Topical Review

PAIN®

The pain switch: an "ouch" detector

Karen D. Davis[a,b,*], Aaron Kucyi[c,d], Massieh Moayedi[e]

"Ouch!" This is a primal, intuitive, and fundamental expression of pain. We all say it, and we all know what it signifies. For centuries, scientists have struggled to elucidate the neural mechanisms of pain. The most prominent theories can be encapsulated by ideas based on *specificity*, *patterns*, or *gates* in the nervous system.[13] A common framework of pain put forth by Melzack and Casey in 1968[11] divides pain experience into 3 dimensions: sensory–discriminative, cognitive–evaluative, and motivational–affective. This served as a useful framework that ignited and shaped pain research, including the highly influential concept of a "neuromatrix,"[10] for 5 decades. However, despite substantial advances, the specific mechanism of how our brain "creates" or "reflects" pain still eludes us. The complexity of pain may have obscured a straightforward path to its understanding.

We propose that the fundamental, and often forgotten, aspect of pain is the simple "ouch"; the feeling that something hurts. This is basically an on/off switch—like the "all or none" response of a neuron—it simply is or is not. Many types of conscious experiences have been classified dichotomously as such—a subjective report either confirms or disconfirms its existence,[6] but this simple concept gets muddled or disappears in our discussions on detecting pain.

Our simple concept is that there is a biological "pain switch" that represents the detection of and ongoing feeling of a fundamental "ouch". This "ouch" is at the core of the pain experience (**Fig. 1**) and is present regardless of the degree of contribution of the 3 dimensions described by Melzack and Casey.[11] It does not have a magnitude but simply is or is not. Neurons can encode the intensity and other features of a noxious stimulus or pain, which have been the focus of much research. But intensity coding need not occur for the basic "ouch". Everyone inherently knows when they feel pain or that something hurts; whether it is evoked by a normally painful stimulus, in an allodynic state, or even in a chronic state. The intensity and quality of pain certainly colors the experience and gives it meaning, but these features are secondary to the fundamental presence of the "ouch" itself that signifies primary sense of pain. The pain switch can be thought of like a light switch. There is light as long as it is turned on to keep a circuit functioning, but there is no light when the switch is turned off or the circuit is interrupted.

This fundamental concept is timely and critically important to debate because of its scientific and clinical value and a rapidly emerging societal and medicolegal need.[12,14] Pain imaging research has been chasing the dream of a brain signature for pain that can be easily and objectively identified and used for diagnostic, prognostic, and evaluative purposes.[16] This is a lofty goal and like other medical advances, it has far-reaching consequences that raise ethical issues. These issues are no longer only of future concern. The definition of pain and whether it can be measured with neuroimaging techniques is currently a hotly contested issue in both scientific and legal realms, ignited by the recent United States court case that deemed admissible a functional magnetic resonance imaging (fMRI) "pain-o-meter" test as evidence of pain in a personal injury case.[14] At issue are not only the technical limitations of current brain imaging methods but also the pain concepts on which "pain-o-meter" tests are based.

Companies that administer (at substantial cost) such pain tests, and other brain-decoding efforts, are emerging—not unlike the companies that opened up shop a decade ago claiming to have an fMRI-based lie detector test. So there is now a plainly visible outcome of the theoretical and academic discussion of the nature of pain and how it is represented in the brain. Published scientific claims of identifying "pain-specific brain activity" now have far-reaching effects, directly impacting the well-being of society-at-large.

The truth remains, however, that we still do not know what is biologically necessary and specific for an "ouch" to occur. The pain switch is not "here" or "there" in the brain. It is reflected by the activity within a complex, dynamic brain network, called the dynamic pain connectome. We recently defined this as "the spatiotemporal signature of brain network communication that represents the integration of all cognitive, affective, and sensorimotor aspects of pain."[9]

We do not yet know how a pain switch operates. One concept is that it occurs through a state change in functional connectivity within the dynamic pain connectome. Functional connectivity state changes are now being intensely studied and modeled across neuroscientific domains, and they could occur during acute noxious stimulation or be sustained in chronic pain conditions. A full understanding of the dynamic pain connectome will certainly require a concerted effort that merges information derived from various research techniques and approaches ranging from electrophysiology to imaging to computational modeling.

