been, uh, shown using, uh, TMS and fMRI, that lefties and even righties with a less strong lateralization are more resistant to, um… to models temporary lesions in the brain for instance, which we all know to be

the case. And I'll just say also that to, to Stephen's point about lateralization being an important factor of language, we think that different aspects of language has different degrees of lateralization, and so that probably matters in terms of resilience to stroke for different, different processes. So the fact for instance, that narrative comprehension is less lateralized, may not mean anything bad about the task of narrative comprehension, it may just mean that the processes that are involved in narrative comprehension are more bilateral than the processes that are involved in semantic judgment for instance. And that I think is important to recognize.

Alright, so the rest of the talk is about changed related to… recovery. And what do I mean by recovery? Well what I mean is changes in behavior that occur after the stroke. So, some of these changes just have to do with biological factors that surround a stroke. So loss of blood flow that then gets restored through re-profusion, resolution of brain swelling which takes a week or two after the stroke. There's some brain tissue that's just stunned by the lack of blood flow, but then comes back online, maybe partially damaged and just starts working again. So these factors account for some of the, uh, the early recovery. I think most of the rest of recovery, um, has to do with changes in the spared parts of the brain.

The one part, the one area where I, where I struggle with this a little bit is, uh, compensatory strategy. So if a person takes on a new compensatory strategy, is that really a change in the spared part of the brain? I think from a philosophical standpoint, the answer is yes, but from a practical standpoint it probably doesn't matter that much, if there's some minor change in the brain that lets a person use a strategy. But I will say, when people start using these strategies regularly, and they incorporate them into their routine for performing a language function, then that probably is instantiated as a static change in the brain. Alright, and many sorts of changes occur in the brain, and for many reasons.

Okay, so here's, uh, a figure that Stephen showed you also. This is our, uh, meta-analysis. This is now several years out of date, so this doesn't include all studies. And the way that we do this meta-analysis requires exclusion of a lot of studies. But still, it was a representative sample at the time. And, what it shows again is that people with aphasia are using to some degree different parts of the brain than a healthy control subject to process language. And the questions that we'd like to answer are what are these areas doing, and why are they there. How did they come to be involved in language?

So… there's a lot of great work on this in animal models. And, I will point you to Theresa Jones is probably the single best person to look up if you're interested in this, in this topic. So there's a lot of good work in, in, uh, in rats in particular, looking at the ways brains change after stroke, the interaction between behavioral experience before and after the stroke, and the way their brans change. And the findings are that there's a degenerative phase which goes on for a week or two, and then a regenerative phase that involves a lot of changes at the neuronal and synaptic levels like axonal sprouting and growth dendritic growth, new synapses. The cell migration is probably a little bit overstated. And then large scale changes like functional reorganization, and that these changes tend to occur in the same kinds of places that we see the in our patients. So around the area of the, of the lesion, and then opposite in the other, opposite the lesion in the other, uh, hemisphere.

And so I'll just say upfront, I'm gonna talk about a, a number of different ways that I think the biology can drive reorganization. And all of the ways that I'm gonna talk about have some evidence in the animal literature to support the fact that they occur. How important they are is another question.

So here's a short list of, of ways that biology can drive changes in the brain. I'm gonna come back to some of these and explain them in more detail in a little bit. So I just wanna flash this up to point out that there's a lot a different ways that brains change after stroke, that might be important for our patients. And this is a really short list. There's a lot of other ways that I'm not including here. And there are ways that can positively impact outcome and potentially ways that they could negatively impact outcome.

And here's a short list of ways that I think behavior can drive brain changes. This is a different level of explanation than the prior one. The prior one focused on sort of neuronal level mechanisms, and this one is focusing on, on aspects of behavior that can, that can drive change. And uh, again, I'll come back to these a little bit later.

