

THE NEUROSCIENCE OF PAIN

Brain imaging is illuminating the neural patterns behind pain's infinite variety.

By Nicola Twilley



Brain imaging is illuminating the neural patterns behind pain's infinite variety. Illustration by Anna Parini

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On a foggy February morning in Oxford, England, I arrived at the John Radcliffe Hospital, a shiplike nineteen-seventies complex moored on a hill east of the city center, for the express purpose of being hurt. I had an appointment with a scientist named Irene Tracey, a brisk woman in her early fifties who directs Oxford University's Nuffield Department of Clinical Neurosciences and has become known as the Queen of Pain. "We might have a problem with you being a ginger," she warned when we met. Redheads typically perceive pain differently from those with other hair colors; many also flinch at the use of the G-word. "I'm sorry, a lovely auburn," she quickly said, while a doctoral student used a ruler and a purple Sharpie to draw the outline of a one-inch square on my right shin.

Wearing thick rubber gloves, the student squeezed a dollop of pale-orange cream into the center of the square and delicately spread it to the edges, as if frosting a cake. The cream contained capsaicin, the chemical responsible for the burn of chili peppers. "We love capsaicin," Tracey said. "It does two really nice things: it ramps up gradually to become quite intense, and it activates receptors in your skin that we know a lot about." Thus anointed, I signed my disclaimer forms and was strapped into the scanning bed of a magnetic-resonance-imaging (MRI) machine.

The machine was a 7-Tesla MRI, of which there are fewer than a hundred in the world. The magnetic field it generates (teslas are a unit of magnetic strength) is more than four times as powerful as that of the average hospital MRI machine, resulting in images of much greater detail. As the cryogenic units responsible for cooling the machine's superconducting magnet clicked on and off in a syncopated rhythm, the imaging technician warned me that, once he slid me inside, I might feel dizzy, see flashing lights, or experience a metallic taste in my mouth. "I always feel like I'm turning a corner," Tracey said. She explained that the magnetic field would instantly pull the proton in each of the octillions of hydrogen atoms in my body into alignment. Then she vanished into a control room, where a bank of screens would allow her to watch my brain as it experienced pain.

During the next couple of hours, I had needles repeatedly stuck into my ankle and the fleshy part of my calf. A hot-water bottle applied to my capsaicin patch inflicted the perceptual equivalent of a third-degree burn, after which a cooling pack placed on the same spot brought tear-inducing relief. Each time Tracey and her team prepared to observe a new slice of my brain, the machine beeped, and a small screen in front of my face flashed the word "Ready" in white lettering on a black background. After each assault, I was asked to rate my pain on a scale of 0 to 10.

Initially, I was concerned that I was letting the team down. The capsaicin patch hardly tingled, and I scored the first round of pinpricks as a 3, more out of hope than conviction. I needn't have worried. The patch began to itch, then burn. By the time the hot-water bottle was placed on it, about an hour in, I was surely at an 8. The next set of pinpricks felt as if I were being run through with a hot metal skewer.

"You're a good responder," Tracey told me, rubbing her hands together, when I emerged, dazed. "And you've got a lovely plump brain—all my postdocs want to sign you up." As my data were sent off for analysis, she pressed a large cappuccino into my hands and gently removed the capsaicin with an alcohol wipe.

Tracey didn't need to ask me how it had gone. The imaging-analysis software, designed in her department and now used around the world, employs a color scale that shades from cool to hot, with three-dimensional pixels coded from blue through red to yellow, depending on the level of neural activity in a region. Tracey has analyzed thousands of these "blob maps," as she calls them—scans produced using a technique called functional magnetic resonance imaging (fMRI). Watching a succession of fiery-orange jellyfish flaring up in my skull, she had seen my pain wax and wane, its outlines shifting as mild discomfort became nearly unbearable agony.

For scientists, pain has long presented an intractable problem: it is a physiological process, just like breathing or digestion, and yet it is inherently, stubbornly subjective—only you feel your pain. It is also a notoriously hard experience to convey accurately to others. Virginia Woolf bemoaned the fact that "the merest schoolgirl, when she falls in love, has Shakespeare or Keats to speak her mind for her; but let a sufferer try to describe a pain in his head to a doctor and language at once runs dry." Elaine Scarry, in the 1985 book "The Body in Pain," wrote, "Physical pain does not simply resist language but actively destroys it."

