Muscle Evoked Potential Operant Conditioning (EPOC) to Improve Sensorimotor Functions in People with Spinal Cord Lesions

You can view this presentation at: youtu.be/2vIuOF6tOXA

[00:00:04] **Dr. Aiko Thompson:** Thank you, the SRNA and the organizing committee, for having me here and then giving me an opportunity to talk about the research studies and programs that we've been running in my lab. So, today, I'd like to talk about operant conditioning of stimulus-triggered muscle responses as a neurobehavioral training method to address different sensory and motor impairments in people with chronic spinal cord injuries and lesions.

[00:00:42] So, with this approach, we use these muscle responses to brain stimulation or peripheral nerve stimulation. These are super-fast and usually involuntary responses, and, importantly, they reflect the state and activity of the brain and the spinal cord just before the time of stimulation.

[00:01:07] And through operant conditioning, modification of a behavior is brought about by the consequence of that behavior. So simply, when the consequence of a behavior is positive, its occurrence increases. When the consequence of the behavior is negative, its occurrence decreases. It's very straightforward.

[00:01:27] But when we put these two things together, we can train specific sets of brain and spinal cord pathways and their activity that are reflected in the specific muscle response. For the interest of today's talk, I won't go over the historic detail of this approach, but I'd just like to point out that this reflex operant conditioning approach that we've been doing is based on more than 45 years of animal basic research and human research.

[00:02:00] And then, through all those studies, we've learned that changes in neural property and activity at all those many different sites in the central nervous system are involved in this neurobehavioral training approach. So, there's about lots of science behind this. I just won't get into it today.

[00:02:22] So, right now, there are a few different conditioning protocols that are being developed and tested in my lab and elsewhere. And because these protocols can be customized to meet each individual's needs and neural pathways available, there are a lot of possibilities for a wide range of conditioning applications in the future.

[00:02:46] In this talk, I'd like to show you a few different examples of therapeutic applications of operant conditioning in people with chronic incomplete spinal cord injury and lesions and other central nervous system disorders.

[00:03:04] The first example is: operant down-conditioning of the soleus H-reflex in people with spastic hyperreflexia due to chronic incomplete spinal cord injuries and lesions. I'm going to start this with: why? Here's why we decided to do down-conditioning of the soleus H-reflex.

[00:03:28] Normally, the excitability of the spinal pathway -- the spinal stretch reflex pathway, -- you can see here, is modulated from sitting, to standing, to walking, to running, to more complicated movement such as dancing, jumping, or kicking the ball, so that this pathway can function appropriately in each one of these movement skills and motor behaviors.

[00:03:54] However, when people go through spinal cord lesion, regardless of the activity being performed, the excitability of this pathway can be stuck high -- not moderated nor useful -- but rather being detrimental, and a part of problematic spasticity that many of these people experience.

[00:04:15] So, to target and improve behavior of this reflex pathway, we applied operant down-conditioning to the soleus H-reflex -- the calf muscle's H-reflex -- in people with spastic hyperreflexia due to chronic spinal cord lesions. This protocol consists of six baseline sessions, and then, 30 conditioning training sessions that occur at the pace of three times a week, followed up by a few follow-up sessions over a few months.

[00:04:49] In each of these sessions, the participant receives 20 contour reflex trials and then three blocks of conditioning trials. During these reflex trials, the participant received the visual feedback on the ongoing calf muscle activity. When the participant has kept the calf muscle activity in the shaded zone for a few seconds, the stimulation is triggered, and reflex is elicited.

[00:05:14] During the conditioning trial, the participants see the size of the reflex response that was just elicited on the right side of the screen here. This person is going through this training exactly right now. Let’s see if we can do this. Yeah. When the reflex is small enough to remain within the shaded area on the right-hand side, the bar becomes green, and the ongoing success goal rate goes up.

[00:05:44] If the bar exceeds or gets out of the shaded zone, the bar color becomes red, and the trial registers as a failure, and the ongoing success rate goes down. It's fairly straightforward, as you can see here.

