Transcript of Typical and Atypical Development of Brain Connectivity: The Case of Hemispherectomy
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Thanks, it's really great to be back here after a few years, I am happy to share some of the work we have been doing and to learn about all the advances that have occurred since my last visit to this meeting.

I wanted to talk to you today a little bit about typical and atypical brain development, especially about development of brain connectivity and what we've learned about hemispherectomy from some of our recent work. I wanted to start by just introducing this idea that for a long time people wanted to focus on thinking about brain regions as, 'well the frontal lobe does this, the temporal lobe does that, the occipital lobe does something else', but we've come to realize that that's just too overly simplistic of a viewpoint. We really have this very interconnected system and it's not just one region doing one function.

So we tend to think more in terms of using principles from network science nowadays to think about networks of regions that are highly interconnected and interdependent on each other. So some of these ideas come from work that has been around in the literature for a while but really now is taking up steam and that's the idea that everything we do like language or memory or any kind of process is really sub served in the brain by these interconnected neurocognitive networks that span the entire brain and that behavior then comes from multifocal, multiple levels, multiple neural systems and that means that any kind of relationship between the brain and some behavior, at the same time there is some area in the brain that might be specialized for it like reading for example, but it's also distributed because that region is highly interconnected with other brain regions and that interconnectivity is really critical for the function. So it's not just that one brain region does reading but it is really its position in a larger network is what enables these kinds of complex functions that we think about all the time.

And so what we'd like to think about in our lab is these critical research questions of how large scale these neurocognitive networks, how they developed from childhood, adolescence going into adulthood and how that has consequences for growing skills and abilities in what we call cognitive maturation; learning new things from a childhood to adulthood. Then of course, what are the consequences when something goes wrong in this developmental pathway? We like to focus a lot on studies of children with autism spectrum disorder in the lab and also attention deficit hyperactivity disorder. Those are some of the prevalent disorders that are out there so we spent a lot of time thinking about what happens in the brain of children with autism or ADHD and how does that affect their behaviors and their learning? Of course, we are also having to collaborate which we have been doing with [---03:16] UCLA and other places to look at brains of children who underwent hemispherectomy and look at how their brains are adapting to that surgery.

So aside from the work that we're telling you about today what we do is start with the question, what does a typical adult brain look like if we put someone in the MRI? Because that lets us make developmental theories about how it got to that point. If you compare a child who is 7 years old to the adult who's 30, what are the differences in their brain connectivity patterns in the typical pathway and what does that tell us about normative brain development? Then of course when we get to other populations whether it is autism, ADHD, or other developmental disorders, children who have undergone a hemispherectomy, what can we learn about and how can we understand those differences in the context of what we already know in typical and atypical developing brains?

If we're interested in connectivity, which we are, there's a few ways that you can study it without actually going into the brain and those are the non-invasive techniques that you all know about. MRI, functional MRI in particular which relies on the blood flow changes to different parts of the brain and structural MRI or structural connectivity which you can actually measure with diffusion tensor imaging and many of you probably seen some figures like this earlier today they let you look at the structure of large fiber bundles that connect the brain regions.

I want to show you this video which I always like to show. Can anyone guess what this brain is doing?

Nothing?

It's actually true this brain is doing nothing in the sense of we're never doing nothing. Even if you think that you're zoning out and completely daydreaming, there's something going on. There's no level of nothing in the brain; the brain is always using energy, it's always consuming energy and some parts of the brain are cohering or synchronizing together and other parts are not synchronized. For a long time people thought this sort of spontaneous nothing activity was just noise, it was, 'OK the brain is just doing nothing, it's idly, it's not doing anything of import', but turns out that there is some systematic structure to this noise. In fact, if you look carefully you'll see the red areas are areas that are correlated with each other and if I let it cycle through you'll see that once in awhile the language network seems to pop up. Frontal lobes and parietal lobes seem to go together and at a different time maybe some systems important for attention or memory seem to be correlated with each other. This is all spontaneous activity when the subject isn't asked to do anything but it turns out that the brain likes to sort of maintain these systems at a very slow frequency in a coherent way so that some people think that this is actually helping us set the stage for the kinds of processes or maybe it's helping to consolidate memories or whatever it is it's preparing us for the next step. So we like to use these sort of correlations between brain regions in the spontaneous, doing nothing state to give us an insight into how the brain is connected, how it's wired up and how that wiring can change with different conditions.

