# Webinar Transcript: Comparing Neuroplastic Changes in Ocular versus Cerebral Causes of Visual Impairment with Dr. Lotfi B. Merabet

So good afternoon. It's a pleasure to be here this afternoon at the Perkins School for the Blind and to talk to you about some of the research that we do here in Boston. While I'll be talking specifically about the neuroplastic changes in ocular versus cerebral causes of visual impairments, myself as a clinician and as a neuroscientist, working in this arena is extremely interesting on two levels.

First, obviously blindness and visual impairment is a concern not only here in the United States, but worldwide, and has a tremendous effect on a person's well-being, education, and rehabilitation. So from a clinical and education side, it's a very, very important subject. At the same time, from a neuroscience standpoint, it's also a wonderful opportunity to study the brain in action and how the brain develops and adapts to the loss of vision. So it's a great, great opportunity as well to understand the brain's potential over time and over development as well. So those are really the two main reasons why I'm in this particular field of research.

One place I always like to start when I talk about this particular type of research is to remind you that when we talk about vision, we talk about the eye and of course we talk about the brain, and both those pieces are very, very important in understanding visual function. So what a lot of people also need to realize is that the brain dedicates an enormous amount of resources to the process of visual function, and this has actually been quantified. And a useful way to separate the brain is to think of it from motor actions or motor things that the brain does, acting, versus sensory functions. Or in other words, the brain is taking in sensory information and integrating it.

And it turns out, if you just look at the cortex, about 44% of the cortex is for motor function, whereas 66% is for sensory function. And of this 66%, you can see that vision plays an enormous amount of parts-- an enormous amount of tissue is dedicated for the process of vision, more than touch, more than hearing, more than smell, which gives you a sense that, again, vision is an extremely important sense, and at the same time the brain dedicates an enormous amount of resources for this process.

Now you might ask, how can we quantify something like this? And the reason-- or the way that we could do this is to look at the cortical surface. And you can put electrodes in various areas and see that when you stimulate that particular part of brain, what type of sensation does that person have? Is it a sensation of smell? Is it a sensation of touch? Is it a sensation of vision, for example?

Similarly, we know from brain injury patients-- so these are patients who have damage to a particular part of the brain-- when that part of the brain is damaged, what is the sensory deficit that that person has? So over the years we've been able to get a good sense, you know, what is the relative contribution of all these brain areas to particular senses and function?

Notice that that's very, very different than a statement like this, where we say, do we really use only 10% of our brain capacity? And the first question I have in this particular case is-- this question, I should say-- is is this even true? And first of all, what does it mean to even quantify capacity? How does one measure that? It's not really a very, very easy concept to measure.

And second of all, if we only use 10% percent of our capacity, it then means that somebody has to be 100% in order for us to know what the relative difference is between the two. And again, that's also something that's not understood. So this is really what I call a neural myth. This is something that gets passed around at cocktail parties and so on without any real scientific or objective evidence.

And the reason why I think this is an important thing to bring up is because the reality is we use all our brain all the time. And studying neuroplasticity, how the brain changes over time and development and particularly in the case of sensory deprivation, like vision, is a wonderful example to demonstrate that indeed the brain uses itself 100%, 100% of the time. So it's a very, very important principle, too, to think about.

So I just mentioned this term, "neuroplasticity," and the term "neuroplasticity" comes from the Greek word "plastikos," which is also where we get the word "plastic," which means to mold or to shape or to form. So just like a piece of plastic can change its shape and its form under the right conditions, so too can the brain.

So this is a nice definition of plasticity. It is the ability of the brain to change its structural and functional organization in response to development, experience, the environment, or damage. And again, notice here that structural and functional are underlined, because it's important that when we talk about neuroplasticity, we need to talk about the brain's structure, and we need to talk about the brain's function.

It's also important to realize that it's not a guaranteed fix. We have this idea that neuroplasticity is this wonderful thing that will sort of solve all these brain lesion or brain damage problems, and unfortunately that's not the case. It's not a guaranteed fix. It's the inevitable consequence of how the brain works throughout a lifetime. Our goal is to understand those parameters and understand them in a manner that we can shape that and drive it in a manner that is beneficial for education, for clinical outcomes, for rehabilitation, and so on.

When we talk about neuroplasticity, particularly in the case of vision, we really should acknowledge the work of these two gentlemen. This is David Hubel and Torsten Wiesel, who shared the Nobel Prize in 1981, and essentially discovered everything we know about the visual cortex and how it's organized, its physiological properties.

And among some of the groundbreaking work that they did is they had these experiments where they worked with kittens, and they would rear kittens under different conditions. So they would keep both eyes open, for example, look at the visual properties of the visual cortex. They would cover one eye. They would cover both eyes. They would change the timing of that, and they would over time understand the importance of visual input into the visual cortex and overall brain development and how that related to visual function.

So this is extremely important work, not only from a neuroscience perspective, because this also laid the groundwork for what we do today when it comes to treating amblyopia, for example. This timing issue, the fact that we have a window of opportunity to fix various problems, is an important one, and that came directly from this work. This idea of patching, where the idea is that if you have a weak eye and a strong eye, the idea is to patch the strong eye to give the chance for the weak eye to take space into the visual cortex and regain as much visual function as possible, is a product of this neuroscience work. So that's why I think the importance of understanding neuroplasticity and neuroscience in general has a direct relation in the way that we take care and educate and rehabilitate individuals with visual impairment.

I always like to share stories about neuroplasticity. And here's one that is very important to me, one of my favorite stories. What you see in this particular picture here is a young man, a young boy. This was taken after the Second World War. This was a young child born blind, and like many children in his situation, learned to read braille.

Unfortunately, one day he was out in the field playing with his friends, and he picked up a landmine, and the landmine exploded and destroyed both his hands and he became a double amputee. And what you see in this picture is that he still can read braille, except he's not seeing the dots, he's actually using the tip of his nose and the surface of his lips to read the braille dots. And you can see in the second picture here that by using this sort of magnified braille text, he's able to go through and still read the text. So really a beautiful, incredible example about brain plasticity, how the brain under certain conditions can adapt and learn to do remarkable things.

In contrast, there are examples of negative plasticity. A good example of that is something like phantom limb pain. So these are patients who have an amputation of a hand or an arm or a leg, and feel that there's tremendous pain coming from that limb that's been amputated, and the reason why is because the brain has not been able to adjust to the fact that that limb is missing, and it manifests itself as pain. So that's an example of maladaptive plasticity.

So again, important to realize that plasticity has a positive and a negative. It's not necessarily a good or a bad thing. It's an inevitable consequence of how the brain adjusts over time.

Going back to this question of blindness, one of the interesting questions that got me interested in this particular arena was this idea that somehow people who were born blind were at an advantage. So you hear this idea that people who are blind hear better, have a keener sense of touch, a keener sense of smell. And it's really quite interesting to see that there was some scientific work in this particular arena.

So just as a thought experiment, let's take the example of Stevie Wonder, and I think an interesting philosophical question is that would Stevie Wonder be the incredible artist, talented artist that he is today, had he not been born blind? So in other words, if he was sighted, would he be the person that he is today? So how much did his blindness actually contribute to his development and his overall life?

And of course, there are many examples like Stevie Wonder, and not just in the musical arena, but other areas as well. I also have a picture here of Andrea Bocelli, who was a very famous opera singer. An interesting case about him is that he was not born blind. He lost his sight in his teens, and I think another interesting question to ask is that if you're born blind versus losing your sight later in life, how does that manifest in terms of brain development and your abilities as well? Something else that neuroscience is in the position to try to answer also.

So let's just go over very quickly some of the scientific evidence addressing this question of whether or not blindness is an advantage, and indeed there is quite a bit of scientific evidence out there. It's been shown that in the tactile domain, people who were born with ocular blindness have a keener sense of touch. They also seem to have a keener sense of hearing in terms of localizing sound in space.

They're also-- they show advancements in terms of identifying smells, compared to their sighted counterparts, and also show enhanced verbal memory. It's very interesting that if you give a list of words to a blind person, then you ask them to recall them, and then ask them a week later or a month later or months later, it turns out that blind individuals are able to recall many more words than their sighted age-matched controls are. So there seems to be quite a bit of scientific, behavioral evidence that blindness somehow confers an advantage.

Now that being said, there are a number of important caveats that have to be taken into consideration when we look at this data. First and foremost is that a lot of this evidence comes from scientific very, very well-controlled laboratory settings. Now it doesn't necessarily mean that if that manifests itself in the lab that it's necessarily going to manifest itself in the real world. So it's under very, very specific conditions that we see these advantages.

Secondly, what drives these advantages? Is it really a sense of sensory thresholds? In other words, do blind people have a keener sense of touch because somehow they have more neural machinery available at their fingertips? Or is it a different shift of attention?

And it seems that it's the latter. It seems that in the case of blindness, blind individuals are able to shift more attentional resources to that particular sense, compared to a sighted person, and that's how it manifests, as these enhanced behavioral functions.

