Researcher discusses neurological underpinnings of pain

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Pain—feared, misunderstood and even poeticized in works of art and literature—has long captivated the scientific imagination of Clifford Woolf since his days as a medical student in South Africa.

Woolf, a Harvard Medical School professor of neurobiology and

neurology at Boston Children's Hospital, has been on a quest to understand the basic mechanisms of pain and to help spark the development of more effective therapies to alleviate pain, especially ones that don't have the abuse potential of opioids.

Woolf is the senior author of a newly published study using optogenetics—a technique that uses genetic engineering to render neurons in living tissue sensitive to laser light.

Using this approach in mice, Woolf and colleagues successfully identified the exact cascade of pain-related behavioral responses evoked by stimulating neurons that exclusively sense pain-inducing stimuli.

The findings, published July 5 in *Cell Reports*, reveal some big surprises and cast a new light the classic dogma of pain reflex responses first described a century ago by the neurophysiologist and Nobel laureate Sir Charles Sherrington.

Woolf sat down with Harvard Medicine News to discuss his latest research and his journey to unravel the mysteries of pain.

HMN: One of the central themes in your research is pain. Why study pain?

Woolf: When I was on the surgical wards as a medical student, there were many patients complaining of terrible postoperative pain. I asked the surgeon, "Why aren't you doing anything to treat them?" And he replied "They've just had an operation. That's what happens. They have pain. They will get over it." I thought "That just sounds crazy! There must be something to relieve their suffering." So that led me to do my PhD thesis on pain, and I rapidly came to recognize that pain is both a protective mechanism and something that needs to be controlled in

patients.

Why do we feel pain? Because it warns us of danger in our environment. Without that warning, we are at high risk of damaging ourselves. Individuals born with congenital insensitivity to pain, for example, suffer repeated injury. They're not aware of the difference between food and their tongues, so they chew their tongues. They burn themselves because they cannot differentiate between something warm or scalding hot.

HMN: So pain is good, except when it isn't?

Woolf: Pain as a physiological response is really good. It's a key adaptive mechanism that has a protective function against danger and is a warning signal of infection, tissue damage or disease. Increasingly, we have come to recognize that it also can become a disease in its own right. This typically happens when the nervous system is damaged and the original trigger for the pain may long have disappeared but the pain persists. It no longer has a warning role but is now a pathological state.

The challenge then is to tease out the different kinds of pain to preserve the "good" pain and control the "bad" pain. Here's an example: If you injure yourself and you have pain, you shouldn't overly exercise the affected body part until healing has occurred—that's good pain, protecting the damaged tissue by making it pain hypersensitive until it has healed. But if you have damage to a peripheral nerve and experience episodes of shooting electrical-shock like pain, that pain has no protective function.

HMN: From biological and evolutionary points of view, there are quite a few things we know about pain. But what are some of the challenges that lie ahead?

Woolf: From an evolutionary point of view, even single cell organisms like an amoeba need to be able to detect their environment and react to it by moving away from any danger. So, the drive to detect potential harm has been there right at the beginning of the formation of living organisms. Obviously as higher species with complex nervous systems evolved, it's become much more complicated, involving sensations, mood, memory and movement. Nevertheless, pain is sufficiently important—80 percent of our peripheral sensory neurons are pain fighters activated by pinch, pinprick, excessive heat or cold and other noxious stimuli.

When we sit, we squeeze the blood from our skin at the point of contact with the chair; if that persists, as it does in some patients, they develop bed sores. Yet, we normally keep moving because at the first hint of pain, even at such a low level that we are hardly aware of it, we shift our position to restore blood supply; this is happening all the time and is just one of our many protective pain mechanisms to avoid damage.

HMN: That's beautiful.

Woolf: It is. That is physiological pain. Everyone thinks of pain as bad but it isn't. That is why it's critical in developing analgesics—you've got to preserve these protective mechanisms and not switch off the entire system. That's one of the big challenges. If you switch these danger signals off, you're going to create as many problems as you solve. In a clinical context, it means getting rid of the pain that is pathological while preserving the pain that is protective.

Today, it is possible for people to live with severe damage to the nervous system, either their brain or their peripheral nerves, and survive. Evolution has not caught up with this. In the hunter-gatherer society, you wouldn't be able to hunt and survive if you had damaged your sciatic nerve or spinal cord, so there was no advantage to develop means of

controlling chronic pathological pain. Now you can survive such injuries and typically they are associated with severe pain.

This is true also for the pain associated with the wearing out of our bodies. These are the age-related defects like the collapse of our intervertebral disks or the wearing out of the cartilage in our joints that in the past people didn't live long enough to develop. Pain is now the most common reason why people see a physician. It also, obviously, was the trigger for the opioid epidemic. Opioid use has expanded beyond severe injury and palliative care to being used for everyday common pain complaints. At last, the National Institutes of Health

are waking up to this. NIH Director Francis Collins has called for a major investment in the study of pain. The development of novel analgesics that do not have an abuse potential is a national priority. We have to replace opioids.

Another challenge is teasing out the genes that drive the development of chronic pain and establishing how they work. How do they increase the risk of a transition from acute to chronic pain and how do they help identify potential targets for new therapy? Something like 50 percent of pain is inherited—so the risk of acquiring chronic pain is not just that you happen to have a disease or particular injury but that you have a genetic susceptibility to developing those changes in the nervous system that maintain pathological pain. We need to be able to identify who is at risk and protect them.

HMN: How does your latest work fit into all that?

