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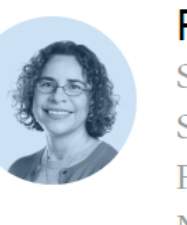
Feature. The Promise of Targeted Neurostimulation in SCI Treatment



Monica A. Perez, PT, PhD
Scientific Chair, Arms + Hands Lab, Shirley Ryan AbilityLab | Professor of Physical Medicine and Rehabilitation, Northwestern University

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Last month, The National Institute of Neurological Disorders and Stroke (NINDS) — part of the National Institutes of Health (NIH) — awarded its prestigious R35 grant to Monica A. Perez, PT, PhD, to fund eight years of research into the long-term benefits and mechanisms of neurostimulation on patients with spinal cord injuries (SCI).

Read on to learn how Dr. Perez and her lab team — which joined Shirley Ryan AbilityLab from The Miami Project to Cure Paralysis in May 2019 — use precisely targeted neurostimulation to overcome damaged communication links between the brain and the body in patients with SCI.

Also, be sure to sign up for the 44th Annual Interdisciplinary Spinal Cord Injury/Disease Course: A Focus on Neuromodulation, a comprehensive online course chaired by Dr. Perez.

How has the use of neurostimulation evolved?
The stimulation we use is not completely novel, but the *way* we're using it is. Most protocols using paired associative stimulation (or "targeted neurostimulation") in humans have targeted the primary motor cortex. For the first time, we are using paired associative stimulation to target spinal synapses in patients with SCI with the goal of enhancing motor output. In our protocol, we activate spinal motor neurons (via retrograde peripheral nerve stimulation) within a few milliseconds of the arrival of corticospinal action potentials (induced by magnetic and electrical stimulation of corticospinal axons). The key novelty of our approach is that we have found a way to target multiple upper- and lower-limb muscles *simultaneously* and combine this approach with physical therapy to achieve *functional* recovery. Neurostimulation is, by far, one of the most promising tools we have today to promote recovery in these patients — there is no doubt. As we enhance the efficacy of these protocols, improvements in recovery may continue to advance.

Tell us about your research.
Voluntary movement depends on synaptic connections between corticospinal axons — which encode the brain's intent — and spinal motor neurons. Throughout life, synaptic connections are forged, in part, by activity-dependent plasticity. SCI eliminates spinal connections, resulting in devastating paralysis. Re-establishing these connections by inducing endogenous neural plasticity mechanisms could potentially restore voluntary movement. Our noninvasive paired associative stimulation protocol targets synaptic connections between corticospinal neurons and spinal motor neurons — a key site where descending commands influence motor output — to improve arm and leg function in patients with different levels of SCI.

The key breakthrough in using this protocol is that we can target multiple upper- and lower-limb muscles simultaneously by using the right timing. It is critical to ensure that the volleys elicited by stimulation of descending neurons reach the spinal cord in a precisely timed manner in relation to antidromic volleys elicited by stimulation of a peripheral nerve. This plasticity depends on the relative timing of pre- and postsynaptic action potentials. We do not just randomly stimulate the brain or the peripheral nerve. Instead, we use electrophysiology to measure the transmission times from the brain to the spinal cord, and the periphery to the spinal cord. These electrophysiological outcomes allow us to make these estimations.

This coordination effectively mimics a complete communication circuit between the brain and body based on fundamental principles of neuroplasticity.

What types of gains have your research subjects made?
To date, more than 60 subjects with chronic incomplete SCI have participated in our studies. They are randomized into two groups that receive either 30 minutes of targeted neurostimulation sessions followed by approximately 60 minutes of physical therapy, or sham neurostimulation followed by approximately 60 minutes of physical therapy. An additional experiment tests the effect of neurostimulation without physical therapy in a similar cohort. The targeted neurostimulation protocol has been customized to include patients with different levels of injury (cervical, thoracic or lumbar). We take measurements before the intervention, immediately following the intervention and then six months later.

We've found that corticospinal excitability and the magnitude of maximal voluntary contractions in targeted muscles increase by 40%-50% after targeted neurostimulation with or without therapy, but that increase is not seen in the sham experiment. Individuals who also undergo physical therapy improve their walking speed and are able to grasp different objects more quickly. We've found that functional gains can last at least six months — a dramatic result for this patient population. Standardized assessments have revealed significant improvements in the quality of life of our patients.

One of our research subjects, who initially was told she would never walk again following her SCI, was able to take more than 60 steps independently following 40 sessions of noninvasive neurostimulation and physical therapy. Following the same protocol, other research subjects experienced additional, significant, first-time gains, including using a manual wheelchair independently, dressing independently and gaining sensation where it had been lost.

