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Topical review

A neurobiologist's attempt to understand persistent pain

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HIGHLIGHTS

- To explain persistent pain we must integrate biologic, mental and behavioural levels.
- Pain may be understood as a result of an interpretation of the health of the body.
- Many small challenges may together bring pain networks in a state of hypervigilance.
- The meaning of the pain to the patient is crucial if the goal is to reduce suffering.

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ABSTRACT

This topical review starts with a warning that despite an impressive wealth of neuroscientific data, a reductionist approach can never fully explain persistent pain. One reason is the complexity of clinical pain (in contrast to experimentally induced pain). Another reason is that the "pain system" shows degeneracy, which means that an outcome can have several causes. Problems also arise from lack of conceptual clarity regarding words like nociceptors, pain, and perception. It is, for example, argued that "homeoceptor" would be a more meaningful term than nociceptor.

Pain experience most likely depends on synchronized, oscillatory activity in a distributed neural network regardless of whether the pain is caused by tissue injury, deafferentation, or hypnosis. In experimental pain, the insula, the second somatosensory area, and the anterior cingulate gyrus are consistently activated. These regions are not pain-specific, however, and are now regarded by most authors as parts of the so-called salience network, which detects all kinds of salient events (pain being highly salient). The networks related to persistent pain seem to differ from the those identified experimentally, and show a more individually varied pattern of activations. One crucial difference seems to be activation of regions implicated in emotional and body-information processing in persistent pain.

Basic properties of the "pain system" may help to explain why it so often goes awry, leading to persistent pain. Thus, the system must be highly sensitive not to miss important homeostatic threats, it cannot be very specific, and it must be highly plastic to quickly learn important associations. Indeed, learning and memory processes play an important role in persistent pain. Thus, behaviour with the goal of avoiding pain provocation is quickly learned and may persist despite healing of the original insult. Experimental and clinical evidence suggest that the hippocampal formation and neurogenesis (formation of new neurons) in the dentate gyrus are involved in the development and maintenance of persistent pain.

There is evidence that persistent pain in many instances may be understood as the result of an interpretation of the organism's state of health. Any abnormal pattern of sensory information as well as lack of expected correspondence between motor commands and sensory feedback may be interpreted as bodily threats and evoke pain. This may, for example, be an important mechanism in many cases of neuropathic pain. Accordingly, many patients with persistent pain show evidence of a distorted body image.

Another approach to understanding why the "pain system" so often goes awry comes from knowledge of the dynamic and nonlinear behaviour of neuronal networks. In real life the emergence of persistent pain probably depends on the simultaneous occurrence of numerous challenges, and just one extra (however small) might put the network into a an inflexible state with heightened sensitivity to normally innocuous inputs.

Finally, the importance of seeking the meaning the patient attributes to his/her pain is emphasized. Only then can we understand why a particular person suffers so much more than another with very similar pathology, and subsequently be able to help the person to alter the meaning of the situation.

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1. Introduction

1.1. Complex problems require an integrated approach

1.1.1. The failure of reductionism

"The brain is not merely complex – it is fantastically complex. There are too many degrees of freedom to allow any practical constraint on the possibilities for our understanding." This statement by the British neuropsychologist Weiskrantz [1, p. 10] comes to mind when trying to explain persistent pain by reference to neural structures and processes. The complexity of the brain and the multitude of factors determining human mental life and behaviour strongly suggest that persistent pain cannot be understood by a reductionist approach alone [2–4]. As expressed by Keele in 1957 [5, p. 188]: "Perpetuated pain is... always complex pain, containing many components built into a pain edifice the exploration of which presents the clinician with a very different problem from the physiologist's analysis of experimental pain." This complexity may explain why – despite an exponential rise in publications – the translation of experimental pain research to clinical applications has been disappointingly slow [6,7]. The clinician cannot permit himself the luxury of focusing solely on one aspect, such as peripheral mechanisms, dorsal horn plasticity, or cognitive-emotional factors. In such a situation, it might be advisable to adopt a "bird's eye view" rather than addressing single factors in detail. This Topical Review is an attempt at such an approach.

1.1.2. Degeneracy and reductionism

A further reason why the reductionist approach fails is that complex biologic systems exhibit *degeneracy* – that is, an outcome does not have a unique basis, and similar patterns of activity can be produced by different mechanisms [8–10]. For example, several kinds of ion channels can render nociceptors hyperexcitable, and if one is blocked others take over [10]. Furthermore, neural networks typically exhibit degeneracy – that is, more than one neuronal system can produce the same response [11,12]. For example, pain with the same location and of the same character may be associated with different cortical activation patterns [13]. It is indeed striking how pain therapies aiming at eliminating one apparently crucial component in the "pain edifice" (e.g. cordotomy, dorsal rhizotomy, nerve section, blocking specific ion channels) so often give only temporary relief [10,14–16]. That persistent pain is associated with hyperexcitability (sensitization) in parts of the CNS begs the question of what causes the hyperexcitability and why it occurs in one person but not in another.

2. Pain and nociceptors – a conceptual note

2.1. What pain is and what it is not

Unfortunately, the "pain" literature is often conceptually unclear due to a lack of an explicit distinction between pain as a sensation (experience) on the one hand and its causes and underlying mechanisms on the other. Pain is a sensation, and in common with other sensations (e.g. itching) it has a bodily location. Nevertheless, pain is obviously not a *thing* that can be physically localized, in contrast to neurons and their activities (pain is not in the brain), inflammation, a herniated disc, and so forth. Neither is pain a perception: an object or event exists regardless of whether it is perceived or not, whereas a pain (e.g. in the knee) exists only as it is felt [17]. A perception may be falsified (I thought my pain was caused by a torn meniscus, but it turned out to be something else), while a sensation cannot. *Whether* pain is felt and the intensity of suffering, however, depend critically on how the person perceives the situation. In other words, we must distinguish between the experience of pain and the meaning that the person gives to it. It obviously does not make sense to say that "my knee hurts but I do not feel it", but the person's beliefs about the cause of pain may be right or wrong. It is an example of conceptual confusion when the doctor questions the patient's report of pain because he does not find a plausible cause by his examination. The pain is exactly as the person describes it (if we exclude persons that for some reason lie); the cause of pain, however, may be located somewhere else or not be what the person believes. As pointed out by Bennett and Hacker [17, p. 123]: "So-called referred pains (e.g. sciatica, referred toothache) are not pains which the subject *mistakenly* thinks are where he points or assuages, but rather pains that are felt in places other than the locus of the injury, infection, etc. ... So, the *location of the cause of a pain* must be distinguished from the location of the pain itself."

