[MUSIC PLAYING]

ELIZABETH SKIDMORE: So good evening. It's my pleasure to be here to talk to you tonight about something that I think about, and it is, what is the rehabilitation that we provide for individuals with traumatic brain injury, and what are the opportunities that rehabilitation can offer in terms of harnessing some of these regenerative capacities that we've been learning about?

So as an occupational therapist, people, and even among my colleagues of physical therapy and speech language pathology, one of the things that we do is once those injuries have occurred and everything's that's been done in terms of acute medical management has happened, we work with folks with the behavioral symptoms and see what we can do to help them return to their everyday lives.

And so we've already learned a lot about traumatic brain injury. It actually can come through a variety of different models and I think Dr. Kahanic talked about animal models that I think are representative of the clinical models, whether it's due to force of the brain bouncing off the side of the head, whether it's due to some sort of air concussive force or a penetrating injury, but regardless, what's pretty common in TBI is there's a disruption in a number of functional phenotypes.

And so we often will see clients who've had changes in their sensory function, their movement, their thinking abilities, their motivation, and their mood, as well as the ability to regulate their behavior. And these symptoms can vary greatly among people, and it doesn't always track with the type of pathology that caused the brain injury. It's often due to the phenotype that we treat or that we look at, the specific phenotype actually has to do with the constellation of behavioral symptoms.

So as a practitioner, as an occupational therapist, and as a rehabilitation scientist, I always look at the problem through the eyes of my client. And I have permission to share this story with you. This is the story of Mike, who at the time that I met him was a VP of Financial Services for a very large regional financial organization and on his way to becoming the CFO of that organization. He was unmarried, very active lifestyle in addition to working probably 80 hours a week. He was very active in golf and skiing and a number of active sports, but he sustained a traumatic brain injury.

And as a result of his brain injury, he sustained a constellation of changes. So he had weakness in his left arm and leg, difficulty moving his hand, which you'll get to see in some video here. He had pervasive challenges with his cognitive function, which are less easy to see in video, so I'm going to ask you to take my word for it, but he was often disoriented, had difficulty attending to a task for more than 30 to 40 seconds.

And he had difficulty with higher-level cognitive abilities, the ability to attend to multiple stimuli at once, prioritize information, set-shift, all the things that would be important for him to return to his previous lifestyle.

In addition, he had some behavioral disruptions. Sometimes there were outbursts in the clinic, disruptions around our own people. So again, we've got to come up with an approach that meets the needs of this gentleman, and he's unable at this point to return to work or return to those leisure activities that are so important to him.

And that's his goal, right? Is to get back to life prior to brain injury. And so what I spend a lot of my time thinking about as a rehabilitation scientist is, how do we optimize rehabilitation to best meet the needs of these individuals? And I tend to think of it a little bit like a pharmacologist because I've had good scientific mentoring. And what I want to think about is what are the key active ingredients?

So one of the things that Dr. Kahanic talked about is the heterogeneity of rehabilitation. How do we get to personalized rehabilitation? So what are the key behavioral phenotypes, and how do we match that with the best active ingredients of rehabilitation for the needs of our clients?

And what I'm going to maybe brainstorm with you a little bit on tonight is how do we then use this optimized rehabilitation to harness either the endogenous regenerative capacities of the body and the brain, or to augment some of the therapies that we've heard about tonight, whether those are from stem cells, neurotransplantation, or pharmacological interventions.

So there has been some work that's been done in neurotransplantation in animal models augmented by rehabilitation. And so I started, when I was asked to do this talk-- and I really think mostly about people-- I started by diving into the literature. And I should let you know that I do collaborate with some of Dr. Kahanic's colleagues where we try to reverse engineer rehabilitation therapies for these animal models. I've done a little bit of thinking about that.

One of the things that I found in the literature is this really nice quote from Steve Dunnett's work who recently wrote a chapter on the state of neurotransplantation about four years ago now. But one of the things that really struck me is that he said it's not enough just to transplant cells and create a structural change in the brain, we have to help those cells integrate or create a microenvironment that integrates those cells into those functional networks.

And because we're talking about a damaged nervous system, we have to retrain the lost functions that that nervous system was responsible for. And so this begets the need for rehabilitation to augment these therapies.