The more static part of it is the structural connections, so those were moment to moment variations in connectivity that happen as correlations between brain regions but underneath it all there is this sort of skeleton or the fibers that connect areas to each other and we can infer the existence of these structural connections just by the fact that water diffusion is actually restricted in parts of the brain where there is a lot pathways going in one direction. Like, if you have electrical wiring that's all going in one direction the water molecules can only flow in one particular way because of that restriction, so basically we can guess at the existence of these large fiber bundles because of this property. So we like to use those two tools and some others to understand connectivity in a typically developing brain.

Just to give you some background we've seen over the years that as you might expect, connectivity changes with development. So if you look at kids and adults for example, and you look at the anterior and posterior parts of the brain and the correlation between those they change between childhood and adulthood so that adults actually have a stronger connectivity between the anterior and posterior parts as compared with children and that structural connectivity (these blue things are representing fiber bundles) you can see there's more of them in the adult brain child areas as you might expect things are getting more connected, more wired up and these relationships also are changing with age. So the structure and function seems to be very highly correlated in the intact adult brain so that they're telling you the same story but in childhood those structural and functional connections are still kind of forming and they're not giving you the same picture.

This is just another study that shows the same concept using different networks but showing that in children compared to adults fiber density and the functional connectivity is lower and this changes across the lifespan. So these are what typical brains do, they strengthen in some areas and at the same time they also weaken their connections in other areas that I'm not showing here.

But then again what happens when we have a case where there's something that's not along the typical trajectory? So in some of our earlier works we looked at these relationships between functional and structural circuit changes after conditions. For example, here there's a patient who had a commissurotomy. So the corpus callosum was split so that the two hemispheres were disconnected from each other and this patient was 24 or so at the time of the surgery and years later when she was in her 70's we collected this data; the resting state FMRI and a structural MRI and even though the hemispheres are completely separated you can see clearly that connections exist between the two hemispheres especially here in the back brain which might surprise you because if you think, 'well, we cut the main system that lets the 2 halves communicate, why are they still communicating'? And this is something I'll come back to.

There are so many pathways for the brain to recover and rewire that it is not always the case that just cutting one thing is going to lead to a drastic reduction in functional activity. In fact, if you take a look at this split brain patient they have a very prominent posterior commissure, that's a very small track that goes across the back of the brain here and if you look at the fibers that go through there they're pretty intact, so it means there are some connections between the left and the right hemispheres. We cut the major ones but the ones that are left still appear to be doing something. So that's often the case in many of these interesting patients, that recovery comes from different ways where you might not expect it.

So I wanted to show you some exciting work that we did in collaboration with [---10:54] which looked at a few patients that had this pretty severe anatomical hemispherectomy. You can see that varying portions of the brain were removed here but you can see it was pretty complete in some cases. Left hemispherectomy. So this question of how do things change with both functional connections and structural connections after a surgery? In this case we tried to use the tools that I've been telling you about to get at this question. Anna Ivanova just published this paper in a journal called Brain Structure and Function, so I can send you the whole PDF is you want to read all the details, I'll give you my email address at the end so please feel free to e-mail me.

So Anna was an undergraduate student in my lab at the University of Miami for three years; she published this paper as part of her work with us as a first author and she's now starting grad school at MIT and she'll be studying language circuits in the brain for her PhD work, so I'm very excited to see what she ends up doing in the future.

For a little bit of background: We know from our previous work and other groups' works that you can find connectivity within these language networks even in the resting state, even if you don't ask people to actively do the test their brains are still going to cycle through some of these networks very spontaneously and these networks tend to involve the inferior frontal gyrus here on the left hemisphere and the parietal lobes and the temporal lobes as you see here which people often call Broadman area 44 and 45. A lot of the work that has been going on in cognitive neuroscience or maps the connections between these areas and how we think that certain parts of the frontal lobe are connected to certain parts of the parietal lobe and what-not and all of these circuits we think are really critical in the intact brain, in the intact left hemisphere of the brain for producing language in the human.

As you can also imagine a lot of people have studied individuals with left hemisphere injury or hemispherectomy to see what their brains are doing when their left hemisphere can't do the tasks that they are supposed to be doing. So in this case you have a series of fluency and language production tasks an in a typical adult brain you'll see that there's more left hemisphere activation while doing these tasks and not so much on the right but in this patient, if they don't really have a left hemisphere to rely on, this patient ends up using the right hemisphere as much as it can be used in order to accomplish the same task. So this is one of the ways that recovery can happen.

This is another example: Even if you are using the right hemisphere instead of the left it is not always the exact same regions that you would expect to see. So in these patients the actual areas of the brain that are used and more posterior than the areas in the control group, which are the yellow dots. So the patient group ends up suing a slightly more posterior part of the brain to accomplish the task – I think it was reading in here in this paper.

