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JOAN BANKS-SMITH 00:09	[music] This is Joan Bank Smith for Kessler Foundation's Fast Hits: Research that Changes Lives. Historically, it was believed that the brain stopped growing after childhood. We now know the contrary to be true. Neuroscience has confirmed that our brains change throughout our lives from birth to death. The brain's ability to rewire its circuitry and make adaptive changes, known as neuroplasticity, is why recovery after injury is possible. Much about neuroplasticity is not well understood. Our researchers are using functional magnetic resonances imaging, fMRI, and real-time neurofeedback capabilities in our Neuroimaging Center, where they are conducting several novel pilot studies funded by the David F. Golger and Craig H. Neilsen Foundation, to understand how and where adaptive changes take place in the brain and correlate changes in the brain to changes in behavior and function.
BANKS-SMITH 01:11	[music] In this episode, I had the opportunity to speak with three of our researchers - Dr. Olga Boukrina, senior research scientist in the Center for Stroke Rehabilitation Research; Dr. Jeanne Zanca, senior research scientist in our Center for Spinal Cord Injury Research and Center for Outcomes and Assessment Research; and Dr. Glenn Wylie, director of the Rocco Ortenzio Center for Neuroimaging - about the research they are conducting on brain activity in people with chronic neuropathic pain and spinal cord injury, identifying a biomarker for fatigue, understanding fatigue across the lifecycle, and using neurofeedback to promote beneficial brain plasticity. These topics were recently published in our 2022 Impact Report.
BANKS-SMITH 02:00	Dr. Zanca, let's talk about your pilot study aimed at empowering people with spinal cord injury to self-regulate chronic neuropathic pain. Why are you using neurofeedback versus medication or surgery as an approach to neuropathic pain treatment?
JEANNE ZANCA 02:17	One of the key problems with neuropathic pain is that we have fewer options to address it. Neuropathic pain is thought to come from a disruption to the nervous system, either the spinal cord or nerves elsewhere in the body, or how the brain is interpreting signals coming from the body. Now, unlike a pulled muscle, we can't use things like exercise or stretching to try to improve that situation. And so we're left with things like surgery that not everyone is a candidate for and it has its own risks, or medications, which presently are the primary means of treating neuropathic pain among people with spinal cord injury. It's often reported that these medications can decrease in their effectiveness over time or have side effects, like drowsiness or constipation, that can affect quality of life. And so we're in a situation where existing treatments aren't capable of eradicating pain completely. And so people with spinal cord injury and neuropathic pain are often told to live with it, but they're not given strategies to learn how to do that over time and to figure out how to cope with that pain in ways that reduce its interference with life.
ZANCA 03:28	So what we'd like to do in this study is to use neurofeedback, which, as described before, as a form of biofeedback for the brain, to help people with neuropathic pain identify strategies that they can use to self-regulate their pain experience, which

	means the intensity and/or unpleasantness of their pain, increase their quality of life and their ability to cope with the pain that's left over after other treatments like medication or surgery are used.
BANKS-SMITH 03:56	How are participants guided while in the MRI scanner to minimize their pain?
ZANCA 04:01	Well, the beauty of this form of neurofeedback is that its intention is to help a person find their own customized strategy for dealing with their pain. So in this particular study protocol, we're offering a menu of options that people can consider. So things like focusing their attention on their breath, shifting their attention from their pain to another thing in the room or their mind, imagining a scene, or manipulating the pain. So, for example, if their pain is a burning pain, they might try an imagery technique where they imagine it transitioning from something burning red to something cool and blue. But we're not actually prescribing what participants have to do while they're being scanned. We're giving them some ideas that they can jump off of, but they can experiment. And the idea is that the neurofeedback will help them learn what's working for them with the idea that they can then use those strategies in the real world to help manage the pain.
BANKS-SMITH 04:58	Dr. Zanca, how will this study help those with a spinal cord injury manage their pain and reduce its interference with daily life?
ZANCA 05:06	One of the challenging aspects of living with chronic pain is the sense that one has little control over it, that it can control one's life instead of the other way around. And so we're very interested in identifying strategies that put the power in the hands of the person who's experiencing the pain to change their experience of it. And so this study, we hope, will be a first step in identifying whether neurofeedback can help people learn strategies that they can employ in their everyday life to manage pain, whether they're having an exacerbation or whether it's their normal level of pain, to give them a way of changing that experience and increasing their feeling of control over their pain so that it doesn't control life.
BANKS-SMITH 05:48	Dr. Wylie, which part of the brain have you found plays a significant role in fatigue after stroke?
GLENN WYLIE 05:54	We've been looking at fatigue in a number of populations, and we just started to look at fatigue and stroke. And in other populations, we found that the basal ganglia is a really important brain area associated with fatigue, as part of a network that also includes areas like the anterior insula and dorsolateral prefrontal cortex. But the basal ganglia seems to really be central to this network. And one of the areas of the brain that's frequently affected by stroke is the basal ganglia, just because of the vasculature and where it's located in the brain. And so that's the area that we're really looking at in this study.
BANKS-SMITH 06:36	How does your study aim to identify the network of the brain associated with fatigue?
WYLIE 06:42	One of the things we're going to do in this study, looking at fatigue and individuals who've had a stroke, is we're looking at fatigue in people who have had a stroke that directly affects the basal ganglia and fatigue in folks who have had a stroke in parts of the brain that do not include the basal ganglia. And that allows us to actually ask the

