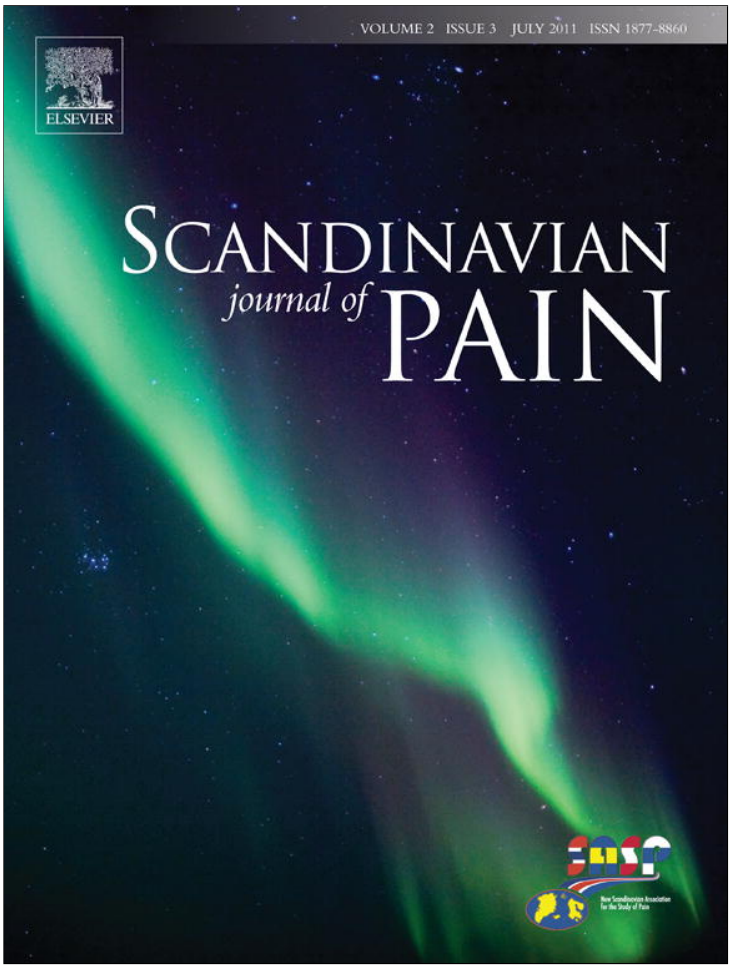
Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

http://www.elsevier.com/copyright

Author's personal copy

Scandinavian Journal of Pain 2 (2011) 105–107

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Editorial comment

The pain modulatory cocktail

Siri Leknes*

University of Oslo, Forskningsveien 3A, Postboks 1094 Blindern, Oslo, Norway

Pain is the subject of a vast field of neuroscientific and medical research. A particular challenge in the study of pain is the subjective and changeable nature of this sensation. The International Association for the Study of Pain (IASP)'s definition of pain highlights its subjective quality:

> 'Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'.

Pain is reliably induced by stimuli which activate nociceptive receptors in the skin, muscle, and gut. Although sensory pains vary qualitatively (consider a sharp pin-prick pain vs. a dull muscle ache), these feelings are similar enough to be classified as pain both in subjective and physiological terms [14,40,44,42]. Chronic pain syndromes such as post-stroke and phantom pain are examples of painful conditions where the pain is not caused by stimulation of peripheral nociceptors. Nevertheless, the subjective hedonic feeling of these pain syndromes mimics sensory pains, and central pain syndromes are encompassed by the IASP definition of pain.

As reviewed by Knudsen et al. [47] in this issue, pain is highly changeable. Somatosensory, affective and cognitive factors have repeatedly been shown to alter both subjective and objective measures of pain. For instance, anxiety can greatly enhance pain and suffering [1,36,24], while expectation of treatment can dramatically reduce pain [41,7,46]. The cognitive context in which pain is perceived also affects the subjective interpretation of a nociceptive event [30,21]. Research on the modulation of pain has mainly concerned itself with pain caused by nociceptive stimulation. The 'pain modulatory cocktail,' i.e. the interaction of nociception and cognitive, affective and other factors, determines the *meaning* of a painful sensation.

1. Measuring pain

Within the neuroscientific and medical communities, numerous approaches exist that use objective measures of pain. Animal pain research largely relies on measures of avoidance behaviours such as tail flick latency. Some research also aims to quantify suffering behaviour, such as licking of the injured paw and reductions in eating [11,37,34]. Many human pain studies use subjective pain ratings to indicate the level of pain. The perhaps most common rating scales for pain are the 11-point pain intensity numerical rating scale (NRS), and visual analogue scales (VAS) anchored "no pain" and "intense pain." These subjective measures are in turn used to inform the interpretation of objective measures of pain-related neural activity, such as functional imaging measures or direct measures of electrical activity from peripheral neurons [28]. An alternative approach relies solely on objective measures of pain-related activity, for instance the quantification of reflexes [19].