Where will your research go from here?
We're not seeing any plateaus in our research subjects; every indication suggests that more promise lies ahead with this protocol.

For the next phase of research — for which we are now recruiting research subjects — we are applying stimulation to the brain and more than one peripheral nerve simultaneously during a functionally relevant motor behavior. Research subjects will undergo this treatment, combined with physical therapy, across 40 sessions.

In addition to researching subjects with chronic injuries, we have gained IRB approval to apply our protocol to patients who have recently experienced an SCI. So far, we have tested nearly 30 inpatients to gain an initial understanding of clinical and electrophysiological changes in this population. We have also used our paired associative stimulation protocol in one of them and seen pronounced improvements in physiological and clinical outcomes. Based on these results and the gains we've observed in the chronic population, it is possible that earlier intervention with this protocol could help to expedite recovery.

How might your research change the standard of care for patients with SCI — and what challenges remain before this change happens?
Right now, we are working on two aspects. One is optimization of the protocol to engage affected pathways: *How can we strengthen these synaptic connections to elicit stronger and long-lasting changes in voluntary behaviors?*

At the same time, we are seeking to determine the best time after injury to use paired associative stimulation for eliciting this plasticity. In this way, our neurostimulation protocol could be used as part of early treatments combined with conventional physical therapy.

Our neurostimulation protocol requires medical personnel with specialized training. The protocol is customized to each patient depending on how pathways are affected. Its use requires someone with knowledge of neurophysiological assessments. Not every physician has this training, but a neurologist or physician trained in physiological outcomes would. We are looking for ways to make the protocol more accessible and standardized so that it can be available in every facility.

Does your research into neurostimulation have potential application in other patient populations?
Theoretically. Because we target and regulate activity in the spinal cord, this kind of neurostimulation could work in people with multiple sclerosis or other disorders that lead to imbalances in excitability in the spinal cord. However, we haven't tested it and don't have any data to support that hypothesis. There's still so much work to be done to make this protocol accessible to patients with SCI, but, yes, the promise exists.

What is your hope for patients with SCI 10 years from now? How might their outcomes and prognoses be different?
I have been working in this field for more than 15 years, and we need to make patient improvements happen faster. We need to shift the timeline for making our protocols stronger and more readily available to different types of patients. We need to expedite the transition from laboratory to use — and effectiveness — in the clinical environment. We need to help our patients soon!

My hope is that paired associative stimulation will become accessible to patients all over the world as the standard of care. We have data that these protocols are working. The key will be to do the intervention earlier in the rehabilitation process.