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The medical profession, too, has often declared itself frustrated at pain's indescribability. "It would be a great thing to understand Pain in all its meanings," Peter Mere Latham, physician extraordinary to Queen Victoria, wrote, before concluding despairingly, "Things which all men know infallibly by their own perceptive experience, cannot be made plainer by words. Therefore, let Pain be spoken of simply as Pain."

But, in the past two decades, a small number of scientists have begun finding ways to capture the experience in quantifiable, objective data, and Tracey has emerged as a formidable figure in the field. By scanning several thousand people, healthy and sick, while subjecting them to burns, pokes, prods, and electric shocks, she has pioneered experimental methods to survey the neural landscape of pain. In the past few years, her work has expanded from the study of "normal" pain—the everyday, passing experience of a stubbed toe or a burned tongue—to the realm of chronic pain. Her findings have already changed our understanding of pain; now they promise to transform its diagnosis and treatment, a shift whose effects will be felt in hospitals, courtrooms, and society at large.

The history of pain research is full of ingenious, largely failed attempts to measure pain. The nineteenth-century French doctor Marc Colombat de l'Isère evaluated the pitch and rhythm of cries of suffering. In the nineteen-forties, doctors at Cornell University used a heat-emitting instrument known as a

“dolorimeter” to apply precise increments of pain to the forehead. By noting whenever a person perceived an increase or decrease in sensation, they arrived at a pain scale calibrated in increments of “dols,” each of which was a “just-noticeable difference” away from the adjacent dols. Last year, scientists at M.I.T. developed an algorithm called DeepFacELIFT, which attempts to predict pain scores based on facial expressions.

The most widely adopted tools rely on the subjective reports of sufferers. In the nineteen-fifties, a Canadian psychologist named Ronald Melzack treated “an impish, delightful woman in her mid-seventies” who suffered from diabetes and whose legs were both amputated. She was tormented by phantom-limb pain, and Melzack was struck by her linguistic resourcefulness in describing it. He began collecting the words that she and other patients used most frequently, organizing this vocabulary into categories, in an attempt to capture pain’s temporal, sensory, and affective dimensions, as well as its intensity. The result, published two decades later, was the McGill Pain Questionnaire, a scale comprising some eighty descriptors—“stabbing,” “gnawing,” “radiating,” “shooting,” and so on. The questionnaire is still much used, but there have been few surveys of its efficacy in a clinical setting, and it’s easy to see how one person’s “agonizing” could be another person’s “wretched.” Furthermore, a study by the sociologist Cassandra Crawford found that, after the questionnaire’s publication, clinical descriptions of phantom-limb pain shifted dramatically, implying that the assessment device was, to some extent, informing the sensations it was intended to measure.

Meanwhile, as the historian Joanna Bourke has shown, in her book “The Story of Pain,” attempts to translate the McGill Pain Questionnaire into other languages have revealed the extent to which cultural context shapes language, which, in turn, shapes perception. In mid-century Montreal, Melzack’s talkative diabetic might have described a migraine as lacerating or pulsing, but the Sakhalin Ainu traditionally rated the intensity of pounding headaches in terms of the animal whose footsteps they most resembled: a bear headache was worse than a musk-deer headache. (If a headache was accompanied by a chill, it was described with an analogy to sea creatures.)

By far the most common tool used today to measure pain is the one I employed in the scanner: the 0-to-10 numerical scale. Its rudimentary ancestor was introduced in 1948, by Kenneth Keele, a British cardiologist, who asked his patients to choose a score between 0 (no pain) and 3 (“severe” pain). Over the years, the scale has

stretched to 10, in order to accommodate more gradations of sensation. In some settings, patients, rather than picking a number, place a mark on a ten-centimetre line, which is sometimes adorned with cheerful and grimacing faces.

