SPEAKER: Dr. Marabet, thank you very much for joining us. Welcome to the show.

DR. MARABET: Thank you very much. Thank you for having me.

SPEAKER: Your research focuses on how the brain adapts to loss of sight, and you've been developing some game based strategies to help specifically blind adolescents. Can you tell us about some of that work?

DR. MARABET: Sure. So our lab focuses on trying to understand how the brain adapts to blindness and visual impairment both of eye related causes as well as brain related causes. So in this direction, we develop a series of assistive technology platforms to try to help and improve compensatory skills, and we use virtual reality to do this as well as game based strategies also. We also combine that with advanced brain imaging techniques because that allows us also to look inside the brain and see how performance and these compensatory behaviors related to changes in the brain as well.

So a very important area of work that we really focus on is trying to create assessment tools and training tools that are what's referred to as ecologically valid. So in words, assessment tools that represent or accurately simulate real world tasks, and this is actually quite important because we know that traditional ophthalmic measures, things like visual acuity, for example, are very limited in terms of telling us how a person functions in the real world. So we need ways to simulate or to assess how a person with a visual impairment uses their vision in real world settings, and that's where virtual reality comes in. So it allows us to close that gap by creating these real world settings, these simulations where we can test performance in real world settings and also use that as a way to train these compensatory behaviors in a safe and controlled manner.

SPEAKER: So you're awarded a pilot grant from the Harvard Catalyst Translational Innovator to improve outcomes for people with a genetic disorder called cerebral adrenoleukodystrophy, or ALD. Can you tell us what ALD is?

DR. MARABET: Yeah. So again, ALD or adrenoleukodystrophy is a specific genetic disorder that affects about one in 17,000 newborns. It's related to a specific mutation called the ABCD1 gene, and this mutation leads to abnormal adrenal nervous tissue development and function. Cerebral ALD, or CALD, is a sub-type, and it's really the most severe phenotype of the disease, and this is seen particularly in children who are young adolescents, 12 or older. In the early stages of disease, we see severe demyelination, in other words, a lack of development of neurons in the brain, and this is particularly in regions of the brain, posterior regions of the brain that are responsible for visual perception.

As the disease progresses, there's loss of language function, seizures also incur, there's paralysis, and ultimately there's death within about 10 years after the diagnosis. So it's ultimately a fatal disease. So the interesting thing is the fact that the earliest manifestations of CLAD seem to be vision related. That's typically what children will first complain about or the first symptoms that we tend to observe. And in particular, they seem to have problems processing complex visual scenes, spatial processing issues. We also know that in the early stages, these patients typically-- we don't see these visual deficits showing up in classic ophthalmic examination like visual acuity, for example, assessments.

So we need a way to pick up on these symptoms and complaints in a way that is more robust or more sensitive than classic ophthalmic testing. The important thing also what we notice is that as these symptoms progress, often it's misdiagnosed. Often, these children are considered, for example, to have other attentional issues like ADHD or perhaps they're just clumsy or something like that when reality that it's a visual processing problem, and we now want to come up with ways to characterize that in a more effective way.

SPEAKER: So you said that typical ophthalmic testing can't pick up these vision differences. Could you tell us a little bit more about why a standard vision test doesn't pick up this issue?

DR. MARABET: Yeah. So maybe I should be a little bit more clear about that. That's not to say that the standard ophthalmic testing cannot pick this up. It just cannot pick it up in the early stages. So by the time the child does manifest with ophthalmic or vision problems that we could pick up on a standard eye test, for example, often it's too late. The idea is to pick up things that are much more subtle when the child is already starting to notice things are not quite right. So very, very often, for example, the child will say, you know, I have I have problems following people in a crowd or maintaining my attention in the classroom. They go and see an eye doctor and then, sure enough, they pass the eye-- you know, they read the eye chart without a problem. So in other words, we need a mechanism to pick up on these subtle visual processing problems sooner than what we would normally get from a standardized test.

SPEAKER: Right. And so that's key to treatment because if you can initiate treatment at the early stage, you can halt the progression of the disorder. And I don't know if you mentioned it, but this is a serious disorder. You've talked about demyelination of the neurons which is, you know, maybe you could describe that a little more. But basically, the neurons can't send signals to different parts of the body.

DR. MARABET: That's right.