Woolf: The standard way that I was taught, and all medical students are taught, is that we respond to an acute noxious stimulus by withdrawing from contact with it. This stems from the work of a very famous neurophysiologist at Oxford, Sir Charles Sherrington, who 100 years ago

discovered the reflex as a fundamental unit of the function of the nervous system.

This was the one of the first rules by which the nervous system works—a particular stimulus provokes a defined, or stereotyped, response by means of a reflex arc that connects the noxious stimulus input and the motor neurons that cause withdrawal.

Sherrington regarded reflexes as fixed and of a defined nature, but our latest work reveals that it is much more complicated than that. Responses are more widespread and varied than anticipated and reflect the overall status of the nervous system. A tiny input can initiate a cascade of interacting behavioral responses, well beyond the reflex, most of which occurs in tiny fractions of a second. We are, I believe, going to have to rethink the way the nervous system works.

HMN: What questions were you trying to answer going into your study?

Woolf: One of the challenges we were trying to overcome with our research was how to study in an awake animal how the nervous system processes pain. By definition, if an animal is anesthetized, it doesn't respond to pain; so we cannot study an anesthetized animal because we've removed the very thing we're trying to study. Yet, how could we provoke this response in a humane way? In our study, we succeeded in activating the nervous system using very brief stimuli—three thousandths of a second—delivered to a very small number of sensory neurons in a very controlled fashion and measuring responses with an extra high-speed camera to reveal new insights into the way the nervous system works. The stimulus was much shorter and much less severe than a mild pinprick. What we do know though is exactly when it occurred, what type of sensory neuron was activated and where, and we could then

measure the responses it elicited.

HMN: How did you achieve that?

Woolf: We used optogenetics. The beauty of optogenetics is that it enables you to use laser light to activate light sensitive proteins engineered to be present only in selected sets of neurons. In our case, the light was applied to the skin so as to activate the branches of sensory neurons in the skin activated only by pain-provoking stimuli. We could do this with exquisite timing by applying very brief laser stimulation of a defined power. Furthermore, using a very high-speed camera, we could tell exactly within a thousandth of a second when we'd activated the system and could then measure exactly when the response occurred and what it was. So, one question we can ask with this strategy is exactly which sensory neurons are required to produce a pain-related behavior. A second question is what is the minimum stimulus required to evoke a pain-related response, and a third question is what is the exact nature and timing of the pain-related behavioral response?

HMN: And what did you find?

Woolf: Something quite unexpected. Instead of just seeing the expected pain withdrawal reflex of the stimulated limb, our approach revealed that the response to this brief and minimal activation was much more complicated than anyone had anticipated and occurred so quickly, in fractions of a second, that you couldn't see it if you tried to observe it by eye. We thought we were only going to see Sherrington's very simple reflexes but at a greater temporal and spatial resolution. Instead we saw things no one has ever seen, things no one expected. The responses to this very brief stimulus of a tiny area of one hind paw elicited global reactions throughout the body that occurred in sub-seconds.

We found that an input as small as it is possible to make with a single trigger to the central nervous system initiates a set of coordinated, preprogrammed activities, which are a diverse and changing repertoire of sub-second behaviors that continue long after the trigger has disappeared. Moreover, the nature of the responses reflected the state of the animal—at rest or moving, awake or asleep. We have, therefore, missed until now a whole sub-second repertoire of behaviors that appear to be key, integral components of pain. How we react or feel is not just a function of what stimuli we are exposed to but also what constellation of neuronal units in the brain get recruited by a tiny brief input.

HMN: So, the nervous system is both exquisitely sensitive to even the tiniest of stimuli, and it also responds in much more complex ways than we thought?

Woolf: And in more widespread ways. Sherrington described this beautiful link: You have a noxious stimulus to one limb and you get a withdrawal of that limb from the stimulus. It turns out that is only the proverbial tip of the iceberg. There is much more happening than the simple reflex, and this gives us new insight into how the brain works and the kind of questions we now need to ask.

HMN: How do these findings propel forward our understanding of pain? What might it mean for research and how we deal with pain?

Woolf: Firstly, we have to recognize and embrace the complexity. We need to move on from simple models of stimulus and a fixed response because our work indicates that is not the way the nervous system works. We also need to exploit the technology by means of which we can

modulate and measure the nervous system at a whole system-level to provide us with tools to look at holistic mechanisms and explore the changes that occur in the context of disease. We can, for example, now trigger different sensory fibers after nerve injury to see why there is heightened sensitivity in neuropathic pain and where this occurs, and we can use these approaches to explore in a very objective way the site of action and efficacy of analgesics.

HMN: What's next for you?

Woolf: In terms of my own lab, I have a particular interest in neuropathic pain, the pain that results from nerve injury or lesions. I also have an extreme interest in spontaneous pain, or pain that arises without any stimulus. Almost all the preclinical measures of pain have been of evoked pain. You touch an animal to see if it's hypersensitive.

There have been no ways of figuring out how pain may arrive spontaneously. These optogenetic and other tools we are developing are going to enable us to tease that out. They will reveal both mechanistic and therapeutic insights into spontaneous pain, and that, frankly, is most of the pain that patients who have nerve injury, shingles, disk prolapse or diabetic neuropathy experience. We now have tools to explore this in ways that have not been possible before.

I am optimistic that we will soon make progress in understanding pathological pain and that this will serve as the foundation for new therapeutic interventions.

More information: Liam E. Browne et al. Time-Resolved Fast Mammalian Behavior Reveals the Complexity of Protective Pain Responses, *Cell Reports* (2017). DOI: 10.1016/j.celrep.2017.06.024