Okay. So, the problem is we see changes in the brain, and how do we know what they're doing, why they're there, what, what are they. And I think, um, I think of this problem as sort of similar to the problem of… uh, identifying birds. So, uh, let's say you're out on a hike, and you see an interesting bird, and you wanna know, what is that bird. And, the way that you figure this out is you make careful observations of the bird. You… look at where it lives. Are you in the forest or in, are you in the marsh? What part of the United States are you in? Are you somewhere else? What does the bird look like, how is it behaving, what's its flight pattern, what's its song, these kinds of things, right. And then if you're lucky, you have your, your Peterson guide to, to birds with you, and you look up what are the traits of different kinds of birds, and you figure out what kind of bird it is. Right? Make sense? Okay. So, I'm gonna propose that, uh, if we wanna understand the, uh, brain basis of aphasia recovery, that we need a similar kind of field guide. So this is a Peter Turkeltaub field guide to brain changes after stroke. (A few people react to that.) I spent a lot of time on Photoshop working on this. (Several people laugh) You should spend some time interrogating what I've done here. (Several people laugh) So, um… okay. So the first question is, uh, is, is it really a change, or is it something that's not really a change? And we can provide different kinds of evidence for whether it's a change or not. Whether there's a difference between the patients and the controls, whether there's evidence for longitudinal changes. When you just think about where it is in the brain, just absolutely where it is in the brain. So is it the right STS or is it the left inferior frontal gyrus? Is it the supplementary motor area? And then we also need to think about the relationship between the stroke and the, and the change that we're, that we're seeing, to understand what it means. We need to think about the timing of the change. So both relative to the stroke and relative to any kind of change in the environment like, uh, like treatment. And then we need to think about how this change behaves. So, is it there for everyone, is it, does it, is it specific for certain functions, does it positively or negatively affect outcomes? Um, is the relationship between, uh, the, the function or the structure of this area the same in patients as it is in control, or is it, or is it different? And these are the kinds of things that will help us understand what these changes mean.

Okay, so now I'm gonna take you through some of these and just give you examples of how I think this kind of information can be informative. And I'm gonna start with changes; I'm gonna spend most of my time on changes that are primarily driven by biology. I do wanna restate that none of this is absolute; all of these changes are driven by both biology and the environment. But I think these changes are the ones that are primarily driven by biology, in that… that regardless of behavioral exposure, these things would be happening anyway.

Okay, so the first one I wanna talk about is axonal collateral sprouting, and some people talk about this as synaptic competition. So this is something that occurs throughout the nervous system, both the central nervous system and the peripheral nervous system. To exemplify that point, I pulled this figure from a Neurology 101 textbook. I think I had this from medical school. And what I'm showing you is not the brain, but I'm showing you the neuromuscular junction. So where, uh, peripheral neurons innervate the, uh, the muscle unit. And… so you've got 2 neurons here. Let's see if I can get mine here. You've got 2 neurons here that are innervating different motor fibers in, uh, in a muscle. And what happens when one of these neurons dies, is that the other sprouts these new collaterals from the axons, to take over the, um… the muscle unit, or the, or the neurons in the brain, okay. So now this, this single neuron is now taking over the synapsis that used to be base, uh, used to, uh, uh, be from a Neuron B. Okay, so that's good. So, uh, so now we have a way to use those muscle fibers or those, or, or those neurons. But the consequence of this, is that in this case, you have 2 neurons controlling this set of, uh, of muscle fibers. And so if you ask a person to produce a slight activity of the hand, they can produce this nice coordinated contraction of the hand. But if there's only one neuron controlling all those muscle fibers, what happens when you ask a person to produce flight activity is you get very disorganized, uh, giant motor unit action potential. So that one neuron just can't ever do the job of the two neurons as well. And I think that's an important point to recognize here.

Okay. So I am a big fan of this, uh, of this particular mode of reorganization. I think this actually explains a lot of what we see in real change that occurs after stroke. And so I'm gonna take you through a couple of examples here.

So I'm gonna use these toy brains to illustrate different ways that brains change after stroke. A couple of just points about this. The particular areas that I'm showing you aren't of any significance. So the fact that they're in opposite hemispheres here, is only because it's easier to show that visually. But I'm not saying really anything at least in most of these models, specifically about left versus right hemisphere. And these are just toy models. They're meant to illustrate, uh, a point.

Okay, so let's say you have, um, a situation like this, where you've got 2 areas that are involved in a function, and they share axonal projection targets. Here I'm showing them as, uh … basal ganglia but that's not really important. So what happens when you have a stroke to one of them? Well the axons die off from that area, and, the other region that innervates the same, uh, the same, uh, the same, uh, region, will take over the synapses through axonal collateral, uh, sprouting. And the ability of this new area to take over the function of the prior area, will depend on the degree to which it's similar to the lesioned area, in terms of its place in the network. So, whether it shares a lot of connections, and whether it performs a similar computation, to that area, as, as baseline. Does that make sense to everybody? Okay.