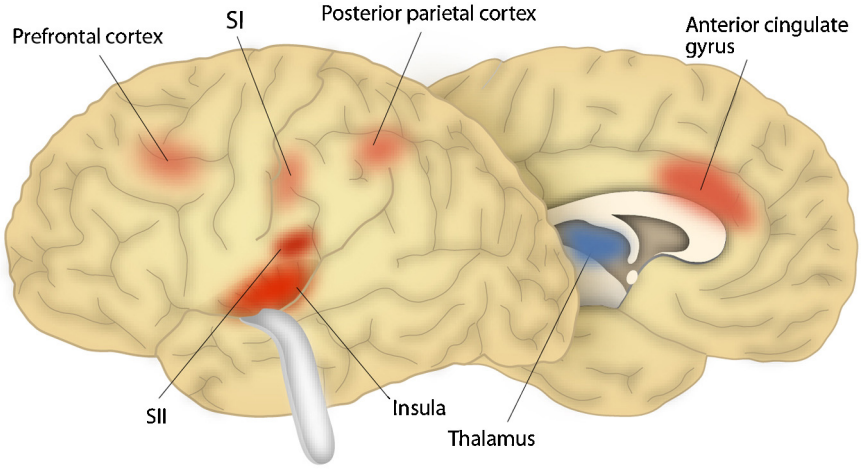

Fig. 1. Regions of the cerebral cortex showing increased activity during experimental pain, as studied with functional MRI. Based on [25].

2.2. Homeoceptor rather than nociceptor?

The use of words such as "nociceptor", "pain system", "pain receptor" and "pain matrix", may restrict our thinking unduly. For example, the basic properties of nociceptors enable them to constantly monitor the composition of the tissues and the mechanical and thermal forces they are subjected to, whereas they evoke pain only under certain conditions and in certain contexts. That is, the main task of nociceptors appears to be to detect and signal *homeostatic threats* [18,19], and only when the threat requires conscious action do we feel pain. Consequently, "homeoceptor" might be a more appropriate term than nociceptor. Daily activities that are not experienced as painful such as using scissors, opening a jar, playing the guitar, riding a bicycle etc. nevertheless must be expected to excite many mechanosensitive nociceptors [20]. Also, when we turn over in bed, change our position in a chair, or move a leg to alter the strain on ligaments it is most likely initiated by signals from polymodal nociceptors. Furthermore, microneurographic studies [20,21] show that considerable firing of human C-fibres can be evoked by non-noxious stimuli. Even in controlled, experimental situations the relationship between C-fibre firing-frequency and pain is far from linear [21]. Thus, firm mechanical stimulation of the skin (pinching, pressing with a pointed object) can make C-fibres fire with a high frequency (10/s) without evoking pain, whereas radiant heat causes pain with a C-fibre firing-frequency of 2/s. Even with radiant heat the nociceptors begin increasing their firing rate at temperatures well below the threshold for eliciting pain [21]. In conclusion, all sensory signals must be evaluated in a broad context to be useful, and signals from nociceptors are no exception. As expressed by Prescott and Ratté [22, p. 632]: "...noxious stimulation, although crucial for normal (i.e. nociceptive) pain, is neither necessary nor sufficient to evoke pain...There is nothing innate to primary afferent nociceptors that endow them, and only them, with the capacity to evoke pain."

3. The relationship between brain activity and pain

3.1. Network activity and the feeling of pain

The brain correlate of our mental life is most likely synchronized, oscillatory electrical activity in distributed neuronal networks [23,24]. This pertains also to the feeling of pain [25–27], and numerous neuroimaging studies (PET, fMRI) have revealed a consistent pattern of activated cortical sites when people are subjected to experimental pain [28–30]. The assumption that these sites constitute nodes in a "pain network" is strengthened by the demonstration that the nodes are functionally connected [26]. The anterior cingulate gyrus, the insula, the second somatosensory area (SII), and the thalamus (less consistently some other parts) show enhanced activity during acute, experimental pain (Fig. 1). As might be expected, these sites are also targets of nociceptive signals carried in the spinothalamic tract [31]. However, activation of the typical "pain network" correlates with pain experience even in situations with no nociceptive input, such as in persons under hypnotic suggestion [32,33]. Indeed, excruciating pain can be experienced in situations where a person mistakenly perceives a serious injury [34]. Furthermore, merely anticipation of pain activates the "pain network" [35,36], whereas perceived ability to control the intensity of an impending nociceptive stimulus reduces the network activity and subsequent pain experience [37]. The link between network activity and pain sensation is further strengthened by the finding that network activity increases in parallel with reported pain intensity rather than with stimulus intensity [36]. Fig. 2 gives a highly schematic presentation of various inputs that may drive the "pain network" and thereby evoke pain sensation.

