Novel neural stimulation protocol for treating chronic pain

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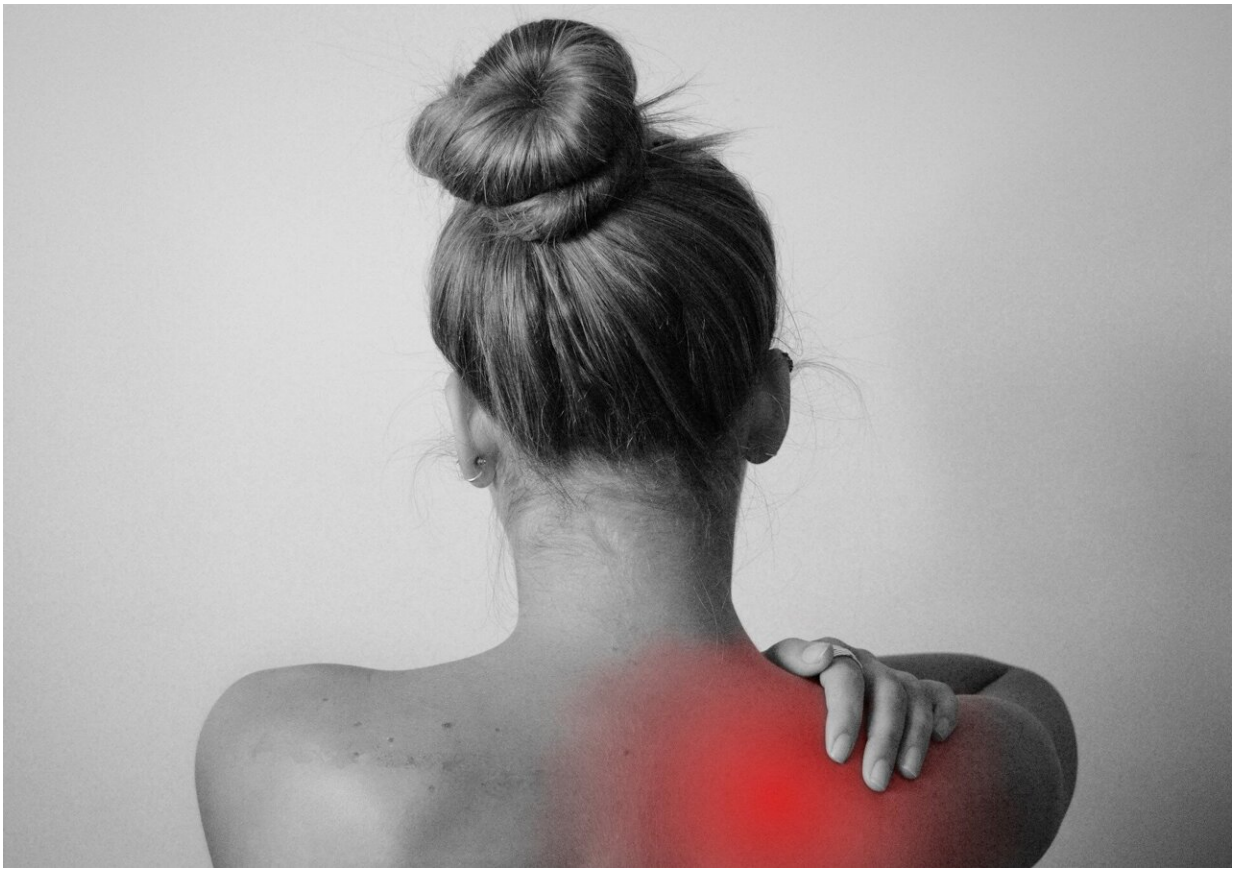

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Any pain you experience is all in your head—really. When we feel pain in response to a stimulus, whether stubbing a toe, burning a finger, or

something more severe, the feeling of pain is the result of a complex signaling pathway in the nervous system.

Pain starts with a stimulus that can potentially cause damage to your body. These stimuli, which include things like extreme cold or heat, and mechanical tear and pinching, are known as "nociceptive stimuli."

Some of our sensory neurons, known as "nociceptors," have nerve endings in our skin or deeper in the body to sense and respond to nociceptive stimulation. Nociceptors send signals to our spinal cord, which then communicates this information to our brain. It is the brain that tells us we are in pain and makes us feel the painful sensation.