In 2000, Congress declared the next ten years the “Decade of Pain Control and Research,” after the Supreme Court, rejecting the idea of physician-assisted suicide as a constitutional right, recommended improvements in palliative care. Pain was declared “the fifth vital sign” (alongside blood pressure, pulse rate, respiratory rate, and temperature), and the numerical scoring of pain became a standard feature of U.S. medical records, billing codes, and best-practice guides.

But numerical scales are far from satisfactory. In Tracey’s MRI machine, my third-degree burn felt five points more intense than the initial pinpricks, but was it really only two points less than the worst I could imagine? Surely not, but, having never given birth, broken any bones, or undergone serious surgery, how was I to know?

The self-reported nature of pain scores leads, inevitably, to their accuracy being challenged. “To have great pain is to have certainty,” Elaine Scarry wrote. “To hear that another person has pain is to have doubt.” That doubt opens the door to stereotyping and bias. The 2014 edition of the textbook “Nursing: A Concept-Based Approach to Learning” warned practitioners that Native Americans “may pick a sacred number when asked to rate pain,” and that the validity of self-reports will likely be affected by the fact that Jewish people “believe that pain must be shared” and black people “believe suffering and pain are inevitable.” Last year, the book’s publisher, Pearson, announced that it would remove the offending passage from future editions, but biases remain common, and study after study has shown shocking disparities in pain treatment. A 2016 paper noted that black patients are significantly less likely than white patients to be prescribed medication for the same level of reported pain, and they receive smaller doses. A group of researchers from the University of Pennsylvania found that women are up to twenty-five per cent less likely than men to be given opioids for pain.

In addition, once pain assessment became a standard feature of American medical practice, doctors found themselves confronted with an apparent epidemic of previously unreported agony. In response, they began handing out opioids such as OxyContin. Between 1997 and 2010, the number of times the drug was prescribed annually grew more than eight hundred per cent, to 6.2 million. The disastrous results in terms of addiction and abuse are well known.

Without a reliable measure of pain, physicians are unable to standardize treatment, or accurately assess how successful a treatment has been. And, without a means by which to compare and quantify the dimensions of the phenomenon, pain itself has remained mysterious. The problem is circular: when I asked Tracey why pain has remained so resistant to objective description, she explained that its biology is poorly understood. Other basic sensory perceptions—touch, taste, sight, smell, hearing—have been traced to particular areas of the brain. “We don’t have that for pain,” she said. “We still don’t know exactly how the brain constructs this experience that you absolutely, unarguably know hurts.”

Irene Tracey has lived in Oxford almost all her life. She was born at the old Radcliffe Infirmary, went to a local state school, and studied biochemistry at the university. Her husband, Myles Allen, is an Oxford professor, too, in charge of the world’s largest climate-modelling experiment, and they live in North Oxford, in a semidetached house comfortably cluttered with their children’s sports gear and schoolwork. In 1990, Tracey embarked on her doctorate at Oxford, using MRI technology to study muscle and brain damage in patients with Duchenne muscular dystrophy. At the time, the fMRI technique that she used to map my brain in action was just being developed. The technique tracks neural activity by measuring local changes associated with the flow of blood as it carries oxygen through the brain. A busy neuron requires more oxygen, and, because oxygenated and deoxygenated blood have different magnetic properties, neural activity creates a detectable disturbance in the magnetic field of an MRI scanner.

In 1991, a team at Massachusetts General Hospital, in Boston, showed its first, grainy video of a human visual cortex “lighting up” as the cortex turned impulses from the optic nerve into images. Captivated, Tracey applied for a postdoctoral fellowship at M.G.H., and began working there in 1994, using the MRI whenever she could. When Allen, at that time her boyfriend, visited from England one Valentine’s Day, she cancelled a trip they’d planned to New York to take advantage of an unexpected open slot on the scanner. Allen spent the evening lying inside the machine, bundled up to keep warm, while she gazed into his brain. He told me that he had intended to propose to Tracey that day, but saved the ring for another time.