[00:05:59] What we saw in this earlier study is that people with chronic spinal cord lesion can decrease the soleus reflex size over the course of 30 conditioning sessions just over 10 weeks, just as much as people without injury are able to do over 24 sessions over eight weeks. And in these individuals, when the down-conditioning training reduces the reflex size -- as you can see in here -- in standing, it changed the reflex activity during walking.

[00:06:38] This is showing the reflex size across the gait cycle before and then after. And then, the small reflex size was accompanied by changes in the calf muscle activity during the gait cycle. In this example, the tonic soleus activity throughout the short step cycle here was replaced by a phasic suppression of the soleus after reflex down-conditioning.

[00:07:06] And that's shown in here. Muscle activity was also improved, not only in the strained calf muscle, but in many other muscles of both upper and lower leg in both legs. And with that, these people were able

to increase the walking speed by about 60%, which converts to about 0.2 m/sec, which if you know how this measurement works, it's a tremendous improvement that you can see very clearly.

[00:07:36] And then, these people also walk, were able to improve their right-left step symmetry. So, overall, the study showed that H-reflex down-conditioning training can improve walking in people with chronic spinal cord lesions. And here is the summary of reflex conditioning as a potential therapy for people with spinal cord lesions.

[00:08:01] The first, the rationale: reflex conditioning induces a targeted change in a specific reflex pathway, towards normalizing the excitability of that pathway. As a result, behavior and the function of the targeted pathway can be improved. The scientific background, as I mentioned earlier, is based on more than 45 years of basic and in human research. So, it's not like I'm making up this thing, importantly.

[00:08:26] And the therapy dose: so, typically, people start to see some functional improvements after 12 sessions over four weeks. But, at this point, we do not know the optimum dose for this treatment yet. The training on therapy technique itself is highly recommended and is available through the National Center of Neuromodulation for Rehabilitation, which is based at the Medical University of South Carolina, and as well as my lab, MUSC's EPOC Lab. And risks: so far, no significant risk has been noted.

[00:09:07] So, next, I'd like to move on to give you the second example, which is operant up-conditioning of the motor evoked potential in the ankle dorsiflexor tibialis anterior in people with foot drop. So, just like the other one, I'm going to start with the reasoning: why?

[00:09:25] So, we decided to do this conditioning to target the brain-to-spinal cord connection, brain-spinal cord pathway, in people with spinal cord lesions. And this is because when an injury or disease cause a partial damage to the spinal cord, here, or the specific pathway -- the corticospinal pathway -- it affects not only its function but it affects the measure that's called motor evoked potential, which we can measure in the muscle.

[00:10:00] So, this measure can reflect the strength of this connection and that's why it has some diagnostic usefulness. What we have found over many years is that, when we have people with spinal cord lesions, this response gets weaker and smaller. And then, those smaller and weaker responses are related to more severe foot drop in people with lesions.

[00:10:28] So, in our study, we decided to up-condition the ankle dorsiflexors' MEP, the muscle response, to increase and strengthen this corticospinal drive for the dorsiflexor to alleviate the foot drop. Here's the overview of the MEP up-conditioning protocol. It is very similar to the reflex down-conditioning I was showing you earlier.

[00:10:54] Three things are different. First, here we are targeting the ankle dorsiflexor tibialis anterior. Second, stimulation is now swapped to non-invasive brain stimulation over the head, called transcranial magnetic stimulation, instead of giving the stimulation to the leg. Third, now the participant is encouraged to increase the response instead of decreasing it. So, it's an upregulation training.

[00:11:14] And this is how the actual training looks like. Let's see if I can play this. Good. When the sitting participant has maintained a predetermined level of dorsiflexor activity -- looking at the screen right here -- the stimulation is triggered and muscle response is elicited. We can also see in here -- this side -- immediately after the response is elicited, the feedback bar refreshes and indicates the size of MEP that was just elicited. You can see here on the right side.

[00:11:57] And just like the reflex example earlier, when the bar reaches the shaded area, the bar is green, and success rate goes up. If the bar does not reach the shaded area, the bar becomes red, and the success rate goes down.