So this is one mechanism by which we might see an area that increases in activity. Now this area was involved before, but it increases, uh, in activity after, um, after the lesion. And so we can predict some things about when, uh, what this should look like when we see it in a brain. So the first thing is that this is a structural change. So it's not going to happen right after the stroke. It's gonna take at least a couple of weeks. And this will also be a change, that if we see this as product of an intervention like a behavior, this should be the kind of change that takes time to occur. This isn't the kind of thing that will occur after a single session of therapy, this is the kind of thing that will occur after weeks, uh, of therapy. The region where this should occur, should be one that shares axonal targets with the lesion tissues. So these are not necessarily areas that are connected to each other, they're areas that share projection targets. And when we see increased activity in these areas, we should see increased performance on the behavior that's served by the lesion tissue, but that change is likely to be less effective than the original tissue was.

Okay, so I'm gonna show you an example from our work that I think suggests this pattern, although we can never, in our work, clearly prove that this is the case. So this is a study we did, we put out last year, where we looked at naming activity, despite the problems with naming. We looked at picture naming, (Some people laugh) uh, activity. It's useful that picture naming relies to some degree on, on both hemispheres here for our purpose. So what we're looking at is activity in the right mouth area of motor cortex. And we're gonna look at whether activity in the, in the right motor cortex depends on whether a person has a stroke that impacts left motor cortex. And the reason for this is the mouth areas, uh, motor cortex in both hemispheres project to similar targets in the brain stem. And so this is a, this is a good candidate for exonal collateral sprouting, in that both regions project to the same, same area. So when you lesion one, you should you should have some takeover from, from the other one. And so we took our, our chronic patients with left hemisphere stroke, and we separated them into a group that had a lesion in motor cortex, and a group that didn't have a lesion in motor cortex. We account for, for overall lesion size here, and when we compare the two, we find that the group that has lesions involving left motor cortex have more activity in right motor cortex than the group that, that doesn't. 'Kay. So that's what we expect to see. And then the second thing that we expect to see here is that that activity should be important for speech production, but only in the group that have left motor cortex lesions. And so that's what we're showing here. So if we just do a correlation, and again, this accounting for lesion size and other factors, between the activity of right motor cortex with, in this case it's picture, it's picture naming, because that was the fMRI test, but, uh, picture naming performance, we see no relationship of that activity in people who don't have a lesion in left motor cortex, but we see a positive correlation in people who have a lesion in left motor cortex. So this suggests again, that now the right hemisphere motor cortex is increasing its activity in response to the stroke only when there's a left motor cortex lesion, and that that activity is helpful. And we think that that has to do with the shared axonal targets, although we can't prove that here. Okay. And we also can't prove that this, uh, that that change relates specifically to axonal collateral sprouting. But it does fit into, uh, a family of changes that encompasses the idea of, or some versions of axonal collateral sprouting, which is increased reliance on spared pathways. Either spared pathways that are currently used or ones that are sort of latent remnants from development that aren't used in, in people, in, in day to day life at least. And so that's shown here. So we have two different networks; in this case one in the left, and

one in the right hemisphere. The end point of the network shares a common outflow pathway, and when you have a stroke, you have up regulation of the alternative pathway. And this doesn't have, it's, probably a lot of this I think has to do with axonal collateral sprouting at a microscopic scale, but some of it may have to do with just changes at the synaptic level. So increased number of synapses on neurons that are already connected to each other, or changes in the, in the nature of those, uh, of those synapses. So that may be at play here. There are situations where I think axonal collateral sprouting though gives potentially better explanations for phenomenon that we see. And so one of these is perilesional recruitment. So, here we've got another toy network with two regions that interact. Again it's not important that these are left and right, these could be any two regions. So what happens when you get a small cortical lesion in the left hemisphere to a region that's important? Well it cuts off the ends of these axons that project to it, but it cuts them off right near their target. And so in that case, you can get sprouting of collaterals that feed areas that are neighboring the, the stroke, and you could get recruitment of these new areas that are right next to the stroke because of these collaterals. Okay. Now what happens when you have a big stroke in this case? Well the axons are now cut off much farther from. From the cortex, and there's no good axonal guidance system in the central nervous system. And so these axonal collaterals they'll sprout, but they can't find their target, and so they're not helpful. And in the, the case of a big stroke, then you wouldn't expect to get peri, uh., much perilesional recruitment, and that I think is what we see phenomenologically. 'Kay.

Now I'm not saying that that is the answer, I'm saying that that's a hypothesis for it that might explain the patterns that we see.

So how am I don' on time? Okay.