It was toward the end of her fellowship in Boston that Tracey first began thinking seriously about pain. Playing field hockey in her teens, she’d had her first experience of severe pain—a knee injury that required surgery—but it was a chance conversation with colleagues in a pain clinic that sparked her scientific interest. “It

was just one of those serendipitous conversations that you find yourself in, where this whole area is opened up to you,” she told me. “It was, like, ‘God, this is everything I’ve been looking for. It’s got clinical application, interesting philosophy, and we know absolutely nothing.’ I thought, Right, that’s it, pain is going to be my thing.”

By then, Tracey had been recruited to return home and help found the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain. Scientists had already largely given up on the idea of finding a single pain cortex: in the handful of fMRI papers that had been published describing brain activity when a person was burned or pricked with needles, the scans seemed to show that pain involved significant activity in many parts of the brain, rather than in a single pocket, as with hearing or sight. Tracey’s plan was to design a series of experiments that picked apart this larger pattern of activity, isolating different aspects of pain in order to understand exactly what each region was contributing to the over-all sensation.

In 1998, while her lab was being built, she took her first doctoral student, a Rhodes Scholar named Alexander Ploghaus, to Canada, their scientific equipment packed in their suitcases, to use a collaborator’s MRI machine for a week. Their subjects were a group of college students, including several ice-hockey players, who kept bragging about how much pain they could take. While each student was in the scanner, Tracey and Ploghaus used a homemade heating element to apply either burns or pleasant heat to the back of the left hand, as red, green, and blue lights flashed on and off. The lights came on in a seemingly random sequence, but gradually the subjects realized that one color always presaged pain and another was always followed by comfortable warmth. The resulting scans were striking. Throughout the experiment, the subjects’ brain-activity patterns remained consistent during moments of pain, but, as they figured out the rules of the game, the ominous light began triggering more and more blood flow to a couple of regions—the anterior insula and the prefrontal cortices. These areas, Tracey and Ploghaus concluded, must be responsible for the anticipation of pain.

Showing that the experience of pain could be created in part by anticipation, rather than by actual sensation, was the first experimental step in breaking the phenomenon down into its constituent elements. “Rather than just seeing that all these blobs are active because it hurts, we wanted to understand, What bit of the hurt are they underpinning?” Tracey said. “Is it the localization, is it the intensity, is it the anticipation or the anxiety?” During the next decade, she designed

experiments that revealed the roles played by various brain regions in modulating the experience of pain. She took behavioral researchers' finding that distraction reduces the perception of pain—as when a doctor tells a child to count backward from ten while receiving an injection—and made it the basis of an experiment that showed that concentrating on a numerical task suppressed activity in several regions that normally light up during pain. She examined the effects of depression on pain perception—people suffering from depression commonly report feeling more pain than other people do from the same stimulus—and demonstrated that this, too, could change the distribution and the magnitude of neural activity.

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One of her most striking experiments tested the common observation that religious faith helps people cope with pain. Comparing the neurological responses of devout Catholics with those of atheists, she found that the two groups had similar baseline experiences of pain, but that, if the subjects were shown a picture of the Virgin Mary (by Sassoferrato, an Italian Baroque painter) while the pain was administered, the believers rated their discomfort nearly a point lower than the atheists did. When the volunteers were shown a secular painting (Leonardo da Vinci's "Lady with an Ermine"), the two groups' responses were the same. The implications are potentially

far-reaching, and not only because they suggest that cultural attitudes may have a neurological imprint. If faith engages a neural mechanism with analgesic benefits—the Catholics showed heightened activity in an area usually associated with the ability to override a physical response—it may be possible to find other, secular ways to engage that circuit.

Tracey's research had begun to explain why people experience the same pain differently and why the same pain can seem worse to a single individual from one day to the next. Many of her findings simply reinforced existing psychological practices and common sense, but her scientific proof had clinical value. "Countless people who work in cognitive behavioral therapy come up at the end of talks or write to me," Tracey told me. "They say how helpful it has been to empower their education of the patient by saying that, if you're more anxious about your pain, or more sad, look, here's a picture telling you it gets worse."