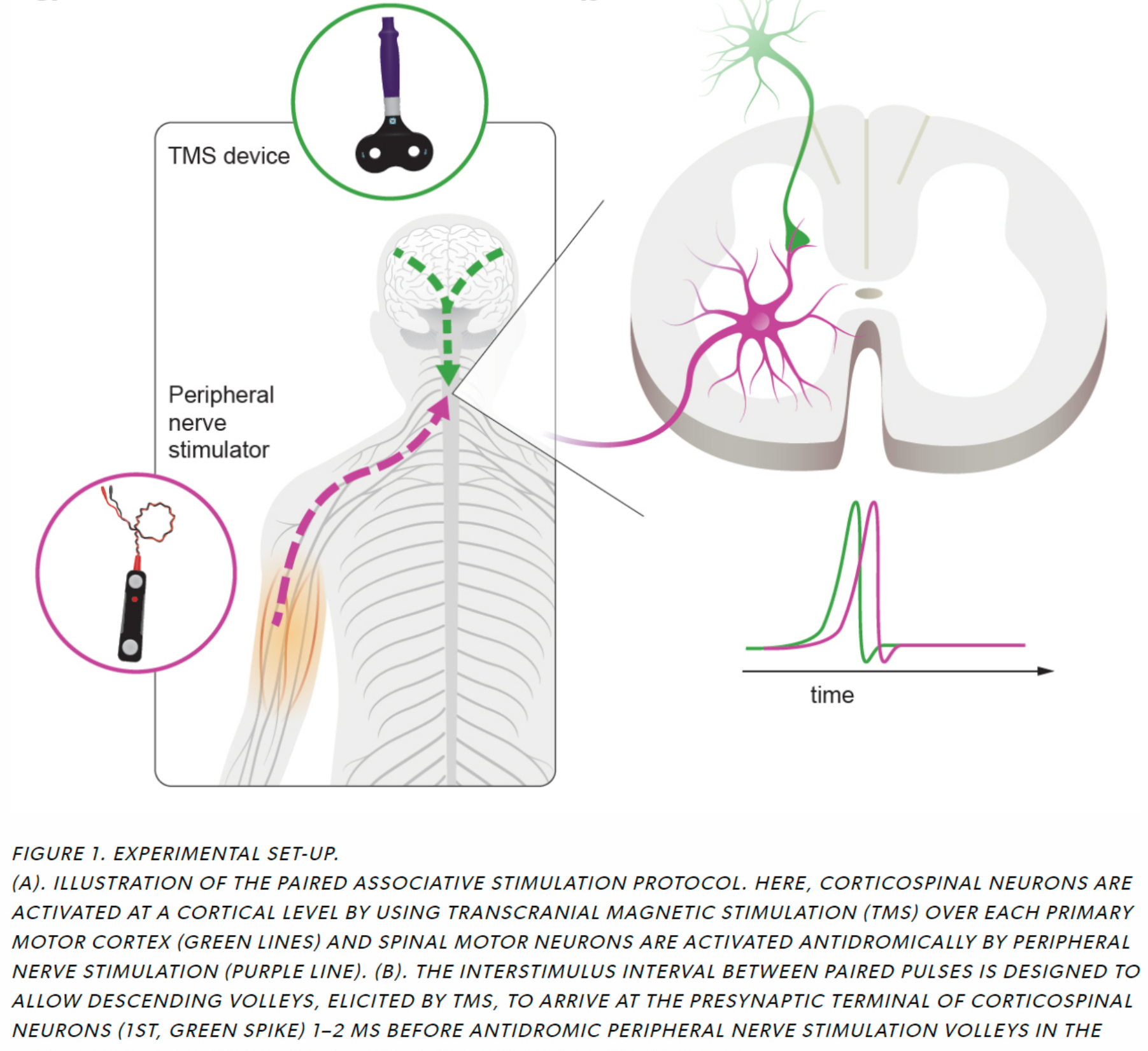

FIGURE 1. EXPERIMENTAL SET-UP.
(A). ILLUSTRATION OF THE PAIRED ASSOCIATIVE STIMULATION PROTOCOL. HERE, CORTICOSPINAL NEURONS ARE ACTIVATED AT A CORTICAL LEVEL BY USING TRANSCRANIAL MAGNETIC STIMULATION (TMS) OVER EACH PRIMARY MOTOR CORTEX (GREEN LINES) AND SPINAL MOTOR NEURONS ARE ACTIVATED ANTIDROMICALLY BY PERIPHERAL NERVE STIMULATION (PURPLE LINE). (B). THE INTERSTIMULUS INTERVAL BETWEEN PAIRED PULSES IS DESIGNED TO ALLOW DESCENDING VOLLEYS, ELICITED BY TMS, TO ARRIVE AT THE PRESYNAPTIC TERMINAL OF CORTICOSPINAL NEURONS (1ST, GREEN SPIKE) 1–2 MS BEFORE ANTIDROMIC PERIPHERAL NERVE STIMULATION VOLLEYS IN THE SPINAL MOTOR NEURONS REACHED THE DENDRITES (2ND, PURPLE SPIKE).

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Buzzworthy. A Neurologist's Take: Earlier Rehabilitation Care for Parkinson's

Jennifer G. Goldman, MD, MS
Section Chief, Parkinson's Disease and Movement Disorders

MENTIONED IN THIS ARTICLE →

A movement disorders neurologist by training — Jennifer G. Goldman, MD, MS, leads the Parkinson's Disease (PD) and Movement Disorders program at Shirley Ryan AbilityLab. The kind of interdisciplinary team with which she collaborates will be familiar to any physiatrist.

"I've always collaborated with other specialties in an interdisciplinary care approach," Dr. Goldman said. "To tackle the cognitive and behavioral issues that patients with PD and movement disorders face, I've worked closely with neuropsychologists, social workers and psychiatrists, but also with speech-language pathologists, physical therapists and occupational therapists. This level of collaboration may not be the most typical for others in my field, but to me, it's so important to interface with multiple disciplines and not stay in a silo."

For Dr. Goldman, the benefits of this approach are clear: a team with different clinical training perspectives is able to provide more patient-focused and complementary disease management and treatment options, including medication, surgery and rehabilitation therapy. Moreover, a team-based approach to care has been associated with improved mobility and quality of life among people with Parkinson's.