So, uh, another mechanism that we could talk about is Deafferentation Atrophy. This is a specific, uh, consequence of a general phenomenon of disconnection within networks. And I'm gonna go back to the same figure I showed you for axonal collateral sprouting here, to show you that even though Neuron A can take over some of the synapses, it can't get them all. And so the motor units that don't receive input here, or the neurons that don't receive input just whither and, and die off, okay. And so that's Differentiation Atrophy. And so it looks like this; you have a stroke here, you lose the input to this area, and that area then shrinks because it's not receiving adequate input anymore. And, now it's an interesting again, sort of philosophical question to ask whether this is an effect that you could say is the stroke itself. Should I have put this in the first category of consequences of the stroke itself, or should I have put this in the recovery category?" But nevertheless, I think it's a phenomenon that we need to think about. And we see this just grossly in brains of people with stroke. So if you look at the caudate nucleus and the thalamus of this person who has a big left hemisphere stroke, and we just compare the size of these regions in the right hemisphere to the left hemisphere, we can see that these regions that for these, that, um, that prece—that, um, that receive a lot of axonal projections from the cortex have shrunken down because of this, this process. Whether that has a functional consequence is I think a matter of debate. Julius and Leo Bonilha have shown some evidence that it is important.

Okay, so if we think about, um, what we should expect to see in this case, again this is an anatomical effect, so this is gonna be delayed by weeks or even months after, uh, a stroke. The location of the effect should be one that receives axonal projections from the lesion tissue, and if

this is functionally important, then decreased size of these areas, which may also be manifested by decreased fMRI signal for instance, should relate to poorer performance on the behavior that's served by the atrophied tissue, not by the lesion itself, 'kay. Does that make sense? Okay, good.

Alright, so next thing I wanna talk about is diaschisis. This is another one that could of gone somewhere else in my, in my taxonomy, but I, I put it here. So the phenomenon of diaschisis is basically distant dysfunction that's caused by, uh a lesion. Classically this is thought to be due to noisy signal from damaged neurons, but it may also be, some people apply this just to talk about dysfunction caused by disconnection for instance. And the idea here is this; you have, uh, uh, a network of brain regions that are working together to perform some function, you have a lesion in one of these brain regions, and then that has effects on the functioning of the rest of the, of the network, because the other nodes in the network don't really know what to do when they're not getting the right input from the, from the lesion area. And so an important point here is that this doesn't just affect regions that are directly anatomically connected to the le—to the lesion; this will affect regions that are part of a functional network.

So… this is a, an electric physiological effect, not an anatomical effect. And so we expect that this should occur immediately after the stroke, to the extent that it has to do with this noisy input, as the degenerative phase of, of change after stroke occurs, this actually may die down to some degree, but it'll probably never go away completely. And the regions where we should expect to see this kind of change, are those that form a functional network with the lesioned area, and decrease in function in these areas should relate to decreased performance on behaviors that are served by the dysfunctional tissue. Again, not necessarily the lesion tissue specifically, but the entire network, okay. And I'll point you to several recent papers. There's like a dozen of these now in the past 2 or 3 years by Mike Fox's group, where he's mapping what he expects to be the network consequences of individual patient's lesions, and explaining syndromes that have poor localization. So, uh, so things like Peduncular Hallucinosis, on the basis of network dysfunction. And I'll show you our, a very recent evidence for this. So Andrew DeMarco in our lab has been working on this new technique that we're calling Functional Anomaly Mapping, where we take a resting state activity, so fMRI activity just while people are laying in the scanner, not doing anything in particular. And then we're looking for regions of the brain that are just behaving anomalously in patients compared to control subjects in this technique. And one of the nice things about this method is that, uh, it finds the anatomical lesions, and it's very highly reproducible from, from day to day. So we have a dice index that's, uh, about the same or, or maybe a little higher than Stephen's first fMRI test. And what you can see here is not only does it find the anatomical lesion, but in people with subcortical lesions, what it tends to show is dysfunction throughout the cortex on the side of the, of the lesion, which is what we expect to see for distant dysfunction. And maybe even more interestingly, we find these effects in the right hemisphere that are reproducible over time, right. Uh… in individual patients. And that when we analyze where this dysfunction occurs, it corresponds very strongly to the abnormality of the signal in the same area of the left hemisphere. So it's homotopic to functional abnormalities that we see in the left hemisphere, which suggests that it's a transcallosal diaschisis; that it's dysfunction that's caused by the lesions in the left hemisphere. And we can demonstrate that this is functionally important by using these maps and correlating them across the group with behavioral outcomes. And I'll show you a nice synergy between what Stephen

showed you and this map. So this is a map of the functional anomalies associated with mean length of utterance on a picture description task. And the first thing is that we find the expected region that should be associated with this behavior in the left interior frontal jo--- uh, lobe, and also in the left basal ganglia. But then we also find this region of the right cerebellum, similar to what Stephen showed you before, where the functional anomalies in this area relate to… mean length of utterance. And this is an area that we know to be involved in speech production, and in particular this lateral aspect of the cerebellum is involved in, in tests like verbal fluency at least in control subjects. So this isn't a completely unexpected finding.