[00:12:13] What we found in this study is that people with spinal cord lesion can increase the muscle response size over 24 up-conditioning training by about 50%. And this is actually exactly the same as people without any injuries achieved over 24 sessions. It was pretty impressive.
[00:12:35] This increase in the dorsiflexor muscle response was accompanied by the consistent changes in the dorsiflexor activity and the ankle joint motion during walking across different individuals with spinal cord lesions.

[00:12:49] Here are the key parts: in these people, swing-phase dorsiflexor activity was increased, the ankle angle at the foot contact was increased, the ankle range of motion across the step cycle was increased, the peak dorsiflexion angle was increased, and the median angle across the gait cycle was also increased.

[00:13:14] So, what we are seeing here is the dorsiflexor MEP up-conditioning seems to alleviate foot drop and improve walking in people with chronic spinal cord lesions. And importantly, this is not limited to people with spinal cord lesions only; this seems to be true in individual with stable secondary progressive multiple sclerosis.

[00:13:41] In this particular person with MS, the ankle dorsiflexor MEP size increased clearly significantly over 24 conditioning sessions. Most importantly, and most remarkably, this really restored this person's swing-phase activity in the tibialis anterior.

[00:14:03] Here, this second half part of this chart is showing the dorsiflexor tibialis anterior muscle activity. Before the conditioning, she had no activity. After 24 conditioning, she actually had clear dorsiflexion activity. And at this point, she, actually, did not show any visible foot drop.

[00:14:23] And what's really exciting is that beginning of the study, she was coming in with cane because she needed it. But towards the end of the training, towards the end of the eight-weeks' period, she started to forget to bring in the cane because she didn't need it.

[00:14:37] And then, with that, my neurologist was very surprised, "I've never seen this happen," and that's important. So, with this person, she told me she needs to keep coming back because she got something good. So, importantly, I was able to get three and a half years of follow-up with the same person.

[00:14:55] She's no longer coming back in for the regular training. She just came back when she felt like coming back. And then, with that, with this person with MS, we were able to really maintain her improvement for another three and a half years, despite she went through a few episodes of relapse and then few other life events that was really stressful, as somebody was talking about. So, what I want to say is, this is because she worked for it, she earned it, that became her own new habit to engage the right pathway in the right way.

[00:15:28] So, now I want to move on to the third example, which is operant conditioning of non-receptive cutaneous reflexes in people with neuropathic pain due to chronic spinal cord lesions. This is our newest and then probably most experimental approach that we are developing in our lab.

[00:15:48] So, I'm going to give you the key background facts. The first is that, people with chronic spinal cord lesions, cutaneous reflexes to non-painful stimulation are present. The reflex is there, but it's small, and it's quite often abnormally modulated, but it's there. So, there's something.

[00:16:06] The other important thing is that this pain pathway and non-pain pathways are mutually suppressive in the spinal cord in theory, and this is something people in the field have known for many years in theory. So, if we can put these things together, and then, now we are trying to see if we up-regulate or we encourage a non-pain pathway to get stronger, can we then suppress the pain pathways overactivity to alleviate neuropathic pain in people with the spinal cord lesion? So, that's the idea.

[00:16:43] So, this is how it looks like. Appearance-wise, the protocol is very similar to the H-reflex and MEP conditioning, like I was showing you earlier. The only difference is, now we are stimulating the cutaneous nerve, which really convey the skin sensation. So, instead of doing motor-nerve stimulation, we're doing skin stimulation, and then we're doing up-training, and that's what it is.

[00:17:00] And here is what we saw in our very first person who went through this training. He was able to gradually increase the cutaneous reflexes -- it's shown here -- over the course of 24 sessions, and that was accompanied by the gradual increase in the pain threshold, or the very systematic increase in the pain threshold, over the course of this 10-weeks' training.

[00:17:36] So, this is really exciting, and this supports the possibility that operant conditioning training of the non-painful pathway may be able to alleviate pain in people with chronic spinal cord lesions. This is really the beginning of our ongoing clinical trial, and I hope, next time when I'm back here -- I hope I get invited again -- I get to share the exciting news about this approach.