We can and should capitalize on what neuroimaging technologies can tell us about pain, but we must also accept technical limitations inherent to those methods,[5] and it should be noted

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] Division of Brain, Imaging & Behaviour Systems, Toronto Western Research Institute, Toronto, ON, Canada, [b] Department of Surgery and Institute of Medical Science, University of Toronto, Toronto, ON, Canada, [c] Department of Psychiatry, Harvard Medical School, Boston, MA, USA, [d] Department of Psychiatry, Massachusetts General Hospital, Charlestown, MA, USA, [e] Department of Neuroscience, Physiology and Pharmacology, University College London, London, United Kingdom

**Corresponding author. Address: Toronto Western Hospital, Toronto Western Research Institute, 399 Bathurst St, Room MP14-306, Toronto, ON M5T 2S8, Canada. Tel.: (416) 603-5662. E-mail address: kdavis@uhnres.utoronto.ca (K. D. Davis).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 156 (2015) 2164–2166

http://dx.doi.org/10.1097/j.pain.0000000000000303

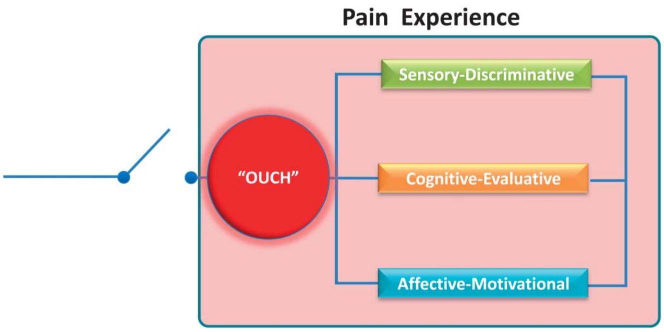

Figure 1. We propose that a fundamental "ouch" acts like a switch being either on or off, and this core sensation determines whether or not someone is experiencing pain. The full pain experience is comprised of this scale-free attribute plus varying amounts of the 3 defined sub-components of pain (ie, dimensions) classically described by Melzack and Casey[11] as sensory–discriminative, motivational–affective, and cognitive–evaluative.

that a future novel approach or technology may be more suited to reveal the complexities of the pain connectome. Each step toward understanding pain and its representation in the brain creates new knowledge and is invigorating. But we are in an age in which scientific findings are immediately made public, and they can have profound social impact before being subjected to the lengthy due process of scientific debate. Given what is at stake, we would do well to temper our enthusiasm at each advance, frequently falling back to contemplate the big picture.

To guide the pain community in understanding neuroimaging findings, we offer 5 key well-established, but often ignored, facts to keep at the fore of our thinking about a pain switch and its representation in the brain:

(1) Pain, by definition, and like all other conscious experiences, is subjective. Thus, only a self-report can truly represent its existence.[1] The special cases in which a self-report is not obtainable and instances of feigning pain have driven the focus of research away from this basic tenet of pain subjectivity and is driving the search for an "objective" brain proxy of pain, which ultimately relies on self-report as ground truth.

(2) The fundamental "ouch," pain threshold, and complexity of the pain experience are highly variable from person to person and brain responses to noxious stimuli are not precisely the same for everyone. There are some brain regions that typically "light up" when pain is evoked, but pain can be present when those typical pain responses cannot be detected with neuroimaging. The situation is even more complex for chronic pains because brain plasticity associated with injury and disease can alter sensory representations. An example from a different field is instructive. Consider that the visual cortex can be activated by Braille reading in blind individuals. Clearly, detecting visual cortex activity in this situation does not prove that an individual has vision!

(3) The fundamental "ouch" is present regardless of the intensity or the complexity of the overall experience. Thus, the "ouch" need only be modeled by an on/off step function.[15] Univariate statistics (subtractions, regression, contrasts) typically used in brain imaging analyses can remove nonspecific confounds and link brain responses to pain magnitude, but these can also remove responses that are present across all pain conditions—the simple "ouch." Thus, the search for the "ouch" may necessitate a similarity or conjunction analysis that requires a brain response to be present in all subjects who experience varying pain intensities and qualities—an approach that uncovered paradoxical heat and prickle percept–related activations using percept-related fMRI.[2–4]

(4) There are no specific, exclusive, and dedicated pain "spots" in the brain, despite the existence of specialized primary afferent nociceptors in the periphery and nociceptive-specific neurons in the brain. These dedicated potentially pain-signaling neurons ultimately share brain real estate with other systems (tactile, thermal, cognitive; eg, see below). This sets up a situation in which brain decoding can fall prey to the problem of reverse inference.[8] We propose that pain is more likely to arise from a complex "pain code" within these neurons and systems that are not easily identifiable using indirect measures from neuroimaging, but rather may be gleaned from large-scale direct neural recordings and modeling.