Third point is the importance to understand that when we say that the blind are better than the sighted, it's also important to realize that maybe sighted people are just really poor when you ask them to do the same thing without their sight. So is it really the fact that the blind are better, or just are the sighted really, really bad when you ask them to do this under nonvisual conditions? So there's two sides of that coin, as well.

And the last thing that's important to realize is that this is not universal. It's not every blind person that seems to show this, or manifest these behavioral advantages, and we really don't know why. We don't know what the contributing factors are. Is it the onset of blindness? The profoundness? Is it the fact that you're a braille reader? Is it the fact that you're very, very independent in your mobility? We don't know what these factors are, and I think that's an important line of research that neuroscience has to consider as well.

That being said, I think it's interesting to look at the level of the brain directly for structural changes that manifest itself. So in this figure here, I'm just showing you sort of a cartoon representation of how the five senses are processed in different parts of the brain. So we have an area for touch. We have an area for smell, for taste, for hearing, and vision, of course, is represented in the back of the brain, what we call the occipital visual cortex.

From the structural side, there's quite a bit of interesting evidence. I'll just share with you one of them that I think is quite nice. This was a study done by Annette Sterr in 1998, and what she did was an individual mapping of the fingers of sighted controls versus blind individuals. So you probably already know that each individual finger is mapped in the brain, in the somatosensory cortex, so each part of the-- each finger has its own individual representation.

And what she found is that in proficient braille readers, that representation was actually fused, as if it was one finger, and you don't see this in sighted people. And the idea was that the somatosensory fusion was a product of the enhanced braille reading ability. So in the same way that it's as if they're reading with one finger, it's interesting that from a structural standpoint as well, that representation at the level of the somatosensory cortex manifests that way also. So there's an association with enhanced braille reading and the ability of the brain to integrate the information from the individual fingers.

On the functional side, I think a very, very interesting question is to wonder what happens to the fate-- or what is the fate of parts of the brain responsible for vision? You'll recall at the beginning of my presentation I said that a very, very large portion of the cortex is dedicated to visual processing. So the question now is, well, what does that all do if you were born blind? Does it stay silent? Does it do something else? Can it take on another function?

And this has actually been an interest of ours in our lab here in Boston, and also by other groups, and I'll share with you a summary of how we were able to answer that question. The technique we use is called functional magnetic resonance imaging, and you're all familiar with MRI. This is a way to get structural images of the brain.

What functional magnetic resonance imaging does is that it takes pictures of the brain in action, and the rationale is the following-- as certain parts of the brain work harder, it's going to command more blood and more oxygen, and that sets up a signal, a contrast, that the scanner can detect, and by mathematical analysis we could figure out parts of the brain that are going to be working harder than others on a particular task. So we put someone in the scanner. We ask them to do something, then we ask them to rest, and when we subtract the two, what's left over is theoretically areas that are associated with that particular task.

So let's look at one of the very, very first examples in this particular area. So what we see here is a sagittal section through the brain, and you'll notice in this blue circle area here, this robust signal, this hotspot of activity in the occipital visual cortex. Now this particular individual is congenitally blind, so the question is why would the occipital cortex-- why would there be such strong activation in the visual cortex of an individual who has never seen?

And the answer is this person is reading braille, and this was the very first demonstration of what we call crossmodal neurosensory plasticity. In other words, parts of the brain that are normally associated with a particular sense are functionally recruited to process other senses in the absence of vision.

And of course, interesting enough, there are other great examples of how this happens. It's true not only for braille reading. There is evidence that this is true for identifying smells. This is true also for localizing sounds in space. It's also true for language and it's also true for verbal memory. So when a blind individual carries out these nonvisual tasks, it's using the part of the brain that is normally ascribed to vision. And this gets back to my earlier point that you use all your brain all the time, and this is, I think, a really dramatic example that the brain is going to use all the resources at its disposal.

Some interesting follow-up questions came from this, leading to this idea that if you're born blind versus losing your sight later in life, is there a difference? Well, this was studied also by a group of scientists. This was work by Harold Burton and what he did is he compared early blind individuals who were proficient braille readers with late blind individuals-- in other words, individuals born blind but lost their sight in their teens or as adults, who were matched for their braille reading ability. And it's important to realize that their braille reading skill was the same in both groups.

And what you see here in these two red circles is that in both cases, the occipital visual cortex was active, but you'll notice that in the case of early blindness, there was more recruitment of the visual brain for this process than the case of late blindness, as if to suggest that the earlier and the more profound this blindness happens, the more likely the brain is going to recruit the visual brain, visual parts of the brain, to do nonvisual things. So the timing issue is very, very important.

An interesting experiment that I was involved with when I was-- my first few years here as a fellow was something called the blindfold experiment, and the interest in this experiment came from two observations. The first was this question of whether or not you have to be born blind to have these changes in the visual cortex, and did you have to be a proficient braille reader or blind for a long period of time for these changes that happen, or we could somehow create artificially or induce these changes in the brain in experimental fashion.

The second was this observation that we had talking to various braille instructors, telling us that sometimes-- at least anecdotally-- when they had children trying to learn braille who had some sort of residual function, often what they would do is blindfold those individuals, and they found that this was enhancing their braille reading abilities. We wanted to study this in a more scientific fashion, and this is how we did it.

So we conducted an experiment called the blindfold experiment, and we took normally sighted adults who came and lived at the hospital for five days. So for five days they were living at the hospital, and they were intensively taught braille by a professional braille instructor for four to six hours a day, by the same instructor. You'll notice that in this picture here they are wearing a blindfold. So they were blindfolded throughout this period of the five-day experimental period, as I said, living at the hospital, learning braille four to six hours a day.

What we would do is we would take these individuals after their braille learning session and we would put them in the scanner, just like I showed you in the previous slides. And you're looking here on day one at the back of the brain. We asked this individual to lie on the scanner and we stimulate the tips of their fingers.

And if you notice at the back of the brain here there really isn't much going on. It's very, very quiet. But if you look at the top left here, you'll see that that little hotspot activity corresponds to the activation of their finger. What's interesting is that as the week progresses, as they get better and better at the braille reading skill, notice how the back of the brain here on the bottom row is becoming online.

So in other words, it's becoming responsive to tactile stimulation as the week continues. So five days is enough to make these crossmodal changes happen. You do not have to be born blind or be blind for a long, long period of time. You can actually induce these crossmodal changes in the brain with very, very rapid consequence.

Interesting thing after this is that after the fifth day, we take the blindfold off. We give the individuals 24 hours to recover their vision, and we put them back in the scanner. And after-- on the sixth day, as I mentioned, after 24 hours, you'll notice that that activity is essentially gone. So almost back to what it was on day one, in terms of baseline. So you can reverse these changes very, very quickly as well.

The other piece of evidence that's quite interesting is that if you look at the behavioral evidence, so what happens to their braille reading ability over time, so what I'm showing you here in this blue line is over time the error rates that these individuals are making on a braille recognition task. So this is what's called the control group, the nonblindfolded group. We had a group who were blindfolded throughout the five days, and we also had a control group who were also living at the hospital, learning braille with the same instructor four to six hours a day, but who were not blindfolded. So we're controlling for the effect of the blindfold.

So what you see here is that normally sighted individuals who were not blindfolded, who went through the five-day training, their error rate was getting lower and lower as the week progressed, as you might imagine. As they get better and better at learning to read braille, they get better and better at the task. The interesting thing is that if you compare the performance of those who were blindfolded, their performance was actually better. So in other words, somehow blindfolding enhanced their braille reading ability. You can see on day one, they're starting at essentially the same level, but they're making fewer mistakes after day five than the group that were sighted throughout the week.

The other thing that was interesting is that if you take the blindfold off, and you give them again those 24 hours of recovery, and you test their ability, you find that their braille reading skill actually gets worse. So somehow putting vision back into the equation almost reverses these effects, in a sense, showing you again how rapidly and dynamic these changes occur at the level of the brain.

So one last piece of evidence I want to share with you on this particular case of ocular blindness, because you may ask yourself, well, you know, it's one thing to see this activation in the brain, but does this activation actually tie in to the abilities that we're talking about? And I want to show-- or share with you, I should say, a clinical example that really answers that question specifically. And this was a patient I had the chance to work with when I first started my fellowship, but I was not there when this actual event happened, so I'm telling you the story the way that it was told to me.

So the case report sounds a little something like this. So this was a 63-year-old right-handed female, at the time, who was blind from birth. She had retinopathy of prematurity, and her reported visual acuities were no light perception in either eye, so in other words she had very, very profound blindness. She hits normal milestones. She learns to read braille at the age of six, and she's a highly proficient reader. 120, 150 symbols per minute is a very, very fast braille reading time.

One day she wakes up in the morning and she's not feeling well. And she worked as an editor for a braille journal, so she took her job, obviously, very, very seriously. She said, you know, I'm going to go to work nonetheless. I'm sure it will pass.

She still feels very, very lightheaded. She has difficulty swallowing. She then loses consciousness. She actually passes out. She's rushed to the hospital and she falls into a coma for 24 hours.

She wakes from the coma. She's alert and she's interactive. She feels fine. In fact, she's given a normal physical and neurological exam by the attending doctors, and they said, you're all right, you're in the hospital, everything's OK.