Bin Feng, associate professor in the Biomedical Engineering Department, a shared department in the schools of Dental Medicine, Medicine, and Engineering, led the discovery of how electrical stimulation of the dorsal root ganglia (DRG) can block nociceptive signal transmission to the spinal cord and prevent the brain from perceiving chronic pain signals. DRG are clusters of sensory neural cell bodies.

This research has inspired the design of a new neural stimulation protocol that targets the neural tissues in the foramen, the bony tunnels in the vertebrae, to selectively block nociceptive signals. UConn Technology Commercialization Services has filed a patent application for this technology.

For decades, doctors have been implanting electrical devices in patients to treat chronic pain. Typical devices deliver electrical signals to the peripheral nervous system and spinal cord to block nociceptive signals from reaching the brain.

A significant problem with these devices is that some patients find them

beneficial in relieving their chronic pain, while others see little to no change in their pain. Despite incremental developments of neurostimulator technologies, the proportion of patients with beneficial responses has not been markedly improved over the years.

"The trouble with this technology is that it can benefit a portion of patients very well, but for a larger portion of patients it has little benefit," Feng says.

These issues root from the fact that scientific research on the mechanisms underlying why these neurostimulators work has lagged behind their clinical applications.

"We're sitting on a huge pile of clinical data," Feng says. "But the science of neuromodulation remains understudied."

Feng has dedicated his research career to better understanding this process in the hopes of making neuromodulation a more effective treatment to benefit a wider patient population. He hopes that further research and development of this approach can also move neurostimulators up from being a last resort for patients, as they are currently.

Neurostimulators alleviate pain according to a "gate control theory." Our bodies can detect both innocuous stimuli, like something brushing against the skin, and painful stimuli, through low- and high-threshold sensory neurons, respectively.

The "gate" in the spinal cord can be closed by the activation of low-threshold sensory neurons. When that happens, the painful nociceptive signals from high-threshold sensory neurons can no longer cross the spinal cord to the brain.

Neurostimulators reduce pain in patients by activating low-threshold sensory neurons with electrical pulses. This usually causes a non-painful tingling sensation in certain areas of the skin, or paresthesia, that masks the perception of pain.

Following FDA approval of DRG stimulation in 2016, many patients receiving this treatment reported pain relief without the expected paresthesia.

Feng and his lab set out to solve this puzzle using pre-clinical animal model studies. They discovered that electrical stimulation to the DRG can block transmission to the spinal cord at frequencies as low as 20 hertz. This is in contrast to the previous findings in the literature that this blocking requires kilohertz electrical stimulation.

"The cell bodies of sensory neurons form a T-junction with the peripheral and central axons in the DRG," Feng says. "This T-junction appears to be the region that causes transmission block when DRG is stimulated."

More remarkably, Feng's group has found that sensory nerve fibers with different characteristics are blocked by different electrical stimulation frequency ranges at the DRG. This has allowed the development of new neural stimulation protocols to enhance selective transmission blocking based upon different sensory fiber types.

"A-fiber nociceptors with large axon diameters are generally responsible for causing acute and sharp pain," Feng says. "It is the long-lasting and dull-type pain that bothers the chronic pain patients mostIn a chronic pain condition, C-fiber nociceptors with small axon diameter and no myeline sheath play central role in the persistence of pain. Selectively blocking C-fibers while leaving A-fibers intact can be a promising strategy to target the cause of chronic pain."

Feng's group has reported this discovery in the recent issue of *PAIN*, the flagship journal for the field of pain research.

Feng's research has provided enough evidence to justify adding more electrodes to devices that target the DRG and surrounding neuronal tissues. This will allow doctors to provide more precise neuromodulation.

"The next-generation neurostimulators will be more selective with fewer off-target effects," Feng says. "They should also be more intelligent by incorporating chemical and electrical sensory capabilities and ability to communicate bidirectionally to cloud-based server."

Given the increased selectivity of this method, Feng predicts neurostimulators will be able to help more people suffering from chronic pain.

"All this technical improvement will likely dramatically enhance patient-specific neuromodulation to allow neurostimulators to benefit a larger patient population," Feng says.

Feng is now working toward conducting clinical studies with his collaborators at UConn Health to test the efficacy of this method in humans.

More information: Longtu Chen et al, Blocking peripheral drive from colorectal afferents by subkilohertz dorsal root ganglion stimulation, *Pain* (2021). DOI: 10.1097/j.pain.0000000000002395

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