So what's been done in the animal models? There's been quite a bit of work has been done in environmental enrichment. I know that this is a model that's used in several labs cross the country in traumatic brain injury. And environmental enrichment is really the idea of putting these animals in these highly-stimulating environments. They involve colorful objects, lots of different activities that they can do, and the idea is that it will stimulate their engagement with their environment, and as a result of that, will stimulate recovery.

In a traumatic brain injury models with animals, they actually have shown pretty good gains not only in neuroplasticity and structural and functional changes within the brain, but also behavioral functional changes in terms of better motor function and cognitive function.

So Dr. Dunnett and a few of his colleagues have actually done some work to see if you use environmental enrichment models in combination with neural transplantation, do you in fact get better outcomes?

And there's a couple of key findings that I glean from the literature. One of the first things is they saw an increase survival of graft cells. I don't know how long they pursued it over time, I didn't look into whether they sustained over time. They saw elevated synaptic densities, they saw increased dopaminergic afferentation, an increased BDNF in the regions where those cells were grafted.

So that's all sounding positive, but again, what I think about are the behavioral changes, and what I thought was really intriguing is in models where there was an environmental enrichment, there were significantly higher skilled reaching and manipulation games as well cognitive gains as measured through learning and memory retention, and I'll show you some data here in a moment.

The other thing that stuck out to me in the literature is that treadmill training in particular does not necessarily yield the same gains. And in this slide right here, this is from Dr. Dunnett's work from his lab. You can see, this is a measure of the amount of BDNF change or BDNF present in the grafted cell region.

And animals that were in a standard cage environment-- so just a regular cage without all that exciting environment to deal with, they did not see as high a level of BDNF levels as they saw in the enriched environment, even without the treadmill. Now what I would point out is, the rich environment includes a treadmill, but it's not a forced-- they had to get-- the rats had to get on the treadmill and use it a forced period of time.

So there's something about environmental enrichment that seems to be positive. I didn't pull all of the different data from these articles, but I saw additional examples related to grass cell health and just-- synaptic density. I also saw similar findings with respect to motor recovery and cognitive changes.

So this is kind of interesting, and I thought, perhaps if I was not a rehabilitation scientist, this would seem like the environment enrichment and the lack of gains from a nonspecific treadmill training conflict with one another. And I'm going to maybe make a case to you that they don't, but there's probably an answer of what's unique in an enriched environment that is not present in this kind of nonspecific treadmill training activity for neurological recovery.

So in clinical rehabilitation studies, we have shown that nonspecific activity does not promote the same level of neurological recovery as specific task practice. And that specific task practice are practical everyday tasks that we do throughout our day that involve a lot of variation in how we move and how we think, that involve a lot of behavioral control, motivation and mood, and they integrate multiple regions throughout our brain.

And so there's been a number of studies that have been done in clinical rehabilitation studies that have shown that task-specific training approaches are actually optimal for promoting motor recovery, cognitive recovery, and even reducing depressive symptoms in people with brain injury over time.

Now hear me clearly, I'm not saying that exercise is bad. Clearly exercise is very important and has multiple benefits that are thorough throughout the system, including vascular system, our muscle or skeletal system, but if you want to retrain a hand that does not move as a result of a neurological injury and force it to get skilled movement back, you need to move beyond just exercise into specific task practice, and the literature is fairly robust about that in clinical studies.

There are examples of specific task practice used in animal models. I thought this is a good model, and I've actually seen this in working. What you can't see very clearly is there's a slotted window and the animals having to reach through that very narrow-slotted window with a level of precision of paw control and grab that tiny little pellet. It's on a platform, and the therapist, if you will, can adjust the height of that platform to make that task easier or harder.

So that's very similar to what we would see in a clinical rehab model. We use specific functional tasks, we make them harder as people start to build skill, and it's that grading that seems to facilitate promotion of control over time and recovery.

So what does that look like in human studies? I'm a little bit more familiar with. It can vary greatly according to the client. But there are some key active ingredients that good task-specific or specific task practice programs should include that are based on the neuroscience, and I'm just going to lay them out for your consideration.

So these active ingredients that I'm going to talk to you about that are related to specific task practice, interestingly enough, have shown to affect multiple domains of brain function.

So when you have a TBI that has diffuse effects across the brain and diffuse effects across our behavior, there is potentially an intervention that could be beneficial as it relates to behavioral gains that translates across multiple domains, and that needs to be tweaked depending on which of these specific behavioral phenotypes are most problematic for a client. And most of these principles are derived from neuroscience, either an animal or clinical studies.