Due to the complexity of clinical pain, the responsible networks are harder to identify than those related to experimental pain. Accordingly, results vary among studies and are often difficult to interpret. Nevertheless, it seems safe to conclude that persistent clinical pain does not necessarily have the same cerebral "signature" as acute experimental pain [38]. The involvement of the medial prefrontal cortex [38,39] seems particularly interesting, since this region is thought to be implicated in making meaning of sensations from one's own body [40]. Less consistently, several cortical and subcortical regions outside the "pain network" have been associated with persistent pain (e.g. the amygdala, the accumbens nucleus, and the cerebellum). This should perhaps not be surprising, since persistent pain influences most cognitive and emotional processes.

Numerous MRI studies have reported widespread cortical grey matter reductions (less often increases) in patients with persistent pain [41,42]. Regions with alterations differ considerably among studies, however, and the significance of such findings is unclear. Broadly speaking, the findings indicate that persistent pain leads to changes in large-scale networks, and that core pain-related regions may be affected in most persons with persistent pain whereas alterations in other regions may be pathology-specific [42]. The grey matter alterations may be a result of persistent pain rather than a cause [43,44], since they seem to disappear when the pain is relieved (e.g. after surgery for painful hip osteoarthrosis, [43]).

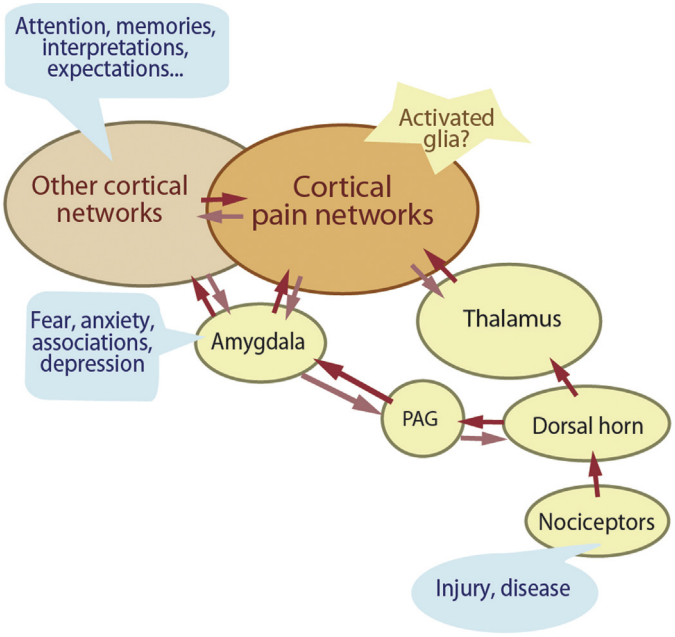

Fig. 2. The cortical pain networks and modes of activation. Schematic to show how quite different inputs can activate the network – from peripheral nociceptors triggered by tissue injury to purely mental processes.

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3.2. Is the "pain network" specific for pain?

The foregoing account strongly suggests that the feeling of pain is correlated with activation of certain cortical networks. These networks are most likely not *specific* for pain, however. Thus, the nodes of the pain network are activated in conjunction with other mental phenomena than pain. For example, the anterior cingulate gyrus has been implicated, among other tasks, in self-control and monitoring of goal-directed actions [45]. The insula shows increased activity in tasks evoking emotions, responds to inputs from various sensory modalities, and is related to bodily awareness [46,47]. Both the anterior cingulate gyrus and the insula seem to be involved in attentional processes [45–47]. Overall, the "pain network" activity seems mainly to reflect the *salience* of a stimulus regardless of its modality [47–49]. Accordingly, both the anterior cingulate gyrus and the insula are included in the so-called salience network [50,51], characterized by its activation by any event that catches our attention and increases arousal. Certainly, pain is a highly salient feeling not meant to be ignored.

Nevertheless, the question of whether cortical networks show some degree of pain specificity is not finally settled. For example, some experimental and clinical findings may indicate that the posterior parts of the human insula at least show some degree of pain specificity [52–54]. Furthermore, Wager and coworkers [29] identified what they interpreted as a "neurologic signature of pain", based on fMRI and machine-learning analysis. They found that experimental pain is associated with a specific pattern of cerebral activation that differs from activation patterns caused by other salient sensory signals (see, however [55] for a critical discussion of Wager and coworkers' conclusions).

Finally, it should be emphasized that the fact that certain patterns of network activity are *correlated* with pain experience does not prove that its activation is *necessary* for the feeling of pain. Indeed, a patient suffering a cerebral lesion (due to herpes simplex encephalitis) encompassing the amygdala, anterior cingulate, and the insula reported normal pain sensations to nociceptive stimulation [45,56]. This may probably be an example of network *degeneracy* [11,12], as discussed above.

4. What drives the "pain network" in patients with persistent pain?

4.1. Many false alarms preferable to a few missed ones

The importance of the ability to feel pain is demonstrated by the sad fate of individuals born without pain sensations [57]. Pain may be viewed as one among several alarms that serve to protect our physical and mental integrity by forcing us to change behaviour. In contrast to other sensory events that tend to adapt when a stimulus continues unaltered, alarms would not serve their purpose if they adapt, and the neural elements responsible for producing pain sensitise rather than adapt. Also, the relationship between pain and a specific event must be quickly learned and remembered. This requires that responsible neuronal groups are highly *plastic*. It follows also that the detector must be very *sensitive*; no threats should be missed, and it is better for survival with many false alarms than a few missed ones. This further implies that the system cannot be very *specific*; genetic pre-specification of all possible noxious life events would be impracticable. Instead, the system is highly adaptable due to its capacity for fast learning. These properties make the system prone to learning from alarms that were meant to be transitory, and may help, at least in part, to explain why the system so often goes awry. A misunderstanding concerning the cause and consequences of an event or situation is remembered (subconsciously), and continues to influence behaviour.