SPEAKER: But maybe you could explain a little bit more about that.

DR. MARABET: I think you characterized it perfectly. That's exactly right. So demyelization, or myelination, I should say, is an extremely important process in terms of brain cell development because it acts as an insulator. It's what allows a brain cell to fire properly, and when that myelination doesn't occur, the cell does not fire properly. And again, it's interesting that this demyelination seems to be focally localized within occipital and posterior regions of the brain which we know are responsible for spatial visual processing. As the disease progresses, we know that this demyelization, extends to other areas that include language, motor function, cognition, and so on.

SPEAKER: And so your project, or the grant you received, is looking at improving detection. Let's talk a little bit about how ALD is treated because, from what I understand, there are good treatments for it. But again, it's about getting started at an early stage. So could you tell us a little bit about how ALD is treated?

DR. MARABET: Yeah, absolutely. So there is a treatment for CALD, and it's ex vivo lentil viral gene therapy. There's some very strong early clinical evidence that this approach is extremely successful in halting disease progression. Dr. Florian Eichler, who is the collaborator on this project, he's the director of the MGH leukodystrophy clinic which currently is running the largest gene therapy clinical trial worldwide. The caveat to this treatment is that the timing is absolutely crucial. The timing needs to be as early as possible to halt the progression. But again, it can't be too early because you're putting the patient at undue risk, and it can't be too late because once the progression is so far along, it's very, very difficult to to halt progress or even reverse that process.

So timing's an extremely important issue. So again, the critical gap in this particular scenario is coming up with a way to pre-detect or detect this pre-symptomatic visual processing defects or impairments, and at the same time, correlating that with subtle changes at the level of the brain as well, looking how the brain is wired. Its connectivity. How the brain activates as well beyond what we can do which is standard MRI testing as well. So there's really two aspects to this study. The first is assessing and being able to detect these visual deficits. And second, looking at these fine details and changes at the level of the brain. And right now, the fact that there isn't really a robust mechanism or a more sensitive mechanism, I should say, is really what I think is hindering the fact that treatment can save lives and neurological function obviously. So we can do it. The treatment does exist, but we need to fine tune it in a manner where we can actually optimize that treatment window.

SPEAKER: Great. And you hinted at, or you described the sort of dual aims of this project. Could you give us a little more information about the project itself? I know there is a component of VR piece to it, and that's work you've done previously, as you said, with some game based strategies that you've been looking at, and you've also worked with imaging. So maybe talk about-- and we can talk about the imaging in a little bit, but just tell us about sort of the specifics of the project and how this assessment is going to work.

DR. MARABET: Yeah. So from the virtual reality standpoints-- you know, in our experience, using virtual reality is very effective because we can create these ecologically valid, these scenarios that simulate real world situations. So examine, you know, imagine for a second that you find yourself in a busy hallway where there's lots of people walking around and so on. We've created a simulation where an observer is standing from the first person perspective looking through this hallway where people are walking around, and the task is to find a target, which in this particular case is the principal of a fictitious school that's walking in the corridor.

And what we do is we change the number of people who are in the crowd in order to make the crowd busier and more action going on. The task of the observer is to observe the visual scene, locate the principal, and track them as they're moving in the visual scene, and we use eye tracking methodology to see where they're looking at all times. And what we find, and perhaps this isn't surprising, is that the more people in the crowd, the harder it is to find the target and to track the target. What's interesting is that when we test this in adolescence with CALD, their performance is actually much worse.

So in other words, as the crowd gets bigger and bigger, they have a much harder time finding the target and tracking the target. And we think that this sensitivity to task demands is the signal that we're looking for to pick up on these subtle visual impairments that otherwise we wouldn't get with, say, an acuity test. So that's really where the virtual reality comes in. It seems to give us this opportunity to define right away these subtle visual impairments that we're trying to pick up on. The second piece that you mentioned about the neuroimaging is to trying to correlate, you know, very fine grained and subtle changes at the level of the brain with these visual impairments, and we use two techniques to do that.

The first is what's referred to as diffusion based imaging, and that allows us to look at the white matter connections of the brain, so how the brain is connected with itself. And the second is functional magnetic resonance imaging which allows us to look at activation of the brain on this particular task. So we see which parts of the brain are active and how that activation is different compared to individuals with neurotypical development. So we have multiple signals to look at, at the level of visual performance, and at the level also of how the brain is wired and activates. Putting all that together, we think we come up we can come up with a more sensitive way to assess these individuals to figure out the optimal timing of treatment.