And she goes, I'm glad to hear that. Could you please give me my phone book-- which is written in braille-- because I'd like to contact some of my friends and family and tell them what happened.

And the interesting thing is that when they handed her her braille phone book, she starts reading the braille text and she recognizes that it's braille, but she realizes that she can't make sense of any of the text that's there. In other words, she knows, she feels the dots, she knows it's braille, but it's almost as if it's written in another language.

She says, I don't understand. I can't make sense of any of the dots or the patterns that are here. So the interesting thing, or the unfortunate thing that happened in this particular case is she had a stroke in her visual cortex. So what I'm showing you in this scan here, and the red arrow is showing you these white areas here are infarcted tissue. This is areas of the visual cortex that are-- that have completely died off because of the embolism, the stroke that she suffered.

So she became alexic for braille, meaning the acquired inability to read braille, following on occipital stroke. Not damage to the brain responsible for language, or the part of the brain responsible for touch, the part of the brain that's normally ascribed to visual processing. So pretty pervasive-- or unfortunate evidence, I should say, that what's happening in the visual cortex is indeed part and parcel to these compensatory behaviors that we see in the case of ocular blindness.

So just as an introduction, I hope I was able to kind of give you this sense that in the case of ocular blindness, the occipital visual cortex-- that's to say the part of the brain normally responsible for visual processing-- is functionally recruited to process nonvisual information-- everything from touch, braille reading, to memory, to smells, to localizing sound in space. And this, we believe, is very, very important to-- related to the compensatory behaviors that we see in people with ocular blindness.

Now, I think an interesting question to ask is what about individuals who are not necessarily ocular blind-- or visually impaired due to ocular cause, I should say-- but rather have congenital damage to their occipital visual cortex? How does this manifest itself in terms of neural plasticity and these behaviors?

So of course, there is a condition where this actually exists, and this really leads to my link of how we evolved from the case of ocular blindness to the situation of CVI. And I just want to share this picture with you at Perkins. During my time here, when I was an intern, I was already becoming aware that the profile of the classic Perkins child was changing.

So of course Perkins has a very, very long history with the blind community, and the classic presentation of a blind child here at Perkins was one of an individual who had some sort of ocular cause or ocular problem, but the rest of the brain was largely intact. And as time sort of moved on, the profile of that child changed tremendously. So there were individuals who had particular cognitive problems, perceptual problems, multisensory deficits, deafness and vision as well as cognitive issues as well. So the profile of visual impairment, or the profile of the classic individual who was going through the Perkins system-- and again, not just here at Perkins but other schools as well-- was changing fundamentally.

So what it means to be visually impaired today is very, very different than, say, 30, 40, 50 years ago. And we're very, very intrigued in this, because again, going back and talking to some of the educators and our colleagues here, they were telling us that a lot of the strategies, a lot of the things that they were developing that has worked time and time again for individuals with ocular blindness, didn't seem to work as well in the case of individuals with these other issues. And we were very interested to try to understand what was the difference, from a brain plasticity standpoint, that might explain this observation.

So of course, the population that we're talking about is CVI, so this is cortical or cerebral visual impairment, and in my mind is really a public health crisis. So CVI affects nearly two out of every thousand live births and accounts for nearly 20% to 25% of visually impaired children in developed countries. And it's important to stress that this is in developed countries, not developing countries.

I'm showing you here some statistics. This was an article in 2002 from the United States looking at the causes of vision loss in students from schools for the blind in the United States with a very, very large study sample. And what you notice is that cortical visual impairment is the number one cause of visual impairment in the kids who were enrolled in this school. So you can see that the demographics, the epidemiology of this condition is quite alarming.

You look at other causes, for example, like syphilis or herpes or rubella, well, these are all infectious. These are things that over time we're going to get a better and better handle on. You would think that these incidences are going to decrease. At the same time, think of conditions like Leber's or retinitis pigmentosa. These are conditions that have a genetic basis, and you would think again, with our advances in genetic therapy, for example, these will also decrease over time. ROP, or retinopathy of prematurity, was something that was very, very common in the past and fortunately it is decreasing now, because we know that this is something that we were doing in the neonatal care units and we have a better understanding of this condition.

So you might ask yourself, well, why is CVI so prevalent? Why are these numbers so high? And the reason is that there's a strong association to the fact that we are getting better and better at saving premature babies. Very, very often, these kids who have CVI are also born premature. And the fact that these babies are now surviving, these babies are living and living longer and living with various consequences, and their visual problems is just part of that problem.

So let's talk a little bit more about the case of cortical or cerebral visual impairment, or CVI. The major causes of CVI are perinatal hypoxic or ischemic events. In other words, in a sense the developing baby has a stroke in utero. Other causes that are quite common are head injury or trauma, as well as infections, such as encephalitis and meningitis.

It's also useful to separate cases of CVI in terms of preterm versus term born babies. In the case of preterm, the common sequelae of this particular situation is periventricular leukomalacia-- "periventricular" meaning surrounding the ventricles, "leuko" meaning white, and "malacia" meaning soft, because that's the appearance it has on various types of brain imaging.

So again, what happens is that essentially the baby suffers a stroke during development, and there is blood that rushes into the cerebral ventricles. And as that blood is resorbed, you see this enlargement of the ventricles, the characteristic shape of PVL, or manifest of PVL. But the problem is that surrounding these ventricles there is death of these white matter tracts that course through, which are very, very important for sensory and motor functions.

Contrast that in the case of term born babies, which we refer to as hypoxic-ischemic encephalopathy, or HIE. In this particular case, again, there is some sort of diffuse hypoxic or ischemic energy-- excuse me, injury-- but again, in this particular case, because the baby is born term, it's under different circumstances. And again, we see this diffuse white matter injury, due again to this oxygen-poor, oxygen-starved areas of the brain, but we do not see this characteristic enlargement of the ventricles as we do see in preterm or PVL.

Other things to keep in mind in terms of CVI. So CVI is suspected by, quote, "a normal eye examination," but I think a more-- or more accurate way to think about this is that a situation where ocular findings do not correspond to the visual impairment that's detected. In other words, there are all sorts of manifestations that cannot be explained by any type of pathology at the level of the eye. Visual acuity can range from near normal to profound blindness, and typically visual field deficits are also present, and this is often in the inferior visual field.

There are characteristic neuroradiological findings-- again, as I mentioned, PVL or some form of white matter injury that results. And often there is a medical history that includes some sort of neurological impairment. This could be cerebral palsy or epilepsy, for example.

But really the key thing to keep in mind is that very often in the case of CVI, there is the presence of unique visual or behavioral dysfunctions, for example, some sort of visual spatial impairments, or difficulty in motion processing, difficulties with complexity and crowding and attention deficits.

Very often these children will tell you that they cannot recognize their favorite toy in a toy box, for example. Sitting by itself they can identify it, but when you put it in a complex environment, they can't find it. Or they cannot find their parents or their friends in a large group of individuals, or they have a hard time following a TV program that has a lot of action, a lot of complexity to it as well. And again, this is something that cannot be explained by some sort of pathology or problem with the eye. It's a manifest of what's happening at the level of the brain.

Another question that I hear a lot that I think is worth spending perhaps a minute or two is discussing the C in CVI, in other words, cortical versus cerebral visual impairment. Is this the same thing? Is it two separate things?

Unfortunately, I think it really starts off with the fact that cortical visual impairment is a misnomer. When it was-- the term was originally coined, we called this cortical visual impairment to differentiate that from problems related specifically to the eye. But the fact is that it's not just simply a cortical phenomenon. It manifests at the level of the optic nerves, the subcortical structures, the optic radiations, and of course cortical areas as well.

So in many ways, "cerebral" is a more encompassing and perhaps more appropriate term. But at the same time, I think it's also from a functional standpoint worth separating cortical and cerebral visual impairment from a functional standpoint. So cortical visual impairments-- and one way to think about it is damage to early visual areas and/or the optic radiations. And typically this results in poor visual acuity and manifests also in terms of visual field deficits.

In contrast, cerebral visual impairment tends to be damage to higher order visual areas, so parietal cortex, temporal cortex, frontal areas. And typically visual acuity in this particular setting can be normal or as moderate visual impairment, but there are also-- what manifests as these higher order visual perceptual deficits, like motion perception, complexity, and so on. The important thing to think about is that these two terms are not-- or these two scenarios are not mutually exclusive, so cortical and cerebral visual impairment do not necessarily occur separately. They can certainly manifest at the same time. So on one level, separating cortical and cerebral might be useful just to kind of get a sense of what we can anticipate the problems or the deficits the individual has.

Let me now describe the profile of the individuals who are involved with our CVI study, and to date we have nine participants who were involved in our study of CVI. These individuals are aged between 14 and 21 years old. And to give you an explanation of why we chose this category, it's largely based on technical and IRB considerations, IRB meaning the Investigative Review Board. This is the ethics committee of our hospital that decides what we can do in terms of our studies.

First and foremost, we cannot anaesthetize our individuals in our brain scanner because they have to be able to, one, carry out the task that we're asking them to do, and of course they have to be awake for that. And there's also associated risks, as you might imagine, anaesthetizing individuals. We wanted to avoid that.