4.2. Pain, learning, and memory

When pain becomes persistent without a continuous nociceptive input, learning (in the form of widespread synaptic changes) must have taken place. In natural situations, much of the learning is conditioned rather than a direct response to a nociceptive input [58]. For example, in a situation requiring movement of a recently injured body part, the alarm may sound even before movement has started. The person learns to avoid everything that is expected to cause the pain [59,60]. Memory traces are presumably consolidated every time pain is temporally linked with the *intention* to move – it need not be an overt movement. To the person, the pain (or merely the expectation of pain) means that the body part is injured, regardless of the doctor's assertions to the contrary. However, while learning avoidance behaviour is an important factor in maintaining pain [59], complex natural situations certainly include more varied learning opportunities [61]. It is how the person perceives the total situation – including nociceptive input, other sensory inputs, social context, previous experiences, expectations, mindset, and so forth – that will determine what is learned and the subsequent pain-related behaviour (Fig. 2). We will return to this under "The meaning of pain".

A role of *memory* in persistent pain is exemplified by case reports of a few persons who, after becoming amnesic due to (most likely) transitory brain ischaemia, experienced relief of persistent pain and opiate dependence [62,63]. It should be noted that the patients had somatic diseases (bone metastases and complications from abdominal and back surgery) that seemingly explained their severe pains as caused by nociceptive signals. The kind of amnesia in these patients strongly suggests injury to the hippocampal formation. That this part of the brain should be involved in persistent pain may perhaps seem surprising since it is related mainly to explicit (declarative) and episodic memory [64]. However, further support for hippocampal involvement in persistent pain comes from a study showing that transition to persistent back pain was

associated with altered hippocampal functional connectivity, notably with the medial prefrontal cortex [65]. Interestingly, connections between the medial prefrontal cortex and the hippocampal formation are involved in extinction of contextual fear [66]. Finally, animal experiments indicate that reduced adult hippocampal neurogenesis is related to development of persistent neuropathic pain [67]. Collectively, it seems plausible that deficits in contextual processing [66] – depending on disturbed interactions between the medial prefrontal cortex and the hippocampus – contributes to making pain persistent. Unfortunately, we cannot yet answer the clinically most relevant question: what might cause a disturbed contextual processing in patients with persistent pain?

4.3. Pain as result of an interpretation of the state of the body

In their book "Phantoms in the brain" [68, p. 54] Ramachandran and Blakeslee aptly states: "..pain is an *opinion* of the organism's state of health rather than a mere reflexive response to an injury". Accordingly, pain is felt (the alarm bell rings) whenever a homeostatic threat is considered sufficiently serious by our bodily surveillance systems. To reach an optimal conclusion, many kinds of information must be evaluated and integrated (presumably by the salience networks): is bodily homeostasis threatened? How serious is the threat? What does the threat mean? For a correct interpretation of the multitude of sensory signals arising in the body, a proper balance among the various somatosensory modalities seems necessary. Loss of sensory information – regardless of whether it concerns low-threshold mechanoreceptors, thermoreceptors, nociceptors, or all – may cause persistent pain [69–71]. Furthermore, to feel the body as normal, motor commands need to be matched by expected sensory feedback from the moving parts [72,73]. Phantom pain, for example, may probably be understood in the context of distorted sensory and motor information processing. Thus, there is no flow of afferent signals from the missing body part, and motor commands are not matched by the expected sensory feedback. Often the person experiences that the missing body part is in a painful position, which cannot be altered voluntarily [74]. The above explanation is supported by the relief of pain with mirror visual feedback [75]. Presumably, this induces an illusion of normality and movement control of the missing body part, and perhaps "resets" networks that monitor bodily homeostasis so that the alarm is shut off. The illusion of normality created by mirror therapy seems to depend both on visual and proprioceptive feedback [76]. Mirror visual feedback has been found to reduce pain also in paraplegic patients with spinal cord injuries [77,78].

4.4. Disturbed body image and persistent pain

The foregoing account suggests that persistent pain can be reduced by therapies that alter (normalize) the person's perception of her own body. Indeed, patients with persistent pain often show evidence of disturbed ownership and body image (the latter term used here in a broad sense, including both implicit and explicit body knowledge) [79–83]. It is plausible that neural networks processing bodily information are changed after deafferentation, but as mentioned above, grey matter alterations occur in virtually all kinds of persistent pain conditions [41–44], presumably as an expression of network plasticity. For example, most patients with complex regional pain syndrome shows neglect-like symptoms and a distorted perception of the affected limbs [81], and patients with chronic back pain showed a disrupted body image of the back [82].

4.5. Network locking and persistent pain

So far, we have discussed evidence that persistent pain is correlated with plastic changes in neural networks, including all levels of the CNS. At the highest level the changes seem to concern networks related to sensory processing, to stimulus salience, memory, body image, and body ownership. The widespread alterations are most likely functionally correlated, and may help to explain core features of persistent pain at a mechanistic level. However, we still have only partial answers to what drives the plastic changes in the first place. After all, most people do not develop complex regional pain syndrome after an injury, not all persons with deafferentation develop persistent neuropathic pain, not all diabetics with peripheral neuropathy experience pain, only some suffer from persistent postoperative pain, and so forth. Many gene polymorphisms [84,85], personality characteristics [86,87], and neuroimaging data [55,88] are associated with individual variations in the tendency to develop persistent pain. Nevertheless, we are far from being able to predict with any clinically useful degree of certainty who will and who will not develop persistent pain. As concluded by Denk and McMahon [85]: "Just like life itself, some aspects of chronic pain may end up remaining irreducibly complex and ultimately unpredictable." It may be that just one small added negative influence – that would be impossible to identify–is the final straw initiating an avalanche that alters networks responsible for homeostatic surveillance. A hypothesis based on the Ising model from physics [89] explains how acute pain becomes chronified when small changes (of one or more among numerous factors) suddenly leads to large changes. The networks may then be brought to a state that, for example, locks the "homeostat" at a high and inflexible level of sensitivity (Fig. 3). It should be realized that neither neurons nor complex interactive networks behave linearly [90], and that brain functional networks are continuously shaped and reshaped by synchronization (by phase and frequency locking) and desynchronization. The normal functioning of the brain is characterized by constantly shifting activity within and between large-scale networks [90,91].