So I think it's probably well-known among the audience that what you do can shape your behavior, we saw that early on. We know that the amount of practice that we have with a task absent a brain injury can actually change the way our neurons organize themselves and communicate with each other.

This is a clinical study that showed in the top half of the slide. They did an imaging to see the population of neurons that represented-- or that were responsible for controlling the thumb, and this is actually in a stroke model. And they looked at it in the unaffected and the affected hemisphere, and what you may notice is that the affected hemisphere had about half the population neurons active related to controlling a thumb, and that corresponded with poor behavioral function.

But after a specific task practice program that was highly intense over three weeks, they reimaged and looked at whether there were changes in the population of neurons responsible for that thumb control, and in fact, you see a doubling in the affected hemisphere as a result of that specific task practice.

You also see a reduction in the unaffected hemisphere. And what you may not know is, this is an old study and this was back in the day when we would restrain the unaffected hand, put a mitt on it or a splint to try to prevent people from behaviorally using that hand. We've now shown that that restraint is unnecessary and that normal movement is enough to facilitate/promote changes over time.

So what does that look like in Mike? And this is where I need help-- there we go. So we identify a number of practical functional tasks that are going to have high repetition throughout an experience. And here, he's just trying to do a very simple thing of coordinating that arm to get up and flip a light off.

Light switches are great because they are immediate response and immediate feedback when you're successful, and they have to spend a lot of time flipping light switches, opening doors, those kinds of things throughout the day. So this is just a very simple example.

Now obviously we would not sit and do that 5,000 times in the period of a couple hours, we're going to derive a variety of tasks, but it just gives you an idea of some of the kinds of tasks that can happen.

Mike in particular ended up adapting his light switches in his apartment so he could get more practice that ended up being harder for him over time, so he really bought into this idea.

OK. So we also know that the more we use specific task practice in a given routine, the more likely we're going to see gains. This is work form-- Catherine Lang's work at Washington University. Her laboratory has been studying this dose response relationship in task practice, and what she's shown is there's a direct relationship to the more opportunities to practice using that hand-- it doesn't matter what the activity is, but using that hand or arm is correlated directly and strongly with the amount of improvement we see in measures of hand and motor function, arm function, and so this is some pretty compelling work.

But you notice the amount of activity that she's looking at here is in the thousands, 4,000 to 5,000 reps. And while that sounds like a lot for an hour therapy session, if we build a program for clients to use their arm as much as possible throughout the day, this is very achievable. And actually, some people can get as high as 10,000 to 11,000 based on activity monitors that we use.

The other key principle in task practice, it's not enough that it needs to be a practical task and it needs to be specific, it needs to embed some sort of novelty and complexity. So really easy tasks usually do not get us to really good gains. And so there's been some really good studies in the neuroscience, particularly looking at animal models that show that if we engage in novelty and complexity in practice, we actually engage our cognitive systems, which then promotes better learning and retention of gains over time.

And so this particular article talks about the importance of novelty and exploration for promoting plasticity in the hippocampus, which is where we form our new memories, as well as stimulate dopaminergic neuromodulation, particularly in the striatal areas, and the striatal areas I'll point out in a moment are a really important areas wher you're trying to get someone to relearn new behaviors.

So novelty and complexity, what does that look like in a clinical rehabilitation setting? It's usually very practical tasks. Most of the tasks that we do every day are multi-step. They require a variety of strategies, and they require us to think about how when we're relearning how to use an arm or pay attention to sequence and problem solve, and so they are multi-step in nature.

And you're going to see him struggle. This is his first day in therapy about a month after treatment as an outpatient, so we're just doing a little bit of baseline testing with him to see what he can and cannot do. You're going to see him struggle with it a little bit, but you'll see him improve here, I promise.

See how he kind of experiments with different strategies? That's what the novelty is about, is trying different ways and then figuring out with practice what works best. What we've learned is the inefficient problematic patterns will fatigue out and people will go back to the most efficient patterns, which is good function.

It does take a little bit of patience. People have to try different strategies.

So you get the idea of how we try to use multi-step tasks as much as possible to promote that complexity. Can we go to the next one, please? The next slide?

It's not only the tests need to be specific, they need to be novel and complex-- they need to have a goal in that, and I'll explain what I mean by this. Often you'll see sometimes in rehab clinics people doing very kind of boring, non-goal-orientated tasks like stacking cones or moving a block from one side of the table to the other. That gets us movement, but it generally does not lead to good gains in movement or retention recovery over time, so goal-oriented tasks matter.