Secondly, we have the advantage of working with slightly older individuals. We have the advantage of these individuals being able to report their particular visual deficits and describe. So we get a lot of feedback directly from these individuals, telling us what they have difficulties with and so on.

And finally, the last piece to think about is that working with this age category also is much easier from a data analysis standpoint as well. A lot of the algorithms and the data analysis packages that we use are designed for adolescent and adult brains, so carrying that over to a pediatric brain is very, very difficult. So in our first early phases, we wanted to spend time focusing on this particular age category.

I think these individuals can be characterized as having moderate to-- or being moderate to high functioning in terms of their verbal abilities and mobility. We use varied assessments for-- to characterize this level of function, and this is equivalent to phase three on the CVI range assessment by Dr. Christine Roman. Again, these individuals all carry a previous diagnosis of CVI.

Three are PVL and two are non-PVL, in other words, three preterm and two term born babies, or two term individuals. Visual acuity ranges are from 20/20, so that's normal, to 20/100, and associated comorbidities include one with cerebral palsy, one with spastic diplegia, and one has seizure activity. And in terms of education, three were mainstreamed through high school, one was homeschooled, and one was through a residential school program.

What I want to show you here is using standard MRI imaging, giving you a sense of what the brains look like in these particular individuals. In A, in the top left, I'm showing you an axial cut through the brain. And you're looking at a 17-year-old female with 20/20 vision. This is a normally sighted control. And you can see, again, the great, beautiful detail that these MRI images give us.

And if you compare that to B, this is an ocular blind girl. She's 25 years old. She is blind from Leber's congenital amaurosis. Her visual acuity is light perception, and you can see immediately that from the base in terms of the structure of the brain, they look virtually identical. In other words, looking at an ocular blind versus sighted control individual in terms of their brain structure, or at least grossly, tells you absolutely nothing in terms of who is the blind versus who is the sighted individual.

In contrast, if you look at individuals with CVI, in C, in the lower left, I'm showing you a picture of an individual with PVL, or periventricular leukomalacia. This is a preterm born individual, 16 years old, female, with 20/60 visual acuity. And the arrow shows you this characteristic enlargement of the lateral ventricles that you see here, again, a very typical telltale sign of periventricular leukomalacia.

In D, in contrast-- this is also an individual with CVI-- a 16-year-old male non-PVL, and notice here that the size of the ventricles appear quite normal, but the arrow here is showing you this area of damage in the frontal cortex which is quite extensive. And notice also that this person's visual acuity is 20/100, actually worse than the individual that I'm showing you in part C, but the morphology of the brain, the structure of the brain, looks very, very different.

So again, already separating CVI in the case of PVL versus CVI non-PVL seems to manifest very, very differently. And we were very interested in understanding how from a brain wiring standpoint this was associated or related to visual deficits in these individuals.

So the hypothesis that we were working on is the following-- our thought is that CVI is a disorder of brain connectivity. In other words, how the brain is wired, put together. And this underlying connectivity is associated with the observed visual dysfunctions. If we understand the wiring of the brain, we will have a better understanding of how these dysfunctions actually manifest themselves.

So the question is how can we actually map the wiring of the brain? And we use a technique called diffusion based imaging, or the particular variant that we use is called HARDI, which is High Angular Resolution Diffusion Imaging. And the point is the following-- is molecular motion inside the brain, or in any part-- or anywhere in the world, is affected by the properties or the medium in which it occurs?

So let me explain it to you this way. If we were to track the motion of water, of, say, in the ventricles of the brain, the motion of that water molecule would be completely random in 360 degrees and in three dimensions, and we call this isotropic diffusion. So at any given time, that motion of that water molecule could be anywhere in three dimensional space.

In contrast, if we looked at water motion in the white matter of the brain, where the axons, where the connections of the brain are passing through, we call that motion anisotropic, which means that the water molecule is more likely to travel down one axis versus the other, because it's constrained by the fact that it's contained inside the axon. So in other-- why is that motion constrained? Well, If it's associated with an axon, a nerve cell, that tells us something about the orientation of that nerve cell. So in other words, we track the motion of water to tell us a little bit about how that axon is oriented. And again, with high-powered computers we were able to make these multitude and multitude of computations and recreate the three dimensional architecture of white matter connections, and this is what I'm showing you in this figure here.

So in this video you are seeing a three dimensional rotation of the brain. These are all the white matter connections inside the brain. So you can see that as the brain is spinning here, another nice thing we can do is virtually dissect pathways of the brain as well. So here we asked the software to just show us the connections of the back of the brain, the visual cortex, to the rest of the brain.

So just to give you some explanation, the colors here represent orientation, so pathways that you see in green are pathways going from the back of the head to the front. Pathways that you see in blue are going from the top of the head to the bottom, and pathways that you see in red are pathways that go from the left and right hemisphere and back and forth. So this is our technology that we use to look at the brain wiring or the brain connectivity.

So if we look at this same imaging technique in those four individuals I mentioned previously, let's take a look and see how these pathways manifest themselves. And in particular we're going to concentrate on the visual pathways. Again, we asked the software to simply focus on the connections of the visual brain, the occipital visual cortex, to the rest of the brain.

And what we find is that there are three major pathways of interest that show up. The first is what's called the SLF, and this corresponds to the dorsal pathway, or the Where pathway, which is involved with spatial processing. So we now have the white matter correlate, or the white matter pathway, that corresponds to the spatial processing or the Where processing pathway.

In contrast, what you see here in red, diving from the back of the visual brain into temporal cortex corresponds to the ILF, and this represents the ventral pathway, or the What pathway, involved with object processing. And this third pathway, which represents direct connections from the occipital cortex to the frontal cortex, which also incidentally is part of the dorsal stream, is called the IFOF, and this is a pathway involved with attention processing.

So what we have here is the opportunity to dissect these three pathways involved with visual processing. If we do exactly this same sort of analysis, we look at the connectivity of individuals with ocular blindness, you'll notice that it looks very, very similar. In other words, the SLF, the IFOF, and ILF are all very, very well developed, so what this tells you then, even in the case of ocular blindness the connectivity of the brain is largely there. So it seems to be largely intact.

In contrast, if you were to look at an individual with CVL, and particularly a case with periventricular leukomalacia, you see right away that there are much fewer connections there. In this particular case, you see there are very, very few connections going from the occipital cortex through the dorsal stream, larger amount of connections going through the ventral stream or the object identification pathway.

And what's interesting is that if you look at the functional assessment of this particular individual, this individual had very, very strong spatial deficits and spatial awareness deficits, again, fitting with the fact that a dorsal pathway didn't seem to be as well developed. Mild object identification deficits, again, largely because the ventral pathway seems to be there, and had very, very strong attentional deficits, and you can see that this seems to be associated with the fact that those direct connections from the occipital visual cortex to the frontal cortex seem to be missing as well. So it seems that the white matter pathways seem to fit the functional profile of these individuals.

In contrast, if you look at an individual with CVL-- or CVI but is non-PVL, was born term, you'll see that the pathways seem to be much more robust, much more intact. And this already gives us a sense that CVI in terms of PVL versus CVI non-PVL form seems to be already very, very different in terms of the connectivity that is there.

Let's look now a little bit more at characterizing the visual functions or visual deficits that we see in individuals with CVI. So we are developing a number, or a battery, of tests that are tablet-based, or touch-tablet-based, so the individual doesn't necessarily have to be verbal in these particular tasks, and by touching various targets on the screen they can tell us what we see, and we have been measuring everything from contrast sensitivity to biological motion. Virtually any type of psychophysical test you want can be done in this-- using this particular apparatus or this setup.

But one particular test that we were interested in is looking at optic flow of motion, and this relates to the fact that a lot of the individuals we've been working with have been telling us that they have deficits in terms of perceiving complex motion. So when they walk, for example, through the corridor, or when there are a lot of individuals walking around them, they get very, very disoriented. They have a very, very hard time finding their way. So we used a psychophysical test to try to emulate-- to replicate that in a scientific and controlled fashion. And the way that we do that is a task called optic flow of motion.

So in this video here I'm going to ask you to look at the center of the screen there. There's a green dot, and when I play this video, you'll see there are all these little dots moving. But if you look very, very carefully, get a global sense of the motion of these dots, you'll notice that the dots are moving away from you. Now they're moving towards you, moving away, and now moving towards you. Right?

So we call this optic flow of motion, and we simply ask the individual to look at this pattern, and we ask them, tell us when the dots are expanding or tell us when the dots are contracting. We quantify this by something called a motion coherence threshold. In other words, the percentage of dots that have to be moving together tells us something about how well your visual system is able to integrate that information in a meaningful way. In other words, are you moving through the environment, or are you moving out of the environment?

So this has a lot of ecological relevance, obviously. The other nice thing about this is that you'll notice that whether you're looking at the green dot in the middle or looking off to the side, you can still do the task. So in other words, this is fixation invariant, so even if you have an individual who cannot look at-- maintain fixation at the center, we can still get an accurate assessment of what their motion threshold is. So it's a pretty robust way of allowing us to quantify how well you're able to integrate these motion signals at a global level.