Relief of persistent pain by seemingly nonphysiologic measures, such as caloric or galvanic vestibular stimulation [92] transcranial motor cortex stimulation [78,92], and electroconvulsive therapy [93] may perhaps be due to a sudden input that releases a locked network and restores plasticity [94].

5. The meaning of pain

5.1. The need for a higher level of explanation

Much of the discussion in the foregoing section dealt with mechanistic explanations of persistent pain. Knowledge about neurons, transmitters, and neural networks is, however, insufficient when trying to understand and alleviate the suffering of real people. More and more detailed knowledge down to the molecular level does not answer the clinically most important questions, namely what "drives" the pain network in one person, and what determines that nociceptor signals are prevented from evoking pain in another person with very similar injury or disease? To answer such questions, we need to go beyond the biologic and mechanistic level and search for the *meaning* the person ascribes to the pain (Fig. 3).

5.2. Evaluation of the total situation determines pain experience

Eric J. Cassell in his book "The nature of healing" [95, p. 2] puts pain in a broad context: "Sickness and its manifestations are inextricably bound up with the phenomenon of meaning. Everything that happens to people – events, relationships, every sight and sound, everything that befalls the body – is given meaning." A pertinent example is the apparently paradoxical finding that a large proportion (37%) of persons with acute injuries arriving at an emergency clinic do not feel pain [96], and a much higher number among

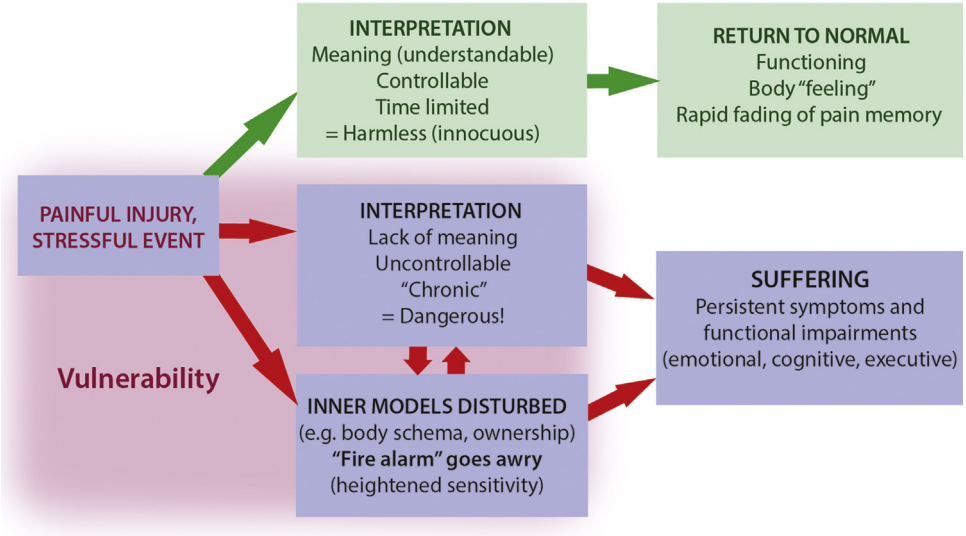

Fig. 3. Persistent pain and meaning. Possible steps and factors that may differentiate the normal situation, in which pain abates in pace with the healing, from situations with development of persistent pain.

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wartime casualties have a pain-free period [97]. Henry K. Beecher, studying pain in wounded soldiers evacuated from the frontline in the Second World War, could find no relationship between the extent of the injury and experienced pain, and concluded [97, p. 1609]: "The intensity of suffering is largely determined by what the pain means to the patient." With our present day knowledge, we can explain the freedom from pain at a mechanistic level as due to descending inhibitory connections that effectively shut off transmission of nociceptive signals [98], but this begs the question of what controls the descending inhibitory system. P.D. Wall discussed what the meaning might be in the examples with injury and no pain, and proposed [99, p. 260] "..that injury may be followed by circumstances in which treatment of the injury does not have the highest biological priority. Pain does not occur in this phase. The three obvious high priority behaviours are fighting, escaping and obtaining aid." Perhaps the most clear-cut example of this kind of meaning is life-threatening situations in which continued physical activity is more important for survival than passivity. Likewise, an athlete may feel less pain because the goal of winning is more salient than the fear of later physical incapacity [100].

The importance of meaning for pain experience is not limited to the examples of acute injuries discussed above [101,102]. For example, whatever the cause of pain, fear of future consequences will influence its intensity and unpleasantness: Does the pain mean prolonged suffering or death? Will the condition prevent me from pursuing activities and goals that are dear to me? Will I lose my job and face economic problems and social isolation? Fear and anxiety are intimately coupled with the meaning the person attributes to the pain – they are aspects of the same phenomenon [95,99].

Experimental studies also support the importance of meaning for pain experience, and also the impact of verbal suggestions. For example, ischaemic arm pain in healthy volunteers was tolerated considerably longer when the person was told that ischaemia is good for muscle cells [103]. It was also shown that this effect could be abolished completely with administration of naloxone and rimonabant (blocking opioid and cannabinoid receptors). One study using hot and cold stimuli applied to the neck showed that expectation of tissue damage increases the experience of pain [104]. This is of course just two among many studies demonstrating effect of expectation – placebo and nocebo – on pain experience [for a recent review see 105].

Ethical issues

There are no ethical issues to report.

Conflict of interest

None declared.