With the advent of functional brain imaging, many hope that a technique which will provide a conclusive objective measurement of pain has been found, obviating the need to rely on subjective measures. A large number of brain regions are activated in most neuroimaging studies of pain. Some, notably the insula, thalamus, and dorsal anterior cingulate cortex (ACC), are reported with great consistency [38]. More than a decade ago, Rainville and colleagues [27] used hypnotic suggestion to show that activity in the ACC varies with the affective component of pain processing. This left the thalamus and the insula as the main candidate regions for an objective marker of nociceptive input. Direct electrical stimulation of insular cortex in epilepsy patients causes intense feelings of pain [22]. Interestingly, however, both the insula and the thalamus have recently been shown to activate during hypnotic suggestion of pain in the absence of nociceptive stimulation [26]. That no brain region has been identified unequivocally as *the* objective marker of nociceptive input after a more than decade of functional imaging research of pain highlights the complexity of the perceptual decision underpinning the pain experience.

2. The descending pain modulatory circuit

Animal research has greatly enhanced our knowledge about the mechanisms involved in modulation of pain. The well-described descending pain modulatory circuit in the brainstem consists of excitatory and inhibitory cells, and communicates with neurons in the prefrontal cortex, anterior cingulate cortex (ACC), hypothalamus, and amygdala to control the nociceptive afferent pathway in the spinal and trigeminal dorsal horn [16,39]. This decision circuit exerts bidirectional control over pain [15]. The circuit consists of ON- and OFF-cell populations in midbrain and medullary pain-modulatory nuclei, notably the periacqueductal grey (PAG) and the rostro-ventral medulla (RVM). Cells within this circuit have a

DOI of refers to article:10.1016/j.sjpain.2011.05.005.
* Tel.: +47 92622872.
E-mail address: siri.leknes@psykologi.uio.no

1877-8860/$ – see front matter © 2011 Scandinavian Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.sjpain.2011.05.007

Author's personal copy

reciprocal activity pattern where OFF-cell silence *permits* a pain response and ON-cell activity facilitates it. Conversely, OFF-cell activity reduces responses to noxious stimuli [15].

It is likely that opiate drugs and endogenous opioids act on this descending system to produce pharmacological, placebo, stress-induced and pleasure-related analgesia [37,12,17,18,23,29,45,15,16,39]. Neuroimaging studies of various factors which modulate pain have implicated brainstem regions within this circuit during up- and down-regulation of pain [40,44,3,13,42,10,43].

3. Why is pain so changeable?

Unpleasant sensations such as pain, itch and nausea have probably evolved as homeostatic alarm signals, notifying us of imbalances in the mechanical, thermal or chemical status of the tissues of the body [33]. Pain encourages the constant optimization of our internal homeostatic balance. The notion of homeostasis was first introduced in relation to automatic regulatory processes such as thermoregulation [6]. Later findings have highlighted the relationship between homeostasis and subjective experience. Cabanac showed that the subjective experience of an event depends on how the event affects homeostasis [5]. For instance, when someone's core temperature is abnormally low, cool stimuli become unpleasant, whereas stimuli which would normally feel too hot (and activate nociceptors) become pleasant [4]. In other words, homeostatic utility or disutility determines the subjective value of a stimulus. This effect is well-documented for primary rewards such as food and drink, which are more pleasurable when relieving a hunger or thirst state [31,9,20]. Since a painful experience constitutes a deviation from homeostatic balance [8], the same principle can be applied to pain. When the perceived threat to the organism becomes greater, pain unpleasantness increases, enhancing defensive and avoidance mechanisms [25].

According to Fields' Motivation-Decision model of pain, the processes underlying the subjective interpretation of a nociceptive stimulus can be understood as the manifestation of an unconscious decision process [15,16]. The decision process requires information about the homeostatic state of the individual (inflammation, hunger, etc.), sensory input, and knowledge about impending threats and available rewards. The basic premise for the decision process is that anything potentially more important for survival than pain should assert antinociceptive effects. This allows the animal to ignore the pain and attend to the more important event. One answer to why pain should be so malleable therefore directly relates to survival. Essentially, pain caused by nociception should be down-regulated if this stimulus occurs in competition with an even which is more important for survival, such as a worse pain or other stressful events, a salient reward, or during goal-related movement. Conversely, pain can be upregulated due to increased attention in contexts where it is the most important event or there is a bias towards negative aspects of the pain experience for reasons such as anxiety, catastrophizing, or depression. Such a negative bias can be transient or due to personality traits [35,2].