(5) Salience and pain are invariably intertwined and necessarily share neural representation. The simple "ouch" will inherently engage the brain's salience network. The converse, of course, is not the case—activity in the salience network does not necessarily signify that a person is experiencing pain. This highlights the issue of reverse inference, which is an inherent problem in ideologies of a "pain matrix"[7] and is critical to be considered in evaluating pain tests.[8]

Thus pain is subjective, individualized, binary, complexly encoded, and salient. With all this in mind, we encourage the pain research community to develop fresh and innovative ways to identify the neural code of the *pain switch*. This is no simple task—it requires a deep understanding of the workings of the nociceptive system, how it interacts with other cognitive processes, temporal dynamics, technical limitations of our measurement tools, clever experimental designs that exploit these factors, and crucially, some big-picture thinking. Discussion and debate stemming from these ideas would accelerate the development of scientifically sound objective pain measures and the identification of new therapeutic targets, which could lead to personalized pain management strategies. The outcome is worth the journey—understanding the pain switch neural code and what turns it on (and off) could be the key to alleviating chronic pain.

Conflict of interest statement

The authors have no conflicts of interest to declare.

K. D. Davis is funded by a Canadian Institutes of Health Research operating grant.

Supplemental Digital Content

An audio introduction associated with this article can be found online at http://links.lww.com/PAIN/A166.

Article history:
Received 25 April 2015
Received in revised form 10 July 2015
Accepted 14 July 2015
Available online 20 July 2015

References

[1] Davis KD. Is chronic pain a disease? Evaluating pain and nociception through self-report and neuroimaging. J Pain 2013;14:332–3.
[2] Davis KD, Moayedi M. Central mechanisms of pain revealed through functional and structural MRI. J Neuroimmune Pharmacol 2013;8: 518–34.
[3] Davis KD, Pope GE, Crawley AP, Mikulis DJ. Neural correlates of prickle sensation: a percept-related fMRI study. Nat Neurosci 2002;5:1121–2.
[4] Davis KD, Pope GE, Crawley AP, Mikulis DJ. Perceptual illusion of "paradoxical heat" engages the insular cortex. J Neurophysiol 2004;92: 1248–51.

[5] Davis KD, Racine E, Collett B. Neuroethical issues related to the use of brain imaging: can we and should we use brain imaging as a biomarker to diagnose chronic pain? Pain 2012;153:1555–9.
[6] Dehaene S, Changeux JP. Experimental and theoretical approaches to conscious processing. Neuron 2011;70:200–27.
[7] Iannetti GD, Mouraux A. From the neuromatrix to the pain matrix (and back). Exp Brain Res 2010;205:1–12.
[8] Iannetti GD, Salomons TV, Moayedi M, Mouraux A, Davis KD. Beyond metaphor: contrasting mechanisms of social and physical pain. Trends Cogn Sci 2013;17:371–8.
[9] Kucyi A, Davis KD. The dynamic pain connectome. Trends Neurosci 2015;38:86–95.
[10] Melzack R. Phantom limbs and the concept of a neuromatrix. Trends Neurosci 1990;13:88–92.
[11] Melzack R, Casey KL. Sensory, motivational, and central control determinants of pain: a new conceptual model. In: Kenshalo D, editor. The skin senses. Springfield: C.C. Thomas, 1968. p. 423–39.
[12] Miller G. Neuroscience. Brain scans of pain raise questions for the law. Science 2009;323:195.
[13] Moayedi M, Davis KD. Theories of pain: from specificity to gate control. J Neurophysiol 2013;109:5–12.
[14] Reardon S. Neuroscience in court: the painful truth. Nature 2015;518: 474–6.
[15] Seminowicz DA, Davis KD. Interactions of pain intensity and cognitive load: the brain stays on task. Cereb Cortex 2007;17:1412–22.
[16] Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med 2013;368: 1388–97.