So in our own data here this is a comparison group to look at what happens to connectivity of this sort of [---14:24] left frontal region in the control brain and of course it's connected to the temporal and parietal areas as one would expect and if you look at the right hemisphere in the control you also have a little bit of temporal parietal connectivity so there is a right hemisphere network that is a homologue of the left hemisphere even though it doesn't look exactly the same as the one you see in the left hemisphere. This is in control group individuals.

Now if you look again at these 4 children who had hemispherectomy this is again the control at the top and the 4 different children here, you can see varying degrees of connectivity there. So some patients tend to have almost a full temporal parietal lobe network, others have very little connectivity, some are intermediate. So every patient is different, every brain is different, and each of these individuals have varying degrees of recovery in terms of reading and language as you would expect. So what we tentatively say that these patterns of functional connectivity of the right hemisphere language network is partially preserved in the patients who underwent left hemispherectomy. So it's not all exactly the same as the left and it's not entirely there but there are parts of it that you can see still remaining and possibly are related to the recovery of function. There's so much variability in this, this is just to illustrate that. These are 4 patients in different colors and it is just showing you the strength of the connectivity between the right frontal lobe and other regions here. This is frontal, parietal, superior, and temporal and you can see by the dots that there is a lot of variability; every subject seems to be different. The box represents the control group and the dots are where the patients fall within the connectivity value. So it is sort of all over the places as one might expect.

And just another quick look at this data, this is from 5 subjects and I am circling the parts of the brain, the parietal and temporal areas that we think are highly connected to the frontal lobes in the right hemisphere and I am also showing you this which is the age at surgery for each child and then the age at which the other group we are collaborating with collected the data (we're just analyzing the data). You can see that we have no control over this, when the surgeons decide to operate, when the MRI data are collected and there are great differences but for this particular patient who had pretty good recovered connectivity in the right hemisphere, surgery age 9, scanning happened at age 21. That was the particular individual who had the highest vocabulary and comprehension scores so it's not one to one: This one had good connectivity but not as great recovery.

So it is almost like there is some indication that seeing the intact connectivity gives us a clue that that individual will have good recovery in terms of function but it's not necessarily always so straightforward. This patient is obviously one case of less connectivity but in this case the one with the highest one was this individual here and you might not necessarily be able to know that just from looking at the brain but it's nice to try to map out some of these connectivity values to what actually happens in terms of the functional outcomes and we did what we could to try to map that here.

So basically I want to give lots of time to our next speaker who will be talking more about reading specifically but from this data I wanted to just give you the take home message that the right hemisphere language networks can be detected in some of the patients we look at who have undergone left hemispherectomy. So right hemisphere networks that we think underlay language processing we can get some sense that they're there and these red hemisphere networks may be responsible for some of preserved capacities of language that you see in terms of recovery in certain individuals.

Hopefully, the idea is to get more data. Longer term follow up, more data from more patients so we can see really where these individual differences come from and chart them in a more systematic way but I'm thinking that you know the kind of data, the resting state and DTI data that I've been talking about they can be useful for a lot of things. Perhaps eventually we will work with surgeons to think about how to determine an optimal age of surgery, is there a way to determine that using some of the imaging data? Can we track recovery of function and how those circuits redevelop or reemerge post-surgery in ways that help with recovery? Can we predict whether any particular intervention will do better or do poorly if we know something about the brain changes that occur alongside interventions? And what about other functions, not just language, motor or other kinds of sensory motor processes or higher cognitive language or other processes - what else can we track using some of these tools? So I'm hoping that this will encourage anyone who has access to do so to keep collecting MR data at various time points so that we have a better sense of how these things unfold. Maybe early on in life during onset, after hemispherectomy, during the course of intervention, during recovery, what does the break look like? As someone mentioned earlier we just don't know because no one is really collecting this data at several points to see what changes are occurring in brain.

This is the paper and like I said. If you want to go ahead and e-mail me I'll put my email on the last slide, I'm happy to send it to those who want to get more into the details of the analyses that I have mentioned. This work was done at the University of Miami, mostly by Anna Ivanova who has now moved on to MIT, and colleagues at UCLA, [---20:33] kindly provided the data and my work at Stanford was more brain development in atypical brains and my work at NYU when I was a post op there was looking at language systems and this is the funding that we have right now and again I will leave this up here for a minute if anyone wants to email me: l.uddin@miami.udu. Thank you very much.

For more information on the development of brain connectivity and hemispherectomy, go to www.brainrecoveryproject.org