You're going to see in a moment that it makes a big difference when a client thinks about opening her hand versus just doing something simple like grasping a pen, and I'll illustrate that for you here.

This is a client a few years after her brain injury. And that is a video that will need to run. She's going to do two things for you. She's going to show you how much movement she has in her hand and then try to make a fist and open it.

And what I want you to pay attention to is when she goes to open her fingers, look at how much they open up, how much extension she has, OK? Now I want you to look at how much those fingers open up when we give her a goal-oriented task, this is just a few seconds later.

So automatically, we see a very different approach to movement, right? Because now she's not thinking about opening her fingers, she's thinking about grabbing the pen, and that goal changes the performance of her hand function. So it automatically looks better right away.

And if you repeat the task again here, again just a few seconds later, you're going to notice yet more improvement. So now look at how much those fingers open up.

So quite a bit of difference over time, and it can happen quite quickly within a session. And if we want to retain those gains, we want to look at ways to increase that in their daily routines both in therapy and outside of therapy.

So tasks that have implicit goals generally get us better performance right away, better retention of that performance session to session, and better generalization to real-world tasks over time, which is ultimately what I care about.

The last principle I'm going to leave you with is that goals need to be-- tasks need to be specific. They need to have high repetition, they need have some novelty and complexity to them, they need to be goal-oriented, and they need to be personally meaningful to a client-- they need to be interesting.

There's a big difference between doing non-interesting tasks and doing interesting tasks in terms of the degree to which it benefits your overall motor control and result improvement in neurological recovery.

Again, there's some really good neuroscience-- I just pulled kind of one of the classic examples-- that looks at the degree to which the meaning of a task can really have a lot of value in learning motivation and carry over learning generalization beyond therapy.

And so Mike is a poker player. And he's a social guy, so we put together some colleagues in the clinic and started working on playing poker. He's thinking more about playing poker, a little less about his hand, although right now, because he's struggling with it, you're going to see him thinking about it a lot.

And he's going to try to do a simple thing like picking that card up and putting it on the table. He's got a discard. I think this is poker, this may be rummy, I don't remember.

This is like doing the exact same task in the next slide. Doing the exact same task two weeks later after doing an intensive, task-specific practice program. So he still has some gains to make, but he's making quite a bit of gains. He's getting more efficient. He's got enough confidence and he's continuing his practices on his own. And we're starting to see that finger separate, which is a major success for a therapist when we start to see individual finger movement.

So just two weeks was enough for him to start to promote those gains. And most people, if we can get them early enough, if they're in that mild-to-moderate stage, we can actually see this progression happen very quickly. The more severe stage, there are some other augmentative interventions that we would add to that intervention to get to this stage.

So the last kind of guiding principle-- as I already said, last guiding principle, those are the last guiding principles related to motor recovery, but as Gwen told you, I'm very interested in the cognitive, emotional, behavioral changes that also accompany with TBI.

So we just spent time getting people to move better, that's not going to be enough to really translate for them to be independent in their communities. They're also going to need to be able to think differently, they're going to need to be able to manage their emotional symptoms, they're going to need to motivate themselves to reengage in life, and they're going to need to be able to manage behavioral changes.

And so what I study is an intervention that I call guided problem solving. It's a very simple intervention where we take the client-- we take the therapist out of the role of teacher, telling clients what to do, and we put them in the role of coach or facilitator. And we teach clients to start to identify problems in their behavior and come up with solutions to address them.

And this is an intervention that we're running right now, we're running a clinical trial right now in six of the inpatient rehab units here at UPMC Rehabilitation Institute. We've just randomized I think participant 249 of 250, so close, and we're testing to see the degree to which these 10 sessions of therapy really translate to gains-- I'll show you the pilot data that led us to that trial.

A couple of things that we've learned is that by teaching people to problem solve, not just move and do what we tell them to do, but to come up with their own strategies, we've seen really good gains immediately and we see them retain those gains.

And this is actually some nice work from Lara Boyd and Carley Weinstein. Lara is at Kansas, and what she did here is the dotted line group is a guided problem solving group that's learning a new motor strategy. Down is better, and the further down is best, that's good improvement.

And what you see is, in the course of a session, we see remarkable change whether we guide them with a dotted line or we tell them what to do. But the thing that's really remarkable is those gains continue with guided problem solving over the days, and wherever they left off on day one, they pick up on day two, so we see good retention, and that carries over to day three.