References

[1] Weiskrantz L. Consciousness lost and found. A neuropsychological exploration. Oxford: Oxford University Press; 1997.
[2] Cohen SP. Botulinum toxin type B for chronic pain: panacea or snake oil? The need for more and better preclinical studies. Anesth Analg 2015;121:20–1.
[3] Marchettini P, Laceranza M, Formaglio F. Experimental pain models and clinical chronic pain: is plasticity enough to link them? Behav Brain Sci 1997;20:458–9.
[4] Miles A. On a medicine of the whole person: away from scientistic reductionism and towards the embrace of the complex in clinical practice. J Eval Clin Pract 2009;15:941–9.
[5] Keele KD. Anatomies of pain. Oxford: Blackwell Scientific Publications; 1957.
[6] Jensen TS. Focus foreword: from molecules to suffering. Nat Rev Neurosci 2005;6:505.
[7] Wolff C. Overcoming obstacles to developing new analgesics. Nat Med 2010;16:1241–7.
[8] Edelman GM, Gally JA. Degeneracy and complexity in biological systems. Proc Nat Acad Sci U S A 2001;98:13763–8.
[9] Marder E, Goaillard J-M. Variability, compensation and homeostasis in neuron and network function. Nat Rev Neurosci 2006;7:563–74.
[10] Ratté S, Prescott SA. Afferent hyperexcitability in neuropathic pain and the inconvenient truth about its degeneracy. Curr Opin Neurosci 2016;36:31–7.
[11] Tononi G, Sporns O, Edelman GM. Measures of degeneracy and redundancy in biological networks. Proc Natl Acad Sci U S A 1999;96:3257–62.
[12] Price CJ, Friston KJ. Degeneracy and cognitive anatomy. Trends Cogn Sci 2002;6:416–21.
[13] Hashmi JA, Baliki MN, Huang L, Baria AT, Torbey S, Hermann KM, Schnitzer TJ, Apkarian AV. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. Brain 2013;136:2751–68.
[14] Noordenbos W, Wall PD. Implications of the failure of nerve resection and graft to cure chronic pain produced by nerve lesions. J Neurol Neurosurg Psychiat 1981;44:1068–73.
[15] Cetas JS, Saedi T, Burchiel KJ. Destructive procedures for the treatment of nonmalignant pain: a structured literature review. J Neurosurg 2008;109:389–404.
[16] Devor M, Tal M. Nerve resection for the treatment of chronic neuropathic pain. Pain 2014;155:1053–4.
[17] Bennett MR, Hacker PMS. Philosophical foundations of neuroscience. Oxford: Blackwell Publishing; 2003.
[18] Craig AD. A new view of pain as a homeostatic emotion. Trends Neurosci 2003;26:303–7.