These early experiments repeatedly demonstrated that pain is neurologically complex, involving responses generated throughout the brain. Nonetheless, by identifying regions that control ancillary factors, such as anticipation, Tracey and her team were gradually able to zero in on the regions that are most fundamental. In 2007, Tracey published a survey of existing research and identified what she called "the cerebral signature of pain"—the distinctive patterns produced by a set of brain regions that reliably act in concert during a painful experience. Some of these regions are large, and accommodate many different functions. None are specific to pain. But, as we stared at the orange blobs of an fMRI scan on her laptop screen, Tracey rattled off the names of half a dozen areas of the brain and concluded, "With a decent poke, you'd activate all of that."

In 2013, Tor Wager, a neuroscientist at the University of Colorado, Boulder, took the logical next step by creating an algorithm that could recognize pain's distinctive patterns; today, it can pick out brains in pain with more than ninety-five-percent accuracy. When the algorithm is asked to sort activation maps by apparent intensity, its ranking matches participants' subjective pain ratings. By analyzing neural activity, it can tell not just whether someone is in pain but also how intense the experience is. "What's remarkable is that basic pain signals seem to look pretty much the same across a wide variety of people," Wager said. "But, within that, different brain systems are more, or less, significant, depending on the individual."

Among the brain's many pain-producing patterns, however, there is only one region that is consistently active at a high level: the dorsal posterior region of the insula. Using a new imaging technique, Tracey and one of her postdoctoral fellows, Andrew Segerdahl, recently discovered that the intensity of a prolonged painful experience corresponds precisely with variations in the blood flow to this particular area of the brain. In other words, activity in this area provides, at last, a biological benchmark for agony. Tracey described the insula, an elongated ridge nestled deep within the Sylvian fissure, with affection. "It's just this lovely island of cortex hidden in the middle, deep in your brain," she said. "And it's got all these amazing different functions. When you say, 'Actually, I feel a bit cold, I need to put a sweater on,' what's driving you to do that? Probably this bit."

The importance of the dorsal posterior insula had previously been highlighted in a somewhat horrifying experiment conducted by Laure Mazzola, a neurologist at the Lyon Neuroscience Research Center, in France. It is common for surgeons treating patients with drug-resistant epilepsy to disable the portions of the brain in which the seizures are occurring. Before surgery, neurologists often stimulate the area and its surroundings with an electrical probe, to make sure they're on target. Taking advantage of this opportunity, Mazzola stimulated various parts of the posterior insula in pre-surgical patients and recorded their responses. When she reached the dorsal region, Tracey told me, the patients "were leaping off the bed." The presence of a probe in the brain shouldn't in itself hurt, because there are no pain receptors there. Yet activating this area was apparently enough to create a brutally convincing synthetic pain.

The day after my fMRI scan, Tracey took me to her department's Clinical Pain Testing lab, a room that she refers to as her "torture chamber." A red illuminated sign blinked "Do Not Enter," and Tracey removed a retractable belt blocking the door. Inside were all the devices that she and her team use to hurt people scientifically. As I reclined in a blue dentist-style chair under the room's lone fluorescent light, she and a couple of her colleagues burned the back of my hand with a laser. Someone pressed a device about the size of a camera's memory card against my forearm. It was rippled with heating elements, which were covered with a thin layer of gold foil to conduct the heat to the skin. "We can raise the temperature by thirty degrees in under a second," Tracey said.

Each of the methods has a particular use. Lasers and electrodes can deliver precise increments of pain in experiments requiring a quick transition between different

levels of stimulation. Capsaicin, because it sensitizes the central nervous system, is best for simulating chronic pain. Inflatable rectal balloons mimic the distinctive pain caused by damage to internal organs. All of them have been designed with the aim of reliably producing in laboratory conditions sensations that hurt enough to mirror real life but don't cause lasting harm, which would be unethical. A scientist hoping to gather publishable data can't just hit someone with a hammer and hope that each blow is as hard as the last one, even if an institutional ethics committee would permit such a thing.