Neuroimaging studies of pain modulation in humans have often, but not always implicated the descending pain modulatory circuit in the brainstem. In addition, as reviewed extensively by Knudsen and colleagues in this issue, a number of cortical and subcortical brain regions are thought to play a role in determining the subjective experience of pain. The studies reviewed demonstrate clearly that no region within the 'pain neuromatrix' is consistently unaltered by factors which modulate the experience of pain. Therefore, a putative primary nociceptive cortex in the human brain which reflects only nociceptive input irrespective of factors relating to homeostasis, has yet to be identified. In fact, primary sensory cortices such as visual area 1 (V1) are also modulated by attention and other factors [32]. Whether the changeability of pain is unique is thus uncertain. Importantly, however, the 'pain modulatory cocktail' reviewed by Knudsen and collegues forms the basis of the challenge as well as the promise of many treatments of chronic pain.

References

[1] Arntz A, Dreessen L, De Jong P. The influence of anxiety on pain: attentional and attributional mediators. Pain 1994;56(3):307–14.
[2] Berna C, Leknes S, Holmes EA, Edwards RR, Goodwin GM, Tracey I. Induction of depressed mood disrupts emotion regulation neurocircuitry and enhances pain unpleasantness. Biol Psychiatry 2010;67(11):1083–90.
[3] Bingel U, Lorenz J, Schoell E, Weiller C, Buchel C. Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain 2006;120(1–2):8–15.
[4] Cabanac M. Physiological role of pleasure. Science 1971;173:1103–7.
[5] Cabanac M. Sensory pleasure. Q Rev Biol 1979;54(1):1–29.
[6] Cannon WB. Organization for physiological homeostasis. Physiol Rev 1929;9(3):399–431.
[7] Colloca L, Benedetti F. Placebos and painkillers: is mind as real as matter? Nat Rev Neurosci 2005;6(7):545–52.
[8] Craig AD. A new view of pain as a homeostatic emotion. Trends Neurosci 2003;26(6):303–7.
[9] de Araujo IE, Kringelbach ML, Rolls ET, McGlone F. Human cortical responses to water in the mouth, and the effects of thirst. J Neurophysiol 2003;90(3):1865–76.
[10] Derbyshire SWG, Osborn J. Offset analgesia is mediated by activation in the region of the periaqueductal grey and rostral ventromedial medulla. Neuroimage 2009;47(3):1002–6.
[11] Dickinson A, Dearing MF. Appetitive–aversive interactions and inhibitory processes. In: Dickinson A, Boakes RA, editors. Mechanisms of learning and motivation. Hillsdale (NJ): Erlbaum; 1979. p. 203–31.
[12] Dum J, Herz A. Endorphinergic modulation of neural reward systems indicated by behavioral changes. Pharmacol Biochem Behav 1984;21(2):259–66.
[13] Fairhurst M, Wiech K, Dunckley P, Tracey I. Anticipatory brainstem activity predicts neural processing of pain in humans. Pain 2007;128(1–2):101–10.
[14] Fields HL. Pain: an unpleasant topic. Pain 1999;l6:S61–9.
[15] Fields HL. A motivation-decision model of Pain: the role of opioids. In: Flor H, Kalso E, Dostrovsky JO, editors. Proceedings of the 11th world congress on pain. Seattle: IASP Press; 2006. p. 449–59.
[16] Fields HL. Understanding how opioids contribute to reward and analgesia. Reg Anesth Pain Med 2007;32(3):242–6.
[17] Forsberg G, Wiesenfeld-Hallin Z, Eneroth P, Sodersten P. Sexual behavior induces naloxone-reversible hypoalgesia in male rats. Neurosci Lett 1987;81(1–2):151–4.
[18] Gear RW, Aley KO, Levine JD. Pain-induced analgesia mediated by mesolimbic reward circuits. J Neurosci 1999;19(16):7175–81.
[19] Gerdelat-Mas A, Simonetta-Moreau M, Thalamas C, Ory-Magne F, Slaoui T, Rascol O, Brefel-Courbon C. Levodopa raises objective pain threshold in Parkinson's disease: a RIII reflex study. J Neurol Neurosurg Psychiatry 2007;78:1140–2.
[20] Kringelbach ML, O'Doherty J, Rolls ET, Andrews C. Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. Cereb Cortex 2003;13(10):1064–71.
[21] Moseley GL, Arntz A. The context of a noxious stimulus affects the pain it evokes. Pain 2007;133(1–3):64–71.
[22] Ostrowsky K, Magnin M, Ryvlin P, Isnard J, Guenot M, Mauguiere F. Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. Cereb Cortex 2002;12(4):376–85.
[23] Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia – imaging a shared neuronal network. Science 2002;295(5560):1737–40.
[24] Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, Matthews PM, Rawlins JN, Tracey I. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. J Neurosci 2001;21(24):9896–903.
[25] Price DD, Harkins SW, Baker C. Sensory-affective relationships among different types of clinical and experimental pain. Pain 1987;28(3):297–307.
[26] Raij TT, Numminen J, Narvanen S, Hiltunen J, Hari R. Brain correlates of subjective reality of physically and psychologically induced pain. PNAS 2005;102(6):2147–51.
[27] Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 1997;277(5328):968–71.
[28] Raja S, Meyer R, Ringkamp M, Campbell J. Peripheral neural mechanisms of nociception. In: Wall P, Melzack R, editors. Textbook of pain. London: Harcourt Publishers Ltd.; 1999. p. 11–58.
[29] Reboucas EC, Segato EN, Kishi R, Freitas RL, Savoldi M, Morato S, Coimbra NC. Effect of the blockade of mu1-opioid and 5HT2A-serotonergic/alpha1-noradrenergic receptors on sweet-substance-induced analgesia. Psychopharmacology (Berl) 2005;179(2):349–55.
[30] Salomons TV, Johnstone T, Backonja M-M, Davidson RJ. Perceived controllability modulates the neural response to pain. J Neurosci 2004;24(32):7199–203.