When we tested normally sighted controls in this particular case and in our age category, we found that typically individuals will score between 5% to 25%. So what does this mean? In other words, 5% to 25% of the dots have to be moving together in order for the individual to tell us what direction those dots are moving in. And when we tested our particular age-matched cohort, we found a threshold of about 16%. In other words, 16% of the dots have to be moving together in order to tell us what direction this is moving in.

In contrast, when we tested our CVI subjects, we got a threshold on the order of 43%. In other words, it takes about three times more information, three times more coherence, in order for the individual to tell us what direction those dots are moving in, which fits in terms of the clinical manifestation these individuals have. So it tells us that in this particular case, in the case of CVI, their ability to integrate motion signals or complex motion signals seems to be impaired.

So the next step we were interested in is going back to the brain and figuring out how did this manifest itself in terms of the functional activation of the brain? So you might be familiar with the fact that there is a part of the brain specifically responsible for motion processing, and that's called area MT, for middle temporary area, or area V5. And that pathway sits actually on the dorsal stream in the Where pathway. So a specific part of the brain responsible for motion integration.

So we went back, took this same task, and had our individuals do exactly the same thing in the scanner. And here you're looking at a brain. This is the right hemisphere of a control individual looking at this motion coherence task at 30% coherence. In other words, we know that this is a value that's higher or allows them to do the task very, very easily, but we know that's a coherence level that it's lower than what we've seen in terms of our CVI subjects. And what you see here, this little yellow hotspot of activity, is area MT, and you can see very, very strong, robust activation in this hemisphere in response to looking at this motion coherence stimuli.

In contrast, if we look at an age-matched individual with CVI with exactly the same level of coherence, you see that there's virtually no activation here. You see the small red spot there. You can see that that part of the brain is not anywhere as active, as robust, as it is in the case of the sighted control.

The interesting thing is that if you take this same individual and you now use 100% coherence, in other words, you make all the dots move in the same direction, all movement is coming in and out, and we scan them again, now you see robust activation in area MT, which tells us that in these particular situations, if you increase the coherence of that signal, you can actually drive the system to comparable levels. So that gives us a sense, or at least a neurophysiological basis, telling us that coherence is probably a very, very important signal in terms of improving the saliency of the visual percepts for these individuals.

We've also looked at the connectivity of this particular pathway as well. We've asked the software here to ask-- or to show us connections between the primary visual cortex and area MT. On the left, I'm showing you in a control, you can see this very, very nice arborization of pathways and nice connections between the two areas.

In contrast, when you would do exactly the same area in CVI, you could see that this pathway is much thinner. It's still there, but much, much thinner in terms of the information that's flowing. And this again kind of fits with this idea that because the pathway is reduced, you have to drive that information that much harder for the signal to actually get through. So the structure and the function and the percept seem to all go together.

Another thing we've done from an analysis standpoint is looked at network connectivity. So in other words, not just the occipital cortex and visual pathways, but the brain as a whole. And the way that we do this is a technique called graph theory. So what we do is we take the brain and we separate it or parcellate it into many, many different areas. So we divide the brain up or we chop the brain up in different areas, and each particular area is represented by a dot that you see here. And of course, we do this throughout the whole brain.

Then we ask the computer to tell us how strong is the connection from one part of the brain to another? And when it's strong, it puts a line between the two, and the thicker that line is, the better the connection is between those two parts of the brain. And of course it goes through multiple, multiple calculations and does this throughout the brain to develop a complete network.

When you do this in our sighted controls-- you're looking at the network here-- you can see very, very strong connections throughout the brain in the case of sighted controls. If you compare this now in the case of ocular blindness, you see also very, very strong connections throughout the brain. And again, this probably is not surprising to you, because in the case of ocular blindness, we see these compensatory behaviors, largely because the brain network is largely intact, and all the pathways are there, and it's simply a question of shifting attention through these pathways to allow these compensatory behaviors.

In the case of CVI, however, what we see is a much thinner network. So in the particular case here, you would see lots of blue indicating weaker connections, red meaning strong connections. In the case of CVI, it is essentially an underconnected brain throughout. And we think this represents the fundamental difference between ocular blindness and CVI. In the case of ocular blindness, you have a largely intact and perhaps in some particular pathways are even enhanced compared to sighted controls. But in the case of CVI, you have an underconnected brain. I think this fundamentally represents the connectivity question that we're trying to get at and explaining these neuroplastic differences between ocular blindness and CVI.

So our overall goal is to correlate clinical, structural, and functional findings in CVI. The idea is that if we can clinically describe as best as possible the functional deficits that these individuals have, from visual acuity to contrast to mobility and overall functionality, tie that in to the structural connectivity of the brain, and I've showed you how we used this technique of diffusion based imaging to tell us how the brain is wired, added to the piece of functional neuroimaging showing which parts of the brain are active during certain tasks, the idea is that all three of these pieces should be interconnected, and by knowing one, I should be able to understand the other two. So for example, if you show me the connectivity, I should be able to predict the clinical manifestations of that, and at the same time, if you showed me the functional activation, I should get a sense of what that connectivity looks like as well. So this is the overall theme of the project that we were pursuing.

So in the last part of my presentation, I want to just share some last thoughts with you that I think is a way to kind of take these principles of neuroplasticity and generalize in the case of CVI and ocular blindness and brain development in general. A question that I often get is how does damage to particular parts of the brain relate to different types of deficits? And I certainly think this is an important concept to think about. Of course, it's difficult to generalize, because every individual is very, very different, but I think it's useful to break down the brain into three parts and kind of get a sense of how those three parts relate to different deficits.

So think of the gray matter of the brain as where all the processing actually occurs, in contrast to the white matter deep inside the brain, where all the information is being shuttled around back and forth. These are the pathways. And the thalamus, where all sensory information enters the brain initially and then is sent to higher areas for processing. So those are the three levels-- white matter, gray matter, and the thalamus.

And the analogy I'd like to use is to think of your brain as a high rise tower, for example, and all the operations that happen inside that building. Think of the gray matter or the cortex as the cubicles where all the decisions are being made. In contrast, think of the white matter as the elevator system that's shuttling information from the various floors, to one floor to another. And finally, think of the thalamus as the lobby of the building, where people are coming in and exiting the building.

So using this same analogy, if you have damage to the cortex, typically what the brain does is it tries to recruit the cubicles next to it in order to try to process that same information. And this is exactly what I mean by crossmodal sensory plasticity. The brain will try to use other parts of the cortex to try to do exactly that same function.

In contrast, if you have damage to the elevator system, then it's very, very hard for information to go from one area to another, but there may be other ways to get there. There might be a stairwell. There might be other pathways that you haven't discovered yet. But it certainly challenges how information is exchanged from one part of the brain to another.

And the last thing to think about is that if you have damage to the thalamus, then now it's really, really hard for information to enter and exit the building, in the same way that if you had damage to the lobby, then nobody can really get in or get out of the building, and that obviously has quite important repercussions in terms of processing as well. So this might be a useful way to kind of use an analogy to understand how different parts of the brain work and how damage to different parts will also manifest in terms of sensorimotor deficits.

Getting back to this idea of the thalamus, we started to look at this initially from a structural standpoint. We're very interested in trying to understand how does thalamic damage manifest, or how does that relate to the case of CVI versus normal development or in the case of ocular blindness? So if you look at the actual volume of the thalamus, which I'm showing you here in yellow, so in yellow you have an outline of the thalamic volume, and you can actually quantify this.

In the figure on the right, you see in red the normal volume of the right thalamus and the left thalamus in normal developed controls. In contrast, in the case of CVI, you'll notice that in both hemispheres, both the right and left thalamus are showing decreased volumes-- in other words, are underdeveloped in terms of their size.

And also interestingly, if you separate CVI versus-- excuse me, PVL versus non-PVL CVI, you notice that in the case of PVL the thalamus is even smaller than in the case of the non-PVL CVI. In this particular case, the thalamus is much larger. And again, this may relate to the differences that we see in non-PVL versus PVL forms of CVI. When the thalamus is larger in terms of development, we may have a greater possibility of information entering and being channeled through the brain, whereas we don't seem to see-- have this same sort of manifest in the case of PVL forms of CVL-- of CVI, excuse me. So looking at thalamic volume may give us an indication about overall sensory function as well.

Another area that I hear a lot about that I think is worth reviewing is this idea that the visual system is divided in terms of its functional specialty. So as I mentioned earlier, pathways from the back of the visual brain, the occipital cortex, entering the parietal cortex and terminating in the function-- in the frontal cortex is called the dorsal stream, or the spatial pathway. This is responsible for telling us where objects are in space.

In contrast, the pathway from the occipital cortex through the temporal lobe, or what's called the ventral stream, is responsible for object identification. This allows us to identify objects, identify what they are, faces, houses, and so on. And this is-- this division of labor, if you will, is something that's been very, very well known in the neuroscience and visual science literature for quite some time.