Tracey has developed protocols to inflict the maximum amount of pain with the minimum amount of tissue damage. Using psychological tricks and carefully choreographed shifts in intensity, she has also devised ways of heightening a subject's perception of pain. At the same time, research identifying the regions most crucial to the experience of pain has inadvertently pointed the way to the creation of artificial pain purely through targeted neurostimulation. It does not take much imagination to discern the potential for misuse of this kind of knowledge. For this reason, the International Association for the Study of Pain (I.A.S.P.) has a code of ethics, and its members are pledged not to inflict or increase pain except in an experimental setting.

A more nuanced ethical issue involves the potential use of neuroimaging as a sort of lie detector—to expose malingerers or increase payouts in injury-compensation suits. “Pain is enormously important in law,” Henry Greely, the director of the Center for Law and the Biosciences, at Stanford University, told me. “It's the subject of hundreds of thousands of legal disputes every year in the United States.” Many are personal-injury cases; others involve Social Security and private-insurance disability. Greely pointed out that the lack of an objective test for pain means not only that people who deserve compensation miss out (and vice versa) but also that millions of billable hours are spent on these suits. With an agreed-upon empirical metric for pain, he estimates, the vast majority of cases would be settled rather than litigated.

Greely believes that the routine use of fMRI evidence in court is likely a decade away, but there are already signs that it is coming. In 2008, a colleague of his, Sean Mackey, was asked to serve as an expert witness in the case of a man who was suing an asphalt manufacturer after suffering first- and second-degree burns. The man's lawyers were planning to use brain-imaging data to show that the injuries had left him in chronic pain. The company's legal team wanted to put Mackey on the stand to argue that the current state of pain science could not justify this as an objective

assessment. The case was eventually settled out of court, but the judge ruled that, despite a demurring opinion from Mackey, the scans were admissible as evidence.

All the scientists I spoke to were careful to stress that they think the field is not far enough advanced for an fMRI scan to be used as legal evidence of pain, or to overrule a subjective report. Some are convinced that it will never reach that point. Karen Davis, a researcher at the Krembil Brain Institute, in Toronto, told me, “Pain is, literally by definition, a subjective experience. That makes self-report the only true measure.” Greely is less sure: “I’m willing to agree that it’s still truly a subjective state, but there are objective things that can give you more or less confidence in the reality of that subjective state.”

Davis is sufficiently worried about the legal ramifications of pain neuroimaging that she recently chaired an I.A.S.P. task force to consider the subject. Researchers who have spent their careers investigating the ways that pain is altered by mood, context, and suggestion are naturally skeptical of the idea that personal testimony can be proved or disproved by making someone spend an hour lying horizontal and immobile in a rigidly controlled, socially isolated, loud, boring, and claustrophobic environment. Although fMRI is often taken to be a transparent window into brain function, Davis told me that it would be more accurate to think of it as a low-resolution, somewhat out-of-synch set of stills from a black-and-white movie. While electrical impulses that travel along neurons last only about a millisecond, blood, which fMRI measures as a proxy, arrives on the scene slightly after the fact, and dissipates slowly.

Most brain imaging has been carried out in 3-Tesla MRI scanners, which cannot resolve detail below a scale of two millimetres. Neurons are so tiny that a cube of brain tissue that size will contain tens of thousands of them. Even the 7-Tesla that scanned my brain had only a maximum resolution of one millimetre. Tracey cautions against overestimating how much “blob maps” can explain. “Underneath that blob there’s an awful lot of nuance, and there’s an awful lot of anatomy,” she said. To help validate her findings, she often combines magnetic imaging with other techniques, such as measurements of electrical activity using an EEG.

Relatively few people have had their brains scanned while being hurt, and an algorithm like Wager’s, which has correctly predicted pain in the brains of a small cohort of healthy volunteers, cannot be reliably extrapolated to apply to the population as a whole. But Greely believes that overcoming this deficiency is simply

a matter of doing more studies. He predicts that, once researchers have collected enough data and developed standardized protocols, neuroimaging will follow in the path of forensic DNA—a scientific breakthrough whose results were eventually considered robust enough to use as evidence in court. Our trust in DNA evidence is increasingly seen as problematic, but Greely is unperturbed. “No evidence is perfect,” he said. “The stuff courts rely on most—eyewitness testimony—is known to be awful, but we use it anyway.”