question, "Is the basal ganglia just associated with fatigue, or is it really central? Is whatever the basal ganglia is doing-- is that really necessary for fatigue in some way?"

BANKS-SMITH 07:15 Dr. Boukrina, you and Dr. Wylie are examining biomarkers for fatigue and people with strokes. Can you explain to us what that means?

OLGA BOUKRINA 07:25 Stroke affects about 795,000 people annually in the US alone, and a lot of the stroke survivors experience fatigue mentally and physically. As Dr. Wylie mentioned, prior studies on fatigue suggest that the basal gangla may be an important area that is impaired in individuals who experience fatigue. And so among stroke survivors, this area is damaged in about 70% to 80% of individuals. So we're looking at the fatigue and basal ganglia as the kind of source of fatigue, as well as other parts of the fatigue network, to determine whether it predicts the experience of fatigue and stroke.

BANKS-SMITH 08:05 How will this research help people who have had a stroke?

BOUKRINA 08:08 Those who have had a stroke, about 29% to 77% of them will experience mental fatigue, depending on the type of assessment. And post-stroke fatigue has a negative effect on participation in physical and other therapeutic activities during rehabilitation. And also this effect may predict the fact that people with fatigue have worse neurological recovery and actually are predicted to have worse mortality. And so our study is aimed at uncovering the neural mechanisms of fatigue and stroke. Once we have a firm understanding of these mechanisms, we can then begin to develop novel targeted treatments for fatigue and stroke.

BANKS-SMITH 08:49 Thank you for explaining that to us, Dr. Boukrina. We're going to come back to you, Dr. Wylie. Another area of research you are involved in is understanding fatigue across the lifecycle. What does that mean?

WYLIE 09:02 Before, we've looked at fatigue in a number of populations, and one population that we thought would have a significant fatigue was elderly people, and that we thought fatigue might increase as you get older. And so we decided to actually look at that by investigating the amount of fatigue that people report as a function of age. And what we've found so far-- we have a limited sample of individuals who range from 20 years old to around 65. What we've found so far is that actually older people, at least within that age range, don't report more fatigue. They report having about the same amount of fatigue as their younger counterparts on a day-to-day basis. But surprisingly, when we actually ask them to perform difficult cognitive tasks, they fatigue less than their younger counterparts; they report less fatigue sort of in the moment as they're working on these tasks. So now what we're doing is we're recruiting even older individuals to see if that pattern holds as you age beyond 65, because that pattern really surprised us.

BANKS-SMITH 10:18 Dr. Wylie, what is the difference between state fatigue and trait fatigue?

WYLIE 10:23 Trait fatigue is kind of fatigue over a long period of time. So when we assess trait fatigue, we ask people to sort of cast their mind back over the past two weeks or a month and sort of reflect on how much fatigue they've experienced. And that's been the predominant measure of fatigue in the literature. And as you can imagine, if you've been having a tough time because-- if you have something like multiple