And here is another example. This is right hand pinch strength where the, the functional anomaly maps do a really nice job of funding the hand area of motor cortex, and the entire descending cortical spinal pathway. But they also pick up this area of the right hemisphere, which is in the right premotor cortex. And when you read the literature on motor recovery from, from stroke, you find that the right premotor cortex is related to recovery of, of right hand movement.

So these are examples of, of diaschisis I think.

Okay, so… uh, is it; so another one that people talk about a lot, another mechanism of biologically driven mechanism of change that people talk a, a lot about is maladaptive release of, of, uh, inhibition. And in this case, most people talk about this as an interhemispheric phenomenon where the two hemispheres inhibit each other at baseline. We know this is the case in the motor cortex. In the primary motor cortex, this is actually important because it's used in order to be able to do different things with your hands at the same, uh, at the same time. It's a little unclear to me how important this is in the language network. Whether there's interhemispheric inhibition in any parts of the language network that predominates, and how important that is. But nevertheless, this very commonly cited as a, as a mechanism. In fact, to date, this has really been I mean the main biological mechanism of, of change after stroke that people talk about in the aphasia literature, and that's because of the TMS work showing that when you inhibit right Broca's area, you can get improvement in recovery., Cindy's going like this (Gestures) and I agree, that that doesn't mean that this is the mechanism by which you see those effects at all. But anyway, I wanted to show it because people talk about it. So the idea here is that the two hemispheres are inhibiting each other. When you get a lesion to the left hemisphere, what happens is you, you lose inhibition over to the right hemisphere. That becomes overactive, and then that feeds back on what's left in the left hemisphere and over-inhibits the perilesional cortex, preventing what would otherwise be a good, a good outcome. 'Kay. So that's the idea.
And if we think about how, what this should look like, the effects; this is an electrophysiological effect predominantly. So the effects should occur immediately after, after the stroke. It should occur in a regional that's directly inhibited by the lesioned tissue should be increased after stroke, and then that increase should relate to decreases in signal around the area of the stroke. And we should see an inverse relationship between activity of this maladaptive cortex and behavior. Now in our work, we, we have looked for this a number of times and have never found a pattern that looks consistent with this. Some other groups have found evidence of inhibition between different areas in right to left inhibition for instance. And we certainly do see what I think are electrophysiologically mediated up regulation of right hemisphere areas after

temporary lesions in the left hemisphere. So if you use transcranial magnetic stimulations and knock out left Broca's area, you do see immediate up regulation of the right hemisphere. But the degree of up regulation is actually preventative for the deficits that would ordinarily be caused, not maladaptive. 'Kay. So I don't think that this is a very important mechanism, but I did wanna mention it because people talk about it a lot.

Okay, so that's the end of the section on biologically driven changes after stroke. And just to summarize a couple of themes that have run through here. I think what brings the, the biologically driven mechanism together is that the location of the change is in general gonna be related in some way to the stroke lesion. But the specific relationship I think can tell you actually a lot about what the specific mechanism of change might be. Whether it's a direct anatomical connection, whether it's an area that shares axonal targets with the region of the legion, uh, lesion, or whether it's just a region that's part of the same functional network. And even more precise relationships we could talk about later that might mean more, even more specific things. And I think the timing of these changes really depend on whether it's an anatomical mechanism, whether it requires some anatomical remodeling, or whether it's just a direct electrophysiological effect like a dysinhibitation kind of effect.