When I asked Tracey whether she thought her work could eventually rid the world of pain, she snorted in a polite attempt not to laugh. Most pain, she explained, is “the good kind.” Hurting yourself when you touch a hot surface is unpleasant, certainly, but it’s also crucial. While in Oxford, I met one of her frequent collaborators, the neurobiologist David Bennett, whose research involves patients who, because of rare genetic mutations, cannot feel pain. “You might wonder, Why are humans born with this system where they have to feel pain?” Bennett said. “And these patients give you the answer to that very quickly, because not feeling pain is a health disaster.” Often, he told me, such people die young. Historically, they frequently became circus freaks: the earliest clinically documented example was a Czech immigrant to the United States, whose case was described by a Dr. Dearborn in the Bronx, in 1932. According to Dearborn, the patient earned a living on the vaudeville circuit as Edward H. Gibson, the Human Pincushion, inviting audience members to come up onstage and push pins into him.

Bennett said that patients of his have chewed off the tips of their own tongues and scratched their corneas. They suffer hearing loss from untreated ear infections, unwittingly rest their hands on hot surfaces, and walk on broken legs, which leaves their limbs deformed. In an evolutionary context, Bennett explained, it makes sense that we are built in anticipation of pain: we are soft, and the world is a dangerous place. Undergoing an extremely unpleasant response to harm helps us avoid further injury in the moment and teaches us to reduce its likelihood in the future.

But there’s a “bad kind” of pain, too—one that is not the result of any obvious external source. Chronic pain is often defined, somewhat misleadingly, as “pain that extends beyond the expected period of healing.” In reality, once you’ve “gone chronic,” as Tracey puts it, pain is the disease, rather than a symptom. That view represents a shift in understanding, brought about in part by her work. Until recently, chronic pain was thought of merely as prolonged “normal” pain. But neuroimaging has shown that, if a chronic-pain sufferer and an unafflicted person

are given the same burn or pinprick, their brains manifest activity differently. Chronic pain, Tracey said, is now understood as “something new, with a life of its own, with its own biology and its own mechanisms, most of which we really don’t understand at all.”

Until a couple of years ago, Tracey, like most researchers in the field, focussed on the good kind of pain; this was crucial to understanding the basic neurobiology involved. Yet the true problem is chronic pain. Estimates suggest that somewhere between ten and thirty per cent of the American population suffers from chronic pain. Its cost to society is some six hundred and thirty-five billion dollars each year—more than that of cancer and heart disease combined. And behind such statistics is the heavy psychic and emotional toll on those who spend every conscious moment suffering. A journalist who was given a diagnosis of fibromyalgia twenty years ago told me that his entire identity is subsumed by his experience of incessant, whole-body agony: “It’s who I am now. I’m broken. I need to be fixed, but I can’t be fixed.”

Tracey’s latest research has investigated a key neural mechanism of chronic pain. It is situated in the brain stem, a hard-to-reach, tube-shaped mass of gray matter at the top of the spinal cord, which functions as the conduit for communication between the brain and the body. Experiments on animals had identified two mechanisms within the brain stem that, respectively, muffle and boost pain signals before they reach the rest of the brain. Since Tracey’s lab first succeeded in imaging the region, more than a decade ago, she has been able to show how these two mechanisms operate. “It can completely block the signals coming in,” she said of one, explaining that it is responsible for situations in which you don’t feel pain even though you should—for instance, when your brain is distracted by the euphoria of crossing the finish line of a marathon. Unfortunately, in some people the mechanism that exacerbates pain is dominant. Scanning the brains of patients with diabetic nerve pain, Tracey and Segerdahl found enhanced communication from the brain stem, via the spine, to the parts of the brain known to contribute to the sensation of pain.

Tracey told me that it seems we may all be predisposed by our brain stems to feel pain more acutely or less, but that in chronic-pain patients it’s as if the volume knob of pain were turned all the way up and jammed there permanently. No one knows why this hypersensitization occurs. Studies of twins suggest that our pain response is, in part, heritable, but there are close correlations between chronic pain and many other factors—gender, age, stress, poverty, and depression. Tracey has begun to study whether recurrent experiences of acute bodily distress early in life trigger brain-stem

changes that make chronic pain likelier later on. With colleagues in Oxford, she is involved in a longitudinal study of extremely premature babies and another of teenage girls who suffer particularly painful periods.