SPEAKER: So maybe-- how do you put that all together? What does that actually look like?

DR. MARABET: In-- I'm sorry.

[LAUGHING]

I just I just want to make sure I understand the question before I ramble on.

SPEAKER: So you take-- so you have the data from the game or the simulation. You have the diffusion imaging. You have the functional--

DR. MARABET: Functional activation.

SPEAKER: --MRI imaging. Yeah. So then-- I mean, maybe this is too complicated to--

DR. MARABET: No, no. Not at all. I just want I understand the question.

SPEAKER: So I'm just sort of thinking-- so you've run some of these simulations already and done imaging. So I guess I'm sort of thinking of like what's the second half of the process, how does that look?

DR. MARABET: Yeah. So once we have the virtual reality assessments we're able to characterize the visual performance, we then add the neuroimaging from the connectivity and activation standpoint. We take that data and we compare it to neuro typical controls. So individuals who don't have, obviously, the disease. So that's an important piece right away is to differentiate how kids with CALD are different. The second piece is that we also have a subgroup of population in the CALD group who are getting the genetic treatment. So we are following those who are getting treatment versus those who are not. And then, again, using a pre-post assessment, understanding how these outcomes are different.

So what signals, for example, are more useful in determining the kids who did well with treatment versus those who didn't get treatment. And I would say the third piece is to use those outcomes against standards like a standard vision test or standard MRI to see if our outcomes are actually better at picking up those individuals and the timing of treatment versus using, again, these standard measures. So there's multiple facets to the study.

SPEAKER: Great. Yeah. I think that answers my question.

DR. MARABET: Was that helpful? OK. Good.

SPEAKER: Yeah. Just wondering because-- Yeah, you know, you're looking at seeing which of these or which combination of these methods provides a better detection signal.

DR. MARABET: That's right, and the kids who are progressing without treatment are really the baseline. So we see the natural course of the disease versus the kids who get the treatments. We get an idea, do our markers pick up on this? So for example, does this visual impairment level off or actually get better? Do these changes at the level of the brain stabilize? This will allow us, again, multiple ways to assess these individuals in a more comprehensive manner. And again, if you benchmark that against standard measures like acuity, like MRI image or standard MRI imaging, we'll get a sense of whether or not we can pick this up faster.

SPEAKER: And you're working with another researcher on this project you mentioned, and just, you know, maybe stepping back, you're not-- you know, this is not your area of expertise, CALD.

DR. MARABET: That's right.

SPEAKER: You study vision and how the brain adapts to changes in vision.

DR. MARABET: That's right.

SPEAKER: And I think the story of how you became collaborators is interesting because it was sort of, you know, one of those serendipity moments of going to a conference. And so maybe you could talk a little bit about how that collaboration started and how you're working together.

DR. MARABET: That's exactly right. CALD is not a population that we've had experience working with in the past. As you said, our expertise is really working with visual impairment in general, again, based on ocular causes as well as brain based causes. And Dr. Florian Eichler is the director, as I mentioned, of the MGH leukodystrophy clinic, and he has extensive experience with the disease, and he's the principal investigator of this large scale clinical trial, as I mentioned. He was really the first one to recognize that there was a gap in our understanding and a gap in terms of how we were assessing these kids. Through the scientific community, through local presentations, and so on, he had a sense that the way that we approached assessing visual impairment could translate to his population.

So he reached out, became aware of our work, and we did some pilot work with some of his early patients. And indeed, we were able to detect that there was this significant change in performance in this group compared to neurotypical development, and we figured that this could very well be a tractable approach to do so. I do also want to identify other collaborators. There's doctors Chris Bennet and Karina Bauer from our lab who are responsible for the virtual reality development as well as the neuroimaging. So it's a really great example of a project that needs multiple pieces. And you know, this Harvard Catalyst grant allows us to come together in a way that perhaps we wouldn't have this collaborative opportunity otherwise.

SPEAKER: Great. So talk a little bit more about maybe-- Yeah. So I think the, you know, talk a little bit about the Catalyst grant and how, sort of, pilot grant opportunities like this can help researchers that are doing things like you. You know, sort of atypical collaborations or working with newer technology.