It's interesting that individuals in the case of CVI have proposed that CVI is actually a dorsal stream dysfunction, that somehow the dorsal stream may be more vulnerable, if you will, in terms of development compared to the ventral stream, and that may be related to the fact that individuals with CVI seem to have all these spatial problems. So it's interesting that this division of labor may very well also fit in terms of the manifestations, but we found that there really wasn't that strong neurophysiological evidence to support this. And this I think is something that we want to pursue as well in our study of neuroanatomy and structural connectivity to give us a handle in terms of whether or not indeed CVI is a dorsal stream dysfunction.

Dr. Gordon Dutton has come up with a very, very nice figure that you see here in the upper right, what he calls the Tree of Visual Perception, and the idea is that there is the left and the right eye, that information enters into the thalamus and then separates into the dorsal and ventral stream. I think a nice figure to sort of summarize this division of labor and specialty of the visual system, but unfortunately I think it fails to capture a very, very important point about the visual system, in that the visual system is not a linear process where information enters the eye and then just simply enters the brain. The reality is the visual system is much more of a circuit, where information is being constantly being shuttled from higher to lower visual areas. So there's this constant exchange of information that you see in the circuit diagram here as well, which I think is a much more accurate depiction of how exactly information is processed in terms of the visual brain.

I'd like to illustrate an important piece about this idea of visual perception using a very, very famous visual illusion I'm sure you've seen before. If you look at this visual illusion, you'll see one of two things-- either two black faces, two silhouettes looking at each other, or you'll see a white vase, but you'll notice you'll never see both at the same time. And we call this a bistable visual illusion.

And this is really the product of your visual system at work. It is the product of what's referred to as bottom-up influences, in other words, information that's coming from the eye, the image that's captured in your eye entering the brain. And it's also the product of what's referred to as top-down influences, which means all your past visual memories and experiences and recollection.

And what you see is actually a combination of those two processes. The reality is that top-down influences are much larger than bottom-up, and the proof of that is the following-- you'll notice that at no time do I ever change this image. In other words, the image that falls onto the retina is always the same. What changes is your percept, and your percept is changing because of this top-down influence. So it's important to realize that what you see or how you see the world is a product of these two forces.

Let me illustrate this a little bit further or a little bit more in detail. Let's just say, out of curiosity, you were looking at a picture of the Mona Lisa. The bottom-up influence of that picture is these feed-forward projections from the eye into the visual cortex and eventually leading to the dorsal and ventral stream. And this is based on direct visual input, the capture of the visual world that's entering inside-- into the brain. And these are early visual properties, like your stereo perception, contrast, color, orientation, and motion. Right?

In contrast, the top-down influences is your memory of what the Mona Lisa actually looks like. You've seen it in books, you've seen it on TV, in magazines, and what have you. And this top-down influence is a feedback projection from higher order associative areas, areas involved with attention and memory and so on, going back to subcortical areas and early visual parts of the visual system as well. And as I said, this is based on prior visual experience, and these are responsible for higher order visual properties, like expectations, mental imagery, and attention. And it's the exchange of these two processes that leads to the percept, and that's why the image looks so vivid to you, because it's a combination of the information coming in and your expectations of what that image should look like.

Now compare that to the case of CVI. My argument to you is that in the case of CVI, you have an impoverished bottom-up input. Now this could be from damage at the level of the eye, to pathways, and to the thalamus, to the optic radiations directly into the visual cortex, so from the get-go you have an impaired bottom-up information processing stream that's developing. As a consequence, over time, this top-down influence also becomes impaired, because this visual repertoire doesn't develop properly over time as well.

And my argument is that over time, in the case of CVI, there is a mismatch between these two systems, and that's what I believe causes or is associated with these deficits, these perceptual deficits. There is a mismatch between what is actually coming in, what the visual system is detecting, and what the individual is expecting to see. And this mismatch, I believe, can help explain the visual deficits that we observe in these individuals.

Again, this is a model, perhaps a way that may simplify our way or conception of what's happening in the case of CVI. It's inspired from work that's been done in cerebral palsy-- a lot of work, as you might imagine. As we had mentioned earlier, there seems to be a strong association between CVI and cerebral palsy.

A nice paper here showing that in normal development, the sensorimotor pathways, we have information coming from the hands, the legs, entering the thalamus, entering sensorimotor cortex, again going back into the thalamus, and then descending in order for you to move your hand or to move your leg. And this loop is extremely important, and again, information coming in, being processed and that you're acting on it.

In the case of periventricular leukomalacia, what we think is happening is that these ascending pathways are coming into the thalamus, themselves being impaired at the information that enters the cortex, that in turn doesn't develop, and as you see that over time that loop doesn't form properly in the same way that it does in the case of normal development. So the hypothesis, or a possibility, is that CVI is simply just the visual manifestation of exactly this same idea, this impairment of ascending pathways into the brain, this loop that doesn't form overtime, manifesting in terms of a visual percept. So I think there's a parallel in terms of what we see on the sensorimotor side in CP, and as well as the visual perceptual deficits that we see in CVI.

I've had the chance to work, and I travel abroad and see other groups and see what they're doing in terms of their development of CVI. Very recently I was in Italy and had the chance to meet with Dr. [INAUDIBLE]. She is the chief of the unit of neurology and psychiatry at the University of Brescia in Italy. This is one of the largest neuropediatric hospitals in Europe, and it's really quite astounding in terms of their work and how they approach it.

It's heavily, heavily inspired in the medical model. And just to share with you some of their ideas is that one thing that's very, very important for them, that I thought was a great take-home message, is that every single child with CVI who goes through their programs has a very, very comprehensive eye exam, everything from understanding the pathology at the level of the eye, to as much as possible in terms of what's happening at the level of the brain. There is a careful refraction. There is-- every approach or every effort is made to try to enhance the vision as much as possible from an optical standpoint-- in other words, to get the individual working with the best possible perception that they can from the get-go.

From there, they will then enter into a visual rehabilitation program [INAUDIBLE] strategy, and this figure just kind of shows you here some of the key aspects of their approach. One is that it's extremely intensive. It's very, very intensive in terms of what they do, the programs that they employ or that they pursue with each individual. They intervene very, very early. The timing seems to be very, very important as well.

It is very multidisciplinary in terms of speech therapy, sensorimotor, occupational therapists, physical therapists, as well as doctors, as well as psychologists involved with early development and education, so it's a very, very multi-disciplinary approach. It is individually tailored. Each individual has a very, very comprehensive evaluation, and they come up with a strategy that's uniquely tailored for that individual.

And most importantly, which was really quite resonating with me, was the fact that it was largely family-centered. So from day one the family is extremely involved with the processing, to the point that they even have a telemedicine-type approach, where very often the therapist is checking in through digital technology with the individual, with the family, how are the therapies going? How are things going?

They can review some of the tasks through telemedicine, to review if there's any problems with the way the therapy is being done, how the individual is doing, and so on. And they feel that that constant connection seems to be very, very good in improving the outcomes of these children. And I'm just indicating here two very, very nice reviews from her group that I think are worth reading.

And the last slide I will share with you, their visual rehabilitation program, their main goals, multiple levels that I think are important things to think about. On a very, very simple and early level are what they call micro and macro environmental adaptations. This could be everything from lighting to optimizing visual distances, using multisensory targets, color-coding, reducing clutter, to ocular motor function and training. Everything from fixations, smooth pursuit and saccade movements. Their argument is that improving ocular motor function engages the brain at a much higher level. So there is this sensory component of perception. There's the motor component as well.

It also involves attention, and their argument is that this brings in many, many aspects of brain function to try to integrate, and the more you can recruit, in principle, the greater the outcomes of these individuals. For those individuals who are more on the lower functioning side, they spend a lot of time looking at enhanced individual potential and awareness by the child, looking at things that the child likes, brightness, various colors, and so on, trying to engage that child visually as much as possible.

The fourth piece is development of research strategies and environmental exploration, looking at what the child likes and so on, and trying to bring objective measures, objective evidence, to what works and what doesn't. And the last part, as I mentioned, again, supports the integration of other sensory channels and promote child development. Again, working very, very closely with the family on motor, cognitive, communication, activities of daily living, visual attention. Again, using this telemedicine approach, using a very comprehensive and holistic approach to engage not only the child in terms of the development, but also the family. And they find in this particular case they have very, very good outcomes. And I think it was a great visit to kind of get a sense of what other groups are doing worldwide in their rehabilitation of individuals with CVI.

So the last slides I have here are, I think, take-home principles of neuroplasticity. Again, I get asked very, very often what are useful principles that we should take away from this idea of neuroplasticity, and how they relate not only in the case of CVI but in development in general. I want to be clear that these are not hard and fast rules. These aren't things that are necessarily tried and true through experimental procedures. These are just simply ideas that comes out of work in neuroscience and neuroplasticity that I think apply to the case and the conversation that we're having today.

The first is this idea that timing is everything. Timing is an extremely important aspect when it comes to development. Damage that occurs early, but not too early, and damage that tends to happen slowly tends to have better outcomes than damage that happens late and sudden onset. Think, for example, traumatic brain injury or concussions. Right, this happens later in life, typically. It also happens very, very suddenly. Brain is not very, very good at dealing with that.