Although the results of this work won't be known for many years, her brain-stem research is already on its way to a clinical application. A few years ago, in collaboration with the rheumatologist Anushka Soni, Tracey began imaging the brains of osteoarthritis patients before and after knee-replacement surgery. Roughly a fifth of patients who have knee replacements find that the operation doesn't meaningfully reduce their pain, and, again, no one knows why. But when Tracey analyzed the scans she found that the unlucky patients had increased activity in the mechanism of the brain stem known to amplify pain signals. Their brains revealed that they had "gone chronic"; they were not just ordinary people whose knees hurt.

Although it's not feasible to give every prospective patient a brain scan, results from fMRI experiments correlate strongly with responses to a questionnaire called painDETECT, which was developed to diagnose nerve malfunction. Such a questionnaire could predict the likely outcome of surgery, so that patients could make an informed decision about whether the procedure was worth it. Tracey is also testing, on a group of twenty-four volunteers, a compound that she hopes could dampen activity in the problematic brain-stem region. In time, patients who seem predisposed to less successful surgical outcomes may be given a drug that makes relief likelier by adjusting their brain-stem biochemistry.

Drug development could be the most influential result of Tracey's work. Pain medications have become something of a pharmacological graveyard, she told me; their development is often abandoned after patients report no improvement. "But their pain rating might still be up for all these other reasons—they're anxious, they're depressed, they're expecting to be in pain," Tracey said. "We've thrown out drugs that probably had high efficacy because we had the wrong measure—we relied on the subjective rating." She believes that drug tests will become much more reliable once their efficacy can be measured against an objective target. She is part of an academic consortium that has received a large grant from Europe's Innovative Medicines Initiative to help establish a set of measurable biological signs that can be used to ascertain whether new drugs are effective at disarming known pain mechanisms, regardless of whether the person taking them experiences any relief. Ultimately, she expects that various combinations of therapies will need to be

delivered, in order to quiet the particular neural systems responsible for each individual's unique experience of suffering.

A few weeks after my ordeal in the MRI machine, Andrew Segerdahl e-mailed me the resulting images. I looked for the brain regions I'd been told were important, but all I could see was a brain on fire. Everything was orange, particularly in the left hemisphere. (The pain was being inflicted on my right leg.)

Over the phone, Segerdahl talked me through my scans. "That map is actually really difficult to make sense of," he said. "Your brain is really, really, really lit up—there's just a lot going on." But then he showed me a sequence of images that had been processed in such a way that the color coding appeared only in regions that had elevated blood flow while I endured the prolonged pain of the capsaicin cream. The characteristic pattern of pain began to emerge, and Segerdahl recited the names of the active regions like old friends.

Then came a set of maps that showed my brain during the exquisite moment of relief when the cooling pack was applied. There were many regions with activity levels—the images looked almost as busy as the heat maps—but the blobs were subtly different in shape and location. In my brain, pain was shading into pleasure, and, curiously, many of the same regions were involved, activated in a slightly different pattern. "There's quite a lot still to be understood in terms of the relief side of this equation," Segerdahl said. He hesitated. "It's, like, I'm super interested in it, but I almost don't want to touch it yet, because it's the ultimate goal."

Tracey has been looking at pleasure for almost as long as she's been studying pain. "They are two sides of the same coin," she told me. Many signs of their interrelation crop up in her work. Chronic-pain patients typically also suffer from anhedonia—the inability to experience pleasure—and research suggests that their brains' reward systems are wired slightly differently from those in other brains. Pain is naturally a more urgent research priority, given that most of us find it intolerable, but fully understanding it will require a better understanding of its opposite. "There's a Jeremy Bentham quote I like," Tracey said. " 'Nature has placed mankind under the governance of two sovereign masters, pain and pleasure.' These are the two things that drive us, as animals, to do what we do." ♦

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