Author's personal copy

[31] Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M. Changes in brain activity related to eating chocolate: from pleasure to aversion. Brain 2001;124(Pt 9):1720–33.
[32] Somers DC, Dale AM, Seiffert AE, Tootell RB. Functional MRI reveals spatially specific attentional modulation in human primary visual cortex. Proc Natl Acad Sci USA 1999;96(4):1663–8.
[33] Stante M, Hanna D, Lotti T. Itch, pain, and metaesthetic sensation. Dermatol Ther 2005;18(4):308–13.
[34] Stevenson GW, Bilsky EJ, Negus SS. Targeting pain-suppressed behaviors in preclinical assays of pain and analgesia: effects of morphine on acetic acid-suppressed feeding in C57BL/6J mice. J Pain 2006;7(6):408–16.
[35] Strigo IA, Simmons AN, Matthews SC, Craig AD, Paulus MP. Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. Arch Gen Psychiatry 2008;65(11):1275–84.
[36] Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. Psychol Assess 1995;7(4):524–32.
[37] Szechtman H, Hershkowitz M, Simantov R. Sexual behavior decreases pain sensitivity and stimulated endogenous opioids in male rats. Eur J Pharmacol 1981;70(3):279–85.
[38] Tracey I. Nociceptive processing in the human brain. Curr Opin Neurobiol 2005;15(4):478–87.
[39] Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55(3):377–91.
[40] Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, Matthews PM. Imaging attentional modulation of pain in the periaqueductal gray in humans. J Neurosci 2002;22(7):2748–52.
[41] Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in fMRI in the anticipation and experience of pain. Science 2004;303(5661):1162–7.
[42] Wager TD, Scott DJ, Zubieta JK. Placebo effects on human mu-opioid activity during pain. Proc Natl Acad Sci USA 2007;104(26):11056–61.
[43] Yelle MD, Oshiro Y, Kraft RA, Coghill RC. Temporal filtering of nociceptive information by dynamic activation of endogenous pain modulatory systems. J Neurosci 2009;29(33):10264–71.
[44] Zambreanu L, Wise RG, Brooks JCW, Iannetti GD, Tracey I. A role for the brainstem in central sensitisation in humans evidence from functional magnetic resonance imaging. Pain 2005;114(3):397–407.
[45] Zubieta J-K, Bueller JA, Jackson LR, Scott DJ, Xu Y, Koeppe RA, Nichols TE, Stohler CS. Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. J Neurosci 2005;25(34):7754–62.
[46] Zubieta J-K, Yau W-Y, Scott DJ, Stohler CS. Belief or need? Accounting for individual variations in the neurochemistry of the placebo effect. Brain Behav Immun 2006;20(1):15–26.
[47] Knudsen L, Petersen GL, Nørskov KN, Vase L, Finnerup N, Jensen TS, Svensson P. Review of neuroimaging studies related to pain modulation. Scand J Pain 2011;2:108–20.