In contrast, someone-- you hear these stories of an individual that has a tumor, for example, that lives for years and years and years and doesn't even realize that the tumor has been growing. Why? Because it's early on in life. It tends to be very, very slow and indolent, and the brain can figure out how to adapt around it, until unfortunately there is a time to do something about it. So earliness, slowness, very, very different than very, very quick and late onset as well.

But again, in parentheses, you'll notice that I have "early but not too early," and that sort of relates to this idea of PVL versus non-PVL as well. Damage that occurs very, very early in development, particularly during the embryonic stages obviously can be very, very-- can have significant impact as well. So again, the idea of timing tends to be a very, very important aspect in terms of neuroplasticity and development.

Second important point, this was a quote that came from one of my preceptors when I was an intern. He said neurology is just like real estate. The three most important things are location, location, and location. And this is exactly the same thing in the case of neurology, because the site of brain damage tells us something about the deficits that you see. By knowing the deficits, you should be able to predict where the damage is in the brain, and conversely, if you know where the damage is in the brain, you should be able to predict what type of deficits that individual is going to have. And understanding that association between the two is an extremely important tenet in neurology, and I think is also something important that we need to figure out for CVI as well.

Third one is go hard, go big, and get busy. These are, again, three things that I think every individual should consider from the development standpoint as well. The brain likes repetition, it likes novelty, and it likes intensity. You think of the study that I showed you earlier on about the blindfold study. How did we see all these dramatic changes in the brain?

Well, we took individuals under intense conditions, four to six hours of braille reading a day. It was repetitive, constant, and the novelty of the task as well was quite obviously important for these individuals. So these are three things that tends to drive the brain tremendously and I think are important in terms of how we develop novel strategies, as well.

Think of also crossmodal and sensorimotor learning. Notice that the sensory world is mapped in different ways-- the way that we see the world, the way that we hear the world, and the way that we touch the world are mapped from a spatial standpoint. There's a lot of overlap or redundancy in the brain, and I think it's worth trying to take advantage of those pathways as much as possible.

And the third are benefits of physical and cardiovascular exercise. I think there's tremendous evidence in the scientific literature of the benefits of cardiovascular exercise, not only in terms of brain health, but also brain development. Increased perfusion to the brain is very, very good for brain development, for muscle memory, developing executive functions. There is a great article that just came out in the Guardian by a neuroscientist named Ben Martynoga-- I apologize if I haven't pronounced that correctly-- that reviews a lot of the scientific evidence that's coming out and showing how physical exercise makes the brain work better. I think that's an important thing to consider in terms of development as well.

I have a lot of people tell me, he goes, well, that's all well and good, but I'm working with a child that has a lot of physical disabilities, cannot be very, very active. Well, my argument is that start passively. Get the body moving. Get that individual engaged. Get that individual in a routine where this becomes part of what they do, and build on that. I just think there's never an excuse to have that child just doing that nothing. Engaging them as much as possible from a physical standpoint is extremely, extremely important.

And then the last thing, which I think is the most important, is that it's never over. That's the one thing we know from neuroplasticity, is that this is a function, as I said, that exists throughout a lifetime. Certainly things are easier to learn when we're younger than we are when we're older, but the opportunity for change is always there.

And this leads to a great quote of an individual with CVI I started working with very, very recently. "Embrace neurodiversity," he says. "I'm not neurologically impaired. I'm neurodiverse." And I thought that that was actually quite interesting, that there are always things to learn in each particular case, and it's been an absolute pleasure working with these individuals, because I surely get the chance to learn quite a bit.

What is the potential study impacts of what we're trying to do? As I mentioned, first of all, we're trying to bring an evidence-based approach in dispelling neural myths. There are a lot of things that we hear, either in sort of the social media or by other individuals and so on that I think need to be questioned, and I think we need to get a good handle of what's true and what isn't.

Secondly, establishing a neurophysiological basis, structural and functional, for visual dysfunctions associated with CVI, as I mentioned, understanding the relationship between brain damage and visual deficiencies or deficits is extremely important. That may be for understanding the importance of thalamic damage, distinguishing PVL versus non-PVL forms of CVI, all those pieces I think can become very, very important and eventually manifest in the way that we educate and rehabilitate these individuals.

Clearly identifying targets for deficit-based training. By having or developing more comprehensive visual perceptual tasks, we get a better idea of what exactly those deficits are, beyond visual acuity, beyond visual fields. Having an understanding of these higher order visual deficits I think is very, very important, and may become then the subject of the type of deficit training that we want to do further down the road.

Involving the sensorimotor piece, I think is an extremely important aspect. The attentional aspect I think is also very, very important to characterize, because that seems to be a very, very common deficit we see in these individuals. Also something that we're very, very interested in is social cognition, how these individuals interact in the world, their perception of values, their perception of trust, for example. How does brain development manifest-- or how does this manifest in differences in brain development? I think that's an important area to look at and something that we're interested in moving forward.

Longitudinal tracking of development, I think would be a great, great arena to start with. The idea of an individual gets scanned at the beginning of their rehabilitation or educational process. You follow them for four, five, six, seven years. You look at those changes afterwards, and you compare those individuals, who did well versus those who didn't, and how did that manifest in terms of brain connectivity and brain function? I think that would be the ultimate goal in terms of where we're heading.

And fifth and most importantly, community empowerment. I think the most important piece, or the most important part of this project, is this sense of getting engaged with parents and individuals with CVI, with educators, with other clinicians, other providers. Providing this sense of community is extremely important.

I always use the example of autism, for example. It wasn't that long ago that we thought autism was caused by mothers who neglected their children. We couldn't have been more wrong, but as we created this upswell of interest, whether it be parents, scientists, providers, educators, and so on, this focused effort was able to really concentrate and push the field forward in a way that has obviously made great strides for autism, and I think CVI deserves exactly the same thing. So I think that hopefully that's a direction we'll move forward in.

Just to show you here, we do have a Facebook page, if you're interested in following some of our work. We're called the CVI Neuroplasticity Research Group. We post various articles, things that we've seen from the scientific community that may be of interest. Parents and participants also post their ideas and thoughts there as well. Again, getting into this idea of community empowerment that I think is extremely important for advancing this field.

I'd like to finish by just thanking a number of individuals who have had a very important role in this project. Like all studies, it takes the expertise of a number of individuals. At the Laboratory for Visual Neuroplasticity, I'd like to highlight the work of Dr. Corinna Bauer and Gabriella Hirsch, as well as Gena Heidary, who's a neuropediatric ophthalmologist at Children's Hospital of Boston. Peter Bex at Northeastern University, who's a visual psychophycisist and helps us develop those visual perceptual tests. David Somers from Boston University, who helps us with the analysis of the functional neuroimaging.

The New England low vision-- the New England Eye Low Vision Clinic at Perkins and the Perkins School for the Blind. This is Dr. Barry [? Cran, ?] Dr. [? Louisa ?] [? Meier, ?] and [? Garrett ?] [? Wright, ?] who have helped us extensively in the functional evaluation of these individuals, as well as the recruitment of lot of the CVI participants. Carroll Center for the Blind, which we've also had a long tie with. The Boston University Center for Biomedical Imaging, where we do a lot of the imaging work.

And of course support from the National Institutes of Health, National Eye Institute, the Massachusetts Lions, Deborah Munroe Noonan Memorial Research Fund, and most importantly our patients and our families, because this is really why we do the work. And we are very, very grateful for their time, letting us into their homes, telling us what they're going through and their stories and sharing them with us has been extremely rewarding. We thank them for that.

Want to thank you so much as well, [INAUDIBLE], for presenting this material to us. We had invited our participants to submit some questions in advance, and I want to thank you for incorporating them throughout the presentation, as you did. Certainly most people are-- start right with that basic. Why do we say "cortical"? Why do we say "cerebral"? What's the difference?

And I think that giving us that foundation to start with really helps put a lot of this material in perspective, and makes it easier for people to kind of search on their own now that they understand how these terms are used. I also wanted to acknowledge that a lot of questions submitted from outside the United States. This is truly a global issue, and you acknowledged the center in Italy. We also heard from France. We've heard from Spain, Egypt, Israel, so this is not something that is exclusive to the United States, or even something where we can say the United States is necessarily leading the way. What kinds of global-- you mentioned working with the center in Italy. What other kinds of global collegiality have you been able to find?

I would have to say that this is still very, very much in the early phases. And I've really seen sort of two schools of thoughts or two sort of approaches. One is sort of an education-driven type approach, which is what my experience has largely been here in the United States, where teachers of the visually impaired tend to drive the research from an evaluation standpoint, from a rehabilitation and education standpoint.

And the other, which is typically what I've seen in Europe, not just in Italy. There's a group in Belgium also that's very much the same way. Of course, Gordon Dutton himself, which is sort of more the medical model, where it's more sort of diagnosis-driven, and then everything sort of follows from the diagnosis.

So there really seems to be two different approaches that I've seen from that. I certainly cannot say one is better than the other. I certainly don't want to make that comment. But I do think what needs to happen is a closer communication between the two, so that we're not coming up with separate parallel strategies.