DR. MARABET: Yeah. Exactly. I mean, if you think of standard funding mechanisms like the NIH, for example, or perhaps the Department of Defense, other foundations like private foundations as well. Typically, you either need a substantial amount of preliminary data to develop a large scale program, or if you're looking, for example, support from certain foundations, they have a very specific call that they're looking for, specific diseases or specific approaches. So sometimes what you're trying to do just doesn't fit with current mechanisms.

I think with something like Harvard Catalyst allows us to do is take these sort of bold exploratory approaches where we think we have a good idea, bring people together who typically would not necessarily work together in more sort of traditional funding mechanisms, allow us to explore if the idea is indeed solvent, and then collect that substantial preliminary data that's necessary to take that to a much larger formal scale such as the NIH.

SPEAKER: And so what is the goal-- once this pilot study is finished, what's the next step? What's the ultimate goal?

DR. MARABET: Well, my hope is that we can validate that, indeed, this approach allows us to hone in and optimize this treatment window on an individual basis. As I mentioned, once we demonstrate this, we feel that we can capture the signal that we're looking for. The question now, of course, is timing, and how does that compare with standard metrics that we have right now? You can think of a situation, for example, if you were making your determination of when a child was going to get treatment based solely on standard MRI imaging, you know, perhaps that child has access to the imaging every four months or every six months or perhaps even once a year.

If, for example, we're able to benchmark that our virtual reality task is picking up on these deficits, this is something they could easily do on a weekly basis at home, for example, and we would track that data. And we could imagine a scenario where we see, you know, a successive trend of decrease, and that would be the signal to bring the family in to do more formal workup, for example, and then have that conversation that this could very well be the right time to pursue treatment.

SPEAKER: Right. And so for people who are in a location that doesn't afford them easy access to a medical center like in Boston--

DR. MARABET: That's right. Yeah.

SPEAKER: What are these, maybe, how intense are these VR systems? Is it, you know-- I mean, I know consumer VR has gotten a lot more portable and wieldy.

DR. MARABET: Right.

SPEAKER: So is it standard off the shelf hardware or is it something you developed?

DR. MARABET: It's actually interesting because a lot of the VR technology that's available today comes from the gaming industry. So you know, we use a platform, for example, called Unity, which is freely available, and a lot of people use this to develop games and so on, and we use this, like I said, for our purposes. It's quite nice because once you develop the platform, you can package it, and it's essentially an executable file that you can send to someone, and the package opens and runs the test in a manner that allows you to collect data, send it to a file that can be saved, and then the patient can send it to you. The interesting also thing to think about is certainly we're in the middle of the COVID pandemic.

So a lot of things to think about is we may very well be in a situation where regardless of what disease or condition you're working with, we may very well need to continue with mechanisms of remote testing as well as solving the issues of privacy and consent and so on. So we're a little bit fortunate in the sense that we have an approach that we would like to develop from a remote platform, and currently in a situation where now there's a mechanism that exists that allows us to do that.

SPEAKER: Could you see this VR platform being useful for other diagnostics?

DR. MARABET: I would hope so. I mean, as I said, we look at visual impairments in general. So we work with a large population that has what's called cerebral visual impairments, or CVI, and these are typically children who are born with some sort of complication, either prematurity or perhaps some sort of accident that occurs during pregnancy or birth. And, typically, these children have developmental issues, particularly also at the level of visual impairments. So we use these virtual reality platforms, one, to assess them, to make sure we have a good understanding of what their deficits are, and our hope is that moving forward this becomes a platform for eventual training. So we use this system, for example, to see what scenarios do they find most challenging?

What situations are their visual system most likely to break down? What cues could we use to make the visual task easier? So for example, if we lower the complexity of the visual scene, if we increase colors or use of saliency or simplify the visual scene, do we find that performance improves? So it allows us a way to run a simulation in a controlled manner to come up with cues that would ultimately or hopefully translate into the classroom and the real world.

SPEAKER: Great. Well, that was excellent.

DR. MARABET: You think so?

SPEAKER: Dr. Marabet, yeah. Thank you very much. Yeah. Thank you very much for joining us. It was great to have this conversation with you.

DR. MARABET: Thank you very much. I appreciate the opportunity.