[00:18:06] So, to summarize, operant conditioning of stimulus-triggered muscle response can induce targeted change in the targeted pathway in people with chronic spinal cord lesions. And conditioning of stimulus-triggered muscle responses can help to improve sensory and motor function in people with spinal cord lesions. And then, training effects may last for several months, potentially two years.

[00:18:34] So, before I conclude, I want to just list the ongoing clinical trials that we are having. We have four major clinical trials happening in my lab. The first one is the reflex training to target neuropathic pain, as I mentioned. Another one is a reflex down-training to target spasticity. Another one is the brain stimulation training to target foot drop.

[00:18:58] And the last one, I didn't get to show you today, but actually, it's growing; it's really a major part of our lab, is to address all these problems and try to do the same in the arm. And so, we're trying to address the sensory and movement problems in arm and hand in people with spinal cord lesions. So, if you or anyone you know may be interested, please reach out to us. Our QR code is up there, and hope to hear from you. Thank you so much. Any questions?

[00:19:40] **Audience Member 1:** Thank you. Thank you so much for that, doctor. I have a question. Has there been any stem cell therapy provided for MOGAD patients? And if so, what percentage would you put on the improvement in quality of life?

[00:20:00] **Dr. Aiko Thompson:** Sorry, could you say it again, please?

[00:20:02] **Audience Member 1:** Okay, no problem. So, have you had any MOGAD patients that had the stem cell behavior delivery done? And if so, what percentage would you put on their improvement of quality of life after doing the stem cell behavior?

[00:20:22] **Dr. Aiko Thompson:** I do not know if I'm expert enough to be able to answer that question. In terms of our approach though, there's a possibility to be combined with some other treatments, such as stem cell

treatment. But unfortunately, and then sadly to admit that, our therapy approach is really in its early stage, and it's been a slow and hard push to get to where we are. So, again, I hope to share better news next time I'm back.

[00:21:01] **Audience Member 1:** Okay. Well, maybe we could have a clinical trial on that for MOGAD patients.

[00:21:05] **Dr. Aiko Thompson:** That would be great.

[00:21:07] **Audience Member 1:** Thank you.

[00:21:08] **Dr. Aiko Thompson:** Thank you.

[00:21:12] **Audience Member 2:** What type of electrical stimulation are you using to get the muscle movement? And then, have you ever considered a trial or done anything with people that are non-ambulatory and its effect on trunk or upper extremities?

[00:21:30] **Dr. Aiko Thompson:** That's a great question. So, to start, probably from the last one, it's the relatively straightforward. The possibility to apply this training to other parts of the body or different movement problems, it's yes. So, I didn't get to show, but it's there. Our lab, our group, is really moving forward with trying to improve the upper limb functions because that could have a huge impact on the quality of life.

[00:21:58] So, that's something we would really like to go for. And then, RE results are looking great. So, if you actually have a chance to look at the website, Krista, who is sitting in here, she's going to be around for the entire conference, and she'd be more than happy to share our website, which shows all the upper limb testing, improvement, and patient testimonials. So, that's something we're going to do.

[00:22:25] And then, trunk, yes, absolutely, because that now I'm talking about it. So, when we do the upper limb training, another thing we've been seeing is actually coming with a lot better improvement in trunk stability. So, there could be a lot more beneficial outcome by working on upper limb, anywhere from the finger muscles, to the flexor muscles, to the upper arm muscles. So, we are definitely in pursuit of that direction. Yes.

[00:22:59] **Audience Member 3:** Hi. Thank you so very much. Your work and Dr. Wolpaw's work is truly at the basis of neuroplastic changes in spinal cord injury. I wanted to ask a question that will set up a session that occurs a little bit later. And in your first, down-regulation of the spastic ankle, what was the average age of the individual and how long after the onset of injury? And again, it's to set up some answers in the future.

[00:23:32] **Dr. Aiko Thompson:** I think that's a really fantastic point and we still have it. So, the average age was close to 50 years old in the initial cohort. And then, in our ongoing clinical trials, the age is actually creeping up. The average age is 60 years old, and all of them have chronic spinal cord injury. The shortest, the earliest, is one year, but now we are having a lot many more people who are coming in 10 years post, 15 years post, living with this in different lesion condition for many years. And then, yes. Thank you.