And so this is a pretty consistent finding, that teaching people to problem solve and work through problems and their behavior seems to be a very effective strategy for, again, retention and carryover of gains.

This also translates to improvements in cognitive function. We've demonstrated-- this is a paper published in *Neurorehabilitation and Neural Repair.* That over time, with this strategy/training approach, we give them 10 sessions and then we follow them for six months, we see them make significantly greater gains in the executive cognitive functions.

And executive cognitive functions, so your higher level metacognitive functions that are necessary for you to think and be independent. And in the left side, you see inhibition, the ability to ignore irrelevant stimuli and stay on a task in a distracting environment. In the right, you see cognitive flexibility, the ability to hold more than one idea in your head and set-shift or multitask.

The guidance training group, who use guided problem solving, are the dark circles. And the way you should read these numbers, these are scaled scores. So anything a seven or higher is within normal range after adjusting for age and education. So we're seeing really remarkable gains in executive cognitive function, which is quite remarkable and not something we've seen with a lot of other therapies and rehabilitation. And so this was the promising data that led us to the large trial that we're conducting right now.

We also see good gains in motivation and mood, and I'm just going to share that motivation data with you. The solid line here, again, is the problem solving group. The dotted line in this case is usual rehabilitation. Our solid line group, they had lower apathy to begin with or lower apathy over time, whereas our usual rehab group showed increases in apathy, and apathy is a problematic syndrome after TBI.

Apathy is the opposite of self-initiation or self-directed motivation, and apathy is directly tied to sedentary behavior and inactivity. And so it's a very important thing-- if we can maintain low levels of apathy where we're likely to see folks engage in more task-specific practice over time.

What I think is really interesting, what I'm starting to spend some time on as we think about our next study, is each of these networks-- the motor network, the executive cognitive network, the mood and motivation network-- all have axons that travel through this really important area that's associated with goal-directed behavior.

So the anterior cingulum, the ventral striatum, and portions of the thalamus, this is a highway for goal-directed behavior. So it's not enough that I can just strengthen someone's hand while they're in therapy, I want them to use it in life, and that means I need to be able stimulate their goal-directed function over time.

And so we're looking at the degree to which we actually see changes and activation in those areas associated with our therapy, but I also think it's an interesting area to start to look at if you're trying to have diffuse effects on overall behavior as a potential target to look out for neuromodulation or other types of therapies.

So I've shared with you some neuroscience principles that are the foundation for maybe a more specific, more homogeneous approach to rehabilitation that we've operationalized in a standardized approach that we call specific task practice with guided problem solving. It is a very simple intervention, it just takes us a few hours to train therapists in it, and we get very high fidelity with this intervention, so it carries over very nicely.

We've done some multi-site work with this and it's not been very problematic to train therapists and other sites to carry it through with the same fidelity. So I think it's a promising approach that might be something that you consider in an regenerative approach as an augmentation.

Mike-- everybody wants to know what happened to Mike. Mike actually did return to work. He right now has a very mild discoordination in his hand. He can type on a keyboard, though, and it takes a skilled observer to really see the difference in his hand function, most people don't notice. His attention and executive function have improved remarkably, they actually improved quite well within the first three months. So he was back to work within five months of his injury.

We did make some modifications to his work environment. We moved him from a pool of desks out in a noisy area in a private office and made a few modifications to his workflow, but he was able to resume that. And he went back to golf with no adaptations. He still skis with an adapted pole because we're still a little worried about his safety and his reaction time. He likes those black diamond slopes, so just a little bit of extra safety for that. But as far as he's concerned, he's back to that activity.

So I'm going to just throw up for consideration and be a little provocative and suggest that it's probably-- what's probably happening in those enriched environments is an opportunity for a lot of task-specific practice, and a variety of practice with a variety of objects in a variety of ways. And you'll notice the treadmill is one of them, but it's not the only option. And it's the combination of those-- it's the variety of routine that maybe is leading to better neurological recovery in these animal models.

I do think that exercise is still important, we have shown that an exercise in populations with cognitive impairments do stimulate angiogenesis and to show cognitive benefits, but if you're looking for more precise behavior management, you probably need a combination of both.

And I'll just thank those who have funded the research that I do, as well as the many people on my team or people that I collaborate with that's contributed to the work that I've shared with you today.