Now, there's reason to initiate this collaboration between neurologists and physiatrists earlier in the treatment of patients with PD and movement disorders. The latest science shows positive benefits for the brain, with increased neurotrophic growth factors, neuroplasticity and neurochemicals, as well as reduced inflammation and stress responses when people with PD exercise (including soon after diagnosis). With greater recognition of the importance of physical activity, Dr. Goldman stressed that, moving forward, the partnership between physiatrists and neurologists will be critical in the treatment of patients with PD.

“We’re really entering a new phase of Parkinson’s care,” she said. “Instead of only offering rehabilitation for people at more advanced stages of the disease — when they have already started experiencing falls, dysphasia or dementia — we are moving the clock backward. Now, rehabilitation can be part of early and continuing care from the get-go. People’s eyes have been opened to the role of physical therapy, exercise physiology and overall fitness in managing the disease and potentially slowing disease progression.”

This new philosophy is possible, in part, because of recent advancements in the early diagnosis of PD. In the past, patients might not have been diagnosed for several years. “Now, thanks to greater awareness and the use of new tools to spot the disease earlier, we might see PD patients just a couple of months into the disease, when symptoms are mild,” Dr. Goldman said.

To facilitate an earlier focus on rehabilitation, it will be pivotal for physiatrists and neurologists to increase their collaboration.

“Neurologists are good at recognizing the benefits of rehabilitation, but don’t necessarily understand that they can refer a patient to a physiatrist, who can guide a program that addresses the rehabilitation needs of PD patients across various stages of disease progression,” she said. “In the spectrum of rehabilitation diagnoses, Parkinson’s may represent a smaller cohort compared with brain injury, stroke and spinal cord injury, but there’s a really important role for physiatry and allied health therapists in the care of this patient population.”

Moreover, physiatry is important for PD patients because of the limitations of currently available treatments. “Yes, we have medicines. Yes, we have surgery, but those interventions help with symptoms,” she said. “They don’t always get at the root cause or slow disease progression. We need something else to fill that void. Therapy can serve as that complement.”

Dr. Goldman hopes to encourage the next generation of PD-focused physiatrists with a new fellowship program dedicated specifically to movement disorders. Commencing in July 2021, this program will provide hands-on clinical experience as part of a collaborative team, along with opportunities for research and mentoring.

“As we study Parkinson’s disease, it will be more important than ever to know how best to treat patients through science — whether it’s through pharmacological or nonpharmacological approaches. New approaches may incorporate exercise, cognitive rehabilitation, technology and robotics. It will be critical to understand how these therapeutics affect neurobiological systems and patient outcomes. We need to know how to ask new scientific questions and how to design new studies,” she said. “A collaborative, interdisciplinary approach is key.”

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Science IRL. Can Drone Technology Help Drive Wheelchairs?

Sandro Mussa-Ivaldi, PhD
Senior Research Scientist, Shirley Ryan AbilityLab | Professor, Physiology, PM&R and Biomedical Engineering, Northwestern University

MENTIONED IN THIS ARTICLE →

For decades, traditional control methods, such as joystick and sip-and-puff systems, have helped patients get where they need to go — though not always easily. Sandro Mussa-Ivaldi, PhD, Shirley Ryan AbilityLab research scientist, offers his take on “Data-driven body–machine interface for the accurate control of drones,” which highlights how body-machine interface technology could offer new — and better — control methods for assistive devices.

What’s the big deal?
Remote control technology can be used to fly airplanes, complete search-and-rescue missions and even perform surgery! All of this technology relies on some type of body-machine interface (BoMI) to translate body movements into commands. This study developed a BoMI that used upper-body movements to control a drone, and it has implications for control methods that may better assist patients in the future.

What did researchers find?
Subjects first participated in a virtual reality (VR) simulation in which they moved their upper bodies in response to a training video. Researchers measured both muscle activation (with EMG electrodes) and motion (with markers) to determine what kind of movements felt most natural to participants. Some people used only the torso, while others used both the torso and the arms. Then, participants used these movements to fly a simulated drone and a real drone (Fig. 1). Researchers found that participants who used torso movements alone demonstrated the most accurate control with the least amount of training. The BoMI was even easier to learn than a joystick!

How does this affect how I treat patients?
People with neurologic conditions such as cervical spinal cord injury or amyotrophic lateral sclerosis (ALS) rely on interface systems to control assistive devices (e.g., powered wheelchairs). However, it can take a lot of time and practice to master traditional control methods, such as joystick or sip-and-puff systems. If this BoMI is applied to assistive devices, our patients could learn to control them faster and with more accuracy. Plus, they can tap into the type of movement that is already easy for them, which makes the control much more intuitive!