[19] Xanthos DN, Sandkühler J. Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. Nat Rev Neurosci 2014;15:44–53.
[20] Torebjörk HE, Hallin RG. Identification of afferent C units in intact human skin nerves. Brain Res 1974;67:387–403.
[21] Van Hees J, Gybels J. C nociceptor activity in human nerve during painful and non painful skin stimulation. J Neurol Neurosrug Psychiat 1981;44:600–7.
[22] Prescott SA, Ratté S. Pain processing by spinal microcircuits: afferent combinatorics. Curr Opin Neurosci 2012;22:631–9.
[23] Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007;8:700–11.
[24] Singer W. Distributed processing and temporal codes in neuronal networks. Cogn Neurodyn 2009;3:189–96.
[25] Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin 2000;30:263–88.
[26] Ohara S, Crone NE, Weiss N, Lenz FA. Analysis of synchrony demonstrates 'pain networks' defined by rapidly switching, task-specific, functional connectivity between pain-related cortical structures. Pain 2006;123:244–53.
[27] Ploner M, Sorg C, Gross J. Brain rhythms of pain. Trends Cogn Sci 2017;21:100–10.
[28] Duerden EG, Albanese M-C. Localization of pain-related brain activation: a meta-analysis of neuroimaging data. Hum Brain Map 2013;34:109–49.
[29] Wager TD, Atlas LY, Lindquist MA, Roy M, Woo C-W, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med 2013;368:1388–97.
[30] Borsook D, Sava S, Becerra L. The pain imaging revolution: advancing pain into the 21st century. Neuroscientist 2010;16:171–85.
[31] Dum RP, Levinthal DJ, Strick PL. The spinothalamic system targets motor and sensory areas in the cerebral cortex of monkeys. J Neurosci 2009;29:14223–35.
[32] Derbyshire SWG, Whalley MG, Stenger VA, Oakley DA. Cerebral activation during hypnotically induced and imagined pain. Neuroimage 2004;23:392–401.
[33] Raij TT, Numminen J, Närvänen S, Hiltunen J, Hari R. Brain correlates of subjective reality of physically and psychologically induced pain. Proc Natl Acad Sci U S A 2005;102:2147–51.
[34] Fisher JP, Hassan DT, O'Connor N. Minerva. Br Med J 1995;310:70.
[35] Porro CA, Baraldi P, Pagnoni G, Serafini M, Facchin P, Maieron M, Nichelli P. Does anticipation of pain affect cortical nociceptive systems? J Neurosci 2002;22:3206–14.
[36] Koyama T, McHaffie JG, Laurienti PJ, Coghill RC. The subjective experience of pain: where expectations become reality. Proc Natl Acad Sci U S A 2005;102:12950–5.
[37] Salomons TV, Johnstone T, Backonja M-M, Davidson RJ. Perceived controllability modulates the neural response to pain. J Neurosci 2004;24:7199–203.
[38] Apkarian AV, Hashimi JA, Baliki MN. Pain and brain: specificity and plasticity of the brain in clinical chronic pain. Pain 2011;152:S49–64.
[39] Schultz E, May ES, Postorino M, Tiemann L, Nickel MM, Witkovsky V, Schmidt P, Gross J, Ploner M. Prefrontal gamma oscillations encode tonic pain in humans. Cereb Cortex 2015;25:4407–14.
[40] Seitz RJ, Franz M, Azari NP. Value judgements and self-control of action: the role of the medial frontal cortex. Brain Res Rev 2009;60:368–78.
[41] Smallwood F, Laird AR, Ramage AE, Parkinson AL, Lewis J, Clauw DJ, Williams DA, Schmidt-Wilcke T, Farrell MJ, Eickhoff SB, Robin DA. Structural brain anomalies and chronic pain: a quantitative meta-analysis of gray matter volume. J Pain 2013;14:663–75.
[42] Cauda F, Palermo S, Costa T, Torta R, Duca S, Vercelli U, Germiani G, Torta DME. Gray matter alterations in chronic pain: a network-oriented meta-analytic approach. NeuroImage Clin 2014;4:676–768.
[43] Rodriguez-Raecke R, Niemeier A, Ihle K, Ruether W, May A. Brain gray matter decreases in chronic pain is the consequence and not the cause of pain. J Neurosci 2009;29:13746–50.
[44] Ruscheweyh R, Deppe M, Lohmann H, Stehling C, Flöel A, Ringelstein EB, Knecht S. Pain is associated with regional gray matter reduction in the general population. Pain 2011;152:904–11.
[45] Heilbronner SR, Hayden BY. Dorsal anterior cingulate cortex: a bottom-up view. Annu Rev Neurosci 2016;39:149–70.
[46] Menon V, Uddin LQ. Saliency switching, attention and control: a network model of insular function. Brain Struct Funct 2010;214:655–67.
[47] Mouraux A, Diukova A, Lee MC, Wise RG, Iannetti GD. A multisensory investigation of the functional significance of the "pain matrix". Neuroimage 2011;54:2237–49.
[48] Lötsch J, Walter C, Felden L, Nöth U, Deichmann R, Oertel BG. The human operculo-insular cortex is pain-preferentially but not pain-exclusively activated by trigeminal and olfactory stimuli. PLoS ONE 2012;7:e34798.
[49] Liberati G, Klöcker A, Safranova MM, Ferrão Santos S, Ribeiro Vaz J-G, Raftopoulus C, Mouraux A. Nociceptive local field potentials recorded from the human insula are not specific for nociception. PLOS Biol 2016;14:e1002345.
[50] Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007;27:2349–56.
[51] Taylor KS, Seminowicz DA, Davis KD. Two systems of resting state connectivity between the insula and cingulate cortex. Hum Brain Map 2009;30:2731–45.
[52] Garcia-Larrea L. Insights gained into pain processing from patients with focal brain lesions. Neurosci Lett 2012;520:188–91.
[53] Mazzola L, Isnard J, Peyron R, Mauguière F. Stimulation of the human cortex and the experience of pain: wilder Penfield's observations revisited. Brain 2012;135:631–40.
[54] Segerdahl AR, Mezue M, Okell TW, Farrar JT, Tracey I. The dorsal posterior insula subserves a fundamental role in human pain. Nat Neurosci 2015;18:500–3.
[55] Hu L, Iannetti GD. Painful issues in pain prediction. Trends Neurosci 2016;39:212–20.
[56] Feinstein JS, Khalsa SS, Salomons TV, Prkachin KM, Frey-Law LA, Lee JE, Tranel D, Rudrauf D. Preserved emotional awareness of pain in a patient with extensive bilateral damage to the insula, anterior cingulate, and amygdala. Brain Struct Funct 2016;221:1499–511.
[57] Brand P, Yancey P. Pain: the gift nobody wants. New York: Harper-Collins; 1993.
[58] Wiech K, Tracey I. Pain, decisions and actions: a motivational aspect. Front Neurosci 2013;7:46, http://dx.doi.org/10.3389/fnins.2013.00046.
[59] Leeuw M, Goosens MEJB, Linton SJ, Crombez G, Boersma K, Vlaeyen JWS. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. J Behav Med 2006;30:77–94.
[60] Meulders A, Vansteenwegen D, Vlaeyen JWS. The acquisition of fear of movement-related pain and associative learning: a novel pain-relevant human fear conditioning paradigm. Pain 2011;152:2460–9.
[61] Wideman TH, Asmundson GJG, Smeets RJEM, Zautra AJ, Simmonds MJ, Sullivan MJL, Haythornthwaite JA, Edwards RE. Rethinking the fear avoidance model: toward a multidimensional framework of pain-related disability. Pain 2013;154:2262–5.
[62] Choi DS, Choi DY, Whittington RA, Nedeljkovic SS. Sudden amnesia resulting in pain relief: the relationship between memory and pain. Pain 2007;132:206–10.
[63] Chon JY, Hahn YJ, Sung CH, Moon HS. Amnesia and pain relief after cardiopulmonary resuscitation in a cancer pain patient: a case report. Korean Acad Med Sci 2012;27:707–10.
[64] Eichenbaum H. Memory: organization and control. Annu Rev Psychol 2017;68:19–45.
[65] Mutso AA, Petre B, Huang L, Baliki MN, Torbey S, Herrmann KM, Schnitzer TJ, Apkarian AV. Reorganization of hippocampal functional connectivity with transition to chronic back pain. J Neurophysiol 2014;111:1065–76.
[66] Maren S, Phan KL, Liberzon I. The contextual brain: implications for fear conditioning, extinction and psychopathology. Nat Rev Neurosci 2013;14:417–28.
[67] Apkarian AV, Mutso AA, Centeno MV, Kan L, Wu M, Levinstein M, Banisadr G, Gobeske KT, Miller RJ, Radulovic J, Hen R, Kessler JA. Role of adult hippocampal neurogenesis in persistent pain. Pain 2016;157:418–28.
[68] Ramachandran VS, Blakeslee S. Phantoms in the brain. Probing the mysteries of the human mind. New York: William Morrow; 1998.
[69] Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. Neurobiol Dis 1998;5:209–27.
[70] Parry CBW. Pain in avulsion lesions of the brachial plexus. Pain 1980;9:41–53.
[71] Ng Wing Tin S, Ciampi de Andrade D, Goujon C, Planté-Bordeneuve V, Créange A, Lefaucheur J-P. Sensory correlates of pain in peripheral neuropathies. Clin Neurophysiol 2014;125:1048–58.
[72] Harris AJ. Cortical origins of pathological pain. Lancet 1999;354:1464–6.
[73] McCabe CS, Blake DR. Evidence for a mismatch between the brain's movement control system and sensory system as an explanation for some pain-related disorders. Curr Pain Headache Rep 2007;11:104–8.
[74] Ramachandran VS, Hirstein W. The perception of phantom limbs. The D.O. Hebb lecture. Brain 1998;121:1603–30.
[75] Chan BL, Witt R, Charrow AP, Magee A, Howard R, Pasquina PF, Heilman KM, Tsao JW. Mirror therapy for phantom limb pain. N Engl J Med 2007;357:2206–7.
[76] Chancel M, Brun C, Kavounoudias A, Guerraz M. The kinaesthetic mirror illusion: How much does the mirror matter? Exp Brain Res 2016;234:1459–68.
[77] Moseley GL. Using visual illusion to reduce at-level neuropathic pain in paraplegia. Pain 2007;130:294–8.
[78] Soler MD, Kumru H, Pelayo R, Vidal J, Tormos JM, Fregni F, Navarro X, Pascual-Leone A. Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. Brain 2010;133:2565–77.
[79] Haggard P, Iannetti GD, Longo MR. Spatial sensory organization and body representation in pain perception. Curr Biol 2013;23:R164–76.
[80] Senkowski D, Heinz A. Chronic pain and distorted body image: implications for multisensory feedback interventions. Neurosci Biobehav Rev 2016;69:252–9.
[81] Lewis JS, Kersten P, McCabe CS, McPherson KM, Blake DR. Body perception disturbance: a contribution to pain in complex regional pain syndrome (CRPS). Pain 2007;133:111–9.
[82] Moseley GL. I can't find it! Distorted body image and tactile dysfunction in patients with chronic back pain. Pain 2008;140:239–43.
[83] Haugstad GK, Haugstad TS, Kirste UM, Wojniusz S, Klemmetsen I, Malt UF. Posture, movement patterns, and body awareness in women with chronic pelvic pain. J Psychomot Res 2006;61:637–44.
[84] Lee M, Tracey I. Neuro-genetics of persistent pain. Curr Opin Neurobiol 2013;23:127–32.
[85] Denk F, McMahon SB. Neurobiological basis of vulnerability: why me? Pain 2017, http://dx.doi.org/10.1097/j.pain.0000000000000858.