Okay. So the last bit is about, um, changes that are driven by behavior. I'm gonna give this somewhat short shrift, because I think the last 3 talks are gonna focus a lot on, on these issues. But I will, I do wanna point out a couple of things. So we tend to focus on changes that are induced by aphasia treatment here. And I think that makes sense from an experimental standpoint, from a practical standpoint because we have great experimental control if we can apply a specific behavioral intervention and then look at a specific change in the brain, we could probably you know, draw very specific conclusions about that. But I do wanna point out that there, I think there are lots of different ways that the behavior of a person with aphasia will impact their brain organization. Um, so there are these explicit compensatory strategies that people use, whether or not they learned them in therapy. So I constantly hear, patients tell me in clinic, that when they can't retrieve the, the name of a word, they, they visualize the spelling, I know that Pagie (inaudible word), that they visualize the spelling of the word as a way to cue themselves, right. And then they incorporate that strategy into their daily lives, and that probably impacts the organization of the brain to some degree. There's increased reliance on preserved ability. So Stephen mentioned the idea that domain general cognitive networks may be important for recovery, and I think that falls into this area, so people end up relying on the things that are preserved more. One that I think we don't talk about enough is learned nonuse. So this is, uh, this is talked about a lot in the motor literature, but not as much in language. So what happens to people when they sit at home and watch TV all day and they don't talk anymore. So there's gonna be some atrophy of, of networks that are involved in, in language because of behavior like that. And we can try to measure those behaviors and incorporate them into our models I think. And then there are some things that are just purely artefactual. So Stephen talked about issues with interactions between effort in the scanner, and activity. And I, I put those into these, into this camp also, as things that we need to think about.

So just some rules of thumb for behaviorally driven changes. So the first is what I already said. They're not just associated with treatment. So just because you see a change that occurs across a population, or in a particular kind of patient, but patients who have received all different kinds of

treatment doesn't mean that that change isn't related to something about their behavior that's driving, driving the change. The function of the brain regions that are involved in this kind of change will mostly be the same as in controls. So for things like compensatory strategies. But that relationship may be enhanced or diminished. And so that means that the loc—the localization of these kinds of changes will tend to be fairly consistent, regardless of, of lesion location. There are some caveats to that. And so that, and so and so also related to that, the changes that we see especially with compensatory strategies, will likely be systematically related to a pattern of deficits and spared abilities, rather than to lesion location. So for instance, people who use this spelling visualization strategy will be the people who have trouble with phonological retrieval, but they can retrieve orthography a little bit, a little bit better, and so we should expect that pattern in those people.

Okay. So just a quick couple of examples of things, of patterns that I've seen in papers that I think suggest this kind of, of change. So the first is in the meta-analysis result that you've seen a couple of times. We found this area in the left hemisphere across 12 different studies, where the left dorsal lateral prefrontal cortex was active in our people with aphasia but not in control subjects. This is the same location across 12 different studies. It's not there in every study, it's, but it's in, there in a significant proportion of the studies. Doesn't matter where the lesions were in this case, it's there. And so that suggests I, I think that this is… a use of, uh, a domain general cognitive process which is subserved by the, by this area of the brain to compensate for aphasia deficits. You've also seen this figure; this is from Julius's lab. These are, these are the areas of the lesion in these patients, and these are areas where increased activity corresponds with better naming ability. And again, the localization is consistent here, um, across a variety of lesions which doesn't necessarily mean that this is behaviorally driven, but I think gives the hint that maybe, maybe it may be. And I'll sh—and, and another set of findings that I think may be mediated by behavior, this is a paper that we published a few years ago, where we; this is the first time we really took this systematic approach where we tried to first explain the, the degree of outcome that was related to the stroke itself by building a model that had to do with stroke location. Stroke size, and then other demographic factors to figure out what we expected the outcome for individual patients to be. and then we looked at the gray matter volume in the rest of the brain using a technique called voxel based morphometry to see if that told us anything more about, uh, about the outcomes. And the finding here was that people who had, um, uh, denser gray matter in this area of the right hemisphere, in the posterior temporal and interior parietal lobe, had better than expected outcomes on a couple of measures, on the WAB naming, and word finding, on WAB repetition, and you can see the areas are a little bit different here, but overlapping, and spontaneous speech. And one thing that we found only for spontaneous speech, was also a relationship in the cerebellum. This is actually a different part of the cerebellum than the one I showed you before. This, this medial area of the cerebellum is really involved in articulation; it's involved in speech production specifically, and you can see it's bilateral, and I think that's important for reasons that I'll explain in a second.

Now one of the interesting findings from this; these are all structural changes, these are not functional changes. And I say they're changes, because they were different than in control subjects. So we, when we compared the gray matter density of these regions in our patients to a set of control subjects, and even a group of people who had stroke, left hemisphere stroke, but not aphasia, never had aphasia by history at, at least, we found that the volume of these areas

were different our patients with, with aphasia. And interestingly, in the right posterior temporal lobe, the patients had greater gray matter density than the control subjects, but in the cerebellum they had less. So these are two different processes that we're observing here. One is atrophy, and the other is hypertrophy, so growth. At least we think that's the case. It could be a mismatch with our control subjects, but this kind of, this kind of dissociation where some areas decrease and some areas increase suggest it's not.