I really think what I've learned-- particularly, again, from my experience with this group in Italy-- is this multidisciplinary approach, engaging the family also, I felt was really, really-- was quite striking to me. And I cannot say in terms of hard evidence that their outcomes are necessarily better, but I had the impression that more people knew what was going on, in a sense. And I can't help but think that that ultimately has a benefit in the end, not just for the child, but also for the community.

No doubt. And certainly in some of these countries that are smaller than ours, where the networking is just smaller, you're closer to someone who might have information that you can use, where in the United States it's very common to be hundreds, thousands of miles away from someone who's having your experience.

Yeah, I think that's true. A final thought about that is I think another aspect that I've learned is sort of the cultural piece to it, as well. In Europe, where you have universal health care and socialized medicine, there seems to be this sort of social responsibility about people with disabilities in general, not just CVI, which really, really struck me.

That's not to say that we're not responsible in the United States. Of course we are, but I think our approach is a little bit different. In Europe they seem to think that this is sort of just part of life and we all have to kind of pitch in. We all have to do something at all levels of society, which I think was really quite striking and something that I took away, whereas here in the United States, we tend to be a little bit more problem-based. You have this problem, you go see this specialist, and that specialist will take care of it, and then that's sort of the end of the conversation. I think there's something to be said for this sort of more inclusive community-based approach that I think in the end will have positive repercussions

Certainly worth looking at other models and other examples. Your summary points at the end were really so practical and so useful, kind of just reminders. And I'd like to revisit this topic about timing, and sort of when we were talking about this earlier, before we got started about how often children are-- I don't want to say misdiagnosed, but maybe incompletely diagnosed, and the impact of this brain dysfunction is sort of lost. And so the family spends some time identifying themselves as one kind of concern that they're all working toward, and then suddenly there's this other thing. I just-- could you say a little bit more about the timing of reaching these-- and they're not always children. Certainly young people and adults. Is it ever too late?

Yeah, fair question. I think there's two ways to answer it. One is from sort of the clinical approach, and I'll answer the second one from a neuroscience perspective. The first, from the clinical approach, is-- being a clinician myself and working with individuals with brain damage and so on, there's a great saying in medicine is that if you really want to be sure about the diagnosis, you just wait long enough. And I think that's very, very true, but unfortunately we don't have that luxury in this particular case.

In the case of a child and developments, the problem is, I think, there are a lot of ways to explain the deficits that you see. It may not be necessarily one condition, or one particular disease, or one scenario. And there's a lot going on at that time as well, and there's also the danger of perhaps incorrectly diagnosing, not only from a medical standpoint, but also from a labeling standpoint as well. So you're walking a fine line by being as sure as you possibly can, but also at the same time this principle of trying to intervene and doing something as quickly as possible.

And it's just simply not easy. The argument traditionally has been that we just need better ways to characterize, better ways to test, and so on. And this has gone on throughout the history of medicine in general. In the case of visual impairment, for example, early childhood screening, going out to various schools and so on is a great example of saying, look, we need to get out there so we have a better handle of just how big the problem is. I think that's from the clinical perspective.

From the neuroscience perspective, I certainly cannot say with hard evidence that intervening at this time versus that time and so on leads to better outcomes or so on. It just stems from the logic of what we know from decades and decades and decades of work in this area. But that certainly has evolved as well. As I mentioned, much easier to learn a language when you're very young versus much later, but that's not to say that you can't do it. You just have to be that much more creative, that much more intense, that much more focused when you're later on, when you're older.

I'll give you another perfect example. When I was going through school, amblyopia, which I mentioned early on in the conversation, the idea is that if you did not take care of this in the early ages, you just didn't have-- there was no point in doing this afterwards. So we called it then this idea of a critical period, that this was sort of the window of opportunity to do something. But you're seeing a lot of studies now that are going back and revisiting this idea, and looking at trying to treat amblyopia in teens and in early adults and so on, which goes to say that that's not so much a fine window or a fine window of opportunity, but rather a little bit more diffuse.

And we start using terms now "sensitive period," as opposed to "critical period," where the opportunity is still there, but as time goes on, you need to be that much more intense, that much more creative, that much more forceful, in order to induce those changes, because as the brain kind of goes down this sort of path, and it starts deciding what it's going to do and dedicating resources for various things, it's harder to kind of bring it back. But I do fundamentally believe that this neuroplasticity is something that you have for life and it's throughout a lifetime. Doesn't mean it's always going to be easy, but the opportunity is certainly there.

What are your thoughts on some of the alternative therapies-- or maybe I should more accurately call them alternative methods-- that have been suggested? Some of it's popular science, but we've certainly heard about oxygen therapies, stem cells, cannabis therapies. What are your thoughts about some of these other approaches?

You know, that's interesting. I get a lot of emails and questions from parents and other providers and educators what my thoughts are on this, and I think it's just like any other situation. There's a great saying in medicine is that sometimes the hardest thing to do is to do nothing.

And it's normal. We want to do something. As parents, as providers, as educators, we feel that we need to intervene. We need to do things. So it's not surprising that people are willing to think out of the box and try various ideas.

I can tell you that in my own personal experience, I have not seen any clear objective evidence in terms of any of these alternative approaches that you've mentioned. That being said, I think there are a couple things to kind of keep in mind. Even if you do try something, these sort of alternative remedies and what have you and you see a benefit, A, it doesn't mean that it's universal. It doesn't mean it's going to work in everybody, so that's the first thing to keep in mind.

Second is this question of causality. In other words, if you took this particular supplement or what have you and you saw a benefit, it doesn't mean that that benefit was caused directly by that intervention. That's another important thing to think about.

The third thing that I think is very, very crucial, and again, speaking to parents in the past, is really the danger of doing some sort of intervention that does not have a scientific basis. So for example, I've heard of parents who spend a lot of money traveling throughout the world for things like stem cell therapy and so on, and not trying to decide what's going to happen.

So first of all, I'm not a molecular biologist, so I cannot comment in terms of stem cell therapy and gene therapy and so on, apart to say from the fact that it's a very, very important and growing scientific field. There's an enormous amount of effort and some very, very brilliant people working in this area. But from what I understand, it's still very much in the early phases.

So in other words, work is still in pre-clinical animal models into the early safety phases before things are really going to be commonplace, and I see that slow probably down the road. So I get very, very nervous when I hear about a family saying that they're going to do stem cell therapy or something along those lines, and the first question I have is what is the credentials of the people who are offering this?

And second of all, from what I understand, because this is still very much in the early phases, typically if you're going to be involved in a stem cell study, because it's still the early phases of the study, you're being recruited as a participant, which you should never pay for. So it just simply doesn't make any sense that when somebody tells me, oh, there's a stem cell therapy. I'm going to pay and I'm going to try it. I'm quite certain we're not at that phase where it is a viable therapy that this is something you should pay for.

So the first question I-- or the first thing I would say in that particular situation is try to get a sense of what the credibility is or the reputation of that individual. Are they affiliated with an institution, for example? Is this something that they've published on? My belief is that if they've been out in the public and they've told that story, then they are free to critique. They're not afraid of what they're saying. So I think that that's an important sign to keep in the back of your mind as you think about these other approaches, alternative approaches.

Thank you. And just as a radical idea, what would you say to a family who said, well, you know what? If my child's visual functioning isn't working, I'm going to raise them as a child without sight. I'm going to try blindfold therapies, or I'm going to try to not have them depend on that.

I think that's an excellent question, and that goes back a little bit to the blindfolding study that I mentioned, and that was very, very much, as I mentioned, the impetus of why we looked into it, and did somehow accepting blindness or becoming a profoundly blind individual somehow kickstart these changes? And that's really what we were interested in.

And of course, there are different schools of thoughts on this. There are institutions who say, yeah, the sooner you accept this blindness, the better it is for you to induce these changes. And there's others that say, no, you should use as much as you have, whatever residual function you have.

So I certainly understand that, from an ethical standpoint, there are differences. The neuroscience certainly suggests that this shocking the system, if you will, induces these changes. Recall I showed you in that data that when we took the blindfold off, they actually regressed. So putting vision back into the equation doesn't necessarily give you the outcomes that you want as well. So that's an important thing to think about.

The second thing I would think about also is distinguishing the case of CVI with ocular blindness. In the case of ocular blindness, who are profoundly blind, who obviously go and learn to read braille and things like that, I think that actually makes sense, and I've showed you how the wiring is fundamentally different so that the brain takes on these other functions.

In the case of CVI, more often than not there is some degree of visual function. It's an impaired visual function, and I would argue that it's a visual function that kind of is lagging behind in terms of the other senses and the other development capacities as well. So given that there is some degree of visual function there more often than not, my argument would be to somehow bootstrap the other senses from a sensorimotor standpoint, using audition, tactile information, the sensorimotor interaction that I mentioned as well, to try to help the visual system catch up, so to speak.

That to me would seem like a more reasonable scenario than simply just saying, you know what? We're going to take vision out of the equation so that the other senses could kind of come in. I think it's a very, very different scenario from a plasticity standpoint than it is in the case of ocular blindness, and again, the networking data suggest that's the case as well.

Well, thank you. Thanks again for your time with us today, and we look forward to working with you in the future.

Thank you. My pleasure.