[86] Wade JB, Dougherty LM, Hart RP, Rafii A, Price DD. A canonical correlation analysis of the influence of neuroticism and extraversion on chronic pain, suffering, and pain behavior. Pain 1992;51:67–73.
[87] Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders – pathways of vulnerability. Pain 2006;123:226–30.
[88] Tracey I. Can neuroimaging studies identify pain endophenotypes in humans? Nat Rev Neurol 2011;7:173–81.
[89] Granan L-P. The Ising model applied on chronification of pain. Pain Med 2016;17:5–9.
[90] Chialvo DR. Emergent complex neural dynamics. Nat Phys 2010;6:744–50.
[91] Tognoli E, Kelso JAS. The metastable brain. Neuron 2014:35–48.
[92] Utz KS, Dimova V, Oppenländer K, Kerkhoff G. Electrified minds: transcranial direct current stimulation (tDCS) and Galvanic Vestibular Stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology – a review of current data and future implications. Neuropsychology 2010:2789–810.
[93] Rasmussen KG, Rummans TA. Electroconvulsive therapy in the management of chronic pain. Curr Pain Headache Rep 2002;6:17–22.
[94] DosSantos MF, Ferreira N, Toback RL, Carvalho AC, DaSilva AF. Potential mechanisms supporting the value of motor cortex stimulation to treat chronic pain syndromes. Front Neurosci 2016, http://dx.doi.org/10.3389/fnins.2016.00018.
[95] Cassell EJ. The nature of healing: the modern practice of medicine. New York: Oxford University Press; 2012.
[96] Melzack R, Wall PD, Ty TC. Acute pain in an emergency clinic: latency of onset and descriptor patterns related to different injuries. Pain 1982;14:33–43.
[97] Beecher HK. Relationship of significance of wound to pain experienced. JAMA 1956;161:1609–13.
[98] Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: specificity, recruitment and plasticity. Brain Res Rev 2009;60:214–25.
[99] Wall PD. On the relation of injury to pain. The John J. Bonica lecture. Pain 1979;6:253–64.
[100] Geva N, Defrin R. Enhanced pain modulation among triathletes: a possible explanation for their exceptional capabilities. Pain 2013;154:2317–23.
[101] Ferrell BR, Dean G. The meaning of cancer pain. Sem Oncol Nurs 1995;11:17–22.
[102] Smadar B. A scientific and philosophical analysis of meanings of pain in studies of pain and suffering. In: van Rysewyk S, editor. Meanings of pain. Cham: Springer International Publishing; 2016. p. 107–28.
[103] Benedetti F, Thoen W, Blanchard C, Vighetti S, Arduino C. Pain as a reward: changing the meaning of pain from negative to positive co-activates opioid and cannabinoid systems. Pain 2013;154:361–7.
[104] Arntz A, Claassens L. The meaning of pain influences its experienced intensity. Pain 2004;109:20–5.
[105] Frisaldi E, Piedimonte A, Benedetti F. Placebo and Nocebo effects: a complex interplay between psychological factors and neurochemical networks. Am J Clin Hypnos 2015;57:267–84.