Okay, so the, these could be biologically driven changes, but I think there are some clues as to why they're not. Um, I, and why I think they're behaviorally driven changes. The first is that the structure behavior relationship was consistent across patients, and was not strongly related to lesion size or location in this group. In fact, we incorporated lesion size and location into the model beforehand, and still found these areas. So it's relatively independent of those, of those factors, so it doesn't relate to features of the stroke itself. The cerebellar atrophy is bilateral, which means that this can't be deafferentation. I actually said in the paper that I thought it might be, but then after thinking about it for a couple a years, I realized I was wrong. So, so, uh, the right cerebellum hooks up to the left hemisphere, and it medi—it's a two syna—at least two synapses between this part of the cerebellum and the, and the left hemisphere, so it can't be deafferentation atrophy, especially if we see it in the left size of the cerebellum, which doesn't connect to the left side of the, of the cerebrum. So these factors suggest to me that this may be a behaviorally mediated change, although it's hard to be more specific than that in this case. And that's where I think the targeted behavioral intervention studies where we can provide a specific behavioral intervention, and then it would serve change over time, become important to test these kinds of hypotheses when we observe a change here.

Okay, actually before the take home points, I just wanna show you one, one more slide that I didn't include for time, but I just wanna show it to you because this is the same thing that Stephen found with a slight difference. So this is a study where, uh, where we used an fMRI naming task, uh, and looked at regions of the brain that were greater in patients than controls, and where the activity related to their outcomes. And, this is another paper where we incorporated features of the stroke into the baseline models. So these are areas that where activity relates to outcome above and beyond what we already know about the person from their, from their stroke lesion, and we find a very similar area of the right superior temporal sulcus to what Stephen showed you before in this task. In our case, this is a naming task now, and I don't know, maybe this shows you some advantages of having tasks that activate the right hemisphere. The, the, uh, the patients with aphasia activated this task more than controls, and the activity was related to their naming outcome. Again, above and beyond what we already knew about them. One a the interesting features of, of this finding is, that goes also along with the one patient that, uh, that Stephen showed you individually, is that interestingly we find that this area unlike the motor cortex in the right hemisphere that I showed you before, is not recruited if a person has a lesion in the corresponding area of the left hemisphere. So these people who have lesions back here, did not recruit the right hemisphere. The people that recruited the right hemisphere were those who had frontal, uh, frontal lesions. And so this is a more complicated network effect that we're gonna have to spend some time figuring, uh, figuring out. Or, it may have some behavioral explanation that has to do with the types of deficits that people who have these lesions have, and people who the, who have these lesions don't. But I think you know, the, the really

exquisite anatomical relationship between this finding and this suggest that it's a direct biological effect.

Okay, so… the take home points again. I think it's, uh, important, um, to understand the grand basis of language outcomes after stroke, and I think it's useful to separate that in to the impact of the stroke itself, and the relationship of the rest of the brain to outcomes. And I think we need to think of the rest of the brain in terms of both factors that contribute to resilience to the stroke, and those that change with recovery. Those changes can be driven by lots of different things, but roughly you can categorize those into biological factors and behavioral factors. And I think the pattern of findings that we see can be really informative about specific mechanisms, allow us to design more precise studies to study those mechanisms, and really get a more fine grain understanding of how we might intervene to improve recoveries.

And I'll just thank all of my collaborators on this work, including people that are still in the lab now, like Andrew DeMarco who's done a significant amount of work on this functional anomaly mapping technique, and people like Shihua Xing who is a visiting neurologist who was with me for a couple a years who did a lot a these studies. Laura Skipper Kallal; I didn't add her married name there. Laura Skipper Kallal who's now at the NSF. Thanks very much. (Applause)

MODERATOR: Okay so we're, we're in break right now, so for those of you who need to take a quick bio break, do that, but we can take a couple of questions, and then we'll get into more informal discussion. Yes, there's one all the way in the back.

MARGARGET: Actually we're gonna start with our RMPTA folks, and then we'll get there, 'cause that was the promise.

Q: Hi. I was curious. You talked about, uh, how learned nonuse results in, um, disease atrophy. And you mentioned this in the context of individuals who may be isolated at home watching TV. But what about individuals with severely limited verbal output; maybe only one or two words, but they're consistently making attempts to communicate? Does this prevent some of the disease atrophy, or are the effects still pretty significant?