	sclerosis or if you've had a stroke, then casting your mind back over the past two weeks, these other things that you've been struggling with probably influence your response to how much fatigue you've had. We think that trait fatigue might be contaminated by other influences.
WYLIE 11:07	State fatigue, on the other hand, is asking people to report the amount of fatigue they feel in the moment. We have them do a task and we say, "Okay, how fatigued are you right now, at this moment?" While that kind of self reported fatigue is not completely free of other influences, it is much less contaminated by other influences. And so we've started using state fatigue measures to look at brain activation associated with fatigue.
BANKS-SMITH 11:36	How does this apply to the work you're doing?
ZANCA 11:38	So in the work we're doing, we acquire both types of fatigue reports, both trait fatigue and state fatigue. And we do that because so much of the literature has used trait measures to study fatigue, and we want to relate what we find to the existing literature, but also we feel that state fatigue measures are much less contaminated by other sources of variance and other things that are going on in people's lives. And so that's really the kind of fatigue that we think is probably going to be most informative when we try to associate fatigue with activation in the brain.
BANKS-SMITH 12:15	How will this research help people who have had a stroke?
WYLIE 12:18	As Dr. Boukrina said, what we first have to do is to understand fatigue. And people have known-- clinicians have known that clinical populations, such as individuals who have sustained a stroke, suffer from high levels of fatigue. They've known this for 100 years, but no one has really been able to understand what fatigue is, part because we haven't had the tools. And so now that we have the tools of neuroscience where we can actually look at brain activation as people become more fatigued and see which parts of the brain are critical for that feeling of fatigue, now that we have that, we can begin to study fatigue to understand it, and then based on that foundation, we can develop interventions.
BANKS-SMITH 13:08	Dr. Wylie, thank you for helping us better understand this. Dr. Boukrina, you're using real-time fMRI neurofeedback to help people with stroke overcome persistent reading and language skills. Can you explain to us what real-time fMRI neurofeedback is?
BOUKRINA 13:26	Real-time fMRI neurofeedback is really a form of biofeedback where the modern technology allows us to provide information about the level of activity in one brain area or in many brain areas to the participant, and the key is that we provide that information with minimal time delay. So as participants engage in self-regulation strategies which can help them activate a particular part of the brain, we can use the real-time fMRI neurofeedback method to inform them about how well they're doing in this task, and the feedback can be in the visual or auditory form, such as a pleasant sound or a smiley face or a thermometer value with some numbers on it.
BANKS-SMITH 14:15	How does using this method promote beneficial brain plasticity or neuroplasticity for your participants?

BOUKRINA 14:22	If we know what brain mechanisms are dysfunctional, we can then use self-regulation strategies in combination with fMRI neurofeedback to allow participants to change their brain activity so that it is more similar to the way that healthy participants, healthy people, activate their brains.
BANKS-SMITH 14:41	Can you explain how participants are learning to regulate their own brain activity by combining mental strategies with neurofeedback?
BOUKRINA 14:51	We know that after stroke to the left hemisphere of the brain, the level of activity in the left hemisphere is decreased among stroke survivors. Similarly, blood flow is decreased. And our goal is to actually bring back that activity in the left side of the brain so that participants can more effectively engage it as they recover from stroke. The left part of the brain supports language processing, and in particular, we're interested in improving the ability to process written language, so when we engage in reading. Reading is such a critical part of life, and having impaired reading severely impaired someone's autonomy, ability to participate in a variety of different activities. So we use a combination of motor imagery and reading to help participants increase activation of the left side of their brain and help them recover the ability to read.
BANKS-SMITH 15:50	How can the strides you are making with the study help others with stroke?
BOUKRINA 15:55	Stroke first and foremost leads to neurologic deficits, and our goal, of course, is to find ways to alleviate them through research. Once we have a full understanding of the relationship between brain activity in the left hemisphere and the time course of language recovery, then we can begin to implement other interventions that support kind of the return of more healthy pattern of brain activity after stroke.
BANKS-SMITH 16:21	[music] To learn more about Drs. Boukrina, Wylie, and Zanca; the Centers for Spinal Cord Injury Outcomes and Assessment and Stroke Research; the Rocco Ortenzio Neuroimaging Center; the studies mentioned in this podcast; or to join a study, links are on the program notes. Tuned in to our podcast series lately? Join our listeners in 90 countries who enjoy learning about the work of Kessler Foundation. Be sure and subscribe to our SoundCloud channel, Kessler Foundation, for more research updates. Follow us on Facebook, Twitter, and Instagram. Listen to us on Apple Podcasts, Spotify, SoundCloud, or wherever you get your podcasts. This podcast was recorded remotely on May 16, 2022, and was edited and produced by Joan Bank Smith, creative producer for Kessler Foundation. [silence]