Reference: Miehlbradt, J., Cherpillod, A., Mintchev, S., Coscia, M., Artoni, F., Floreano, D., & Micera, S. (2018). Data-driven body–machine interface for the accurate control of drones. *Proceedings of the National Academy of Sciences, 115*:7913-7918. https://doi.org/10.1073/pnas.1718648115

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Influencer. From EMG to CAPMR

Lawrence R. Robinson, MD, FABPMR (’85 Residency)
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and John and Sally Eaton Chair in Rehabilitation Sciences,
Sunnybrook Health Sciences Center, Toronto, Canada
President, Canadian Academy of Physical Medicine & Rehabilitation

Larry Robinson, MD, discusses his enthusiasm for electromyography (EMG) and his focus as the new president of the Canadian Association of Physical Medicine & Rehabilitation (CAPMR).

Tell us about your work.
I’m in full-time academic medicine, with two institutional leadership roles. First, I’m the Division Director for PM&R at the University of Toronto’s Faculty of Medicine, which is the largest PM&R department in Canada. Additionally, I’m the Program Chief of Rehabilitation Services and the St John’s Rehab Program at Sunnybrook Health Sciences Centre, which is the largest rehabilitation hospital in the Greater Toronto Area with 178 beds. I also hold the John and Sally Eaton Endowed Chair in Rehabilitation Sciences at Sunnybrook.

What is your research specialty?
My clinical specialty is electrodiagnosis or electromyography (EMG) — using electrical tests to diagnose diseases of nerve and muscle. We stimulate nerves and record from muscles or nerves to see how fast and how well a nerve conducts. We also put small needle electrodes in the muscle to record the muscle’s electrical activity.

My interest in EMG started while I was a PM&R resident at the Rehabilitation Institute of Chicago (now Shirley Ryan AbilityLab), during my rotation with Dr. Ian MacLean. EMG instantly appealed to me. To understand why a muscle is weak, you think about the wiring diagram, design testing to distinguish the different options and then come to a diagnosis. This logical approach fits well with my thinking style.

Your biggest claim to fame is arguably the Combined Sensory Index (CSI) — commonly called the “Robinson Index” — for carpal tunnel syndrome. What does CSI do?
About 20 years ago, I realized there were many different tests to assess carpal tunnel syndrome — probably a dozen of them — but the tests sometimes give different results. It was a real challenge to know what tests to perform and how to reconcile these differences. The Robinson Index takes the three best tests available and aggregates the results into a single number. I liken the approach to board examinations, when people take multiple tests and then the results are averaged for a result.

From there, the focus was on knowledge translation and acceptance — getting people to change to a new method requires a sustained, multifaceted approach, including national and international presentations, publications, and one-on-one discussion. Ultimately, the index has taken off, but it’s been a 20-year process.

Congratulations on your recent election as President of the Canadian Association of Physical Medicine & Rehabilitation (CAPMR). What are your goals over your two-year term?
I grew up in Boston and spent all my life in the U.S. until I moved to Canada in 2014. I became a Canadian citizen in 2019, and it was only a year later, in 2020, when I was elected President of CAPMR. One goal for my presidency is to use my background and experience in the U.S. to increase our international collaboration. We’ve arranged for the *American Journal of Physical Medicine & Rehabilitation* to become our official journal — now, the *AJPM&R* has the CAPMR logo on it. We’ve also been more active in the International Society of Physical and Rehabilitation Medicine.

The other goal is to build our virtual education resources. Before COVID-19, we typically had one annual meeting a year. Now, we’ve totally switched — and rather quickly too, I have to say — to virtual connections. Every couple of weeks we have a webinar, and people from all over the world attend. Clinicians from places like Bangladesh, Singapore and Malaysia, who normally would not be able to travel to Canada, can now access this education.

In addition to being elected to the CAPMR presidency, what other professional honor has meant the most to you?
Winning the Lifetime Achievement Award from the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) in 2017. I’ve gone to every meeting of AANEM since 1986, so it was great to be recognized by the organization.

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CME Opportunity.

Title: Disability, Ethics and COVID-19: How COVID has Exposed and Amplified the Gaps and “Clash of Cultures” between Persons with Disabilities and our Healthcare System

Presenter: Kristi Kirschner, MD, University of Illinois College of Medicine, Department of Medical Education

Learning Objectives: At the conclusion of this activity, participants should be able to:

1. Characterize the health equity issues that existed pre-COVID pandemic for people with disabilities
2. Identify the problems of health care access, bias, and equity exposed during the COVID pandemic for PWD
3. Generate possible solutions for redressing the inequities and planning for the next pandemic

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