PETER TURKELTAUB: Well I think we don't know is the bottom line. I think, uh… the, I, you know, some of these things that I raised are sort of theoretical things that I could affect, uh, that I think could affect brains, could affect outcomes, but that we don't have enough data on to, to support. I, I bring them up because I think they're really important things to think about, and you know, we, we, when we study people in the lab, we have a tendency to focus on what they're doing in the lab, and not think as much about what they're doing at home. And so I think these things are really important to consider, but I just don't think we know yet.

Q: 'Kay, thank you. I'm Gerald.

PETER TURKELTAUB: Can you wave? I can't tell where you are.

Q: yeah. (Laugh)

PETER TURKELTAUB: Oh there you are.

Q: (Laughs) So I'm just curious to know to what extent do you think that, um… suppression (inaudible word) activation of certain brain regions used in maybe TMS and the (inaudible word) training can like facilitate the (inaudible word). And I'm also curious to like, um… ask if… like how do you think, let me say this idea of in the hemispheric inhibition can be like investigated in healthy populations.

PETER TURKELTAUB: Um, so… I think Julius is gonna talk more about brain stimulation in the second half. Um, I, I'll say my take, uh, I think brain stimulation TMS, uh, and TDCS are both really promising ways to manipulate these networks. I think we don't have as good an understanding as we need to of how they affect the brain in order to use them in the best way possible to manipulate these networks. I think that the pairing of that kind of stimulation with behavior potentially is a really powerful way to, to… try to coax neurons into forming new networks the way they ought to, or maybe re-wading inhibitory excitatory balance between different brain areas that can then potentially reopen critical periods for recovery. I think that's a real possibility. But I think we don't know enough about the mechanisms right now to say for sure. Now the second question was about, uh, whether this, um, interhemispheric inhibition is important in without the stroke; is, is that what you're asking in, in language? Again, I think we don't really know. There are, there are some imaging papers using a technique cause—uh, called dynamic causal modeling, that tries to look at time courses in the brain and the way different regions interact with each other that do suggest that there's some inhibition between the hemisphere in, in language areas. And, the TMS papers, there's a couple of these where people inhibit one side of the brain, and, uh, although we don't know what TMS does long term, we're, we're quite confident that when you zap an area of the brain, that that inhibits that area of the brain. So when you do that short term, you see immediate increases in activity in the right hemisphere. And that suggests at least an immediate electroci, electrophysiological response. I do wonder a little bit about these effort confounds that Stephen brought up, if, if because you zapped the language area in the left hemisphere, a person has to work a little harder for the task, you might see up regulation of the, of the right hemisphere. Some of the patterns suggest that that's not the mechanism, but. Uh, so I think we don't really know is the answer, and I think it's kind of a hard thing to measure unfortunately. The reason that we know so much more about the motor system is we just have much better measures of the motor systems. And, so it's much easier to figure these things out in the motor system.

HELEN: Time for one last question.

Q: Thank you Dr. Peter for an informative presentation. But still touching upon the same things that you just mentioned, about bimanual moments, especially when we have brain stimulation protocols that inhibit for a shorter duration, but still have the effect for related longer duration. What influence can it have on bimanual moments? Like can you, uh, explain more based on your experience of it? Does it have an influence on the speech or the contribution from right language, to the right hemisphere to the language? Based in terms of stress of (inaudible word)?

PETER TURKELTAUB: So in terms of bimanual movement, I' not sure, I'm not sure I understand how the bimanual movement part relates to the, the speech part. Can you explain that a little bit more?

Q: My understanding is that they have been extrapolating more direct systems even to the language systems. (Yeah) So is there any possibility or based on your experience, this inhibition can indirectly influence the language systems also?

PETER TURKELTAUB: Inhibition of the, of the motor area; I don't think so. And the, and the reason is, that when you're using TS, so TMS is the tool that you're using for this. When you use TMS you use, uh, uh, a coil, an electrical coil that really stimulates a pretty small area; it's about a cubic centimeter of tissue that you stimulate. And so, um… so TMS can be used for instance for mapping out the motor, uh, the motor cortex for pre-surgical purposes. And so when you're stimulating the hand area of motor cortex, which is what people do in these, in these studies, you're just, you're not stimulating the, the mouth area of motor cortex. I don't think it should, it should impact language.

Q: Okay, thanks.